Oncoplastic and Reconstructive Breast Surgery

Second Edition

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Editors

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Springer

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ISBN 978-3-319-62925-4 ISBN 978-3-319-62927-8 (eBook)
https://doi.org/10.1007/978-3-319-62927-8

Library of Congress Control Number: 2018968556

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To Professor Umberto Veronesi, whose philosophy guided us to oncoplastics journey.

To our mentors, models of integrity and discipline for our surgical practice, and who left an indelible mark on us with their skills, creativity, and love of science and art of oncoplastic and reconstructive surgery of the breast.

To all the patients who allowed us to repair an important part of their lives. We got it right many times, but sometimes made unavoidable mistakes when we were not able to achieve the best outcome. This is the experience we want to share in this book, in order to help surgeons make positive decisions.

To our families, particularly our wives and children, for whom we want to create a better future, and try to leave a better world.

Cicero Urban (Curitiba)
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Foreword to First Edition

Surgical management of malignant diseases represents an exemplary model of multidisciplinary management. The combined modality approach to the treatment of breast cancer patients that includes primary surgical treatment, radiation therapy, and chemotherapy needs careful integration of these modalities with the new methods of reconstructive breast cancer surgery. This book provides such a practical approach to the successful management of the disease. For this endeavor, the authors have assembled leaders in the field of oncoplastic breast surgery from around the globe to provide a truly international flavor for the reader. The content of this textbook is therefore relevant to clinicians around the world.

There are 49 chapters, with major sections covering topics ranging from the basic principles of plastic surgery to the difficulties of partial breast reconstruction, to the most advanced field of breast repair after mastectomy. Furthermore, there is a special section dealing with reconstruction in particular subgroups of patients, such as the elderly, pregnant patients, and previously irradiated patients.

The breast is the heart of femininity, and although it is often exploited for commercial reasons, it remains in the mind of every one of us as the true symbol of womanhood, with the role of nurturer, nourisher, and comforter. These gestures evoke a strong sense of affection and the importance that this delicate organ has in the minds of women, who combine the seductive aspect as well as the maternal role, of men, capturing the source of pleasure and desire, and also of children, who find satisfaction and the bond to life itself.

Here, therefore, the desire surfaces for every woman who has experienced breast cancer to rediscover pleasure in her own company, to reconcile with her own shaken femininity, offering the possibility to look in the mirror and rediscover the beauty of her own body, to develop the desire of pregnancy, to hold to the breast and nurture her own baby, and to be able to return to normal daily life, also grateful for the goals achieved by science today: increasingly more conservative surgery, with respect for women's physical and psychological integrity, and reconstructions that allow the restoration of a natural looking breast, with minimum scarring.

In conclusion, this textbook is an excellent, user-friendly guidebook for anyone who cares for or treats patients with cancer of the breast, particularly residents, fellows, and practitioners of general surgical oncology, and, for this reason, it would be a worthy addition to most surgical and oncological libraries.

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Foreword to First Edition

Surgery is still an important part of breast cancer treatment. *Oncoplastic and Reconstructive Breast Surgery* edited by Mario Rietjens and Cicero Urban is a major contribution to the surgical literature in the field of breast cancer. Although mastectomy and axillary lymph node dissection have been well-known techniques for many years, a novel approach for mastectomy should be reconsidered in the case of risk-reducing mastectomy or when a nipple-sparing mastectomy is proposed for selected breast cancers. Conservative treatment is now widely proposed in stage I and II breast cancer leading to wider glandular defects requiring immediate remodeling to avoid disabling cosmetic results. The attitude toward the axillary lymph nodes has changed in the last few years. Sentinel node techniques have been introduced successfully in patients with no tumors and can even be performed twice in cases of local recurrence after conservative treatment.

But the most recent change in breast surgery is the development of oncoplastic indications at the time of the primary surgery. A huge armamentarium of plastic surgery techniques is now available for performing immediate breast reconstruction or remodeling of the breast tissue in cases of wide tumorectomy. The technique of lipofilling represents a true revolution in plastic surgery and can be applied in many situations of breast cancer surgery, provided that statistical studies confirm the safety of the procedure in cancer patients. Indications for implants or autologous myocutaneous flaps should be discussed for each patient requiring an immediate total breast reconstruction. The most sophisticated techniques such as those using microsurgery require close collaboration between the different specialties as well as a high level of competence. This book provides an extensive description of all the techniques available today, with a most practical presentation for surgeons who want to extend their surgical knowledge. The chapters include not only details regarding surgical indications but also data about the risk of complications. The book will be extremely useful for both cancer surgeons trained in oncoplastic surgery and plastic surgeons called upon to reconstruct the breast or to improve the breast morphology after extensive tumorectomies.

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Foreword to Second Edition

The state of the art in oncoplastic surgery is to cope with unfavorable anatomy of relative tumor size and tumor location, to challenge complex local treatments and post-radiation breast surgery, and to remove cancer without mutilation and tumor not touching ink for invasive disease and at least 10 mm in ductal intra-epithelial neoplasia (DIN). Oncoplastic surgery was not invented to extend unnecessary margins but to reduce re-excisions and recalls for distortion after prior breast conserving surgery (BCS) and to lower the rate of mastectomies to save social and medical resources.

Oncoplastic techniques are composed of aesthetic surgical interventions to solve benign, malignant, and aesthetic problems according to the individual anatomy of the breast, the culture of the given individual, and the available resources for the best treatment.

Radiotherapy is an integral part of BCS. Hence, breast conserving surgery can be considered in cases where radiotherapy is an oncological indispensable modality and the preservation of a natural breast is achievable by oncoplastic surgery. Tumor-adapted reductions represent the main purpose of OPS based on a variety of techniques by the use of local breast tissue. The local breast tissue requires RT, and hence, reductions are the ideal oncoplastic method without "jamming" of cosmetic outcome and oncology. The shifting of healthy tissue during the oncoplastic reduction dislocates the tumor bed after excision. In order to avoid a local miss of the boost, the electron IORT, in our hands by the use of in situ application before the tumor removal, is proved advantageous to an external focusing.

The experience from post-radiation surgery after BCS for recurrence or aesthetic correction led to new promising protocols of primary radiotherapy (PRT) in locally advanced breast cancer (LABC) or more difficult cases.

The leading term, tumor-specific immediate reconstruction, was given by my teacher, John Bostwick III, to define oncoplastic surgery. This leading notion opens the perspective of multiple transitions from breast conserving and partial reconstruction to conservative mastectomy and immediate or delayed total reconstruction including backup techniques after prior BCS. Due to the increasing number of breast cancer in primarily aesthetic patients after prior augmentation and cancer complicated implants, new oncoplastic techniques of implant-based breast conserving and implant-based conservative mastectomy and reconstruction have been successfully developed.

Finally, the surgical surface of the operated breast and the individual body image in the mirror after oncoplastic surgery and immediate reconstruction after conservative mastectomy are uniform and sometimes better than before together with a psychological relief from cancer trauma.

In my view, the capacious textbook written by the most experienced and skilled breast surgeons in the world will be a milestone in the establishment of an acknowledged specialization and certificate in the form of a breast surgery license to cover comprehensively oncologic, reconstructive, and aesthetic surgery of the breast. Patients affected with breast cancer, female and male, can be saved without losing their belief in body image and beauty.

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Foreword to Second Edition

It is with great pleasure that I write these introductory comments for the second edition of this important body of work on oncoplastic surgery. Most contributors to this text have dedicated their careers to improving the surgical care of patients faced with the traumatic diagnosis of breast cancer—a unique entity and a life-changing moment for each and every patient.

Historically, the surgeon has been the "quarterback" in the breast cancer patients' care. We must ask why, and perhaps the answer lies in the depths of history and the halls of institutions that have pioneered treatment options for many decades. Reaching far into ancient history we learn that if left untreated, breast cancer becomes a ravenous enemy of a woman's body destroying the breasts' shape, form, and dignity by local consumption of normal tissues engulfing the breast with fulminating spread of malignant disease. Not a pretty picture by any stretch of the imagination.

The field of oncoplastic surgery has come of age and is currently undergoing a long-awaited period of tremendous enthusiasm from surgeons around the world. For decades, surgeons met this philosophical approach to the breast cancer patient with trepidation—thinking it might compromise the surgeons' ability to adequately treat the tumor effectively with the ominous prediction that poor patient outcomes could be the end result. However, history has proven otherwise. The few long-standing pioneers in oncoplastic surgery have proven that outcomes are not only substantiated, but in many if not most cases, patient outcomes are improved. The principles of oncoplastic surgery embrace the multidisciplinary approach with the highest standards placed upon the onocologic assessment and outcome—but without the need for total disregard and sacrifice of aesthetic principles.

Rather, oncoplastic surgery seeks the perfect blend of planning and execution of the surgical procedure(s) most appropriately aligned with multiple factors such as the patient's personal risk factors, tumor location, histologic subtype, size, shape, contour of the breast, and most importantly, the patient's desires. How does the patient feel about the breasts? What is their preference? Perhaps they have long awaited a breast reduction—and this would be the ideal procedure to remove a tumor in the lower pole of the breast? Or perhaps the patient has a genetic predisposition that is best treated with skin/nipple sparing mastectomy and immediate reconstruction?

In the past, the surgical management of breast cancer was judged solely on the basis of "survival rates" as the critical endpoint. However, from decades of experience we are clearly aware that in most cases, women with early breast cancer will achieve and enjoy excellent survival rates. Utilization of the oncoplastic approach to surgery facilitates a comprehensive surgical plan for most patients and ultimately will lead to improved patient outcomes that focus not only on the benefits of the oncologic treatment, but also on the benefits of achieving improved aesthetic outcomes customized to each patient in order to improve the quality of life women can enjoy for decades to come. This exciting textbook embodies the current "Renaissance Period" for oncoplastic surgery—bringing together the science and art of optimizing breast cancer treatment in an efficient, cost-effective, and humanitarian manner.

I congratulate Dr. Cicero Urban and his colleagues on their achievement once again in bringing this important body of work to surgeons around the world seeking to integrate oncoplastic techniques into their practice for the benefit of their patients. It has been my pleasure to contribute, and I hope each of you will reap the pleasure of seeing your patients not only survive but thrive throughout the years.

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Preface to First Edition

Non enim vivere bonum est, sed bene vivere
It is not well living, but living well.

Seneca

The unprecedented progress that breast surgery has experienced in the past century has led to a radical change of paradigms. It is no longer possible to dissociate aesthetic and oncology surgery. This interdisciplinary and translational feature represents a new stage for both breast surgery and plastic surgery all over the world.

Breast surgeons must have a thorough knowledge of the existing concepts in plastic surgery of the breast, as a plastic surgeon who regularly performs breast reconstruction procedures must also be familiar with oncologic principles of breast cancer surgery and keep up to date with developments in chemotherapy, hormonetherapy, radiotherapy, and monoclonal therapies which will influence surgical decisions. Many results considered unsatisfactory in reconstructive surgical procedures in the past are due to this lack of interdisciplinary understanding. Good reconstruction depends on choosing the technique that is most suitable for each patient's aesthetic-functional condition and for the oncologic and clinical factors involved. It all begins with a well-performed and properly balanced oncologic surgical procedure—radical where it needs to be, but conservative and carefully performed in order to preserve breast tissue that will improve the patient's quality of life while maintaining local control of disease.

Nevertheless, most breast cancer surgical procedures do not follow oncoplastic standards, and so patients still experience mutilation resulting from mastectomy without immediate reconstruction. It is important not simply to preserve life but also to preserve a good quality of life and to understand women in a holistic manner. The breast represents more than just its shape or function during the breast-feeding period. It is the true feminine identity itself, which goes through a period of great conflict when cancer is diagnosed. Surgery is a difficult and traumatic event that will affect one in every eight women, and it places breast cancer at the center of public health measures all over the world.

The scope of this book, with its 49 chapters written by renowned and experienced authors, is new. It approaches oncoplastic and reconstructive breast cancer surgery from the viewpoints of the fundamentals of molecular biology and breast anatomy, the basics of diagnosis and clinical therapeutics, ethics and bioethics, clinical oncology, psychology, and quality of life, evaluation of aesthetic outcomes, and oncoplastic and reconstructive techniques, which are described in detail. There is also an accompanying website where one can view videos of surgical procedures conducted by the Plastic Surgery Division of the European Institute of Oncology in Milan (Italy) and from Hospital Nossa Senhora das Graças (HNSG) Breast Unit in Curitiba (Brazil). The various surgical techniques are clearly explained and demonstrated. By such an approach, we aim to link oncologic surgical principles with aesthetic-functional and reconstructive ones, which were in opposition for many decades. The radical approach of the past is now obsolete, with the utmost effectiveness obtained with minimal mutilation. More conservative breast surgical procedures, less radical mastectomies, preservation of the axilla with the sentinel lymph node technique, less aggressive techniques (such as recently developed intraoperative radiotherapy), individualized chemotherapy and target therapies through predic-

tive factors, and more accurate prognoses are all achievements associated with the development of reconstructive techniques that are more efficient but less traumatic. They are what is today an inseparable oncologic-reconstructive-aesthetic-functional combination.

The patient, who is seen in a holistic way, doubtlessly enjoys the great benefit of this change in paradigms: physically, psychologically, and spiritually. It was exactly by bearing this thoroughness in mind that this work was designed, dedicated to all the professionals involved in breast health care and especially to surgeons. We would like to thank all the authors and colleagues who kindly and selflessly helped with the chapters, and especially Jim Hurley II, a dear friend and a skilled oncoplastic surgeon from Chambersburg (USA), for his final review of the English. We also sincerely thank and acknowledge Umberto Veronesi and Jean-Yves Petit, who have dedicated a great deal of their lifetime to patients with breast cancer and therefore have allowed women all over the world to benefit from their creativity and scientific knowledge.

Milan, Italy — Mario Rietjens
Curitiba, Brazil — Cicero Urban

Preface to Second Edition

Since the first edition of this great and successful book, significant advances have been made in oncoplastic and reconstructive breast surgery. There is no doubt anymore about the importance of preserving the breasts, symmetry, and quality of life to breast cancer patients. These principles have overlapped old prejudices and fears about combining in one surgery the goals of oncology and aesthetics.

Professor Umberto Veronesi, who wrote the foreword for the first edition, and the leader of breast conserving movement, sadly passed away in 2016. He left his legacy to new generations of breast surgeons in the twenty-first century. More, today, is not better. More radicalism, most of the time, means unnecessary mutilation and suffering to the patients. Without the consolidation of breast conserving surgery in Milan trials in the 1980s, we probably would be spending more years doing mastectomies and axillary dissections, without reconstruction. Oncoplastic concept had arisen in this fertile field in the 1990s in Europe.

The spirit of this book remains the same—to provide in-depth concepts and techniques to all breast specialists by internationally recognized authors. This is not directed to one single specialty, but across specialty lines, covering a broad range of topics related to breast cancer treatment. It is necessary to recognize the positive impact of body integrity on the quality of life of breast cancer patients, who are living more, but sometimes, unfortunately, not better. So, all efforts should be done in order that all these advances in breast surgery reach most patients around the world.

With the significant improvement in survival, the medical community became more cognizant of the quality of life after breast cancer. Patients' satisfaction and assessment of their quality of life seem to directly correlate with their final appearance after breast cancer surgery, hence the growing interest and enthusiasm among surgeons in the field of oncoplastics and breast reconstruction. The debate about which specialty is entitled to perform this kind of procedure, or, if it is better to have a single or a double-team approach, is obsolete. Since both oncoplastics and breast reconstruction are methods, not specialties, we ought to focus on training to render these techniques available to all breast cancer patients. The real challenge to be faced is not "who" should or can do it, but on "how" best to do it. How to train surgeons, how to replicate it, and how to expand it? Training facilities and skills are worldwide the subject of debate, but the goals are the same.

Plastic surgery creativity and expertise, associated with surgical oncology principles, are the inspiration and mentors for the future of breast surgery. It should be a strong alliance. Effective surgical management of breast cancer requires a complete and deep understanding of both fields, since the patient is unique, and both long-term and disease-free survival should be accompanied with a good quality of life.

South America, Europe, and the United States were together here. Many of the pioneers and leaders in this field are sharing their experiences in this unique book. *Oncoplastic and Reconstructive Breast Surgery* Second *Edition* was updated and extended with more chapters, authors, and videos. We deeply acknowledge all the contributors for their superb chapters and our families for their love and support.

Curitiba, Brazil — Cicero Urban
New York, NY — Mahmoud El-Tamer
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List of Videos

Electronic Supplementary Material: Electronic supplementary material is available in the online version of the related chapter on Springer Link: http://link.springer.com/

Part I

Basic Principles for Oncoplastic and Reconstructive Breast Surgery

Oncoplastic Surgery: The Renaissance for Breast Surgery

1

Gail S. Lebovic

1.1 Background

Since the beginning of recorded time, the breast has been a symbol of motherhood, femininity, and sexuality. It has been portrayed throughout history in works of art symbolizing each of these aspects of a woman's life—and even in religious works of art, the breast has been memorialized as a central focus of a woman's anatomy. Similarly, there is evidence of the challenges and ravages of breast cancer dating back as far as the seventeenth century B.C. [1]. Many accounts of this dreaded disease are documented throughout history, and in some regards, the psychological fear and trauma associated with breast cancer have not changed much at all through the ages—even though our diagnostic abilities and treatment options have managed to dramatically improve the outcomes of women with breast cancer. One of the most comprehensive examinations of the breast throughout history was written by Dr. Marilyn Yalom. Her work illustrates how and why the breast has become such an important symbol of femininity throughout history and why the breast continues to be so important to women in today's modern societies [2]. Her description of the breast as both "life-giving" and "life-destroying" gives us the essence of why breast surgeons must be trained with a keen sense of blending science and art.

When we examine the disease processes that affect the breast(s), the historical journey becomes complex and is one that is quite triumphant when looking at how far we have come. Early cases of breast cancer reported large fungating tumors that killed women quickly, and the entire experience was no less than horrific. Unfortunately, even though modern methods of detection have improved early diagnosis, physicians still see late-stage tumors such as those described hundreds of years ago (Fig. 1.1a, b).

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As far as we can tell, although Hippocrates discussed the potential for removal of the breast, the first documented account of mastectomy is credited to Johan Schultes (1595–1645). However, a detailed description of the operation was only published after his death in 1665 [3–5]. Early mastectomies were made possible with the introduction of surgical instruments that allowed for very rapid removal of the diseased tissue. Although the idea of removing the diseased area gained popularity, women often died from bleeding, infection, shock, or anesthetic complications. However, once anesthetic techniques were perfected, and antibiotics became a routine part of surgical regimens, success with removal of the breast was accomplished. As surgeons go, Halsted is most often credited as the innovative surgeon that perfected the technique of radical mastectomy in the United States in 1882. In fact, Halsted achieved a 5-year cure rate of 40% which was highly regarded. In addition to his aggressive removal of tissue, other factors likely contributed to this success rate as well, such as his use of antiseptic techniques and his use of rubber gloves. Apparently, Halsted had asked Goodyear to develop gloves in 1889. Other surgeons such as Crile and Haagensen were also important in the consistent move toward innovation in fighting breast cancer through surgery, and the Halsted radical mastectomy was the mainstay of breast cancer treatment throughout most of the last century. In fact, it was used in over 90% of all breast cancer cases treated between 1910 and 1964 [6].

As we examine the results of the Halsted radical mastectomy (i.e., removal of the entire breast including much of the skin along with the nipple-areolar complex, underlying pectoralis muscles and the axillary contents), we quickly begin to understand the physical and psychological challenges that women face(d) when deciding to undergo this presumed "life-saving" surgery (Fig. 1.2a, b). Although hundreds of thousands of women have lived through this life-altering surgery, it is clear that the psychological impact on women undergoing mastectomy is profound and includes body image changes as well as many other emotional challenges

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_1

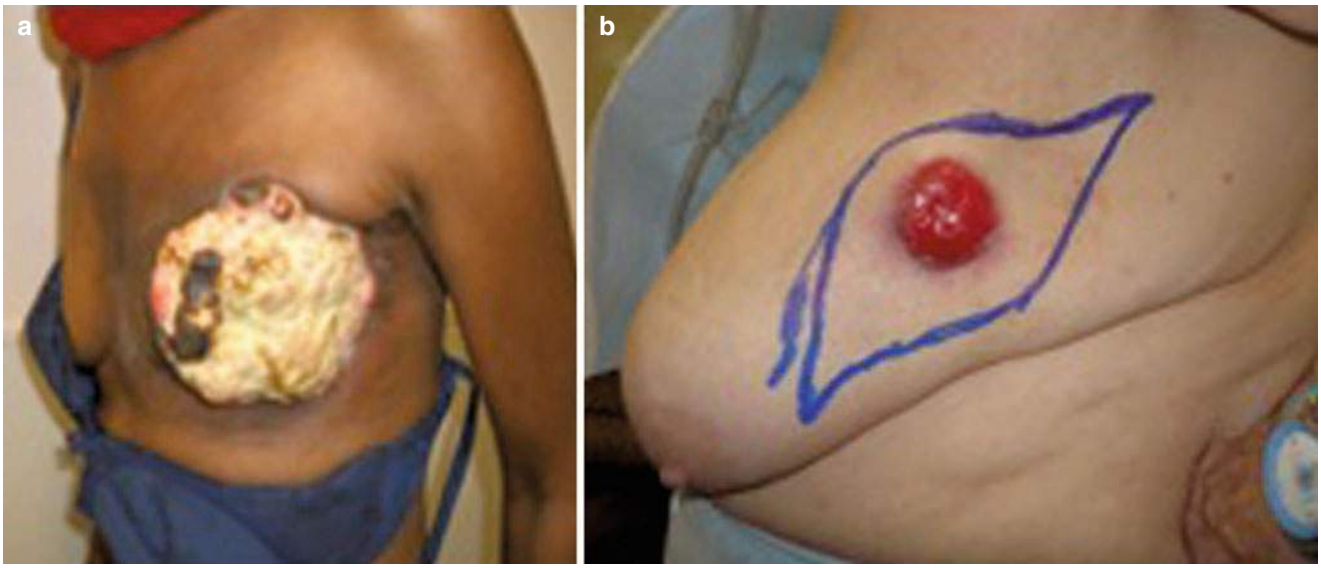

Fig. 1.1 Advanced breast cancer showing fungating lesions extruding through the skin

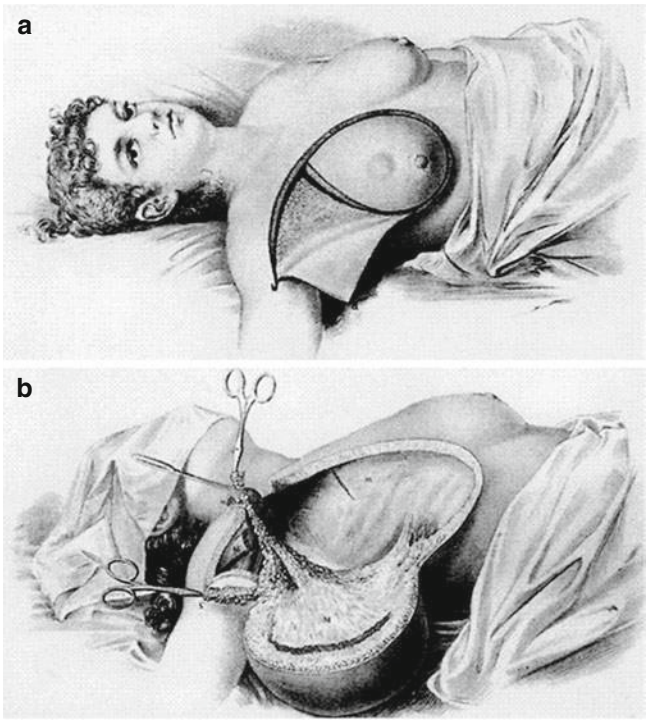

Fig. 1.2 Etchings of Halsted radical mastectomy showing enormous en bloc resection of the breast, underlying muscles, and overlying skin

Table 1.1 Emotional issues and breast cancer

• Fear, anxiety, and distress
• Depression
• Grief
• Body image
• Sexuality
• Fertility
• Planning for the future
• Social support system

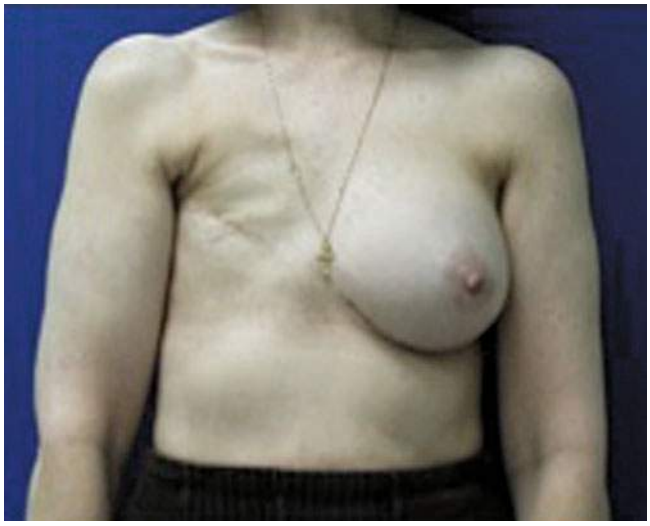

Fig. 1.3 Patient following standard radical mastectomy. Note the body posture with the right shoulder slightly forward as if "guarding" or "hiding" the mastectomy site

that must be addressed in order for successful adaptation to a "new way" of life. Table 1.1 illustrates some of the critical issues that most women struggle with after receiving a diagnosis of breast cancer. Each and every woman will weigh in differently on the priority of these things in their own particular life, but for most women, the single greatest challenge is the adjustment to their new body image.

The photo in Fig. 1.3 shows a woman many years after radical mastectomy of the right breast. In this photo her body language speaks to us, as it shows her stance with her right shoulder angled upward and forward in a manner

Table 1.2 Emotional pros and cons of breast reconstruction

Pros	Cons
Feel whole again	Fear
Maintain femininity	Not essential for well-being
Balanced physically	Too old to matter (i.e., being vain)
Marital/sexual acceptance	Interfere with treatment
Avoid embarrassment of prosthesis	Concern about masking disease
Surgeon's recommendation	Uncertainty about breast appearance
Forget about disease	Requires additional surgery, risk of complications

suggestive of protecting, guarding, and/or trying to "hide" the area of her mastectomy. Many studies confirm that breast reconstruction assists women in their adjustment to mastectomy; however, it does not eliminate the need for psychological adjustment, and in fact, consideration to undergo breast reconstruction brings with it additional and somewhat different issues for a woman to grapple with (Table 1.2). It is essential for the breast surgeon to be trained—not only in the technical aspects of dealing with breast cancer—but with the skills to assist women struggling with these difficult and often very delicate psychological challenges as well.

1.2 Breast Surgery: Evolution of the Science

With women's advocacy groups forming throughout the 1960s–1970s, social awareness about breast issues and breast cancer began to change dramatically. Just a few decades ago, women were loathed to speak about breast cancer in social circles, whereas today, women take to the streets, gather by the thousands, and celebrate their successes in conquering their battle with breast cancer. This awakening coupled with the "feminist movement" of the 1970s created an environment for women to begin questioning their "rights" in the treatment of breast cancer. At the time, most women underwent open surgical biopsy with preoperative consent for the surgeon to proceed with mastectomy if the frozen section was positive for cancer. One can only imagine how traumatic it was for women who faced the uncertainty of waking up from surgery with or without their breast(s). This practice soon came under scrutiny and ultimately called for the standard of care to include a preoperative confirmation of the diagnosis of cancer prior to mastectomy, as well as informed patient consent prior to surgery. There is no doubt that the work of well-known patient advocate Rose Kushner irreversibly changed history in regard to breast cancer treatment. She was the first breast cancer survivor to bring these issues to Washington and create legislation that helped fuel many changes in the United States. Her efforts were of paramount importance.

Although surgical removal of the breast was touted as a giant step forward in the treatment of breast cancer, no doubt surgeons and their patients both struggle(d) to accept this method as the "best" possible solution. For decades, a growing consciousness began to form about the possibility of imaging the breast in order to find tumors at an earlier stage. Thankfully, through the development of imaging techniques that ultimately led to screening mammography programs, the diagnosis of smaller and often "earlier" cancers was made possible. Thus, with the advent of modern-day breast imaging and the diagnosis of earlier and often noninvasive tumors, improved survival rates and better treatment options became a reality [7–9]. For the breast surgeon, this included the notion that perhaps surgical treatment need not be so aggressive. In addition, the interaction between physicians in different sub-specialties became popular as it was noted that a more comprehensive plan could be developed if and/or when a patients' treating physicians communicated directly with one another in the best interest of the patient.

As radiologists began to diagnose smaller tumors, surgeons began to modify the techniques of Halsted, and they began saving the pectoralis muscles and more of the overlying skin of the chest. Studies quickly noted that survival rates were equivalent to radical mastectomy, and thus the "modified" radical mastectomy became popularized. This huge change in breast surgery was most likely due to the earlier stage of disease at the time of diagnosis, but nonetheless, this changed breast surgery forever. As can be seen in Fig. 1.4, the standard modified radical mastectomy has a typical horizontal scar across the breast area and in most cases does not require a skin graft for closure which was quite commonly needed with the radical mastectomy.

From here, surgeons began to hypothesize that perhaps the breast tissue itself (including the nipple-areolar complex) could be preserved if additional therapy (such as radiotherapy and/or chemotherapy) were administered to help decrease or eliminate potential for recurrent disease. Of course the scientific community required classic studies to be performed in order to prove this hypothesis, and through decades of tedious clinical trials, Dr. Umberto Veronesi and his clinical group at the Milan Cancer Center ultimately proved this to be the case. Veronesi's pioneering work and numerous other scientific studies by various surgeons around the world have shown that survival rates for women undergoing breast conservation are equivalent to those having mastectomy if, and only if, many factors are also taken into consideration such as appropriate selection of patients, wide excision of tumor with substantial clear histologic margins, and the use of adjuvant therapy (chemotherapy and/or radiation therapy) as needed [10, 11]. Ultimately, with these critical decisions being made in the field of breast surgery and through the extraordinary courage and foresight of innovative surgeons, scientists, oncologists, radiation oncologists,

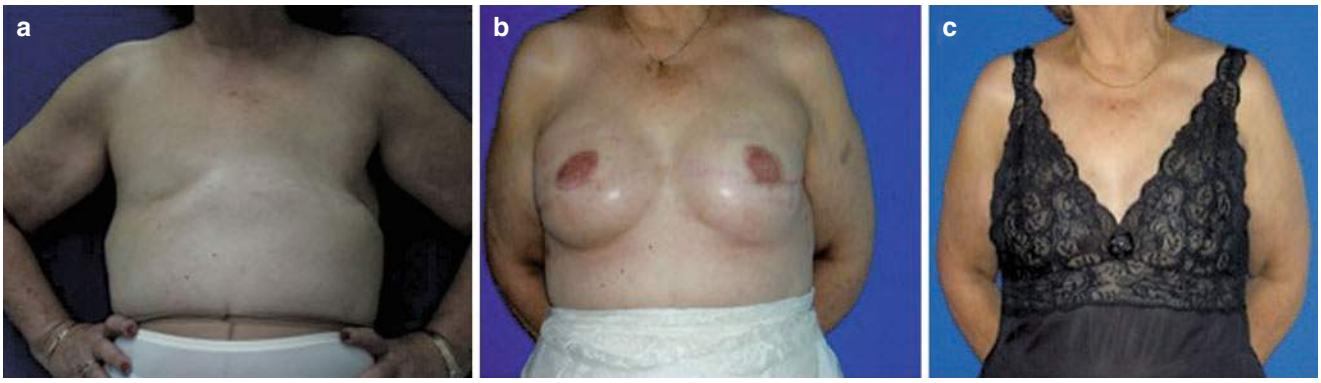

Fig. 1.4 The *left image* (1.4a) shows the patient 30 years after bilateral modified radical mastectomies. She requested and underwent bilateral breast reconstructions (1.4b) which shows how the horizontal incisions result in a somewhat globular shape of the reconstructed breasts leaving them flattened at the central nipple-areolar area. Normally, this is the area of the breast with the most projection, but this limitation of the horizontal incision is quite signficant and also commonly results in the "dog ear" of excess tissue *left behind* at the lateral aspect of the breast. Even with these limitations, we can see that the breast reconstructions have had a positive impact on this patient's body image with her regained self-confidence evidenced by her new lingerie (1.4c)

and other breast cancer specialists working together, the field of breast surgery began to evolve dramatically, and it has never been the same since.

While the idea of breast conservation surgery became a reality, and surgeons and patients alike hoped that mastectomy would become a distant historical footnote, studies ultimately showed that not all women were truly good candidates for breast conservation. Interestingly enough, not all women choose breast conservation either, and so the mastectomy has remained a mainstay in the treatment of breast cancer. Two important questions remain, "how can we best identify suitable candidates for breast conservation" and, equally as important, "how can we improve the aesthetic appearance of the breast(s) following mastectomy?" In fact, the selection of appropriate patients for the appropriate procedure becomes the critical question for the breast surgeons' judgment.

Given today's current imaging techniques, as well as other sophisticated methods to assist with patient assessment such as genetic testing, the selection of appropriate patients has become much more comprehensive and precise. Today, preoperative assessment is the cornerstone of effective, efficient, and appropriate breast surgery, and it is a vital expertise that the breast surgeon must be able to offer in order to provide optimal care to patients.

Simultaneous to the changes occurring in the evolution of the "science" of breast cancer surgery, changes in the evolution of the "art" of breast surgery were occurring as well. These changes resulted in dramatic achievements in the field of plastic and reconstructive surgery, and breast reconstruction became the pinnacle achievement for many surgeons.

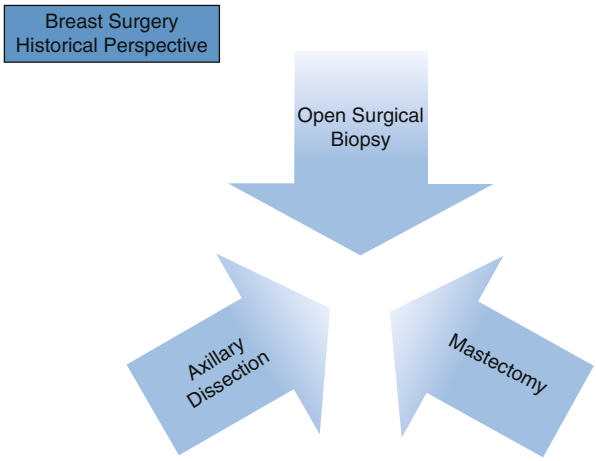

Fig. 1.5 Historical perspective of breast surgery with a few of the procedures available throughout much of the last century

Prior to the parallel changes occurring in each subspecialty involved in the care of the breast cancer patient, the surgeon had few choices in the decision-making process. The treatment of breast cancer was obvious and monotonous—mastectomy (radical or modified radical) (Fig. 1.5). However, as diagnostic techniques improved and as treatment options became more complex, the evolution of the multidisciplinary approach to the breast cancer patient became widely popularized, and today, the multidisciplinary approach is recognized as a much more efficient and effective method for treating patients. Today, this approach serves as the ideal model for treatment of breast cancer as well as many other diseases, and this approach allows us to achieve much better surgical outcomes (Fig. 1.6a–c).

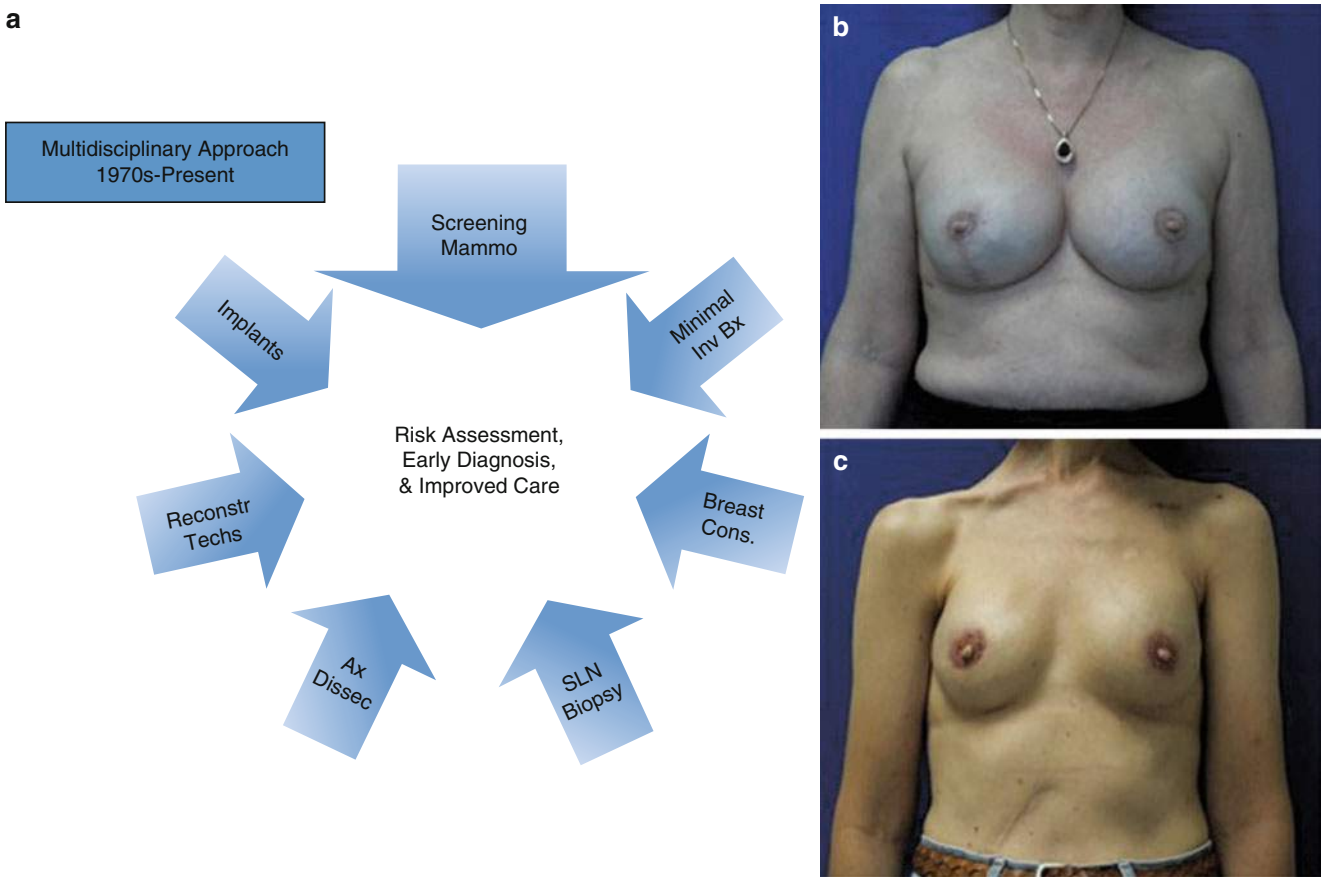

Fig. 1.6 (**a**) Multidisciplinary approach showing many aspects to patient evaluation and work-up that can be used to assist with preoperative planning and surgical decision-making. *Mammo* mammography, *Inv Bx* invasive biopsy, *Cons.* conservation, *SLN* sentinel lymph node, *Ax Dissec* axillary dissection, *Reconstr Techs* reconstruction techniques. (**b**) Case example using a multidisciplinary approach and oncoplastic surgical techniques. The patient presented with BRCA mutation, following bilateral prophylactic mastectomies with bilateral breast and nipple reconstructions. The final result shows skin-sparing mastectomies, tissue expansion with ultimate bilateral submuscular saline implants, and nipple reconstructions. (**c**) Case example using a multidisciplinary approach and oncoplastic surgical techniques. The patient presented with bilateral ductal carcinoma in situ. Mastectomies with bilateral breast and nipple reconstructions were performed. The final result shows total skin-sparing mastectomies, with ultimate bilateral submuscular saline implants (no expansion needed) and nipple reconstructions

1.3 Breast Surgery: Evolution of the Art

In parallel, to the changes occurring in the diagnosis of breast disease and the improvements in the treatment of breast cancer, the focus on the female breast became much more socially acceptable. With the introduction of television, magazines, pornography, and more sexually directed marketing, the world's view of a woman's breast began to change since breasts were literally much more visible each and every day. Historically, being "well endowed" has long been a "virtue" that artists and writers have documented throughout the ages.

In the seventeenth century, Marinello became very interested in methods for preserving the beauty of the breast and his account of the perfect breast: "The breast of a beautiful woman should be wide and full of meat so that no sign of underlying bone be detected and the skin colour should be 'snow-white'. The beautiful neck is like snow but the breast is like milk ... the best breasts are small ones, round, firm, like the round and beautiful apple; they should neither be too attached nor too small ... two raw apples looking like ivory." His description gives us a clear idea of how dedicated he was to developing the art of surgical methods to restore the breasts' own natural beauty [3]. Many others were equally as interested in the "art" of breast surgery, and thus this field began to blossom and take shape.

Some of the earliest methods for breast enhancement relied simply on garments such as corsets and brassieres. These external means of enhancing the breasts, such as padded bras, remain popular today and are well evidenced by the multibillion-dollar lingerie industry. However, surgical enhancement and correction of breast "deformities"

has been an alluring challenge to surgeons since the late 1800s. By the twentieth century, many surgeons were developing and refining various surgical techniques for improving the size, shape, and general appearance of the breasts.

While correction of large and ptotic breasts seemed important and interesting to women and the surgical community, many women were even more interested in methods for enlarging the breasts, and some of the earliest methods for breast enhancement utilized injectables such as paraffin wax and other substances. Unfortunately, most of these methods proved disastrous. In fact one of the first to inject paraffin into the breast for enlargement was Robert Gersuny, and he was also the first to describe paraffinomas in 1899. Later, Buck and Brockaert also described the poor results with this technique, and in fact the results were so bad that decades passed before other invasive techniques were even considered for breast enhancement.

However, as we all know, "necessity is the mother of invention," and in 1950 J.H. Grindlay and his colleagues implanted polyurethane sponges in an attempt to achieve permanent breast enlargement. While this technique was considered quite innovative, it too proved to be disastrous with the end result yielding severely fibrotic, hardened (calcified) breasts that were usually misshapen and very unattractive in appearance.

Later, substances like silicone oil and gel were introduced into the breast(s) via injection. Scientists and surgeons originally believed that these materials were biologically inert. However, injection of these materials into the breasts often results in a substantial inflammatory response, infections, etc. and ultimately led to the abandonment of these techniques. Instead, the innovative idea of encapsulating these materials within a silicone rubber shell and placing these gel implants into the breast took hold, and the first implantable breast-enhancing "implant" devices were developed [3]. The ability to create a rubber silicone shell filled with physiologic saline created a lot of excitement as well, but the first saline-filled implants were fraught with problems including frequent rupture and severe rippling. Since virtually all of the first breast enhancements (augmentations) were performed in the subglandular position, the results were less than optimal aesthetically. These initial saline implants were also prone to rupture because the shell was too thin and fold-fault fracture causing leaks and deflation were very common which led to the demise of the early saline-filled implants. The next monumental phase in the development of breast implants was continued refinement in the production of various silicone materials and implants. These gels have various degrees of viscosity, making multiple different types of implants possible, including shaped implants for special situations. At last, the era of breast augmentation was on its way to success.

Numerous different types of breast implants were produced and marketed through the 1970s and 1980s, some with better rates of surgical success than others. It didn't take long for surgeons to figure out that the utility of breast implants could be expanded to the realm of breast reconstruction. However, the paucity of the skin left after mastectomy created some difficulty in regard to closing the skin wound over an implant. Once again the entrepreneurial spirit led to the development of the "tissue expander," and this wonderful new implant allowed surgeons to begin the era of "immediate" breast reconstruction. Often these expanders can be left in place as the permanent implant. Most importantly, breast reconstruction with tissue expanders is much less invasive and difficult for patients than other types of reconstruction such as myocutaneous flaps. Thus, the patient has less pain, less recovery time, and less time away from work. Expanders are widely used throughout the world, and they remain the "workhorse" for breast reconstruction since they can be used for immediate and/or delayed reconstruction and can maximize the efficiency of breast reconstruction [12].

Breast reconstruction following mastectomy became hugely successful and popular in the 1980s until suddenly in 1990 when implants were banned from clinical use in the United States by the FDA. This sparked a global examination of silicone gel implants in an attempt to examine various problems that some felt might be associated with breast implants. Ultimately, after extensive review and with additional changes and new developments in the manufacturing process, silicone gel implants were reintroduced into the surgical domain. Currently, they are widely used throughout the world and allowed limited use once again in the United States under guidelines outlined by the FDA [13].

Many scientists agree that in fact, it is not the implants themselves that are responsible for some of the difficulties encountered following breast augmentation and/or reconstruction. There are numerous factors that contribute to outcomes following aesthetic and reconstructive breast surgery including patient selection, surgical technique, and postoperative complications such as seroma, hematoma, or subclinical infection. While selection of a specific implant is important, other factors such as surgical approach (submuscular versus subglandular) and surgical technique are also critical in achieving optimal outcomes.

In reviewing the enormous changes that have occurred in breast surgery during the past 40 years, it is quite interesting to note the parallel changes that occurred in breast cancer surgery as well as cosmetic and reconstructive breast surgery. Interestingly, while the process of breast augmentation may seem very different from breast reconstruction, most of the critical issues needed to obtain excellent outcomes are shared in common between the two. This includes many of the psychological and preoperative patient assessment issues as well. Consider first those patients undergoing

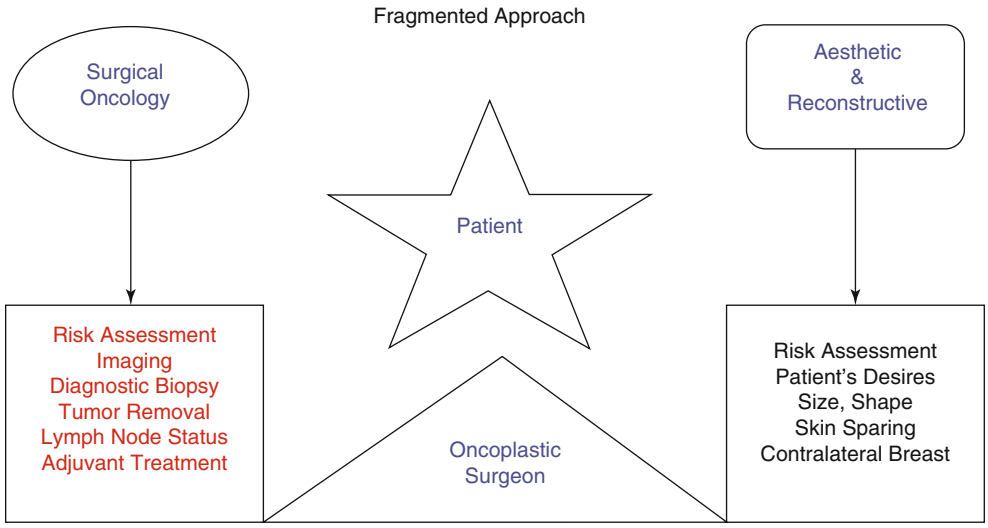

Fig. 1.7 Most commonly, the approach to the breast surgery patient is fragmented. This usually requires two surgeons with distinctly different goals and concerns

augmentation or other elective breast surgery. These women should undergo a thorough multidisciplinary preoperative work-up quite similar to those that all breast cancer patients endure. Although in one group of these patients cancer has already been diagnosed, women undergoing elective breast surgery should be screened for potential breast cancer risk since later in life they will face the need for screening mammography, etc. [14]. This consideration is critical to the patient when choosing various aspects of the augmentation such as implant type, placement, etc. Thus, we see how quickly the lines begin to blur between surgical oncology and aesthetic breast surgery.

It is precisely for these types of observations that in the late 1980s and early 1990s, a few surgeons scattered around the world began to have similar thoughts about the approach to breast surgery. Independently, each of them began to blend the principles of surgical oncology with those of aesthetic and reconstructive surgery resulting in the birth of oncoplastic surgery. At least a decade later, surgeons began to subspecialize in breast surgery; however the evolution of the training programs for this sub-specialty has varied widely in various environments and is in critical need of updating and expanding the curriculum and standardization.

1.4 Oncoplastic Surgery: Blending Science and Art

Part of the difficulty for today's breast surgeons stems from the historical development of surgical sub-specialties and breast surgery in particular. Because most breast cancer surgery was performed (and often still is) by general surgeons, and because reconstructive surgery remained in the solitary domain of the plastic and reconstructive surgeons, the care of breast patients has been quite fragmented in its approach; see Fig. 1.7. Historically the general/breast surgeon was primarily concerned with issues relating to cancer. Their focus was primarily on the oncologic portion of the surgical intervention, and their surgical plan remained separate from the patients' needs, wants, and desires in regard to reconstructive and/or breast surgery to create symmetry between the two breasts. Since breast cancer surgery inherently creates a "net asymmetry" between the two breasts, the surgeon cannot ignore the impact this has on the patients' psychological well-being and feeling of "wholeness" since most women are seeking symmetry as the ultimate outcome.

As described in the sections above, the way that breast surgery evolved resulted in a fragmented approach and often did not result in the best outcomes for the patient. Thus, those surgeons committed to sub-specializing in breast surgery began to practice "oncoplastic surgery" by combining or blending the principles of surgical oncology with those of plastic and reconstructive surgery. As illustrated in Fig. 1.8, the objective is to change the fragmented surgical approach to one that is more complete utilizing a multidisciplinary approach to the patient and planning the patients' surgery in a comprehensive fashion. The ideal situation would be to have each and every "breast surgeon" trained as an "oncoplastic surgeon"—that is to say that the terms would be synonymous. This would allow the breast surgeon to take care of the patients' needs, wants, and desires. There are numerous advantages to this approach for the patient and for the surgeon as well. While this may be possible for the future, unfortunately, due to the way that breast surgery evolved, at this point, relatively few breast surgeons are trained and competent in all of the skills required to practice in this manner.

The term "oncoplastic surgery" was first coined by Dr. Werner Audretsch and was meant to describe this integrated "holistic" approach to the breast cancer patient. In

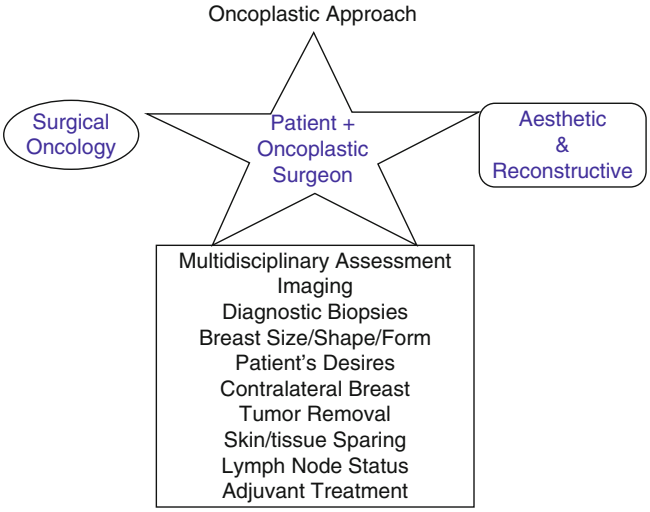

Fig. 1.8 An integrated approach will result from changing the training curriculum and skills requirements of the multidisciplinary breast fellowships. In this manner, the breast (oncoplastic surgeon) will be knowledgeable to work either in a team setting or independently with the required skills to care for the patient in a more integrated fashion

effect, it is also used to describe the training required by the breast surgeon in order to be fully aware of the available and appropriate procedures for each patient seeking care. That is not to say that every breast surgeon *must* perform these procedures alone. On the contrary, oncoplastic surgery can be practiced in a team setting where a surgical oncologist works directly with a plastic and reconstructive surgeon, but this should not preclude the ability of the breast surgeon to be trained and become proficient in all of the procedures necessary to perform all aspects of breast surgery.

Although the surgical community in general lagged well behind in their acceptance of this approach, eventually in the late 1990s, a multidisciplinary breast training fellowship was established in the United States. However, these fellowships were limited in their scope and did not train fellows to perform the cosmetic and/or reconstructive breast procedures necessary to practice in a comprehensive fashion. Since the year 2000, much debate has ensued over this issue, and unfortunately much of the debate stems from deeply ingrained territorial discussions between specialists rather than a productive realignment in the best interest of the patient. The goal ultimately is to provide patients with the most effective and efficient care, and in doing so, it will be necessary to revitalize and expand the curriculum for the multidisciplinary breast fellowships [15, 16]. Since it has now been more than 10 years since the inception of the multidisciplinary breast training fellowships, expansion of the training curriculum is most appropriate at this time. Table 1.3 illustrates the various surgical procedures that the current US fellowship trained breast surgeons are skilled in versus those

Table 1.3 Recommended curriculum for oncoplastic surgery training

Oncoplastic curriculum		
Levels	Disciplines	Credits/hours
Basic core disciplines	• Breast cancer molecular biology	10/20
	• Anatomy and physiology of the breast	10/20
	• Epidemiology	5/20
	• Bioethics and legal medicine	5/20
	• Medical photography	5/10
	• Radiology of the breast	10/20
	• Breast pathology	10/20
	• Radiotherapy	5/10
	• Breast cancer clinical oncology	10/20
	• Psychosocial aspects of patient care	
Basic surgical training	• Minimally invasive biopsy techniques	10 cases
	• Sentinel lymph node biopsy techniques	10 cases
	• Level II techniques	10 cases
	• Level III techniques	10 cases
Advanced surgical training	• Level IV techniques	10 cases
Total minimum credits		70 credits/160 h

that need to be added to their training curriculum in order to be competent in oncoplastic surgery.

The international community has been farther ahead in the adoption of oncoplastic surgery as compared to the United States. Thus, in order to formulate criteria for updating the multidisciplinary breast fellowships, an International Steering Committee was convened. This team of breast specialists included all disciplines included in breast healthcare as well as highly regarded oncoplastic/breast surgeons from seven different countries. Representative breast surgeons with their board certifications in general surgery and ob/gyn and plastic and reconstructive surgery were all present at the meeting and contributed to the outline for the recommended training guidelines. Each of the surgeons on the committee had been practicing oncoplastic surgery for a minimum of 10 years, and all were in agreement on formulating these guidelines for future breast surgery training programs.

As with all specialties establishing guidelines for training, it is important to consider those clinicians already currently in practice that may be "grandfathered" in to a newly established program. Furthermore, it is important to consider various practice environments and the locoregional differences in training. However, as a result of the discussions with this esteemed group of clinicians, a consensus among them was reached and included a classification system for those surgeons already trained in breast surgery that do not have the training or skills to provide comprehensive types of breast

Table 1.4 Additional procedures to be added to breast surgery training programs

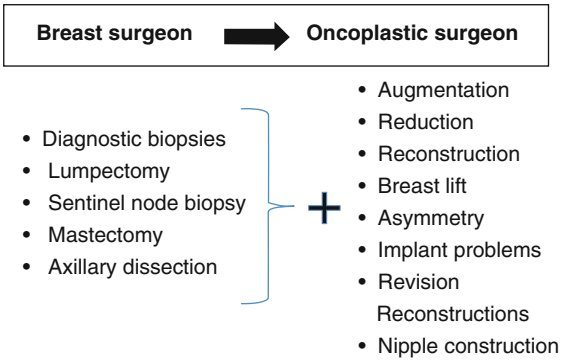

Table 1.5 Guidelines for training in oncoplastic surgery

Guidelines for standardized training in oncoplastic surgery	
Level I	Risk assessment using multidisciplinary model
	Aesthetic principles, evaluation, and techniques
	Comprehensive surgical plan diagnosis, Rx, and follow-up
	Aesthetic approach to incisions
	Large resections with breast conservation
	Reconstructions with local tissue flaps
Level II	Perform skin/nipple-sparing mastectomy
	Perform breast reduction with/without nipple transfer
	Perform mastopexy
Level III	Perform augmentation mammoplasty
	Perform mastopexy with implants
	Perform skin/nipple-sparing mastectomy + reconstruction
	Perform reconstruction with implants/expanders
	Perform nipple reconstruction with skin flaps
Level IV	Specialty training to include myocutaneous flaps

surgery as well as those that already do have these skills. This is most important as the training fellowships revisit their current curriculum and prepare to update and expand their program training modules.

Table 1.4 illustrates the definition of the four different levels of oncoplastic surgery practice, and Table 1.5 defines recommended curricular activities necessary to gain competence in each area. Of key importance is Level IV since this requires additional specialty training in myocutaneous flaps in order to be proficient in this area.

1.5 Conclusions

Often as surgeons we become so focused on the conquest of eliminating disease that we forget about the "person" sitting in front of us who has just had their life turned on its end, and from that day forward, they will never be the same again. The role of the surgeon in this dynamic process can be good news, or it can be very bad news. Even more difficult are the images that are conjured up within a patient's mind in regard to how they will look after surgery and how their friends, family, and partner will feel about their newly formed body. These questions loom large over every woman facing breast surgery—and many of these same questions apply whether or not a woman faces a diagnosis of breast cancer or she is having elective breast surgery. Any woman who has decided or who needs to have breast surgery understands their life will never be the same in some manner. We as surgeons need to truly understand this, and our approach to patient care must revolve around this premise.

Most women seeking breast surgery (cosmetic and/or reconstructive) prefer having one surgeon that they trust perform their surgery, and they do not take kindly, nor do they understand the logic behind having two surgeons or having to see a surgeon who might not "specialize" in breast surgery for a procedure such as a breast reduction. Likewise, it makes no sense that a "breast surgeon" does not know how to perform a breast reduction or breast lift. As evidenced by the extraordinarily low numbers of women having breast reconstruction after mastectomy, it becomes clear that this current, fragmented approach to breast surgery actually acts as a deterrent to patients seeking optimal breast care and it is time for a change in the training of breast surgeons around the world. Being a breast surgeon with the ability to guide a patient through the challenging journey of breast cancer is most certainly a privilege; however the only greater satisfaction comes with being able to practice fully integrated breast surgery with the skills of an oncoplastic surgeon—a breast surgeon skilled in the science and art of helping a patient fulfill their needs, wants, and desires.

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Oncoplastic and Reconstructive Anatomy of the Breast

2

Mahmoud El-Tamer, Cicero Urban, Mario Rietjens, Flavia Kuroda, and James Hurley II

2.1 Introduction

Breast cancer surgery has gone through various changes, and has become more complex and biologically individualized. Although the concern with local control of disease has still persisted, this is currently associated with an aesthetic-functional concept. Therefore, breast anatomy in the way it was traditionally approached requires updating. Form, volume, inframammary fold (IMF), height, and breast projection, as well as size and shape of the nipple and areola complex, lipo-substitution level, and ptosis, are some of the points concerning surface anatomy that have acquired more importance within the oncoplastic and reconstructive context. Similarly, the abdominal wall and the dorsal structure of the thorax must be part of the surgeon's background, as one needs to have a full reconstructive and oncoplastic view in order to make more adequate surgical decisions. In this way, aesthetic-functional breast anatomy is essential to reconstructive breast cancer surgery. The spatial organization of the mammary ducts, the vascularization, and the innervation involve relevant therapeutic implications in the era of sentinel node and oncoplastic surgery, so the reconstructive breast surgeon must be aware of all of these anatomic relationships. It is within such a perspective that this chapter has been developed, to detail the anatomical nuances of the breast and their respective impact on different oncoplastic surgical procedures to achieve an excellent cosmetic result with the lowest complication rate.

2.2 Surface Anatomy of the Breast

The breasts are the most superficial aspect of the anterior chest wall. The skin immediately over the breast tissue is characterized with a nipple-areola complex (NAC), centrally located in young adults.

The breasts extend between the second and the sixth ribs, overlying the pectoralis major muscle superomedially, and the serratus anterior muscle in the lower third and medial areas. In women with large cup size, the breast may reach up to the clavicle. Considering horizontal dimensions, they lie from the lateral edge of the sternum up to the mid axillary line [1, 2]. This extension is critical, as it represents the size of the IMF, the so-called breast base, frequently used as a reference for the choice of implants or flaps in breast reconstruction. Differences in this base are known as a significant cause of asymmetry, and it is critical that the IMF is maintained or reconstructed in breast cancer surgery.

The breast extends into the axilla beyond the anterior axillary line; this extension is called the tail of Spence. In adult women, after puberty, the breast has the shape of a drop, assuming the shape of a cone in nulliparous women, and a more pendulous contour in multiparous women.

Determining factors for mammary aesthetics are volume, parenchyma distribution, tissue elasticity, location and appearance of NAC, quality of the skin envelope, and the relation between the final shape of the breast, thoracic wall, and the body [10].

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_2

The normal breast has good skin and parenchyma elasticity, and most of the volume is located at the inferior and lateral pole. The NAC is generally located in the fourth and fifth intercostal spaces in males and prepubescent children. In an adult woman, the position of the nipple areola varies depending on the degree of ptosis and size of the breast. The areola is usually round with variable diameter. The nipple, placed at the central region of the areola, has between 4 and 15 mm of projection, and is where the lactiferous ducts converge in a number ranging from 15 to 20 (5–9 true mammary duct orifices and other sebaceous glands, tubercles, and tubes) [3]. It contains a huge concentration of nerve sensorial terminations and an abundant lymphatic system called the subareolar or Sappey's plexus [4–6].

Many studies have reported that women's breasts are more frequently asymmetric [7, 8]. In a recent study, Avsar et al. measured anthropometric breast values in 386 female students and reported symmetric breast volume in only 35% of subjects [9]. Multiple studies have been done over the years on all aspects of breast anatomy, including arterial supply, venous drainage, and lymphatic patterns. Discrepancies have existed in the published literature in aspects such as lymphatic mapping, dominant arterial supplies, and general vascular patterns. Information presented in the following paragraphs represents the most current research and findings. Along with the currently supported theories, we have also listed papers of historical precedence that are of interest and relevance to all surgeons.

The blood is supplied to the NAC by the internal mammary artery via its perforating branches, by the anterior intercostal arteries, by the lateral thoracic artery, and by branches from the axillary artery. The internal mammary artery is the main and constant contributor of blood to the NAC by means of its perforating branches numbering from 1 to 4, and anterior intercostal branches numbering from 4 to 6 [2–6, 10].

The color of the NAC has particular importance, as it varies according to ethnicity. It is a factor to be considered for reconstruction and for the final aesthetic result of the breast. It contains sebaceous and sudoriferous glands as well as an intermediate type of mammary and sudoriferous gland called Montgomery's glands. These open at the Morgagni's tubercles and are able to secrete milk. There are also smooth muscle fibers in the areola, and through certain stimuli, they can contract, reducing the size of the areola and projecting the papilla forward [2, 4, 5].

The relationship between NAC and the IMF, within this context, can also differ according to the breast and the patient's age. The nipple is usually located between 19 and 25 cm from the manubrium, between 9 and 12 cm from the medial line of the sternum, and between 7 and 10 cm from the IMF. These distances are relative and may vary according to the ethnic origin of the patient, though not representing an anatomical abnormality (Fig. 2.1).

2.3 Surgical Anatomy of the Breast

2.3.1 Fascia

The breast is enveloped by a pseudofascial plane: the superficial fascia of the anterior thoracic wall. This fascia splits into an anterior and a posterior layer. The posterior or deep layer of the superficial fascia is found posterior to the breast tissue, overlying the retromammary space and pectoralis muscle fascia. The retromammary bursa is a distinct space between the posterior fascia of the breast and the pectoralis fascia, which facilitates mobility of the breast over the chest wall. The superficial fascia joins the cervical fascia at the level of the second intercostal space and superficial abdominal fascia of Camper below the inframammary line. The anterior border of the breast is thought to lie in the subdermal plane [11].

2.3.2 Raising Flaps

The identification of the appropriate plane is crucial when creating flaps for breast-conservation surgery or mastectomy. Immediately below the skin lies the subdermal system, the subcutaneous tissue, and, finally, the breast parenchyma (Fig. 2.2) [11].

A dissection in between the subdermal and subcutaneous system results in excision of all breast tissue and preservation of adequately perfused flaps (Fig. 2.2, Plane 1). Figure 2.3 shows the actual plane during a mastectomy. While raising flaps for the repair of the defect, we recommend that flaps be raised between the subcutaneous tissue and the breast (Fig. 2.2, Plane 2), a plane we have labelled as the glandular plane.

When utilizing tumescent injection and sharp dissection for creating flaps, the tumescent solution is injected into the subcutaneous space, and dissection proceeds between the subcutaneous space and the subdermal system. Skin flap thickness varies between patients. In the same patient, the thickness of the flaps varies in different locations. We suggest using the superficial fascial plane as a guide for raising skin flaps during a mastectomy in lieu of a specific flap thickness. Blood loss is minimal when surgeons use the appropriate plane because the connecting vessels between the breast and the subdermal tissue are miniscule. The superficial fascial plane should be used in all type of therapeutic or prophylactic mastectomies (Fig. 2.3).

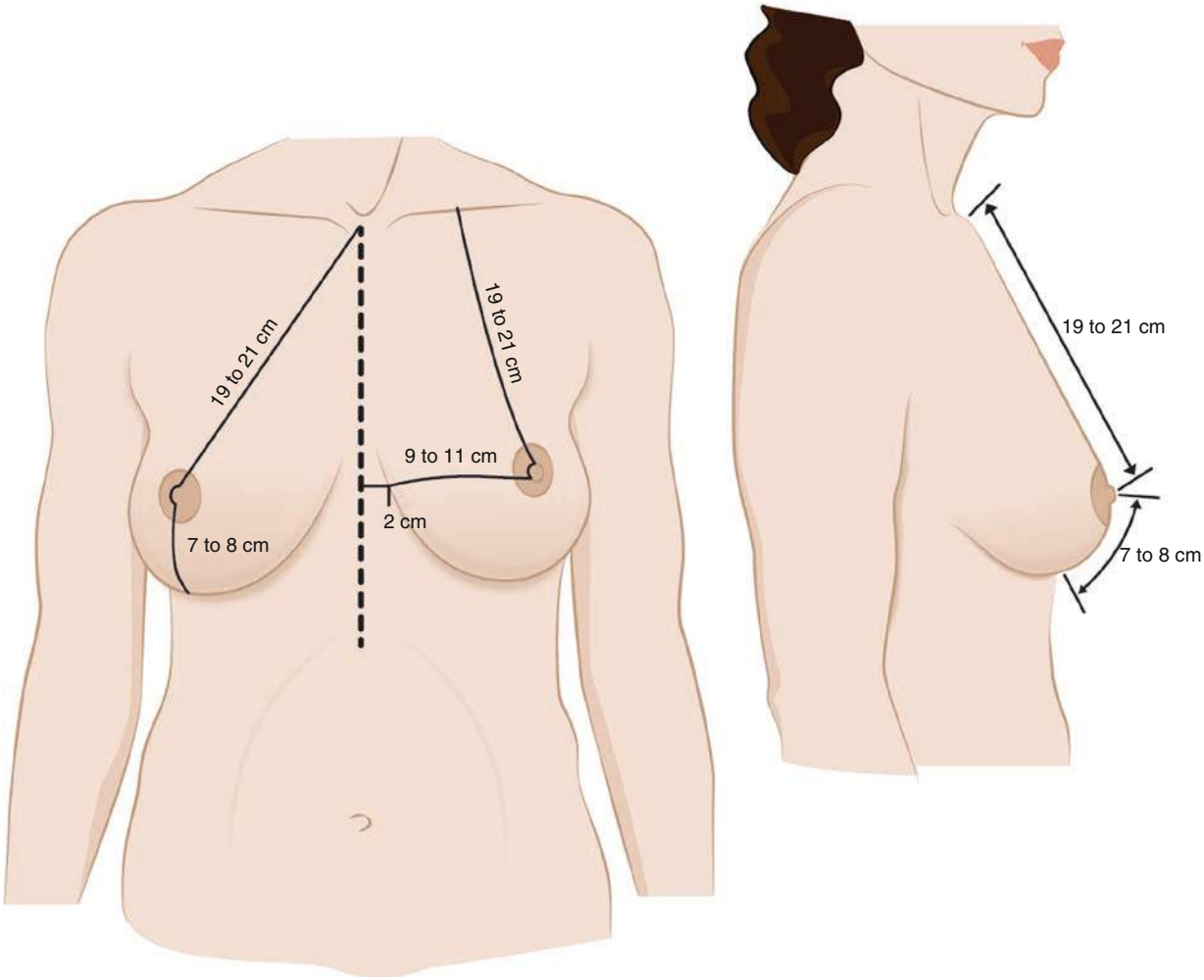

Fig. 2.1 The relationship between the nipple-areola complex and the inframammary fold

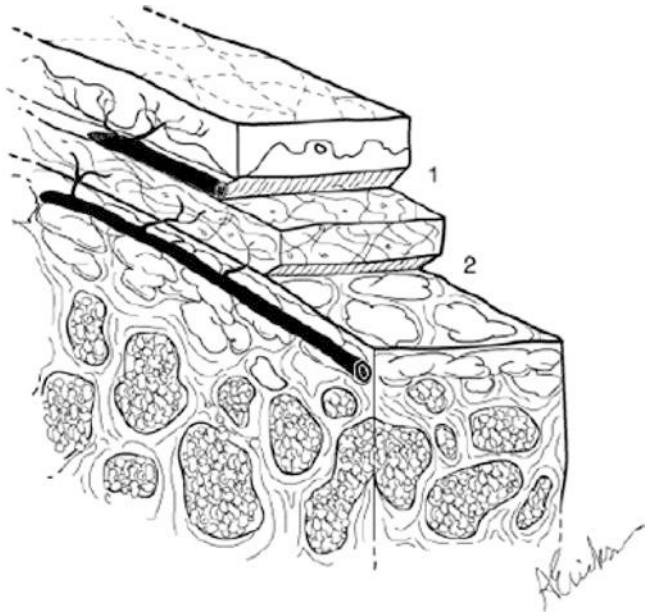

Fig. 2.2 Raised flaps between the subcutaneous tissue and the breast. (*1*) Subdermal plane. (*2*) Subcutaneous plane (Used with permission from El-Tamer M, ed. *Principles and Techniques in Oncoplastic Breast Cancer Surgery*. World Scientific Publishing 2013; Singapore)

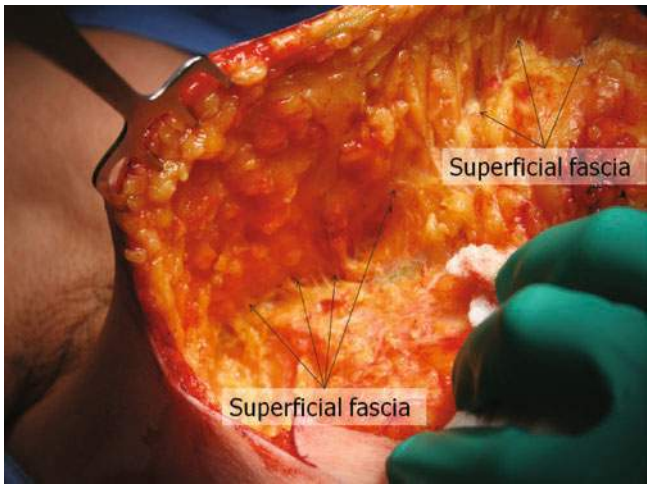

Fig. 2.3 Actual plane during a mastectomy (Courtesy of Dr. Mahmoud El-Tamer, Memorial Sloan Kettering Cancer Center, New York, NY, USA)

2.3.3 Ligaments of Cooper and Horizontal Septum

The deep and superficial layers of the superficial fascia are linked through fibrous bands, known as ligaments of Cooper. These ligaments originate from the pectoralis fascia at the level of the fifth rib and extend into the overlying skin as well as the pectoralis major muscle, dividing the breast tissue into septae and aiding in suspending the breast to the chest wall [12, 13].

A ligamentous septum comprising a horizontal fibrous septum originating from the pectoralis fascia at the level of the fifth rib and its vertical ligamentous suspension provides medial and lateral lines of fixation on either side of the breast [13]. This also gives rise to a superficial aspect that merges into the overlying skin [13]. The medial superficial ligament is thought to be weaker and stretches into the skin overlying the sternum. The lateral stronger superficial ligament creates a strong connection between the pectoralis minor as well as the skin and overlying fascia of the axilla along the midaxillary line, producing the axillary hollow [13]. The superficial part of the horizontal septum is a thickening of the ligaments of Cooper, stretching for the same origin at the level of the fifth rib to the inframammary line [13].

The horizontal ligamentous septum guides the neurovascular supply of the breast and NAC. Varying degrees of ptosis are a direct reflection of the laxity of the ligaments of Cooper.

Between the breast and the pectoralis major fascia exists the space known as the retromammary bursa, which facilitates the mobility of the breast on the chest wall. Adhering to this space while raising local flaps for breast-conservation surgery is crucial to the viability of the breast tissue; it will preserve the integrity of the neurovascular supply to the breast tissue and minimize fat and tissue necrosis, particularly in older women with fatty breasts.

2.3.4 Blood Supply to the Breast and Overlying Skin

Salmon developed a successful injection technique in cadavers that allowed him to delineate the arterial supply of the breast in fine detail [14]. He found that the blood supply to the breast originated from three systems, the axillary, internal mammary, and intercostals, which are more commonly known today as the lateral mammary, internal mammary, and intercostal branches. The inferior and central pedicles of the breast were thought to be hypovascularized [15]. This idea was challenged by Salmon, who attributed this misconception to an inadequate injection technique. He has proposed that the inferior and central portions of the breast receive arterial supply from perforators through the pectoralis muscle. These perforators are well visualized during a mastectomy while taking the breast off the pectoralis major muscle. Figure 2.5 represents a magnetic resonance imaging (MRI) reconstruction of the blood supply of the breast, clearly showing the lateral mammary, internal mammary, and intercostal perforators.

2.3.5 Lateral Mammary Artery

This artery supplies the lateral aspect of the breast; it is a direct branch of the axillary artery or one of its tributaries [16]. Salmon has observed the lateral mammary artery to arise from the external mammary artery, lateral thoracic artery, or directly from the axillary artery [14]. Occasionally, it is referred to as the lateral thoracic artery, which is thought to be incorrect, as the lateral thoracic artery supplies the lateral upper chest wall. The lateral mammary artery enters the breast over the axillary tail laterally at the level of the third or fourth rib. The artery runs superficially and takes an anterolateral course, sending branches into the breast tissue, the overlying skin, and the chest wall (Fig. 2.4). This artery consistently contributes deep subcutaneous branches to the NAC [12] and has been cited as contributing 30% of the blood flow to the breast [17]. The branches of the lateral mammary artery travel diagonally in a medial direction until fading beyond the lateral aspect of the inframammary line (Fig. 2.5). The lateral mammary artery connects with the medial artery

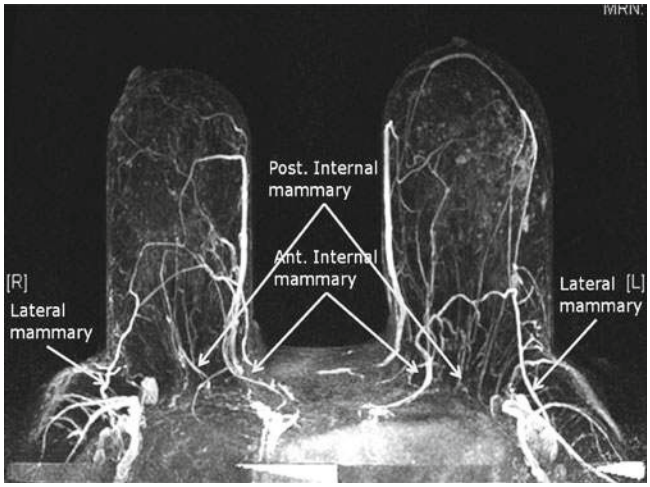

Fig. 2.4 MRI reconstruction of the vascular supply of the breast. Notice the two main branches of the lateral mammary originating from the axillary artery and the internal mammary artery, originating medially through the chest wall. The internal mammary has anterior and posterior branches as seen here. The posterior or deep branches of the internal mammary artery travel under the pectoralis major and perforate through the muscle into the breast, as seen in the center of the breast (Courtesy of Dr. Jennifer Kaplan, Memorial Sloan Kettering Cancer Center, New York, NY)

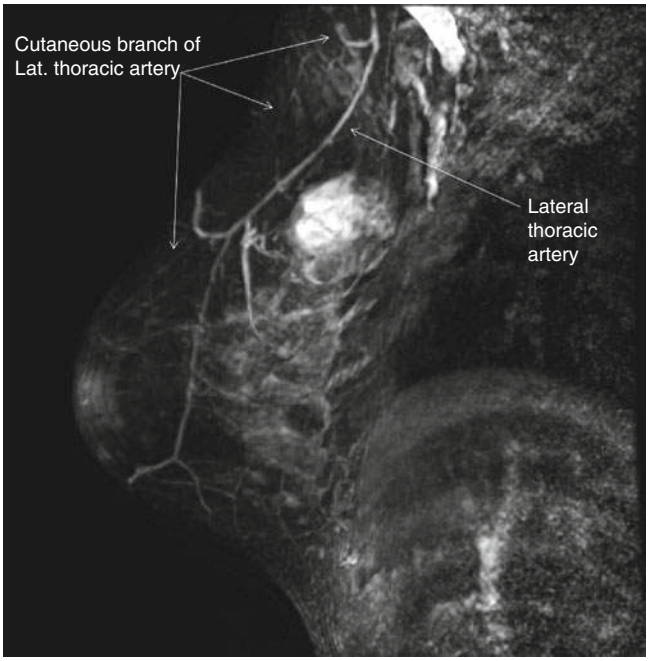

Fig. 2.5 Lateral mammary artery, traveling through the breast (Courtesy of Dr. Mahmoud El-Tamer, Memorial Sloan Kettering Cancer Center, New York, NY, USA)

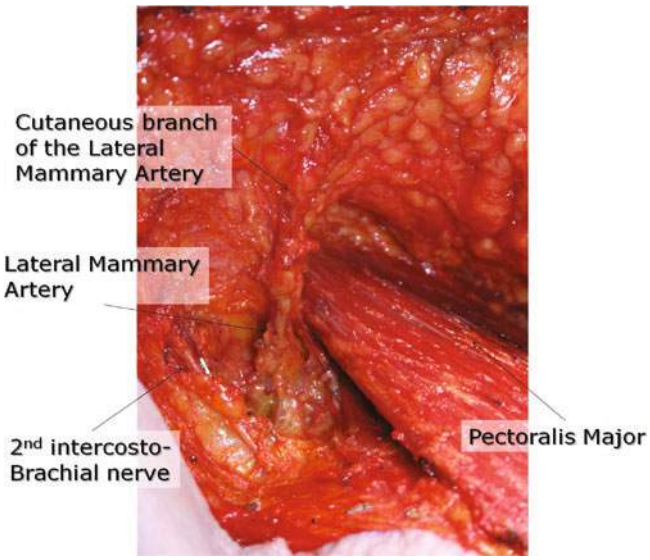

Fig. 2.6 The lateral mammary artery seen after completion of a mastectomy and a sentinel node dissection; notice its cutaneous branch that has been preserved (Courtesy of Dr. Mahmoud El-Tamer, Memorial Sloan Kettering Cancer Center, New York, NY, USA)

around the NAC either through the superficial or posterior branches (Fig. 2.4). The lateral mammary artery is pivotal for the survival of the laterally based breast reduction. This artery may frequently be ligated during an axillary node dissection. When planning an oncoplastic procedure in a patient who is undergoing an axillary node dissection, one has to avoid mammaplasties that are laterally based. Occasionally, the lateral thoracic artery may be used for breast reconstruction procedures that demand microsurgical anastomoses. The lateral thoracic artery sends a dermal branch to the lateral skin of the breast; one has to attempt to preserve it when feasible, particularly in nipple- and skin-sparing mastectomies (Fig. 2.6).

2.3.6 Internal Mammary Artery

The internal mammary artery (internal thoracic artery) originates from the subclavian artery, traveling parallel and posterior to the lateral border of the sternum. This artery provides up to 60% of the blood supply to the breast, mostly the medial portion. It sends anterior and posterior perforating branches through the parasternal and intercostal spaces. The largest branches perforate through one of the first few intercostal spaces. The anterior perforators arise from the first four intercostal spaces, just medial to the sternum. Perforators from the second and third intercostal spaces are the most consistent, while those from the first and fourth are not as common [18]. These anterior perforators split into cutaneous and breast branches (Fig. 2.4). Preserving the integrity of the cutaneous branches is crucial when performing a skin-sparing or nipple-areola-sparing mastectomy (Fig. 2.7).

The posterior medial perforators of the internal thoracic artery (only described by Salmon) arise more laterally from the intercostal spaces through the pectoralis fascia into the breast and supply the deep portion of the breast tissue. These vessels appear to be branches of the internal thoracic artery, emerging from the fourth and fifth intercostal spaces. These vessels may have been reported by others and referred to as branches of the intercostals. Figure 2.4 is an MRI reconstitution of the branches of the internal mammary, showing the anterior and the posterior branches.

This blood supply supports a significant portion of the medial aspect of the breast as well as the NAC. This is the main blood supply for medially based breast reduction. The posterior medial mammary arteries are important contributors to the arterial blood supply of the inferiorly based breast reduction pedicle.

Van Deventer has recently dissected 27 breasts after intra-arterial latex injection [6]. He reported that the blood supply to the NAC originated from:

- The internal thoracic branches in 27/27
- The anterior intercostal in 20/27
- The lateral thoracic in 19/27
- A direct branch from the axillary artery in 2/27
- The posterior intercostal in 1/27

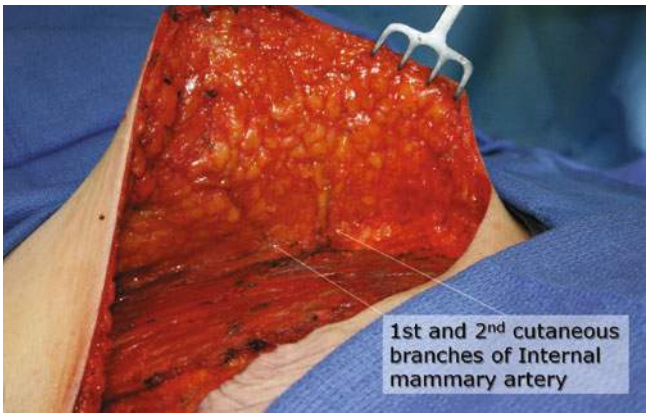

Fig. 2.7 Preservation of the integrity of the cutaneous branches is crucial when performing a skin-sparing or nipple-areola-sparing mastectomy (Courtesy of Dr. Mahmoud El-Tamer, Memorial Sloan Kettering Cancer Center, New York, NY, USA)

2.3.7 The Venous Drainage

It is formed by a deep system and a superficial system. Low-caliber vessels that drain just below the superficial fascia form an interconnected traversal longitudinal network, like a knit cloth, which drains to the internal mammary vein, and the anterior superficial jugular vein forms the superficial system. In the deep system, the afferent branches discharge into three main pathways: tributaries of the internal mammary vein, tributaries of the intercostal veins, and the vertebral system. There is special interest in the mammary venous drainage due to the potential use of certain branches in breast reconstructive surgeries. The drainage follows the course of the arteries, with a large number of anastomoses between the superficial and the deep system, and has the axillary vein as its main system. Around the areola, the veins form a venous circle which, together with the drainage of the mammary tissue, follows a peripheral course up to the internal thoracic, axillary, and intercostal veins [2, 5]. Metastases can pass through any of these routes, following their way to the heart and then to the lung capillaries. Due to a system of avalvular venous drainage that connects Batson's venous vertebral plexus to thoracic, abdominal, and pelvic organs, one can explain the route of metastases to the vertebra, ribs, and central nervous system from the breast, mainly through intercostal posterior veins.

The interest for studying *lymphatic drainage* has increased due to sentinel node (SN) studies. In most cases, the SN position is at level I. The breast lymph vessels have their drainage established by two plexuses: superficial or Sappey's subareolar, and deep or aponeurotic. The former is made up by collecting trunks, which gather skin drainage, superficial breast planes, nipple and areola, as well as the upper limb, supraumbilical region, and dorsum. The latter follows through the pectoral muscles up to Rotter's lymph nodes (situated between the pectoralis major and the pectoralis minor muscles) and then toward the subclavian lymph nodes. It is relevant to mention that though the lymphatic flow is unidirectional, there is a great interrelation between the superficial system and the deep as to breast drainage, which explains the broad variation of lymph drainage found in breast cancer [19]. Approximately 3% of the breast lymph flows to the lymph nodes in the internal mammary chain and 97% to the axillary lymph nodes. Any quadrant of the breast is able to drain to the internal mammary chain. Axillary nodes vary in number from 20 to 60. Lymph node groups of axillary drainage can be divided into [1]:

- An axillary vein group or lateral group, consisting of four to six lymph nodes located medial or posterior to the axillary vein, holding most of the drainage from the superior portion of the breast.
- An external mammary group, also called pectoral group, situated at the inferior border of the pectoralis minor muscle in association with the lateral thoracic vessels. It consists of four or five lymph nodes and holds most of the lymphatic drainage from the breast.
- The subscapular lymph node group or posterior lymph node group, which consists of six or seven lymph nodes situated along the posterior wall of the axilla up to the lateral border of the scapula and which is associated to subscapular vessels. They also contain drainage from the cervical posterior region and the shoulder.
- The central group, which consists of three or four lymph nodes situated posterior to the pectoralis minor muscle, interwoven with the adipose tissue of the axilla. They hold drainage from the three groups mentioned above, and they can also contain drainage directly from the breast. A sequence of this drainage moves on to the subclavicular lymph nodes or to apical lymph nodes. Clinically, this is the most palpable group, which is something of extreme relevance to the clinical evaluation of axillary metastases.
- The subclavicular or apical group, consisting of 6–12 lymph nodes, which is situated posterior and superior to the border of the pectoralis minor muscle. It gets drainage directly or indirectly from all of the other groups. The lymphatic efferents of these ducts form the subclavian trunk, which pours into the right lymphatic duct and to the left side to the thoracic duct. Through this route, there is also the possibility of drainage for lymph nodes from the deep cervical area.
- The Rotter's group or interpectoral group, which consists of one to four small lymph nodes situated between the pectoralis major and the pectoralis minor muscles associated with branches of thoracoacromial vessels.

It is relevant to mention that there is another division of axillary lymph nodes that is routinely used by surgeons, taking into account the relation between the axilla and pectoralis minor muscle. The lymph nodes that are situated lateral and below the pectoralis minor muscle are referred to as Berg's level I and encompass the external mammary group, axillary vein, and subscapular vein. Those situated behind this muscle are referred to as level II and correspond to the central group and part of the subclavicular group. The lymph nodes situated above the superior border of the pectoralis minor muscle are referred to as level III and include the subclavicular group [13].

The lymph nodes of the internal mammary chain are situated in the intercostal spaces of the parasternal area. They are close to the internal mammary vessels, in the adipose extrapleural tissue. They are found medial to the mammary vessels in the first and second intercostal spaces and lateral in the third space [13]. There are also other accessory networks such as the one that connects the two breasts, called trans-mammary and paramammary, which is related to the hepatic lymph nodes and subdiaphragmatic nodes (Fig. 2.8).

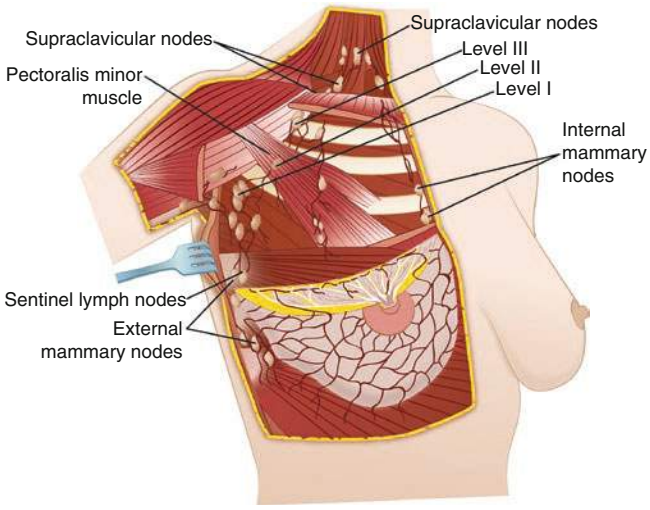

Fig. 2.8 Lymphatic drainage of the breast nodes

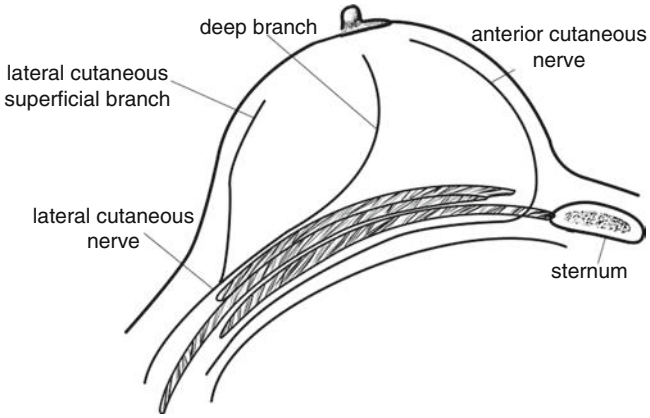

Fig. 2.9 Nerve supply to the breast. The lateral cutaneous nerve divides into superficial and deep branches

2.3.8 Breast Innervation

Initially described in detail by Sir Astley Cooper in 1840, the breast has since been consistently found to be innervated from the lateral and anterior cutaneous branches of the second to sixth intercostal nerves [20, 21]. The lateral branches pierce the chest wall musculature at the midaxillary line and travel medially. These nerves divide into a superficial branch and a deep branch at the edge of the pectoral muscle (Fig. 2.9).

The superficial branch travels subcutaneously, whereas the deep branches travel along the pectoralis fascia for a few centimeters and then merge through the breast tissue to the surface at the midclavicular line. The superior area of the breast also gets innervation from the cervical plexus by the supraclavicular nerve.

The anterior cutaneous branches merge through the chest wall at the edge of the sternum and travel superficially toward the nipple, thereby innervating the medial aspect of the breast.

The NAC innervation is not consistent, hence the controversy. It is agreed upon, however, that the innervation of the NAC is from the anterior and lateral branches of the third to fifth intercostal nerves. The fourth lateral cutaneous nerve is the most frequent source of sensation to the NAC, mostly via its deep branches.

Hamdi and colleagues have reported that in 93% of breasts, the deep branch of the lateral cutaneous nerve innervates the nipple. As previously described, the deep branch runs within the pectoralis fascia, curves straight up through the glandular tissue at the level of the midclavicular line, and sends its terminal branches straight to the nipple [22].

The third, fourth, and fifth anterior branches innervate the medial aspect of the NAC. The nerves enter the NAC superficially at its medial edge, mostly between 8:00 o'clock and 11:00 o'clock for the left breast and 1:00 o'clock to 4:00 o'clock for the right breast. When planning a terminal duct excision or removing a centrally located tumor, we strongly recommend avoiding a medial periareolar incision because it will interrupt the anterior cutaneous branches that may be the only innervation to the NAC. Understanding the innervation of the NAC is important in planning incisions and access for resection of a tumor. Historical papers on breast innervation are included [23, 24].

2.3.9 Chest Wall Muscles

The most important *muscles* related to breast are as follows:

- The *pectoralis major* muscle is in a close relation with most of the breast surface. It is a flat muscle, and it is divided in two portions: clavicular and costosternal. The latter originates from the sternum and from the costal cartilages of the second and sixth ribs. It inserts in the major tubercular groove of the humerus and in the bicipital groove. The cephalic vein, which many times is used for long-term catheters in chemotherapy, is the separation point between this muscle and the deltoid muscle, at the deltopectoral groove. Its function is flexion, adduction, and medial rotation of the arm. The medial and lateral portions of the pectoral nerves innervate it. These nerves, if sacrificed in axillary surgery, may cause retraction, local fibrosis, and loss of function [25]. The pectoralis major muscle is used for the protection of implants during mammary reconstructive procedures and also in aesthetic surgeries. Sometimes the implant coverture is compromised when there is an anatomical variation, as it occurs when the inferior insertion of the muscle is in an upper part of the thoracic wall.
- The *pectoralis minor* muscle appears on the sternal fascia of the third, fourth, and fifth ribs and inserts in the coracoid process of the scapula. It is innervated by the medial pectoral nerve, which is a branch from the brachial plexus (C8-T1) [25]. It travels posteriorly to the axillary muscle and anteriorly to the axillary vein.
- The *serratus anterior* muscle originates on the surface of the upper eight ribs and inserts along the vertebral border of the scapula. The function of this muscle is to keep the scapula pressed against the thorax wall, and it is innervated by the long thoracic nerve (Bell's nerve), originating from posterior branches of C5, C6, and C7 of the brachial plexus. The path of this nerve is posterior to the axillary vein and then emerges in the medial level of the subscapular fossa. It is important that this nerve be preserved during axillary dissection to avoid instability of the scapula, therefore reducing the strength of the shoulder, a condition known as winged scapula.
- The *latissimus dorsi* muscle originates on the spinous process and supraspinous ligaments of the seventh thoracic vertebra and on all sacral and lumbar vertebrae. It inserts the bicipital sulcus of the humerus. The thoracodorsal nerve originating from the brachial plexus rooted in C6, C7, and C8 innervates it. The nerve passes by the axilla and is contained in the axillary lymph nodes of the subscapular group. In the case of an injury to this nerve, there is no motor disability; however, it is not possible to use this muscle for breast reconstructions. Their arterial supply is shown in Fig. 2.10.
- *Rectus abdominis* muscle: this is the muscle that recovers the anterior wall of the abdomen. Its insertion is the inferior margin of the fifth, sixth, and seventh costal cartilage. As it goes down to the pubis, this muscle becomes narrower and is inserted into the body of the pubis inferiorly. It also has the so-called tendineae (areas of interruption of the muscle), which usually are four in number. One is positioned at the navel level, two are above it, and one is below it. The muscle is enveloped by a fibrous fold that originates in the aponeurosis of the internal oblique muscle, external oblique muscle, and transverse abdominis muscle, which joins along with the medial line forming the linea alba. This is the inferior limit for the muscle dissection in TRAM flaps. The posterior face of this muscle lies on the subpectoral tissue. Concerning its blood supply, from bottom to top goes the inferior epigastric artery, which is a branch of the external iliac artery. From the superomedial portion comes the supply of the superior epigastric artery, which is a branch of the internal thoracic artery, originating at the subclavian artery. These two arteries produce a rich network of anastomoses among them (the choke system), therefore establishing communication between the subclavian artery and the external iliac

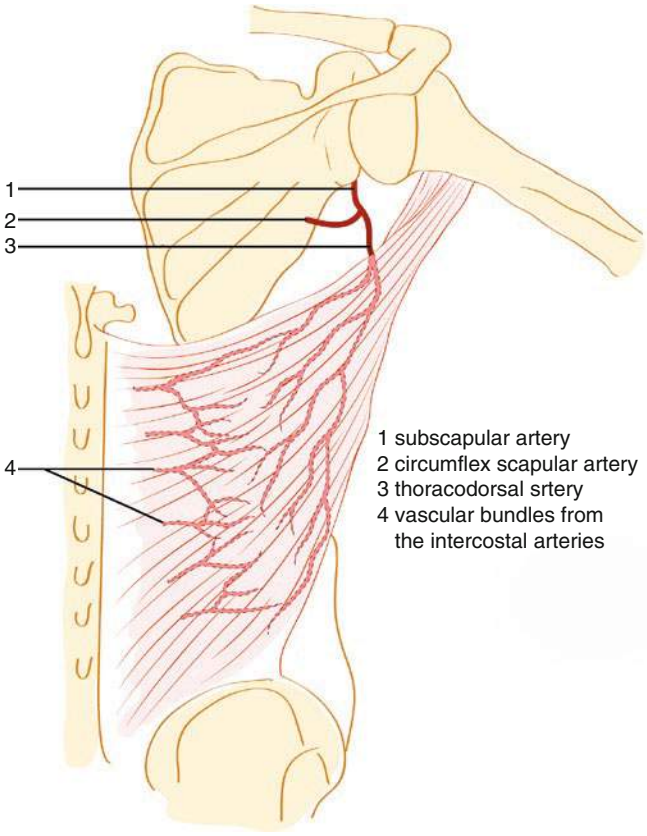

Fig. 2.10 Arterial supply of the latissimus dorsi

artery. This anatomy is very important for breast reconstruction. This type of surgery can be performed by using the rectus abdominis muscle either unilaterally or bilaterally together with the subcutaneous tissue and skin, tying off the inferior epigastric artery and rotating the flap through a tunnel previously prepared toward the mammary site, or simply by using subcutaneous tissue and abdominal skin and performing microanastomoses between perforating vessels and either internal mammary vessels or lateral thoracic vessels (Figs. 2.11 and 2.12).

2.3.10 The Inframammary Fold

The *IMF* has been subject of special attention lately because of its importance to immediate reconstruction in skin-sparing mastectomy (SSM) and nipple-sparing mastectomy (NSM). It is situated at the fifth rib level in a medial position, and in its lateral portion, it overlies the sixth intercostal space. It is an important anatomic landmark in breast surgery, because it defines the shape and structure of the breast, and a boundary for reconstructive and aesthetic surgeries. From the onset of breast development, it anchors the inferior pole of the breast to the chest wall, and with age, the breast begins to sag or become ptotic relative to this point [26, 27]. The relationship between it and the pectoralis major muscle is also important with respect to breast implant support. It is located inferior to the inferior origin of the pectoralis major muscle [28]. Considerable attention should be paid to its role in creating a natural-appearing breast in different techniques. In augmentation mammoplasty, the IMF provides a relatively well-hidden site for an incision to place a mammary implant and provides inferior support for subpectoral implants that is essential to prevent migration [29]. Its distance from the areola and its bilateral symmetry preservation are some points that must be observed for a satisfactory aesthetic-functional result. It represents a zone of adherence of the superficial fascial system as well as an increase in dermal collagen [26, 27, 30]. It has a ligament that originates at the periosteum of the fifth rib medially and the fascia between the fifth and the sixth rib laterally, inserting into the deep dermis [29]. However, the existence and origin of this ligament are not universally agreed upon among anatomists. Preserving it in mastectomies is still object of debate due to the possibility of remaining mammary tissue at the site. Gui et al. [31] found that 28% of their IMF specimens contained breast tissue and lymph nodes. However, aiming to explain this,

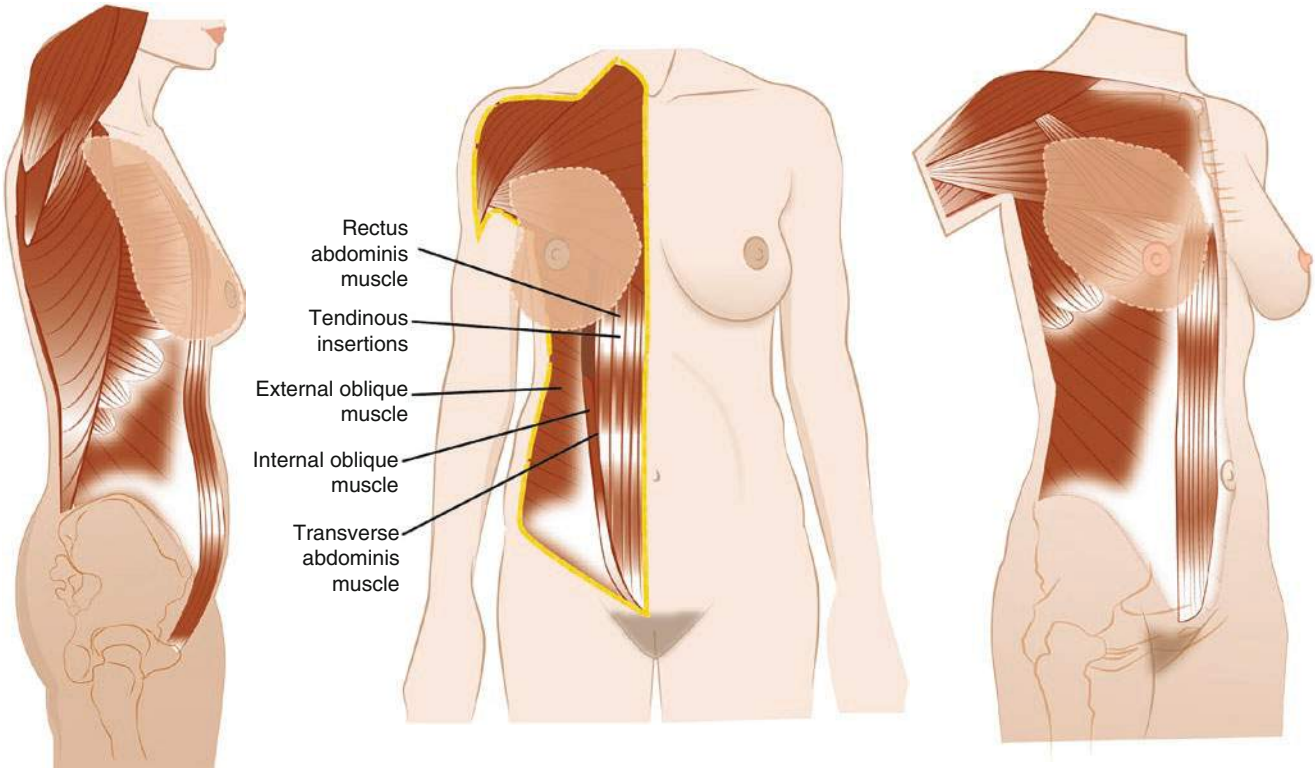

Fig. 2.11 Rectus abdominis muscle

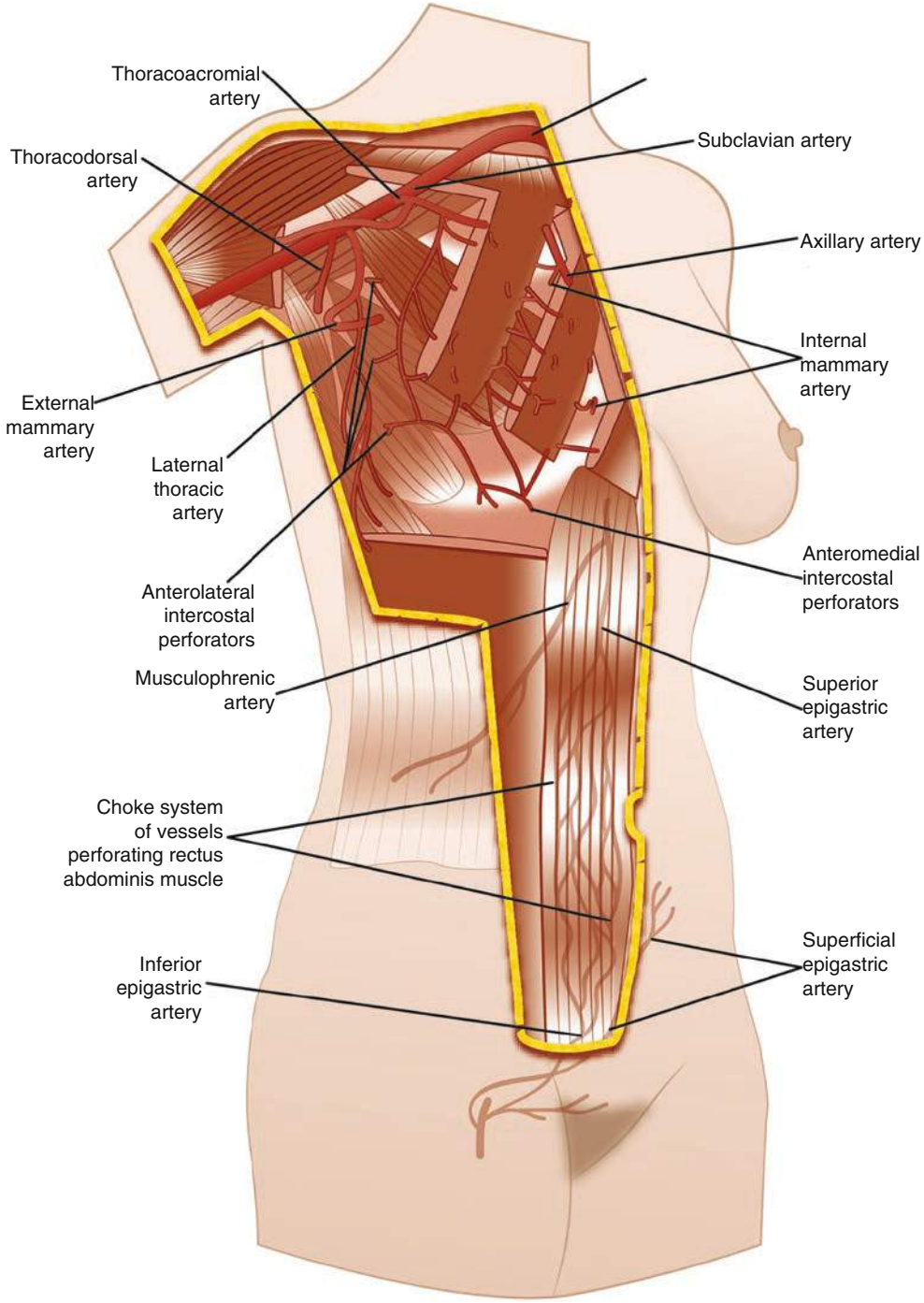

Fig. 2.12 Arterial supply to the rectus abdominis muscle

Carlson et al. [32] showed that preserving it keeps less than 0.02% of the total mammary tissue. If the IMF is breached, it must be repaired to reconstitute the natural breast crease at the time of breast reconstruction to maintain the correct breast implant position and achieve an optimal final aesthetic outcome [30, 31]. There is a specific chapter about IMF reconstruction in this book.

2.4 Conclusions

Aesthetic-functional breast anatomy is essential to reconstructive breast cancer surgery. The spatial organization of the mammary ducts, the vascularization, and the innervation involve relevant therapeutic implications in the era of SN and oncoplastic surgery, so the reconstructive breast surgeon must be aware of all of these important anatomic relationships.

Disclosures: Portions of the text of this chapter are adapted with permission from El-Tamer M, ed. *Principles and Techniques in Oncoplastic Breast Cancer Surgery*. World Scientific Publishing 2013; Singapore.

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Breast Cancer Reconstruction Epidemiology

3

Joanna C. Mennie, Jennifer Rusby, David A. Cromwell, and Richard Rainsbury

3.1 Background

The psychosocial impact on women with breast cancer who undergo mastectomy has been well documented. In 2013, approximately 12,500 mastectomy procedures were performed for breast cancer in England alone, representing 34% of all index breast cancer procedures [1]. With the improvements in screening and adjuvant therapies prolonging breast cancer survival, women are living with the psychosocial morbidity associated with mastectomy for longer. Breast reconstruction, however, has been shown to improve women's emotional well-being and confidence and is now regarded as an integral part of breast cancer services worldwide [2–4]. Among women with breast cancer, studies have shown women's desire for reconstruction to range from 28 to 50% across Europe [5–7]. This chapter explores the longitudinal trends of post-mastectomy breast reconstruction uptake and procedure type. Reconstruction trends and techniques following partial mastectomy procedures are discussed in Sect. 3.3.

3.2 Breast Cancer Reconstruction Service Development

In 1885, the first post-mastectomy breast reconstruction procedure was attempted when Heidelberg transplanted a lipoma from the flank [8]. Eleven years later Tanzini was the first to describe the use of latissimus dorsi to reconstruct the large soft tissue defects resulting from Halsted's radical mastectomy as an alternative to skin grafting [9]. In the early 1900s, surgeons developed further autologous techniques in breast reconstruction including the rediscovery of the latissimus dorsi flap [10]. The 1960s marked the advent of silicone breast implants, and during the 1980s, further innovation occurred with the invention of expanders [11] and development of free flaps for use in breast reconstruction [12]. Access to breast reconstruction, however, remained limited.

As breast cancer treatments have evolved, care pathways and services have been subjected to several reorganisations. In the last decade, improvements have included the development of referral pathways, integration of regional services, the adoption of a multidisciplinary approach to care, and national guidelines [13, 14]. In the USA, a significant reform was the Women's Health and Cancer Rights Act, which came into effect in 1999 and mandated that health insurance providers cover costs for reconstruction after mastectomy. Subsequently, reconstruction techniques have been further refined with an emphasis on reducing donor site morbidity. Evolving mastectomy approaches have also influenced reconstruction practice as studies have shown no difference in survival between conventional and skin-sparing techniques [15].

3.3 Current Practice

Currently women have several breast reconstruction options available to them either at the time of mastectomy or at a later date. These include implants, autologous pedicled flaps with or without implants, and autologous free flap reconstruction [16]. In recent years, there has been the development of materials that facilitate direct to implant reconstruction (such as acellular dermal matrices (ADM) and titanium mesh), with reports of improved aesthetic outcomes, and a reduction in capsular contracture rates [17, 18]. Evidence of long-term benefit is lacking, however [19].

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_3

Post-mastectomy reconstruction can be classified as either immediate or delayed. The main advantages of immediate breast reconstruction are that the skin envelope is retained and the patient undergoes fewer operations [20]. Whilst in delayed reconstruction, reported complication rates are lower [21]. Whether a women's specific treatment pathway results in immediate or delayed reconstruction is dependent upon several factors including disease stage, comorbidities, the availability of appropriate skills, and patient choice. Service quality and service availability are key issues [22, 23]. Selective offering of reconstruction to women has been reported by Alderman et al., who found breast reconstruction was discussed in only 33% of patients [24]. Finally adjuvant therapy, in particular radiotherapy, may also influence practice. Some surgeons argue that reconstruction should be delayed if radiotherapy is anticipated [25]. Whilst this is acknowledged in terms of implant reconstruction [16], other authors have shown the sequence of autologous reconstruction to hold no difference in subjective aesthetic outcomes or complication rates in women receiving adjuvant radiotherapy [26]. What is clear is that current evidence is limited and surgeon opinion divided [27].

3.4 Post–mastectomy Reconstruction Uptake

In recent years, numerous studies have provided encouraging evidence indicating a rise in reconstruction rates (see Table 3.1). In the English National Health Service, immediate reconstruction has risen annually from 10% of all unilateral index mastectomies for breast cancer in 2000 to 23% in 2013. The uptake of delayed reconstruction has also increased in the last decade; however, rates in England plateaued at around 350 procedures per quarter from 2007 onwards [1].

In Catalonia, Spain, rates of immediate post-mastectomy reconstruction have similarly increased [28]. However the sample size in this regional study was limited to around 900 women per year. In France, a national database review reported a smaller increase in immediate reconstruction [29]. Further national European studies evaluating trends in reconstruction are limited. This may be due to a lack of reliable national registries, or investigation of the data within.

Trends in post-mastectomy reconstruction also remain underreported in Asian countries. A single-centre study from China evaluated 17,040 women undergoing mastectomy between 1999 and 2014 and reported a stable reconstruction rate of 3.5% [30]. It should be noted however that significant differences between China and Europe exist in breast conserving and mastectomy practice; in China 81.2% of breast cancer is resected by mastectomy. As such, a direct comparison of reconstruction practice is difficult. In Korea, Kim et al. have reported an increase in national reconstruction rates, alongside a proportional increase in BCS [31].

In the USA, rates of immediate reconstruction have been higher than in Europe and Asia [32–35]. In one nationwide study of 178,603 women, immediate post-mastectomy reconstruction rose from 21% in 1998 to 38% in 2008 [36]. However, the authors reported on both unilateral and bilateral mastectomy cases together. Furthermore prophylactic procedures were included. Considering contralateral prophylactic mastectomy rates are significantly higher in the USA (49%) compared with Europe (<10%) and that reconstruction is more likely after bilateral mastectomy, this may explain some of the differences in reported practice between countries [37, 38]. Lang et al. reported only on those women undergoing index mastectomy for stage I–III breast cancer in the USA and found a similar increase in immediate reconstruction rates to Europe [23].

Outside the UK, trends in delayed reconstruction have been less well reported. This is possibly related to the difficulty in tracking patients over time. Studies have typically been limited by short follow-up periods or have combined immediate and delayed reconstruction rates [28, 39]. A Danish registry study of 13,379 women found an overall rate of 13% for delayed reconstruction from 1999 to 2006 [40].

3.5 Factors Influencing Reconstructive Uptake

3.5.1 Patient Factors

Advancing patient age has been reported to influence immediate post-mastectomy reconstruction uptake [41, 42]. A national study from English NHS hospitals reported that 31% of women aged 40–49 underwent reconstruction, compared with 2.1% in women aged 70–79 years [22]. A number of factors may reduce uptake in the elderly. Increasing comorbidity heightens the risk of more major surgery, and the more advanced tumours presenting in this age group may require post-mastectomy radiotherapy. As such, a lower percentage of these women are likely to be suitable for immediate reconstruction. Eaker et al. adjusted for disease stage and comorbidities across age groups and still found an association with age [43]. They also found substantial differences in disease management with less diagnostic activity and less aggressive treatment in women aged 70–84 years.

Increasing deprivation, lower income, and education have also been associated with lower immediate reconstruction rates [22, 35]. A review of cancer screening pathways has

Table 3.1 National or regional studies reporting the proportion of women undergoing immediate reconstruction across time following mastectomy

Author	Study year	Country	Data source	Population	Mastectomy total (*n*)	Immediate reconstruction (%)
Morrow [32]	1985–1990 1994–1995	USA	Retrospective national cancer database	All women with breast cancer	155,463 68,348	1985–1990, 3.4% 1994–1995, 8.3%[a]
Agarwal [33]	1998–2002	USA	Retrospective SEER database	All women with breast cancer	52,249	1998,15.3% 2002, 15.9%
Reuben [34]	1999–2003	USA	Retrospective nationwide inpatient sample database	Women with breast cancer, an increased risk, or benign disease	469,832	1999, 22.9% 2003, 25.3%
Merchant [35]	2005–2009	California	Retrospective health-care cost and utilisation project database	Women with in situ or invasive breast cancer	48,414	2005, 21% 2009, 33.6%
Albornoz [36]	1998–2008	USA	Retrospective nationwide inpatient sample database	Women with breast cancer or an increased risk	178,603	1998, 20.8% 2008, 37.8%
Lang [23]	1998–2008	USA	Retrospective SEER database	Women with index stage I–III breast cancer	112,348	1998, 11.7%[b] 2008, 21.7%[b]
Escriba [28]	2005 2011	Spain	Retrospective discharge database	Women with invasive index breast cancer	953 867	2005, 13% 2011, 22.8%
Rococo [29]	2005 2012	France	Retrospective hospital episode statistics database	Women with in situ or invasive breast cancer	18,314 19,574	2005, 11.4% 2012, 13.4%
Kim [31]	2002–2012	Korea	Retrospective Korean breast cancer society registry	Women with index in situ or invasive breast cancer	2002, 4628 2012, 5746	2002, 8.2% 2012, 15.8%

[a]Immediate reconstruction defined as reconstruction within 3 months of mastectomy
[b]Immediate reconstruction defined as reconstruction within 4 months of mastectomy

found that those women from deprived areas and low-income households are less likely to attend for screening [44]. Current differences in the presentation route among these women may therefore impact on a woman's suitability for reconstruction, and these could be amenable to targeted improvement initiatives.

The relationship between ethnicity and immediate reconstruction varies across countries, which is likely to be representative of cultural differences. In the USA, authors consistently report greater post-mastectomy reconstruction in women of white ethnicity [34, 35, 41], whilst in the UK, women of black ethnicity are more likely to undergo reconstruction than women of white ethnicity [22].

3.5.2 Disease Factors

Disease factors have had a substantial influence on the integration of immediate reconstruction. In those women with in situ disease, reconstruction is more likely than in women with invasive disease [22, 35, 45]. Lang et al. performed a multivariate national analysis of 112,348 women in the USA undergoing mastectomy and found immediate reconstruction to be less likely with increasing stage, larger tumour size, negative oestrogen receptor status, and more than four positive lymph nodes [23]. Anticipated adjuvant therapy also reduces the likelihood of women being offered reconstruction. Those women that do not receive radiotherapy or chemotherapy are more likely to have immediate reconstruction [23, 33, 39].

3.5.3 Structure of Health-Care Systems

The structure of women's breast cancer care within countries is also a factor in reconstruction uptake. For example, in Australia and the USA, those women with private insurance are more likely to receive immediate post-mastectomy reconstruction [35, 46]. Further, care that is delivered in a teaching hospital increases likelihood, as well as a greater plastic surgeon density and urban location of treatment [34, 39, 41]. In France, mastectomies performed in 1 of the 20 dedicated cancer centres were most likely to receive immediate reconstruction compared with other public hospitals or private hospitals [29].

3.5.4 Region of Treatment

Another common feature of patterns of surgery has been regional variation. In 1988–1995, during the development of breast cancer services, variation of 3.3–16% was reported by Polednak across regions in the USA [47]. However in recent years, despite established breast cancer care pathways, national studies have found this variation still exists despite adjustment for disease and patient factors Table 3.2.

The variation reported across studies suggests there is potential to increase the proportion of women receiving post-mastectomy reconstruction. Further, it suggests that the structure and process by which care is delivered play an important role in determining the specific pathway women access and follow.

Table 3.2 National studies reporting on regional variation of immediate post-mastectomy reconstruction

Author	Study year	Country	Region definition	Number of regions	Immediate reconstruction variation (%)	Adjusted for confounders
Jagsi [39]	1998–2007	USA	State	50	19–76	Yes
Jeevan [22]	2006–2009	UK	Cancer networks	28	8–29	Yes
Mennie [1]	2009–2014	UK	Cancer networks	28	13–37	Yes

3.5.5 Education and Training

The provision of breast surgical services varies enormously around the world. Traditionally, general surgeons have been trained in the surgical management of breast cancer in many countries, including most of Europe, North America, the Middle and Far East, and Australasia. Gynaecologists undertake this work in Austria, Germany, Switzerland, Luxembourg and the Czech Republic, and in parts of South America. Wide differences in availability and provision of breast reconstruction services have emerged over the last decade, both between and within countries. In 2005, fewer than 25% of women in the USA were referred for a reconstruction opinion, as most general surgeons felt this was an unimportant aspect of treatment [48].

Access to reconstruction is influenced by the way in which the service is delivered—either by breast and plastic surgeons working either independently or together or by an oncoplastic team with cross-specialty skills. Growth and development of the 'oncoplastic' model of service delivery and greater cross-specialty collaboration have taken place in recent years. This has underpinned the increasing availability of reconstruction reported above, particularly in the UK and some other parts of Europe.

In 2000, a position paper was published by the European Society of Breast Cancer Specialists (EUSOMA) which described the key requirements for multidisciplinary specialist breast units [49]. The principles of this landmark document were adopted by the European Parliament in its 2003 and 2006 Resolutions on Breast Cancer, recommending that breast disease should be diagnosed and treated in dedicated breast centres, backed up by a robust framework of quality assurance and accreditation [50, 51]. These documents triggered off a range of interrelated developments which have had a direct impact on the availability and quality of breast reconstruction.

In 2007, revised EUSOMA guidelines set down new standards for the training of breast surgeons [52]. These recommended the introduction of an explicit curriculum, which required surgeons (general, gynaecological, and plastic) to develop the knowledge, expertise, and skills in oncological and reconstructive surgery to enable them to practice independently within a multidisciplinary team. A more recent EUSOMA publication has gone further and has established the requirements of a specialist breast centre [53]. These requirements include the availability of surgeons who are able to undertake basic reconstruction and oncoplastic procedures, as well as nominated reconstructive surgeons with a special interest and expertise in reconstruction and reshaping techniques.

The last decade has seen an increased demand for training in breast reconstruction in response to public, patient, and provider expectations. Many European breast surgeons remain concerned about the lack of opportunities to develop these skills, coupled with poor patient information and access. Most support the implementation of specialty curricula, specialty-specific examinations, and the development of a new specialty in breast surgery [54]. Efforts have been made to address their concerns, with the introduction of a breast specialty examination by the European Union of Medical Specialists (UEMS) [55].

Training in reconstruction has also been supported by a range of developments in the UK. Firstly, the implementation of a nationally appointed centrally funded Oncoplastic Fellowship Programme in 2002 [56]. More than 100 surgeons from a background of general and plastic surgery have completed these fellowships in large regional oncoplastic centres. The programme has generated a new cohort of consultant oncoplastic surgeons with sufficient experience to support a modern reconstructive service and to train the next generation. Secondly, the UK General Medical Council has recently approved new curricula in general and plastic surgery, supporting the acquisition of reciprocal cross-specialty skills in oncological and reconstructive breast surgery. Lastly, oncoplastic training is supplemented by postgraduate courses, including an online interactive Oncoplastic Masters Programme [57]. Meeting the future demand for breast reconstruction will require much more structured, explicit training opportunities, coupled with closer cross-specialty collaboration, both at national and international levels.

3.6 Trends in Type of Procedure

3.6.1 Immediate Reconstruction

Studies from the early 2000s revealed a preponderance of autologous reconstruction over implant-based procedures with a ratio of 2:1 [47, 58]. However, practice in both Europe and the USA has changed considerably in recent years. Early results evaluating 21,862 women undergoing unilateral index mastectomy with immediate reconstruction in England

revealed a strong trend toward implant-based reconstructions, rising from 30% in 2007 to 54% in 2013 [1]. Free flap reconstructions increased marginally from 17 to 21%, whilst the proportion of pedicled autologous procedures, with or without implant, decreased (see Fig. 3.1).

In the USA, this trend toward implant-based procedures is even more pronounced. Cemal et al. reported national implant procedures to rise from 39% of all unilateral immediate reconstructions in 1998 to 63% in 2008 [59]. For those women undergoing bilateral reconstruction as a result of contralateral prophylactic mastectomy, implant-based techniques also rose from 54 to 73%, but unilateral and bilateral autologous immediate reconstruction decreased from 59% in 1998 to 32% in 2008 [36]. This significant increase in immediate reconstruction with implants is likely to be attributable to the advent of ADMs facilitating a direct to implant reconstruction.

3.6.2 Delayed Reconstruction

Compared to immediate reconstruction, procedural trends reported in the delayed setting differ substantially (Fig. 3.1). In the UK, free flap reconstructions were seen to dominate, rising from 25% of all delayed cases in 2007 to 42% in 2013. Pedicled procedures decreased, whilst implant-based procedures remained relatively stable around 25% [1]. These differences are likely to be influenced by the more complex reconstruction needs in the delayed setting, such as the requirement for the skin, alongside the possibility of an irradiated field. We are not aware of trends in delayed reconstruction being reported at a national level outside the UK.

3.6.3 Interpretation

The recent national trends toward increasing rates of immediate implant reconstruction are surprising when considering the results from several outcome studies. Authors have not only found autologous reconstruction to be more stable with greater longevity of aesthetic results than implant-based procedures, but Patient-Reported Outcome Measures (PROM) results following free flap reconstruction are significantly higher [60, 61]. The structure and process of breast cancer services may offer an explanation. For example, autologous reconstruction takes considerably longer than an implant procedure and as such may exceed the operating room capacity and threaten cancer waiting targets [62]. Integrated

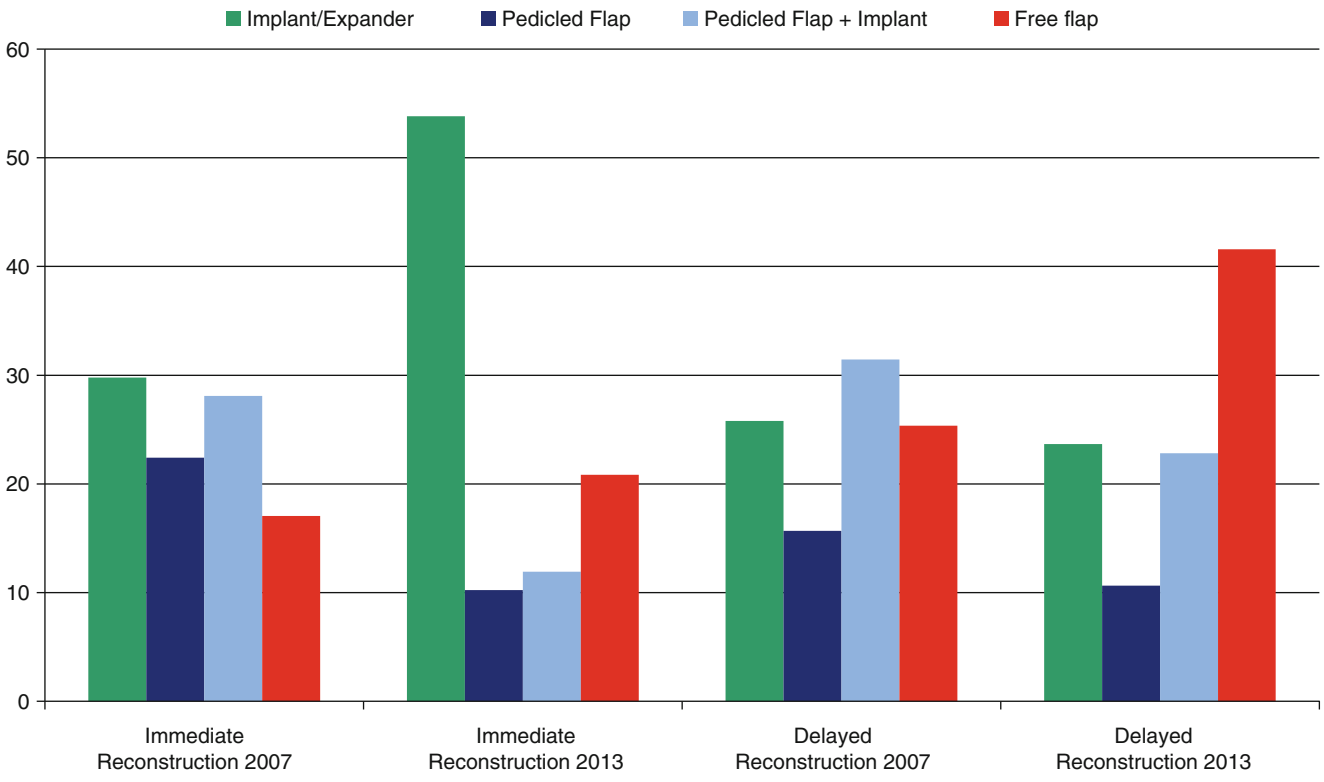

Fig. 3.1 Proportion of type of immediate and delayed post-mastectomy reconstruction procedures performed in English National Health Service hospitals during Hospital Episode Statistics (HES) year 2007 and 2013

workforce training and availability has a major influence on practice. It is known that the distribution of microsurgical breast surgeons varies across the country in the USA and Europe. Moreover, recent studies have revealed significant regional variation in the type of reconstruction procedure offered to women [36, 39]. In the UK, the proportion of immediate reconstruction using free flaps ranged from 9 to 63% across microsurgical regions during 2010 and 2014 [1]. These inequalities can be only addressed by the implementation of national guidelines defining best reconstructive practice, backed up by innovative approaches to the acquisition of reconstructive skill.

A study from the USA has also speculated that cost may also be a factor. Surgeons' hourly rate for an implant reconstruction in the USA is $587 whilst for an autologous procedure is $322 [59]. Given the procedural reimbursement policies in the USA, this may well explain the pronounced trend toward implant-based reconstructions [63]. Surgical factors and patient choice also need to be considered. In recent years, experience with implants in the setting of radiotherapy has increased, and studies have demonstrated acceptable outcomes [64, 65]. Further, women with breast cancer have far greater access to information nowadays, and rates of prophylactic contralateral mastectomies are increasing [36]. In contralateral prophylactic cases, implant reconstruction is more likely, as patients favour a symmetrical result with quick recovery [37, 66]. Women's cultural beliefs and choice also play a role. In China, traditions about cancer treatment, prosthesis, and body image may help to explain the low reconstruction uptake and the low proportion of implant reconstructions [30].

3.7 Future Considerations

The benefits of post-mastectomy reconstruction have been widely accepted, and the integration of reconstruction services into breast cancer pathways has been a huge achievement in the last decade. The reported increase in uptake is encouraging and looks set to continue. However, the significant geographical variation that exists between and within countries cannot be overlooked, both in terms of the uptake of reconstruction and procedures used. Further investigation is required to determine how much of this variation is related to training, service provision, or capacity barriers. Countries should ensure appropriate mechanisms are in place to monitor pathways and address any inequalities.

The scarcity of reports on national trends particularly in relation to delayed post-mastectomy reconstruction should be addressed. The collection of an agreed dataset would allow trends and patterns of breast reconstruction to be audited and compared both at national and international levels. Dissemination of this type of information will be crucial in guiding and shaping future practice.

Prospective data collection at a national level is particularly important when assessing the impact of new developments, such as the rising popularity of implant/ADM reconstruction. The regulation of medical devices received significant attention following the PIP scandal [67], but long-term data on the use of ADMs is sparse. Whilst ADM/implant reconstruction appears cost-effective in the short term, it will be important to establish that this approach is not creating significant problems in the longer term.

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Hereditary Breast Cancer: Prophylactic Mastectomy, Breast Conservation, and Rates of Cancer

4

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Hereditary breast cancers represent 5–10% of all breast cancer diagnoses [1] and up to 40% of all breast cancer diagnosed in women 35 years of age or younger [2]. In 1886 the French physician Paul Broca first noticed and described a familial clustering of breast cancer [3]; in his wife's family, 10 out of 24 women, spread across four generations, reportedly died from breast cancer. In addition, several other family members died from other malignant diseases. Broca astutely concluded that this high incidence of cancer in a single family was too high to be attributed to chance. In 1990, p53 mutations were identified in Li-Fraumeni syndrome, a disorder with a high predilection for breast cancer [4, 5]. Subsequently, in 1994, using positional cloning methods, a strong candidate for the 17-q-linked BRCA1 gene was identified [6]. Probable predisposing mutations detected included an 11-base pair deletion, a 1-base pair insertion, a stop codon, a missense substitution, and an inferred regulatory mutation. The BRCA1 gene was found to be expressed in numerous tissues including the breast and ovary. In 1994 Wooster et al. [7] performed a genomic linkage search with 15 high-risk breast cancer families that were unlinked to the BRCA1 locus on chromosome 17q21 and were successful in localizing a second breast cancer susceptibility locus, BRCA2, to chromosome 13q12–13. In 1995, in a collaborative effort between the University of Utah and the Institute of Cancer Research in the United Kingdom, a set of families with a predisposition to breast and ovarian cancers were studied and reliably excluded from linkage to BRCA1, leading to the landmark discovery of the second breast cancer gene, BRCA2 [8].

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Since these landmark discoveries, there has been extensive research into the implications of these genetic mutations and their optimal management. Patients who are diagnosed with these mutations are faced with challenging decisions regarding surveillance and prophylactic surgery. The surgical management of breast cancer, and the choice and timing of prophylactic surgery are discussed in this chapter. Some of the principles discussed may be extended to include the management of patients with mutations in genes other than BRCA which also predispose to breast cancer, as well as patients who are estimated to be of high risk due to significant family history without a defined genetic mutation.

4.1 Associated Risks

Since the discovery of BRCA1 and BRCA2, there have been many epidemiological studies attempting to define the risk of ovarian and breast cancer associated with these mutations. Much variation has been reported, possibly due to heterogeneity in study designs and the populations which were included.

Hartmann and Lindor [9] combined the data from 2785 families, of which 537 carried BRCA1 or BRCA2 mutations, and estimated the cumulative risk to breast cancer by the age of 80 years to be 67% among BRCA1 carriers and 66% among BRCA2 carriers. The lifetime risk was found to be dependent on age; for example, a 60-year-old unaffected BRCA2 carrier has a lifetime risk of breast cancer of 48%, as compared to 66% for an unaffected 30 year old. The authors include tables stratifying risk by age, which may be useful for counseling patients regarding risk.

The cumulative lifetime risk of ovarian cancer by age 80 years was estimated to be 45% for BRCA1 carriers and 12% for BRCA2 carriers. For men, the cumulative risk of breast cancer by age 70 years was estimated to be 1% for BRCA1 carriers and 7% for BRCA2 carriers.

This study also replicated the previously seen difference in the subtype of breast cancer diagnosed in these groups.

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_4

In the cohort with BRCA1 mutations, more than 75% were estrogen receptor (ER) negative, and 69% were triple negative. In contrast, 77% of patients with BRCA2 mutations were diagnosed with ER positive tumors, and only 16% developed triple negative breast cancers. An earlier large analysis of 19,731 carriers of BRCA1 and BRCA2 mutations detailed the distribution of ER positive disease in BRCA2 carriers and ER negative disease in BRCA1 carriers [10]. The CIMBA (Consortium of Investigators of Modifiers of BRCA 1/2) group collected pathological data from 4325 BRCA1 and 2568 BRCA2 mutation carriers, and identified that the proportion of ER negative breast tumors decreased with age at diagnosis among BRCA1 carriers but increased with age at diagnosis among BRCA2 carriers. In contrast, the proportion of triple negative breast cancers decreased with age at diagnosis in BRCA1 carriers but increased with age at diagnosis of BRCA2 carriers [11].

Contrary to popular belief, carriers of BRCA 1/2 have not been shown to have worse survival than non-BRCA mutation carriers with breast cancer. A recent meta-analysis, which included 66 studies comparing breast cancer patients with and without BRCA mutations, only found sufficient evidence for a 10% worse unadjusted recurrence-free survival for BRCA1 mutation carriers, but the evidence for differences in other outcomes in BRCA 1/2 carriers was judged to be indecisive [12]. In contrast, a population-based cohort study of 3220 women with breast cancer found that BRCA2 carriers had worse outcomes but that BRCA1 carriers did not, when compared with patients with sporadic breast cancer [13]. However, after adjustment for age, tumor stage and grade, nodal status, and hormone receptors, BRCA status was no longer a risk factor for death or distant recurrence. Only two studies reported breast cancer-specific survival (BCSS) in patients undergoing breast-conserving surgery (BCS) for genetic mutation-related breast cancer—one showed no difference between carriers and non-carriers. However, in the other [14], which compared 56 Ashkenazi Jewish BRCA carriers with 439 non-carriers, BCSS was worse in women with BRCA1 mutations than in those without (62% at 10 years versus 86%; $p < 0.0001$), but not in women with the BRCA2 mutation (84% versus 86% at 10 years; $p = 0.76$).

4.2 Surgical Management of Breast Cancer in BRCA Carriers

4.2.1 Breast-Conserving Surgery

The current standard surgical treatment for women with unifocal, unilateral breast cancer is wide-local excision, followed by radiotherapy. This strategy has been shown to have comparable long-term oncologic outcomes to mastectomy [15, 16]. In recent years, the breast surgery has become increasingly conservative, with "no tumor at the inked margin" currently accepted as adequate resection [17]. However, for carriers of BRCA mutations with breast cancer, the choice of appropriate local management is more complex. Options include BCS, unilateral mastectomy, or bilateral mastectomy. Important considerations include the risk of ipsilateral breast cancer recurrence and risk of contralateral breast cancer (CBC). One important area of uncertainty is whether there is a survival advantage to be gained from prophylactic surgery in the setting of a recent breast cancer diagnosis.

The safety of BCS for BRCA mutation carriers was addressed by Valachis et al. [18], who performed a systematic review and meta-analysis. The final cohort included 526 patients with BRCA mutations and 2320 controls. Among the BRCA carriers, 17.3% had reported ipsilateral breast recurrence (IBR), as compared with 11% of the control group. This difference was not statistically significant ($p = 0.07$). Only four studies differentiated between BRCA1 and BRCA2 mutation carriers, and although numbers were small (405 with BRCA1 mutations and 203 with BRCA2 mutations), no difference in IBR was seen between the two groups. It is important to note that the follow-up was short in many of the studies included (2.1–14 years). Longer follow-up may have shown a larger discrepancy in IBR between those with and those without genetic mutations. A case-control study carried out in Milan compared 54 mutation carriers undergoing BCS for breast cancer with 162 matched controls with sporadic breast cancer [19]. With a follow-up of 10 years, there was a significant difference in IBR (27% versus 4%, hazard ratio [HR] 3.9, $p = 0.03$). Similarly, a study from Yale showed increased rates of IBR after 12 years of follow-up in mutation carriers age ≤42 years treated with BCS and radiotherapy, compared with non-carriers of the same age (49% versus 21%, $p = 0.007$) [20]. In contrast, a similar case-control study carried out at the Institut Curie showed that with a follow-up of 13 years, there was no difference in IBR between carriers and non-carriers of BRCA genetic mutations who had BCS for breast cancer [21]. Pierce et al. compared mastectomy and BCS in a clinic-based ascertainment of 655 women with BRCA1/2 mutations and found that ipsilateral cancer rates were higher in the BCS group (23.5% vs. 5.5%, at 15 years, $p < 0.0001$). This study, like others, did not clearly distinguish between true recurrences and metachronous ipsilateral second primary malignancies. The rate of CBC was 40%, with no perceived difference between those receiving BCS and mastectomy. Regional and systemic recurrence rates, along with overall survival rates, were similar in both groups [22].

In the systematic analysis by Valachis et al. [18], the results of two studies [23, 24] were combined to investigate risk factors for IBR after BCS in BRCA carriers. Two risk

factors were identified: receipt of adjuvant chemotherapy and oophorectomy. This suggests that conservative treatment may be safer in women who opt for or have already undergone oophorectomy.

Other factors should also be taken into consideration before proceeding with aggressive surgical therapy for BRCA carriers with breast cancers. Gangi et al. [25] studied a cohort of 135 BRCA carriers diagnosed with ovarian cancer and found that 12 (8.9%) were subsequently diagnosed with breast cancer during follow-up. Bilateral mastectomy was performed in 6 (50%) and the rest had lumpectomy. Most of the ovarian cancer patients (82%) were diagnosed at stage III/IV, and the majority of the breast cancers (83.3%) were stage 0/I. Of the 12 patients diagnosed with breast cancer, 4 died of recurrent ovarian cancer. The overall 10-year survival of the entire cohort was 17%. The low rate of breast cancer in this group may be attributed to the high rate of platinum-based chemotherapy (99%), which has a risk reductive effect for BRCA mutation carriers, or may just be due to the competing risk of mortality from ovarian cancer. A similar study from Memorial Sloan Kettering Cancer Center and the University of Pennsylvania identified 18 metachronous breast cancers in a cohort of 164 BRCA-mutated patients diagnosed with ovarian cancer (11%), of which 12 of the breast cancers were stage 0/1/2 [26]. Ten-year overall survival was 68% in this cohort. None of the reported deaths were breast cancer related. These findings suggest that aggressive surgery may not be necessary for BRCA carriers with breast cancer who have previous ovarian cancer, although stage, disease status, and time since ovarian cancer diagnosis should be taken into consideration.

Overall, these results suggest that the risk of IBR in BRCA carriers does not appear to be significantly increased over the short term, suggesting that radiotherapy is as effective in carriers as in non-carriers. However, there appears to be an increased risk of ipsilateral events with continued follow-up, which may represent an ongoing risk of new primary malignancy in intact breast tissue that still harbors the underlying predisposition.

4.2.2 Contralateral Prophylactic Mastectomy

One of the clinical dilemmas when breast cancer is diagnosed in a BRCA mutation carrier is whether a contralateral prophylactic mastectomy (CPM) should be required. While the addition of radiotherapy to BCS appears to reduce the risk of IBR to the level of non-carriers over the short to intermediate term, the rate of CBC has consistently been shown to be substantially higher than patients with sporadic breast cancer [18, 20, 22]. BRCA carriers treated for unilateral breast cancer have been shown to be approximately three times more likely to develop CBC than non-carriers [18, 20, 27]. The cumulative 5-year risk of CBC for BRCA1 and BRCA2 mutation carriers has been shown to be 15% and 9%, respectively, and the 10-year risk has been shown to be 27% and 19%, respectively [28]. The 5-year cumulative risk was remarkably lower in non-BRCA carriers (3%; 95% confidence interval [CI] 2–5%) and remained so over subsequent years (5%; 95% CI: 3–7%). This is consistent with other descriptions of women diagnosed with sporadic breast cancers, who have a risk of 3% at 5 years and 5% at 10 years [28]. A recent case-control study by Garcia-Etienne et al. reported a CBC rate of 25% at 10 years in mutation carriers, as compared with 1% in the control group of patients with sporadic breast cancer [19]. The meta-analysis by Valachis et al. [18] reported pooled CBC rates of 23.7% among BRCA carriers and 6.8% in non-carriers (risk ratio [RR] 3.56, $p < 0.001$), based on 11 studies, bearing in mind that some had short follow-up of less than 5 years. Combining the results of the seven studies that differentiated between BRCA1 and BRCA2 carriers, they found that patients with BRCA1 mutations had a higher CBC rate than those with BRCA2 mutations (21% vs. 15%, RR 1.42, $p = 0.04$). Oophorectomy and increased age were associated with decreased risk of CBC (RR 0.52, RR 0.57, respectively). In patients who had not undergone bilateral oophorectomy, the use of tamoxifen significantly reduced the risk of CBC (RR 0.42). Graeser et al. followed a cohort of BRCA carriers for 25 years and reported a CBC rate of 47.4% [29]. Patients who were initially diagnosed before the age of 40, and who carried the BRCA1 mutation, had an even higher rate at 25 years (62.9%). A recent Dutch review of 6294 patients, of whom 271 carried a mutation of BRCA1/2, reported a 10-year cumulative CBC risk of 5.1% for non-carriers, 21.1% for BRCA1 carriers, and 10.8% for BRCA2 carriers [27]. Younger age at diagnosis was associated with higher risk of CBC in mutation carriers (23.9% vs. 12.6%), but not in non-carriers. Conversely, systemic therapy was associated with lower risk in non-carriers, but not in mutation carriers. Metcalfe et al. found that the number of first-degree relatives affected with breast cancer was also a predictor of the development of CBC [30].

The increased risk of CBC in BRCA mutation carriers raises the question of whether these patients derive a survival benefit from CPM. Metcalfe et al. followed 390 BRCA-mutated patients treated with mastectomy for unilateral breast cancer for 20 years [31]. Of these, 181 also had a contralateral mastectomy. At 20 years the overall survival of those who had contralateral mastectomy was 88%, as compared with 66% of those who did not, and the death-from-breast-cancer rate was 9.9% vs. 29.2%, respectively ($p < 0.0001$). In the multivariable analysis, contralateral mastectomy was associated with a 48% reduction in death from breast cancer, but this was not significant in the propensity score-adjusted analysis. It is important to note that this study was retrospective and not

randomized. One of the major criticisms of this paper has been that many of the CPMs were carried out years after the initial diagnosis and that the survival was calculated from the time of initial diagnosis, leading to a significant survival bias. A prospective study of 583 BRCA mutation carriers, diagnosed between 1980 and 2011 in The Netherlands, compared those who had CPM and those who did not [32]. Among the 242 patients who had CPM, 2% developed CBC, after a median follow-up of 11.4 years, as compared with 19% of those who did not. Mortality was lower in the CPM group (9.6 versus 21.6 per 1000 person years of observation). Those diagnosed before the age of 40, and those who did not receive chemotherapy, derived the most benefit from CPM. Again, the result of this study may overestimate the benefit of CPM due to selection bias and late CPM in survivors found to be carriers many years after their initial diagnosis. Although many papers reported variable outcomes with and without CPM in high-risk patients, few have examined those with BRCA mutations specifically. Studies examining outcomes following CPM in breast cancer patients with BRCA1/2 mutations are summarized in Table 4.1 [31, 33, 34]. It is important to note that many of the patients included in these studies may have been diagnosed before the widespread availability of MRI screening. With aggressive surveillance, benefit derived from CPM may be lower.

The choice of surgical treatment for first diagnosis of breast cancer is a complex decision based on multiple factors and requires detailed discussion with the patient. If the patient is requesting the highest risk reduction, then mastectomy with CPM may be offered. If the patient has had oophorectomy or is premenopausal and planning oophorectomy in the near future, then BCS with adjuvant radiotherapy is a reasonable option, especially in older BRCA2 carriers, with local recurrence rates in line with those of non-carriers. Patients should be counseled regarding the high risk of CBC. If the patient wishes to preserve the ovaries and manage the affected breast conservatively, then the risk of IBR and CBC should be highlighted, and increased surveillance should be considered. For patients considering mastectomy with or without CPM, and wishing to have reconstruction, the need for postmastectomy radiation therapy should be taken into consideration, as this may have an impact on cosmetic outcomes [35].

Table 4.1 Studies examining outcomes following contralateral prophylactic mastectomy in breast cancer patients with BRCA1/2 mutations

Study	*n*	Contralateral breast cancer rates		Survival	
		With CPM (%)	Without CPM (%)	With CPM (%)	Without CPM (%)
Metcalfe [31]	390	0.6	33.5	88	66
Heemskerk-Gerritsen [32]	583	2	19	92	81
Evans [33]	698	0	25	89	71

CPM contralateral prophylactic mastectomy

4.3 Surgical Management of Unaffected BRCA Carriers

4.3.1 Risk-Reducing Mastectomy

Several studies have examined the effect of bilateral prophylactic mastectomy on outcomes of BRCA1/2 carriers. The results are summarized in Table 4.2 [36–41]. The majority of studies showed a significant reduction in the risk of breast cancer, although there is no convincing evidence of improved mortality. There are no randomized controlled trials to date examining the benefits and risk of risk-reducing mastectomy (RRM). A recent meta-analysis by de Felice et al. [42] demonstrated a significant reduction in the risk of breast cancer in mutation carriers receiving RRM (HR 0.07; 95% CI 0.01–0.44; $p = 0.004$). It is important to note that there is significant morbidity associated with RRM, with complication rates reaching 40–64% [43–45] and with significant proportions expressing dissatisfaction with their appearance and decreased breast sensation postoperatively [46, 47]. A systematic review by Razdan et al. [48], however, reported high satisfaction rates and favorable psychosocial outcomes in patients undergoing RRM. Sexual well-being was unfavorable in 38% of patients in the 11 studies which reported it.

National Comprehensive Cancer Network (NCCN) guidelines [49], the U.S. Preventive Services Task Force (USPSTF) guidelines [50], the Society of Surgical Oncology (SSO) guidance [51], and The National Institute for Health and Care Excellence (NICE) recommendations [52] acknowledge that while the risk of breast cancer is reduced by 85–100% and breast cancer-specific mortality is reduced by 81–100% by RRM, the procedure carries significant morbidity. It is therefore recommended that the decision to proceed with RRM in an unaffected individual be made with multidisciplinary input and after detailed discussion with the patient.

4.3.2 Nipple-Sparing Mastectomy

Recently, it has been shown that almost 70% of BRCA mutation carriers undergo reconstruction following prophylactic mastectomy, and this is even higher (77.6%) in those who are 35 years of age or younger at the time of surgery [53]. It has been shown that preservation of the nipple-areolar complex (NAC) is associated with improved body image, patient satisfaction, and breast sensation [54]. Local and distant recurrence rates, along with cancer-specific survival rates, have been shown to be comparable with patients who have had conventional mastectomy [55]. There has been debate in

Table 4.2 Studies examining the effect of bilateral prophylactic mastectomy on outcomes of BRCA1/2 carriers

			Breast cancer risk		Survival		
Study	Year	Total *n*	With RRM	W/o RRM	With RRM	W/o RRM	Comments
Rebbeck [36]	2004	483	2/109 (1.9%)	184/378 (48.7%)	N/R	N/R	Retrospective case-control study
Heemskerk-Gerritsen [37]	2007	145 (with BRCA)	1/145 (0.7%)	–	100% OS	–	Retrospective analysis of high-risk patients with RRM
Domchek [38]	2010	1619	0/257 (0%)	98/1372 (7.1%)	N/R	N/R	
Skytte [39]	2011	307	3/96 (0.8% per person year)	16/211 (1.7% per person year)	N/R	N/R	
Ingham [40]	2013	691	7/126	220/565	98%	86.7%	Median follow-up 13.3 years
Heemskerk-Gerritsen [41]	2013	570 (405 BRCA1)	0/212 (0%)	57/358 (16%)	100% (breast cancer-free survival) 99% OS	74% (breast cancer-specific survival) 96% OS	

RRM risk-reducing mastectomy, *N/R* not reported, *OS* overall survival

recent years regarding the safety of nipple-sparing mastectomy (NSM) in BRCA mutation carriers. The rate of cancer, either invasive or in situ, identified in the NAC of prophylactic specimens of BRCA carriers has been shown to be low [56, 57]. There are no randomized trials comparing prophylactic total mastectomy and NSM in BRCA mutation carriers, and the available evidence is limited to small retrospective studies. A cohort of 89 BRCA mutation carriers who had NSM were followed for a median of 28 months and found to have no local recurrence in those with breast cancer and no subsequent diagnosis of breast cancer in those who had prophylactic surgery [58]. Excision of the NAC was subsequently performed in five patients, of whom one was for further investigation of ductal carcinoma in situ which was found in the margin of the mastectomy specimen, and there was no disease found in the NAC of any of these five patients. Yao et al. reported a series of 201 BRCA1/2 carriers who had NSM, of whom 150 were for risk reduction and 51 were for cancer [59]. Of those who had prophylactic surgery, 4 (2.7%) were found to have incidental cancers. Only one of these patients had a cancer event at a mean follow-up of 32.6 months.

Patients should be counseled regarding the risk of nipple necrosis (5–26%) and risk of need for surgical debridement of the NAC (3.5–18%) [58–60].

Although these early studies are encouraging regarding the oncologic safety of prophylactic NSM for BRCA mutation carriers, larger studies with longer follow-up will be helpful to assure patients and physicians of the safety of the procedure.

4.3.3 Prophylactic Oophorectomy

Current guidelines recommend prophylactic oophorectomy after completion of childbearing for carriers of BRCA1/2 mutations. The NCCN, the USPSTF, and the SSO all recommend prophylactic bilateral salpingo-oophorectomy (BSO) at the age of 35–40 for BRCA mutation carriers while factoring in patient and family choices [49–51]. Despite the strength of this recommendation, the data on the effect of prophylactic oophorectomy on risk of breast cancer is conflicted. It is important to bear in mind that the procedure is associated with significant side effects, including menopausal symptoms, infertility, and osteoporosis [61].

A retrospective study by Rebbeck et al. [62] of 551 BRCA carriers demonstrated a risk reduction of 96% for ovarian cancer and 53% for breast cancer with prophylactic BSO. A prospective study by Kauff et al. [63] yielded similar findings, with BSO conferring a 85% risk reduction for BRCA1-related gynecological malignancy and 72% for BRCA2-related breast cancer. There was no effect on the risk of ER negative breast cancer. A meta-analysis by Rebbeck et al. [64] showed significant reduction in the risk of breast cancer in BRCA1/2 mutation carriers undergoing prophylactic BSO, with similar rates of reduction in BRCA1 and BRCA2 carriers (HR 0.49; 95% CI = 0.37–0.65, BRCA1 mutation carriers HR 0.47, BRCA2 mutation carriers HR 0.47). Domchek et al. also reported lower all-cause mortality and breast-specific mortality in those undergoing BSO (10% vs. 3%, HR 0.4 and 6% vs. 2%, HR 0.44). More recent studies have been less encouraging. A recent study carried out in The Netherlands followed a group of 104 BRCA1 and 58 BRCA2 mutation carriers who had RRSO at premenopausal age and identified 18 breast cancers in 18 women during 532 women-years (34/1000 women-years), indicating a lower reduction in the risk of breast cancer than expected [65]. Another group described outcomes in 3722 BRCA mutation carriers, of whom 1522 had bilateral oophorectomy [66]. Overall, oophorectomy was not associated with decreased breast cancer risk. Age-adjusted HR

associated with oophorectomy was 0.96 (95% CI 0.73–1.26) for BRCA1 and was 0.65 (95% CI 0.37–1.16) for BRCA2 mutation carriers. However, in stratified analyses, the effect of oophorectomy was significant for breast cancer in BRCA2 carriers diagnosed prior to age 50 (age-adjusted HR 0.18, 95% CI 0.05–0.63), but still not in BRCA1 mutation carriers.

With regard to the impact of oophorectomy on breast cancer outcomes, Narod et al. described a cohort of 676 BRCA mutation carriers with a diagnosis of breast cancer, of whom 345 subsequently underwent oophorectomy, and suggested that BRCA1 carriers with ER negative disease derived the greatest benefit from oophorectomy (HR 0.07, $p = 0.01$) [67]. There was no effect on the risk of disease-specific mortality in ER positive breast cancers. This counterintuitive result may result from selective survival bias, given that the oophorectomy was performed at a mean of 6 years after the diagnosis of breast cancer and given that triple negative breast cancer typically recurs 1–3 years after the primary diagnosis. At this time, there is insufficient evidence to recommend oophorectomy as a therapeutic intervention in patients with BRCA-associated breast cancer, and the major benefit of the procedure appears to be in the prevention of ovarian cancer.

4.4 Surveillance of Patients with BRCA1/2 Genetic Mutations

Patients with diagnosed genetic mutations that predispose them to breast cancer may elect to defer risk-reducing surgery. These patients require surveillance to detect cancer at an early operable stage. NCCN guidelines [49] recommend that these patients become "breast aware" from the age of 18 and commence clinical examination every 6–12 months from age 25. Radiological screening should commence at 25–29 years of age and continue to the age of 75, with annual MRI, and from age 30, annual mammogram should also be performed. There is no proven clinical benefit to mammographic screening before the age of 30 [68]. Internationally, there is some variation in surveillance protocols, with MRI screening only being carried out to the age of 49 and mammographic screening to the age of 69. Regarding surveillance post risk-reducing surgery, there are no established guidelines. A recent international survey revealed that in most countries, clinical examination is still performed either annually or semiannually post risk-reducing surgery [69]. In Austria and Israel, annual MRI and ultrasound are still performed after RRM, and in other countries, MRI is carried out after NSM, to assess the volume of remaining breast tissue, in order to assess for further need for surveillance.

4.5 Chemoprevention for BRCA Carriers

There is a growing body of evidence to support the use of chemoprevention of breast cancer in certain high-risk patients. The International Breast Intervention Study (IBIS) 1 trial showed a risk reduction with tamoxifen in the incidence of ER positive breast cancers (HR 0.65) and ductal carcinoma in situ (HR 0.66), but not ER negative breast cancers [70]. The Royal Marsden breast cancer prevention trial also showed a significant reduction in the risk of ER positive breast cancer with the use of tamoxifen (HR 0.48), at 20 years of follow-up [71]. However, neither of these studies had sufficient numbers of BRCA mutation carriers to examine the preventative effect of tamoxifen for these patients. The NSABP-P1 Breast Cancer Prevention Trial randomized 13,338 women to receive tamoxifen or placebo, and at a median follow-up of 54 months, a risk reduction of 49% was seen in the tamoxifen group [72]. Of the 288 breast cancer cases, 19 were carriers of a BRCA mutation. Analysis of these patients showed that tamoxifen reduced the incidence of breast cancer in carriers of BRCA2 by 62%, but not carriers of BRCA2 [73]. However, two small case-control studies [74, 75] showed a reduction in the risk of CBC in carriers of BRCA1 and BRCA2. There have not, to date, been any randomized controlled trials examining the effect of chemoprevention on the risk of breast cancer in BRCA carriers.

It has been hypothesized that environmental and behavioral factors may influence the development of breast cancer in patients with genetic mutations. A meta-analysis by Friebel at examining modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers concluded that although several associations were identified, including age at first live birth, smoking status, breastfeeding, and oral contraceptive use, the data assessing modifiers were inadequate, and further studies were warranted [76]. There is a randomized controlled trial currently assessing the efficacy of a lifestyle intervention program for BRCA mutation carriers [77].

4.6 Conclusions

Hereditary breast cancer accounts for up to 10% of all breast cancers and up to 40% of breast cancers diagnosed in younger women. Although treatment has traditionally been more aggressive in these women, their risk of local recurrence is lower than previously thought. Due to their increased risk of CBC, they are often offered risk-reducing surgery at the time of diagnosis.

Women diagnosed with a genetic mutation associated with increased risk of the development of breast cancer are faced with options regarding surveillance and prophylactic surgery. The evidence suggests that while risk-reducing BSO

and mastectomy can dramatically reduce the risk of developing breast and ovarian cancer, the use of modern imaging techniques for aggressive surveillance may reduce the urgency of surgery. Further research is needed to investigate the use of chemoprophylaxis and other risk modifiers in women with a genetic mutation that predisposes them to breast cancer.

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Breast Imaging in Oncoplastic and Reconstructive Breast Surgery

5

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5.1 Introduction

Breast cancer represents one of the most complex diseases in medicine [1, 2]. It is a broad universe of diseases with different biological profiles, clinical manifestations, and prognoses, whose common history began with mutilating surgeries in the late nineteenth century and reached a better understanding with the development of molecular biology in less than 100 years. The replacement of the Halstedian paradigm, associated with the early diagnosis, changed the treatment of this disease, personalizing and improving the patients' quality of life while increasing their cure rates with less mutilating approaches [3, 4]. The multidisciplinary model of disease management and the rapid incorporation of new diagnostic and therapeutic technologies were the main responsible for this [5]. Thus, in this chapter the main aspects related to breast imaging will be discussed.

5.2 Diagnostic Methods of Breast Cancer

Mammography (MG) is, currently, the most important method in breast evaluation. Other diagnostic methods, such as ultrasound (US), magnetic resonance (MR), tomosynthesis (TMS), scintigraphy, and PET-CT, are used as auxiliary methods in the diagnosis of breast cancer, and they are chosen according to the lesion that will be evaluated [6].

There are two different levels of approach for breast evaluation, which have an influence on the choice of imaging methods: asymptomatic patient evaluation for breast cancer screening and symptomatic patient to diagnose either a benign or a malignant tumor.

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5.2.1 Breast Cancer Screening

The aim of breast cancer screening is to spot the tumor at an early stage, before its clinical manifestation, increasing the chances of patients' extended life. Mammography is the only method that pointed to an absolute reduction in mortality rate (between 25% and 30%) among patients undergoing regular screening, due to detection of ductal carcinomas in situ and infiltrating carcinomas of a smaller size and staging when compared with the group of non-tracked ones [7–15]. US and MR have appeared useful in specific groups of patients; however no long-term study has been carried out to determine the impact on mortality.

MG can detect 5–7 cancer cases in every 1000 asymptomatic women undergoing the first exam and 2–3 cases at every 1000 women undergoing annual screening [16]. The HIP (*Health Insurance Plan)* study was the first evidence of the mammographic potential to reduce mortality rate. Within this study, performed in the 1960s, around 6000 women were randomized in two groups, a control one and another one undergoing physical exams and mammograms. After a 7-year follow-up, a 30% mortality rate reduction in the group of women that underwent screening [17, 18] was noticed. After that study, mammography began to be widely used for screening breast cancer. By the end of the 1980s, a variety of other studies confirmed reduction of mortality rate of 50-year-old patients and above, undergoing regular screening [7–15]. There are also benefits, though not so evident, to women between 40 and 50 years old. Although no piece of study has demonstrated an association between self-exam of breasts and lower mortality rate, this type of test has to keep being encouraged.

US is not appropriate as an initial method for tracking, mainly due to its limitation to evaluate microcalcifications, which are the early cancer manifestation in 50% of cases. Some studies have proposed the use of US as the method for screening of asymptomatic patients with negative mammogram, though dense (density categories BI-RADS 3 and 4) [19]. Kolb et al. [20] have published a study performed with

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_5

11,130 asymptomatic patients undergoing mammography and US, which shows that additional US and mammography have increased the detection of breast cancer in dense breast patients at 42%. Nevertheless, so far there are not enough randomized studies showing a decrease in mortality rate among this group of patients, which is a requirement for application of the method as a screening method in large populations.

RM appears to be the most sensitive method for detecting breast cancer among high-risk patients, mainly for those with identified genetic alterations (BRCA1 and BRCA2) or a marked family history [16, 21, 22]. Krieger et al. [21] followed up 1909 women with marked family history or with genes BRCA1 and/or BRCA2 positive for an average period of 2.9 years, showing 33.3% sensitivity to mammography and 79.5% for MR. Kuhl et al. [23] evaluated 529 asymptomatic women for a period of 5.3 years, with marking family history or genetic mutation, and they observed 33% sensitivity for mammography, 40% for US, and 91% for MR. More recent studies have confirmed these findings. Riedl et al. in 2015 reported an overall sensitivity similar for MG and US, isolated, 38% and, when combined, 50%. Isolated MRI showed sensitivity of 90% and, combined with mammography, 93%, with no increase when combined with US [24]. However, randomized prospective studies are required in order to establish the impact of mortality on these new tracking methods.

In Brazil, the Brazilian College of Radiology and Diagnostic Imaging (CBR), the Brazilian Society of Mastology (SBM), and the Brazilian Federation of Gynecology and Obstetrics (FEBRASGO) published their recommendations for the screening of breast cancer [25]. The recommendations are the following:

(a) Women aged under 40.
- Mammography—Generally, at this age range mammography is not recommended, except on an individual basis for women at high risk for breast cancer, as shown on Table 5.1.
- Ultrasonography—At this age range, sonographic screening is not recommended, except on an individual basis for women at high risk for breast cancer in whom screening by magnetic resonance imaging might be appropriate but, for any reason, cannot be performed.
- Magnetic resonance imaging —At this age range, breast MRI screening is not recommended, except on an individual basis for women at high risk for breast cancer, as shown on Table 5.2.

(b) Women aged between 40 and 69.
- Mammography—At this age range, mammography is recommended for all women with annual periodicity.
- Ultrasonography—Generally, at this age range, sonographic screening is not recommended, except on an individual basis for women in the situations described on Table 5.3.
- Magnetic resonance imaging—Generally, at this age range, MRI screening is not recommended, except on an individual basis for women at high risk for breast cancer, as shown on Table 5.4.

Table 5.1 Recommendations for mammographic screening for high-risk women aged under 40

Women with genetic mutation (BRCA1 or BRCA2) or with first-degree relatives with proved mutation	Starting at 30 years of age (but not before the age of 25)
Women at lifetime risk of ≥20%, according to one of the mathematical models based on the patient's family history	Starting at the age of 30, or 10 years before the age of diagnosis of the youngest relative affected by the disease (but not before the age of 25)
Women with previous history of chest irradiation between 10 and 30 years of age	Starting 8 years after the radiotherapy treatment (but not before the age of 25)
Women with Li-Fraumeni or Cowden syndrome, or family history (first degree relatives) of such syndromes	Starting at the time of the diagnosis (but not before the age of 25)
Women with personal history of lobular neoplasia (ALH and LCIS), ADH, LCIS, invasive breast cancer or invasive ovarian cancer	Starting at the time of the diagnosis (but not before the age of 25)

Note: *ALH* atypical lobular hyperplasia, *LCIS* lobular carcinoma in situ, *ADH* atypical ductal hyperplasia, *CDIS* in situ ductal carcinoma

Table 5.2 Recommendations for screening with magnetic resonance imaging for high-risk women aged under 40

Women with genetic mutation (BRCA1 or BRCA2) or with first-degree relatives with proved mutation	Annually, starting upon confirmation of the genetic mutation (but not before the age of 30)
Women at life time risk of ≥20%, according to one of the mathematical models based on the patient's family history	Annually upon risk calculation or 10 years before the age of diagnosis of the youngest relative (but not before the age of 30)
Women with previous history of chest irradiation between 10 and 30 years of age	Annually, starting 8 years after the radiotherapy treatment (but not before the age of 30)
Women with Li-Fraumeni or Cowden syndrome, or family history (first degree relatives) of such syndromes	Annually, starting at the time of the diagnosis (but not before the age of 30)
Women with personal history of lobular neoplasia (ALH and LCIS), ADH, ISDC, invasive breast cancer or invasive ovarian cancer	Annually, starting at the time of the diagnosis (but not before the age of 30)
It may be considered in women with recent diagnosis of breast cancer and with a normal breast at conventional imaging methods and physical examination	Single evaluation of the contralateral breast at the moment of the diagnosis

Note: *ALH* atypical lobular hyperplasia, *LCIS* lobular carcinoma in situ, *ADH* atypical ductal hyperplasia, *CDIS* in situ ductal carcinoma

Table 5.3 Recommendations for screening with ultrasonography for women aged between 40 and 69

It may be considered in high-risk women, particularly those where MRI screening might be appropriate but, for any reason cannot be performed	Individualized
It may be considered for women with dense breast tissue, as an adjuvant to mammography	Individualized

Table 5.4 Recommendations for screening with magnetic resonance imaging for high-risk women aged between 40 and 69

Women with genetic mutation (BRCA1 or BRCA2) or with first-degree relatives with proved mutation	Annually, starting upon confirmation of genetic mutation
Women at lifetime risk of ≥20%, according to one of the mathematical models based on the patient's family history	Annually, upon risk calculation
Women with previous history of chest irradiation between 10 and 30 years of age	Annually, starting after 8 years of treatment
It might be considered for women with personal history of lobular neoplasia (ALH and LCIS), ADH, DCIS invasive breast cancer or invasive ovarian cancer	Annually starting at the time of the diagnosis
It may be considered in women with recent diagnosis of breast cancer and with a normal breast at conventional imaging methods and physical examination	Single evaluation of the contralateral breast at the moment of the diagnosis

ALH atypical lobular hyperplasiam, *LCIS* lobular carcinoma in situ, *ADH* atypical ductal hyperplasia, *DCIS* in situ ductal carcinoma

Table 5.5 Recommendations for mammographic screening of women aged above 70

Women with life expectancy >7 years, with basis on comorbidities	*Annually*
Women who can be submitted to invasive diagnostic investigation and treatment after abnormal result of screening	*Annually*

(c) Women aged above 70.
- Mammography—At this age range, mammographic screening is recommended on an individual basis, as shown on Table 5.5.

5.2.2 Evaluation of Symptomatic Patients

All imaging methods are useful for the evaluation of a patient with symptoms or signs that point to breast cancer. The combination of MG and US is particularly useful in this group of patients. Moy et al. [26] report that only 2.6% of patients did not have symptoms or signs appearing in mammography and in US from a group of 374 symptomatic women with breast cancer. Kolb et al. [20] also reported that MG itself diagnosed only 48% of the tumors in patients with dense breasts, while MG US together detected 97% of the cases. The possibility of a patient to present with a tumor through negative MG and US goes down to 3%.

The choice of an initial method for a symptomatic patient may be influenced by the patient's age range. If the patient is young (below 35 years old), US is the chosen method for initial evaluation, considering that most patients will show dense breasts. For patients aged 35 years old and above, an initial evaluation with MG is recommendable, and complementary US or MR applies for cases in which clinical suspicion is maintained.

It is relevant to make it clear that there is no test or test group able to guarantee that a patient does not have breast cancer within the effectiveness of a suspicious physical exam. The final conduct in this group of patients must be based mainly on clinical parameters.

5.3 Breast Imaging Reporting and Data System (BI–RADS®)

Breast Imaging Reporting and Data System (BI-RADS®) is the result of a mutual effort between members of the *American College of Radiology* (ACR) with the cooperation of the *National Cancer Institute*, *Centers for Disease Control and Prevention*, *Food and Drug Administration*, *American Medical Association*, *American College of Surgeons*, and *College of American Pathologists*. This system is designed to standardize the medical report, reduce misunderstandings in the interpretation of images, and make patients' follow-up easier, besides allowing for an internal quality auditing system. It should be used in MG, US, and MR [6].

After evaluation of images, the medical report must be written in a clear and concise way, so it can give the professional who requested the test a real idea of what was diagnosed as well as the recommended conduct. The medical report must contain the five parts that follow:

(a) Indication for exam (a brief description of the reason for exam).
(b) Breast composition (description of the breast standard, it indicates the risk of a lesion to be obscured by normal mammary tissue).
(c) Findings (an accurate description of the findings according to established terms and standards must be made).
(d) Comparison to previous studies (important in cases of dubious findings, and less important in cases of either negative or benign mammograms).
(e) Overall assessment (classification of exam in one of the system categories, and conduct recommendation (see Table 5.6):

Category 0: must be reserved for cases in which an additional evaluation has to be performed, such as additional

Table 5.6 BI-RADS® categories

Category	Definition	Risk of malignancy	Recommendation
0	–	–	Additional imaging required
1	Negative	–	Annual follow-up
2	Benign finding(s)	0%	Annual follow-up
3	Probably benign	<2%	Term follow-up
4 (A, B, C)	Suspicious of malignancy	3–95%	Biopsy recommended
5	Highly suggestive of malignancy	>95%	Biopsy required
6	Known neoplasia	–	Conduct according to case

[a]Adapted from Breast Imaging Reporting and Data System (BI-RADS®)

mammographic incidences with local compression or ampliations, or even complementation with other tests (for instance, US or MR). It can also be used in cases that a comparison with previous tests becomes important, before a final impression is reached.

Categories 1 and 2: cases classified as negative (category 1) or with benign findings (category 2) are followed up through annual routine tests.

Category 3: in cases of probably benign lesions, which show risk of malignancy lower than 2%, a semester follow-up is recommendable until 2 or 3 years have been completed (according to the lesion) aiming to determine the stability of the lesion. After such a period, if no alteration in the lesion is noticed, it begins to be classified as category 2, returning then to the annual tracking group.

Category 4: considering lesions classified as 4, the subdivision 4A, 4B, and 4C is optional, though strongly recommended. Category 4A must be used when the risk of malignancy is low and a 6-month control period after biopsy or a negative cytology is indicated. Category 4B indicates an intermediate risk of malignancy, so a good anatomic-radiological correlation is needed. Category 4C includes findings of moderate suspicion in which a malignant result is expected.

Category 5: lesions classified as highly suggestive of malignancy show a risk of malignancy higher than 95%. This group must be reserved for the group of classic tumor lesions such as spiculated masses, pleomorphic calcifications, or ductal calcifications, in which a malignant lesion can only be discharged after surgical evaluation of the region in question.

Category 6: this category is reserved for the group of lesions that already have a diagnosis of cancer, when returning for neoadjuvant chemotherapy control or even in cases that a second opinion is required. This category is not appropriate in cases of follow-up after breast conservative surgery.

5.4 Mammography

5.4.1 Normal Mammographic Findings

There is a big variation in the appearance of a normal breast in a mammogram, mainly as to the size, shape, and parenchyma composition. Parenchyma composition may vary from almost totally substituted to extremely dense, and this composition is directly related with sensitivity to mammography.

Liposubstituted breasts allow for an excellent background tissue for tumor visualization, while high density can obscure cancer visualization.

The BI-RADS® standards the composition of the breast is divided into four categories [6]:

(a) Category a: breasts are almost entirely fatty (Fig. 5.1a).
(b) Category b: there are scattered areas of fibroglandular density (Fig. 5.1b).
(c) Category c: the breasts are heterogeneously dense, which may obscure the small masses (Fig. 5.1c).
(d) Category d: the breasts are extremely dense, which lowers the sensitivity of mammography (Fig. 5.1d).

Younger women tend to have a bigger amount of fibroglandular tissue, although there is considerable variation within the same age range. As the age range increases or when the woman breastfeeds, the fibroglandular tissue tends to be replaced by fat. The replacement always occurs from the posterior region to the anterior one and from medial to lateral, in a symmetric way. An increase in mammary density can be observed during pregnancy and due to the use of hormone therapy.

5.4.2 Abnormal Mammographic Findings

Masses and calcifications are the most common abnormal findings in MG. Other lesions that have been observed are architectural distortion, focal asymmetry, global asymmetry, retraction or cutaneous thickening, mammillary retraction, and axillary lymphadenomegaly.

5.4.2.1 Masses

Masses are described as lesions occupying space that is seen in at least two incidences. They are described according to shape, margin, and density [6].

Shapes can be round, oval, or irregular (Fig. 5.2). While the oval and round shapes are usually related with benign lesions, the irregular shape is more associated with malignant lesions.

Margins are also an important indicator of malignancy, and they are described as circumscribed, microlobulated,

obscured, indistinct, or spiculated (Fig. 5.3). Circumscribed lesions are defined as lesions that show at least 75% of the margins well-defined, and they are associated with a possibility of malignancy lower than 2% [31, 32]. These lesions are classified as probably benign (BI-RADS® 3 category), and it is recommended that a semester control is done. But microlobulated lesions and indistinct ones show a higher risk of malignancy, while spiculated ones are highly suggestive of malignancy.

The density of masses may also point to its etiology, being described as high density, low density, isodense to parenchyma, and fat density (Fig. 5.4). Generally, benign lesions tend to be less dense than malign ones, though this is not always absolutely true. The existence of fat density inside the mass confirms its benign nature.

Finding associated lesions may help define the nature of lesions, such as gross calcifications (associated with fibroadenoma in involution) and pleomorphic (related to malignant lesions), cutaneous retraction and mammillary retraction.

5.4.2.2 Calcifications

Calcifications must be described according to their morphology and distribution. Morphology shows a good correlation with the nature of calcifications, and they can be classified as [6]:

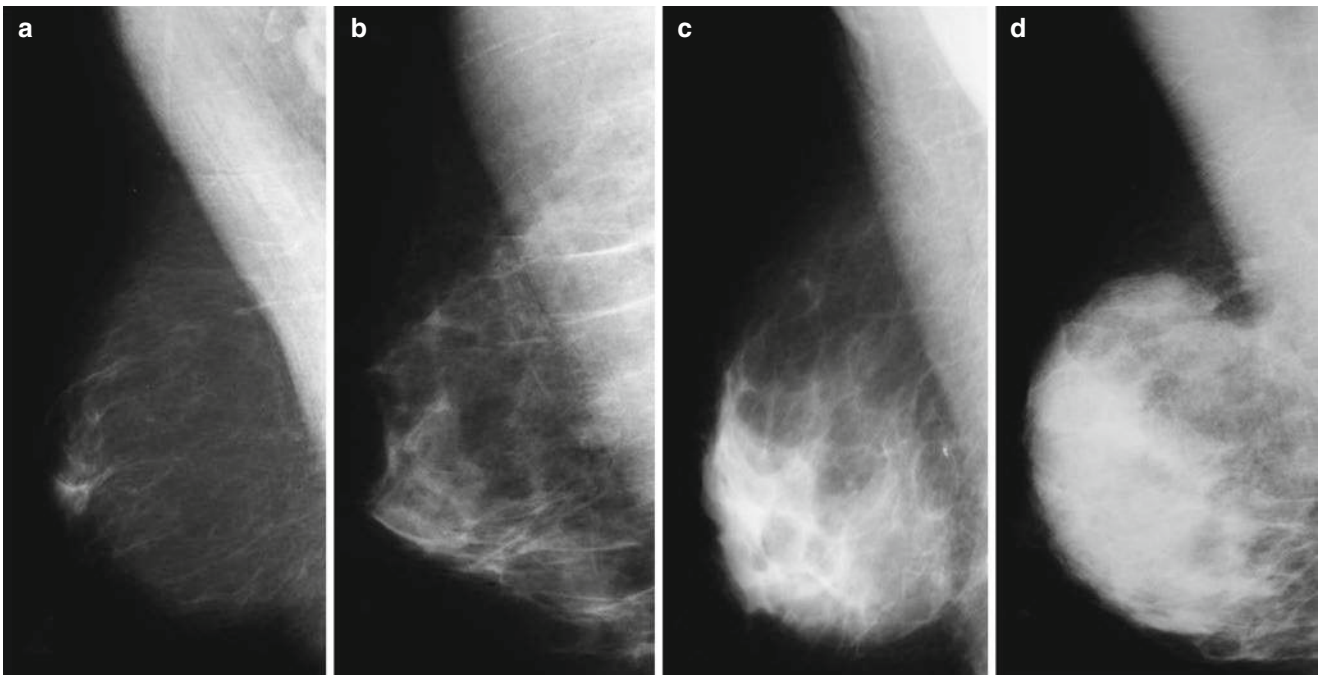

Fig. 5.1 Mammographic patterns of mammary density according to BI-RADS®: breasts are almost entirely fatty (**a**); scattered areas of fibroglandular density (**b**); the breasts are heterogeneously dense (**c**); extremely dense (**d**)

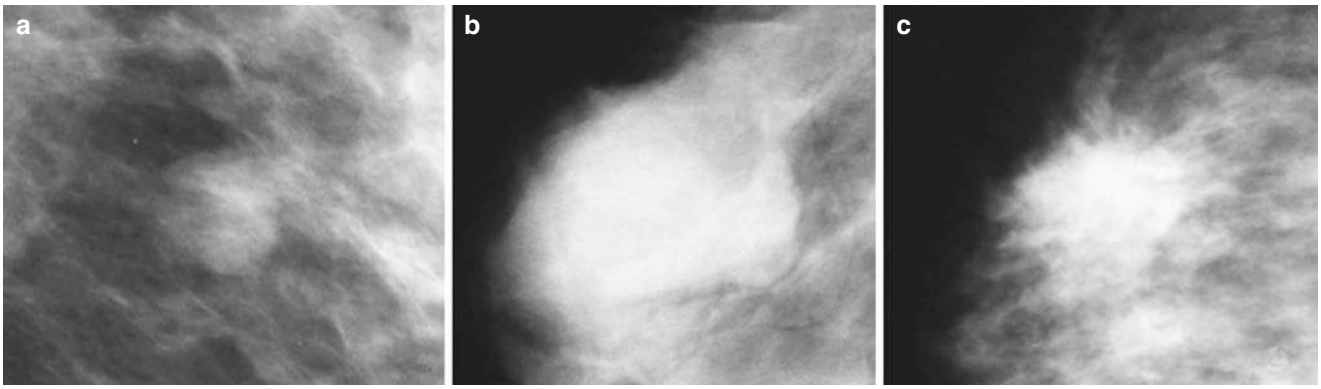

Fig. 5.2 Shapes of masses screened: round (**a**), oval (**b**), and irregular (**c**)

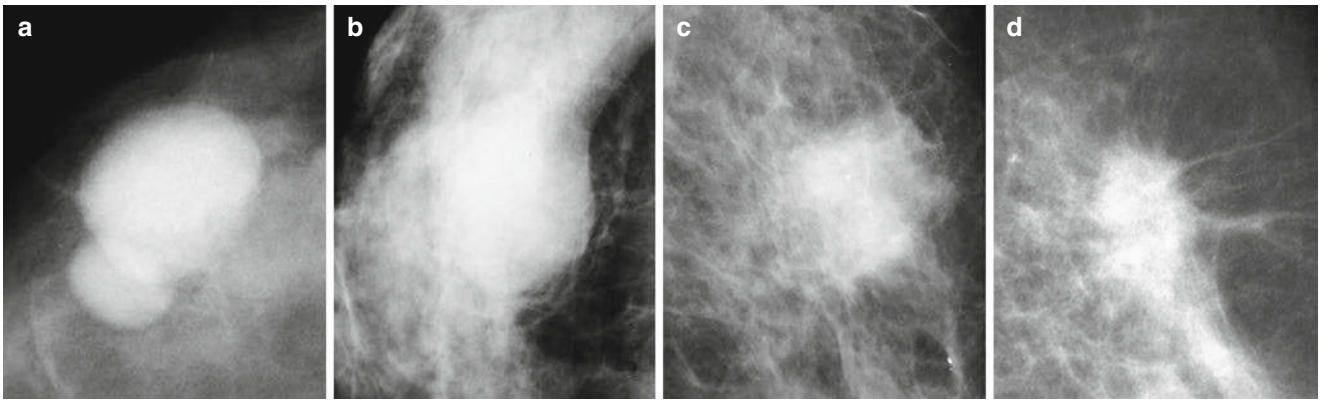

Fig. 5.3 Margins of masses screened: circumscribed (**a**), obscured (**b**), indistinct (**c**), and spiculated (**d**)

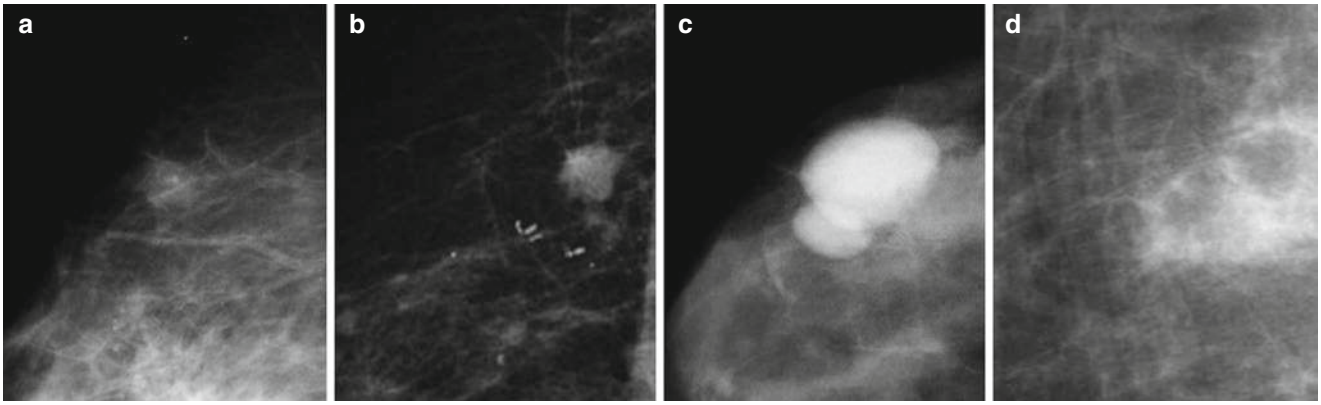

Fig. 5.4 Density of masses screened: low density (**a**), isodense (**b**), high density (**c**), and fat density (**d**)

(a) Typically benign: skin calcifications (lucent-centered), vascular (parallel lines associated with vascular structures), "popcorn" type (coarse and associated with mass images, corresponding to fibroadenoma in involution), gross tubular (associated with duct ectasia), round (frequently formed in acini and lobes), rodlike (lucent-centered), "eggshell" (calcium deposit on the cyst walls or of fat necrosis), "milk of calcium" (sediment calcifications inside the cysts), sutures (formation of calcium around the sutures), and dystrophic (in irradiated breasts and those undergoing traumas) (Fig. 5.5).
(b) Suspicious morphology: amorphous (frequently small and with morphology difficult to define, commonly mistaken as benign calcifications; when grouped they should be correlated with biopsy) (Fig. 5.6a), coarse heterogeneous (they are larger and tend to coalesce, so they can be associated with malignancy or with an initial phase of dystrophic calcifications of fibrosis, fibroadenoma, or trauma) (Fig. 5.6b), fine pleomorphic (they show a wide variety of shapes and sizes, generally less than 0.5 mm) (Fig. 5.7a), and fine linear or fine-linear branching (calcifications on the duct tracks, which suggest that there is participation of the duct through the tumor) (Fig. 5.7b).

Considering calcification distribution, we can describe them as follows:

(a) Diffuse: distributed at random in the breasts, generally found in benign calcifications.
(b) Regional: found in a broad area of the breast, but with no duct track. It may involve one or more quadrants, and the risk of malignancy is associated mainly with calcification morphology.
(c) Grouped: they must be used when at least five calcifications occupy a small volume of the breast, and there is high risk of malignancy.
(d) Linear: they point to a ductal distribution, increasing the risk of malignancy.
(e) Segmental: they point to damage of the ducts and of their branches in an area of the breast, also increasing the risk of malignancy.

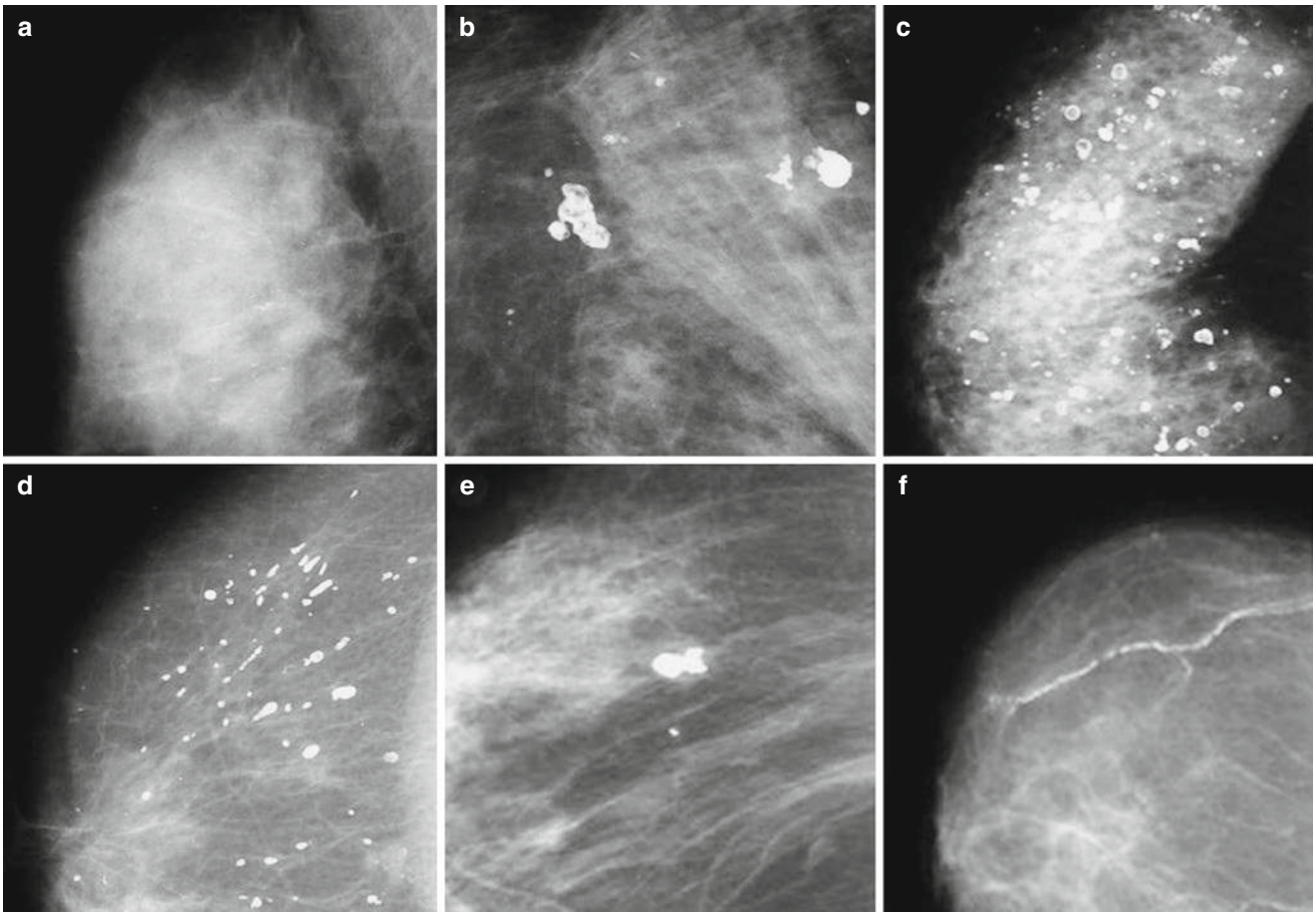

Fig. 5.5 Typically benign calcifications: "milk of calcium" (**a**); dystrophic (**b**), round and rodlike (**c**), gross tubular (**d**), "popcorn" type (**e**), and vascular (**f**)

5.4.2.3 Architectural Distortion

Architectural distortion is defined when normal architecture of the breast is altered; however, there is no evident mass (Fig. 5.8). When there are no records of trauma or of surgery, distortion leads to a condition of highly suspicious of malignancy or a radial scar; therefore, histological evaluation is recommended [6].

5.4.2.4 Asymmetries

(a) Asymmetry: this is an area of tibroglandular-density tissue that is visible on only one mammographic projection. Most such findings represent summation artifacts, whereas those confirmed to be real lesions may represent one of the other types of asymmetry or a mass.
(b) Global asymmetry: it generally represents an anatomic variation, which is identified during the comparison with the contralateral breast. It cannot be associated with the palpable mass, the architectural distortion area, masses, or microcalcifications.
(c) Focal asymmetry: defined as a lesion that cannot fill the criteria of mass required, visualized in both incidences as similar shapes. It may represent a normal parenchyma island; however, many times it presents with non-specific characteristics, so it demands additional investigation.
(d) Developing asymmetry: this is a focal asymmetry that is new or more conspicuous than on a previous examination. Approximately 15% of cases are found to be malignant.

5.4.2.5 Special Cases

Some alterations can be seen through mammography, and they are described as follows [6]:

(a) Solitary dilated duct: this is a unilateral tubular structure that likely represents a dilated duct. Even if unassociated with other suspicious clinical or mammographic findings, it has been reported to be associated with noncalcified DCIS.

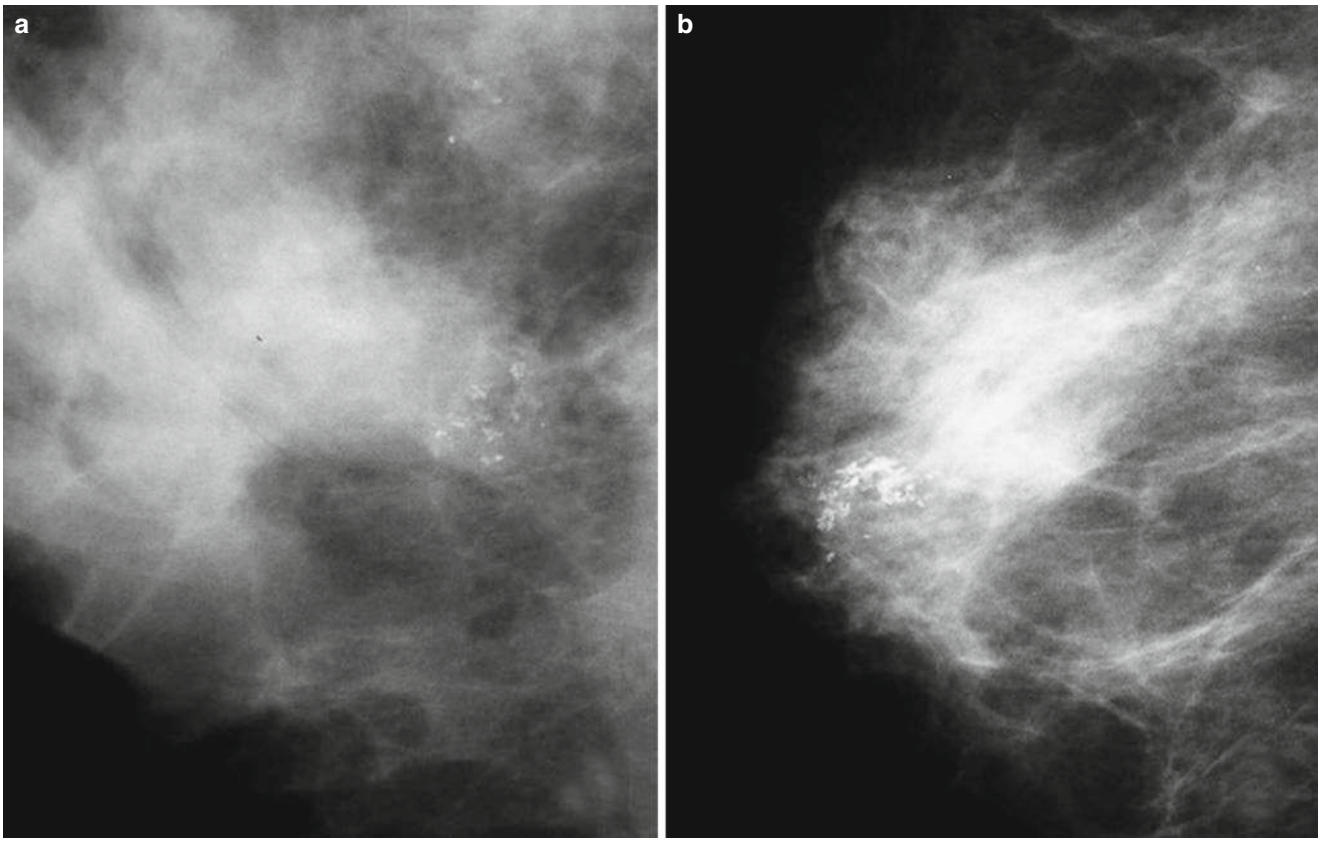

Fig. 5.6 Suspicious calcifications: amorphous (**a**) and coarse heterogeneous (**b**)

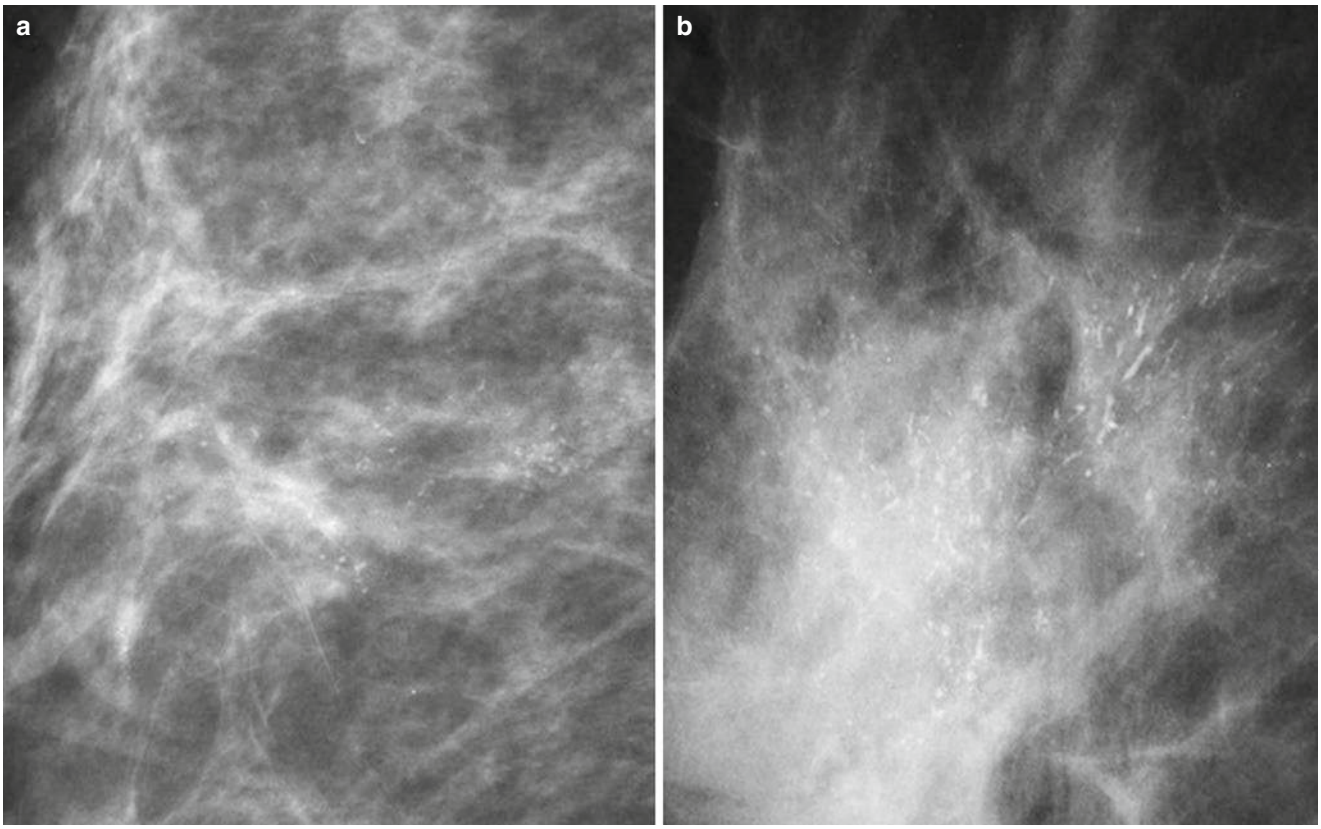

Fig. 5.7 Suspicious calcifications: fine pleomorphic (**a**) and fine linear (**b**)

5.5.2 Abnormal Ultrasound Findings

The evaluation of masses detected both through mammography or through physical exams is the most frequent indication for US. Calcifications are poorly evaluated through this method, as their detection becomes more difficult and their morphological evaluation is not possible.

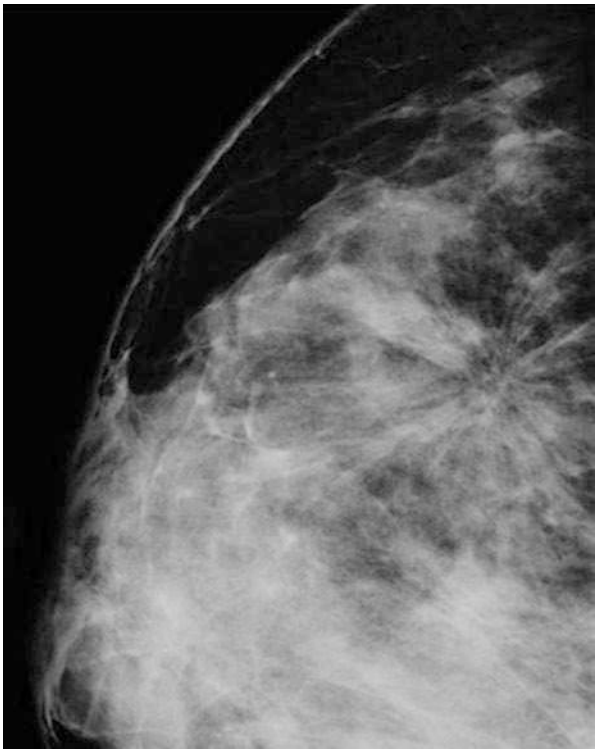

Fig. 5.8 Architectural distortion in mammography

5.5.2.1 Masses

Masses must be detected and analyzed on more than one incidence to differ from normal anatomic structures. They are ecographically described according to shape, orientation, margins, echo pattern, and posterior features [6, 27].

The shape can be defined as round, oval, or irregular (Fig. 5.10). Interpretation of the exam concerning benignity and malignancy of the mass is similar to mammography, and irregular ones are the most suspicious.

Orientation is a particular aspect of US (Fig. 5.11). Masses that are parallel to the skin, that is, wider than higher, are generally benign. When the orientation is vertical, that is, higher than wider, it is more suggestive of malignancy, as it represents a growth through normal tissue plans.

Margins are described as circumscribed and not circumscribed: indistinct, spiculated, angular (projections forming acute angles), and microlobulated (various small lobulations of 1–2 mm) (Fig. 5.12). Except for the circumscribed margin, the various aspects are suggestive of malignancy. The spiculated margins and/or microlobulated are the ones that present with the highest predictive value for malignancy [27, 28].

The echogenicity pattern aids primarily with the differentiation between cystic mass (anechoic) and solid (hypoechoic, isoechoic, hyperechoic, heterogeneous, and complex cystic and solid), defined in relation to fat (Fig. 5.13). The homogeneously hyperechoic masses are considered of higher predictive value for benignity. Solid hypoechoic and isoechoic masses need other characteristics

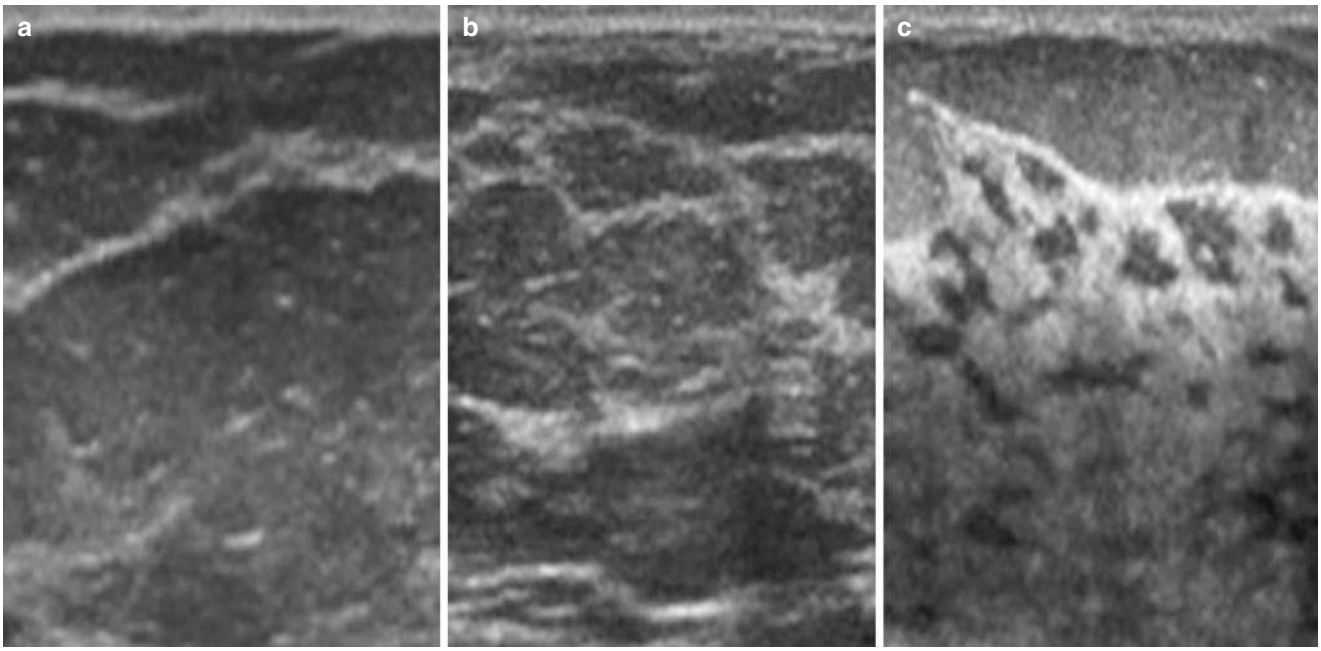

Fig. 5.9 Echotexture patterns in ultrasound according to BI-RADS®: homogeneous, fat (**a**); homogeneous, fibroglandular (**b**); and heterogeneous (**c**)

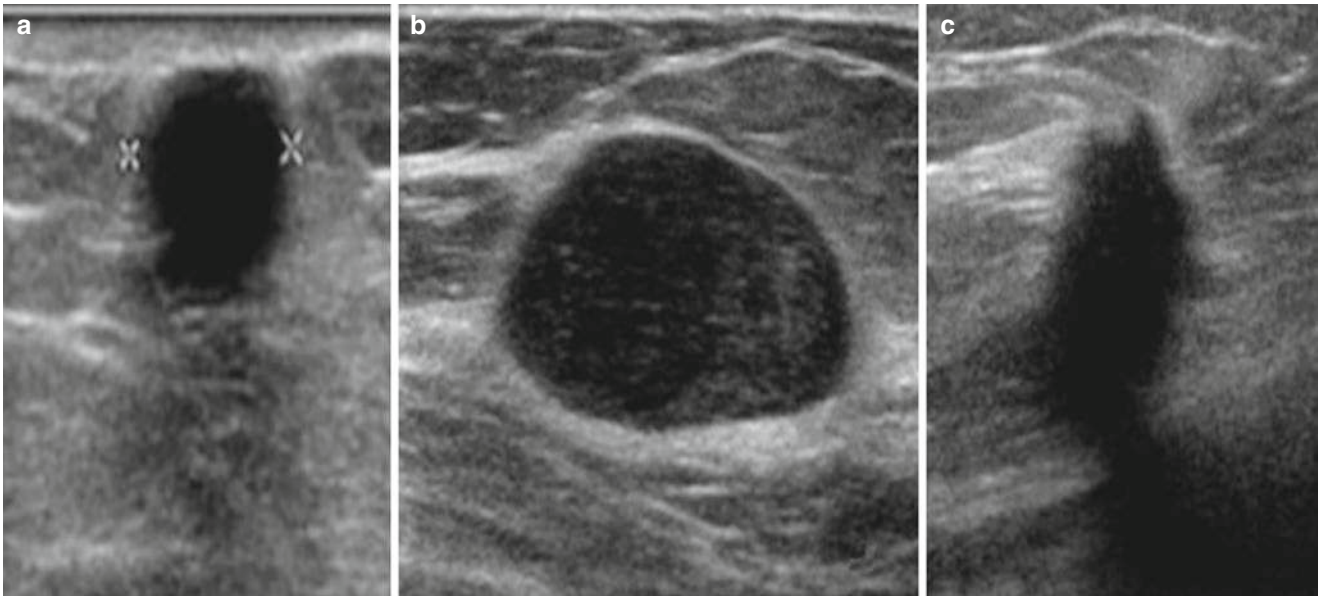

Fig. 5.10 Shape of masses screened through ultrasound: round (**a**), oval (**b**), and irregular (**c**)

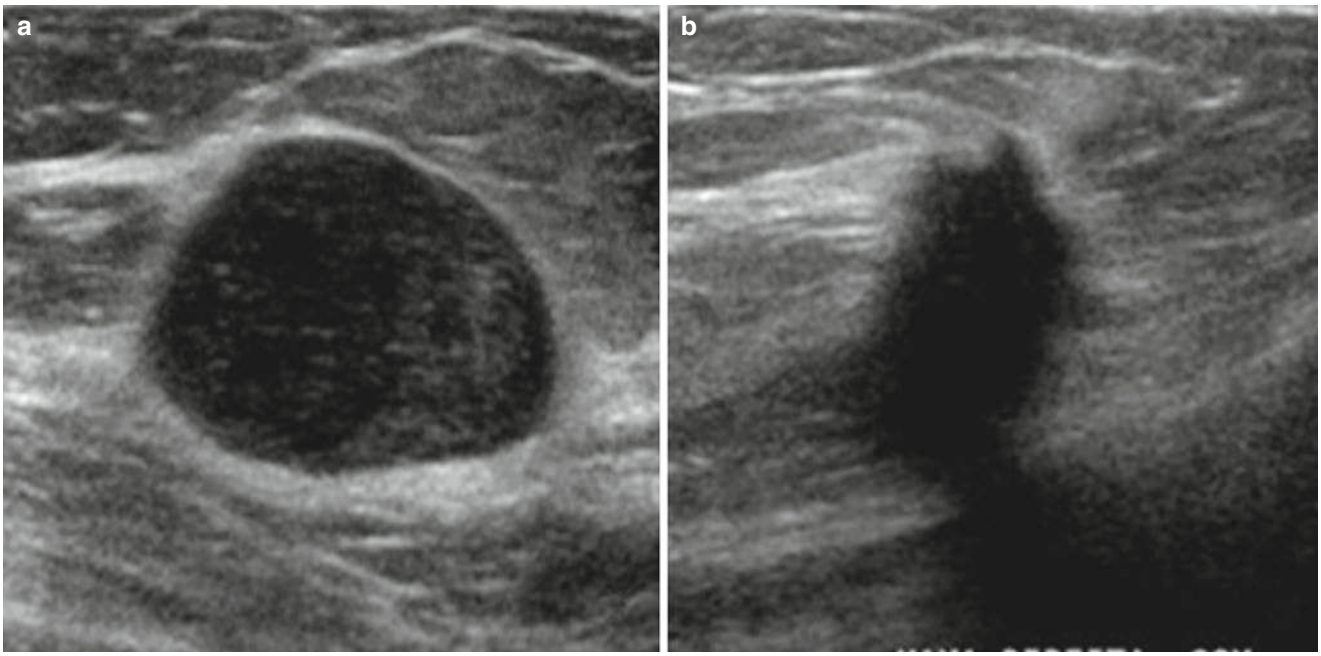

Fig. 5.11 Orientation of masses in ultrasound: parallel to the skin (**a**) and vertical to the skin (**b**)

for evaluation concerning malignancy. Complex masses have mixed echogenicity, with both anechoic and echogenic components [27].

The posterior acoustic phenomena result from attenuation of the mass (Fig. 5.14), except for posterior peripheral shadow, which occurs as a result of an alteration of speed in the acoustic beam of the curved edges in either oval or round masses. These phenomena include acoustic reinforcement, that is, more echogenic posterior area, found mainly in cysts. Also, it has been observed an acoustic shadow, that is, a darker central posterior area, associated with calcifications, fibrosis, or neoplasia with high desmoplastic reaction. Some masses do not cause an alteration of the acoustic beam through the mass. These aspects are not reliable for the definition of benignity or malignancy, and they must be considered in correlation with other aspects [27, 28].

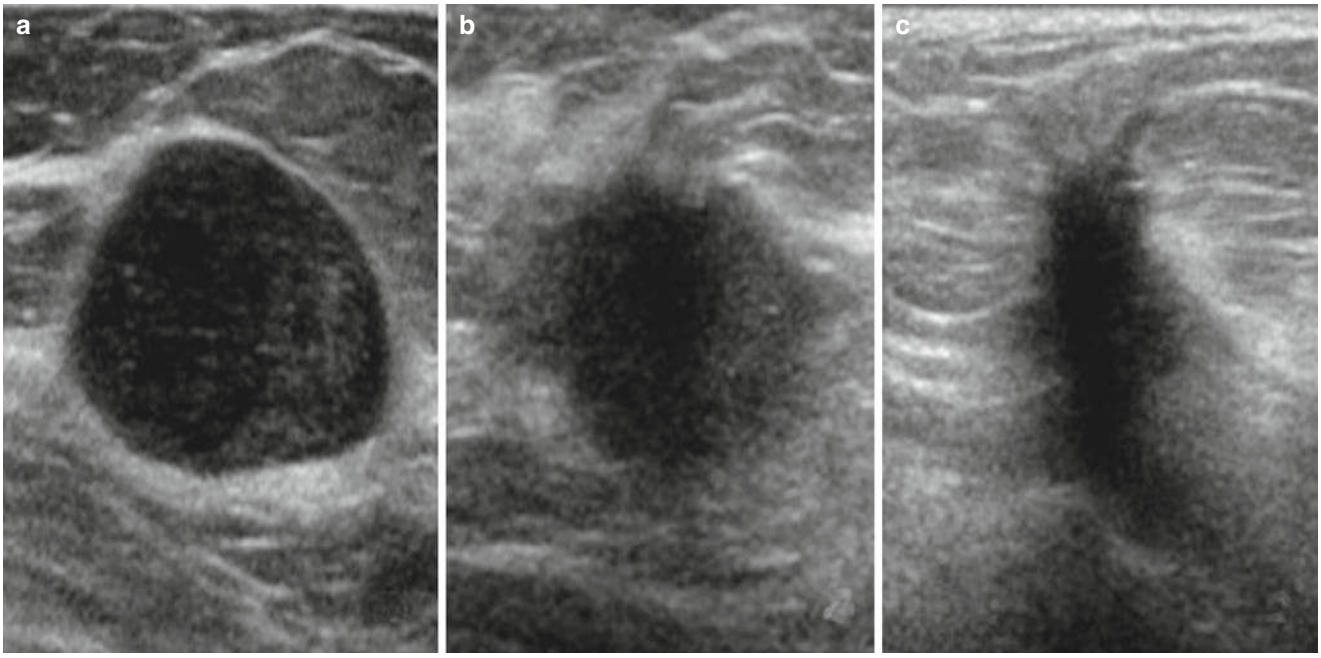

Fig. 5.12 Margins of masses in ultrasound: circumscribed (**a**), indistinct (**b**), and spiculated (**c**)

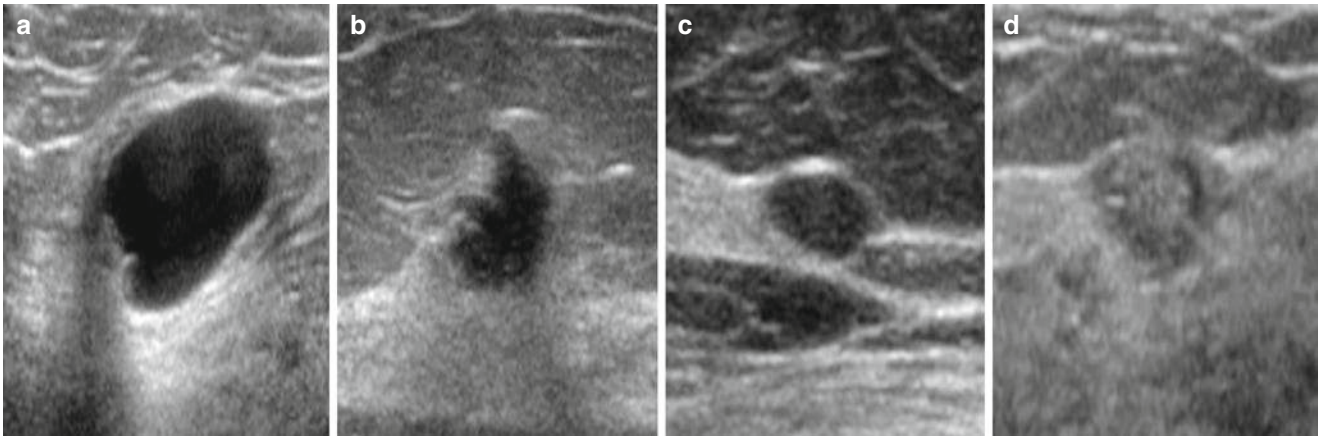

Fig. 5.13 Echogenicity patterns of masses in ultrasound: anechoic (**a**), hypoechoic (**b**), isoechoic (**c**), and hyperechoic (**d**)

5.5.2.2 Calcifications

US has very low sensitivity for the detection of calcifications, especially of microcalcifications. It also does not allow for their morphological analysis, which is an important piece of data to characterize malignancy. Among other factors, the low sensitivity results from heterogeneous breast echotexture and from the small size of microcalcifications (less than 0.5 mm), with no typical posterior acoustic shadow [6, 27].

5.5.2.3 Special Cases

Some alterations show characteristic findings [6]:

(a) Clustered microcysts: defined as small anechoic clustered images (less than 2–3 mm) with thin septations inside (less than 0.5 mm), with no solid component associated. This finding occurs mainly with fibrocystic alterations and in the apocrine metaplasia (Fig. 5.15a).
(b) Complicated cysts: cysts that have thin echoes inside fluid level or even mobile debris, with no solid component attached to the wall (Fig. 5.15b).
(c) Skin masses: they are the so-called epidermal and sebaceous inclusion cysts, keloid, neurofibromas, and accessory nipples. They are classified as benign lesions (category 2).
(d) Foreign bodies: it may correspond to surgery marking clips, threads, catheter, silicon, metal, or glass from trauma. Clinical history is very important for differentiation. Free silicon in the parenchyma has a typical aspect of "snowstorm," that is, an echogenic area that causes a marked acoustic shadow, obscuring the deep structures (Fig. 5.15c).

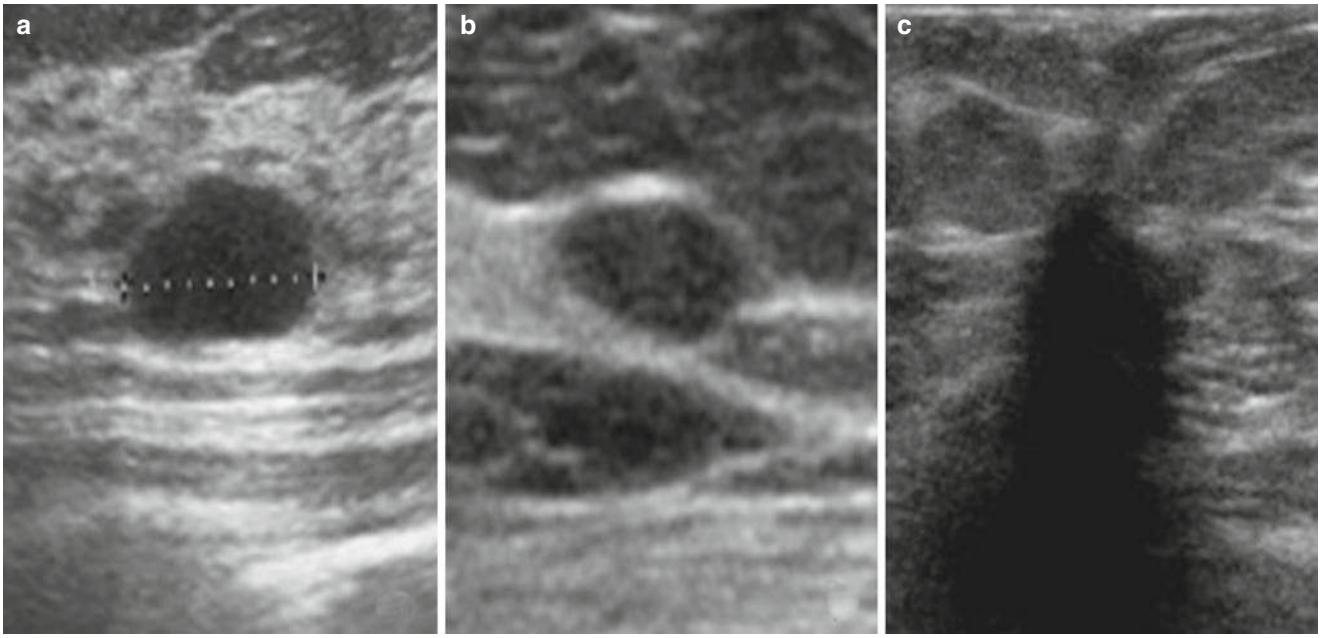

Fig. 5.14 Acoustic phenomena of masses in ultrasound: acoustic reinforcement (**a**), no alteration of the acoustic beam (**b**), and acoustic shadow (**c**)

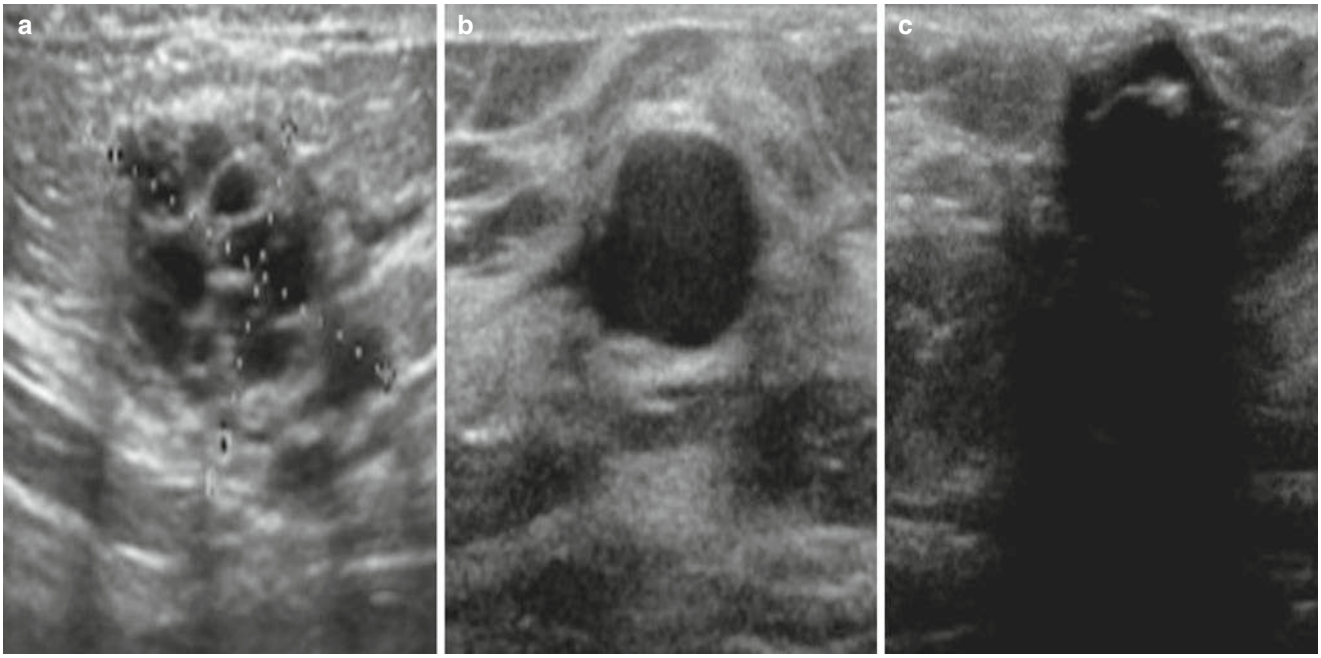

Fig. 5.15 Special cases observed through ultrasound: clustered microcysts (**a**), complicated cysts (**b**), and foreign body related to draining (**c**)

(e) Intramammary lymph node: described as oval masses, circumscribed, with an echogenic center and hypoechoic periphery. They are located mainly in the upper quadrants and sides of the breast, and their size ranges from 3 mm to 1 cm.
(f) Axillary lymph node: the aspects are similar to those of the intramammary lymph nodes, and they can measure above 2 cm. When they are too big (above 4 cm) or with a hypoechoic center, they must be evaluated, so the possibility of a metastatic disease is not ignored.

5.5.2.4 Vascularity and Elasticity

This is an additional piece of data for the evaluation of masses or suspicion areas, though with limited value. The complete absence of vascularity is usually observed in cysts.

A rather increased vascularity may be suggestive of neovascularity, and it is usually observed not only inside the mass (internal vascularity) but also in the peripheral area of a lesion (vessels in rim). The elasticity is described as soft, intermediate, and hard [6].

5.6 Magnetic Resonance

MR is the most accurate method in the detection of breast cancer, and it is indicated in selected cases to increase the sensitivity that results from traditional methods (MG and US). The method holds the advantage of showing a three-dimensional view of the breast, with high sensitivity and no use of ionizing radiation. Among the disadvantages are the high cost of the procedure and its low specificity [29].

Analysis of MR must be made through images obtained from the dynamic technique during the endovenous injection of paramagnetic contrast (gadolinium), associated to enhancement kinetics. Following that, the images obtained with spatial high resolution for a detailed morphological evaluation of the lesion aim to detect characteristics of suggestive malignancy. Interpretation of MR must consider the clinical history data (including physical exams—palpation of the masses, skin appearance, scars; surgical antecedents of those of biopsies; menstrual cycles; hormone therapy reposition; radiotherapy) and comparison with previous exams (MG and US—identification of areas with suggestive lesions, mainly microcalcifications, evaluation of temporal stability, or the appearance of new lesions, among others).

5.6.1 Normal Findings Through Magnetic Resonance

Breast anatomy is thoroughly demonstrated through MR, in which not only the parenchyma can be evaluated but also vessels, lymph nodes (intramammary and those from axillary prolongations), the retromammary area, and the thoracic wall; these latter are difficult to access through other imaging methods.

Characterization and description of the parenchyma are made according to BI-RADS® criteria [6]:

(a) Almost entirely fat.
(b) Scattered fibroglandular tissue.
(c) Heterogeneous fibroglandular tissue.
(d) Extremely fibroglandular tissue.

Characterization of the background parenchymal enhancement according to BI-RADS® criteria [6]:

(a) Minimal.
(b) Mild.
(c) Moderate.
(d) Marked.

Contrary to what occurs in MG, dense breasts are not difficult to diagnose through MR, which minimizes the overlapping effect of the parenchyma, and also through contrast, which makes lesions appear more evident. On the other hand, hormone variations cause an influence on the interpretation of images, mainly considering enhancement and parenchyma edema. In premenopause breasts, parenchyma enhancement varies according to the menstrual cycle, so incidental points of enhancement (uniform, diffuse, or scattered in some areas) are common and more evident on the first and the fourth weeks. Some of these points may present with quick and intense enhancement as in malignant lesions, being differentiated only when disappearing in subsequent exams, in a different phase of the menstrual cycle. The exam must be performed, preferably, on the second week of the cycle (between 7 and 14 days), when the number of points (foci) and speed of enhancement are the lowest when compared with the other phases [30, 31].

In the postmenopause period, the use of combined (estrogen/progesterone) hormone reposition therapy (HRT) can revert the usual atrophy in the period and result in an aspect similar to premenopause and even appear to be a parenchyma edema and a regular edema. When there is any doubt of interpretation, it is recommendable that a reevaluation is made after suspending HRT for 6–8 weeks. In cases of therapy with selective modulators of estrogen receptor (tamoxifen), there is no hormone stimulation, which reduces vascularity and density of parenchyma. Enhancement foci in patients' breasts using tamoxifen cannot be considered as usual ones, for their hormone activity is blocked. Pregnant patients and lactating ones may also experience an increase of breast density and of enhancement, due to an increase in vascularity.

Breast vascularity is important, and it defines a geographic pattern of normal parenchyma enhancement. There is a preferable enhancement in the external upper quadrant and in the inferior portion as well, as the center of the breast is the last one to enhance due to the existence of a different vascular supply. This geographic pattern of the normal parenchyma enhancement occurs symmetrically in both breasts.

The larger ducts that converge below the nipple and drain out each segment are about 2 mm in diameter. Dilated ducts with proteinaceous contents or with hemorrhagic debris can be seen in ponderated sequences in pre-contrast T1 with increased signal, and the post-contrast analysis can be done through images with subtraction to not obscure the area with enhancement.

Lymph nodes are easily detected and characterized through their reniform shape with fatty hilum (high signal in

ponderated sequences in pre-contrast T1, with no fat saturation), besides having a strong enhancement after the use of EV contrast. The T2 ponderated images are also useful for characterizing lymph nodes, as they produce increased signal intensity when compared with the normal parenchyma.

Pectoralis muscles and the thoracic walls are considered anatomically distinctive, and the evaluation of isolated neoplasic involvement of one of these structures or of both of them influences on the staging and surgical treatment. Deep tumors may produce retraction of the pectoralis muscles or get too close and make an obliteration of fat planes but with neoplastic involvement; there is an irregular enhancement through contrast in damaged areas of the muscle. The thoracic wall is made up of the anterior serratus muscle, the intercostal, and ribs. Neoplasic involvement in these structures will also be highlighted as abnormal to MR.

5.6.2 Abnormal Findings Through Magnetic Resonance

MR is evaluated not only through morphological characterization of lesions but also through the type of enhancement by means of contrast and the dynamic characteristics, which may occur not only in three-dimensional lesions, such as masses, but in areas of the parenchyma. Microcalcifications are not demonstrated through MR, and they must be spotted in conventional mammograms for the correlation with magnetic resonance images and detection of suggestive enhancement in the area.

The main visualized alterations to MR are described as follows, according to BI-RADS® [6]:

5.6.2.1 Focus

This is a tiny non-specific enhancement area (<5 mm), too small to be characterized. It does not necessarily represent a lesion that occupies some space, such as a mass (Fig. 5.16).

5.6.2.2 Masses

They are described as three-dimensional lesions that occupy some space. They can be morphologically evaluated (shape and margins) and also through their enhancement patterns (Fig. 5.17).

The shape may be round, oval, or irregular. As in the other methods, the round shape is the one most related with benignity, while the irregular one is related with malignancy.

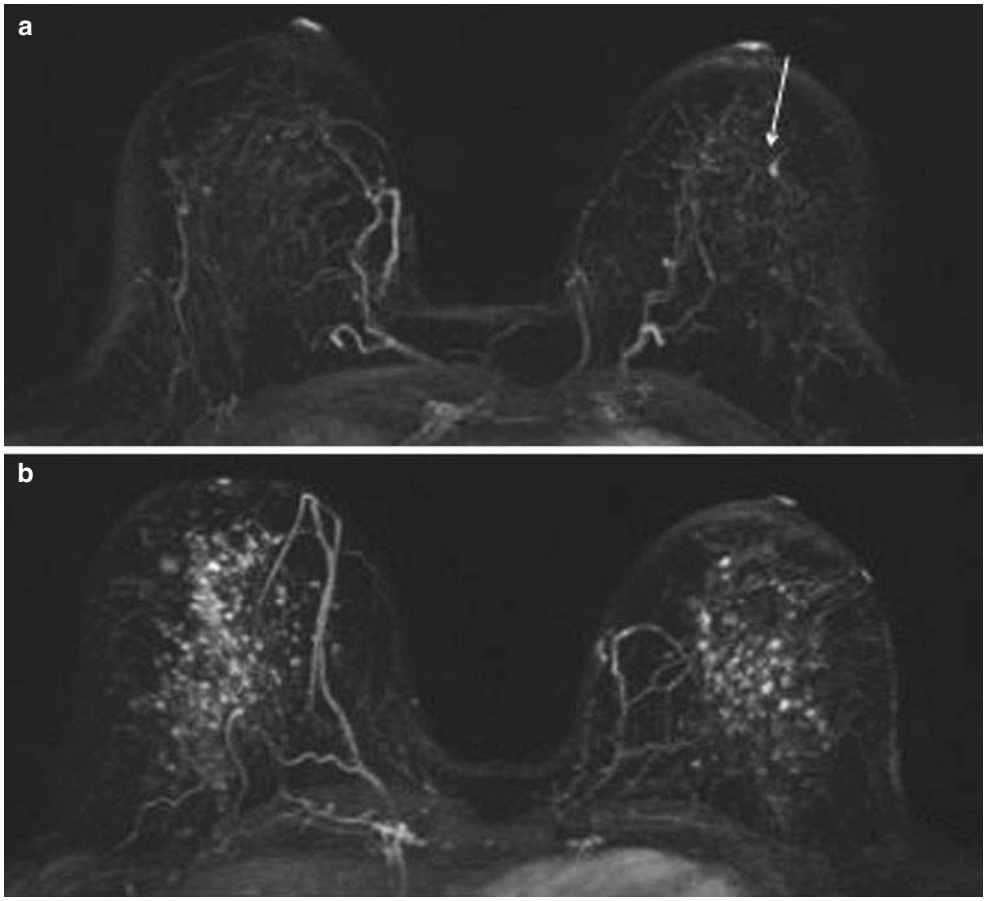

Fig. 5.16 Foci: (**a**) MIP reconstruction showing isolated focus (arrow) in a patient with benign functional alteration; (**b**) MIP reconstruction showing moderate background parenchymal enhancement (previously called diffuse foci)

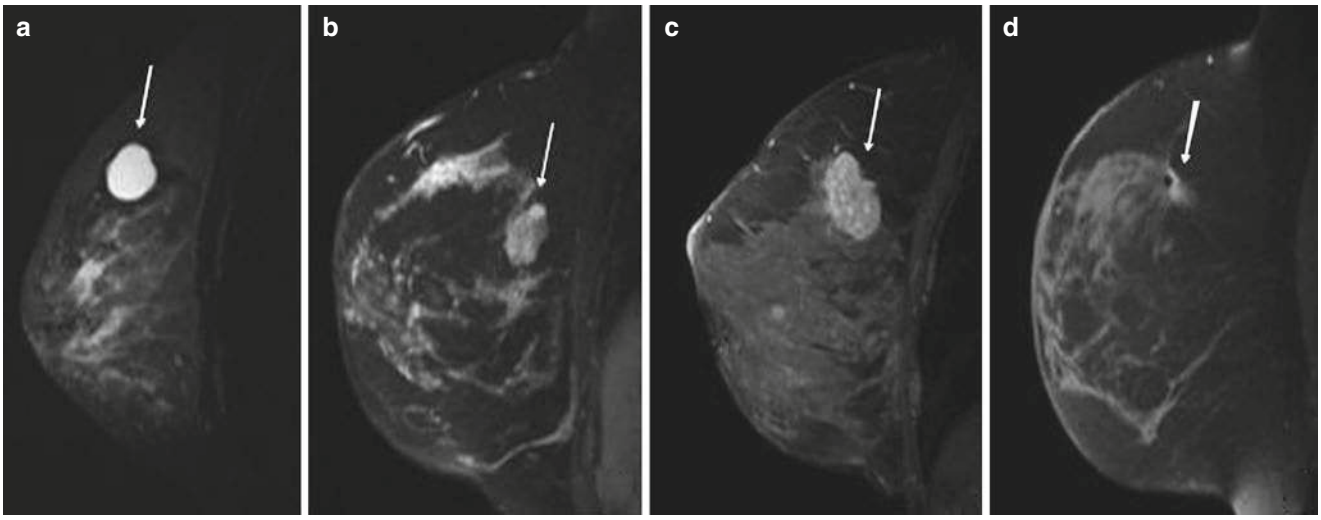

Fig. 5.17 Masses: (**a**) sagittal STIR showing a round mass with regular margins (arrow) (simple cyst); (**b**) sagittal FSE T1 post-contrast showing an oval mass with regular margins and hypocaptation septum (arrow) (fibroadenoma); (**c**) sagittal FSE T1 post-contrast showing irregular mass, with indistinct margins and heterogeneous enhancement (arrow) (invasive ductal carcinoma); and (**d**) sagittal FSE T1 post-contrast showing irregular mass with spiculated margins and peripheral enhancement (arrow) (steatonecrosis)

The analysis of the margins depends on the space resolution of the images. The margin is described as circumscribed and not circumscribed (irregular and spiculated). Irregular margins and spiculated ones are the most suggestive of malignancy.

As an additional piece of data to the morphological analysis, the characteristics of the internal enhancement contribute with the differentiation of benign masses from malignant ones. The enhancement pattern can be described as homogeneous (uniform and confluent—more suggestive of benignity) or heterogeneous (there are variable signal intensities inside the mass). The enhancement can also be described as rim enhancement and with dark internal septations. The heterogeneous aspect is the most suggestive of malignancy, mainly when it is peripheral, though septation enhancement and central enhancement are also suggestive. Inflammatory cysts may have their own enhancement, but they are hyperintense in the ponderated images in T2, due to their fluid content. Fat necrosis may also have a peripheral enhancement with a dark center, but it can be differentiated through the clinical record, through mammographic characteristics and through the signal in the sequences with fat saturation through MR. These two lesions are described as false-positive potentials in the analysis of lesions with peripheral enhancement, which is typical of malignancy. The enhancement pattern with dark internal septations is highly suggestive of fibroadenoma, and it is an indicator of benignity [32].

5.6.2.3 Non-mass-Like Enhancement

Non-mass-like enhancement describes an area of enhancement that can neither be classified as mass nor as focus. This includes patterns that can extend over a region of varied sizes according to a specific distribution, and, except for the internal homogeneous pattern, there will always be areas of normal mammary tissue of fat interspersing the enhancement areas.

Considering distribution, it is described as focal (it generally takes less than 25% of the volume of a quadrant), linear (it follows the duct track toward the nipple, with ramifications, or it can seem like a plane in other incidences, and it does not follow the duct track), segmental (triangular region or in a cone, with apex to the nipple, which resembles a duct and its branches), regional (it encompasses a huge tissue volume, with a geographic aspect and with no relation to the distribution of one duct system), and multiple regions and diffuse (equal all over the extension of the breast) (Fig. 5.18). Regional distribution patterns, in multiple regions and in a diffuse way, are the most suggestive of benign disease, such as the proliferative alterations, while the linear and the segmental patterns are highly suggestive of malignancy (ductal carcinoma).

Internal enhancement patterns can be described, as a whole, as homogeneous or heterogeneous. An additional description can be made when the aspect of the heterogeneous enhancement is considered: clumped and clustered ring.

5.6.2.4 Associated Findings

The associated findings may increase suspicion of breast cancer, and they are considered important because some of them influence on the surgical treatment and on the staging. The associated findings include [6]:

(a) Skin retraction or nipple retraction.
(b) Skin thickening: focal or diffuse (normal thickness up to 2 mm).
(c) Skin invasion: there is an abnormal enhancement of the skin that is also thick in most cases.

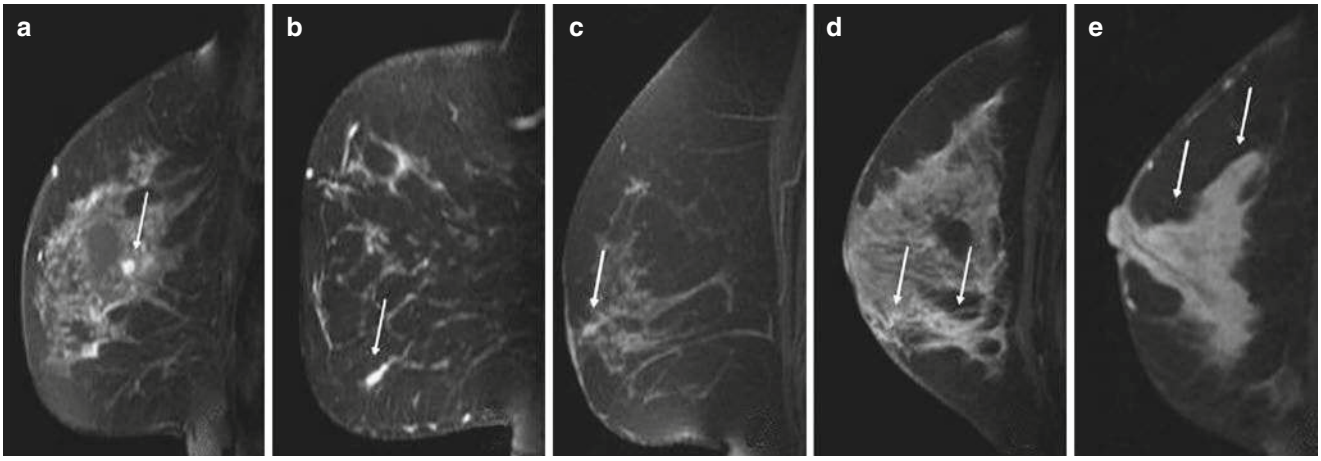

Fig. 5.18 Non-mass-like enhancement: (**a**) sagittal FSE T1 post-contrast showing focal enhancement (arrow) (benign functional alteration); (**b**) sagittal FSE T1 post-contrast showing linear enhancement (arrow) (scar); (**c**) sagittal FSE T1 post-contrast showing linear enhancement (arrow) (intraductal carcinoma); (**d**) sagittal FSE T1 post-contrast showing segmental enhancement (arrows) (invasive ductal carcinoma); (**e**) sagittal FSE T1 post-contrast showing regional enhancement (arrows) (benign functional alteration)

(d) Edema: there is a trabecular thickening with or without associated skin thickening.
(e) Lymphadenomegaly: enlarged and round lymph nodes with loss of fatty hilum signal; they are highly suggestive.
(f) Pectoralis muscle or thoracic wall invasion: abnormal enhancement stretching to the pectoralis muscle with or without retraction, as well as to ribs and intercostal spaces.
(g) Postoperative collections (hematoma/seroma): there is an increase of the signal in the ponderated sequence in pre-contrast T1.
(h) Cyst: it is described as a well-circumscribed structure filled with fluid; it can be round or oval and with an imperceptible wall. In the ponderated margins in T1, the cysts appear with a hypointense signal to the adjacent tissue, except for cysts with protein content due to blood products. In pre-contrast sequences, only the inflammatory cysts will present with peripheral enhancement.

5.6.3 Kinetic Curve

The kinetic curve is obtained from a dynamic sequence performed when an endovenous injection is applied in a contrast environment (gadolinium) and it describes the enhancement characteristics of a specific region determined by ROI (*region of interest*). This region must be specially the one with the largest and fastest enhancement or the most suggestive area.

The physiopathological basis has not been properly elucidated yet, but it is known that the intensity of enhancement depends not only on the increase of vascularity and the permeability of the vessels, commonly found in malignant lesions, but also on the interaction of the contrast with the lesion tissues.

Considering the enhancement pattern in dynamic series, two phases can be distinguished according to BI-RADS®: initial phase (the period between the injection and the second minute post-contrast) and the delayed phase (period that starts after 2 min from the contrast injection). Fischer [33] considers the initial phase to be the one up to the third minute after the endovenous contrast injection and the delayed phase to be the one between 3 and 8 min.

In the initial phase, signal intensity after contrast is quantitatively evaluated, and enhancement speed is classified as slow, medium, or rapid. Mainly in malignant lesions, the maximum intensity of enhancement tends to be reached in the initial phase. In a study, Kuhl et al. [34] evaluated 266 lesions with mean enhancement to malignant lesions at 104% ± 41 and for benign lesions at 72% ± 35, with sensitivity of 91% and low specificity at 37%. Low specificity was attributed to the fact that benign lesions can also have fast and intense enhancement.

The delayed phase is evaluated in a qualitative way through the morphology curve. Visual classification is made as follows:

(a) Type 1 curve (persistent)—signal intensity increases throughout the dynamic series, and the highest point is obtained in the last post-contrast series (Fig. 5.19a). According to Fischer [33], signal intensity in the delayed phase increases at 10% above the initial rise by 3 min.
(b) Type 2 curve (plateau)—signal intensity reaches a balance after the initial phase, and it does not vary significantly in the subsequent phases (Fig. 5.19b). The

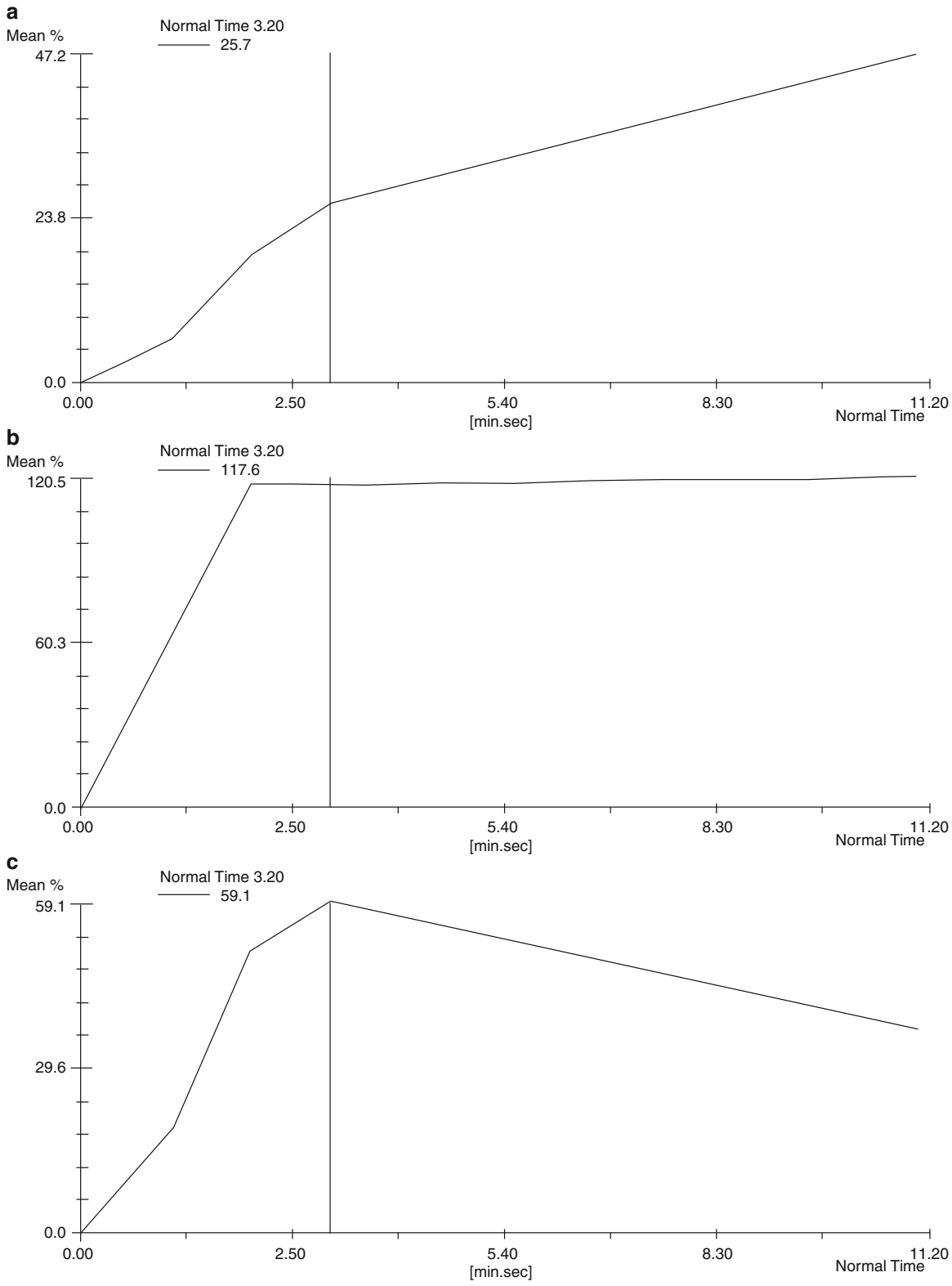

Fig. 5.19 Types of kinetic curve within dynamic magnetic resonance evaluation: pattern type I (**a**), pattern type II (**b**), and pattern type III (**c**)

maximum signal intensity is reached by 2 or 3 min. A variation of signal intensity by ±10% of the initial rise value at 3 min is acceptable [33].

(c) Type 3 curve (washout)—signal intensity goes down right after it reaches its highest point, usually on the first or second post-contrast sequence (Fig. 5.19c). According to Fischer [33], the signal intensity on the late phase reduces by over 10% of the initial peak value by 3 min.

As a general rule, the big majority of benign lesions follow a persistent curve pattern, and the malignant ones follow a washout pattern or a plateau one. The probability that each type of curve is associated with breast cancer was studied by Kuhl et al. [34], and the following results were found: type 3 curve, 87%; type 2 curve, 64%; and type 1 curve, 6%. In the same study, it was demonstrated that the analysis of the curve aspect is more specific (83%) than the quantitative analysis of the signal intensity (37%), though both methods present with the same sensitivity (91%).

5.6.4 Current Clinical Applications of Magnetic Resonance

Clinical indications are still discussed in some aspects, with the best cost-benefit relation for patients with high risk to develop breast cancer or for those proven to have cancer. Among them we can highlight:

5.6.4.1 High-Risk Patients for Breast Cancer

Women considered high risk for developing breast cancer are those with documented mutations in genes BRCA1 and BRCA2, a marked family history (estimated risk over 20% according to the risk calculation models), personal history of breast cancer, previous biopsy showing lobular carcinoma in situ, or atypical ductal hyperplasia, besides previous thoracic radiation between 10 and 30 years of age (Fig. 5.20) [35].

The importance of mammographic tracking in this group is low, as most of the subjects will develop breast cancer during their premenopause period, a stage when the mammary parenchyma is denser. Another limiting factor is the higher radiosensitivity in this group, as reported in some studies. Kriege et al. [36] compared the accuracy diagnosed through MG, US, and MR in 1904 patients of both genetic and family high risk, showing sensitivity figures of 33%, 60%, and 100%, respectively. Other six multicentric studies have shown similar results [37–42]. The most recent one of them was published by Kuhl et al. [42], demonstrating sensitivity to cancer detection of 33% for MG, 37% for US, and 92% for MR in high-risk patients, with 98% specificity for all methods. No case of hidden carcinoma was found, as well as all tumors were below 1 cm (46% invasive carcinomas and 53% carcinomas in situ).

Based on these pieces of data, in 2007 the American Cancer Society (ACS) published recommendations for the performance of MG and MR annually for all patients with confirmed mutation, first-grade patients with confirmed mutation, patients with risk to develop breast cancer above 20%, and patients undergoing thoracic radiation for over 10 years [43]. These recommendations have been recently confirmed in a publication of the ACR and the Society of Breast Imaging (SBI) [44].

5.6.4.2 Detection of Hidden Primary Tumor of Breast with Positive Axillary Lymph Node

The hidden tumor is defined in patients with axillary lymph node metastasis of breast cancer with no primary focus detected through conventional methods (MG and US), corresponding to less than 1% of all breast cancer cases [45, 46]. Contrasted MR is highly sensitive for the detection of a hidden tumor, changing the conduct in relation to the treatment of some patients, even to the point of considering a conservative treatment for some selected cases (Fig. 5.21).

For being a common entity, studies up to this moment have a small population, though with stimulating results on the capacity to detect primary lesions through MR. The detection percentage was 75% and 86%, respectively, in the studies by Morris [47] and Orel [48], all of them with proven histological basis. The lesions appear predominantly as mass-like enhancement with morphology suggestive of malignancy and varied sizes between 5 and 30 mm. In spite of the highly predictive negative rate, in case of a negative MR, the possibility of a primary breast lesion cannot be completely excluded.

5.6.4.3 Preoperative Staging of Breast Cancer

The surgical planning depends on a careful preoperative evaluation of the extension of the disease (Fig. 5.22). MR is currently the most sensitive method to detect additional foci of a multifocal disease (detecting a range of 1–20%), multicentric (2–24%), and contralateral (3–24%) not shown by traditional methods (MG and US), besides allowing for an evaluation of the extension for the pectoralis muscle, the thoracic wall, and the papillary-areolar complex. The main point of discussion is whether to find out if these foci of neoplasia represent an increase in the extended life of the patients undergoing conservative surgery [49–51].

Fischer et al. [33] evaluated 463 patients with confirmed diagnosis of breast cancer observing multifocal lesions not detected through other methods in 8.9% of cases, multicentric ones in 7.1%, and contralateral in 4.5%, which results in a change of attitude on therapy using MR in 19.6% of cases. Later, the same author [49] published another study evaluating the influence of preoperative MR on the local recurrence rate of breast cancer and found a reduction from 6.5 to 1.2%

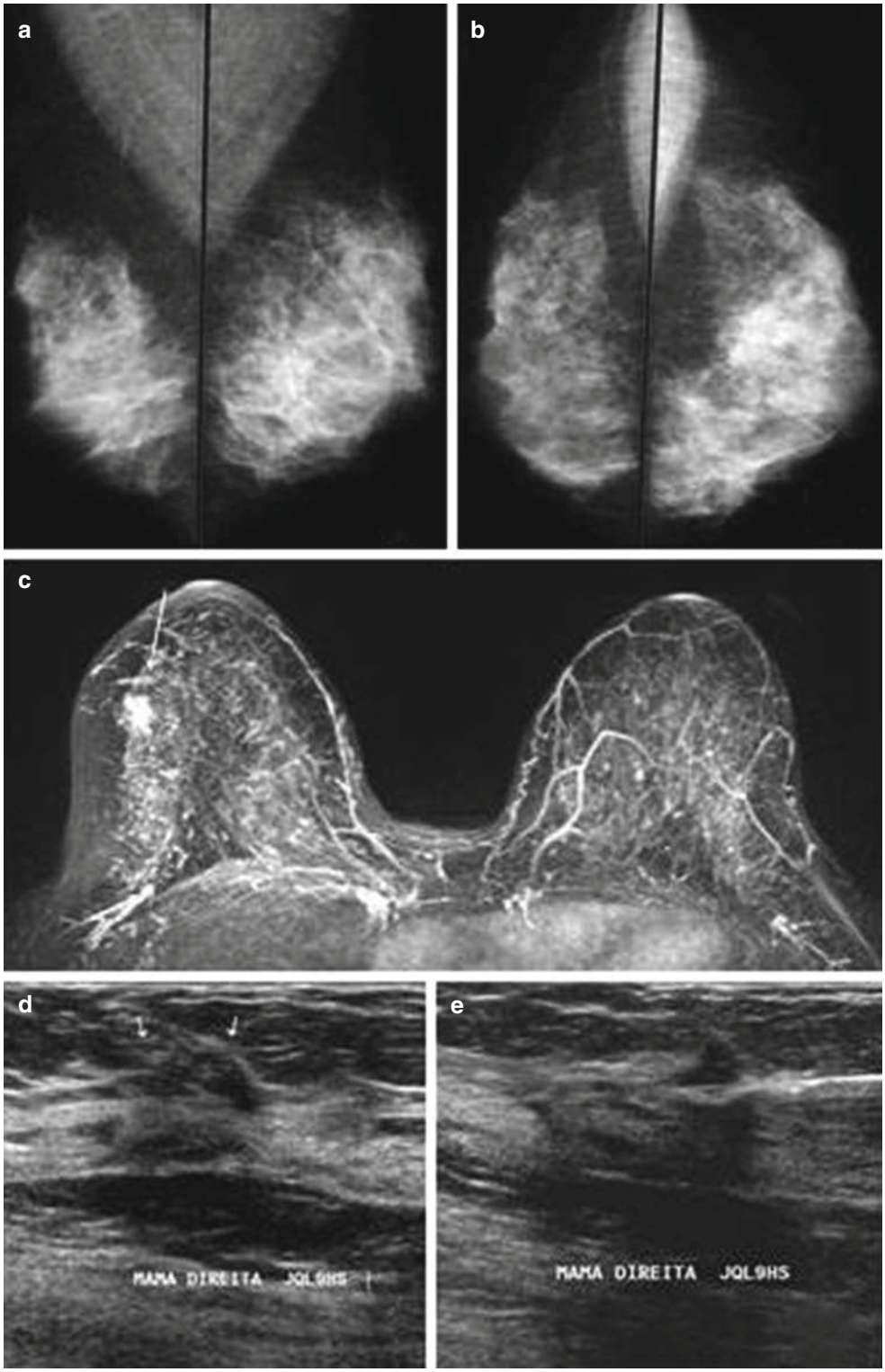

Fig. 5.20 A 45-year-old patient, asymptomatic, with family history of two sisters having breast cancer. Mammography (**a**, **b**) and ultrasound did not show abnormalities. The patient underwent magnetic resonance (**c**) for tracking, which shows a suspicious enhancement area in the right breast (arrow). From ultrasound guided (**d**) performed after the resonance, the irregular hypoechoic area was observed (arrows), undergoing percutaneous biopsy, and (**e**) diagnosed as having invasive ductal carcinoma

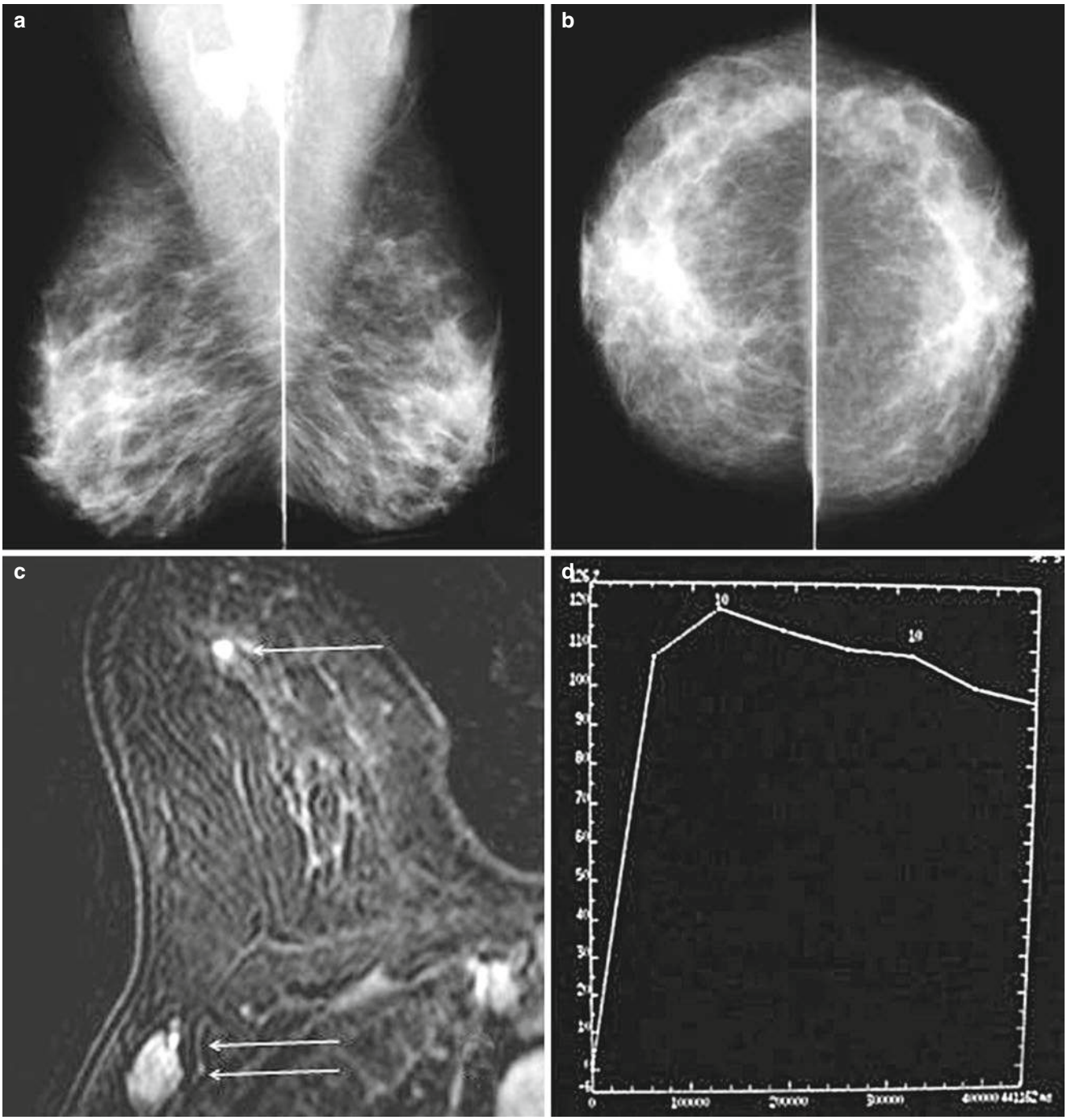

Fig. 5.21 A 55-year-old patient, with palpable lymph node in the right axillary region. Mammography (**a**, **b**) showed a dense lymph node in the axillary region. Ultrasound did not show suspicious findings in the breast. Magnetic resonance (**c**, **d**) confirmed the lymph node enlarging in the axillary region (two arrows) and showed a small captating mass in the superolateral quadrant of the right breast (arrow), with kinetic curve type III, which was confirmed as invasive ductal carcinoma when surgery was performed

among the group undergoing MR. He associated this fact with better diagnosis of the tumor extension and better staging.

On the other hand, another study, published by Turnbull et al. [52], did not show any difference in the percentage of reoperation between the group undergoing MR (19%) and the group that did not undergo it (19%). They also demonstrated that MR contributed for a delay in the surgical procedure and an increase in the number of mastectomies. Therefore, multicentric studies are still not considered necessary to define specific groups that could benefit from routine preoperative staging through MR [53]. An attempt

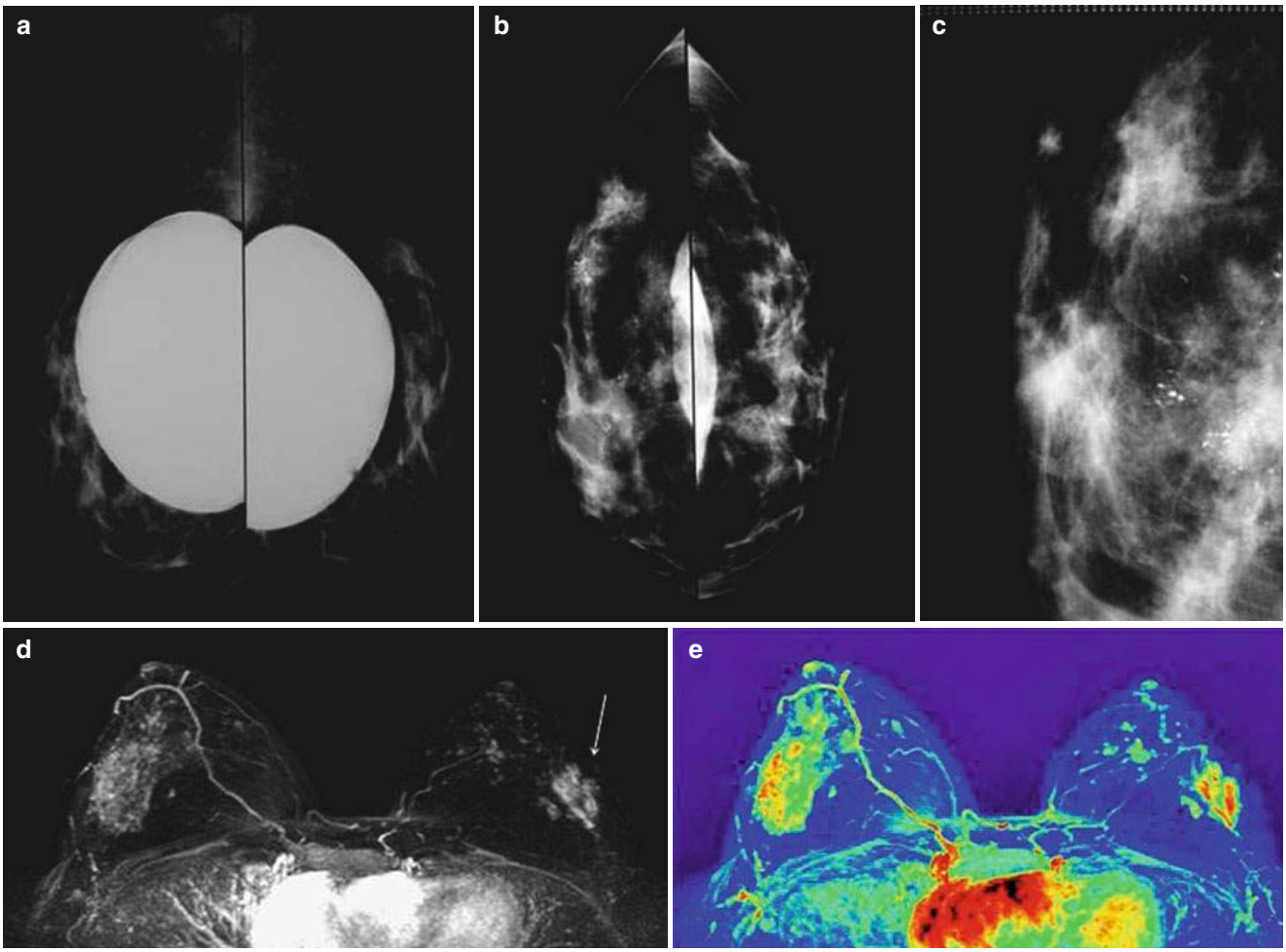

Fig. 5.22 A 51-year-old patient, with mammary prosthesis, undergoing mammography (**a**–**c**) which showed pleomorphic microcalcifications in the superolateral quadrant of the right breast, having the diagnosis of invasive intraductal carcinoma confirmed when biopsied. Magnetic resonance (**d**, **e**) for staging showed that the lesion extended to the papilla, besides having another invasive focus in the contralateral breast (arrow)

to develop a systematization was recently published by *EUSOMA Working Group* recommending preoperative MR for some specific groups, such as patients with multiple undetermined or suggestive lesions with clinical findings that diverge from those findings from screening, with significant familial or genetic risk and with diagnosis of Paget disease or lobular histological subtype, besides those patients with indication of partial radiotherapy [54].

5.6.4.4 Response Evaluation to Neoadjuvant Chemotherapy Treatment

Neoadjuvant chemotherapy is performed on patients with an advanced stage of the disease, aiming to reduce tumor staging before treatment through surgery. Adequate monitoring of the effects of the preoperative therapy is relevant to evaluate the efficacy of medication after the first cycles, which implies the continuation or change of chemotherapy scheme, besides aiding the surgical planning.

Though the response to neoadjuvant chemotherapy is done traditionally through clinical exam, MG and US, the use of MR for this monitoring has shown to be more effective than conventional methods (Fig. 5.23). MR helps differentiate fibrosis induced by chemotherapy of the tumor itself, besides being useful for the evaluation of multicentric, multifocal, and contralateral disease [55].

Even with so many advantages, MR also has some limitations for this group. Chemotherapy drugs reduce vascularization and capillary permeability, besides producing fibrosis, necrosis, and tumor inflammation, which changes the enhancement parameters for this group. This is related with less accuracy in the evaluation of tumor volume, which may be under- or overestimated [55, 56].

Martincich et al. [57] showed that the integration between morphological and functional parameters can improve the precocious response to the neoadjuvant treatment (after the second cycle), with a good histopathological correlation. In

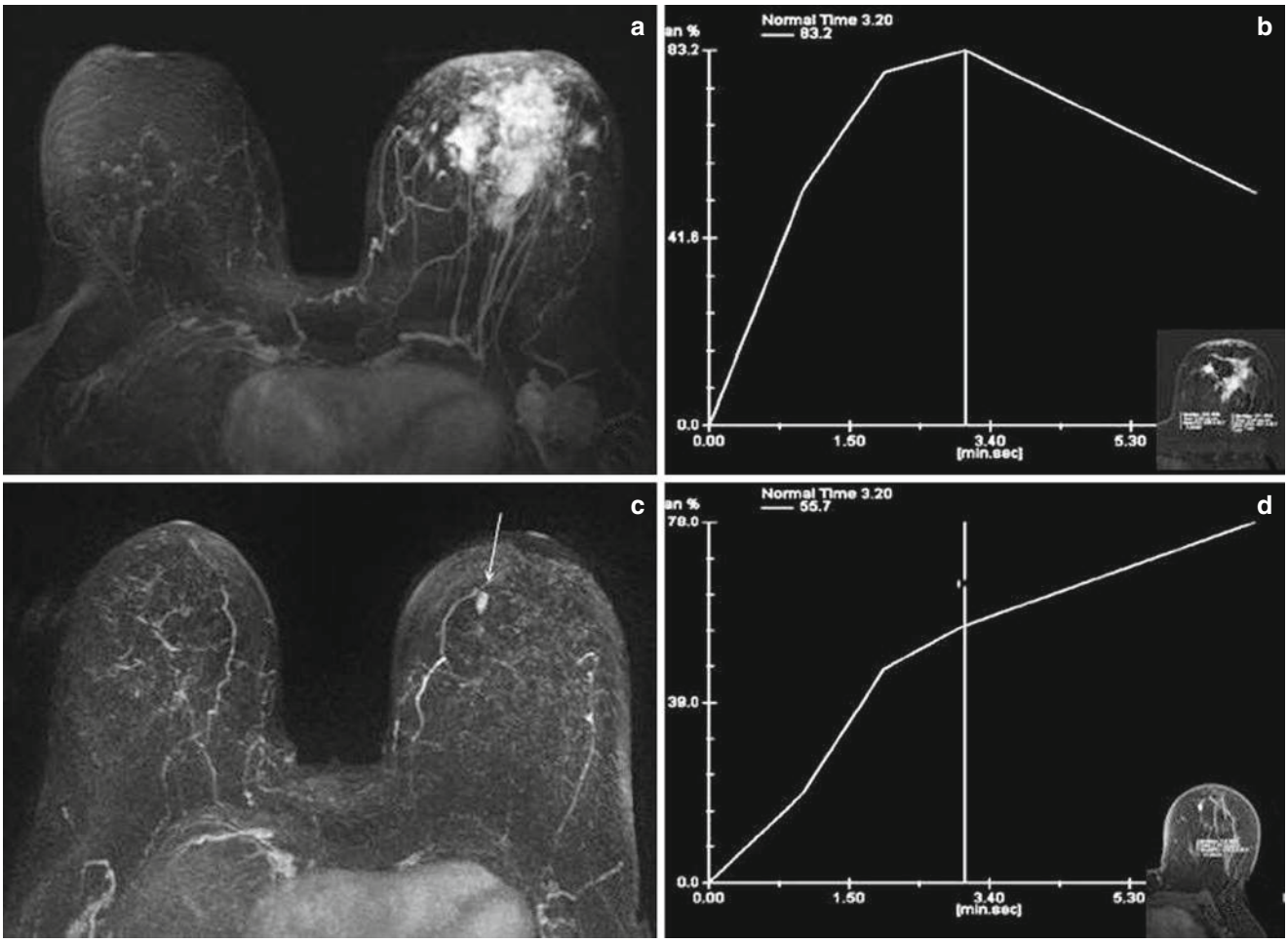

Fig. 5.23 A 36-year-old patient with edema and redness of the left breast. Resonance showed an extensive lesion in the left breast (**a**), with enhancement curves type III (**b**), besides skin thickening and axillary lymphadenomegaly. Patient underwent neoadjuvant chemotherapy and control after the third cycle (**c**); there was tumor regression with a small residual lesion (arrow) and enhancement curve type I (**d**)

this study an accuracy of 93% was obtained to predict the full pathological response, with reduction of the tumor volume and of the enhancement through contrast. Pickles et al. [55] evaluated 68 patients before and during the precocious phases as well as after chemotherapy, showing that quantifying the dynamic parameters of enhancement and the change of tumor volume allow for a differentiation between responsive and unresponsive patients.

5.6.4.5 Papillary Lesion with Pathological Discharge

The papillary flow can be a breast cancer manifestation. MG and US are the first exams to be performed, though many times they do not detect the lesion, due to difficulties to evaluate the retroareolar region. Ductography also helps detect the lesion, though with limitations, mainly for the intermittent papillary flow. MR has appeared as a good choice of diagnosis in this group because it is able to detect small intraductal lesions, therefore giving aid to the surgical planning (Fig. 5.24).

Morrogh et al. [58] evaluated 376 patients with papillary discharge, out of which 306 had negative MG and US. This group then underwent ductogram and MR, and 46 tumors (15% of cases) were observed. Ductography did not detect six tumors (predictive positive value of 19% and negative of 63%), and MR did not detect one tumor (predictive positive value of 56% and negative of 87%). The authors concluded that the ductogalactography presents with low predictive negative value so it may not exclude pathology and that MR can aid the surgical planning, though it does not exclude duct resection when there is suspicion of discharge. But Liberman et al. [58] concluded that MR can be a good alternative to galactography in cases of suspecting papillary discharge with negative MG and US, as it detected the focus in 100% of the evaluated patients. This way, concomitant evaluation with MG and MR is recommended for the patients with suspecting papillary discharge.

5.6.4.6 Postoperative Evaluation to Detect Local Recurrence

Recurrence occurs at an annual rate of 1–2%, and it is uncommon during the first 18 months after the treatment [59]. Evaluation through physical exam, MG, and US is difficult due to postoperative and radiotherapy changes, such

as surgical scar, architectural distortion, calcifications, increase in mammary density, and fat necrosis, which can mimic the appearance of a recurring neoplasia or even obscure it. MR has appeared to be a promising method for the evaluation of local recurrence, mainly in cases of difficult evaluation through conventional methods (Fig. 5.25).

Up until 18 months after the surgical and radiotherapy treatments, MR has limited value, as there is still secondary enhancement to induced inflammation by the treatment both

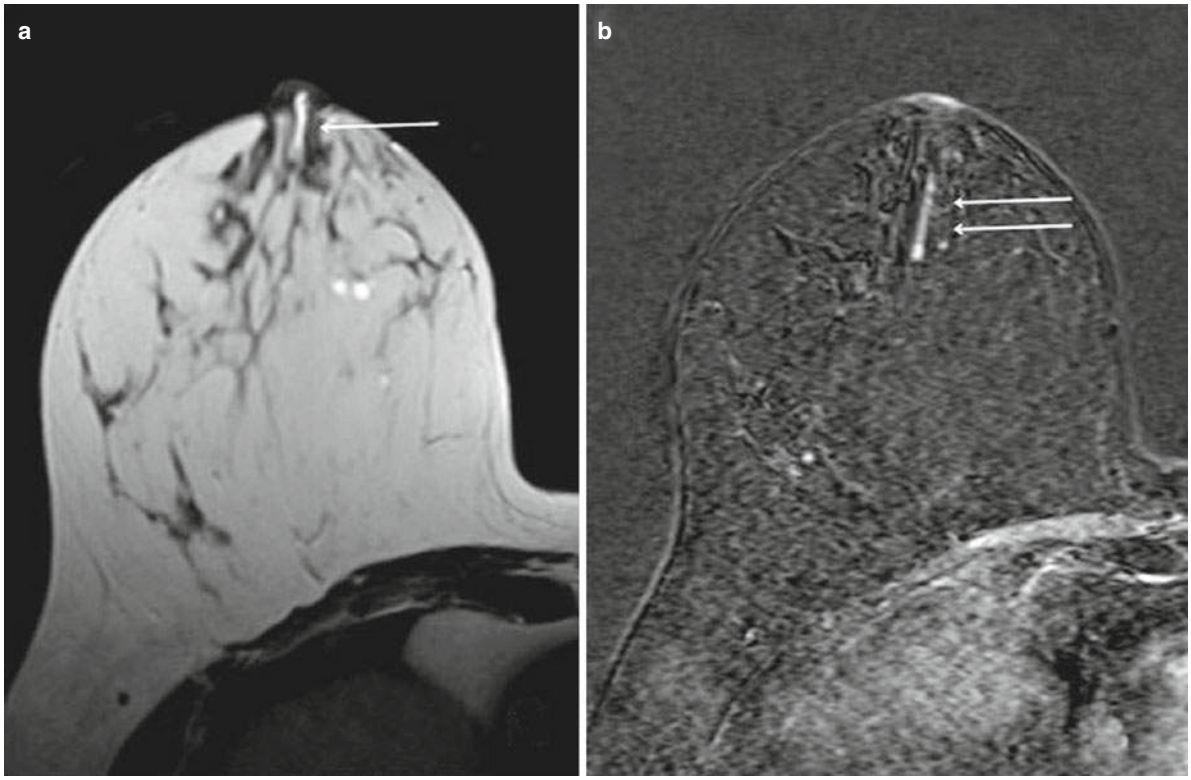

Fig. 5.24 A 43-year-old patient with family history of papillary brain stroke on the right. Mammography and ultrasound do not show abnormality. Resonance showed a small dilated duct (**a**, arrow) with a linear enhancement area no interior (**b**, double arrow). The surgery confirmed the diagnosis of intraductal carcinoma

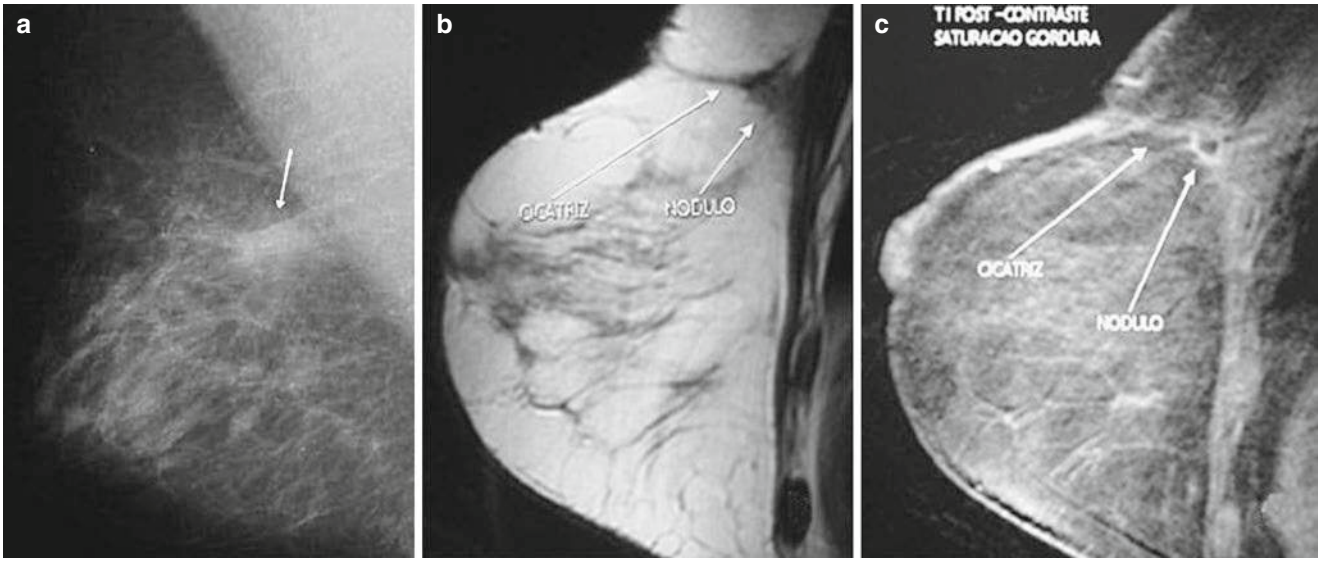

Fig. 5.25 A 63-year-old patient with history of 6-year quadrantectomy. Control mammogram (**a**) shows focal asymmetry of the scar topography. Resonance shows asymmetry (**b**) but with a fat area inside (**c**) confirming the diagnosis of postsurgical of steatonecrosis

in the scar region and in the areas with normal tissue, due to radiotherapy. After this period, MR is able to detect tumor recurrence and differentiate from areas of secondary enhancement to the treatment. Benign sequels such as fat necrosis, seroma, and hematoma can be safely differentiated through MR, because of their signal characteristics [29, 60].

5.6.4.7 Evaluation of Inconclusive Findings Through Conventional Imaging Exams

MR shows morphological and enhancement details that allow for a better differentiation between benign and malignant lesions, when biopsy is not viable and the evaluation through conventional imaging methods are inconclusive. The dynamic study helps differentiate a well-circumscribed carcinoma that morphologically mimics a benign mass or a thick content cyst, as well as to characterize lobular neoplasia that mimics focal asymmetries, cases of palpable lesions that do not appear through the traditional methods, and cases of diabetic mastoplasty that simulate a carcinoma, among others. In cases of suspecting microcalcifications seen in MG, MR cannot be used to keep away the presence of neoplasia, so there is the need of a biopsy, due to limited sensitivity in the evaluation of low-grade intraductal carcinomas (CDIS). But in cases of high-grade CDIS, MR presents higher sensitivity than MG. This was demonstrated by Kuhl et al. [61], who prospectively studied 7319 women. It was observed a sensitivity of 61% for MG and 80% for MR in the detection of low-grade CDIS, while for high-grade CDIS sensitivity was 52% for MG and 98% for MR.

5.6.4.8 Evaluation of Mammary Prosthesis

MR has been more constantly used to evaluate mammary prosthesis for aesthetic or reconstruction (after mastectomy or quadrantectomy). The aims of evaluation through MR of women with prosthesis range from checking implant disruption (Figs. 5.26 and 5.27) to neoplasia research (high-risk women or those with suspicion of alteration in clinical-imagiological exams) and to evaluation of extension of a

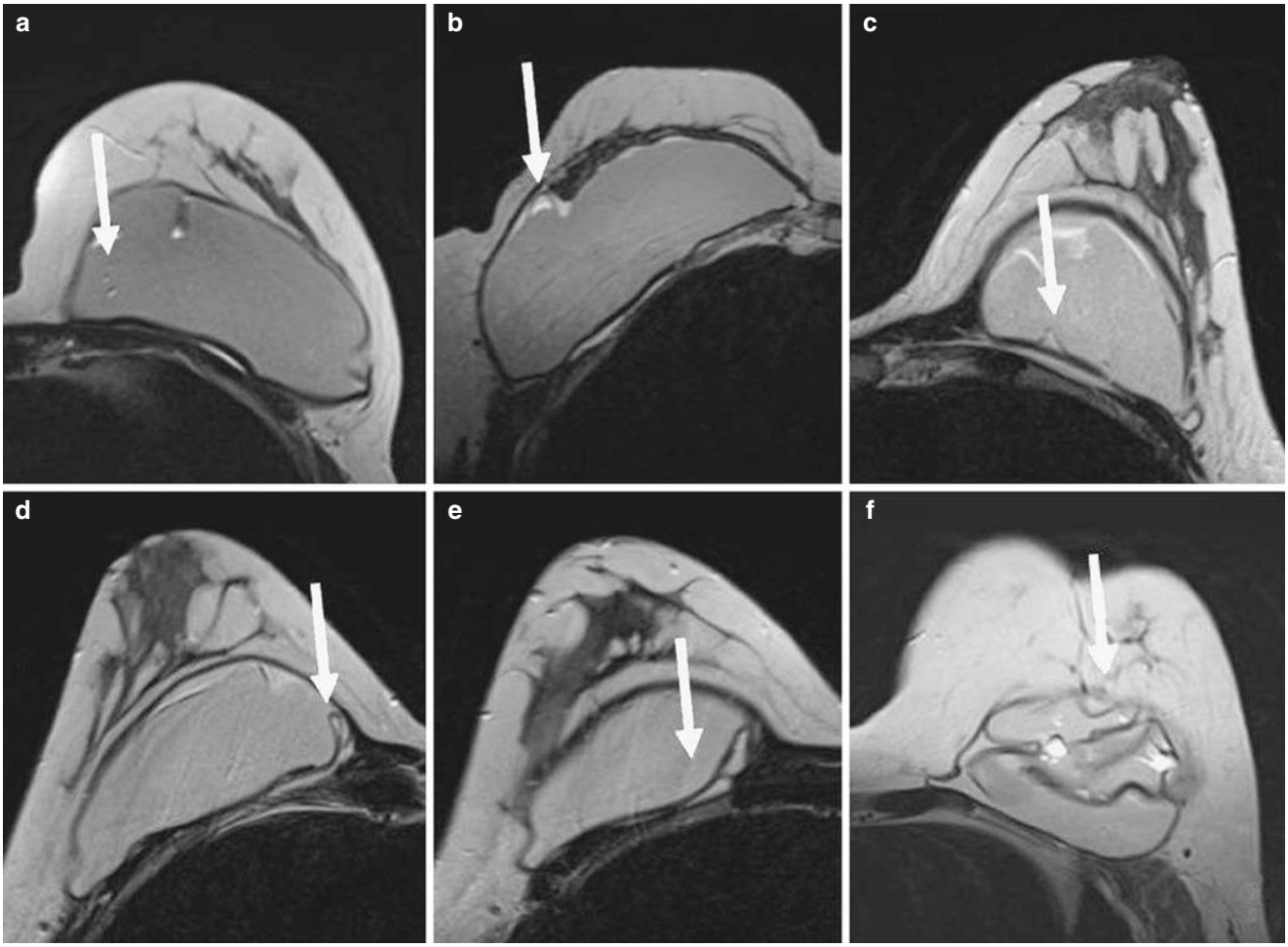

Fig. 5.26 Signs of intracapsular rupture to magnetic resonance: (**a**) thin drops of fluid inside the prosthesis; (**b**) focal area of liquid subjacent to the capsule; (**c**) small leakage of silicon external to the capsule; (**d**) "tear drop" sign; (**e**) "linguini" sign; (**f**) sign of "salad oil"

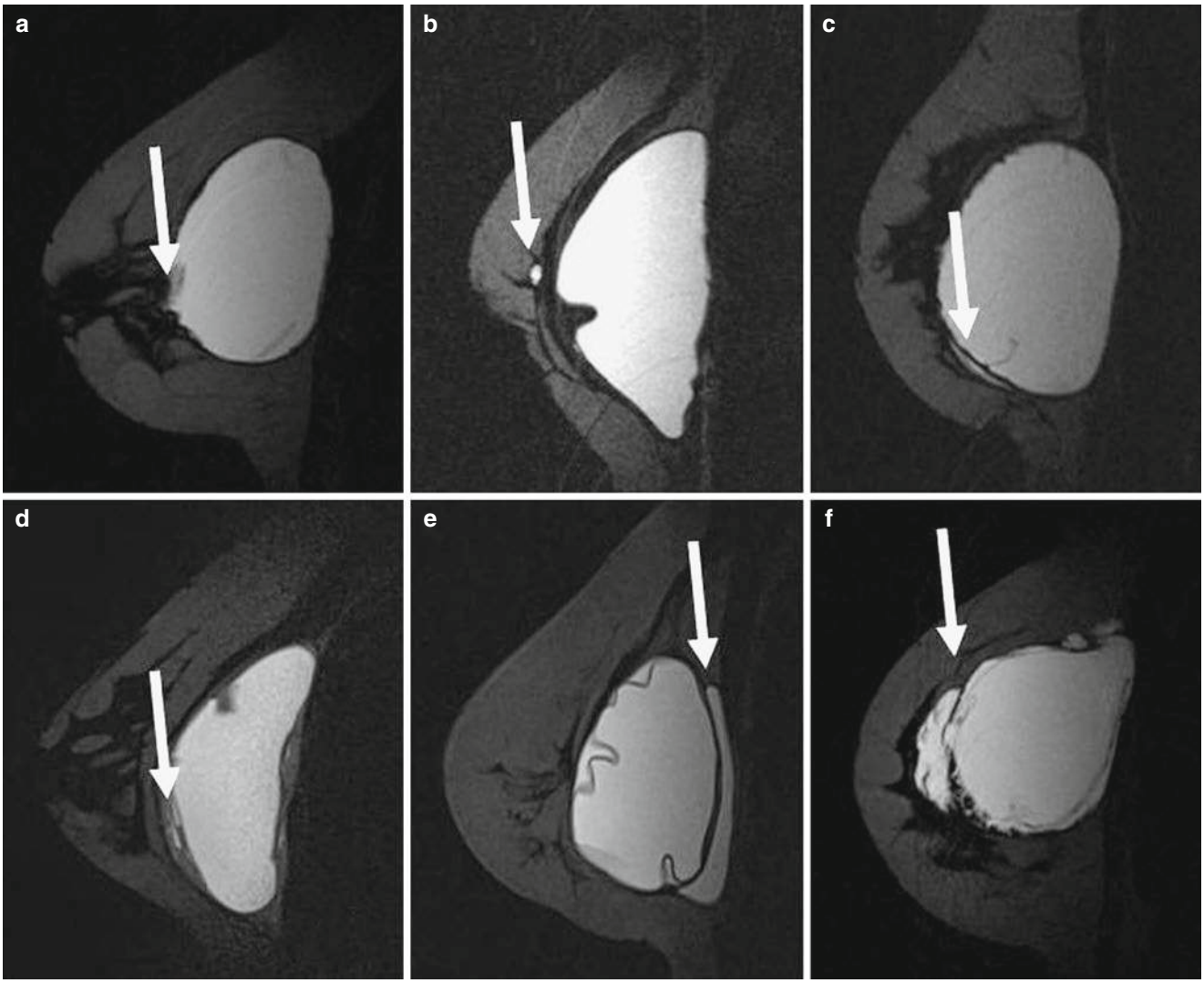

Fig. 5.27 Signs of extracapsular rupture to magnetic resonance: (**a**) focal area of silicon leakage external to the reaction capsule; (**b**) focal silicon area anterior to the pectoralis muscle; (**c**) laminar area of silicon leakage; (**d**) intermediate silicon sign around all the reaction capsule; (**e**) extensive leakage silicon posterior to the capsule; (**f**) leakage and silicon for the parenchyma

confirmed neoplasia and research of recurring tumor in reconstructed breast after mastectomy. In patients with silicon injection in the parenchyma, in which conventional methods have their evaluation limited, MR has appeared to be highly efficient to differentiate siliconomas from carcinomas (Fig. 5.16). In a meta-analysis, Cher et al. [62] concluded that the use of MR to evaluate the integrity of the prosthesis has sensitivity of 78% and specificity of 91%, with predictive value ranging on the works discussed between 50% and 100% and negative predictive value of 70% and 100%. Holmich et al. [63] compared the clinical diagnosis and the MR diagnosis of prosthesis rupture and concluded that the clinical exam focusing on the detection of rupture had little sensitivity and specificity, detecting less than 30% of rupture cases; only 50% of the implants considered clinically intact through MR were actually intact. Therefore, the FDA recommends the annual use of MR from the third year after surgery to detect silent ruptures [64].

5.7 Conclusions

The reduction of mortality from breast cancer is the result of decades of investments focused on early diagnosis and access to adequate treatment for the population. Early detection benefits women with less mutilating surgeries, increases the potential for cure, reduces the ultimate costs of treatment, and maintains a significant range of the female population economically active. The importance of MG in the early detection of breast cancer has been confirmed through large population studies for more than four decades. Other diagnostic methods (US and MRI) have specific indications for breast cancer

screening, such as US for patients with dense breasts and MRI for high-risk patients. On the other hand, in the evaluation of the symptomatic patient, all methods should be used until the diagnosis of benign or malignant disease, as well as percutaneous biopsy and presurgical localization techniques. However, despite all the efforts of the scientific community, breast cancer is still one of the most frequent tumors among women and one of the most deadly. As health professionals, we have an obligation to know and reinforce the importance of constant vigilance on this public health problem, which is breast cancer.

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Magnetic Resonance Imaging of the Breast in Surgical Planning

6

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6.1 Introduction

Magnetic resonance imaging (MRI) has changed the landscape of breast disease diagnosis and management, and it has been incorporated into treatment algorithms according to evidence-based consensus guidelines [1–3]. In oncology, the ability to biopsy a finding seen only on MRI has been a significant advancement in the field [4–7]. Preoperatively, MRI has the ability to detect breast disease occult on other imaging modalities as well as additional sites of disease within the ipsilateral or contralateral breast, assess treatment response to neoadjuvant chemotherapy, and guide preoperative needle localization. Breast MRI also has high sensitivity for the evaluation of residual disease post-lumpectomy with positive surgical margins and the evaluation of recurrent disease [8–12]. Other more controversial and emerging uses for MRI in the preoperative setting include axillary staging and aiding in the planning of reconstructive procedures.

This chapter gives an overview of the indications, uses, and controversies regarding the use of breast MRI in surgical planning.

6.2 Image Acquisition

Although image protocols for breast MRI may vary between institutions, certain minimal technical requirements have been proposed by the American College of Radiology (ACR), with the aim of detecting even small cancers by assessing lesion morphology and enhancement kinetics [3, 13].

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The ACR practice parameters recommend the following minimum requirements for performing breast MRI [3]:

1. Resolution, contrast, and field strength: A 1.5 T magnet has traditionally been considered the minimum technical requirement because of the relationship between field strength and resolution. The slice thickness should be 3 mm or less, and the in-plane pixel resolution should be 1 mm or less to minimize the problem of volume averaging effects. Motion correction may be helpful in reducing artifacts encountered with image subtraction.
2. Simultaneous bilateral imaging.
3. Contrast: Gadolinium contrast should be administered as a bolus with a standard dose of 0.1 mmol/kg followed by a saline flush of at least 10 mL.
4. Scan time: A pre-contrast scan should be obtained. Kinetic information should be reported, based on enhancement data determined at specified intervals separated by 4 min or less. Imaging sites should have an adequate short temporal resolution for an accurate capture of lesion kinetics.
5. Examinations should be performed with a dedicated bilateral breast MRI coil.

The sequence of most value to provide a surgical roadmap is a high resolution (at least 1 mm in-plane resolution), fat-suppressed T1-weighted sequence that is acquired before and at least three points after the administration of intravenous gadolinium. To properly assess enhancement kinetics, the first post-contrast image should be acquired within 2 min of contrast administration. Subtraction images (involving computer post-processing where the signal from the pre-contrast scan is subtracted from each post-contrast image) are useful for the detection of enhancement which may be difficult to ascertain from post-contrast images alone because certain benign findings such as ductal material and complicated cysts will have the same signal as contrast material. Fat generally has a high signal intensity, i.e.,

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_6

it appears bright on standard T1-weighted sequences, and so does the gadolinium contrast material that is administered; therefore, fat suppression is recommended for the pre- and post-contrast scan to increase the conspicuity of enhancing breast lesions relative to the breast background tissue that can contain variable amounts of fat. High spatial resolution techniques allow for the morphologic analysis of lesions, and high temporal resolution (rapid image acquisition) is used for assessing enhancement profiles and minimizing scan time. Enhancement kinetics of lesions seen on MRI may be obtained and analyzed to aid in the differentiation and diagnosis of benign versus malignant findings. A dedicated breast coil must be used with MRI-guided needle localization or biopsy capability for MRI-only detected lesions. The standard protocol at Memorial Sloan Kettering Cancer Center (MSK) is to acquire three-dimensional isotropic images in the axial plane, with cubic voxels of 1 mm, which allow sagittal and coronal reconstructions analogous to that done with computed tomography (CT). This has been made possible with the introduction of phased-array coils and parallel imaging, enabling simultaneous high temporal and high spatial resolution imaging of both breasts [14, 15].

Other standard sequences in the breast MRI protocol include axial T1-weighted without fat suppression and fat-suppressed T2-weighted imaging [3, 13]. T1-weighted images are helpful in characterizing fat-containing lesions (fat will appear hyperintense, i.e., bright), architectural distortion, and post-biopsy/surgical changes. On fat-suppressed T2-weighted images, fluid in the breast will present with varying degrees of hyperintensity, i.e., brightness, depending on proteinaceous and hemorrhagic content, whereas fat will appear hypointense, i.e., dark, as compared with fibroglandular tissue; therefore, benign lesions such as breast cysts (simple or hemorrhagic) can be easily identified, in addition to myxoid fibroadenomas and lymph nodes.

The radiologist's interpretation of the breast MRI is based on reviewing all sequences together which improves sensitivity and specificity, potentially avoiding an unnecessary workup or biopsy. If not all sequences are acquired, then the sensitivity and specificity can be impacted.

6.3 Oncologic Preoperative Planning

6.3.1 Background

Advances in surgical techniques and imaging modalities over the past 30–40 years have paved the way for breast conservation therapy (BCT), rather than mastectomy in most cases of breast cancer [1, 2].

Some of the earliest prospective randomized trials by investigators such as Veronesi and Fisher et al. have clearly established that lumpectomy plus radiation therapy is just as effective as mastectomy for treating early-stage breast cancer, with the overall survival ranging from 38% to 71% in the lumpectomy plus radiation group as compared with 44% to 71% in the mastectomy group [16–22]. During these trials, clinical examination and mammography were the mainstay of treatment and follow-up. However, recurrence rates of up to 10% or greater in 10 years in patients who underwent BCT followed by radiation and chemotherapy highlighted the likelihood that residual disease was still present within the breast [1, 2]. This may be due to the fact that the assessment of lesion size, presence of multifocality or multicentricity, and locoregional involvement of adjacent structures such as the pectoralis muscle and chest wall, which would change surgical management, was performed with mammography, which is suboptimal [1]. Although mammography is beneficial in the overall screening of the average-risk population [23], it has limitations in certain subsets of patients, such as those with dense breasts [24]. More recent imaging modalities such as digital breast tomosynthesis and contrast-enhanced spectral mammography (CESM) may be able to address these problems [25, 26], and several trials are underway comparing the efficacy of MRI as compared with tomosynthesis and CESM.

MRI, however, has already been shown to have superior sensitivity for the evaluation of tumor burden in the breast [27–35]. If used appropriately, breast MRI has the potential to decrease positive margin and recurrence rates in patients with certain cancers who are otherwise candidates for BCT [1]. Breast MRI is increasingly used to define the extent of disease when a patient is newly diagnosed with breast cancer and to help guide management by specifically identifying those who need a mastectomy as first-line therapy based upon surgical guidelines for multicentric disease, thereby obviating the need for multiple surgeries [36]. Mammographically occult additional breast cancer detected on MRI is likely to be clinically relevant disease [37]. Moreover, MRI may help identify occult disease in the contralateral breast, changing surgical management and possibly treatment depending upon differences in immunohistochemical surrogates of breast cancer molecular subtypes [38, 39].

6.3.2 Who Should Undergo Preoperative Breast MR Imaging?

The ACR Committee on Standards and Guidelines published guidelines for the indications and performance of breast MRI in 2004 and published a revision in 2013; the guidelines include the ACR's recommendation of an annual screening MRI examination for certain high-risk women and has helped cement the importance of MRI in breast imaging [3].

The ACR recommends the performance of diagnostic breast MRI for several indications including:

1. For the evaluation of extent of disease of invasive carcinoma and ductal carcinoma in situ (DCIS) in both mastectomy and breast conservation candidates, including locoregional involvement of adjacent structures
2. For patients with a new breast malignancy for the detection of occult cancer in the contralateral breast
3. For the evaluation of occult breast cancer in the setting of metastatic disease
4. When other imaging modalities are inconclusive
5. Post-lumpectomy with close or positive surgical margins
6. Before and after neoadjuvant chemotherapy to evaluate treatment response
7. For the evaluation of suspected imaging recurrence in the breast/chest wall or in the oncoplastic reconstruction including in tissue flaps and soft tissue superficial to the implant

Ideally, every woman with newly diagnosed breast cancer who has access to MR imaging should undergo MRI because it defines extent of disease more accurately then standard mammography and ultrasound as well as physical exam [1, 3]. At this time, however, MRI should not replace diagnostic mammography and ultrasound. The following is a common discussion question requiring further investigation: if something is not seen on MRI, is it clinically relevant? At minimum, we suggest pre-operative MRI for patients known to have high risk of recurrent disease such as young patients, patients with heterogeneous and extreme fibroglandular breast tissue breasts, and patients with a certain tumor histology, the extent of which is known to be difficult to fully assess on mammography and ultrasound alone. These include invasive lobular carcinoma (ILC) [34, 40], DCIS [41], as well as tumors with extensive intraductal component (EIC) which may increase the recurrence rate [42, 43].

6.3.2.1 Evaluating Extent of Disease in the Ipsilateral Breast

Candidacy for Breast Conservation Therapy

Absolute contraindications to BCT, as determined by a joint committee of the American College of Surgeons, include persistent positive margins after reasonable surgical attempts, first or second trimester pregnancy, inability to undergo therapeutic irradiation, and clinical or mammographically detected multicentric cancer [3]. Tumor size is not an absolute contraindication to breast conservation treatment; however, a relative contraindication is the presence of a large tumor in a small breast in which an adequate resection would result in significant cosmetic alteration [3].

Multiple clinical trials in the United States of America and Europe show that, on average, MRI can detect occult disease in the ipsilateral breast in approximately 15% of patients, with reported ranges of 12% to 27% [35, 37, 44–46]. MRI converts a patient to mastectomy approximately 15% of the time [37]. Those who are not in favor of MRI feel that this increased mastectomy rate is not warranted; treatment is based on guidelines which have historically only involved mammography and ultrasound. Nevertheless, we suggest that treatment guidelines should be modified to consider MRI findings. All studies have shown that residual disease or positive surgical margins are associated with local recurrence [47, 48]. Furthermore, preoperative MRI can identify 5%–10% of patients harboring additional multicentric disease that could presumably cause a recurrence[1].

An example of how preoperative MRI has changed surgical management is a study done by Northwestern University in Chicago, Illinois, which included 155 women with newly diagnosed breast cancer [49]. MRI identified 124 additional lesions in 73 patients. Of the 155 patients, change in surgical management occurred in 36 (23%) of 155. Lumpectomy was converted to mastectomy in 10 (6%) of 155 women. In 8 (80%) of the 10 women where lumpectomy was converted to mastectomy, this was beneficial to the patient. Two (20%) of the ten borderline lesions for BCT were converted to mastectomy on the basis of MRI where MRI overestimated disease. Overall, MRI resulted in a beneficial change in surgical management in 10% of newly diagnosed breast cancers, with the authors concluding that the detection of additional ipsilateral and contralateral cancers justifies the role of preoperative breast MRI.

In contrast, two prospective randomized trials assessed the effect of MRI on short-term surgical outcomes [50, 51]. The re-operation rate, including both margin re-excision and conversion to mastectomy, was the primary endpoint in both studies. In the Comparative Effectiveness of MRI in Breast Cancer (COMICE) trial, 23.7% of patients in the MRI group were converted to mastectomy on the basis of MRI results, with no significant difference in re-operation rate seen between the MRI and no-MRI groups [50]. The mastectomy rate in the MRI group was 13.0% compared with 8.8% in the no-MRI group. Limitations of the COMICE trial included the lack of experience of some of the participating centers with MRI and that not all of the MRI detected lesions were biopsied. In the MR Mammography of Nonpalpable BrEast Tumors (MONET) study, the re-excision rate was 34% in the MRI group compared with 12% in the no-MRI group, but the number of conversions to mastectomy did not differ, resulting in an overall re-operation rate of 24 (45%) of 53 patients in the MRI group and 14 (28%) of 50 patients in the no-MRI group [51]. The MONET trial, with only 149 cancers, was likely underpowered, and the very high rate of re-excision in

the MRI group was not justified. Thus, neither the COMICE nor MONET studies showed that MRI significantly reduced reoperation rates.

Although the use of preoperative MRI has not as yet been proven to improve local control or overall survival [2], it is important to note that randomized control trials (RCTs) are not needed to justify the use of a new diagnostic test [52]. For example, RCTs have not been performed for diagnostic mammography although many trials have been performed assessing its use as a population-based screening tool [53].

MRI evaluation of breast carcinoma prior to surgical treatment has also been shown to be useful in both mastectomy and breast conservation candidates to define the relationship of the tumor to the fascia and to determine its extension into pectoralis major, serratus anterior, and/or intercostal muscles [1, 54].

MRI determines the extent of disease more accurately than standard mammography and physical examination in many patients. However, it remains to be shown that this increased accuracy results in any reduction in recurrence rates following surgery, radiation, or systemic therapy.

Prevention of Positive Surgical Margins

The aim of breast conservation surgery is to obtain negative surgical margins, usually defined as the absence of invasive or DCIS at an inked surface; however, there are variations in this definition and what is deemed to be an acceptable margin [2, 3]. Patients who underwent breast-conserving surgery and radiation therapy with negative margins at excision have been consistently found to have lower rates of recurrence, whereas patients with positive margins had higher rates of recurrence [42, 55–57].

Re-excision due to positive margins is associated with increasing patient anxiety, surgical risk related to reoperation, and increasing cost [1, 58]. Positive margin rates have been reported as high as 70%, although more conservative estimates report that 30%–50% of women undergoing breast conservation therapy may require additional surgery for positive margins. Too little or too much tissue may be removed when there is no information about how much residual disease exists. MRI can provide the surgeon with a roadmap defining the amount of residual disease if present. Of note, it is always preferred that a breast MRI be performed before any surgery to define the extent of disease because postoperative change can sometimes be difficult to differentiate from residual disease.

Certain tumor histologies have an increased rate of positive surgical margins and recurrence, including DCIS, ILC, and those with an extensive EIC.

DCIS

Ductal carcinoma in situ (DCIS) is a common non-invasive cancer [41, 59]. Early detection is crucial, as a large proportion of DCIS progresses to invasive cancer. Since the introduction of screening mammography, DCIS now accounts for 15%–20% of all detected breast cancer and for 25%–56% of clinically occult cancers [1, 60]. The extent of DCIS involvement is often underestimated with mammography, especially if the cancer is not associated with calcification [1, 41]. In addition, image-guided percutaneous biopsy underestimates the presence of invasion in over 20% of patients with preoperatively diagnosed DCIS without evidence of an invasive associated component (pure DCIS) [61].

Recent studies showed the importance of preoperative MRI in assessing DCIS extent, with published studies citing sensitivities ranging from 40% to 96% [60, 62–69]. MRI morphology and size features can help identify invasive disease preoperatively, which would impact treatment [47, 70].

On MRI, DCIS is often seen as a clumped non-mass enhancement in either a focal, linear, segmental, regional, or diffuse distribution. MRI can detect not only calcified but noncalcified DCIS. Criteria used to diagnose invasive breast cancer on MRI such as the presence of an enhancing mass with washout kinetics do not always apply to DCIS [71]. For example, 30% of DCIS in one series was reported to exhibit rapid wash-in and washout enhancement; 50% showed intermediate (plateau) enhancement; 15% exhibited slow (progressive) enhancement; and 5% did not enhance at all [1]. Diagnostic criteria based on contrast enhancement kinetics are therefore not reliable to exclude DCIS; rather, if they are suspicious, they can be used to confirm the diagnosis. The accuracy of MRI for the detection of DCIS has improved with advances in MRI technology, specifically improved spatial resolution and use of multiparametric images. For example, combining MRI post-contrast images and DWI improves the accuracy of diagnosing in situ disease [72–74].

ILC

Invasive lobular carcinoma (ILC) accounts for 5%–20% of breast cancers and is the second most common histology [40, 75]. The main difference between IDC and ILC is their growth pattern, with ILC tending to grow more diffusely, typically due to loss of E-cadherin [76]. The "classic type" lobular carcinoma consists of relatively small, uniform cells that grow in a loosely cohesive fashion, forming lines of cells infiltrating the healthy tissue. Targetoid growth, which describes formation of webs around healthy ducts, is often reported. Moreover, synchronous and metachronous contralateral carcinomas are more often observed in ILC [77]. ILC also tends to be larger at detection than IDC [78, 79].

ILC presents a major diagnostic challenge [40]. The diffuse growth pattern of ILC makes mammography and ultrasound unreliable at staging, thus causing high rates of tumor re-excision and leading to a common preference by both patients and surgeons to perform mastectomy [80]. On MRI, the morphologic appearance of ILC is variable with an

enhancing mass being the easiest to detect [81, 82]. In the absence of a mass, diffuse non-mass enhancement infiltrating between normal fibroglandular tissue may be visualized, with this growth pattern most likely explaining why ILC tends to be larger than IDC [79]. Variability in gadolinium uptake and morphology of ILC reflects the tumor histology. However, despite this, retrospective and prospective sensitivity of breast MR imaging for ILC is high, with sensitivity averaging approximately 93.3% and reaching as high as 100% [34, 83–85].

EIC

Extensive intraductal component (EIC) is a histopathologic feature that appears to be associated with a high risk of breast cancer recurrence [86, 87]. First described by the Joint Center for Radiation Therapy, this entity is sometimes classified as DCIS occupying 25% or more of the area comprising the primary invasive tumor and DCIS in the surrounding normal breast tissue. Approximately 20% of women with early-stage breast cancer undergoing breast conservative surgery and radiation for invasive ductal carcinoma have an EIC. Several series have reported an increased risk of breast recurrence in women with EIC-positive tumors, ranging from 2% to 32% at 10 years, and this may be related to the presence of a significant residual tumor burden following gross excision [2]. However, a number of more recent studies have shown that negative resection margins diminish the risk of breast recurrence in EIC-positive tumors [42, 43, 57]. Therefore, while the presence of an EIC is a pathologic indicator that disease in the breast may be more extensive than what is clinically appreciated, it does not appear to be an independent risk factor for local recurrence [2].

6.3.2.2 Examining the Contralateral Breast

The contralateral breast can be screened at time of MRI to define disease extent. The American College of Radiology Imaging Network (ACRIN) 6667 trial reported that MRI was able to detect a malignancy in the contralateral breast in 3.1% of women who had been newly diagnosed with breast cancer [39, 88, 89]. Follow-up studies including a series at MSK also corroborated these findings, with detection rates for a contralateral malignancy ranging from 2.7% to 6.0% [39, 44, 45, 89, 90]. Knowledge of a contralateral breast malignancy changes surgical management [2] and would enable discussion of all treatment options at the very start based on the bilateral synchronous tumor molecular subtypes.

It has been argued that rates of contralateral cancer have been declining steadily since 1985, possibly due to the increased use of adjuvant systemic therapy, and that the low incidence rate makes it difficult to justify the routine use of MRI for contralateral cancer detection [91, 92]. However, we argue that ignoring the opposite breast and assuming that the adjuvant chemotherapy will treat unsuspected contralateral disease cannot make clinical sense as we expend so much energy, time, and resources to treat the known cancer [1]. The assumption also fails to take into account that breast cancer is a heterogeneous disease and treatment is becoming increasingly personalized based upon knowing probable molecular subtype through immunohistochemical surrogates.

6.3.2.3 Assessment of Postoperative Residual or Recurrent Disease

Breast MRI may be used in the evaluation of residual disease in patients whose pathology specimens demonstrate close or positive surgical margins for residual disease; this is recommended by the ACR [3]. Moreover, suspected recurrent disease within lumpectomy sites and reconstructed breasts can also be assessed.

Residual Disease

Residual disease following lumpectomy is suspected when the initial attempt at surgical resection is incomplete and there are positive surgical margins [1]. Specimen radiography is useful to determine lesion retrieval [93]. If the initial carcinoma contains calcification, then post-lumpectomy mammogram with magnification views can be performed to assess whether there are remaining residual suspicious calcifications [94]. If present, these can be localized under mammographic guidance, which can then direct the surgeon to area of residual disease.

However, this is not possible if the original tumor does not contain calcifications. In addition, the ability to detect residual disease radiographically at the lumpectomy site is often limited as post-operative distortion and changes such as hematoma/seroma obscure the evaluation [1]. In these cases, the patient returns to the operating room and the surgeon excises the positive margins of the lumpectomy cavity. Breast MRI can offer important information regarding the presence of residual disease in these cases, particularly in young patients with dense breasts, cancers with EIC, certain breast cancer molecular subtypes like Her2 overexpressing, and ILC [95].

The role of MRI in the case of close or positive margins is to evaluate for the presence of bulky residual disease [1, 96]. Residual microscopic disease at the surgical margin is not well evaluated with MRI as it cannot be differentiated from enhancing granulation tissue but will usually be successfully re-excised from the seroma cavity, regardless of the imaging results. The major role of MRI is in the assessment of measurable residual disease at the resection margin or distant from the lumpectomy site, and this information can guide surgical management. If re-excision with the goal of breast conservation is performed, pre-operative MRI needle localization can be used to facilitate complete resection.

Recurrent Disease

In the breast, recurrence is thought to be due to either undetected tumor that was not adequately treated at the time of detection of the index tumor or the de novo development of cancer [1, 96]. Recurrence may develop despite the presence of negative margins at the time of surgery and the administration of neoadjuvant/adjuvant chemotherapy and radiation. As discussed, rates of recurrence vary and are increased in patients with positive margins, in young patients, and in tumors with an extensive intraductal component.

Residual disease and recurrence are related [1, 96]. Residual disease that is untreated may eventually manifest itself as a recurrence, either early (within the first 2 years) or late (following 2 years). Radiation therapy and/or chemotherapy treats a significant proportion of undiagnosed residual disease. The disease that is not treated presents as a recurrence. It is currently not known which cancer, if any, can be safely left behind in the breast to be effectively treated by radiation therapy and/or chemotherapy. Therefore, at this time, it is surgically necessary to remove all residual disease.

On average, local recurrence is reported in 6.2% of the mastectomy patients and 5.9% of the patients treated with BCT [22]. However, published literature that offers a long-term follow-up of patients BCT indicates that the cumulative local recurrence rate can be as high as 19% and beyond the often quoted 10% in 10 years in most published studies [97–104]. In addition, although it was believed that local recurrences do not have an impact on overall survival, more recent studies demonstrate that local relapse does have an impact not only on disease-free survival but also on overall survival [97, 98, 101, 103, 104]. Therefore, avoiding recurrence or its early diagnosis is considered as important as the early diagnosis of the primary cancer. Since a more accurate local staging translates into improved local control and the evaluation of the post-operative breast can be limited on mammogram and ultrasound, MRI should be considered for evaluating local in breast recurrence.

6.3.2.4 Assessment of Residual and Recurrent Disease in the Reconstructed Breast

MRI has also been shown to be useful for the evaluation of residual or recurrent disease within reconstructed breast flaps [105, 106]. Various surgical methods, including modified radical mastectomy (MRM), simple mastectomy, skin-sparing mastectomy (SSM), and nipple areolar skin-sparing mastectomy (NASSM), can be performed with oncoplastic reconstruction [106–108]. For autologous tissue reconstruction after mastectomy or MRM, the transverse rectus abdominis, latissimus dorsi, or gluteus maximus muscles can be used, with a transverse rectus abdominis myocutaneous (TRAM) flap being most common, followed by the latissimus dorsi flap [105].

After mastectomy and breast reconstruction, the patient undergoes clinical surveillance for recurrence, and imaging (typically ultrasound) is only performed for diagnostic purposes (e.g., palpable area of concern or peri-implant fluid collection). Several studies report a 2.0%–7.5% local recurrence rate after modified radical mastectomy followed by breast reconstruction [109–112]. However, the detection and determination of the extent of recurrence can be challenging. Numerous studies have evaluated the capabilities of MRI for the detection of recurrent malignant disease following breast-conserving surgery with and without adjuvant radiotherapy [113–123] and in patients undergoing breast reconstruction using silicone prostheses [124–126]. Fewer studies have investigated the role of MRI for diagnosing recurrence within an autologous tissue reconstruction (flap) after mastectomy [127]. These studies have outlined the strengths of MRI for this purpose [113]. Most studies have quantified MRI's sensitivity at 100% [118, 119, 128].

Understanding the surgical procedure is crucial in the interpretation of the MRI findings. For example, the contact zone between the flap and surrounding residual mammary adipose tissue can be visualized on T1-weighted images as a line of low signal intensity approximately 1 mm in width. The musculovascular pedicle of the flap can also be clearly visualized with MRI. Typically, the musculovascular pedicles of the latissimus dorsi flaps can be followed laterally and those of the TRAM flaps, caudally.

The absence of contrast enhancement on MRI excludes recurrent carcinoma with a high degree of probability. Fat necrosis after breast-conserving surgery as well as flap reconstruction postmastectomy can sometimes be a diagnostic challenge [113, 115]. The irregular enhancing areas in fat necrosis on MRI correspond to peripherally developing fibrosis and inflammatory cell infiltration, and the non-enhancing area of the central portion corresponds to necrotic fat. Since fat necrosis can occur in 10%–26% of cases after a TRAM flap procedure [129–131], MRI can be useful for differentiating fat necrosis from recurrent disease if it demonstrates a typical appearance. However, fat necrosis particularly in its earliest form can result in a false positive. In our practice, if the radiologist believes the finding is probably benign fat necrosis, a 6-month follow-up breast MRI is recommended.

Changes after radiation therapy can also sometimes be difficult to differentiate from recurrence disease. This includes the thickening of the skin, edema, and a concomitant inflammatory reaction in the fibroglandular tissue, all of which demonstrate contrast enhancement particularly within the first 12 months post-operatively. These changes resolve over time, with the specificity of MRI increasing between 12 and 18 months [116, 124].

Chest-wall recurrence occurs in 0.2%–1% of women who have undergone mastectomy per year [132]. Even though the

patient has undergone mastectomy, an MRI using the breast coil and the standard diagnostic breast protocol, which includes pre- and post-contrast imaging, can assist in surgical planning and determining the extent of disease including if there is rib or lung involvement.

6.3.2.5 Occult Primary Breast Cancer

Breast cancer that presents as axillary metastases with an occult primary tumor that cannot be detected by physical examination, mammography, or ultrasonography is seen in fewer than 1% of cases [133, 134]. Breast MRI is recommended when there is an occult primary. The literature demonstrates that breast MRI can locate the primary tumor in the breast in over 50% of women presenting with metastatic axillary adenopathy and an occult primary tumor [135–137]. The pooled sensitivity for the detection of cancer in a meta-analysis was 90% and the specificity was 31% [137]. The mean pathological size of the occult tumors ranged from 1 to 50 mm, and 82% were infiltrating ductal cancers. Breast MRI can also define the disease extent to facilitate treatment planning.

The identification of the site of malignancy is important therapeutically particularly because of the importance in determining the index cancer's molecular subtype to guide treatment [1, 32, 138]. Traditionally, patients undergo mastectomy if the site of malignancy remains unknown after MRI; however, some patients may receive full breast radiation with careful follow-up with MRI. Identification of the primary tumor allows the possibility of BCT and delivery of radiation to the primary tumor site, minimizing the risk of local recurrence and having obvious advantages compared with radiation of the intact breast without knowledge of tumor extent or characteristics.

6.3.2.6 When Other Reports Are Inconclusive

When mammography and ultrasound are inconclusive, MRI can be helpful in the assessment of the breast [96, 139]. MRI should not be used in place of an inadequate conventional workup. Usually, MRI is used in these situations to exclude the presence of disease. Caution should be exercised, however, as a negative MRI in this setting can be overly reassuring and misleading particularly if the conventional workup has been assigned a BIRADS 0. If BIRADS 0 has been assigned to a mammographic and sonographic diagnostic workup where MRI is recommended for further evaluation, the radiologist should clearly state in the report what the recommendation is if the MRI is negative—specifically that a decision still needs to be rendered regarding the mammographic and sonographic findings [1, 96]. This is so the entire evaluation does not rest with the MRI results.

As discussed, information from the MRI may change the planned treatment management [1]. Caution should be exercised in changing management based on MRI findings alone without initial biopsy confirmation. Additional biopsies and/or correlation with other clinical and imaging information should be used together with clinical judgment. Moreover, inappropriate uses of breast MRI should not supplant careful problem-solving mammographic views or ultrasound in the diagnostic setting [3]. Because MRI will miss some cancers that mammography will detect, it should not be used as a substitute for screening mammograms. MRI should not be used in lieu of biopsy of a mammographically, clinically, and/or sonographically suspicious finding.

6.3.3 Axillary Staging

Axillary staging of newly diagnosed breast cancer is clinically relevant; as a result, it is being evaluated [140]. Sentinel lymph node biopsy (SLNB) is the gold standard for axillary staging of patients with breast cancer who have a clinically and radiologically negative axilla [141–145]. Preoperative ultrasound with fine-needle aspiration (FNA) or core biopsy of morphologically abnormal lymph nodes can be performed to identify node-positive patients if it would alter treatment.

The importance of axillary staging in newly diagnosed T1-T2 breast cancers has been debated [4]. Several studies and trials argue that patients with a low axillary tumor burden do not benefit from an axillary lymph node dissection (ALND) [146–148]. For example, in patients with nodal metastasis who underwent whole breast radiotherapy and systemic therapy, the ACOSOG Z0011 trial demonstrated that omission of ALND led to an extremely low rate of local recurrence and excellent overall survival. Additionally, the International Breast Cancer Study Group (IBCSG) trial 23–01—a randomized, multicenter, phase III clinical trial comparing ALND with no ALND in patients with micrometastases alone in the SLN group—also demonstrated that an ALND can be omitted in patients with very low-volume metastatic nodal involvement [149].

Nevertheless, there is a need for more accurate imaging tools to diagnose and evaluate metastases in axillary lymph nodes particularly with the increasing use of neoadjuvant chemotherapy. Axillary MRI may prove to be an alternative to SLNB in determining axillary lymph node metastases. Several studies are underway to characterize abnormal lymph nodes, with a reported mean sensitivity and specificity of MRI in detecting metastatic lymph nodes as high as 90% [150]. For example, a study found that the presence and number of axillary lymph nodes with no fatty hilum on MRI significantly correlated with pathologic node positivity, while kinetics, node number, and node size did not correlate with these characteristics [151]. Another study compared the axillary lymph nodes on MRI to the actual pathological proven metastases as diagnosed from the surgical specimen and found that an MR short axis threshold of 4 mm yielded

the best predictive value for metastatic nodal involvement with a sensitivity and specificity of 78.6 and 62.3%, respectively. Other factors that significantly correlated with metastatic lymph node involvement were irregular contours (sensitivity 35.7% and specificity 96.7%), central nodal hyperintensity on inversion recovery T2-weighted images (sensitivity 57.1% and specificity 91.4%), and a cortical thickness of >3 mm (sensitivity 63.6% and specificity 83.2%) [152]. Gadolinium is the intravenous contrast used in breast MRI. Research into different contrast agents is being conducted to determine if they can improve the accuracy of MRI. In particular, data from studies using superparamagnetic iron oxide (SPIO) indicate that these contrast agents have sensitivity and specificity for the detection of axillary involvement of 98% and 96%, respectively [153]. Combining radionuclide-based imaging techniques such as PET and single-photon emission computed tomography (SPECT) with MRI has also been under investigation for axillary staging [154].

6.4 Reconstructive Presurgical Planning

6.4.1 Identification of Perforators

Pre-operative anatomic imaging of vasculature is useful for the surgeon to devise a strategy before attempting a breast reconstruction procedure [155, 156]. Prior to the era of pre-operative perforator imaging, a surgeon had little knowledge of an individual patient's vascular anatomy until well into surgery; thus, perforator selection was often a tedious and stressful process at the expense of operating time. The knowledge of location and anatomy of the underlying perforators can increase the predictability and improve intraoperative decision-making to choose the appropriate technique in an individual patient [157, 158]. In addition, there is a high degree of anatomic variability among patients and between individual sides of the same patient [159, 160]. Pre-operative imaging can assist in the selection of appropriate donor sites, flap design, and in determining an individual's unique anatomy.

Traditionally, handheld Doppler and color duplex ultrasonography were used to detect the location of perforators and flow characteristics [161, 162]. However, these techniques have been associated with significant interobserver variability, and high false-positive rates, and can be limited by difficulty in interpretation of findings, reproducibility, and patient body habitus [158, 163].

MR angiography (MRA) has been shown to accurately locate perforating vessel branches and shows vessel anatomy in a format that is easily viewed by a surgeon, providing a 3D road map [159, 164]. Ahn et al. first described the use of MRI for delineating perforators of the lower abdomen for TRAM flap selection without contrast [165]. The use of MRA in the examination of the deep internal epigastric artery perforator (DIEP) vascular anatomy is a relatively newer imaging modality and represents the next generation in preoperative DIEP planning [166]. MRA spatial resolution allows the visualization of 1 mm perforating vessels, permitting a better delineation of intramuscular course of perforators [156, 167]. Disadvantages of MRA are contraindication to use with a cardiac pacemaker or claustrophobic patients, higher costs, longer acquisition times, and motion artifact. Continuing advances in MRA have decreased the procedure time for a single donor site to as little as 20 min but could extend up to 40 min for multiple donor site studies [168, 169].

Currently, at our institution, CT angiogram is used to pre-operatively assess the DIEP vascular anatomy.

6.4.2 Predicting Breast Volume and Outcome

Although tumor size is not an absolute contraindication to BCT, there is little published experience in treating patients with tumor sizes greater than 4–5 cm [2]. A relative contraindication is the presence of a large tumor in a small breast in which an adequate resection would result in significant cosmetic alteration. Therefore, tumor-to-breast volume ratio is a highly informative parameter when deciding on the type of surgery for a particular patient [170]. This ratio is usually subjectively assessed by the surgeon. Cosmetic results are reportedly worse when the volume of tissue excised is >70–100 cm^3. Other factors that affect cosmesis are breast size, how high the ratio is between the tissue excised and the breast volume, and the location of the tumor [171, 172].

Therefore, several studies are underway where breast MRI is used to derive the tumor-to-breast volume ratio using computer software. The first study to assess tumor-to-breast volume ratio as measured on MRI and to correlate it to the type of surgery selected for the patient (BCT vs mastectomy) found the ratio to be predictive of axillary lymph node metastases [173]. MRI-derived breast tumor volume was also shown to be more predictive of recurrent-free survival than tumor diameter in patients undergoing neoadjuvant chemotherapy for breast cancer [10]. Further studies have also shown that 3D MRI as compared with mammography enables a more accurate quantitative assessment of the breast parenchymal volume [170, 174–177]. MRI-derived volume ratio measurements may reliably select the optimal type of surgery for the patient [170].

Subjective observation of the tumor-to-breast volume ratio may lead to the overestimation of this ratio and, subsequently, unnecessary mastectomies [170]. Highly accurate MRI measurements as derived with the aid of computer software allowing quantification may spare mastectomies in

favor of BCT and aid in achieving better cosmetic results with safe margins.

6.5 Neoadjuvant Chemotherapy

6.5.1 Background

Neoadjuvant chemotherapy (NAC) is the administration of chemotherapy prior to the definitive breast cancer surgery [11, 96, 178]. It use has been expanded and can enable breast-conserving surgery and sentinel lymph node biopsy in women who traditionally require a mastectomy and full axillary lymph node dissection. The primary goal of NAC is a pathologic complete response (pCR) defined as the absence of any residual cancer. As a biomarker, pCR serves as an intermediate endpoint for improved disease-free and overall survival. The National Comprehensive Cancer Network guidelines currently recommend a breast MRI pre- and post-NAC (MRI is often used to evaluate treatment response).

Assessing tumor response to NAC can be difficult clinically and on mammography and ultrasound, often due to effects of fibrosis (a response to chemotherapy) and breast density [11, 96, 178]. Numerous studies have demonstrated that MRI has the highest diagnostic accuracy for pCR [8, 9]. Several studies have demonstrated that residual tumor measurements on MRI correlate with the pathologic residual disease following NAC [10–12]. In addition, MRI is able to exploit the functional and biologic information about the tumor by assessing changes in tumor kinetics, which often occurs early in the tumors before volume alterations. Information from MRI pertaining to suboptimal response may lead to the use of alternative treatment regimens.

6.5.2 Response Assessment

Breast MRI has a reported sensitivity of 50%–100% for the assessment of response to NAC [179]. This high sensitivity is dependent on the ability of MRI to differentiate enhancement related to residual tumor from normal background parenchymal enhancement of the fibroglandular tissue. Decreased enhancement of tumors in patients undergoing NAC usually occurs due to the antiangiogenic effects of cytotoxic treatment agent and may compromise the ability to visualize residual viable tumor.

6.5.3 Predictors of Pathologic Response on MRI

MRI may help identify breast cancer features that are predictive of pCR post-NAC. When MRI is performed pre- and post-NAC, an objective tumor response can be assessed by applying Response Evaluation Criteria In Solid Tumors (RECIST) to the primary breast tumor [180], which include complete response, partial response, and progressive disease. Several studies have demonstrated that rates of complete response, partial response, or no response on MRI correlated well with response measurements from the standard clinical assessment [181–183].

Other studies have explored tumor characteristics on MRI early in treatment for their ability to predict the eventual overall clinical or histopathologic tumor response [184–187]. These studies evaluated size and morphologic measurements as well as functional parameters related to the pharmacokinetics of contrast uptake. For example, a study using RECIST criteria evaluated the early size reduction (ESR) of the breast cancer on MRI measured after the first cycle of treatment. ESR was found to correlate with response; patients who had a higher ESR were more likely to have a complete response [184]. Another study measured tumor volume and early contrast uptake in breast cancer patients receiving NAC and found that reductions in tumor volume and early contrast uptake after two cycles of treatment were associated with a major histopathologic response, defined as no residual viable cancer cells or only small clusters of dispersed residual cancer cells found on postoperative specimens [185]. Another group applied MR spectroscopy to measure pharmacokinetic parameters, water apparent diffusion coefficient, fat/water ratio, and water T2 before treatment and after the second of six treatment cycles. Pharmacokinetic parameters and ADC did not detect an early response; however, fat/water ratio and water T2 measurements did correlate with final tumor volume response [187].

Several other studies observed correlations between the initial morphologic patterns of breast tumors on MRI and their likelihood of response to treatment [188–190]. In one study, breast cancers were classified from 1 to 5 according to the degree of tumor containment, where 1 corresponded to unicentric tumors with well-defined boundaries, and 5 corresponded to a septal spreading pattern with ill-defined boundaries [189]. Morphologic pattern was found to be associated with the tumor response, with 77% of type 1 tumors demonstrating a partial or complete response versus 25% of type 5 tumors. A higher rate of breast conservation was also associated with tumors of type 1 morphologic pattern.

The ACRIN Trial 6657 then tested parameters that showed significance in the pilot studies for predicting tumor response and recurrence-free survival [191]. The trial compared MRI findings with clinical assessment for the prediction of pathologic response to NAC in patients with stage II or III breast cancer greater than 3 cm. Women undergoing NAC with an anthracycline-based regimen, with or without a taxane, were enrolled. MRI parameters included measurements of tumor longest diameter, volume, and peak signal enhancement

ratio, and clinical tumor size and response category were also recorded at each time point. Clinical and MRI predictor variables were compared for their ability to predict pCR and residual cancer burden. In the 216 women included in the study, MRI size measurements were superior to that of the clinical examination at all time points, with tumor volume change showing the greatest relative benefit at the second MRI study. Additional predictive value was gained with adjustments for age and race. The authors concluded that MRI findings are a stronger predictor of pathologic response to NAC than clinical assessment, with the greatest advantage observed with using volumetric measurement of tumor response early in treatment.

These studies and others suggest a role for MRI in characterizing the response of breast tumors to NAC in order to facilitate assessment of treatment efficacy [191]. This can be performed non-invasively and repeatedly to evaluate patients during treatment. Imaging techniques that quantitatively assess response, both morphologically and functionally, are being increasingly utilized in oncologic clinical trials to evaluate response to therapy and may help determine the most effective imaging methods and parameters for serial monitoring of patient treatment.

6.5.4 Assessment of Residual Disease After NAC with MRI

Many studies have specifically investigated the role of breast MRI as a diagnostic tool for evaluating the extent of residual disease after NAC [192, 193]. Similar to the assessment of disease extent, MRI has been shown to be superior to mammography, ultrasound, and clinical examination in measuring residual disease after NAC [10, 183, 193].

Despite the superior accuracy when compared with other modalities, MRI can over- or underestimate residual tumor extent. This may be influenced by tumor response, chemotherapeutic agent, or NAC-induced reactive changes within the tumor [194]. What has been consistently observed is that MRI is very accurate for mass-type lesions that show a clear tumor boundary and concentric shrinkage after therapy. In contrast, MRI is not accurate for cancers presenting with non-mass enhancement that are less confluent after chemotherapy, with residual disease presenting as scattered or clustered cells, as seen in previously discussed entities such as DCIS and ILC [195–197]. MRI measurements correlate the best with histopathologic residual disease size compared with the other imaging modalities or clinical examination [181, 182, 198]. MRI has been reported by some to underestimate and others to overestimate residual disease extent in tumors with significant treatment response [199–202].

Molecular characteristics have also been shown to affect the accuracy of MRI in evaluating residual disease post-NAC [195–197, 203–207]. MRI is more accurate in triple-negative or ER-negative/HER2-positive cancers which are more aggressive and also more likely to achieve a pCR post-NAC [196]. MRI is less accurate in ER-positive/HER2-negative breast cancer [203, 205–207]. There are studies, however, that report after multivariate analysis that molecular subtype did not significantly influence the sensitivity, specificity, positive predictive value, or negative predictive value of MRI in predicting pCR [204]. Another factor that can affect accuracy is the spatial resolution (size of the image voxel analogous to a pixel) of the MRI [196, 208] which is increased with MRI magnet strength. Studies have shown no difference in accuracy between 1.5 and 3.0 T [196, 208]. Studies with a dedicated 7 T MRI, which allows for a significantly higher spatial resolution, are now underway for the assessment of accuracy post-NAC [209].

Current research is being performed to determine if percutaneous MRI-guided biopsy can diagnose pCR in breast cancer patients who have had a complete imaging response. If this is possible, this would obviate the need for breast surgery. This novel method challenges the current clinical practice and may ultimately lead to a paradigm shift in treatment practices and the meaning of BCT. In patients who show diffuse disease pre-operatively, some surgeons still lean toward mastectomy even in the setting of a complete imaging response on MRI. Percutaneous diagnosis of pCR or minimal residual disease could potentially aid in determining the optimal surgical procedure [210]. The value of MRI in the NAC setting is an exciting and important evolving field.

6.6 Limitations of Breast MRI

As with any diagnostic imaging modality, several limitations exist for breast MRI. MRI is the most sensitive imaging modality and false positives lower its specificity [96]. False positives can be caused by high-risk lesions such as lobular carcinoma in situ (LCIS), atypical ductal hyperplasia (ADH), and atypical lobular hyperplasia (ALH), as well as benign masses such as fibroadenomas, papillomas, and lymph nodes. False positives can be caused by benign lesions including pseudoangiomatous stromal hyperplasia (PASH), fibrocystic changes, sclerosing adenosis, duct hyperplasia, and fibrosis. With improved experience, many of these lesions can be identified and confidently diagnosed as benign at time of interpretation. An examination of the literature demonstrates that the true positive biopsy rate of MRI-recommended biopsies approaches 45% [211]; however, these results are from large experienced centers. The biopsy rate and positive predictive value is similar to that generated by routine mammography and better than that generated by ultrasonography [35, 212, 213].

False-negative examinations with MRI do occasionally occur and have been reported with some well-differentiated IDCs as well as invasive lobular carcinoma [214] as well as in DCIS and infiltrative ILC. Sensitivity is impacted by such factors as poor spatial resolution and lesions that do not demonstrate avid enhancement. More recent evidence suggest that the sensitivity for DCIS detection may actually be higher than previously reported now that high resolution scanning techniques are available and patterns of DCIS on MRI are more recognized [66, 69].

6.7 Summary

Breast MRI has become an indispensable tool in breast cancer imaging. Indications have become clearer and better defined. Guidelines and recommendations are evolving, and the use of MRI is increasing as surgeons recognize the clinical benefits of performing the most sensitive imaging study, which is the only true three-dimensional imaging study involved in the diagnostic workup of breast cancer before establishing the treatment plan. Increasing use of breast MRI may also provide further insight into tumor biology, microenvironment, and outcome. Where available, breast MRI should be considered in all patients because it behooves everybody to know the disease extent as ultimately this knowledge may lead to a paradigm shift in the understanding and treatment of different breast cancers with different imaging phenotypes. On the other hand, we are limited in what we can learn without this knowledge. Breast surgeons should rely on breast MRI in a similar fashion to surgical colleagues in other fields—as it is often the test of choice (and if it is not, another three-dimensional study is performed). Compared with other imaging modalities, MRI provides knowledge that the patients deserve to have to ensure the best individualized treatment plan.

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Breast Cancer Pathology

7

Hannah Y. Wen and Edi Brogi

7.1 Introduction

Pathologists play a pivotal role in the management of patients with breast diseases, particularly in the current era of multidisciplinary and personalized treatment. The pathologist establishes the diagnosis, assesses the extent of the disease and predictive and prognostic markers, evaluates the tumor response post-neoadjuvant systemic therapy, and also incorporates the latest advances in molecular testing into routine clinical practice. This chapter provides an overview of the approach used by pathologists to examine and sample breast tissue specimens and to interpret and report the microscopic findings including the assessment of margin status and evaluation of the tumor biomarkers.

7.2 Diagnostic Procedures

The definitive diagnosis of a breast lesion is based on the histologic examination of a tissue specimen taken from the part of the breast that appears abnormal either at physical exam or in imaging studies. The histopathologic examination of a biopsy specimen aims to determine whether the area of concern is benign, atypical, or malignant. The diagnostic procedures include fine-needle aspiration biopsy, needle core biopsy, and excisional biopsy.

7.2.1 Fine-Needle Aspiration Biopsy

Fine-needle aspiration biopsy (FNA) is a minimally invasive, rapid, safe, and cost-effective diagnostic procedure. It is a minimally invasive procedure performed using a thin gauge needle and has a very low rate of complications. FNA yields a cell suspension that is smeared onto slides or concentrated into a thin layer or a cellblock. The experience of the cytopathologist plays an important role in the diagnostic interpretation of cytology preparations. Limitations of breast FNA include a high rate of unsatisfactory sampling for small nonpalpable breast lesions and the inability to reliably diagnose invasive carcinoma and accurately assess biomarker status. Due to these limitations, the utilization of FNA in the primary diagnosis of breast lesions has declined in most countries. FNA is a reliable, safe, and cost-effective alternative to needle core biopsy (CBX) in the preoperative evaluation of axillary lymph nodes and in the diagnostic evaluation of possible chest wall recurrence or distant metastases. In the metastatic setting, the assessment of breast cancer biomarkers by immunohistochemistry and/or florescence in situ hybridization [1–4] on formalin-fixed cellblock material obtained by FNA provides reliable information. FNA cytology specimens of good cellularity are usually suitable for the evaluation of genomic alterations by targeted next-generation sequencing.

7.2.2 Needle Core Biopsy

Needle core biopsy (CBX) of a breast lesion is performed to sample indeterminate/suspicious calcifications, a mass with or without associated calcifications, an area of architectural distortion, or an area of mass or non-mass signal enhancement on MRI.

If the CBX is performed to evaluate mammographic calcifications, a radiographic image of the needle cores documenting the presence of the calcifications should be submitted to the pathology laboratory together with the tissue specimen (Fig. 7.1). The pathologists reviewing the CBX slides correlate the number of foci and the extent and characteristics of the calcifications identified in the tissue sections with those of the calcifications visualized in the accompanying specimen radiograph. If the calcifi-

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_7

cations identified in the slides do not account for the number of foci, extent and characteristics of the calcifications seen in the specimen radiograph, additional evaluation is required in the form of deeper level sections of the tissue blocks containing the calcifications. An X-ray examination of the tissue blocks is most useful to locate the calcifications within the tissue blocks (Fig. 7.2). In routine hematoxylin and eosin (H&E)-stained slides, the calcified deposits rich in calcium phosphate appear as dense blue to purple aggregates (Fig. 7.3). Calcium phosphate-rich calcifications can be associated with benign, atypical, or malignant findings. Calcium oxalate crystals appear as translucent triangular or rectangular fragments ("broken glass") and are birefringent under polarized light. Calcium oxalate deposits are usually located in the lumen of cysts, particularly apocrine cysts, and do not associate with malignant findings (Fig. 7.4). In the final diagnostic report of a CBX specimen that sampled an area of calcifications, the pathologist needs to comment on their presence and specify their association with benign, atypical, or malignant findings.

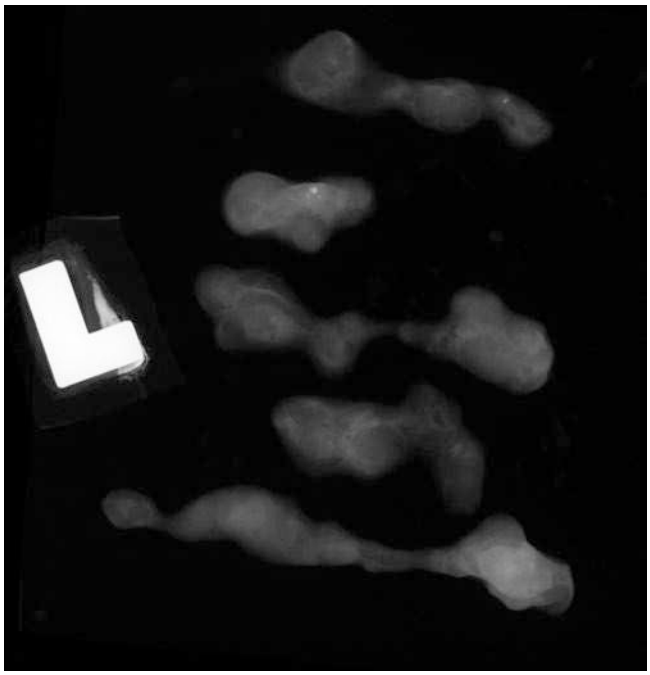

Fig. 7.1 Breast stereotactic biopsy specimen radiograph

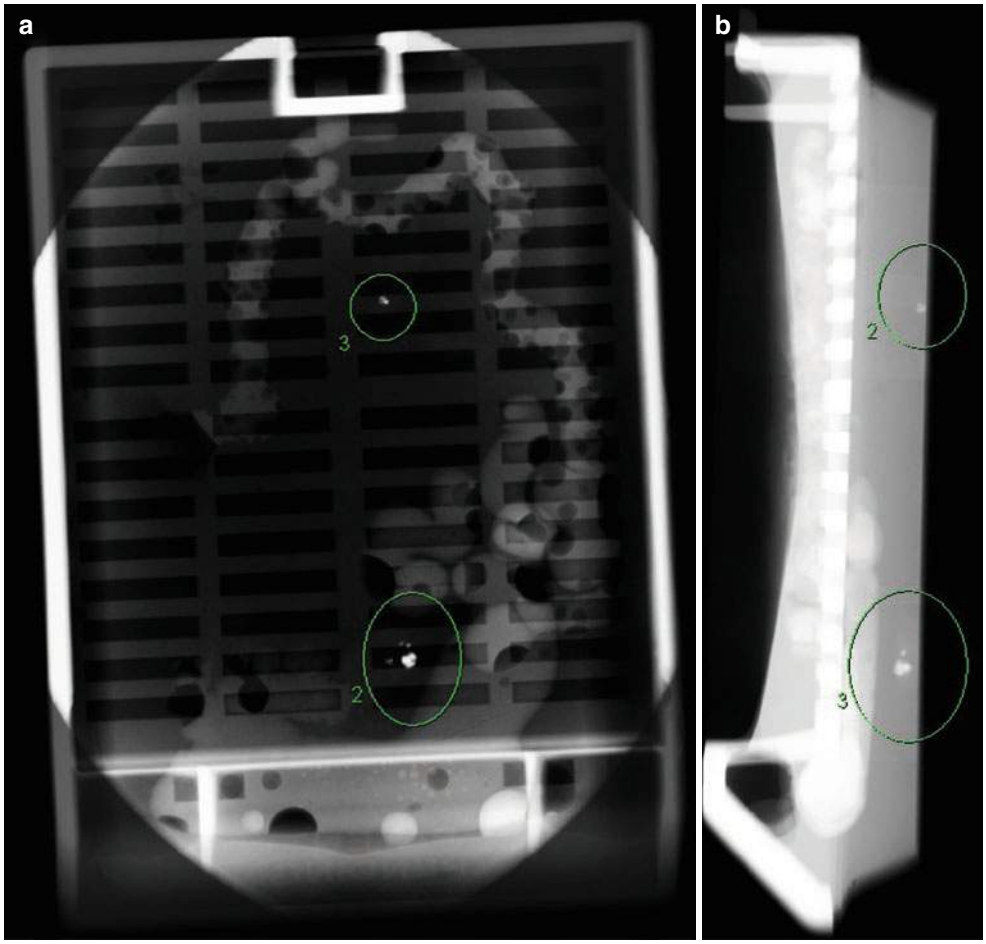

Fig. 7.2 Examination of tissue blocks by X-ray to localize the foci of calcifications. The side view in panel (**b**) illustrates the depth of the calcifications in the block, which helps to determine the depth of sectioning of the tissue block and expedites the histologic identification of the calcifications

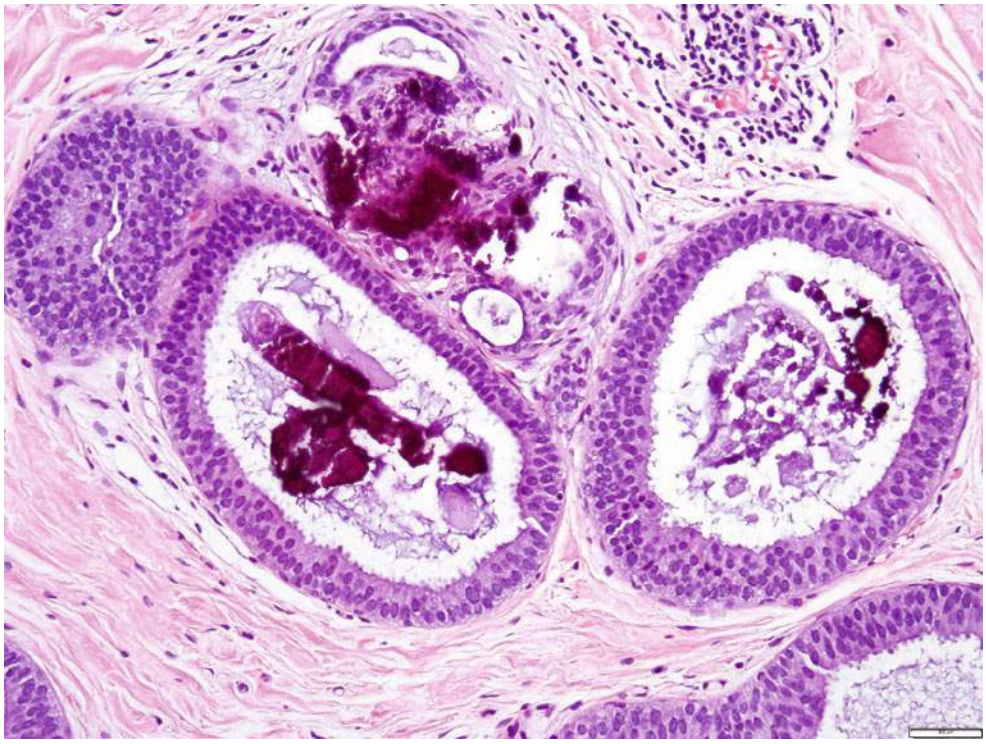

Fig. 7.3 Calcifications (calcium phosphate). Calcium phosphate deposits are associated with columnar cell change with atypia identified in a core needle biopsy

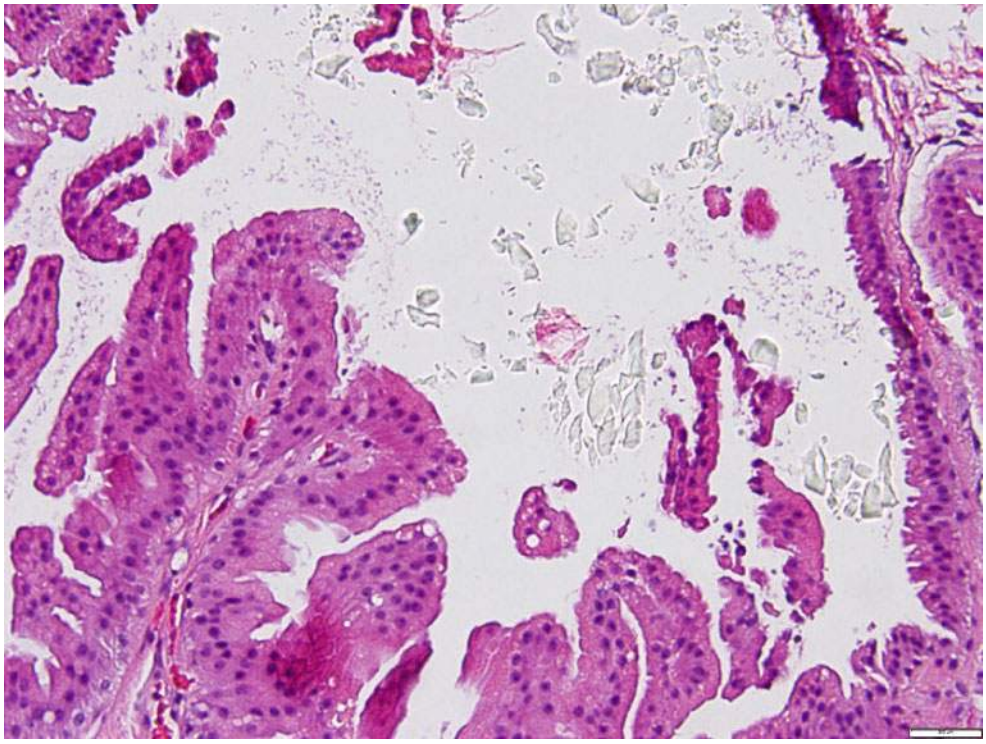

Fig. 7.4 Calcifications (calcium oxalate). Calcium oxalate crystals appear as translucent "broken" glass. They are typically present in the lumen of apocrine cysts

If a CBX was performed to evaluate a mass lesion, and the histologic findings do not account for the latter, further evaluation is required, either as repeat CBX or surgical excision of the mass lesion.

If invasive carcinoma is present in a core needle biopsy, the pathologist reports the histologic subtype and the grade of the invasive carcinoma. The size of the invasive carcinoma in the CBX material often underestimates the actual size of the invasive carcinoma, but it is useful in correlating the histopathologic findings with the clinical and/or radiologic characteristics of the lesion for optimal patient management. In particular, neoadjuvant chemotherapy is not indicated if the CBX specimen of a mass lesion yields only micro- or minimally invasive carcinoma in a background of mass-forming DCIS [5, 6].

The diagnosis of atypical ductal hyperplasia (ADH) on review of CBX material mandates surgical excision of the target lesion to further assess the extent of the atypical ductal proliferation. Flat epithelial atypia (FEA)/columnar cell change with atypia is an alteration of the terminal duct lobular unit. The glandular epithelium shows low-grade nuclear atypia but lacks a complex architecture. FEA may be found in stereotactic needle CBX specimens evaluating indeterminate calcifications detected at mammography. The management of patients with flat epithelial atypia (FEA)/columnar cell change with atypia in CBX material remains controversial. Surgical excision of the target lesion is usually recommended at most centers, but the reported rates of upgrade to carcinoma (invasive carcinoma and/or DCIS) at surgical excision vary greatly in different studies [7–23], and some investigators suggest that close radiologic follow-up might be an adequate management in some patients [19–25], especially if the CBX procedure has removed all mammographic calcifications [9, 17, 18, 24, 25].

Controversy also exists regarding the management of patients with radiologic-pathologic concordant CBX diagnosis of atypical lobular hyperplasia (ALH) and classical lobular carcinoma in situ (LCIS) not associated with other high-risk lesion. In a study of 72 consecutive patients who underwent surgical excision following a CBX diagnosis of LCIS or ALH with concordant radiologic-pathologic findings, there were only 2 (3%) cases of carcinoma (invasive carcinoma or DCIS) [26]. Other investigators also reported 1–4% upgrade rate in similar cases [27–30]. In contrast, the rate of upgrade to carcinoma at surgical excision of ALH/classic LCIS in patients with discordant radiologic-pathologic findings ranges from 18 to 38% [26, 29]. If the needle CBX yields a morphologic variant of LCIS, namely, pleomorphic LCIS and LCIS with necrosis, surgical excision is recommended. Surgical excision of variant LCIS diagnosed at CBX yields (micro)invasive carcinoma in 25–53% of cases [31–34]. Given the frequent association of LCIS variants and (micro)invasive lobular carcinoma, the use of immunohistochemical stains for myoepithelial markers and cytokeratins (such as pancytokeratin and/or cytokeratin 7) should be considered to rule out microinvasion in a CBX sample yielding a LCIS variant, as the (micro)invasive lobular carcinoma can be extremely subtle and/or mimic inflammatory cells.

If the histologic findings in the CBX material are benign and they are deemed concordant with the features of the imaging target, follow-up surgical excision is not required, with only few notable exceptions.

Microglandular adenosis (MGA) is an infiltrative proliferation of benign-appearing monostratified glands devoid of myoepithelium [35–37]. It can present as a palpable mass, or a MRI-detected lesion, or is an incidental finding in a breast specimen targeting another lesion. Rare cases of MGA are reported in BRCA1 germline mutation carriers [38]. Even though MGA is an infiltrative glandular proliferation devoid of myoepithelium and can be extensive, it lacks cytologic atypia and is regarded as a "benign" lesion. MGA, however, often harbors foci of atypia and frequently is found in association with triple-negative invasive carcinoma. Recent evidence suggests that MGA shares similar genetic alteration with MGA-associated triple-negative invasive carcinoma and should be regarded as a non-obligate morphologic precursor of the latter [39–41]. Surgical excision of an imaging target/lesion yielding MGA at CBX is mandated even in the absence of any cytologic atypia.

Surgical excision of the mass is usually recommended if the histologic findings in the CBX material show a fibroepithelial lesion of uncertain classification, to rule out the possibility of a phyllodes tumor. Few retrospective series have evaluated morphologic parameters in CBX material of fibroepithelial lesions and correlated the findings with the diagnosis of phyllodes tumor in the follow-up surgical excision specimen, but no single morphologic feature or combination thereof was definitively predictive [42–49].

The need for surgical excision following CBX diagnosis of papilloma without atypia is also a subject of debate. In contrast to historical data, few contemporary series have documented a low rate of upgrade at surgical excision of papilloma without atypia diagnosed at CBX if the radiologic and pathologic findings are concordant. A retrospective series evaluating 171 patients with radiologic-pathologic concordant CBX diagnosis of intraductal papilloma without atypia documented a 2.3% (4/171) rate of upgrade to carcinoma (DCIS and/or invasive carcinoma) at subsequent surgical excision [50]. Other recent series also reported low rates of upgrade in cases with radiologic-pathologic concordance [51–55], but some investigators still recommend excision based on upgrade rates of 6–14% [56–61]. Some recent retrospective series reported a low rate of upgrade at surgical excision of radiologic-pathologic concordant lesions yielding a CBX diagnosis of radial scar without epithelial atypia

[62–71]. When the information on the upgrade rates at excision of benign lesions diagnosed at CBX needs to be interpreted with caution. In particular, careful assessment of radiologic-pathologic concordance is required to decide whether surgical excision can be safely spared.

7.2.3 Excisional Biopsy

A diagnostic excisional biopsy is performed if the radiologic-pathologic findings at CBX are discordant or the mammographic calcifications are not amenable to stereotactic biopsy. The rate of radiologic-histologic discordance at percutaneous CBX ranges between 1% and 8% [72–78] and is dependent on the characteristics of the radiologic target and the individual's experience. Radiologic-pathologic discordance at CBX mandates re-biopsy or surgical excision of the imaging target. In this setting, the prevalence of carcinoma at re-biopsy/excisional biopsy ranges from 0 to 100% in different series, with average rate of 14% [78].

7.2.4 Intraoperative Frozen Section

The breast is rich in adipose tissue. Fatty tissue does not freeze well at the temperature that is best for cutting non-fatty tissue and therefore is difficult to section. Incomplete sectioning or folding can affect the microscopic evaluation of frozen tissue. Intraoperative evaluation by frozen section technique thus finds limited applications in the primary diagnosis of breast lesions. In the context of nipple-sparing mastectomy, the nipple margin is often evaluated intraoperatively the nipple-areolar complex is removed if carcinoma (invasive carcinoma and/or DCIS) is identified in the nipple margin specimen. Intraoperative evaluation of the margin status in patients undergoing breast-conserving surgery is performed at some centers, but its utility remains debated, particularly in light of the recent recommendations regarding margin assessment for DCIS [79] and invasive carcinoma [80] and the multidisciplinary approach to patient management.

Following the publication of the results of the ACOSOG Z0011 study [81], patients with T1-T2 invasive carcinoma and clinically negative axillary lymph nodes (ALNs) (cN0) who are managed with breast-conserving surgery (BCS) and whole-breast irradiation, undergo ALN dissection only if metastatic carcinoma is identified in at least three (sentinel) lymph nodes. In this context, intraoperative evaluation of the sentinel lymph nodes (SLNs) is not performed routinely. At most centers, intraoperative evaluation of the SLN(s) is usually performed in patients undergoing mastectomy and in cN0 patients who do not meet the ACOSOG Z0011 selection criteria. At many centers, intraoperative evaluation of SLN(s) is also obtained in patients undergoing definitive surgery (either BCS or mastectomy) after completion of neoadjuvant chemotherapy. In all cases, the prosection of SLN(s) follows the same standard protocol. Each SLN is sliced at 2 mm intervals parallel to its longest axis, and all the tissue slices are examined (see also paragraph on SLN evaluation). Frozen section, touch preparation, or smear cytology can be used for intraoperative evaluation with comparable results [82]. The identification of single cells and clusters of carcinoma spanning less than 0.2 mm in greatest dimension or containing fewer than 200 cells in a single lymph node section is classified as pN0(i+) [83, 84] and should not prompt ALN dissection in a patient who has not received neoadjuvant systemic therapy. In the post-neoadjuvant therapy setting, a similar amount of residual carcinoma in a lymph node is classified as ypN0(i+) [84], but constitutes evidence of residual metastatic disease, and should prompt ALN dissection or axillary radiotherapy.

7.3 Gross Examination and Handling of Surgical Specimens

7.3.1 Lumpectomy or Partial Mastectomy

In the past, presurgical localization of nonpalpable breast lesions involved placing a localizing wire near the target lesion under radiologic guidance. Recently, other techniques have been introduced to localize the lesion for surgical excision. Currently, I^{125} radioactive seed(s) localization (Fig. 7.5) has replaced needle wire(s) localization at many institutions, including ours [85–87]. Using appropriate imaging guidance, the I^{125} radioactive seed is placed within the lesion to be surgically removed. Multiple seeds are used to localize multiple foci of lesions or bracket a large area of lesions such as extensive DCIS or calcifications. At the time of surgery, the surgeon uses an appropriate gamma probe to identify the radioactive seed at the nonpalpable surgical target, which is removed together with the lesion. An intraoperative X-ray evaluation of the surgical specimen is obtained to document removal of the radioactive seed (and of any marker clip placed at the time of the CBX). In rare cases, the radioactive seed may be lost or not removed at the time of surgery [85, 88]. The breast specimen containing the radioactive seed is immediately delivered to the pathology department together with a copy of the specimen radiograph. Radioactive hazard tags on the specimen container and on the pathology requisition form specify the number of radioactive seeds (one or more) present in the specimen. The prosector first examines the specimen radiograph to verify the presence and number of the radioactive seed(s), as well as the shape and number of clips in the specimen. Radiographically, the radioactive seed appears as a 4× 0.8 mm radiopaque metal bar with slightly

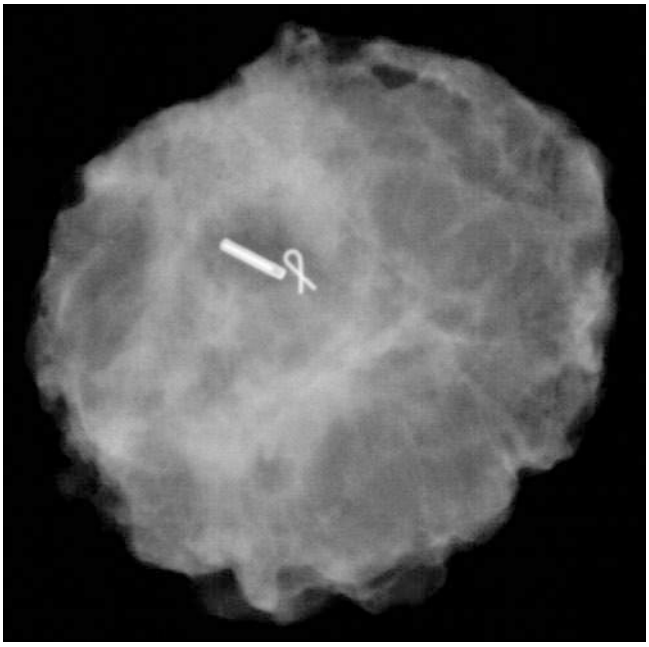

Fig. 7.5 Lumpectomy specimen with radioactive seed. The specimen radiograph of a lumpectomy specimen shows a radioactive seed (linear opacity) adjacent to a ribbon-shaped biopsy clip

translucent tips. The prosector uses a gamma probe to verify the presence and location of the radioactive seed(s) within the specimen, then inks the surface of the specimen (as per protocol) and slices the specimen, and identifies and removes the radioactive seed(s). The radioactive seed(s) is/are placed in a plastic bag labeled with a tag indicating the patient's name and the part and number of the surgical specimen. The bag with the radioactive seed(s) is stored in a lead container, which is periodically disposed by the radiation safety personnel. The prosector always document retrieval of the radioactive seed(s) in the appropriate log to account for all the radioactive seeds received in the laboratory and document chain of custody [88]. The radioactive seed has a sturdy outer shell of titanium, very resistant to injury. The I^{125} could become airborne if the outer shell is cut through, which may cause contamination of the work area and of the personnel handling the seed. This scenario is exceedingly rare, but it is important to be aware of this possibility, particularly when the tissue specimen is extensively calcified [89]. After removing and storing the radioactive seed(s), the prosector uses the gamma-counter to scan the tissue specimen and the work area to make sure that no radioactivity leaked from the seed [87].

The pathologist is responsible for margin assessment and evaluation. If the surgeon specifies the orientation of a breast specimen (usually by placing two sutures: short suture = superior aspect; long suture = lateral aspect), the prosector applies ink of different colors to the six surfaces (anterior, posterior, medial, lateral, inferior, and superior). This method is imperfect, as the shape of a breast specimen changes significantly after the tissue is removed from the patient, is significantly flattened if the specimen is X-rayed. The shape also varies depending on the positioning of the tissue specimen on flat surface. No physical landmark separates two adjacent margins, and by default inking of the different margin surfaces with different colors cannot be absolutely accurate. Furthermore, mixing of inks of different colors can limit the definitive microscopic identification of a margin. An alternative method of margin assessment relies on the surgeon submitting each shaved margin as a separate specimen. In this scenario, the surgeon removes the breast lesion and can submit the specimen without orienting sutures; the main lumpectomy specimen can be inked uniformly with ink of one color (usually black ink). After removing the lesion in the main specimen, the surgeon resects each margin from the wall of the lumpectomy cavity and submits it with its specific and unequivocal designation. The surgeon places a stitch or a clip on the surface representing the final margin, and the latter is inked with one color. The margin specimen is serially sectioned and submitted entirely (or representatively sampled according to a protocol that needs to be validated in each laboratory), so that each section shows a portion of the final inked margin surface. The prosector needs to be aware of the patient's relevant clinical history, including prior breast needle core biopsy procedures and the corresponding diagnoses; the prosector also needs to review the specimen radiograph. The prosector sections the lumpectomy specimen into at 3–4-mm-thick slices and assesses the presence of abnormal areas by gross inspection, palpation, and correlation with the specimen radiograph. The prosector records the size, shape, color, consistency, and texture of any grossly evident lesion and its relationship with the needle core biopsy site(s), marker clip(s), and radioactive seed(s) present in the specimen. If more than one lesion is present in the specimen, the prosector records the characteristics of each lesion separately and documents their spatial relationships. All grossly identified lesions are submitted for histologic evaluation, either entirely or representatively; the breast tissue located in between the lesions is also sampled.

The largest span of a tissue piece that can be placed in a standard histology cassette and onto a standard glass slide is about 2.0–2.5 cm. Most tumors measuring up to 2.0–2.5 cm in greatest dimension are entirely and sequentially submitted for histologic evaluation, and the tissue section spanning across the largest diameter of the tumor is used to measure the size of the invasive carcinoma microscopically (Fig. 7.6). If the tumor is larger than 2.5 cm, a complete cross section through its largest diameter is blocked out and submitted in

two or more tissue blocks (Fig. 7.7), and this information is documented in the gross description of the case. In particular, the adjacent cut surfaces are painted with ink of the same color to facilitate piecing together the tumor at the time of microscopic examination, so that the tumor size can be verified (Fig. 7.7b). Representative sections of grossly unremarkable breast tissue are also submitted for histologic examination. Tissue specimens up to 5 cm in greatest dimension are usually submitted entirely. If a specimen is larger than 5 cm, at least one section per centimeter of the tumor is submitted and representative sections of the surrounding grossly unremarkable breast tissue are also submitted. More extensive specimen sampling is indicated following a core needle biopsy diagnosis of DCIS to exclude the possibility of stromal invasion, and in some cases the entire specimen may be submitted.

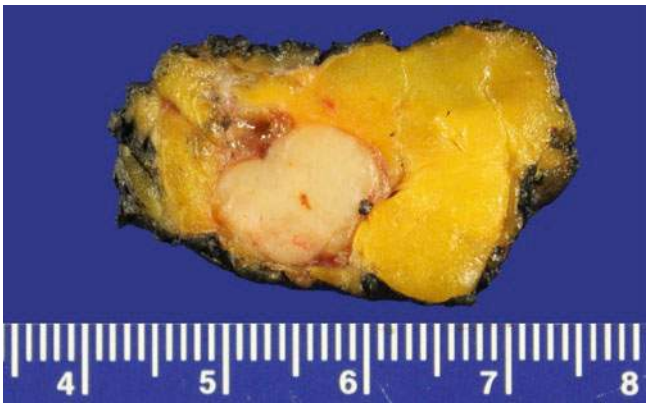

Fig. 7.6 Prosection of a specimen containing a small tumor. A complete cross section of a small tumor and adjacent tissue can be submitted in one tissue cassette, and it can be entirely visualized in the corresponding tissue section

If no grossly evident lesion is identified macroscopically (i.e., excision of non-mass forming DCIS), the entire specimen should be submitted in sequential order. If the specimen is too large for complete histologic evaluation, the entire biopsy site and surrounding tissue (about 2- to 3-cm-wide radius) need to be evaluated, with extensive sampling of the surrounding breast tissue. Review of the specimen radiograph and/or radiologic findings, such as the extent of mammographic calcifications, is necessary to identify the lesion and to determine the extent of the lesion. At the time of prosection, the number of tissue slices across the largest dimension of the specimen is recorded. If the specimen is not submitted entirely, the gross description of the case should specify the tissue slice from which each tissue block was submitted. The pathologist correlates the microscopic findings with the gross description of the case and estimates the extent of disease by multiplying the number of tissue slices with microscopic evidence of tumor by the thickness of the tissue slices.

When cavity shave margins are excised, each margin specimen is a flattened piece of tissue with one side marked with a suture or clip as the new margin. The tissue surface designated as the final margin is inked, and the specimen is sectioned with cuts perpendicular to the inked margin surface. Each margin specimen is submitted entirely. If a margin specimen is large and its complete evaluation would require submitting numerous tissue blocks, each laboratory should work out a reasonable algorithm for optimal sampling of the tissue. If carcinoma or atypia is present in the representative sections, and a large margin specimen was only representatively submitted, all of the remaining tissue, or at least all the inked tissue surface, should be evaluated histologically for the definitive assessment of the margin status. If carcinoma is present, the distance of invasive and /or in situ carcinoma to the closest inked margin is reported.

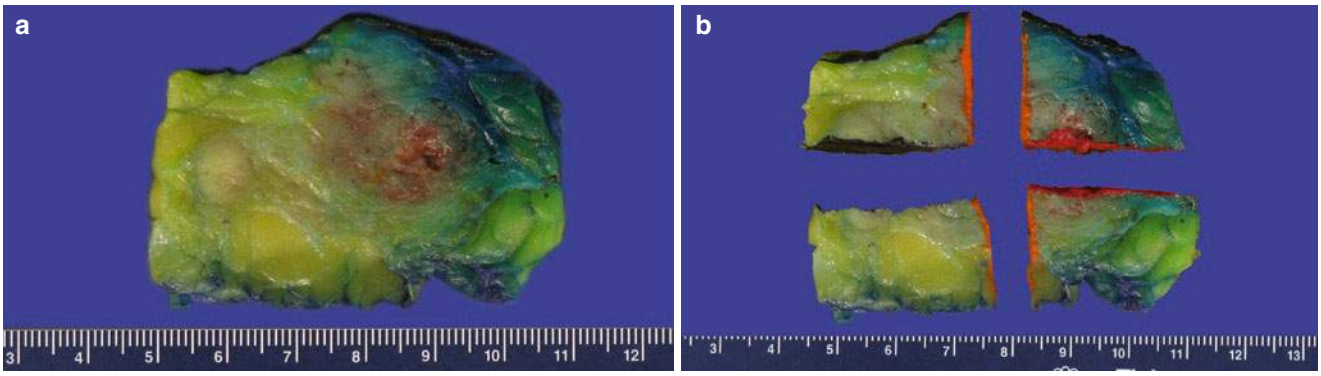

Fig. 7.7 Prosection of a specimen containing a large tumor. Tissue slice encompassing the largest diameter of a tumor which cannot be accommodated entirely in a single cassette (**a**). The slice of tissue shown in (**a**) is blocked out into smaller pieces that are then submitted in multiple cassettes. Matching colored ink is applied to the paired cutting edges of the adjacent tissue pieces so that the cut surfaces can be accurately matched when the slides are reviewed microscopically, to ensure appropriate reassembly of the tumor and its accurate microscopic measurement (**b**)

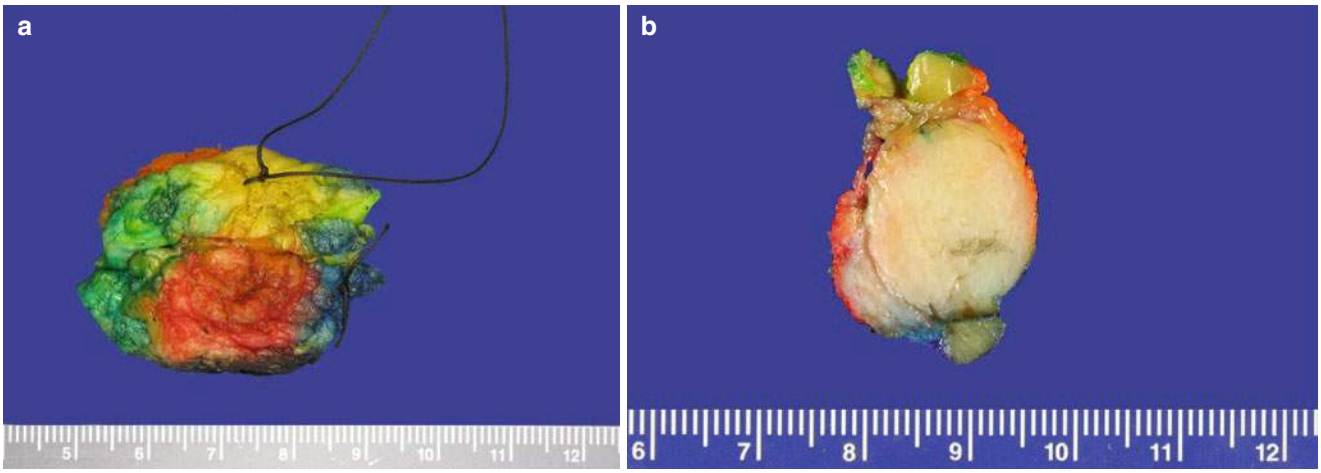

Fig. 7.8 Prosection of an oriented lumpectomy specimen. (**a**) The specimen is differentially inked in six colors to designate the six margins. (**b**) A cross section of the specimen shows the lesion with the adjacent inked margins

If cavity shave margins are not resected, the surgeon usually designates the superior margin of an oriented lumpectomy with a short suture or one clip and the lateral margin with a long suture or two clips. The specimen is inked in the pathology laboratory with six colors to designate the six margins (Fig. 7.8). Alternative techniques for inking the specimen using fewer colored inks exist, but they tend to be more cumbersome and possibly more prone to misinterpretations. Once the specimen has been inked, it is serially sectioned, examined, and sampled akin to an excision specimen received with no orienting marks. If feasible, a section of the lesion with the adjacent closest inked margin is submitted (Fig. 7.8b). If the specimen is large (>5 cm), any gross lesion and/or mass is entirely or representatively submitted. The margins are also sampled, with more extensive sampling of the surface(s) closest to the lesion(s).

Studies have shown that the re-excision rate is significantly reduced if the surgeons submit additional margin specimens taken all around the lumpectomy cavity [90–93] rather than simply excising the lesion in one lumpectomy specimen. In a prospective randomized controlled trial involving 235 patients with stage 0–III breast cancer treated with BCS, patients in the additional shave margin group had significantly lower rate of positive margin than those in the no shave margin group (19% vs 34%, respectively; $p = 0.01$) and significantly lower rate of second surgery for margin clearance (10% vs 21%, $p = 0.02$) [92]. There was no significant difference in the rate of complications and in patients' perception of cosmetic outcomes between the two groups [92].

According to the guidelines issued by the Society of Surgical Oncology and American Society for Radiation Oncology [80], a "positive margin" is defined as "ink on tumor." Conversely, "no ink on tumor" constitutes adequate margin in patients with stage I–II invasive breast carcinoma treated with BCS and whole-breast irradiation. Even though obtaining a wider margin clearance is not required routinely, it may be appropriate in cases with extensive intraductal component (EIC), with multiple close margins, or in younger patients [80]. DCIS should be excised with at least 2-mm-wide margin [79]. The aforementioned guidelines notwithstanding [79, 80], pathologists report margin status as recommended by the College of American Pathologists: a margin should be reported as positive when there is ink touching invasive cancer or DCIS, and the location (superior, inferior, medial, lateral, inferior, superior, anterior, and posterior) of the positive margin should be specified. If no tumor is present at ink ("negative" margin, from a surgical point of view), the actual distance of invasive cancer and/or DCIS to the closest margin(s) needs nonetheless to be specified [94].

7.3.2 Mastectomy (Total, Modified Radical, and Nipple-Sparing)

The gross examination of mastectomy specimen requires knowledge of the clinical indications that led to mastectomy, including information on any prior breast needle core biopsy or surgery, the number and location of the lesion(s) present, and if the patient has received neoadjuvant treatment for breast carcinoma or carries a germline mutation associated with high risk of breast carcinoma. A mastectomy specimen is received oriented, with a suture designating the axillary tail. At our institution, the surgeon also places a suture at the 12 o'clock position. The nipple and areola are present on the anterior aspect of total, simple, and modified radical mastectomy specimens. The deep margin of the mastectomy is inked. In our laboratory, we also paint the anterior surface of a mastectomy specimen. We apply blue ink on the anterior-superior surface of the specimen and green ink on the anterior-inferior surface (Fig. 7.9). The nipple is shaved off, perpendicularly sectioned, and entirely submitted. A section of the nipple base is submitted en face. The specimen is then

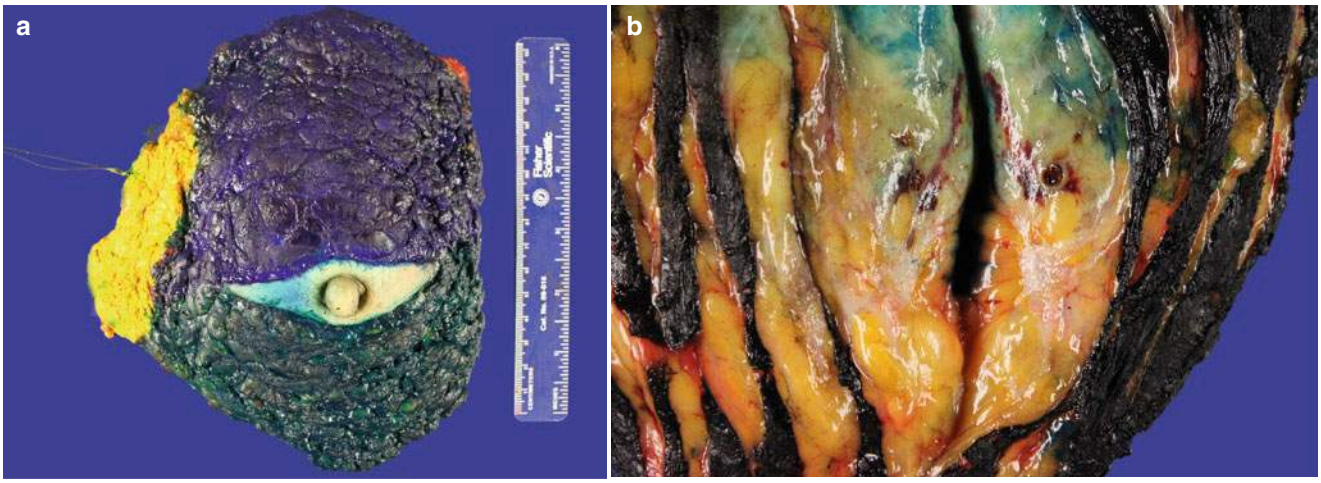

Fig. 7.9 Prosection of a mastectomy specimen. (**a**) The mastectomy specimen is received with a long stitch designating the axillary aspect and a short stitch designating the 12 o'clock aspect (not shown). The deep margin of the mastectomy is inked (not shown). At our institution, the anterior surface of a mastectomy specimen is also inked (anterior-superior = blue ink; anterior-inferior = green ink). We also ink the axillary aspect of the specimen (yellow ink) for reference purpose. (**b**) The mastectomy specimen is serially sectioned from the posterior aspect (black ink) at approximately 0.5 cm intervals to identify the lesion(s)

serially sectioned with sagittal cuts from the posterior aspect of the specimen at approximately 0.5 cm intervals (Fig. 7.9b). The prosector examines each tissue slice and describes any grossly evident lesion(s), recording its size, border, firmness and consistency, and its location within the breast (quadrant and/or o'clock axis), the distance from the nipple, skin, and the deep margin. If more than one lesion is identified, the distance between the lesions is also recorded. All lesions are sampled, and sections of the lesion(s) in relation to the closest inked margin are submitted. A section of the deep margin is submitted. If the tumor mass approaches the deep margin or the anterior surface of the specimen, sections of the aforementioned areas are submitted for histologic evaluation. Two representative sections are submitted from each quadrant of the breast that shows no obvious abnormality. A modified radical mastectomy has an attached portion of axillary soft tissue with level I and II lymph nodes. Sometimes the soft tissue specimen containing the axillary lymph nodes is not attached to the mastectomy, but it is submitted to the pathology department in a separate container. All lymph nodes are dissected, thinly sliced at 2 mm intervals, and entirely submitted. The total number of lymph nodes, and the presence of matted lymph nodes, and the size of the largest lymph node are recorded. In all mastectomy specimens, the axillary tail is always examined to rule out the presence of lymph nodes. If any lymph node is identified, it is sliced at 2 mm interval and entirely submitted for histologic evaluation.

The surgeon designates the nipple margin of a nipple-sparing mastectomy specimen with a suture. The prosector identifies this area, applies ink, and submits the tissue for histologic evaluation with a clear designation in the gross description of the case, so that the nipple margin can be appropriately identified and reported.

A risk-reducing (so called "prophylactic") mastectomy is usually a simple or nipple-sparing mastectomy. It is performed in women who are at high risk of developing breast cancer, including women with documented BRCA1 or BRCA2 germline mutation, women with strong family history of breast cancer, or women with personal history of contralateral breast cancer. By definition, a risk-reducing mastectomy specimen contains no carcinoma, although occasionally microscopic examination may identify small foci of DCIS and/or invasive carcinoma. The breast is thinly sectioned and carefully examined. If the patient has no personal history of DCIS and/or invasive carcinoma, we sample any grossly evident lesion(s) and submit four representative tissue sections from each breast quadrant. If the patient had risk-reducing mastectomy for contralateral carcinoma, we sample any grossly evident lesion(s) and submit only two sections per quadrant. We do not routinely submit sections from the deep margin and the nipple/areola and skin, but if microscopic evidence of DCIS and/or invasive carcinoma is identified in the slides of a risk-reducing mastectomy specimen, the latter is retrieved, and sections of the nipple and deep margins are submitted for complete histologic evaluation.

7.3.3 Breast-Conserving Surgery or Mastectomy After Neoadjuvant Chemotherapy

Pathologic complete response (pCR) has been used as an endpoint for neoadjuvant trials, but there are different definitions of pCR. The FDA currently regards the absence of residual invasive carcinoma in the breast and of residual disease in the axillary lymph node(s) as pCR and regards it as

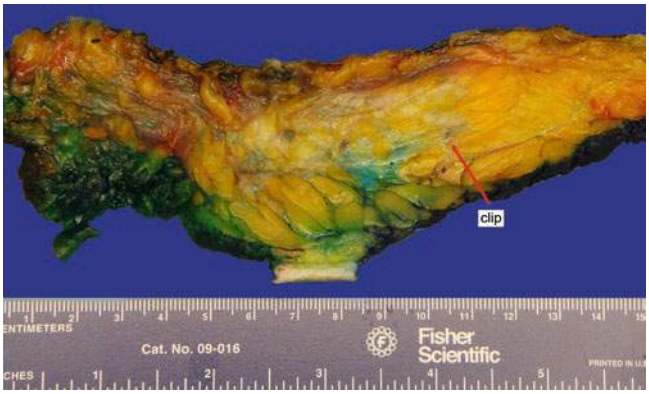

Fig. 7.10 Tumor bed in a mastectomy specimen obtained post-neoadjuvant chemotherapy. The biopsy clip is identified within the tumor bed

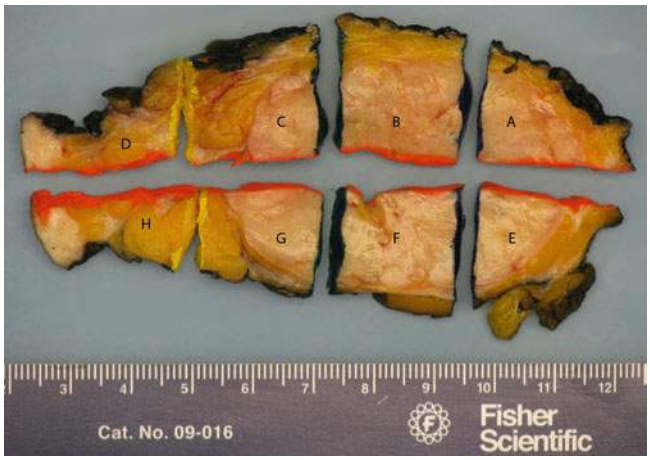

Fig. 7.11 Sampling of the tumor bed in a (mastectomy) specimen obtained post-neoadjuvant chemotherapy. A complete cross section through the largest diameter of the tumor bed is blocked out and submitted in multiple cassettes. Matching colored ink is applied to the paired cutting edges of the adjacent tissue pieces so that the cut surfaces can be accurately matched when the slides are reviewed microscopically, to ensure appropriate reassembly and measurement of the tumor/tumor bed area. Each tissue piece (A through H) is submitted in a cassette, and the corresponding section code is recorded in the gross description of the case

an acceptable criterion for expedited drug approval. According to the aforementioned definition, the presence of residual DCIS does not rule out pCR. Lymphovascular invasion is a form of invasive carcinoma, and its presence rules out pCR.

Only the pathologic evaluation of post-neoadjuvant specimens can reliably assess the response of the carcinoma to the treatment. If the invasive carcinoma responds completely to the neoadjuvant treatment, the area of the breast where the carcinoma previously resided shows some macroscopic and microscopic stromal alterations and appears somewhat different from the adjacent normal breast tissue. The area of the breast where the invasive carcinoma resided before treatment is referred to as "tumor bed." It is important to identify the tumor bed grossly, as it provides an estimate of the size of the untreated invasive carcinoma, and it is the area of the breast that needs to be sampled to rule out the possibility of microscopic foci of residual carcinoma. The tumor response to neoadjuvant therapy tends to be discontinuous, and residual viable carcinoma can consists of single cells and small clusters scattered throughout the tumor bed (Fig. 7.10).

Review of radiologic findings before (and after) neoadjuvant treatment is fundamental to know the size and location of the tumor(s)/residual tumor(s) and of any biopsy clip(s) that can guide the macroscopic identification of the tumor bed. This information should be made available to pathologists together with the post-neoadjuvant surgical specimens [5, 6, 95].

The prosector identifies and records the two largest dimensions of the tumor bed(s) and submits entirely its largest cross section for microscopic examination. It is recommended to retain an image (either a drawing or a photograph) of the sliced specimen with a map of the macroscopic alterations from which the tissue sections are submitted and annotations of the different areas sampled (Fig. 7.11) [5, 6]. Small lumpectomy specimens showing no gross evidence of residual carcinoma should be submitted in their entirety. For large lumpectomy or mastectomy specimens, full-face cross sections should be taken every 1 cm of the tumor bed area, up to a total maximum of 25 blocks [6].

Few different grading schemes have been proposed to quantify the tumor response to neoadjuvant treatment and try to predict the patient's prognosis [95]. The Residual Cancer Burden (RCB) is a prognostic index predictive of the survival of a patient who received neoadjuvant chemotherapy. The calculation of the RCB is based on multiple pathologic parameters, including the size of the largest tumor bed (two-dimensional measurement), the overall cancer cellularity (estimated as an average of the residual tumor cellularity in the tumor bed compared to reference diagrams), the percentage of residual carcinoma that consists of DCIS, the number of lymph nodes with residual carcinoma, and the size of the largest nodal metastasis [96].

7.3.4 Pre-analytic Standardization: Tissue Handling, Type of Fixative, and Duration of Tissue Fixation

The cold ischemia time is the time between surgical removal of the tissue from the patient to the time when the tissue is placed in formalin for fixation. The breast specimen needs to be placed rapidly in an adequate amount of fixative to ensure adequate tissue and antigen preservation, in particular of the estrogen receptor (ER), progesterone receptor (PR), and HER2 proteins. The American Society of Clinical Oncology and College of American Pathologist (ASCO/

CAP) guidelines recommend that the cold ischemia time be shorter than 1 h [97, 98]. Longer cold ischemia time causes a reduction in the staining intensity and percentage of tumor cells showing reactivity for ER, PR, and HER2 by immunohistochemistry [99, 100]. It is recommended that 10% neural buffered formalin (NBF) be used to fix breast tissue specimens to ensure comparable results and optimal immunoreactivity [97, 98]. To ensure adequate tissue penetration, the specimen needs to be cut into 2–4-mm-thick tissue slices and fixed in 10% NBF for at least 6 h, but no longer than 72 h before processing [97, 98].

7.4 Pathologic Features (Type, Size, Grade)

7.4.1 Type

Breast cancer is a heterogeneous disease and consists of different entities with distinct morphology, biological characteristics, and clinical behaviors. According to WHO classifications of the tumors of the breast [101], breast tumors are divided into epithelial tumors, mesenchymal tumors, and fibroepithelial tumors. Epithelial tumors (=carcinomas) are the most common type. They derive from the epithelium lining the breast ducts or lobules and are classified as ductal or lobular carcinoma.

7.4.1.1 Ductal Carcinoma In Situ (DCIS)

Ductal carcinoma in situ (DCIS) is a neoplastic proliferation of epithelial cells confined to the mammary ducts and ductal lobular units, with no invasion into the surrounding stromal tissue. DCIS is a non-obligate morphologic precursor to invasive breast carcinoma, usually of ductal morphology. It accounts for 20–25% of all newly diagnosed breast cancers in the USA [102]. Most cases of DCIS in industrialized countries are clinically asymptomatic, and they are detected by screening mammogram due to the presence of associated calcifications. Much of the increase in the incidence of DCIS in the last two decades is due to the implementation of mammographic screening. DCIS is a very heterogeneous group of lesions. The pathological classification of DCIS is based on architectural pattern, nuclear grade, the presence of necrosis, and additional cytomorphologic features. The architectural patterns of DCIS include solid, cribriform, micropapillary, papillary, solid-papillary, and flat (clinging) (Fig. 7.12); different architectural patterns often coexist in any given case. Necrosis is common in DCIS of intermediate and high nuclear grade. The so called "comedo DCIS" refers to DCIS with solid growth pattern, high nuclear grade, and central necrosis (Fig. 7.13). Modern classifications stratify DCIS based on its nuclear characteristics, including nuclear size and pleomorphism into low, intermediate, and high grade [103].

DCIS of low nuclear grade is composed of small monomorphic cells with smooth nuclear contour, fine dispersed chromatin, and inconspicuous nucleoli (Fig. 7.14a). Mitotic figures are rare. The cells of low-grade DCIS are typically polarized in a gland-like arrangement. The calcifications associated with low-grade DCIS are often small and laminated (Fig. 7.14a). Necrosis is uncommon. DCIS of intermediate nuclear grade consists of cells with intermediate-sized nuclei showing mild to moderate variation in size and shape, variably coarse chromatin, and evident but inconspicuous nucleoli (Fig. 7.14b). Mitotic activity may be present, but it is rarely high. Necrosis and calcifications tend to be present. DCIS of high nuclear grade consists of cells with large and pleomorphic nuclei, irregular nuclear contour, coarse or vesicular chromatin, and prominent nucleoli (Fig. 7.14c). Mitotic activity is easily detected. Necrosis is common. Periductal stromal fibrosis and inflammation are common around high-grade DCIS, which sometimes presents clinically and/or radiologically as a mass lesion. High-grade DCIS is associated with higher risk of local recurrence and progression to invasive carcinoma than low-grade DCIS [104–106]. Other risk factors include young age, symptomatic detection, and positive margin.

Special cytomorphologic variants of DCIS include apocrine, spindle cell DCIS, and solid-papillary DCIS. The cells of apocrine DCIS have enlarged nuclei with prominent nucleoli and abundant eosinophilic or granular cytoplasm (Fig. 7.15). Spindle cell DCIS is composed of monomorphic spindle cells with low to intermediate nuclear grade (Fig. 7.16) and sometimes can mimic the appearance of usual ductal hyperplasia. Solid-papillary DCIS consists of a proliferation of neoplastic ductal cells with low to intermediate nuclear grade, arranged in solid sheets around filiform fibrovascular cores (Fig. 7.12e). The neoplastic cells sometimes show a palisading "picket fence" arrangement along the fibrovascular cores. Spindle cell and solid-papillary DCIS sometimes coexist. They can express neuroendocrine markers such as chromogranin, synaptophysin, and neuron-specific enolase.

Paget's disease of the nipple is characterized by the presence of adenocarcinoma cells (Paget cells) within the squamous epithelium of the nipple (intraepidermal adenocarcinoma). The most common clinical presentation is an eczematous and/or erythematous alteration of the nipple and areola, sometimes with nipple ulceration (Fig. 7.17a). On histologic examination, the Paget cells are atypical cells with abundant pale cytoplasm (Fig. 7.17b). They are present as single cells or small clusters and rarely form glands. In 97–100% of patients with Paget's disease, mammary carcinoma is also found and usually consists of DCIS with or without an invasive component [107–109]. The neoplastic cells of Paget's disease are positive for low molecular weight cytokeratins and CK7; they are HER2-positive in 80–100% of the cases and have variable estrogen receptor (ER) and progesterone receptor (PR) expression.

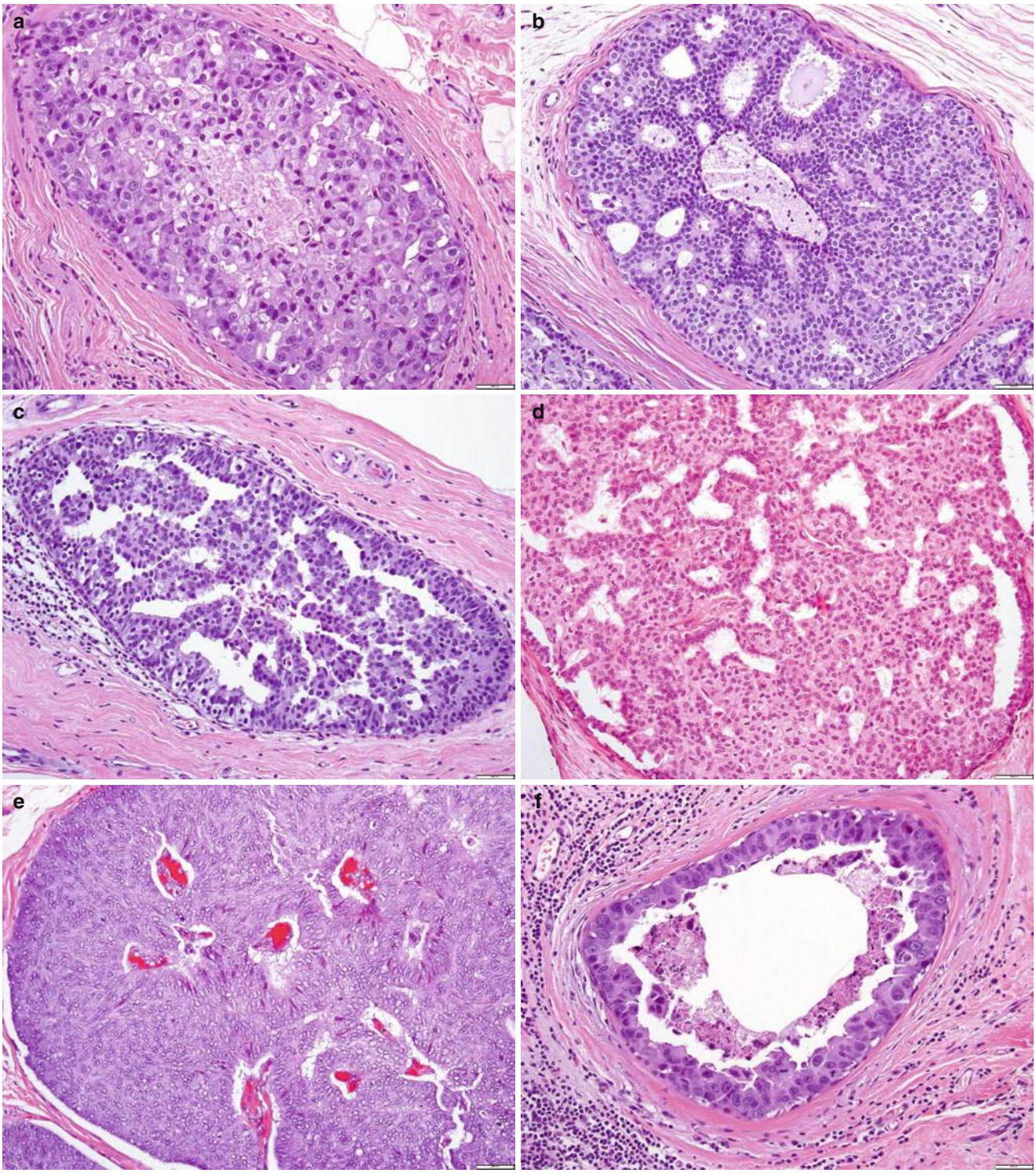

Fig. 7.12 Ductal carcinoma in situ, different architectural patterns. (**a**) Solid with central necrosis. (**b**) Cribriform. (**c**) Micropapillary. (**d**) Papillary. (**e**) Solid-papillary. (**f**) Flat with central necrosis

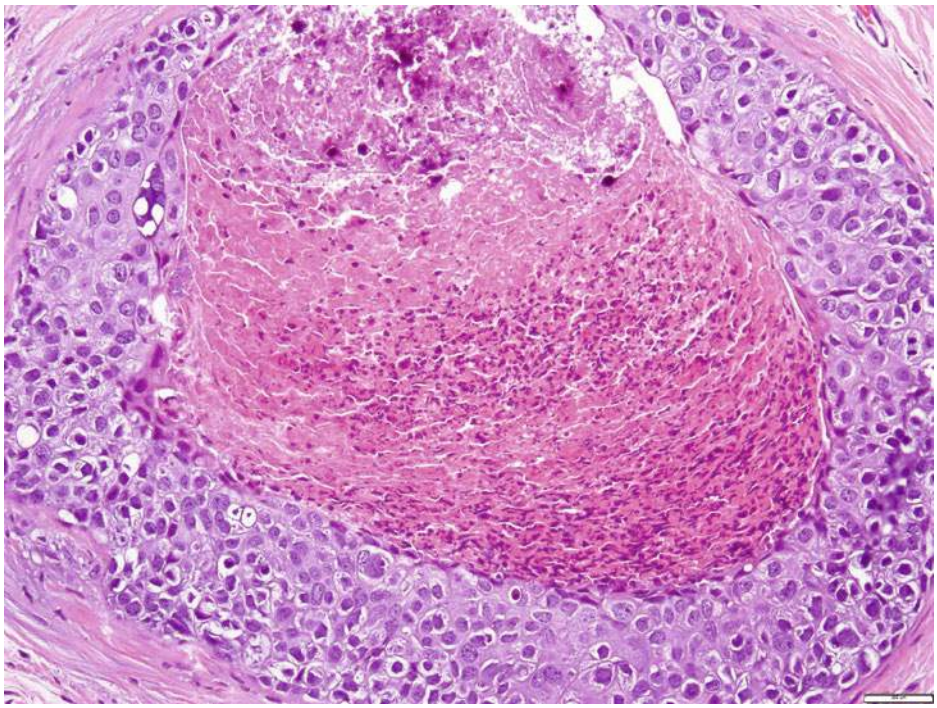

Fig. 7.13 Ductal carcinoma in situ with comedo necrosis and calcifications

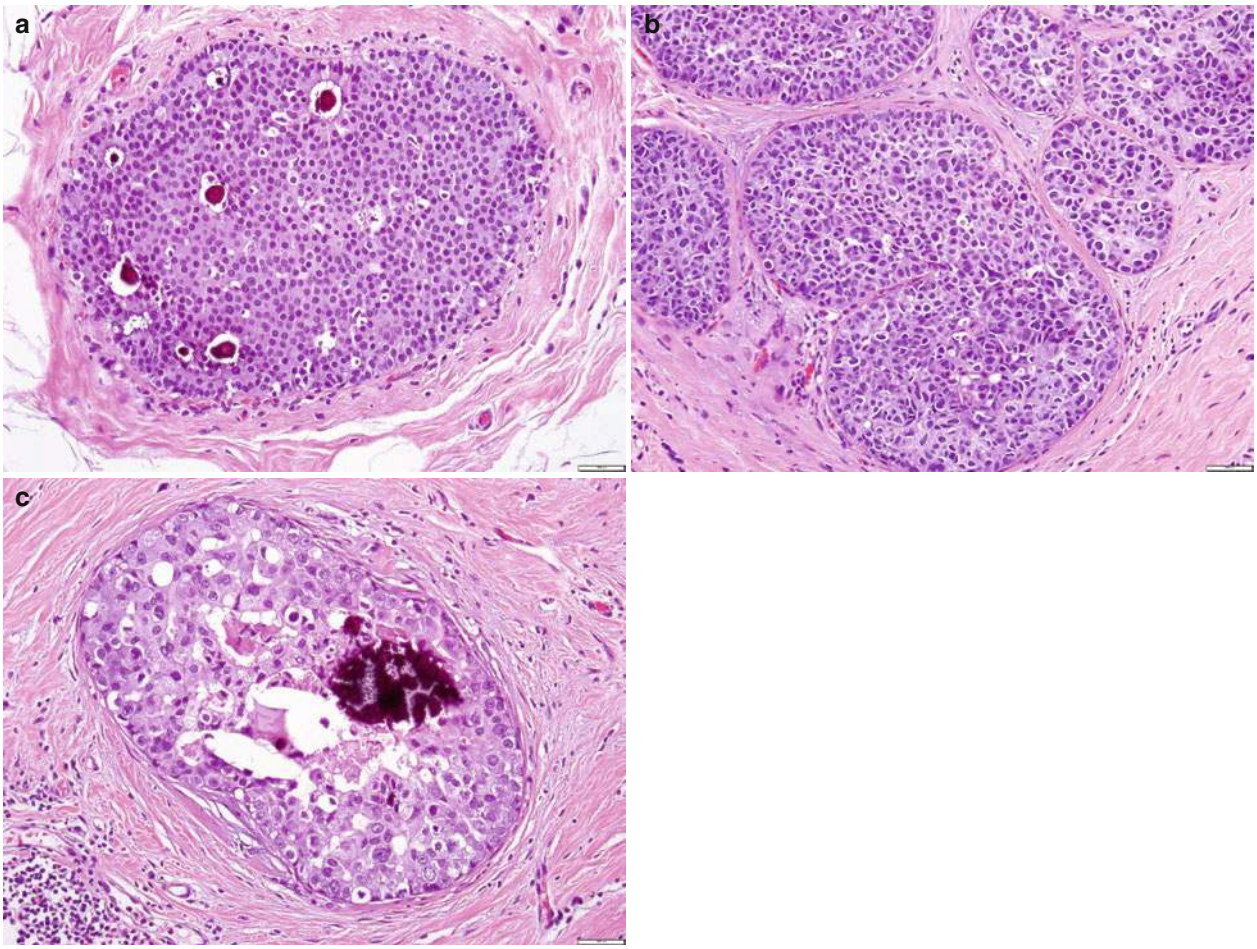

Fig. 7.14 Ductal carcinoma in situ (DCIS), nuclear grade. (**a**) DCIS with low nuclear grade; few small calcifications are present; (**b**) DCIS with intermediate nuclear grade; (**c**) DCIS with high nuclear grade and coarse pleomorphic calcifications

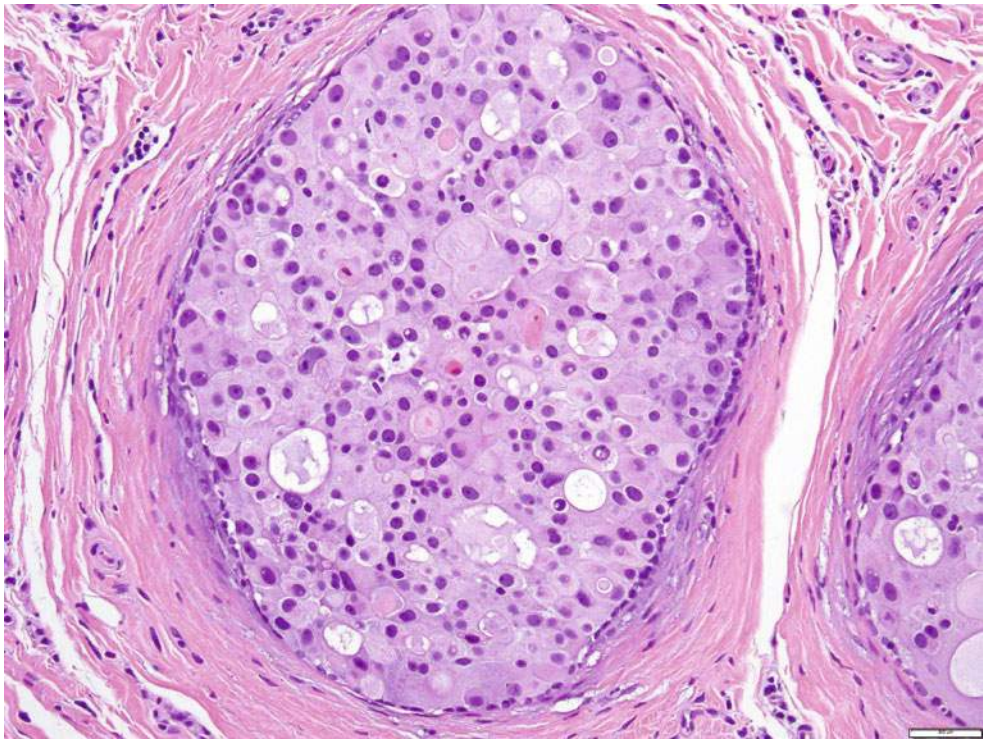

Fig. 7.15 Ductal carcinoma in situ with apocrine morphology. The cells have abundant cytoplasm

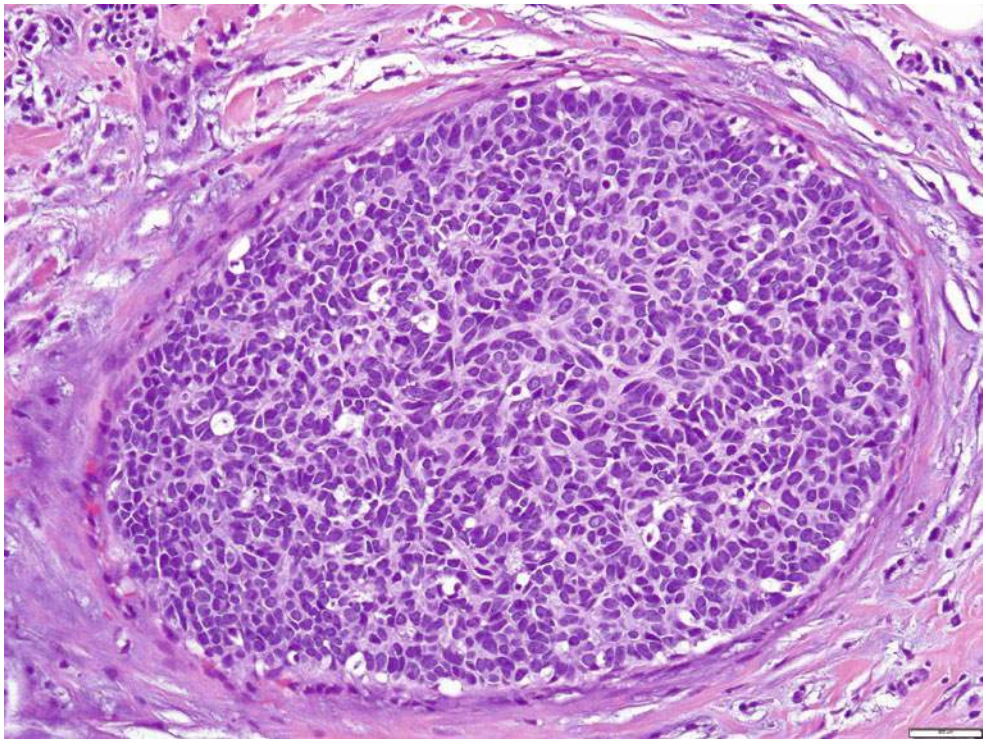

Fig. 7.16 Ductal carcinoma in situ, with spindle cell morphology. In the central portion of this duct involved by DCIS, the neoplastic cells have a spindled shape

Lobular carcinoma in situ (LCIS) (Fig. 7.18) and atypical lobular hyperplasia (ALH) arise within the terminal ductal lobular units and can show pagetoid involvement of the ducts. The acini are expanded by a monomorphic proliferation of dyshesive cells; the nuclei show low-grade atypia and are located in the center of the cells. The cells of LCIS and ALH are cytomorphologically similar, but in LCIS the cells fill and expand more than 50% of the acini of a lobule, whereas in ALH the proliferation is less conspicuous. Classic LCIS and ALH are rarely associated with mammographically detectable calcifications and usually constitute an incidental finding in a biopsy specimen

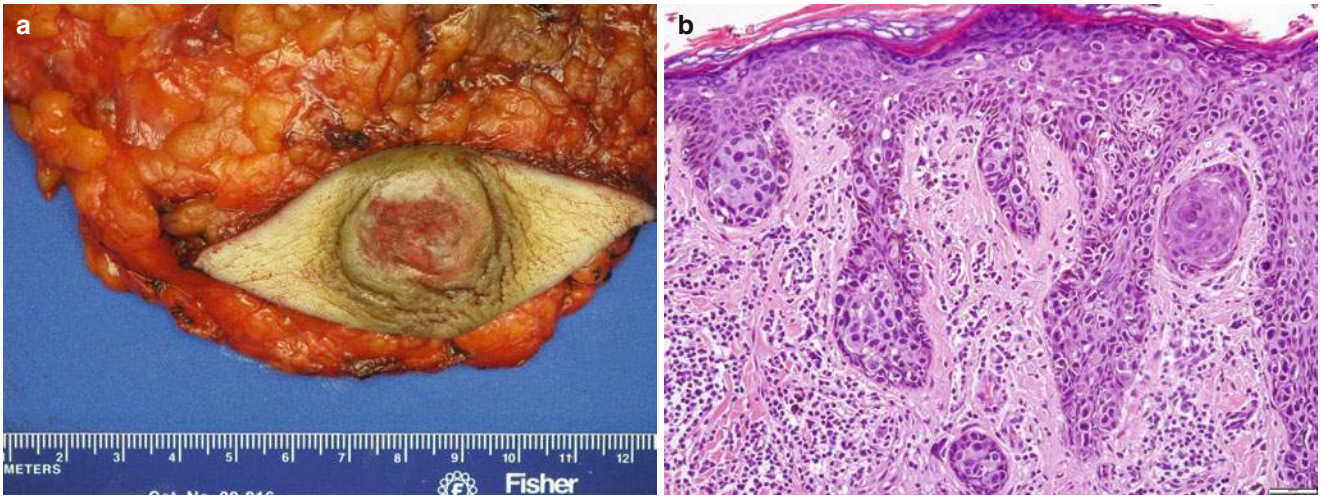

Fig. 7.17 Paget's disease of the nipple. (**a**) The nipple shows an irregular ulceration. (**b**) The neoplastic cells have abundant pale cytoplasm and large dark nuclei. They are distributed as single cells or clusters throughout the entire epidermis. Inflammatory cells are present in the dermis

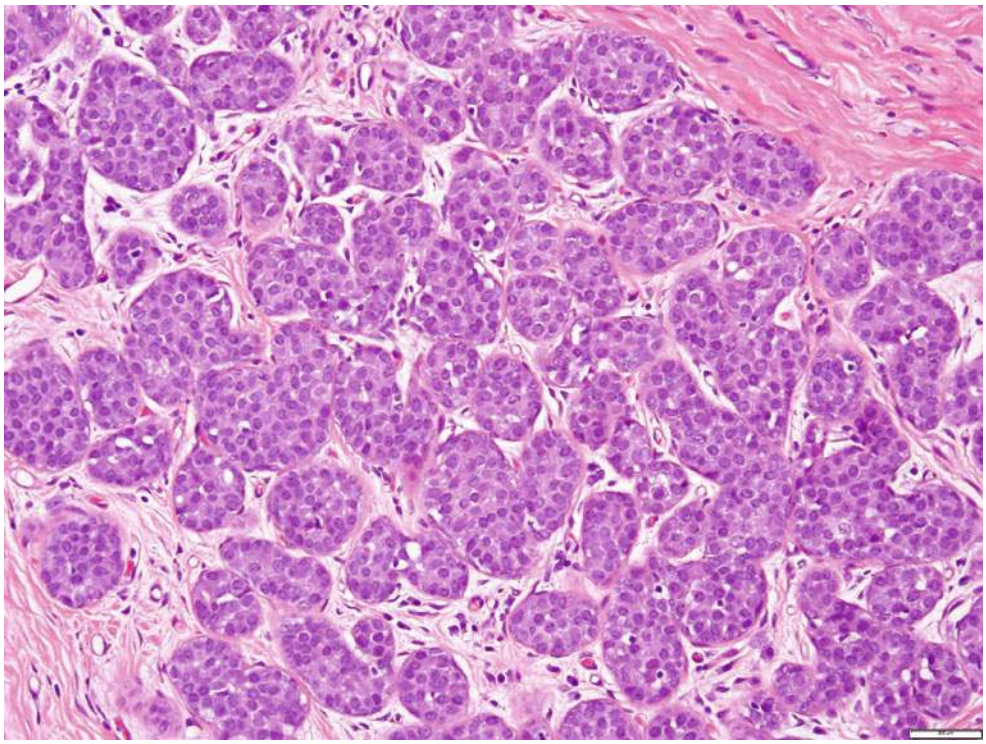

Fig. 7.18 Lobular carcinoma in situ, classic type

obtained to evaluate another lesion. Classic LCIS and ALH are both risk factors and non-obligate morphologic precursors of invasive carcinoma. The risk of progression to invasive carcinoma is very low compared to that of DCIS. E-cadherin is a transmembrane glycoprotein encoded by the *CDH1* gene, which is located on chromosome 16q22.1, and involved in epithelial cell-cell adhesion. LCIS and ALH are characterized by loss of E-cadherin expression by immunohistochemical staining; in some cases E-cadherin staining is attenuated and/or incomplete (Fig. 7.19). P120 links the E-cadherin/beta-catenin complex to the actin cytoskeleton. If the E-cadherin-beta-catenin complex is absent or not functional, p120 loses its membranous localization and is present diffusely throughout the cytoplasm. P120 immunohistochemical staining is useful in the diagnostic evaluation of solid carcinoma in situ that shows ambiguous reactivity for E-cadherin. DCIS with solid growth shows strong membranous expression of E-cadherin and p120 (Fig. 7.20). Pleomorphic LCIS (PLCIS) and LCIS with necrosis are rare variants of LCIS of relatively recent identification. Pleomorphic LCIS (Fig. 7.19a) demonstrates the dyshesive growth pattern

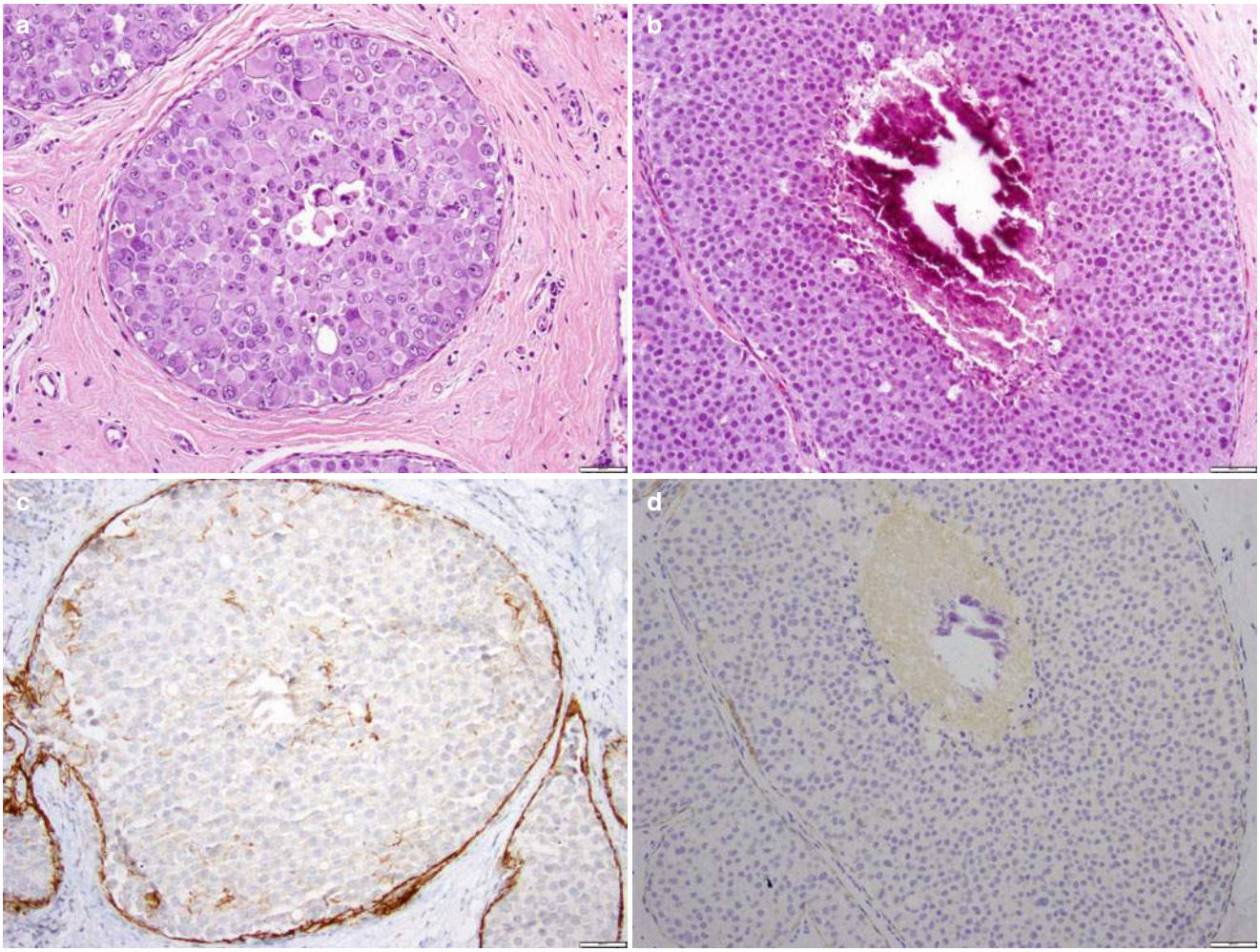

Fig. 7.19 Lobular carcinoma in situ (LCIS) variant forms. (**a**) Pleomorphic LCIS. (**b**) LCIS with necrosis (**c**, **d**). Lack of immunoreactivity for E-cadherin in pleomorphic LCIS (**c**) and LCIS with necrosis (**d**). This result supports a lobular phenotype

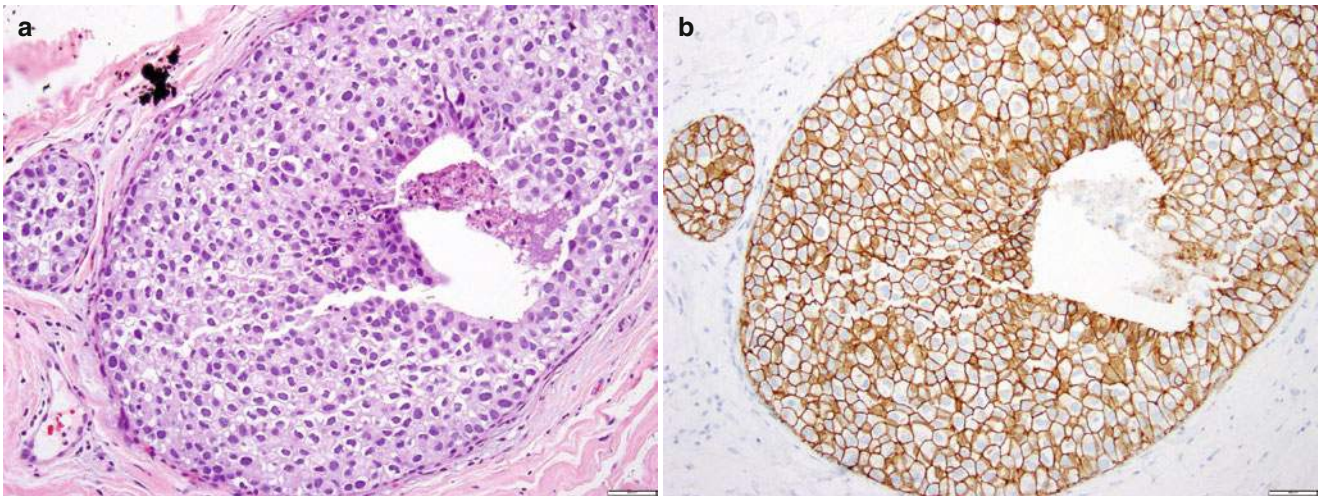

Fig. 7.20 Immunohistochemical stains for E-cadherin in ductal carcinoma in situ. Membranous reactivity for E-cadherin supports a ductal phenotype

characteristic of LCIS, but exhibits moderate to marked nuclear pleomorphism, and can have central necrosis with associated coarse and pleomorphic calcifications. LCIS with comedo necrosis (also known as "florid" LCIS) (Fig. 7.19b) is composed of cells with the cytomorphology of classic LCIS but shows massive acinar expansion, with foci of central necrosis that often harbor coarse calcifications. Both PLCIS and LCIS with comedo necrosis can closely mimic DCIS mammographically and histologically. In cases in which immunohistochemical stain for E-cadherin is inconclusive, p120 catenin (p120) can be used to assess whether E-cadherin is dysfunctional.

7.4.1.2 Invasive Carcinoma

Morphological classification of histologic subtypes of invasive breast carcinoma follows the latest WHO classification of tumors of the breast [101]. Invasive ductal carcinoma (IDC) of no special type or not otherwise specified (NOS) and invasive lobular carcinoma are the most common forms and comprise 60–75% and 5–15% of invasive breast carcinoma, respectively. Invasive carcinomas in which greater than 50% of the lesion displays no special features are classified as IDC-NOS [101]. This designation is a diagnosis of exclusion, as it applies to an invasive carcinoma that does not show morphologic features diagnostic of any special histologic subtype (Fig. 7.21). Invasive lobular carcinoma (ILC) is the second most common histologic subtype of invasive breast carcinoma. ILC (Fig. 7.22) is composed of loosely cohesive or dyshesive tumor cells, which often infiltrate the breast parenchyma in a single linear file. In classic ILC (Fig. 7.22a), the tumor cells are small, round, uniform, with minimal nuclear pleomorphism. Cells with an intracytoplasmic lumen, intracellular mucin, or signet ring morphology are common. Pleomorphic ILC (Fig. 7.22b) has a dyshesive growth pattern as that of clas-

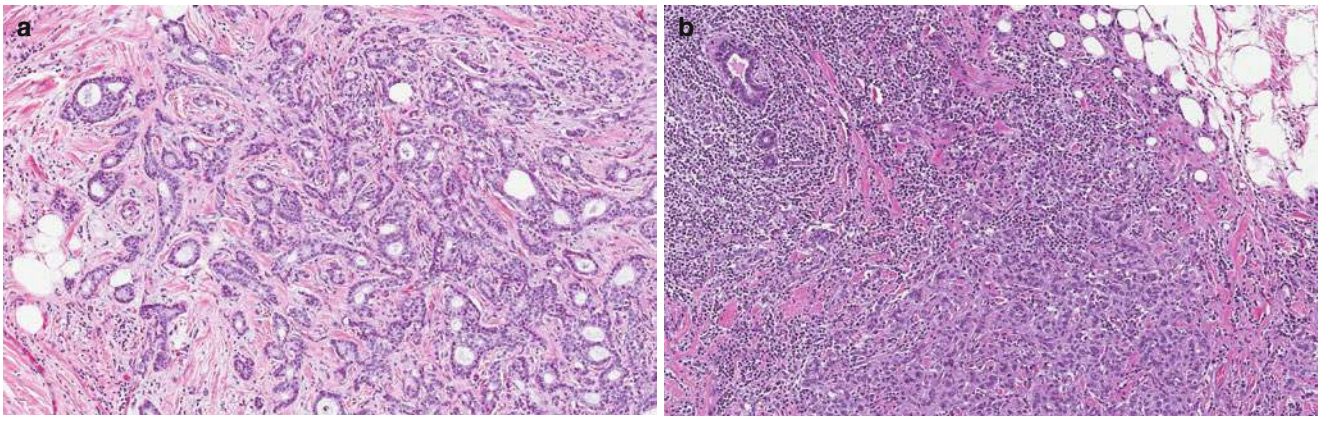

Fig. 7.21 Invasive ductal carcinoma of no special type. (**a**) Well-differentiated invasive ductal carcinoma, with low nuclear grade and evident gland formation. (**b**) Poorly differentiated invasive ductal carcinoma, with high nuclear grade and no gland formation. This carcinoma is associated with a prominent inflammatory infiltrate

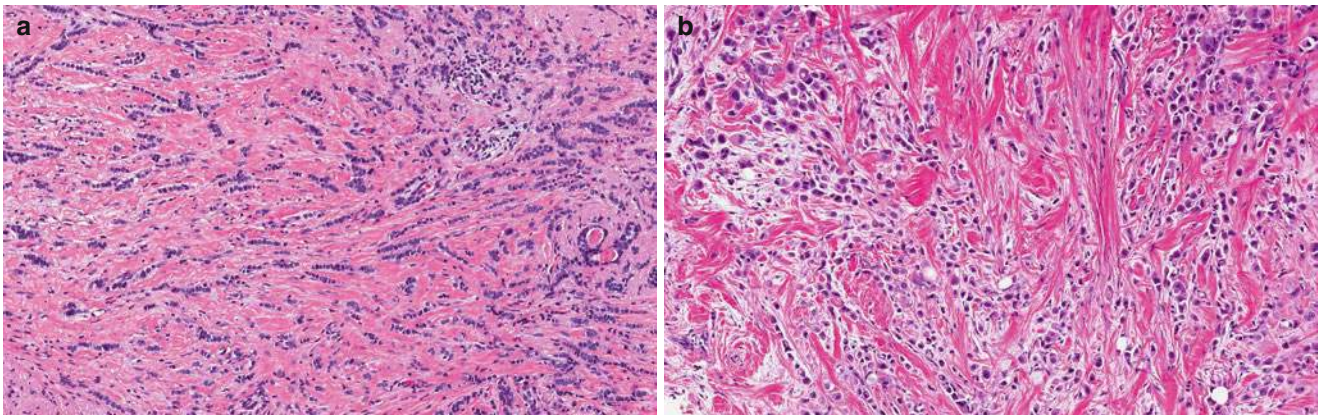

Fig. 7.22 Invasive lobular carcinoma, classic and pleomorphic types. (**a**) Invasive lobular carcinoma, classic type. The cells are small and have low-grade nuclei. (**b**) Invasive lobular carcinoma, pleomorphic type. The cells have abundant cytoplasm and large hyperchromatic and irregular nuclei. The neoplastic cells of invasive lobular carcinoma with classic (**a**) or pleomorphic (**b**) morphology infiltrate the stroma as either single cells or in linear files (so called "Indian files") [Note: images (**a**) and (**b**) are shown at the same magnification]

sic ILC, but the neoplastic cells have large and irregular nuclei, prominent nucleoli, and marked nuclear pleomorphism; binucleation is common. The neoplastic cells often show oval to plasmacytoid morphology, and the nucleus can be located at one pole of the cell. The discohesive morphology in ILC is secondary to the dysregulation of cell-cell adhesion, due to the loss of E-cadherin. ILC displays recurrent copy number alterations including gains at 1q and losses at 16q, chromosomal abnormalities commonly seen in low-grade precursor lesions, and well-differentiated hormonal receptor-positive invasive breast carcinomas [110–112]. Pleomorphic ILC and classic ILC have overlapping genomic alterations: 16q losses and 1q gains [113]. However, pleomorphic ILC harbors additional genetic alterations typically found in high-grade IDC [113]. Somatic *CDH1* gene mutations are identified in over 60% of ILC and often occur in combination with chromosome 16 loss [114–116]. Inherited mutations in the *CDH1* gene cause hereditary diffuse gastric cancer and increased risk of developing mammary ILC of the breast [117–120]. In addition to *CDH1* mutations, alterations in PI3K pathway (*PIK3CA*, *PTEN*, and *AKT1*) are observed in 50% of ILC cases [115, 116]. Mutations in *HER2*, *HER3*, *FOXA3*, and copy number gain in *ESR1* are more frequent in ILC than in IDC [115, 116]. It remains unclear whether patients with ILC have similar or better prognosis compared to patients with stage- and receptor-matched IDC [121].

The special histologic subtypes of breast carcinoma are less common than that of IDC-NOS and ILC [101]. They include tubular carcinoma (Fig. 7.23), cribriform carcinoma (Fig. 7.24), mucinous carcinoma (Fig. 7.25), invasive micropapillary carcinoma (Fig. 7.26), invasive papillary carcinoma (Fig. 7.27), metaplastic carcinoma (Fig. 7.28), carcinoma

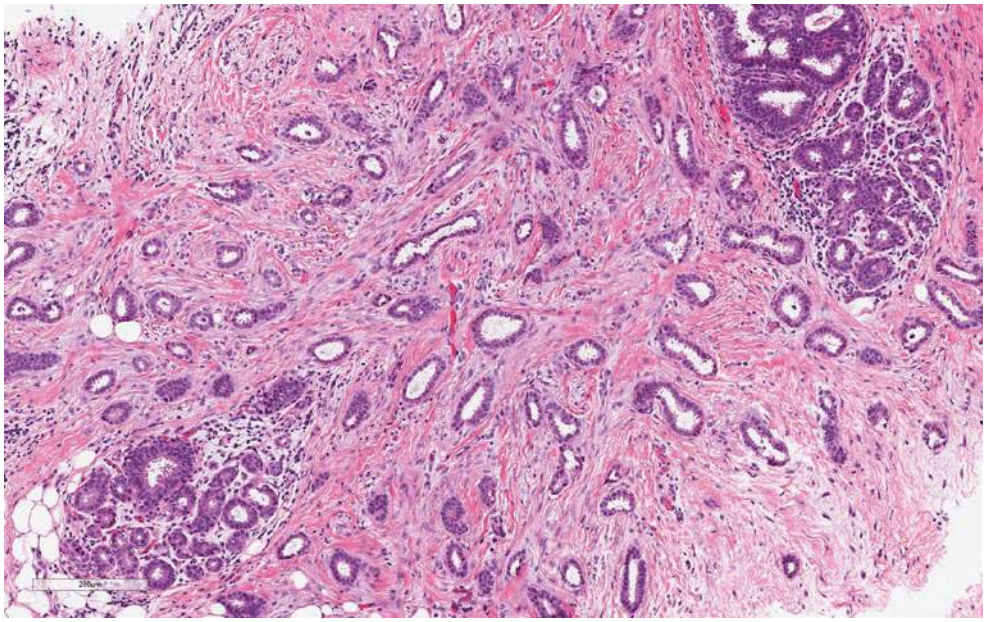

Fig. 7.23 Tubular carcinoma. The invasive carcinoma consists of well-formed monostratified glands with low nuclear atypia

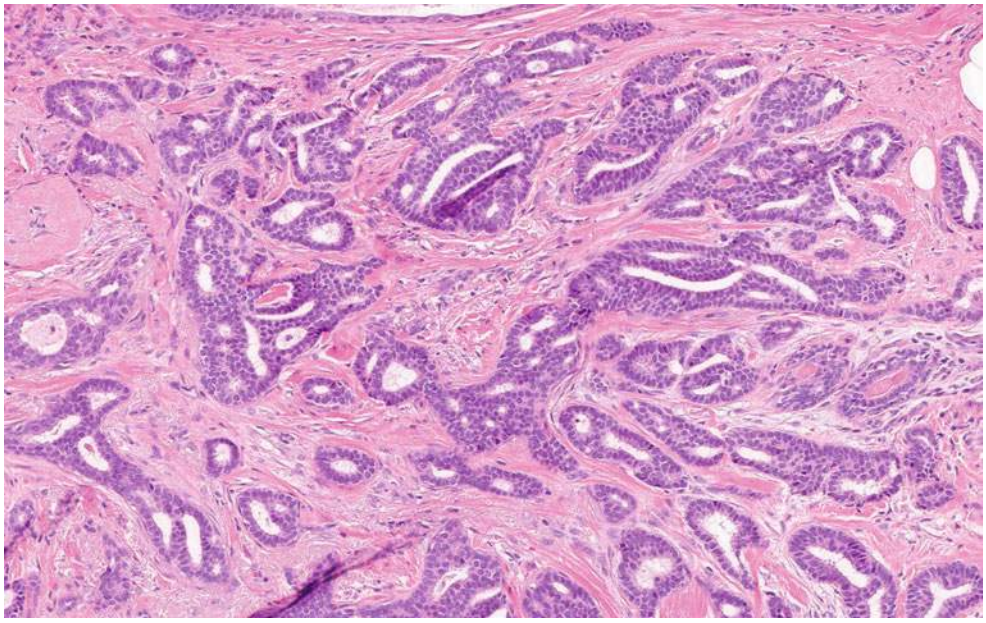

Fig. 7.24 Cribriform carcinoma. An example of invasive cribriform carcinoma. The carcinoma consists of large and cribriform nests with irregular outline and infiltrative pattern

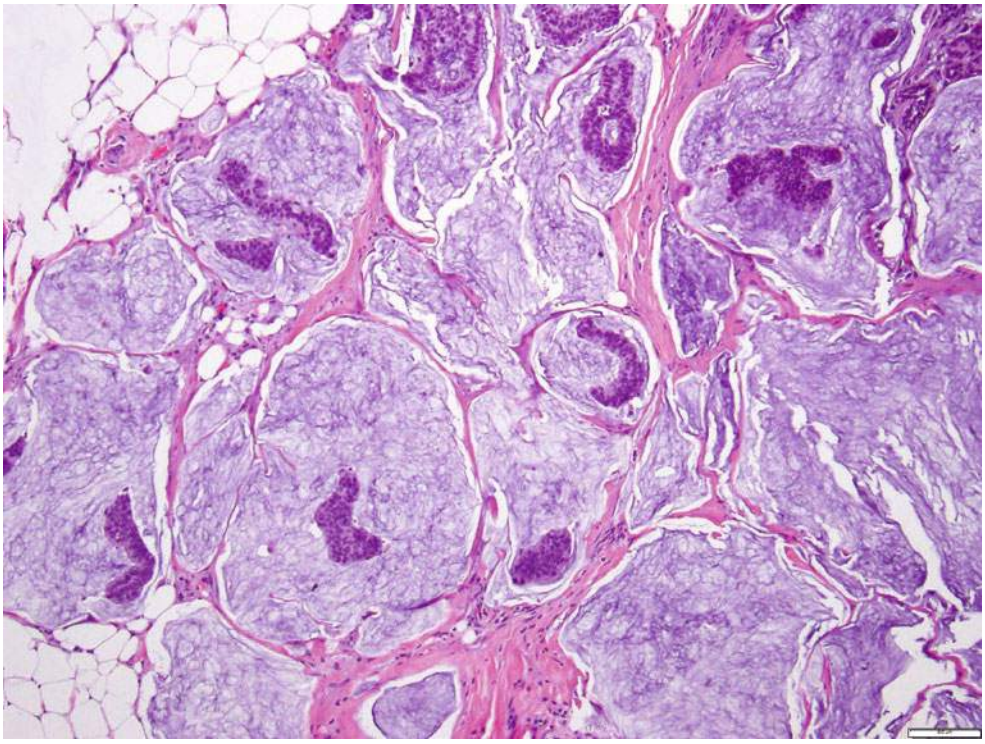

Fig. 7.25 Mucinous carcinoma. Clusters of carcinoma floating in mucin invade into the tissue

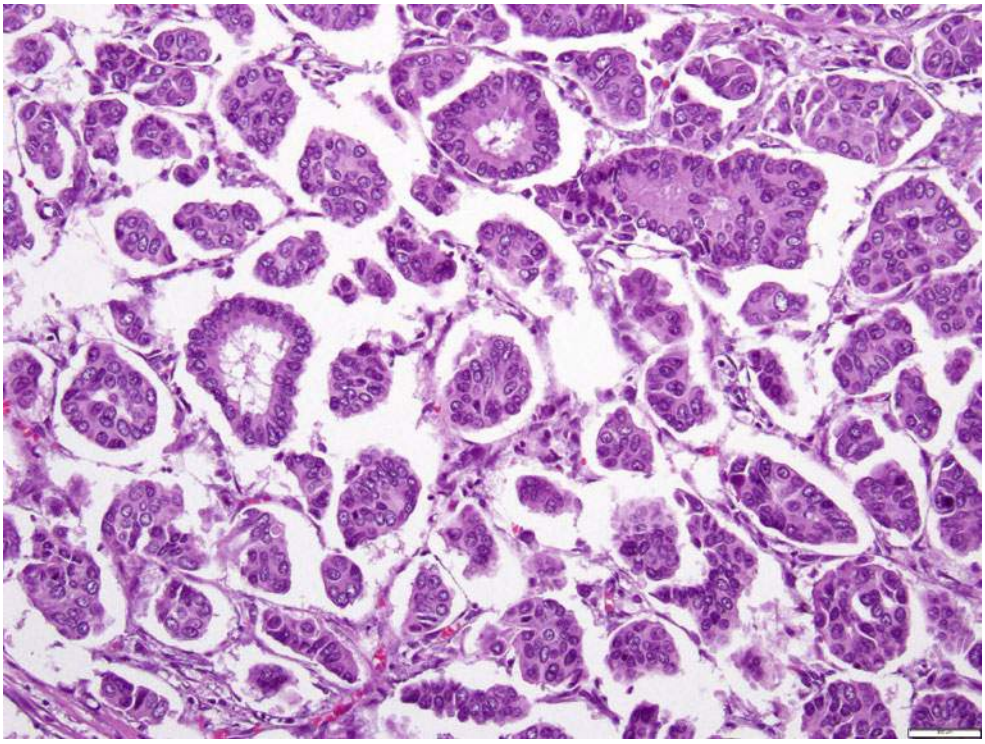

Fig. 7.26 Invasive micropapillary carcinoma. Each of the clusters and rings of invasive micropapillary carcinoma is surrounded by a clear "halo-like" space. This growth pattern can closely mimic lymphovascular invasion

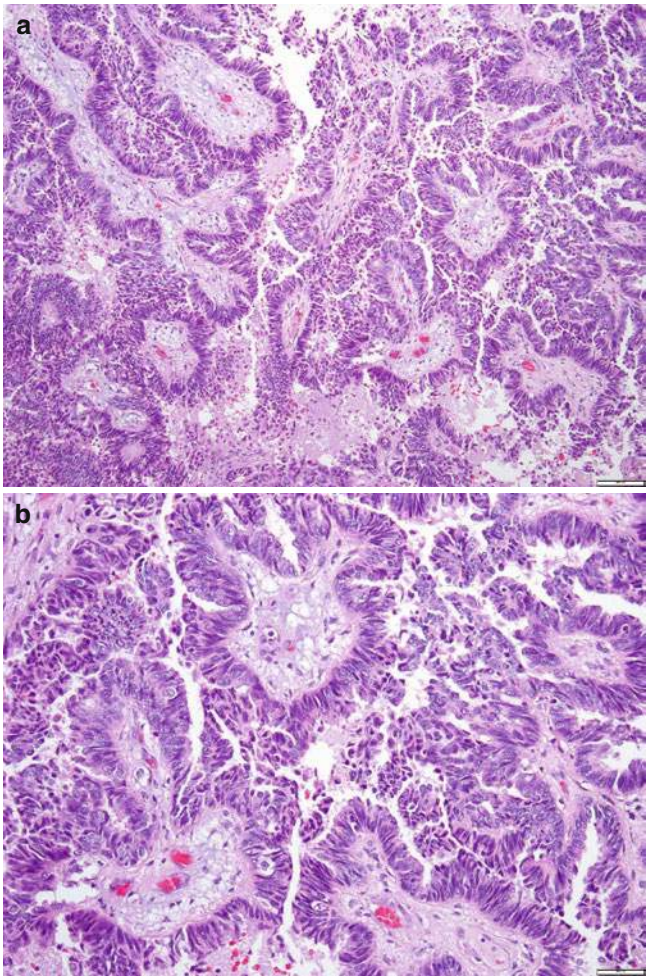

Fig. 7.27 Invasive papillary carcinoma. The neoplastic cells line fibrovascular cores devoid of myoepithelium (not shown). Primary breast carcinoma with exclusively invasive papillary morphology is unusual, and the possibility of metastatic carcinoma from a non-mammary site, such as ovary or female genital tract, should be considered

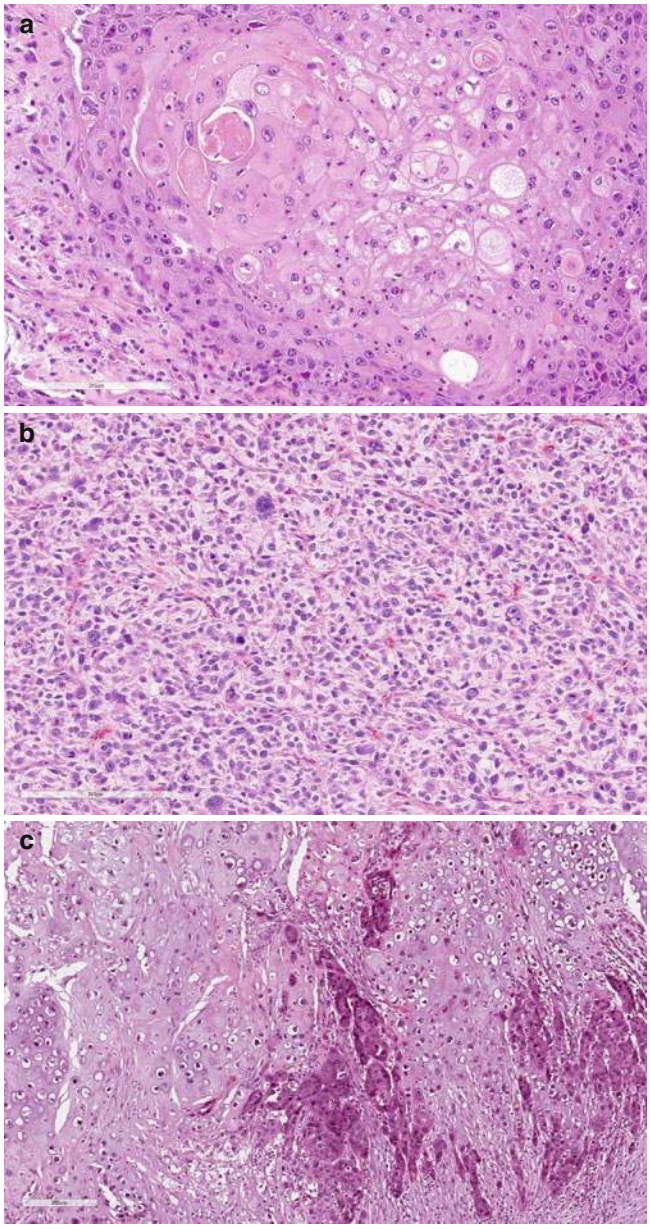

Fig. 7.28 Metaplastic carcinoma, different morphologies. (**a**) Metaplastic squamous cell carcinoma. (**b**) Metaplastic spindle cell carcinoma, with intermediate to high nuclear grade. (**c**) Metaplastic carcinoma with chondroid differentiation

with apocrine differentiation (Fig. 7.29), carcinoma with signet ring cells (Fig. 7.30), carcinoma with neuroendocrine features (Fig. 7.31), adenoid cystic carcinoma (Fig. 7.32), secretory carcinoma (Fig. 7.33), acinic cell carcinoma (Fig. 7.34), and several other exceptionally rare subtypes.

Encapsulated papillary carcinoma (EPC) (formerly referred to as intracystic papillary carcinoma) is a unique variant of papillary carcinoma and usually occurs in postmenopausal women. On gross examination, EPC appears as a circumscribed cystic tumor with a central cavity filled with delicate and friable fronds (Fig. 7.35a). Microscopically, EPC consists of papillary fronds filling a cystic space and surrounded by a thick fibrous capsule (Fig. 7.35b). The neoplastic ductal cells are monomorphous, with low to intermediate nuclear grade, and have cribriform and focally solid arrangement along delicate fibrovascular cores (Fig. 7.35c). Myoepithelial cells are typically absent within the fibrovascular cores as well as at the periphery of the tumor. EPC was traditionally regarded as a form of DCIS, but the absence of myoepithelium at the periphery of the tumor is strong evidence that EPC represents an indolent variant of locally invasive low-grade carcinoma [122–124]. The staging and management of EPC remain controversial. Rare cases of lymph node involvement and distal metastasis are reported

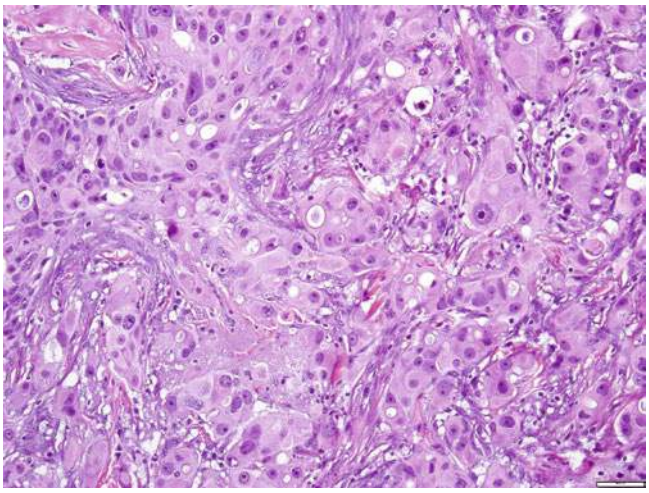

Fig. 7.29 Carcinoma with apocrine differentiation

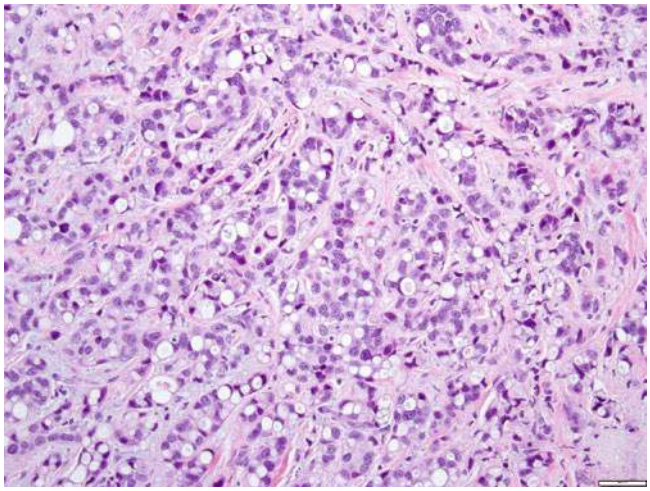

Fig. 7.30 Carcinoma with signet ring cells. Most neoplastic cells have intracytoplasmic vacuole that indent the nucleus, with resulting "signet ring" morphology

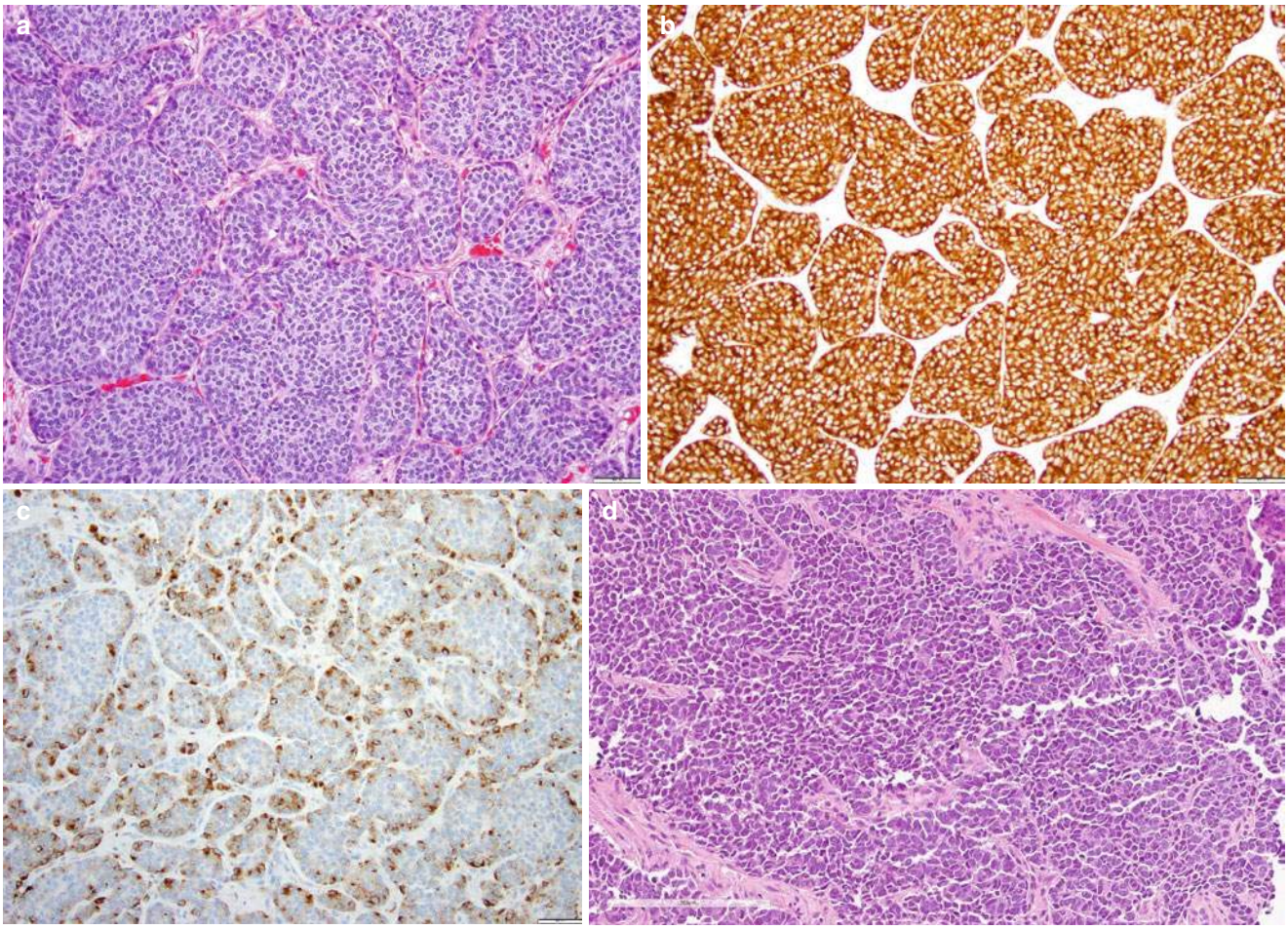

Fig. 7.31 Carcinoma with neuroendocrine features. (**a**) This moderately differentiated invasive carcinoma demonstrates diffuse reactivity for the neuroendocrine marker synaptophysin (**b**), and scattered positivity for chromogranin, another neuroendocrine antigen (**c**). (**d**) This high-grade invasive carcinoma with neuroendocrine features qualifies morphologically as small cell carcinoma of the breast

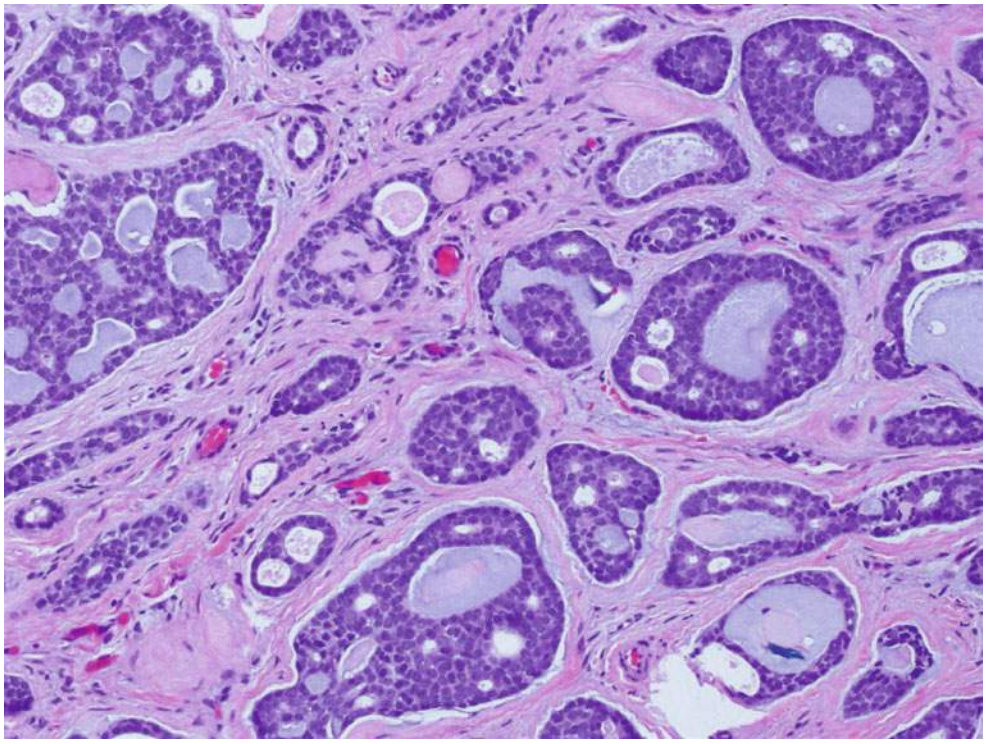

Fig. 7.32 Adenoid cystic carcinoma. Adenoid cystic carcinoma of the breast is morphologically similar to its counterpart in the salivary glands. It is a carcinoma with biphasic (epithelial and basal/myoepithelial) differentiation

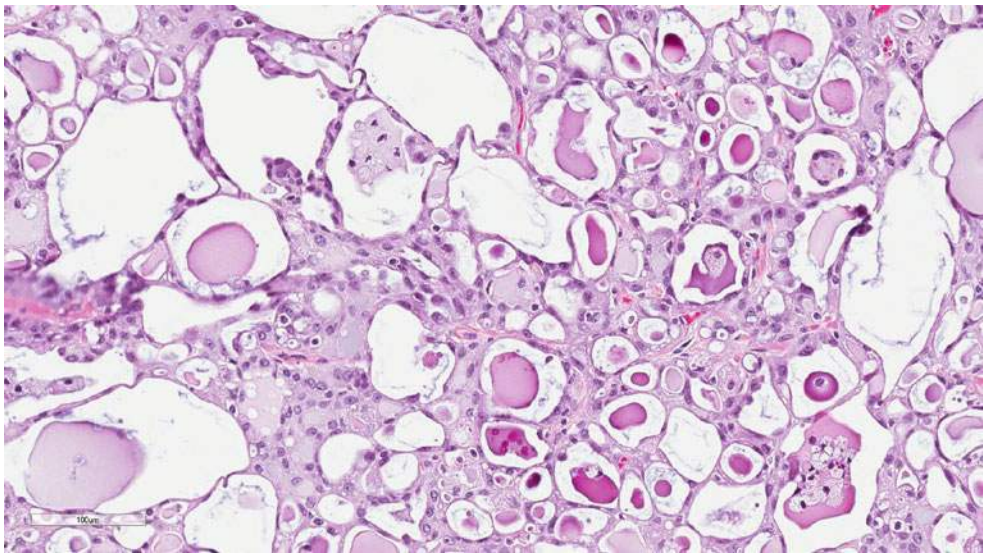

Fig. 7.33 Secretory carcinoma. This rare form of invasive carcinoma consists of cells with abundant vacuolated cytoplasm and intraluminal secretion

[123, 124], but most tumors tend to be indolent. At present, EPC is regarded as an indolent form of invasive carcinoma with excellent prognosis with adequate local therapy and possibly hormonal therapy. The recommendation by the WHO working group is that in the absence of conventional forms of invasive carcinoma, EPC should be staged and managed as Tis(DCIS) disease [101]. If conventional invasive carcinoma is associated with EPC, staging and management should be according to the size of the invasive component [101].

Gene expression profiling and microarray comparative genomic hybridization (aCGH) studies of special histologic subtypes of breast cancer have revealed distinct features at the genomic and transcriptomic level. Tubular carcinoma shares similar transcriptomic profiles to histologic grade- and ER-matched IDC-NOS with just few subtle differences, suggesting that these two entities may evolve through common molecular pathways and have similar precursor lesions [125]. Mucinous carcinoma and carcinoma with neuroendocrine differentiation are transcriptionally distinct from

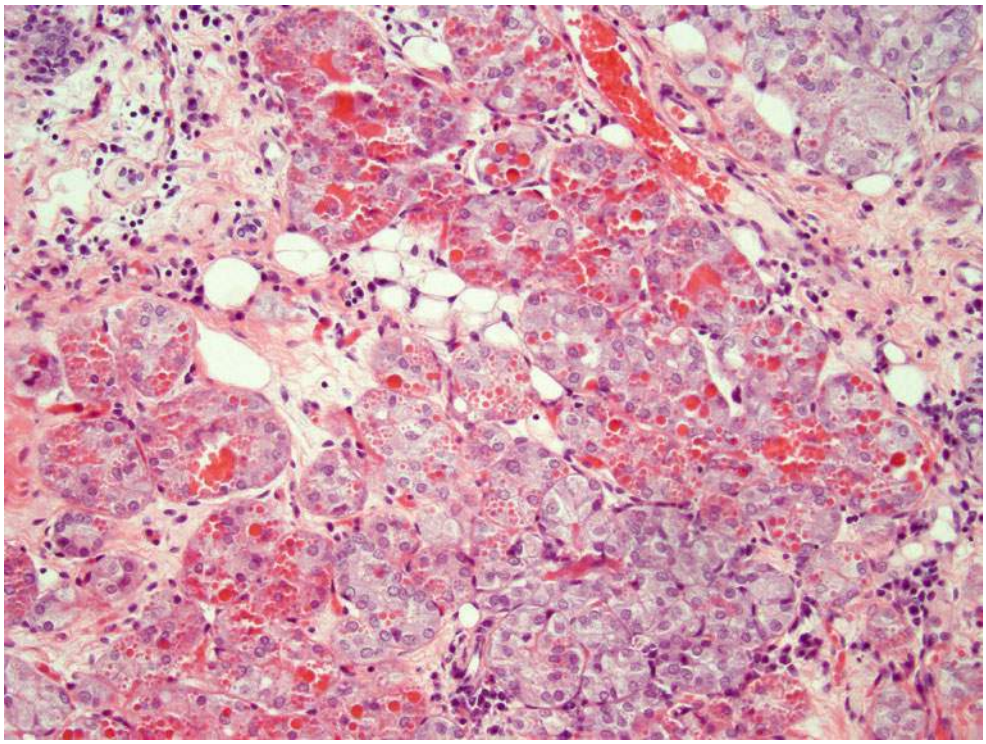

Fig. 7.34 Acinic cell carcinoma. This rare form of invasive carcinoma consists of cells with granular cytoplasm and is morphologically similar to its counterpart in the salivary glands

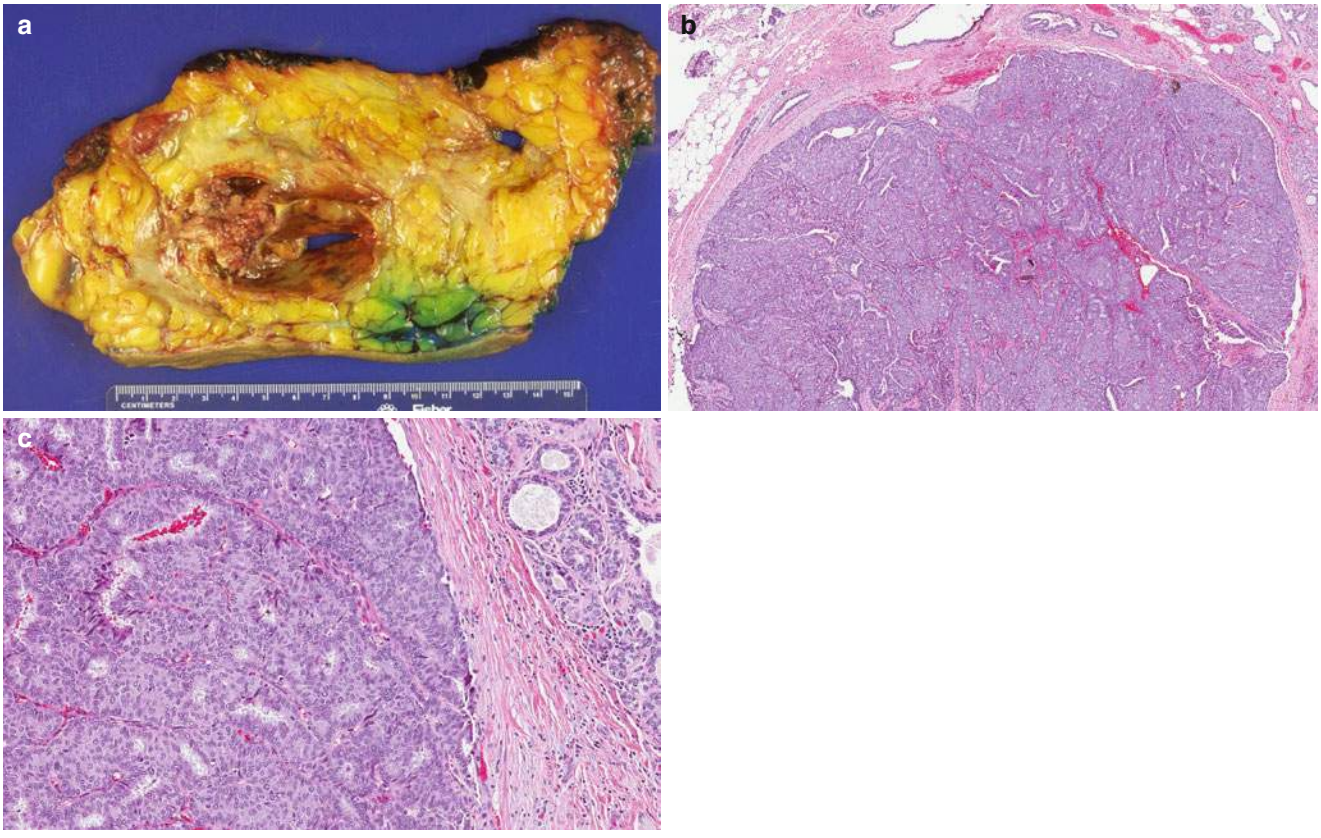

Fig. 7.35 Encapsulated papillary carcinoma (EPC). This tumor typically presents as a solid and cystic lesion in the central breast/subareolar region. EPC is a rare and indolent variant of papillary carcinoma. It is usually surrounded by a thick fibrous capsule and has a broad pushing infiltrative edge (**b**). The nuclear grade of EPC is low to intermediate

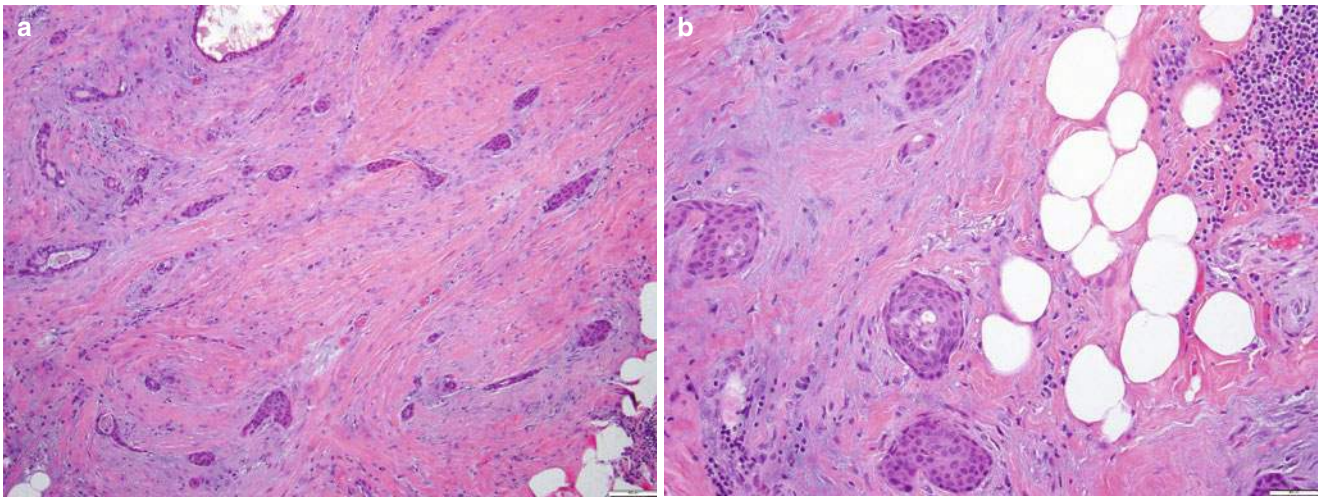

Fig. 7.36 Low-grade adenosquamous carcinoma. This is a biphasic tumor with epithelial/squamous and basal/myoepithelial differentiation. It can be locally aggressive but has limited to no metastatic potential

histological grade- and molecular subtype-matched IDC-NOS by gene expression microarray analysis [126]. Pure mucinous carcinoma displays a relatively low level of genetic instability and less frequent gains of 1q and loss of 16q, the hallmark genetic features of low-grade invasive breast carcinomas, than grade- and ER-matched IDC-NOS. These findings suggest that mucinous carcinoma may evolve through genetic pathways distinct from those altered in the low-grade breast neoplasia family [127]. Interestingly, the mucinous and non-mucinous components of mixed mucinous carcinomas display similar genomic alterations [127]. Similarly, in carcinoma with mixed NOS and invasive micropapillary morphology, both micropapillary and non-micropapillary components harbor similar genomic alterations, which are also similar to those found in invasive micropapillary carcinoma [128]. Invasive micropapillary carcinomas have genomic alterations significantly different from grade- and ER-matched IDC-NOS. High-level gains/amplifications of 1q, 8q, 17q, 20q, and MYC (8q24) amplification are more prevalent in invasive micropapillary carcinomas [129]. Papillary carcinomas display less genomic alterations than grade- and ER-matched IDC-NOS; however, the patterns of gene copy number aberrations found in papillary carcinomas are similar to those of ER- and grade-matched IDC-NOSs, including 16q loss [130]. The histologic subtypes of papillary carcinomas, including encapsulated papillary carcinoma, solid-papillary carcinoma, and invasive papillary carcinoma, have remarkably similar pattern of copy number alterations [130, 131].

Certain special histologic subtypes of breast cancer not only have distinct morphological and molecular features but also distinct biology and clinical behavior. Even in the era of molecular testing, traditional morphologic classification remains valuable for risk stratifications. For example, tubular carcinoma is almost always ER/PR-positive, HER2-negative and is associated with favorable prognosis, even compared to well-differentiated invasive ductal carcinoma [132]. Several special histologic subtypes, such as adenoid cystic carcinoma (Fig. 7.32), secretory carcinoma (Fig. 7.33), and low-grade variants of metaplastic carcinoma including low-grade adenosquamous carcinoma (Fig. 7.36) and low-grade fibromatosis-like metaplastic carcinoma (Fig. 7.37), often exhibit triple-negative phenotype by immunohistochemistry and have basal-like phenotype by gene expression profiling. Nonetheless, these carcinomas are associated with a relatively indolent behavior and good clinical outcome, unlike the triple-negative breast carcinomas with conventional invasive ductal NOS morphology.

7.4.2 Size

The size of the invasive carcinoma is essential for pathologic tumor staging. The prosector records the three dimensions of the tumor at gross examination, but, ultimately, the microscopic measurement is the most accurate method for assessing the tumor size because only the invasive component is to be used to determine the pT stage. If an invasive carcinoma is associated with extensive mass-forming DCIS with high nuclear grade and periductal fibrosis, the gross measurement of the tumor mass will overestimate the size of the invasive component. Such discrepancy can have important consequences, especially if neoadjuvant chemotherapy is being considered. In contrast, the gross measurement of an ILC

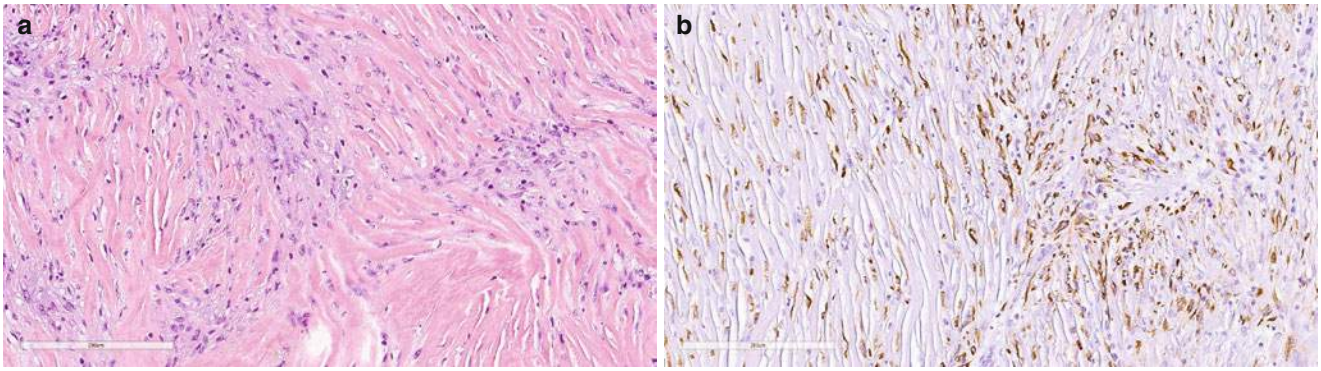

Fig. 7.37 "Low-grade" "fibromatosis-like" metaplastic spindle cell carcinoma. (**a**) H&E stain. (**b**) Immunohistochemical stain for pancytokeratin demonstrates the epithelial nature of the neoplastic spindle cells

may underestimate the tumor T-stage by nearly 50%, due to the lack of desmoplastic stromal reaction and diffuse "single-file" growth pattern [133]. In cases of invasive lobular carcinoma, discrepancies between the pathologic T-stage (based on microscopic measurement) and the clinical T-stage (based on imaging techniques) are not uncommon.

If the tumor mass measures up to 2–2.5 cm grossly, a full cross section of the tumor can be submitted in one cassette, and the largest span of invasive carcinoma is measured microscopically in the corresponding tissue section. If the tumor mass measures greater than 2.5 cm grossly, a full cross section through the tumor greatest diameter is mapped and submitted in multiple tissue cassettes, in a manner that allows the pathologist to reassemble the tissue sections at the time of microscopic examination and accurately assess the size of the invasive component microscopically (see Sect. 7.3). If the lumpectomy specimen was sliced sequentially and entirely submitted, the size of the invasive carcinoma can be calculated by multiplying the number of sequential slices involved by the invasive carcinoma by the estimated thickness of each tissue slice.

Carcinoma in situ is classified as Tis, with an additional parenthetical subclassification indicating the subtype, such as Tis (DCIS) or Tis (Paget's). Although the size of the DCIS is not required for pT staging, the extent of DCIS is a significant parameter that plays an important role when deciding on patient management. If DCIS is present in one slide, the extent of DCIS is measured by the largest microscopic span between the two furthest foci of DCIS [134]. The optimal prosection of an excision specimen known to contain DCIS involves sequential sectioning and histologic evaluation of the entire specimen. The extent of DCIS can be calculated by multiplying the estimated thickness of each tissue slice by the number of slices with microscopic evidence of DCIS [134].

Microinvasive carcinoma is defined as invasive carcinoma spanning up to 1 mm and classified as T1mi by the American Joint Committee on Cancer (AJCC) [84]. Microinvasive carcinoma tends to be associated with high-grade DCIS. It usually consists of rare single cells and small clusters admixed with marked chronic inflammation in the stroma adjacent to high-grade DCIS. In our experience, microinvasive carcinoma is also frequently associated with PLCIS and LCIS with comedo necrosis, while it is uncommon near low-grade DCIS or classic LCIS. Immunohistochemical stains for cytokeratin and myoepithelial markers are often helpful to demonstrate the absence of myoepithelial cells around the microinvasive clusters. If more than one focus of microinvasive carcinoma is present, the pathologist may count and report their number. The incidence of axillary lymph node metastasis (including macro-and micrometastases) in patients with microinvasive carcinoma ranges from 0 to 11% [135–143]. The presence of more than one focus of microinvasive carcinoma was not associated with increased rate of lymph node metastasis or local recurrence [139, 141, 143], but its clinical impact has not been fully investigated.

If two or more separate foci of invasive carcinoma are present, each focus needs to be characterized and documented. The pT stage is based on the size of largest invasive focus. If two or more tumors appear separate but are closely adjacent, the intervening tissue is sampled to determine whether the tumors are truly separated or rather represent one contiguous tumor with dumbbell shape. Foci of invasive carcinoma that are less than 5 mm apart are arbitrarily regarded as part of the same tumor, and the size is measured across the largest span between the furthermost foci, including the intervening stroma (the latter being by definition always less than 5 mm in size).

The size of the residual invasive carcinoma post-neoadjuvant therapy can be difficult to assess, especially when the residual invasive carcinoma consists of scattered

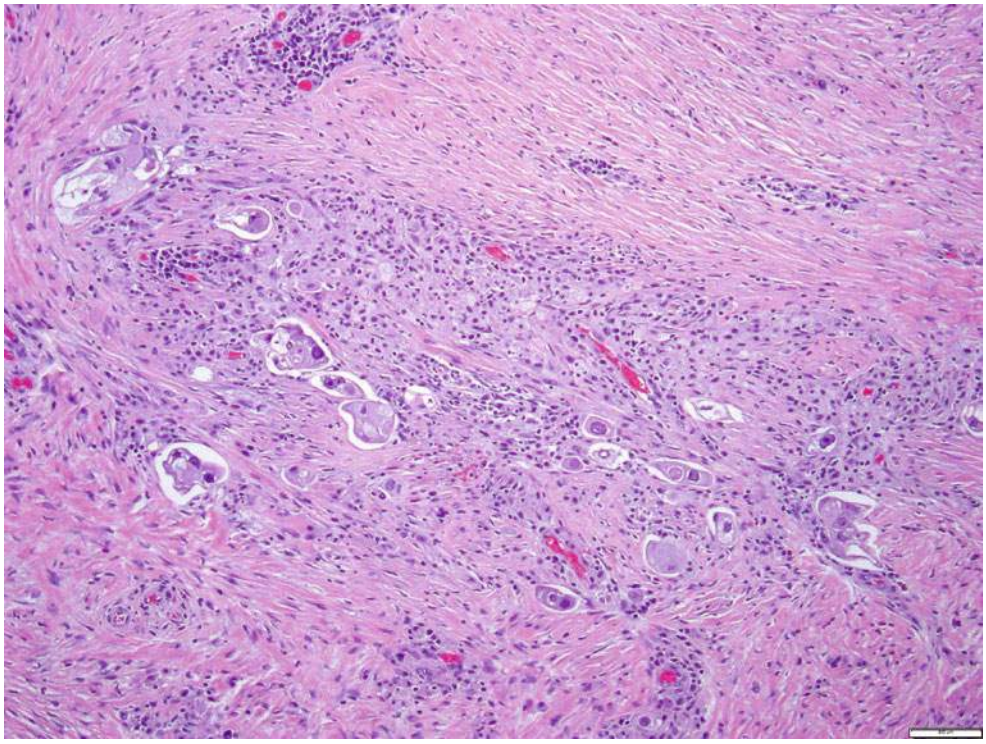

Fig. 7.38 Residual invasive carcinoma post-neoadjuvant chemotherapy. The residual invasive carcinoma is present as few scattered microscopic foci within the tumor bed

microscopic foci within the tumor bed (Fig. 7.38). Adequate sampling of the tumor bed is critical (Sect. 7.3). According to the AJCC Cancer Staging recommendations [84], the residual tumor size (ypT) is the largest single focus of invasive carcinoma; a modifier "m" is used to indicate multifocal disease. According to the Breast International Group-North American Breast Cancer Group (BIG-NABCG) recommendations, the largest span of the tumor bed area involved by residual viable invasive carcinoma combined together with the tumor cellularity constitutes a better indicator of the tumor response and prognosis [5, 6].

7.4.3 Grade

Tumor grade is a prognostic factor in breast cancer. The most used grading system for invasive carcinoma of the breast is the modified Scarff-Bloom-Richardson system [144]. The invasive carcinoma is graded based on three parameters, namely, tubule and gland formation, nuclear pleomorphism, and mitotic count (Table 7.1) (Fig. 7.39).

Tumor grade is not only an important prognostic factor, but it is also a predictor of response to neoadjuvant systemic therapy. The frequency of complete pathologic response in grade 3 tumors is higher than in grade 1 and 2 tumors [145].

Table 7.1 Grading of invasive carcinoma (Modified Scarff-Bloom-Richardson system)

Tubule and gland formation	Score
Majority of tumor (>75% of tumor)	1
Moderate tubule formation (10%-75% of tumor)	2
Minimal or no tubule formation (<10% of tumor)	3

Nuclear pleomorphism	Score
Small nuclei (<1.5 x normal ductal cell) with minimal pleomorphism, even chromatin pattern, nucleoli not visible or inconspicuous	1
Moderate increase in size (1.5-2 x normal ductal cell) and pleomorphism Nucleoli are visible but small and inconspicuous	2
Large nuclei (>2 x normal ductal cell) with vesicular chromatin, marked variation in size and shape, prominent nucleoli	3

Mitotic count[a]	Score
Total number of mitotic figures in 10 high-power fields (400× final magnification) The score 1–3 thresholds depend on the microscope field diameter	1–3

Final grading Add scores for gland formation, nuclear pleomorphism, and mitotic count	Total score
Grade I/III	3–5
Grade II/III	6 or 7
Grade III/III	8 or 9

[a]Evaluation of mitotic requires optimal tissue fixation and good tissue preparation

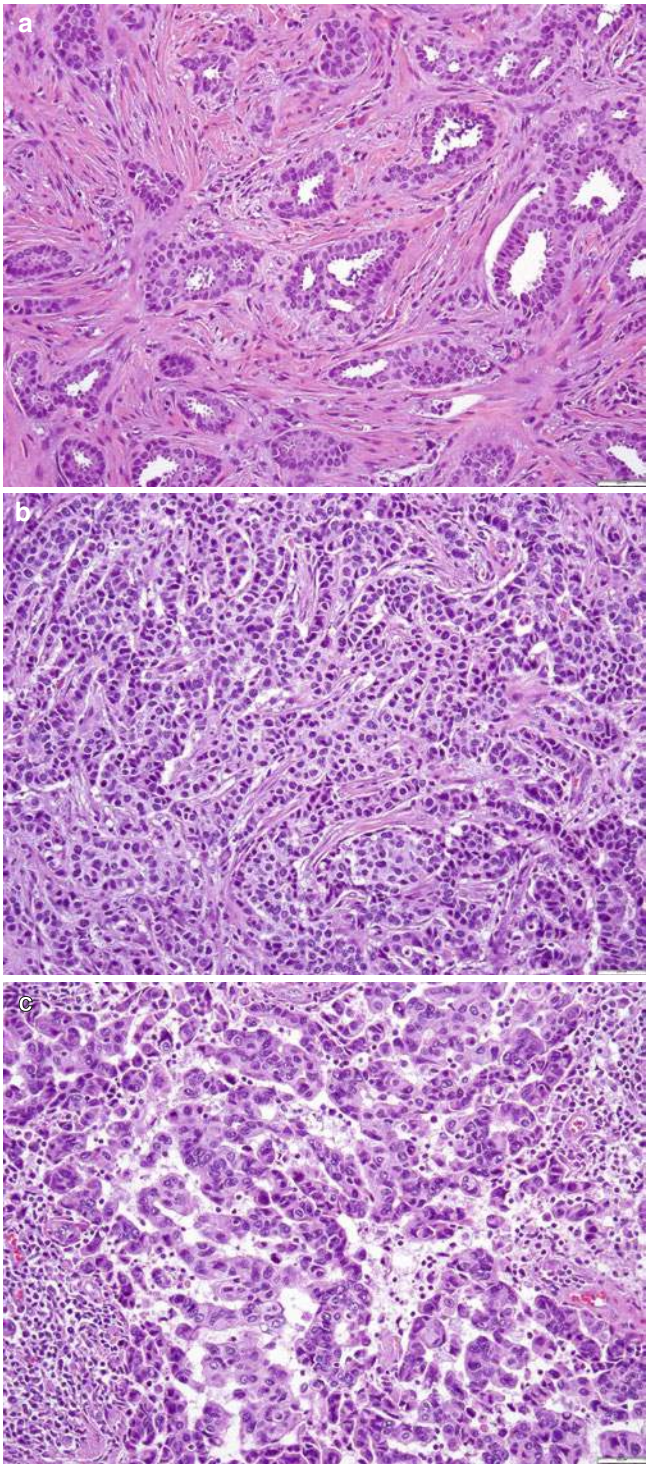

Fig. 7.39 Invasive ductal carcinoma, histologic grade. (**a**) Well-differentiated. (**b**) Moderately differentiated. (**c**) Poorly differentiated

Morphological, immunohistochemical, and molecular studies demonstrated an association between some precursor lesions such as columnar cell changes with atypia, atypical ductal hyperplasia (ADH), lobular neoplasia (ALH and classic LCIS), low-grade DCIS, and invasive carcinomas of low nuclear grade, such as tubular, cribriform, lobular, tubulolobular, and grade 1 (well-differentiated) carcinomas [146–148]. The "low-grade breast neoplasia family" and their non-obligate precursor lesions share similar immunophenotype (ER-positive, HER2-negative) and genetic alterations, with recurrent loss of chromosome 16q, gain of 1p, and low number of genetic alterations per case [110, 147, 149]. In contrast, the immunoprofile and genetic alterations of high-grade DCIS and grade 3 invasive carcinomas are more heterogeneous and have greater genetic complexity [148]. Based on these observations, the low-grade and high-grade carcinomas seem to evolve from distinct molecular pathways, although genetic evidence supports the progression from low- to high-grade carcinoma in a subset of cases.

7.5 Sentinel Lymph Node Biopsy and Axillary Lymph Node Dissection

7.5.1 Sentinel Lymph Node Biopsy

A prospective randomized clinical trial (NASBP-32) demonstrated that ALND can be safely omitted in patients with cT1-T2N0 disease and no evidence of carcinoma in the SLN(s) that were sliced into 2-mm-thick tissue sections and evaluated only with routine H&E-stained slides [150]. As a corollary study, the tissue blocks of the SLNs of patients with no evidence of metastatic disease in the two arms of the study were further evaluated with deeper levels and cytokeratin stains at a central laboratory. The results demonstrated that "Occult metastases were an independent prognostic variable in patients with sentinel nodes that were negative on initial examination; however, the magnitude of the difference in outcome at 5 years was small (1.2% points). These data do not indicate a clinical benefit of additional evaluation, including immunohistochemical analysis, of initially negative sentinel nodes in patients with breast cancer" [151]. Following publication of the aforementioned results, the practice of routinely obtaining additional H&E level sections and cytokeratin stains of SLNs negative for carcinoma in the initial H&E sections to identify occult metastases has been discon-

tinued at most centers, including ours. The results of another prospective randomized clinical trial by the American College of Surgeons Oncology Group (ACOSOG Z0011) [81, 152] led to additional changes in the management of the axillary lymph nodes in patients presenting with cT1-T2N0 disease. The ACOSOG Z0011 study evaluates the survival of patients with cT1-T2N0 disease who were found to have metastatic carcinoma (micro- or macrometastases) in one or two SLNs and treated with breast-conserving surgery, whole-breast irradiation, and systemic therapy as determined by the treating clinician. Four hundred forty-six patients were randomized to SLN biopsy alone and 445 to SLND *and* ALND. The two arms of the study were comparable with respect to patient age, tumor characteristics (grade, size, histology, and estrogen receptor status), and adjuvant systemic therapy [81]. The results of the study, first reported after a median follow-up of 6.3 years, showed no significant survival differences in relapse-free survival and locoregional recurrence between the two groups [81]. At a median follow-up of 9.25 years, no statistically significant difference is detected in local recurrence-free survival between the two groups. The 10-year cumulative incidence of nodal recurrences is 0.5% in the ALND arm and 1.5% in the SLND-alone arm. The 10-year cumulative locoregional recurrence rate is 6.2% with ALND and 5.3% with SLN biopsy alone [153]. Before the publication of the results of the Z0011 trial, SLNs of cN0 patients found to have micro- or macrometastatic disease in the sentinel lymph nodes underwent ALND. In the post-ACOSOG Z0011 era, ALND is limited to cT1-T2N0 patients who do not meet the Z0011 selection criteria, and the practice of routine intraoperative evaluation of SLNs for patients undergoing breast conserving surgery has been discontinued at most centers. ALND is performed if micro- or macrometastatic carcinoma is identified in SLNs from patients with cT1-T2N0 disease surgically managed with mastectomy, because such patients were excluded from the Z0011 trial. Intraoperative assessment of the SLN(s) continues to be performed routinely in this group of patients.

When processing SLNs at intraoperative frozen section or post fixation for permanent section, it is recommended to slice the SLNs into 2-mm-thick sections along the major axis of the lymph nodes [154, 155]. All grossly negative SLNs are entirely submitted for microscopic examination [154, 155]. According to the AJCC staging system, lymph node metastases are classified as macrometastases, micrometastases, and isolated tumor cells (ITCs), based on the size of the tumor deposits [84]. A macrometastasis consists of tumor deposits greater than 2 mm (Fig. 7.40); a micrometastasis is defined as tumor deposits greater than 0.2 mm or greater than 200 cells in a single cross section, but not greater than 2 mm. ITCs are defined as small clusters of tumor cells not greater than 0.2 mm in largest dimension or nonconfluent or nearly confluent tumor cells $\leq$200 cells in a single cross section [84]. The size cutoff values of 0.2 mm and 2 mm were arbitrarily chosen. The size of the tumor deposits is determined by measuring the largest contiguous span of the tumor, and not across the entire span of all tumor deposits. The threshold of 200 cells is especially useful in the evaluation of metastatic lobular carcinoma where the tumor cells are often dispersed instead of forming cohesive clusters. Nonetheless, the quantification of small tumor deposits in lymph nodes continues to be challenging in some cases.

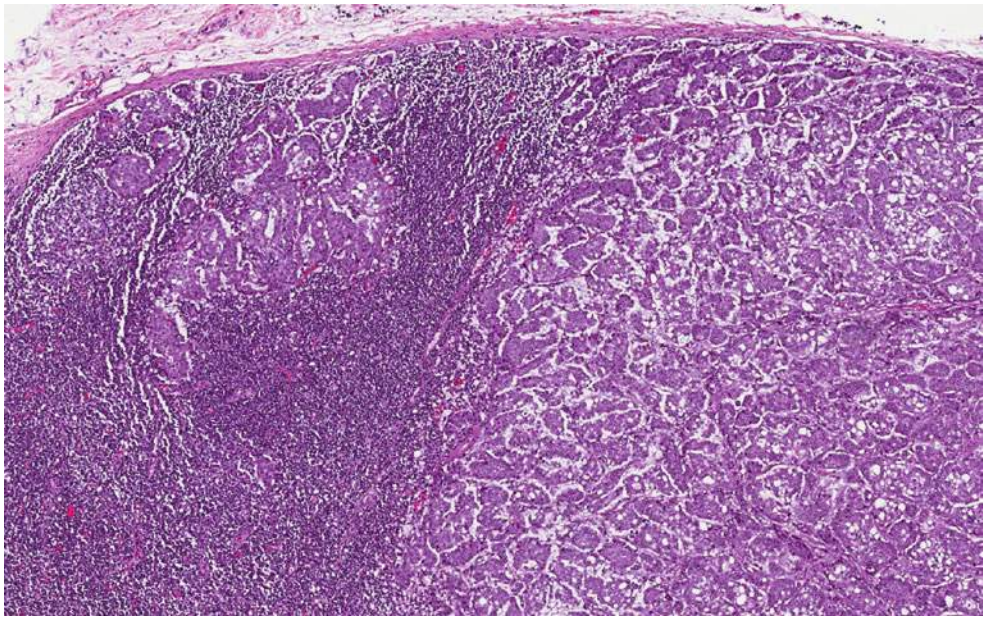

Fig. 7.40 Axillary lymph node with metastatic mammary carcinoma. Metastatic carcinoma extensively involves a lymph node, but does not transgress the lymph node capsule. Residual lymph node tissue is visible

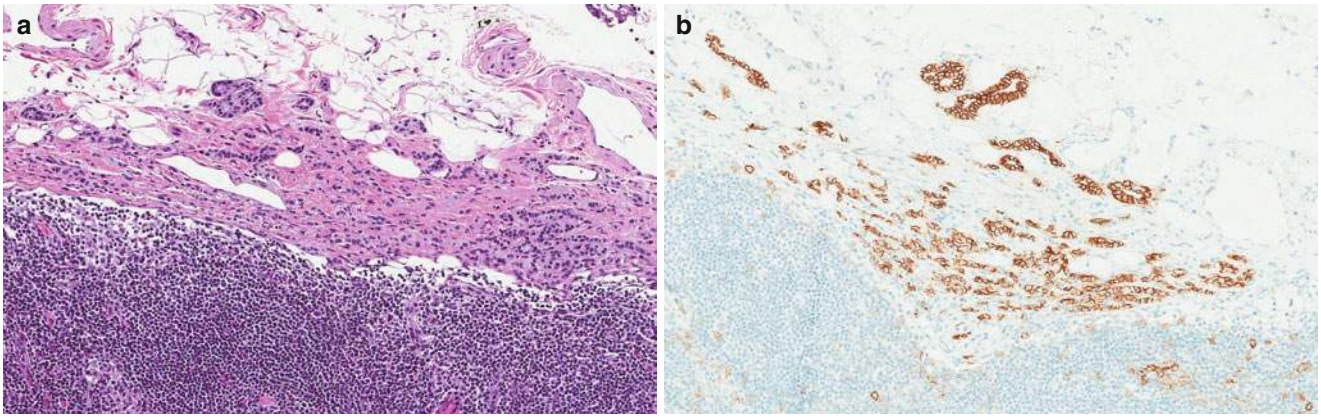

Fig. 7.41 Extranodal extension. In this unusual case, carcinoma was present only in the adipose tissue outside of the lymph node capsule (**a**), but no definite lymph node metastasis was identified. Membranous reactivity for E-cadherin demonstrates that the carcinoma present outside the lymph node has a ductal phenotype

Extranodal or extracapsular extension (ECE) is extension of the metastatic carcinoma beyond the lymph node capsule into the surrounding soft tissue (Fig. 7.41). We routinely report the presence or absence of ECE and the size of the ECE, if present. ECE of the SLN metastasis is significantly associated with non-SLN involvement [156]. Whether ECE is an independent risk factor for locoregional and distant recurrence remains controversial [157–160].

Patients with gross extracapsular extension were excluded from the Z0011 trial, and the significance of microscopic ECE was not evaluated [152]. Gooch et al. retrospectively reviewed patients who would have been eligible for the Z0011 study and underwent ALND at our center, most of them in the pre-Z0011 era [161]. In this study, ECE in SLNs was associated with higher tumor burden in the axillary lymph nodes, and ECE >2 mm was the strongest predictor of additional positive lymph nodes at completion ALND [161]. Choi et al. reviewed data from 208 breast cancer patients with T1-T2 tumors, and 1 or 2 positive SLNs underwent ALND [162]. Patients with ECE (either ≤2 mm or >2 mm) had significantly higher frequency of N2 disease compared to patients without ECE [162]. Patients with ECE ≤2 mm had similar outcome (local, nodal, and distant recurrence) to patients without ECE. Patients with ECE >2 mm had worse survival; however, on multivariate analysis, tumor size and >3 positive node were independent predictors for mortality, while ECE >2 mm was not [162].

7.5.1.1 Sentinel Lymph Node Biopsy Post-neoadjuvant Systemic Therapy

The use of neoadjuvant systemic therapy is increasing, particularly that of neoadjuvant chemotherapy (NACT) for triple-negative and HER2-positive invasive carcinomas. The timing of SLN biopsy in patients receiving neoadjuvant therapy is controversial. Several clinical trials evaluated the feasibility and accuracy of SLN biopsy following NACT. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B27 trial [163] analyzed 428 patients who underwent SLN mapping following NACT. The overall success rate of SLN identification was 84.8% [163]. The success rate was significantly higher when radioisotope was used for the mapping, either alone or in combination with blue dye [163]. The false-negative rate (FNR) of SLN biopsy in predicting the axillary nodal status in 343 patients who also underwent ALND was 10.7% [163]. The SENTINA (SENTinel NeoAdjuvant) study reported a SLN detection rate of 80.1% among 592 patients who underwent SLN biopsy after NACT and FNR of 14.2% among 474 patients who converted from cN+ to ycN0 post NACT [164]. In multivariate analysis, the number of lymph nodes examined was a significant factor. The FNR was less than 10% for patients with three or more SLNs removed, compared to 24.3% when only one SLN was removed and 18.5% when two SLNs were removed [164].

The American College of Surgeons Oncology Group (ACOSOG) Z1071 (Alliance) trial evaluated the false-negative rate of SLN biopsy following neoadjuvant chemotherapy in patients initially presented with biopsy-proven node-positive cN1 breast cancer [165]. The rate of SLN identification in 651 patients with cN1 disease was 92.9%. Of the 310 patients with residual nodal disease, the FNR of SLN biopsy was 12.6%, above the prespecified threshold of 10.0% [165]. Similar to the NSABP B27 trial and SENTINA trial [163, 164], the FNR of SLN biopsy was significantly reduced when blue dye injection and radiolabeled tracer were used together for SLN mapping and if at least three SLNs were identified [165]. The FNR of SLN biopsy among patients with three or more SLNs examined was 9.1% [165]. Although Z1071 failed to meet the prespecified threshold of

a false-negative rate of 10%, further analysis of the data from the Z1071 trial suggested that placing a clip in the biopsy-proven positive lymph node at the time of biopsy and identification and removal of the clipped node at the time of SLN biopsy could improve the FNR [166].

The protocol for prosection and examination of SLNs in patients who have received neoadjuvant therapy does not differ from that of patients who undergo a similar surgical procedure before receiving systemic therapy, but the finding of any amount of residual viable carcinoma constitutes evidence of metastatic disease. In particular, the finding of ITCs is clinically relevant in the neoadjuvant setting. The presence or absence of treatment effects is also documented. The following information is included in the pathology report of lymph node status post NACT: number of examined lymph nodes, number of lymph nodes with viable carcinoma, size of the largest metastatic focus, number of lymph nodes with treatment effect *and* viable carcinoma, number of lymph nodes with treatment effect *without* viable carcinoma, and presence and extent of extracapsular extension, if present.

Additional levels and/or cytokeratin stains are obtained to evaluate suspicious findings, but are not performed routinely [6]. In the Sentinel Node Biopsy Following Neoadjuvant Chemotherapy (SN FNAC) study, the FNR of SLN biopsy was 13.3% but was lowered to 8.4% with the use of immunohistochemical stains for cytokeratins [167].

7.5.2 Axillary Lymph Node Dissection

When handling an ALND specimen, all the lymph nodes are dissected, thinly sectioned, and entirely submitted for microscopic examinations. It is important to give an accurate count of the lymph nodes that are dissected, because the number of positive nodes is an important factor in determining the tumor stage. When reporting the status of the axillary lymph nodes, we specify the number of lymph nodes examined, the number of lymph nodes with metastatic carcinoma, the size of the largest metastatic focus, the presence/absence of extracapsular extension, and when present, the size of the extracapsular extension.

7.6 Staging

Staging of breast carcinoma is determined using the tumor-node-metastasis (TNM) system based on the latest recommendations by the AJCC [84]. Clinical staging is denoted using a prefix "c." Pathologic staging summarizes the clinical staging and the data from pathological examination and is denoted using a prefix "p." Staging of breast carcinoma in patients who have received post-neoadjuvant therapy is designated using a prefix "yc" or "yp."

7.7 Prognostic and Predictive Factors

7.7.1 Estrogen Receptor, Progesterone Receptor, and Human Epidermal Growth Factor Receptor 2

Estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) are the main predictive and prognostic markers for invasive breast carcinoma. The assessment of ER, PR, and HER2 status requires the use of accurate, sensitive, specific, and reliable methods. In the USA, it is mandatory to use US Food Drug and Administration (FDA)-approved assays. ER, PR, and HER2 status should be assessed in all primary, recurrent, and metastatic breast carcinomas. DCIS with no evidence of associated invasive carcinoma is tested for ER (and PR). This practice is based on the results of a subset analysis of NSABP-B24 trial data which showed that adjuvant tamoxifen significantly reduced subsequent breast cancer at 10 years after lumpectomy and radiation in women in ER-positive DCIS, while no significant benefit was observed in ER-negative DCIS [168]. The ER, PR, and HER2 status of metastatic breast carcinoma usually resembles that of the primary tumor, but sometimes it is different, particularly after prolonged hormonal treatment. In a study of 233 primary breast carcinomas and paired metachronous non-osseous distant metastases, receptor conversion for ER and PR was 15.1% and 32.6%, respectively, including 12.4% of the tumors going from ER- or PR-positive to ER-/PR-negative and 8.2% from ER-/PR-negative to ER- or PR-positive [169]. HER2 conversion by immunohistochemical staining was 5.2%; in half of the cases with a change in HER2 status, HER2 was negative in the primary carcinoma, but the metastasis was HER2-positive; in the remaining half of the cases, HER2 conversion was from positive to negative [169].

The ASCO/CAP established guidelines for ER, PR, and HER2 testing in breast carcinoma [97, 98], including standardization of pre-analytic variables, the type of fixative and the optimal length of tissue fixation, the use of validated antibodies and appropriate control tissues, and assay interpretation and reporting. The specimen should be fixed as quickly as possible in an adequate volume of fixative. The cold ischemia time should be documented; the recommend cold ischemia time should be $\leq$1 h. Several studies have shown that prolonged cold ischemia time can alter the detection of ER, PR, and HER2 by immunohistochemistry [100, 170, 171] and the detection of HER2 amplification by in situ hybridization [171]. Significant reduction of ER, PR, and HER2 signal by immunohistochemistry was observed after 2 h for non-refrigerated tissue samples and after 4 h for refrigerated samples [100]. Only 10% neutral buffered formalin should be used as the fixative for breast tissue specimens; the breast tissue specimen should be

sliced into 4–5-mm-thick sections to facilitate formalin penetration, placed in abundant fixative, and fixed for at least 6 h and no more than 72 h [97, 98].

The ER, PR, and HER2 status of invasive carcinoma can be assessed in any tumor tissue sample from the primary or metastatic site, whether obtained by needle core biopsy or surgical excision. The ER, PR, and HER2 status of newly diagnosed breast carcinoma is usually assessed at most centers using core needle biopsy samples, whereas in the past testing was usually performed in the tumor in the resection specimen. This change of practice has been in part driven by an increase in the use of neoadjuvant chemotherapy in patients with triple-negative and HER2-positive carcinomas. A number of studies documented high concordance between the results of ER, PR, and HER2 status assessed in the invasive carcinoma in the core needle biopsy samples and in the paired surgical excision specimens [172–181]. The current ASCO/CAP guidelines for HER2 testing recommend routine evaluation of HER2 in the carcinoma in the needle core biopsy specimen and to repeat the HER2 assessment in the excision specimen if any "histopathologic discordance" is noted [98]. Possible scenarios of "histopathologic discordance" include:

1. The initial HER2 test is positive, and the invasive carcinoma is grade 1 invasive ductal or lobular carcinoma, ER and PR-positive, or the invasive carcinoma is at least 90% pure of the special histologic subtypes such as tubular, mucinous, cribriform, and adenoid cystic carcinoma. A new HER2 test should be ordered on the basis of these criteria.
2. A new HER2 test may be ordered on the excision specimen if one of the following is observed: The initial HER2 test is negative, and the tumor is grade 3; or if the amount of invasive carcinoma in the core biopsy is small, the resection specimen contains high-grade carcinoma that is morphologically distinct from that in the core; or core biopsy result is equivocal for HER2 by both immunohistochemistry and in situ hybridization [98].

Some investigators, however, reported that repeat HER2 testing based on grade 3 histology alone had limited impact [180, 181]. In a study comparing the HER2 results of 400 carcinomas that had been tested both using the core biopsy material and the subsequent excision specimen [180], 8/400 (2%) cases were found to be discordant. Further analysis of the discordant cases showed that the policy of retesting HER2 status in grade 3 carcinomas found to be HER2-negative in the needle core biopsy specimen would have identified only one false HER2-negative carcinoma out of the 116 tumors that were retested [180]. Prendeville et al. assessed the rate of HER2 discordance in the surgical excision specimen with grade 3 invasive carcinomas that were HER2-negative in the core biopsy material [181] and found a 97% concordance rate among 100 grade 3 invasive carcinomas that were HER2-negative in the needle core biopsy [181]. The three discordant cases had equivocal HER2 results by immunohistochemistry (IHC) and low level of amplification by dual in situ hybridization (ISH) [181].

In post-neoadjuvant systemic therapy specimens, retesting ER, PR, and HER2 status is not recommended for any of the marker positive in the pretreatment core biopsy material [6], but should be performed if the biomarker status is unknown, or retesting is required as part of a clinical trial protocol [6]. Retesting should be considered for negative or equivocal results in the pretreatment core biopsy sample, if there was insufficient invasive tumor for accurate assessment on pretreatment core biopsy, or if there is heterogeneous tumor or multiple tumors with different morphologies on resection [6].

7.7.1.1 ER and PR

ER is expressed in approximately 70% of all invasive breast carcinomas. Adjuvant endocrine therapy (i.e., tamoxifen and aromatase inhibitors) is highly effective in patients with ER- and/or PR- positive carcinoma and will lower the risk of disease recurrence. Harvey et al. found that ER status was a highly significant predictor of disease-free survival for breast cancer patients who received adjuvant endocrine therapy either alone or in combination with chemotherapy [182]. In this study, ER by IHC was scored using the Allred scoring system [183] which is based on the percentage of the tumor cells showing positive nuclear staining and the staining intensity. ER-positive tumors were defined as having a score >2, which corresponds to ≥1% positive nuclear staining of any intensity [183]. The same staining cutoff is used for PR. According to the ASCO/CAP guidelines, a tumor is considered ER- or PR-positive if ≥1% of nuclear staining is present in tumor cells by immunohistochemistry [97] (Fig. 7.42). For ER and PR, the pathology report should include the percentage of tumor cells showing positive nuclear staining and the staining intensity (weak, moderate, or strong). The same scoring system applies also to ER/PR evaluation in DCIS.

The selection of antibodies for ER and PR IHC testing should be restricted to those recommended by the ASCO/CAP guidelines, including clones 1D5, 6F11, SP1, and 1D5+ER2.123 for ER and clones 1A6, 1294, and 312 for PR [97]. Positive and negative controls should be included in every immunohistochemical staining assay. Normal breast epithelium has a heterogeneous staining pattern for ER and PR and serves as a valuable internal positive control. In most laboratories, an external positive control tissue is also placed on the same slide with the index carcinoma. The staining should be repeated if the external or internal control tissue does not show the expected reactivity.

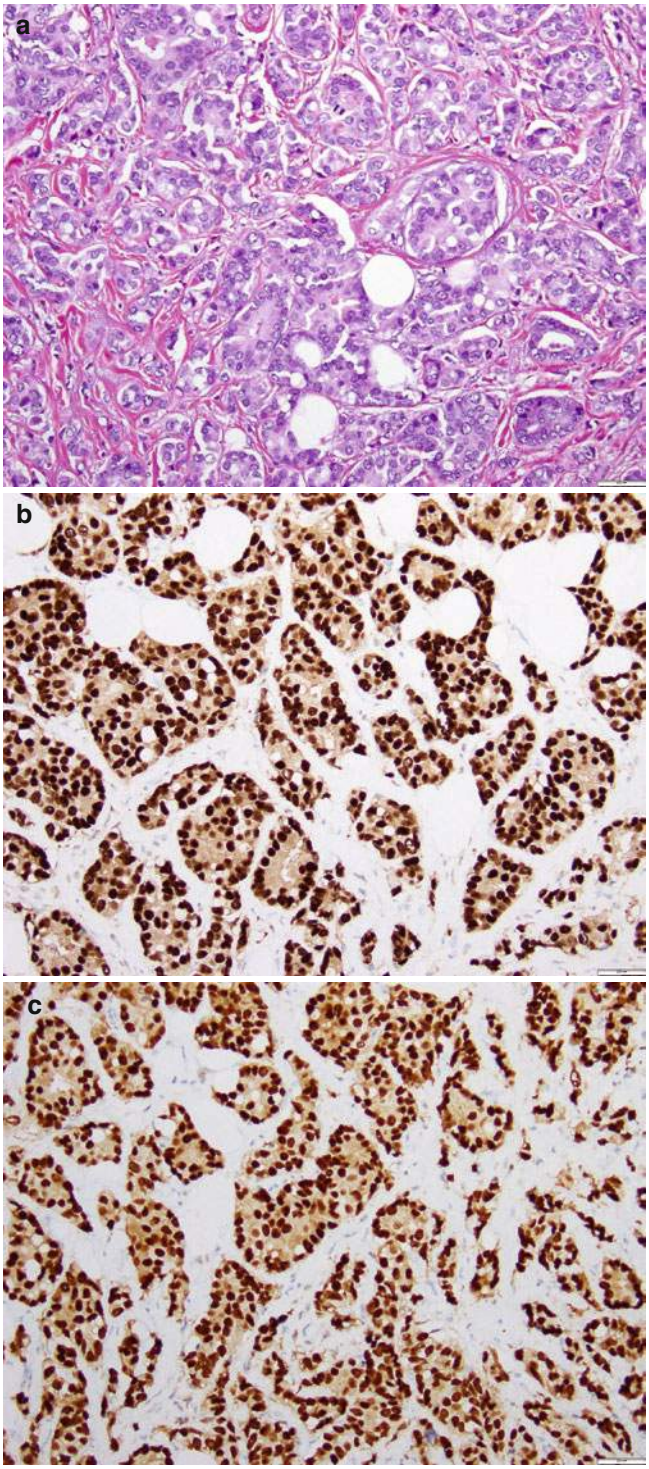

Fig. 7.42 Immunohistochemical stain for ER and PR in invasive ductal carcinoma. (**a**) H&E; (**b**) ER; (**c**) PR

7.7.1.2 HER2

HER2 is a member of the human epidermal growth factor receptor family. Overexpression or amplification of HER2 occurs in approximately 15–20% of the primary invasive breast carcinoma. Trastuzumab (Herceptin), a monoclonal antibody targeting the extracellular domain of the HER2 protein, is the first anti-HER2 drug approved for the treatment of HER2-positive breast cancer. It was approved in 1998 as a first-line treatment in combination with chemotherapy for HER2-positive metastatic breast cancer [184]. In 2006, the FDA expanded the use of trastuzumab for early-stage HER2-positive breast cancer after primary therapy. Trastuzumab plus chemotherapy significantly improved disease-free survival and overall survival in women with HER2-positive early-stage breast cancer [185, 186]. Other HER2-targeted drugs have been approved for the treatment of HER2-positive breast cancer, including pertuzumab (Perjeta) [187, 188], a monoclonal antibody inhibiting dimerization of HER2 and HER3 receptors; lapatinib (Tykerb) [189], a tyrosine kinase inhibitor; and trastuzumab emtansine (T-DM1), an antibody drug conjugate [190]. These new HER2-targeted drugs are now being tested in the adjuvant setting, either alone or in dual antibody regimens with trastuzumab.

The HER2 status of invasive carcinoma is used to identify patients suitable for HER2-targeted therapies. The ASCO/CAP guidelines for HER2 testing in breast cancer were first issued in 2007 [191] and updated in 2013 [192] and in 2018 [98]. The 2013 ASCO/CAP guidelines lower the HER2-positive threshold by IHC from 30 to 10% of tumor cells with strong circumferential staining and by in situ hybridization (ISH) from HER2/CEP17 ratio from 2.2 to 2.0. According to the 2018 ASCO/CAP guidelines [98], HER2 testing by IHC assay is reported as positive (3+) if there is circumferential membrane staining that is complete and intense in >10% of the tumor cells (Fig. 7.43). If the membrane staining is complete but weak/moderate in >10% of tumor cells, HER2 staining is equivocal (2+), and reflex testing is required [98]. HER2-negative staining is either 1+ staining (incomplete membrane staining that is faint/barely perceptible in >10% of tumor cells) or HER2 0 (no staining observed or incomplete membrane staining that is faint/barely perceptible in ≤10% of tumor cells) [98].

The 2018 ASCO/CAP guidelines [98]revised the HER2 testing algorithm to address the less common HER2 dual-probe ISH scenarios and eliminated the ISH equivocal category following the 2013 guidelines. By dual-probe ISH assay, HER2 amplification is defined as *HER2*/CEP17 ratio ≥2.0 and the average HER2 copy number ≥4.0 signals per cell (ISH Group 1) [98] (Fig. 7.44). *HER2*/CEP17 ratio <2.0 and average *HER2* copy number <4.0 signals per cell is interpreted as negative (ISH Group 5) [98]. For the less common HER2 dual-probe ISH groups, concomitant IHC review is required. If HER2 IHC is 3+, the diagnosis is HER2 positive. If *HER2/CEP17* ratio is ≥2.0 but the average *HER2* signals per cell is <4.0 (ISH group 2), and the concurrent HER2 IHC is 0-1+ or 2+, the diagnosis is HER2 negative. If *HER2/CEP17* ratio is <2.0 but the average *HER2* signals per cell is ≥6.0 (ISH group 3), and the concurrent HER2 IHC is 2+ or 3+, the diagnosis is HER2 positive. If *HER2/CEP17* ratio is

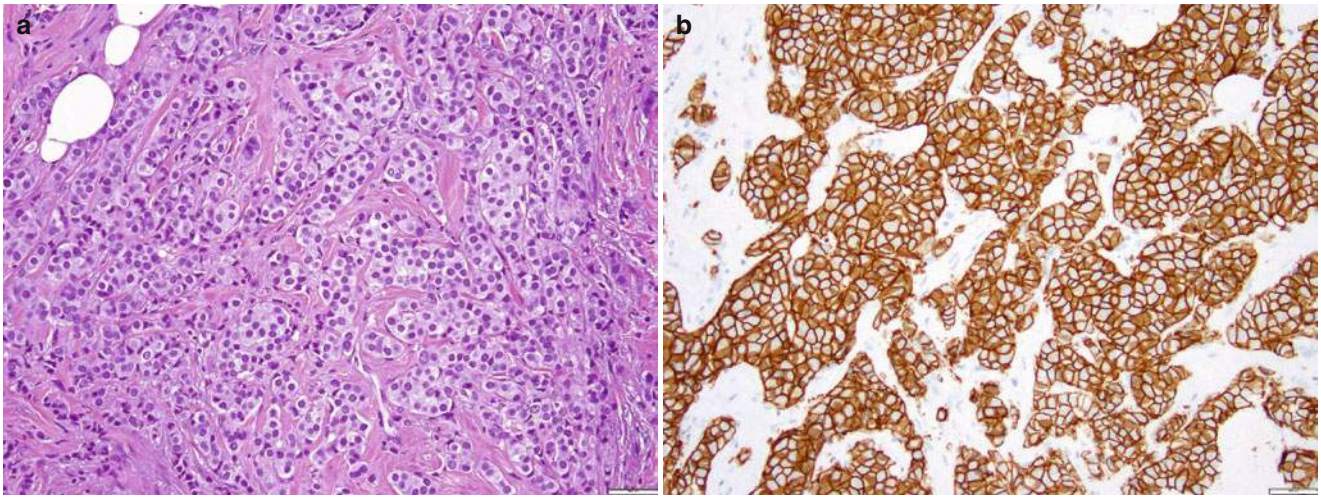

Fig. 7.43 Immunohistochemical stain for HER2 (**a**) H&E; (**b**) HER2 3+ staining is a complete and strong membranous staining in >10% of the neoplastic cells

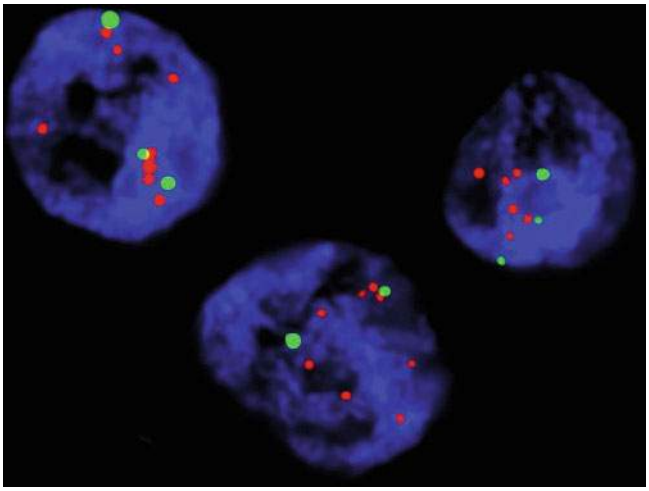

Fig. 7.44 In situ fluorescent hybridization for FISH shows HER2 amplification. The green dots identify the gene for the centromere of chromosome 17 (CEP17). Each red dot corresponds to a copy of the HER2 gene. In each of the three tumor cells shown, the ratio of the HER2 gene copy number divided by the number of the CEP17 is greater than 2 (2.7 ratio)

<2.0 but the average *HER2* signals per cell is ≥4.0 and <6 (ISH group 4), and the concurrent HER2 IHC is 0-1+ or 2+, the diagnosis is HER2 negative (formerly HER2 ISH equivocal).

Although HER2 activation in breast cancer is mainly through *HER2* gene amplification, recent studies have discovered *HER2*-activating mutations as an alternative mechanism to activate *HER2* in breast cancer [193]. Bose and colleagues analyzed data from 8 breast cancer genome-sequencing projects and identified 25 patients with *HER2* somatic mutations, mostly in *HER2* gene amplification negative breast cancer [114, 193]. In 17 of the 25 patients, *HER2* mutation occurred in the kinase domain. Functional analysis of 13 HER2 somatic mutations revealed 7 of these are activating mutations, including G309A, D769H, D769Y, V777L, P780ins, V842I, and R896C [193]. *HER2* mutations are enriched in invasive lobular carcinoma, especially those with high-grade, non-classic histology [116]. Sequencing analysis of 75 relapsed invasive lobular carcinomas identified HER2 mutations in 18% of the cases [194]. These mutations can be potentially actionable with tyrosine kinase inhibitors.

7.7.2 Ki67

Ki67 is a cell proliferation marker and has been shown to be a prognostic factor in breast cancer [195–199]. Cheang and colleagues described a four-biomarker immunopanel (ER, PR, HER2, Ki67) to identify luminal A and luminal B breast cancers defined by gene expression profiling [197]. Both luminal A and luminal B subtypes are ER- and/or PR-positive, HER2-negative. Ki67 index of 14% was used as the cutoff to distinguish between luminal A and luminal B subtypes, luminal A subtype as being Ki67 index <14% and luminal B subtype as being Ki67 index ≥14% [197]. Luminal B tumors are associated with increased risk for recurrence and death from breast cancer as compared with luminal A tumors [197].

Despite evidence that Ki67 is a valuable prognostic marker, assessing Ki67 by IHC has not become routine clinical practice because of the lack of reproducibility across laboratories. An International Ki67 in Breast Cancer Working Group proposed guidelines for the analysis and reporting of Ki67 [200]. Although these guidelines aimed to minimize pre-analytic, analytic, and post-analytic variabilities, a subsequent Ki67 reproducibility study conducted by the same group of investigators observed

large variation among laboratories in the assessment of Ki67 [201]. In addition, Ki67 is a continuous variable, and the cutoff values to distinguish "Ki67 high" from "ki67 low" varied among studies. The lack of a validated cutoff value further limits the clinical utility of Ki67 assessment. The current ASCO clinical practice guidelines do not recommend the use of Ki67 index by IHC to guide choice on adjuvant chemotherapy or endocrine therapy [202].

7.7.3 Androgen Receptor

Androgen receptor (AR) is frequently expressed in breast cancer. AR positivity was reported in 60–80% of breast cancer in various studies [203–208]. The majority (over 90%) of the ER-positive breast cancers are also positive for AR [206, 207]. AR is positive in 10–36% of triple-negative breast cancers (ER-negative, PR-negative, HER2-negative) by immunohistochemistry [206–208]. Farmer et al. described a "molecular apocrine" group of breast cancer by gene expression profiling analysis, characterized by AR positivity and ER negativity [209]. The "molecular apocrine" group is significantly associated with apocrine histology [209]. Lehmann et al. described six subtypes in triple-negative breast cancer by gene expression profiling [210]. Luminal androgen receptor (LAR) is one of the distinct subtypes [210]. Tumors in the LAR subtype have high levels of AR mRNA and protein expression and display luminal gene expression patterns [210]. Although the incidence of AR positivity is lower in triple-negative breast cancer than in ER-positive breast cancer, it's of greater clinical significance in triple-negative breast cancer, because patients with triple-negative breast cancer do not benefit from conventional endocrine therapy. A phase II study investigated the effects of bicalutamide, an AR antagonist in patients with AR-positive, ER-/PR-negative metastatic breast cancer [211]. Of 424 patients with ER-/PR-negative breast cancer, 12% tested AR-positive, defined as greater than 10% nuclear staining in tumor cells by immunohistochemistry [211]. The study observed a 6-month clinical benefit rate of 19% [211]. The drug was well-tolerated with no grade 4/5 treatment-related adverse events. It is therefore important to include AR immunohistochemistry as part of routine testing in triple-negative breast cancer, to identify a subset of patients with triple-negative breast cancer that might benefit from anti-AR therapy. However, currently, there are no FDA-approved standard reagents for AR immunohistochemistry and no guideline recommendations for AR testing and standard cutoff value for AR positivity. Some studies applied the 1% threshold similar to the ASCO/CAP guidelines for ER/PR positivity, while other studies used 10% cutoff.

7.7.4 Multigene Assays

In the past decade, several multigene assays have been developed and showed prognostic value in patients with early-stage breast cancer, such as the 21-gene recurrence score (Oncotype Dx™, Genomic Health, Redwood City, CA) [212], the 70-gene assay (Mammaprint™, Agendia, Amsterdam, the Netherlands) [213], and the prediction analysis of microarray 50 (PAM50) (Prosigna™, NanoString Technologies, Seattle, WA) [214, 215]. The 21-gene recurrence score assay has been validated for its use as a prognostic test to qualify the risk of distant recurrence as well as in predicting benefit of adjuvant chemotherapy [212, 216]. The American Society of Clinical Oncology and National Comprehensive Cancer Network (NCCN) currently include the Oncotype Dx recurrence score in their recommendations for patients with early-stage ER-positive, HER2-negative breast cancer [202, 217].

Oncotype Dx is a multigene assay that estimates the likelihood of distant recurrence at 10 years and chemotherapy benefit in patients with early-stage, node-negative, ER-positive, HER2-negative breast cancer treated with tamoxifen [212]. The assay analyzes the expression of a panel of 21 genes by RT-PCR, including 16 cancer-related genes and 5 reference genes [212]. The recurrence score (RS), ranging from 0 to 100, is calculated from the gene expression results using the prospectively defined algorithm. Five of the 16 cancer-related genes are proliferation genes including Ki67. The score of the proliferation group, together with the scores of hormone receptors, is heavily weighted in the score algorithm. The recurrence score is classified into three categories: low risk (RS < 18), intermediate risk (RS 18–30), and high risk (RS ≥ 31) [212]. The prognostic value of the assay and prediction of chemotherapy benefit in patients with stage I–II, node-negative, ER-positive breast cancer treated with 5 years of tamoxifen were validated by retrospective analysis of 668 samples from the NSABP B-14 study and 651 samples from the NSABP B-20 study [212, 216]. Analysis of a subset of patients in the SWOG 8814 trial found that the predictive and prognostic value of Oncotype DX recurrence score also applies to patients with ER-positive, node-positive breast cancer [218]. A prospective study, the Trial Assigning Individualized Options for Treatment (Rx) (TAILORx), was designed to determine chemotherapy benefit in patients with node-negative, ER-positive, HER2-negative breast cancer and recurrence score in the intermediate risk group [219]. Initial results of TAILORx confirm an extremely low risk of recurrence in patients with RS 0–10, with 99.3% of patients free from distant recurrence of breast cancer at 5 years [220]. The latest results of the TAILORx study showed no benefit from adding chemotherapy to endocrine therapy for women

with intermediate recurrence score (11-25), especially for those older than 50 years of age [221]. At a median follow-up of 7.5 years, endocrine therapy was noninferior to chemotherapy plus endocrine therapy in the analysis of invasive-disease free survival. In women 50 years or younger with a recurrence score 16-25, there is a small benefit from chemotherapy [221]. The recurrence score cutoff values for low risk (0–10) and intermediate risk (11-25) used in TAILORx trial are substantially different from those previously defined [212, 220, 222]. Use of the Oncotype Dx assay significantly impacts adjuvant chemotherapy recommendations in node-negative, ER-positive, HER2-negative, breast cancer patients, resulting change of treatment recommendations in about 30% of the patients [223–227]. The recurrence score is incorporated in breast cancer staging in the 8th edition of the American Joint Commission on Cancer (AJCC) staging guidelines [84].

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Molecular Classification and Prognostic Signatures of Breast Tumors

8

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8.1 Introduction

Breast cancer is a complex and heterogeneous disease where tumors of the same apparent prognostic type can vary widely in their responsiveness to therapy and survival rates. Traditionally the classification of breast cancer is performed based on clinical-histopathological parameters, such as age, tumor size, histological grade, lymph node status and by the analysis of estrogen (ER), progesterone (PR), and human epidermal growth factor 2 (HER2) receptors expression. The evaluation of these combined factors has been widely used in clinical practice and formed the basis to classify patients into various risk categories such as the St. Gallen criteria [1] and the Nottingham Prognostic Index [2]. However, the markedly extensive breast cancer heterogeneity combined with the lack of reliable predictive factors among these categories limits their ability to distinguish subtle phenotypic differences that may present relevant therapeutic implications.

With the extraordinary advances obtained with high-throughput microarray platforms, genome-wide methodologies have been widely employed to molecularly classify breast cancer. The pioneer studies, based on gene expression profiling, have showed that gene expression patterns can classify breast tumors into different subtypes, known as "intrinsic" subtypes, representing a significant improvement over the traditional methods of tumor classification [3, 4]. Subsequent refining of these intrinsic subtypes have led to the identification of subgroups within each and across these subtypes as well as the identification of novel ones, with corresponding clinical implications in treatment response [for review, see [5, 6]]. In addition, with the recent integration of multiomics data, more comprehensive breast cancer signatures with distinct copy number, metabolomics, methylation, gene expression, microRNA, and protein expression patterns [7, 8] have emerged. As results of these studies, several prognostic gene signatures have been proposed to predict clinical outcome and customize therapy, including the ones based on immune response genes, such as the programmed death receptor 1 (PD-L1) and its associated pathways [9].

In this chapter, we will discuss some of these molecular signatures and its significant roles in providing new insights into breast cancer classification and in assessing patient's prognosis and defining therapy.

8.2 Molecular Classification

8.2.1 The Gene Expression "Intrinsic" Subtypes

Genome-wide studies, using microarray hybridization methods, have allowed the analysis of the DNA copy-number changes or gene expression of thousands of genes in one single experiment in a given tumor sample [10–12]. These methodologies revealed at the molecular level the complexity of the notable breast cancer heterogeneity [13–15], as clearly demonstrated by the large variation in the gene expression patterns.

The pioneer study described by Perou et al. [3], using gene expression analysis, sets the basis for the current molecular classification of breast tumors known as the "intrinsic" molecular subtypes. These authors performed cDNA microarray analysis in a set of normal and malignant human breast tissues from 42 individuals. Using a hierarchical clustering method, the samples were clustered into four molecular subtypes according to differences in their gene expression profiles (of 1753 genes): luminal, normal breast-like, HER2, and basal-like. In a very simplistic description, luminal tumors were characterized by high expression of

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_8

hormone receptors and associated genes; normal breast-like cancers were defined by poorly characterized tumors; HER2 subtypes presented high expression of HER2 and other genes located in the 17q amplicon and low expression of ER and associated genes; and basal tumors presented high expression of basal epithelial genes, basal cytokeratins and epidermal growth factor receptor (EFGR), and low expression of ER and associated genes. Morphological and immunohistochemical features of basal-like cancers were similar to those described for tumors arising in *BRCA1* germline mutation carriers [16–19].

In subsequent larger studies from the same group, it was demonstrated that the luminal subtype could be further divided into at least two subgroups (luminal A and B) [4, 20, 21] each with different gene expression profiles and different prognosis (Fig. 8.1). Luminal A tumors presented high levels of expression of ER-activated genes and low proliferation rates and were associated with a good prognosis, whereas luminal B tumors were more often of higher histological grade and presented higher proliferation rates and a worse prognosis. This initial molecular taxonomy has been validated in several other studies, which also identified few less-defined subtypes, including the interferon-rich, molecular apocrine and claudin-low tumors [20–28]. The complete molecular characterization and the clinical implications of these less-defined subtypes are not yet fully identified and/or known.

Extensive work has been additionally performed for a more refinement of the molecular classification of the triple-negative breast cancer (TNBC) tumors. In a seminal study by Lehmann's group [29], this breast cancer subtype was further subdivided by gene expression analysis into six TNBC subtypes (and one unstable group (UNS): basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR)). These subtypes present molecular alterations that target specific cellular processes and signaling pathways; the BL1 subtype is characterized by expression alterations of genes involved in cell cycle and DNA damage response, such as the ones affecting the ATR/BRCA pathways; the gene expression patterns of the BL2 subtype impact growth factor signaling (e.g., EGF, IGFR1, and WNT), glycolysis/gluconeogenesis, and the expression of myoepithelial markers. The IM subtype targets immune-regulatory pathways (e.g., cytokines) and presents gene expression patterns representative of both the tumor cells and infiltrating lymphocytes. Both M and MSL subtypes share elevated expression of genes involved in epithelial-mesenchymal transition (EMT), cell motility, and growth factor pathways (e.g., TGF-beta-, EMT-, IGF-, and PDGF-related markers). The MSL subtype, however, presents decrease expression of genes involved in proliferation, which is accompanied by the expression of genes associated with stem cells. The LAR subtype is characterized by luminal gene expression and is driven by the androgen receptor (AR). Other independent studies have been performed for the subclassification of TNBC subtypes using, in addition to gene expression, an integration of several other genome-wide molecular analysis [see below: [30–32]].

The five major molecular breast cancer subtypes identified in the initial gene expression studies cited above differ not only with regard to their pattern of gene expression and clinical features but also to the response to treatment and clinical outcome [21, 33–37]. Patients with luminal tumors respond well to endocrine therapy; however, luminal A and B tumors respond differently in response to the type of the endocrine agent used (tamoxifen or aromatase inhibitors) and also present a variable response to chemotherapy [38–41]. Patients with luminal A tumors present with an overall good prognosis with a 5-year survival rate of approximately

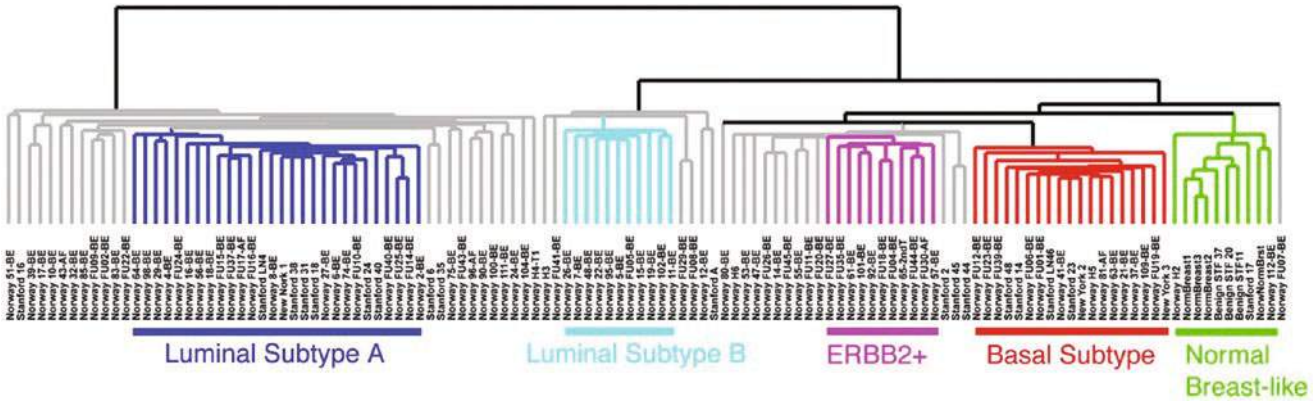

Fig. 8.1 Breast cancer classification into five molecular subtypes. Hierarchical clustering of 115 tumor tissues and 7 nonmalignant tissues using the "intrinsic" gene set. Experimental dendrogram showing the clustering of the tumors into five subgroups. Branches corresponding to tumors with low correlation to any subtype are shown in gray. Source: *Sorlie et al., PNAS U.S.A. 100(14):8418-23, 2003. Copyright (2003) National Academy of Sciences, U.S.A.*

90%. Patients with HER2-amplified tumors respond to the trastuzumab antibody monoclonal therapy and to anthracycline-based chemotherapy; however, they generally present poor prognosis, and their 5-year survival rate can be as low as 20% [42, 43]. Finally, patients with the basal-like tumor subtype present no response to endocrine therapy or trastuzumab; however, they can be sensitive to platinum-based chemotherapy and PARP (poly (ADP-ribose) polymerase 1) inhibitors [44–46]. These tumors are especially common in African-American women and generally confer poor prognosis [47, 48]. Interestingly in the neoadjuvant setting, the intrinsic subtypes have also been found to present different responses to treatment. The pathological complete response (pCR) rates to the standard chemotherapy based on anthracycline and taxane were approximately 7% for luminal A, 17% for luminal B, 36% for HER2-positive, and 43% for basal-like subtype [41]. In the subclassification of TNBC into six different subtypes described above [29], distinct cytotoxic effects of chemotherapeutic agents were also observed, showing the markedly heterogeneity of these tumors in relation to treatment response and the impact of gene expression profiles in conferring distinct outcomes in TNBC patients [for review, see [6, 37]]. More recently, the initial six TNBC molecular subtypes proposed were reduced into four tumor-specific subtypes: BL1, BL2, M, and LAR [49]. In this study, neoadjuvant chemotherapy response was evaluated in over 300 retrospective cases of TNBC subtyped using the molecular classification and demonstrated that the response to similar neoadjuvant chemotherapy varied significantly among the subtypes: 41% of BL1 patients achieved a pCR compared to 18% for BL2 and 29% for LAR.

To study the utility of the major breast cancer subtypes in breast tumor classification, a total of 189 breast tumors across 1906 "intrinsic" genes were initially analyzed by Parker et al. [39]. These authors identified a set of 50 genes that were further validated and compared for reproducibility of classification across different prediction methods and different patient cohorts. This analysis profiled by qRT-PCR (quantitative real-time PCR) a total of 122 breast cancers from the 189 individuals into the "intrinsic" subtypes luminal A, luminal B, HER2-positive, basal-like, and normal-like. Due to its high reproducibility a standardized method of classification was developed, the PAM (Prediction Analysis of Microarray) 50 Breast Cancer Intrinsic Classifier test, which is commercially available (Renamed Prosigna Breast Cancer Prognostic Gene Signature Assay) [50]. The PAM50 assay offers the measurement of the expression level of 55 genes (50 classifier genes and 5 housekeepers) and is recommended for all patients diagnosed with invasive breast cancer, regardless of tumor stage or ER status.

The gene expression intrinsic subtypes are endorsed by the St. Gallen international expert consensus panel since 2011 [51–53]; however, a simplified clinicopathological classification, which defines subtypes based on the immunohistochemical analysis of ER, PR, and HER2 receptors status and the Ki-67 cell proliferation marker, similar to what was proposed by Cheang et al. [38] is adopted (Table 8.1). The breast cancer subtypes defined by this classification are similar but not identical to the five intrinsic subtypes and represent a convenient approximation that can be performed in considerably less expensive and less complexes assays. In general, the therapy recommendations for this classification follow the "intrinsic" subtype classification: luminal A tumor patients generally require only endocrine therapy, considering that they are mostly less responsive to chemotherapy; luminal B patients, in addition to endocrine therapy, should receive chemotherapy (of both anthracycline- and taxane-based); HER2-positive tumors should receive chemotherapy and 1 year of treatment with trastuzumab; and triple-negative tumors should be treated with chemotherapy (also anthracycline- and taxane-based in addition to an alkylating agent (typically cyclophosphamide). The St. Gallen panel recognizes that the precise identification of intrinsic subtypes is based on molecular markers, which can provide the appropriated choices of treatment; however, where such assays are unavailable, the surrogate definitions of breast cancer subtypes by the IHC measurements described above should be used [51–53].

Table 8.1 Intrinsic and IHC subtypes and type of treatment recommended (since St. Gallen conference, 2011)

Intrinsic subtype	IHC subtype	Definition	Type of treatment
Luminal A	Luminal A	HER2 positive Ki67 low	Endocrine therapy alone
Luminal B	Luminal B (HER2 negative)	HER2 negative ER positive PR positive Ki67 high	Endocrine therapy ± cytotoxic therapy
	Luminal B (HER2 positive)	HER2 positive ER positive PR positive	Cytotoxics + anti-HER2 + hormonal therapy
Erb-B2 overexpression	HER2 positive	HER2 positive ER negative PG negative	Cytotoxics + anti-HER2 therapy
Basal-like	Triple negative	HER2 negative ER negative PR negative	Cytotoxic therapy

Table modified from Goldrisch et al. [51] and Perou et al. [3]
ER estrogen receptor, *PR* progesterone receptor, *HER2* epidermal growth factor receptor 2, *ki-67* protein Ki-67

8.2.2 MicroRNA- and DNA Methylation-Based Breast Cancer Subtypes

MicroRNAs (miRNAs) are a class of noncoding endogenous RNA molecules, with approximately 22 nucleotides, that have been identified to play a role in several types of cancers,

including breast cancer [54]. These molecules regulate a range of critical cellular processes associated with tumorigenesis, including proliferation, cell-to-cell signaling, cell death, migration, and invasion [55]. This regulation occurs through the interaction of their target genes. One miRNA can interact with multiple targets, and one gene can be controlled by multiple miRNAs [56]. More than 60% of all protein-coding genes have conserved miRNA binding sites in their 3′UTR region, which affords them the possibility of control by their respective miRNAs [57]. Interestingly, miRNAs are usually located in cancer-associated gene regions [58]. miRNAs that act in the cancer process can present an oncogenic (oncomiR) or tumor-suppressive (tumor suppressor miR) function. OncomiRs are frequently upregulated in cancer, where they target tumor suppressor genes for degradation and promote cancer cell growth; tumor suppressor miRs on the other hand are usually downregulated in cancer, targeting oncogenes for degradation, and have an antitumor function [59].

A number of differentially expressed miRNAs are observed among the breast cancer subtypes, as evaluated in both cell line models and clinical cases [60–65]. Blenkiron et al. [60] assessing the expression of 309 human miRNAs in 93 breast cancer patients showed that 9 of these miRNAs (miR-15b, miR-99a, miR-100, miR-103, miR-107, miR-126, miR-130a, miR-136, and miR-146b) could discriminate the luminal A from the luminal B breast cancer subtypes. Sugita et al. [61] have investigated the TNBC and non-TNBC subtypes of patients from African-American and non-Hispanic White patients. In both populations, significant differentially expressed patterns of miRNAs were observed between these subgroups. In the TNBC subtype, most of the miRNAs involved were identified to regulate cellular signaling pathways associated with tumor aggressiveness. In this study, a panel of 26 miRNAs were able to distinguish the TNBC transcriptome of African-American and non-Hispanic White patients. This panel was identified based on the integration of miRNA expression and DNA copy-number change analysis. Subsequently, others have proposed specific miRNA expression signatures for ER+, PR+, and HER2+ tumors [62, 63] with however variable miRNA contents. These discrepancies can be attributed to the technical variables of each of these studies, including the annotation of miRNAs investigated, type of specimens utilized (fresh, frozen, or archived material), type of miRNA platforms and analysis adopted, as well as variables related to the clinicopathological parameters of the tumors. In any event, as in gene expression studies, these miRNA expression signatures have been shown to present a strong power in discriminating the intrinsic molecular breast cancer subtypes.

DNA methylation patterns, as microRNAs, also present distinct patterns among the breast cancer subtypes. DNA methylation sites were investigated in several studies in relation to their classification power. Bediaga et al. [66] using a panel of 807 cancer-related genes identified specific methylation profiles for basal-like, luminal A, and HER2-overexpressing breast cancers. Using the same gene panel, Holm et al. [67] and Ronneberg et al. [68] classified 189 and 80 breast cancer samples, respectively, into distinct breast cancer subtypes. Interestingly, in these studies, there were differences in the epigenetic profile of breast cancer compared to their respective gene expression patterns, which was supported by larger studies assessing genome-wide methylation with the expression of thousands of gene transcripts [68]. More recent studies have also identified DNA methylation signatures associated with hormone receptor status, breast cancer subtypes, and *TP53* and *BRCA* mutation status [69, 70]. In TNBC in particular, where approximately 10–20% of TNBCs have *BRCA1* mutation, distinct methylation profiles have been observed in these tumors in comparison to TNBCs that are negative for *BRCA1* mutations or to non-TNBC subtypes [71, 72]. These and other methylation patterns across the breast cancer subtypes have also shown to impact response to chemotherapeutic agents and disease-free survival [73–75].

8.2.3 Multiomics Integrated Signature-Based Breast Cancer Subtypes

The integration of multiple distinct “omics” signatures to intrinsically subtype breast cancer has been more recently proposed. The assumption is that the simultaneous measurement of multiple types of biomarkers is likely to provide more accurate classification than that obtained with a single type. One of the most comprehensive molecular integration studies was performed by The Cancer Genome Atlas Project (TCGA) [7]. In this large project network, more than 800 primary breast cancers were profiled at the DNA (i.e., methylation, chromosomal copy-number changes, and somatic and germline mutations), RNA (i.e., miRNA and mRNA expression), and protein (i.e., protein and phosphor-protein expression) levels, using the most recent technologies [7]. The integration of the data from these platforms classified these tumors into four major breast tumor subgroups, luminal A, luminal B, HER2 positive, and triple negative, each with significant molecular heterogeneity, which captures the biological diversity and complexity within and across the breast cancer subtypes. Independently, a study conducted by Curtis et al. [8] described an integrated genomic/transcriptomic analysis of breast cancers with long-term clinical outcomes from the METABRIC (Molecular Taxonomy of Breast Cancer International Consortium) patients’ cohort. Unsupervised clustering analysis of paired DNA-RNA profiles revealed novel subgroups with distinct clinical outcomes, based on the presence of specific copy-number

alterations (CNAs) affecting mainly chromosomes 5, 8, 11, and 17 and gene mutations, such as the ones affecting the known driver cancer genes *KRAS*, *EGFR*, *CDKN2B*, *BRCA2*, *RB1*, *ATM*, and *SMAD4*.

Additional integrated genomic analyses have also revealed intra-subtypes molecular signatures [75–80]. In the study performed by Ciriello et al. [76], where it was performed computational integrated analysis using genomic data from over 1000 luminal A tumors, distinct signatures based on the integration of copy-number and somatic mutations in this tumor subtype were observed. These subgroups presented different clinical prognosis, including response to endocrine therapy. New comprehensive genomic analyses were also performed for TNBC tumors [31, 32, 78, 81, 82]. In the analysis conducted by Burstein [31] four stable distinct TNBC subtypes: (1) luminal androgen receptor (AR; LAR), (2) mesenchymal (MES), (3) basal-like immunosuppressed (BLIS), and (4) basal-like immune-activated (BLIA) with distinct prognosis were observed by integrating copy-number and gene expression profiling. Unique subtype-specific gene amplifications were observed in these subtypes, with *CCND1*, *EGFR*, *FGFR2*, and *CDK1* amplified in the LAR, MES, BLIS, and BLIA subtypes, respectively. Also, distinct prognosis was observed, with the BLIS and BLIA subtypes presenting the worst and best prognoses, respectively (independently of other known prognostic factors).

Collectively, these studies have confirmed, refined, and/or identified novel breast cancer subtypes as determined by the different subsets of genetic and epigenetic abnormalities. The utilization of these integrated molecular tools, with further combination with pathology and epidemiology factors, is critical to better understand the heterogeneous and complex biology of the breast cancer subtypes, which is reflected in their diverse clinical behavior, which directly impacts response to treatment, disease progression, and overall survival.

8.3 Prognostic Gene Expression Signatures

In the daily management of breast cancer, the selection of the most appropriate treatment for an individual patient remains a challenge, despite the excellent assistance of the established therapy guidelines such as the St. Gallen [52], National Institutes of Health (NIH) [83], American Society of Clinical Oncology [84], and others. The ability to identify breast cancer patients with either a very high or very low risk of recurrence, who would need adjuvant systemic therapy from those who could be spared from such type of treatment is critical. The power of making this distinction at the time of diagnosis, from the analysis of the patient's primary tumor, would substantially improve breast cancer survival.

Several multigene signatures that predict outcome and response to therapy in breast cancer have been developed through the data obtained from gene expression profiling [for review, see [5–9, 84, 85]] (Table 8.2). In these studies, major prognostic factors, such as lymph node status or estrogen receptors, were addressed and have allowed that subgroups of tumors with a very distinct clinical outcome that could not

Table 8.2 Most common prognostic gene expression breast cancer signatures commercially available

Gene expression signatures	Patient population	Prediction	Number of genes	Material	Assay	Company
Oncotype Dx	ER positive/negative LN negative Tamoxifen treated	Risk of recurrence (RR)	21 genes	FFPE	RT-PCR	Genomic Health (Redwood City, CA, USA)
MammaPrint	ER positive/negative LN negative Tumor size <5 cm Age <61 years	Risk of distant metastasis	70 genes	Frozen	Microarray	Agendia (Huntington Beach, CA) (Amsterdam, the Netherlands)
PAM50 (Prosigna)	LN negative ER positive/negative No systemic therapy	Risk of relapse (ROR)	55 genes	Frozen/ FFPE	Microarray/ nCounter	Nanostring Technologies—nCounter format (Seattle, WA, USA)
MapQuant DX	ER positive/negative LN positive/negative	Molecular grading	97 genes	Frozen/ FFPE	Microarray	Ipsogen (New Haven, CT, USA) (Marseilles, France)
Breast Cancer Index	ER positive LN negative	Risk of late recurrence Response to endocrine therapy	Two-gene HOXB13:IL17R molecular grade index (MGI)	FFPE	RT-PCR	BioTheranostics (San Diego, CA, USA)

ER estrogen receptor, *LN* lymph node, *FFPE* formalin-fixed paraffin-embedded, *qRT-PCR* quantitative real-time PCR

be predicted by the conventional prognostic factors were distinguished in the analysis of the patient's primary tumors. The main objective in most of these studies was to predict which patients would benefit from a more aggressive treatment from the ones that would be unlikely to respond and therefore not present a significant survival benefit.

Vant'veer et al. [86], one of the pioneers of these studies, proposed a prognostic gene signature to identify a group of good prognosis patients with minimal risk of development of distant metastasis within 5 years after diagnosis. The expression of 25,000 genes were analyzed in primary breast tumors and a set of 70 genes with differential expression profiles, separated the patients into two categories, "poor" and "good" signature groups, based on their risk of developing distant metastasis. Among the genes that were upregulated in the poor signature group were genes involved in the cell cycle, angiogenesis, invasion and metastasis, and signal transduction, such as *CYCLIN E2*, *MCM6*, *MMP9*, *MP1*, *RAB6B*, *PK428*, *ESM1*, and the VEGF receptor *FLT1*. Subsequent studies confirmed the reproducibility of the initial 70-gene signature as a predictor of outcome independently of traditional clinical-histopathological prognostic markers [87–91]. This validation analysis let to the development of the commercial test *MammaPrint* developed by the company Agendia (Amsterdam, the Netherlands). This test is approved by the Food and Drug Administration (FDA) to predict the risk of recurrence within 10 years after diagnosis of stage I or stage II breast cancer that is hormone receptor-positive or hormone receptor-negative. This signature was evaluated in a large clinical trial, the MINDACT (Microarray In Node-negative and 1–3 positive lymph node Disease may Avoid Chemotherapy Trial), which is performed in breast cancer patients with ER-positive, lymph node-negative disease with long-term follow-up and known clinical outcome [92]. The primary endpoint of this trial was to test its robustness and clinical applicability in identifying patients that could be spared from the use of chemotherapy without affecting the survival outcome. The primary statistical test was conducted on patients deemed clinically high risk but genomically low risk who were randomized not to receive chemotherapy. The 5-year distant metastasis-free survival for this group was close to 95%. MINDACT was underpowered to determine whether chemotherapy is beneficial in patients who had discordant test results [93].

The other prognostic signature also commercially available is the *Oncotype Dx* (Genomic Health Inc., Ca). This assay was developed based on the identification of 250 selected genes with different expression profiles [94–96], initially tested in patients from the National Surgical Adjuvant Breast and Bowel Project (NSABP B-20) clinical trial [97]. After statistical analysis and clinical validation, 21 genes (16 cancer-related genes and 5 reference genes) were selected, and their expression analysis was translated into a "recurrence score (RS)" which was then used to assign the patients into 1 of 3 groups, based on the risk of developing distant metastasis: low risk (RS <18), intermediate risk (RS ≥18 and <31), and high risk (RS ≥31) [98]. This validation study was performed in lymph node-negative, ER-positive breast cancer patients who were treated with tamoxifen in the large, multicenter NSABP B-14 trial [99]. Subsequent studies have demonstrated its clinical utility as an independent prognostic parameter in ER and lymph node-positive patients that received adjuvant chemotherapy [100] and also in postmenopausal patients with ER-positive tumors that were treated with aromatase inhibitors [101]. An ongoing large prospective clinical trial, the TAILORX (Trial Assigning IndividuaLized Options for Treatment (Rx)), is further testing the clinical utility of the *Oncotype Dx* with the primary endpoint of accessing whether adjuvant chemotherapy plus hormonal therapy presents a better outcome when compared to hormonal therapy alone in patients that present a low and intermediate score (RS between 11 and 25) [102]. The most recent results from this trials have shown that women with low score present very low 5-year recurrence rates when only treated hormone therapy [103].

Contrary to the *MammaPrint*, which is performed by a microarray assay in frozen tumor tissue samples, the *Oncotype Dx* can be performed by real-time (RT)-PCR in formalin-fixed paraffin-embedded (FFPE) samples, not requiring therefore the highest-quality RNA material. The *Oncotype Dx* prognostic test has been endorsed by the American Society of Clinical Oncology [84] for clinical use and is included in the National Comprehensive Cancer Network guidelines and St. Gallen International Expert Consensus [51–53]. The recommendation for its use is limited to newly diagnosed patients with lymph node-negative, ER-positive breast cancer that were treated with tamoxifen.

The PAM50 multigene gene expression-based assay, described above as an "intrinsic" subtype classification assay, is also used to predict prognosis. This assay is commercially available by the name of Prosigna Breast Cancer Prognostic Gene Signature Assay (Nanostring, Inc.) [50] and was approved by the FDA in 2013. It is applicable to postmenopausal patients with invasive breast cancer stage I or stage II and lymph node negative and stage II with one to three positive nodes, who are hormonal positive and have been treated with surgery and hormonal therapy. It estimates distant recurrence, after 10 years of diagnosis, based on a risk of recurrence (ROR) score, which ranges from 0 to 100: node-negative cancers are classified as low (0–40), intermediate (41–60), or high (61–100) risk, and node-positive cancers are classified as low (0–40) or high (41–100) risk. This assay is now included in the St. Gallen guidelines [53].

Several other prognostic signatures were developed, such as the *MapQuant Dx* (Ipsogen, Marseille, France), a microarray-based assay originally based on 97 differentially

expressed genes, which was validated as strongly associated with risk of recurrence among patients with grade 2 tumors [104]; *Theros Breast Cancer Index* (BCI BioTheranostics, San Diego, CA) is based on a qRT-PCR assay and provides an assessment of the likelihood of distant recurrence in patients diagnosed with ER-positive and lymph node-negative breast cancer. It uses a combination of indices (HOXB13:IL17BR two-gene ratio) and a proliferation-related five-gene molecular grade index (MGI), which discriminates grade 1 from grade 3 breast tumors [105, 106]; *EndoPredict test* is used to predict the risk of distant recurrence of early-stage, hormone-receptor-positive, HER2-negative breast cancer that is either node negative or has up to three positive lymph nodes [for review, see [85]]. Interestingly, although there is very little overlap among these signatures in relation to the gene composition, most of them are related to proliferation and ER-signaling cellular processes [107]. Therefore, the prediction power of most of these signatures is more robust and indicated for ER-positive tumors/luminal subtype and less for the ER-negative subtypes [108].

Recent studies have, however, shown that other cellular processes genes, including the ones involving the expression of immune response genes, have the potential to predict survival, specially in the HER2-positive and basal-like subtypes of tumors [109, 110]. Gene signatures that impact the activation of immune signaling pathways, such as the IRF1/STAT1/IFNG pathway, and the expression of cytokines and chemokines and others have been reported as potential predictors to immunotherapy [for review, see [110]]. In a recent transcriptomic study from HER2+ patients treated on a randomized adjuvant trastuzumab trial, the most significant pathways associated with prolonged relapse-free survival (RFS) were involved with immune response. Based on gene expression of these pathways, the authors identified a 14-gene signature that could stratify patients in immune enriched vs. nonimmune-enriched subgroups. Immune-enriched patients treated with trastuzumab-based chemotherapy presented a better RFS as compared to the nonimmune-enriched ones [111]. Other studies were conducted in TNBC, where it was shown that the expression of the programmed cell death ligand 1 (PDL-1) and tumor-infiltrating lymphocytes (TILs) impacts prognosis [112–114].

Several other immune signatures have been proposed in breast cancer, several of which being tested in ongoing clinical trials in both the neoadjuvant and adjuvant settings. These trials, where stratification of the patients is randomly based on these expression signatures, will provide evidences of their effectiveness for prognosis and prediction of treatment response, specially in patients submitted to immunotherapy [115–117].

Although the importance of the gene expression signature of breast tumors has been well established and represents a more accurate prognostic marker than other well-established clinical-histopathological criteria, one cannot assume that all the genes present in these gene expression signature panels are equally important or have an independent role in breast cancer pathogenesis and recurrence [118, 119]. Additional studies are required to distinguish the unique and the overlapping genes of these innumerous signatures, considering specific clinical settings. It is also critical to assess whether these prognostic signatures observed in patients' tumors are represented in the liquid biopsies (e.g., plasma and/or serum) of the patients, so they can be used for early cancer detection and diagnosis and treatment monitoring.

8.4 Conclusions

The advances in the microarray technology and the ability of perform large-scale validations using bioinformatics tools have allowed the development of integrated "omics" signatures that provide a more comprehensive understanding of the whole genome of the cancer cells, allowing for the intrinsic molecular classification of breast cancer and their respective implications in response to therapy and clinical outcome. It is without question that the continued improvement of molecular tumor profiling with the development of next-generation technologies, such as large-scale and exome sequencing, together with pathological and epidemiological patient' information, will lead to successful application of these and newly developed molecular signatures into the clinical setting. These efforts will certainly be reflected in the stratification of breast cancer disease in a new refined taxonomy, allowing a better understanding of the genetic diversity in the different and even less frequent breast cancer subtypes. In addition, considering that the success of a treatment largely depends on the ability to match a particular tumor phenotype to a specific tumor genomic target, these new technologies would provide the identification of new therapeutic targets, allowing for the development of novel diagnostic tests to guide the most appropriated and individualized cancer therapy. Finally, considering the increasing dissemination of the genomic-based testing and treatment strategies for cancer, in the context of precision medicine, it is imperative to address the use of these tests on the impact of the patient's therapeutic decision-making and health outcome.

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Photographic Principles of Medical Documentation

9

Murillo Fraga, Diego Ricardo Colferai, and Marcelo Sampaio

9.1 Introduction

The standardization in photography in plastic surgery is a very important issue and has been exhaustively discussed in the last years. The documentation of images in scientific research must be done in a systemic and standardized way in order to allow its reproducibility [1]. This enables the validation and comparison of techniques as well as the analysis of results maintaining the scientific accuracy. The clinical photograph must always be taken by the same camera, film, lenses, distances, luminosity, and the same position of the patient [2, 3]. The use of a leveled tripod, electronic flash, spotlights, and markers and the standardization of the distance between the feet and the photographic background are very important technical elements [4]. The photographic background must be of gray color or surgical blue (royal blue), nonreflective. The spotlights (two units) are positioned at 45°, and the leveled tripod allows the adequate framework, which allows the stabilization of the image. The photographic incidences (front, right and left oblique, and right and left side) must be standardized (Fig. 9.1).

It is relevant to highlight the importance of preserving the right of privacy of the patient; therefore, the consent form must be solicited before any photographic documentation [4–6].

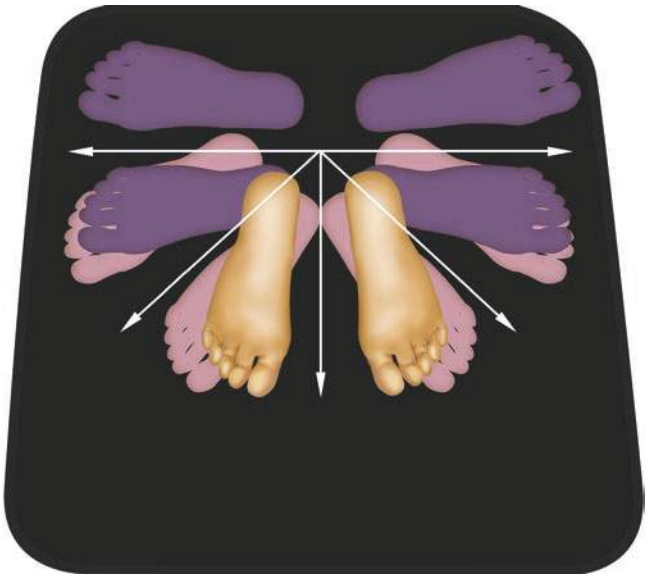

Fig. 9.1 Marking carpet for adequate maintenance of pre and post-surgery positions

9.2 Technical Aspects of the Photograph

9.2.1 Positioning

Aiming at standardizing the distance between the feet and the photographic background, a 1-cm-thick ethylene vinyl acetate (EVA) frame can be used, which keeps the positioning of the patient fixed at 70 cm from the photographic background and the distancing of 30 cm between the feet (Figs. 9.1 and 9.2) [2].

The photographic background made of polyester fabric measuring 1.60 m length by 1.40 m width in blue color is well stretched and fixed to the wall [7]. There is also a care protocol that was developed with the purpose of standardizing and ordering all stages of data collection, aiming at

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_9

systematizing them [8]. A distance of 1.2–1.8 m for the body and the face is adequate. We suggest a 105 mm lens at a distance of 1.5 m for the face and a 50 mm lens or an equivalent for the documentation of the body (Fig. 9.2) [2].

The patient is guided to stay in anatomic position, keeping the eyes' horizontality (Frankfurt plan) during the measuring. The photo framework of the mammary region is defined by the crossline gnathion (chin region) on top and by the bottom edge of the navel at the bottom (Fig. 9.3) [1].

Even though the clinical photographs are taken of five different positions (anteroposterior (AP), right and left side, and right and left oblique [1, 9, 10]), a relaxed and a contracted position of the breast can be added. This maneuver is achieved by pushing the hands against the hip, and it allows a more dynamic assessment. In some particular cases, a leaning forward position is useful to demonstrate asymmetry. Several authors strive aiming at standardizing clinical photographs, but variability remains a challenge [1, 2, 10–12].

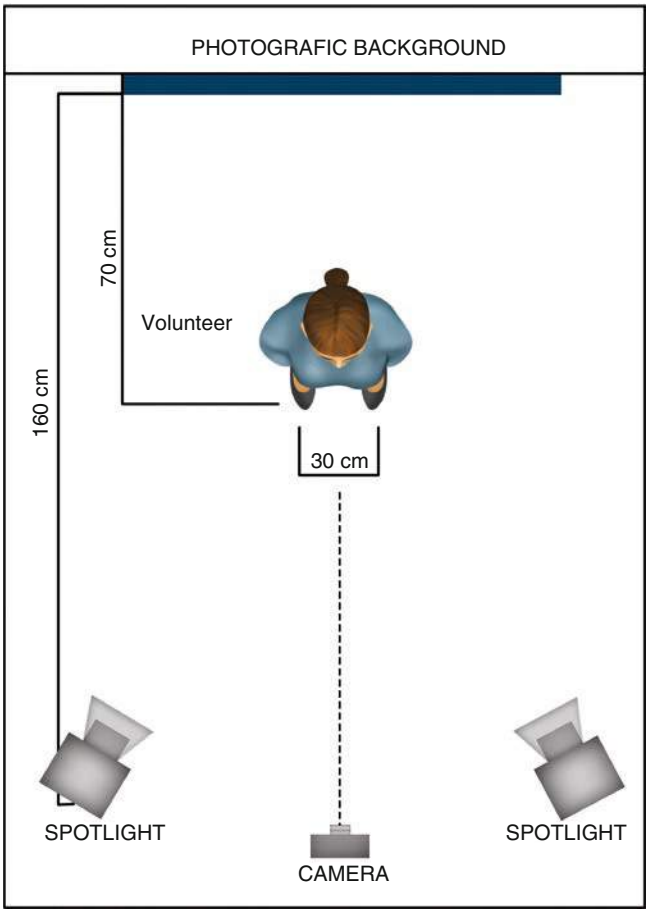

Fig. 9.2 Necessary equipment to assemble a studio in the doctor's office

9.2.2 Lighting

In plastic surgery many lighting ways have been suggested, from flashes of the camera itself to external lights in different configurations [8]. When it comes to a normal and informal picture, we observe a certain asymmetry in lighting; in other words, one of the sides of the body is illuminated differently. Now, when it comes to surgical documentation, there has to be symmetry between the hemibodies, as well as equal illumination of both sides. Thus, we suggest using a pair of umbrellas assembled at the height of the eyes with a 45-degree angulation.

A recurring problem in the lighting of images of the patient is that some details and contours are eliminated of flattened in such a way by the light that they are not visible. The cellulite in the body or certain facial wrinkles are frequently not seen in anterior light (flash) but are extremely apparent in vertical light. In general, skin irregularities are better observed in tangential light. Shapes such as breasts or contours of the body are better seen in slightly shaded light.

Lighting is a topic of extreme importance to preserve the technical accuracy of clinical photograph. Excessive lighting or overexposure can mask furrows, wrinkles, or scars. In the same way, poor lighting or underexposure may cause shades which accentuate folds or scars [4].

9.2.3 Storing of Images

Technology has evolved quickly. Some decades ago, drawings were used and, next, black and white photography, colored transparencies, and films. In the last 15–20 years, digital images have become the new pattern, and analogic photography became obsolete.

There has also been a change in the way images are stored. Diskettes, magnetic tapes, CDs, DVDs, USB drives, external HDs, and network units gave way to data archiving in the cloud [13]. The advance of technology presents challenges concerning technical work (software incompatibility, hardware, execution problems, scanning, and storing) and security. The lack of a specific legislation and clear rules makes the circulation of images through the Internet a weak point.

9.3 New Technologies for Breast Measuring

The three-dimensional surface image has gained popularity in plastic and reconstructive surgery worldwide because the two-dimensional pattern lacked in shape and depth [14]. The 3D image is a significant advance in photographic

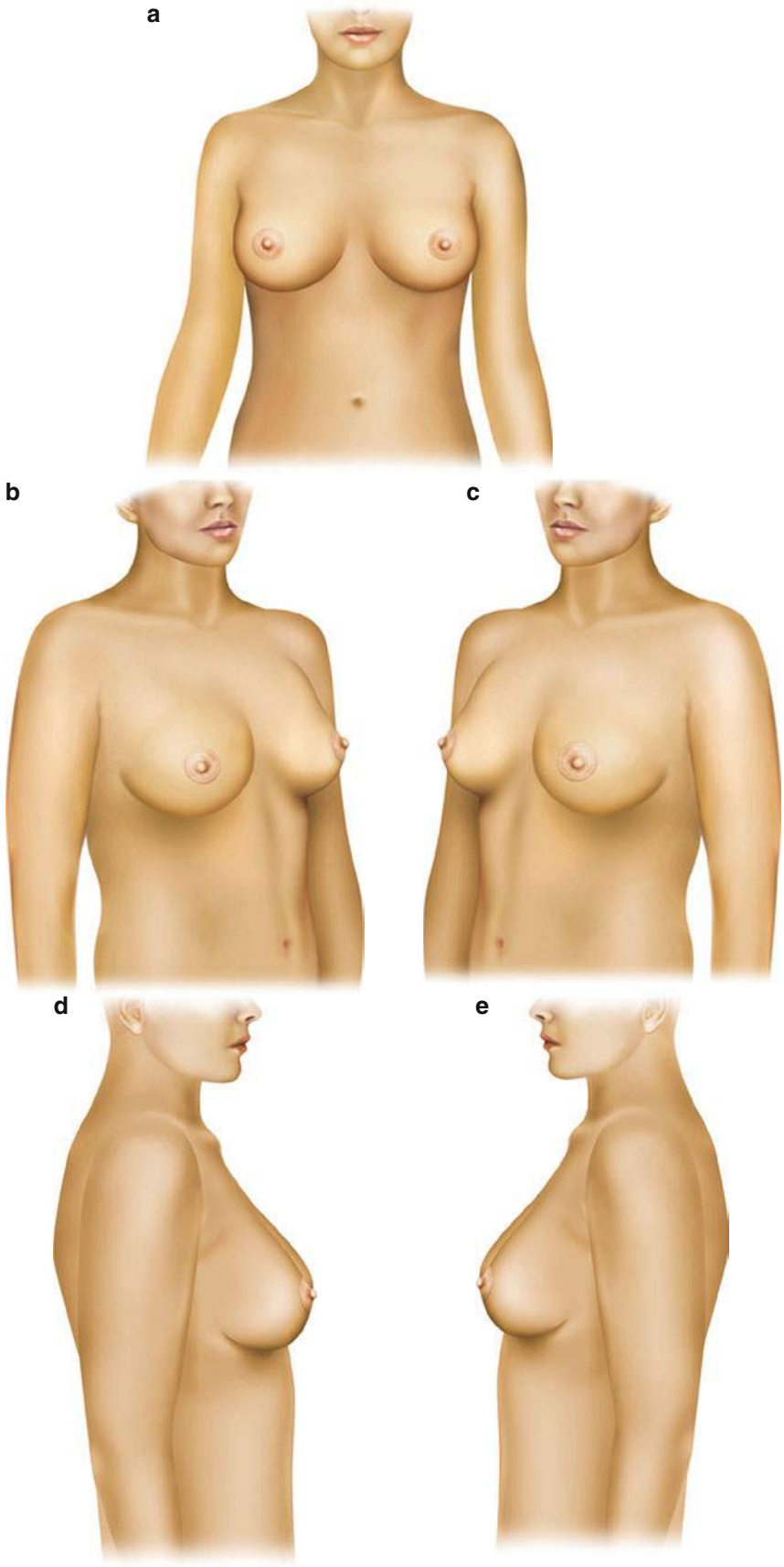

Fig. 9.3 Clinical photographs in the following positions: (**a**) anteroposterior, (**b**) right oblique, (**c**) left oblique, (**d**) right side, (**e**) left side

evaluation, because it is able to calculate measures and carry out clinical analyses in x, y, and z coordinates (three-dimensional). This triangulation allows the creation of 3D images [15].

The 3D image was first described in 1994 to diagnose ortho-dental conditions. It was initially used to highlight facial asymmetry and subsequently used to show alterations in the body contour [16, 17].

In breast surgery, the 3D images help in determining the volumes and shapes of the breast, estimate the differences, and allow the projection of results after the surgery [18]. This tool must be used as an auxiliary, and the virtual post-surgery results must not be promises of actual results. Numerous variables may interfere in the final result (age, BMI, ethnicity, height, gender, quality of breast tissue, lactation period, among others) [19].

It is important to observe the limitation of the use of these images, which still bump into cost, quickness and capture of image processing, portability, and special characteristics of the images [19, 20].

The 3D image is a tool which assists the surgeon in his decisions, besides being an important form of marketing. The quick advance of technology will provide a more efficient communication between the doctor and the patient, allowing a more precise and effective instruction.

The ultimate objective is to bring about a more satisfactory result for the patient.

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Breast Cancer Patient and Reconstructive Consultation

10

J. Michael Dixon and Cameron Raine

10.1 Introduction

Patients with primary or recurrent breast cancer having a mastectomy or very wide excision should be considered for whole or partial breast reconstruction, and therefore it is important to have reconstructive surgeons present at the multidisciplinary team meetings which make such decisions. For patients with larger operable invasive cancers, options other than mastectomy should be considered. Where there are options, these can and should be discussed with the patient. For those women who are deemed suitable candidates for whole or partial breast reconstruction, the timing, options and complications of reconstructive surgery should be considered and discussed.

10.2 Guiding Principles in Breast Reconstruction

Treatment of the cancer should not be compromised by breast reconstruction. The need to achieve an aesthetically satisfactory breast reconstruction, however important this is to the patient, should not stand in the way of ensuring that any surgery removes all disease to limit local recurrence and that radiation and systemic therapy is delivered in a timely manner to maximise long-term local and systemic control. One issue of concern is that if major complications develop after reconstructive surgery, then this can delay administration of radiotherapy and chemotherapy. The overwhelming body of evidence indicates that immediate breast reconstruction is safe and appropriate for the majority of patients undergoing mastectomy and does not impact significantly on the timing of adjuvant therapy [1]. Furthermore studies have indicated that in general, better results are obtained with immediate reconstruction compared with delayed reconstruction because skin and other soft tissues can be preserved, which are normally removed as part of a standard mastectomy [2]. Good oncological surgery which removes all the cancer does not have to be destructive, and in the majority of patients, it is not necessary to remove the skin over the whole breast, the nipple areola complex or the pectoral fascia. This does not mean that excellent results cannot be obtained by delayed breast reconstruction [3].

In every centre, there should be a multidisciplinary team approach to breast cancer management, and a similar multidisciplinary approach should be available when considering breast reconstruction. Any surgical plan must incorporate information from all members of the breast management team including breast surgeons, radiologists, oncologists, pathologists, nurses and support staff. If a plastic surgeon, not present at the multidisciplinary meeting, is to be involved in the discussion about breast reconstruction, then they need to be aware what the patient has been told about their breast cancer and what options have been discussed. If risk-reducing mastectomy is planned, then the reconstructive surgeon needs to know whether it is to be a skin-sparing or nipple-sparing mastectomy before having any discussions with the patient. The best option for the patient is a joint consultation between the oncological surgeon and the plastic surgeon. In some centres, the oncological surgery and reconstruction are performed by appropriately trained oncoplastic surgeons. It is imperative such individuals can offer the same range of procedures that a combination of a breast oncological surgeon and a plastic surgeon together can offer. If the oncoplastic surgeon is not able to offer free-flap breast reconstruction, then onward referral to a suitable plastic surgeon should be arranged if a free flap is considered the patient's best option.

Breast reconstruction is not normally one operation but typically requires two or three operations. Even if breast reconstruction is performed immediately, surgery to achieve true symmetry usually involves additional procedures in the ensuing months. This can include changing a tissue expander

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_10

for a permanent implant, a nipple or areola reconstruction, revision of autologous tissue transfer, liposuction or lipofilling for contour refinement or scar revisions. Patients who undergo unilateral breast reconstruction often require a contralateral breast procedure such as breast augmentation, breast reduction or even a contralateral risk-reducing mastectomy. From the outset, the patient's expectations need to take account of the long-term reconstructive plan, and patients need to be aware that to achieve good symmetry often requires more than one operation.

Patient preference and lifestyle are very important when planning reconstructive breast surgery. Patients may express a strong preference for one type of reconstruction and seek a particular reconstructive surgeon based on the types of surgery they offer. Although an implant-based reconstruction is often considered simple, it can be far from simple to achieve a good cosmetic result and requires considerable expertise and is not without complications [3]. Patients who participate in sports or other activities that require significant abdominal strength may not wish abdominal flap operations. Certain lifestyles may dictate where scars should be placed, for instance, when raising a latissimus dorsi (LD) flap, and so the reconstructive surgeon needs to be aware of the patient's occupation and other aspects of their lifestyle, prior to making any recommendation or discussing options with patients.

10.3 Patient Consultation

The main aim of the discussion dealing with breast reconstruction is to inform women regarding the reconstructive options that are available in general and that are appropriate to them in particular. The current advice is that women should be provided with verbal, written and photographic information regarding the full range of reconstructive options [3]. Any reconstructive options that are unsuitable for the individual patient should be specifically identified and the reasons for this explained. It is also important that women considering reconstruction are seen by specialist reconstructive surgeons. For many patients, this will mean seeing more than one surgeon. Preferably, as outlined above, these doctors should see the patient together and provide the patient with clear information on their reconstructive choices and who will do what during any planned surgery.

There has been some concern expressed in relation to performing breast reconstruction on patients with advanced disease. This includes locally advanced and metastatic disease. There is evidence that removing the cancer even in patients with known metastatic disease improves local disease control but may not improve overall outcome [4, 5]. This means that mastectomy with or without reconstruction should not be discounted in all patients with metastatic disease. For these women, breast reconstruction is entirely feasible once appropriate systemic therapy has produced stabilisation of metastatic disease. In patients with locally advanced breast cancer, systemic therapy can produce dramatic responses allowing both greater tissue and skin preservation [6] and, in patients who require mastectomy, can make breast reconstruction an option for many women in whom reconstruction was not considered feasible at the time of presentation. Even in patients who have locally advanced cancer with skin involvement, breast reconstruction is possible with myocutaneous flaps. Patients with inflammatory breast cancer may also prove suitable candidates for breast reconstruction following response to neoadjuvant chemotherapy.

Having reached agreement that whole or partial breast reconstruction is appropriate for the patient, the aim of the reconstructive consultation is to evaluate the various reconstructive options against the background of the patient's wishes and expectations whilst considering their suitability for any given technique.

There is huge variation not only in the type of reconstructions different units perform but also in the percentage of patients who get immediate or delayed reconstruction across and between countries [1–3]. There is no scientific basis for this huge variation, and steps within countries need to be taken to ensure consistent availability of the whole range of reconstructive options in all regions and centres. It is important that centres that perform breast reconstruction should compare their own use of different reconstructive techniques with those in other centres in the country in which they work. Patients should be informed of all their potential options and get the opportunity to discuss available options in detail. An important part of the initial consultation is that patients are made aware of the rates of post-operative complications and that they are given a realistic perspective on the pain and discomfort associated with the procedure, including realistic outlines of recovery time from each of the various operations and the necessity, in most patients, to undergo more than one procedure to obtain symmetry [3]. One audit showed patients were poorly informed in relation to the pain and discomfort involved and the time it took to recover after various procedures [3]; following the audit, various recommendations were made (Table 10.1). Complication rates, particularly implant loss, have been underestimated and in large series can be significant [3] (Table 10.2). The discussion should include the possible need for symmetrising surgery on the contralateral normal breast to obtain true symmetry.

Patients considering bilateral risk-reducing mastectomy and bilateral breast reconstruction are often referred through family history clinics having discussed options including screening and the use of currently available pharmaceutical agents to reduce the risk of breast cancer development.

Patients wishing to be considered for delayed partial breast reconstruction may attend because of asymmetry fol-

Table 10.1 Recommendations following UK audit of breast reconstruction

Clinicians should act to better inform women about both the procedures they decide to undergo and the reconstructive options available
Clinicians should ensure that women are offered a full range of appropriate reconstructive options, whether or not these are available locally
Clinicians give accurate data on post-operative complications to inform women about risks of different operations
Women considering reconstruction should be informed preoperatively that the chance of requiring further surgery either during their initial admission or post-operatively is around one in ten
Women must be informed how to report their levels of pain and be able to access appropriate pain relief and to be provided with adequate psychological support following their surgery

Table 10.2 Complication rates as reported by patients following mastectomy and immediate or delayed breast reconstruction from the UK National Mastectomy and Breast Reconstructive Audit: Third Annual Report 30 June 2010

Patient-reported outcomes at 3 months: High proportion of reported post-discharge complications requiring intervention after mastectomy (Mx), immediate breast reconstruction (IBR) or delayed breast reconstruction (DBR)			
Post-discharge complication (%)	Mx	IBR	DBR
Readmission for treatment or surgery	10	16	15
Wound infection requiring antibiotics	19	25	28
Unplanned removal of implant	–	10	7
Surgery to remove some or all of flap	–	4	6

lowing breast-conserving surgery and radiotherapy. These patients attend to discuss possible reconstructive options because of the impact that breast asymmetry has on their everyday quality of life.

10.4 Assessing Patient's Fitness for Reconstructive Surgery

There are a variety of factors which need to be considered when considering a patient's suitability for breast reconstruction, including age, co-morbidities, body mass index, smoking history, diabetes, steroid/other drug therapy and religious affiliation [7, 8].

10.4.1 Smoking

There are more than 4000 chemicals present in cigarette smoke including nicotine and carbon monoxide [9]. One effect of nicotine is to cause vasoconstriction of the dermal-subcutaneous vascular plexus. This has important consequences as many tissue flaps rely on this plexus for their survival [10]. As well as inducing a hypoxic state and causing vasoconstriction, smoking can lead to increased platelet aggregation which results in the formation of tiny thromboses in capillaries. This is detrimental to wound healing which relies heavily on blood flow in newly formed capillaries. Smokers have higher levels of fibrinogen and haemoglobin which increase blood viscosity and increase likelihood of blood clotting, and blood flow can be reduced by up to 42% [11]. The combination of decreased oxygen delivery to tissues and the thrombogenic effects of smoking together with increased viscosity and reduced flow is the main reason why wound healing in smokers is significantly impaired.

The link between smoking and wound healing was first documented in the 1970s. Problems with wound healing in smokers have been documented at multiple sites in the body. One study of patients undergoing abdominoplasty found that smokers were 3.2 times more likely to have wound problems than non-smokers. The number of cigarettes smoked in this study was not however a reliable predictor of those likely to develop wound healing complications [12]. Facelifts in smokers have been reported to be associated with a 12.5 times risk of developing retroauricular skin necrosis compared with non-smokers [13]. A study of 425 patients undergoing mastectomy and breast-conserving surgery identified that after adjusting for other confounding factors, smoking was an independent predictor for wound infection and skin necrosis regardless of the number of cigarettes smoked [14]. The odds ratios for infection were 2.95 for light smoking (1–14 g/day) and 3.46 for heavy smoking (>15 g/day). The odds ratios for necrosis and epidermolysis were 6.85 for light smoking and 9.22 for heavy smoking.

In patients undergoing pedicled TRAM flap breast reconstructions, the number of wound infections is higher in both current and former smokers [15]. Complications related to reconstruction are significantly more likely in current smokers (odds ratio 3.9) and former smokers (odds ratio 3.5) compared with non-smokers. A study by Padubidri looking at patients undergoing TRAM flaps and tissue expanders [16] reported the complication rate using tissue expanders for smokers was 37.1% which was statistically higher than the 26.6% for non-smokers. In the TRAM flap group, active smokers had a significantly higher overall complication rate and a significant increase in particular of mastectomy flap necrosis. A study of 716 patients having free TRAM flaps showed abdominal flap necrosis, mastectomy flap necrosis and abdominal hernias were significantly higher in smokers [17]. Mastectomy skin flap necrosis occurred in 18.9% of smokers and 9% of non-smokers, $P = 0.005$. This study did demonstrate a dose effect with smokers who had a history of more than a pack a day for 10 years being at increased risk of developing problems compared with smokers who had smoked for smaller number of pack years (55.8% vs. 23.8%). One observation in this study was that delayed breast reconstruction in smokers was associated with a significantly lower rate of wound complications compared with immedi-

ate breast reconstruction in smokers. The risk of wound complications in delayed reconstructions was in fact similar to the rate in non-smokers. Complications were also less common in women who had stopped smoking 4 or more weeks before surgery. A study by Gill et al. examined risk factors and associated complications in 758 patients undergoing deep inferior epigastric perforator (DIEP) flaps for breast reconstruction [18] and found the risk factors associated with breast or abdominal complications included smoking ($p = 0.001$), post-reconstruction radiotherapy ($p = 0.001$) and hypertension ($p = 0.0370$). Smoking and post-reconstruction radiotherapy were the only significant risk factors for fat necrosis in the breast reconstruction in this study. Implant loss in patients having breast reconstructions with acellular dermal matrix (ADM) was 34.6% in smokers vs. 13.2% in non-smokers ($p = 0.01$) in a recent study reported by Barber [19].

10.4.2 Interaction with Obesity and Diabetes

It is recognised that cigarette smoking, obesity, age, diabetes and nutrition are all factors which play an important role in wound healing. Smokers who are obese or have diabetes are at an even greater increased risk of wound healing problems than smokers without these risk factors. McCarthy et al. studied 1170 patients undergoing expander/implant reconstructions [20]. They maintained a prospective database which included the variables of age, smoking status, body index, history of diabetes, hypertension and/or radiation as well as the timing of the reconstruction, immediate or delayed, and the laterality of reconstruction. The chances of developing complications were 2.2 times greater in smokers and 2.5 times greater in women over the age of 65. Patients who were obese had nearly twice the odds of having a complication. The same was true for patients with hypertension. The odds of reconstruction failure were five times greater in smokers, and failure was nearly seven times greater in obese patients and four times more likely in those who had hypertension. This study concluded that smoking, obesity, hypertension and age over 65 were all independent risk factors for perioperative complications following expander implant breast reconstruction.

10.4.3 Smoking Cessation

There is one small randomised clinical trial of 108 patients with 40 patients in the control group and 68 patients in the intervention group [21]. Patients assigned to intervention were given counselling and nicotine replacement therapy. The study did show a significant reduction in complications in the intervention group with a reduction in wound-related complications and the need for secondary surgery. In this study, patients stopped smoking for 6–8 weeks before surgery and did not smoke for 10 days after the operation. In the literature, there is no consensus on the optimal duration of preoperative smoking cessation, but there is some evidence that there are potential benefits from even a brief period of abstention. The majority of studies are however retrospective and have inherent weaknesses in their design.

10.4.4 Diabetes Mellitus

Studying any risk factor in isolation is always difficult because patients with diabetes often have other associated risk factors such as obesity. One study of complications after breast reconstruction did show a significantly increased risk of skin-sparing mastectomy flap complications in diabetics [22].

10.5 Post-mastectomy Radiotherapy and Its Impact on Breast Reconstruction

Indications for post-mastectomy radiotherapy have expanded over the past decade. One study of 919 patients who had breast reconstruction separated them into three groups: mastectomy with post-operative radiotherapy before reconstruction, $n = 57$; immediate reconstruction and then post-mastectomy radiotherapy, $n = 59$; and reconstruction without post-mastectomy radiotherapy, $n = 665$ [23]. Overall the complication rates for patients having radiotherapy either before or after mastectomy were significantly higher than controls, 40% vs. 23% ($p < 0.001$). Immediate reconstruction before post-mastectomy radiotherapy increased both the overall rate of complications (47.5% vs. 23.2%) and the rate of late complications (33.9% vs. 15.6%) compared with controls (both $p < 0.001$). Delayed breast reconstruction in patients who had either had or not had post-operative radiotherapy produced similar complication and satisfaction rates, but prior radiotherapy was associated with decreased aesthetic satisfaction compared to those who had no post-mastectomy chest wall radiotherapy, with only 50% of patients being happy in the group who had radiotherapy compared with 66.8% in those who did not have radiotherapy. A recent meta-analysis of the effects of radiotherapy on breast reconstruction reported a wide variation in complication rates (8.7–70%) and in acceptable cosmetic outcomes (41.4–93.3%) [24]. There were more complications and a

higher revision rate if an implant reconstruction was used after radiotherapy. There was more fibrosis with autologous reconstructions if the reconstruction was performed before compared with after radiotherapy.

Patients whose preferred reconstructive option involves the use of breast implants and in whom post-mastectomy radiotherapy is considered likely require special consideration. The literature suggests that there is a significantly increased risk of capsular contracture and other secondary complications in patients who receive radiotherapy compared with patients who have breast reconstruction with implants but do not have radiation [25, 26]. Complications after irradiation of implants are also more common than one sees in patients undergoing autologous breast reconstruction who received radiation [27]. In one study of ADM with implants, the implant loss rate was significantly higher (28.1% vs. 13.8% $p = 0.01$) in patients who had radiotherapy [19]. Implant failure is more common in women who have had prior radiotherapy (OR 3.03 (1.59–5.77)) [24]. The scientific data on ADMs and capsule formation around an implant suggests that there may be a lower encapsulation rate because of a reduction in the inflammation described around the implants [28]. There is the belief that reconstructions involving ADMs do better in the setting of radiation despite a lack of evidence from any clinical trials. Many authors have reported retrospective series in patients who have received either pre- or post-operative chest wall radiotherapy. Colwell et al. reported no difference in complication rates in radiated vs. non-radiated patients [29]. Kobraei et al. found that post-operative radiotherapy was the only factor statistically related to implant loss supporting the study by Barber [19, 30]. Animal models support the view that there may be less capsular contracture around implants in the absence of ADM [31]. Some prefer to delay breast reconstruction in patients in whom it is clear post-operative radiotherapy is required, whereas others are happy to use implant or autologous reconstructions. This lack of consensus can make it difficult for patients who are likely to need post-mastectomy radiotherapy when they are considering their options for reconstruction. They may receive conflicting advice from different individuals reflecting the differing approaches of individual doctors when considering breast reconstruction where post-operative radiotherapy is considered likely. Fibrosis in autologous breast reconstruction is more common in immediate reconstructions that are irradiated compared with delayed breast reconstructions [24]. This same meta-analysis showed *no* impact of radiotherapy in patient and physician satisfaction of the final cosmetic result [24].

Table 10.3 Options for breast reconstruction

Technique	Indications for	
	Immediate reconstruction	Delayed reconstruction
Prosthesis	Small breasts Adequate skin flaps	As for immediate reconstruction *plus* well healed scar *plus* no radiotherapy[a,b]
Tissue expansion and prosthesis	Adequate skin flaps Tension-free skin closure Small- to medium-sized breasts	As for immediate reconstruction *plus* well healed scar *plus* no radiotherapy[a,b]
Myocutaneous flaps	Larger skin incision Doubtful skin closure	As for immediate reconstruction
	Large breasts	Can be used if previous radiotherapy

[a]Unless using acellular dermal matrix
[b]Radiotherapy significantly increases complication rates

10.6 Evaluation of Candidates for Breast Reconstruction

Important factors in assessing whether patients are suitable for breast reconstruction and determining the optimal technique include assessment of a patient's general health, their body habitus, breast size and shape, extent of any mastectomy scar, site of any mastectomy scar, the thinness of the mastectomy flaps, previous radiotherapy, their smoking history and patient preference.

It is important to assess the quality of the tissue that is present and is likely to remain when performing a breast reconstruction. There is a need to determine the amount of skin and soft tissue required to create acceptable symmetry, before being able to determine what might be appropriate options (Table 10.3).

10.7 Whole Breast Reconstruction: Patients with Newly Diagnosed Breast Cancer in Whom Mastectomy Is Recommended

10.7.1 Treating the Breast Cancer

For patients undergoing mastectomy as their primary surgical option, it is important not to delay removal of the cancer and removal of or biopsy of regional lymph nodes as this may impact on the patient's long-term prognosis. One study showed huge variation in time patients waited for mastectomy alone compared with mastectomy and immediate breast reconstruction [3]. If it looks as though it is going to take a long time

either for the patient to make a decision on her chosen reconstructive option or to assemble a team to perform a reconstructive procedure, then other options for the patient should be considered. One of these options, which is underutilised in many centres, is to give systemic therapy as the initial treatment. For premenopausal women and those postmenopausal women with large oestrogen receptor-negative or HER2-positive cancers, then neoadjuvant chemotherapy ± trastuzumab is an excellent option, particularly if the oncologist has already considered that it is likely the patient will receive chemotherapy in the adjuvant setting [6]. In HER2-positive cancers, dramatic rates of complete pathology response including disappearance of DCIS are possible with the use of neoadjuvant chemotherapy together with trastuzumab [32]. In postmenopausal women with large tumours, almost 80% are oestrogen receptor-positive, and these cancers respond well to aromatase inhibitors [33, 34]. In such women, prescription of aromatase inhibitors for a number of months to shrink the cancer will allow over half to become suitable for breast conservation, or they can be placed on aromatase inhibitors for a few weeks as a temporary measure, whilst consideration is given to the best form of reconstruction.

Should the scheduling of reconstructive surgery be delayed for any reason, then another option is to excise of the invasive cancer through an appropriately placed incision that does not interfere with later breast reconstruction procedures. This can allow adjuvant systemic therapy to be administered prior to mastectomy and reconstruction.

A useful option in some patients is to perform an initial sentinel lymph node biopsy in a patient with an invasive cancer who has no obvious nodal disease on clinical and ultrasound assessment of the axilla. One value of preoperative axillary assessment using a combination of imaging with fine-needle aspiration cytology and/or core biopsy or sentinel lymph node biopsy is that it allows assessment of the likelihood and extent of any axillary lymph node involvement. This helps evaluate the likely need for post-mastectomy radiotherapy. Although there are some who believe that post-operative radiotherapy has limited impact on the cosmetic outcome from whole breast reconstruction, the majority of surgeons believe radiotherapy does have a significant negative impact on breast reconstructions, particularly if breast implants are being used [23, 25–27], and they advise patients to delay reconstruction until the completion of treatment [35]. Knowledge of the likely requirement for post-operative radiotherapy can influence the decision to proceed with immediate breast reconstruction and if so can influence the preferred technique. Although there are some who believe that it is not possible, with any degree of certainty, to determine whether post-operative radiotherapy is likely to be needed, it is clear that it is possible, with a high degree of accuracy by preoperative assessment of the type and extent of the primary cancer in the breast and any nodal involvement to predict those who are likely to need post-operative radiotherapy

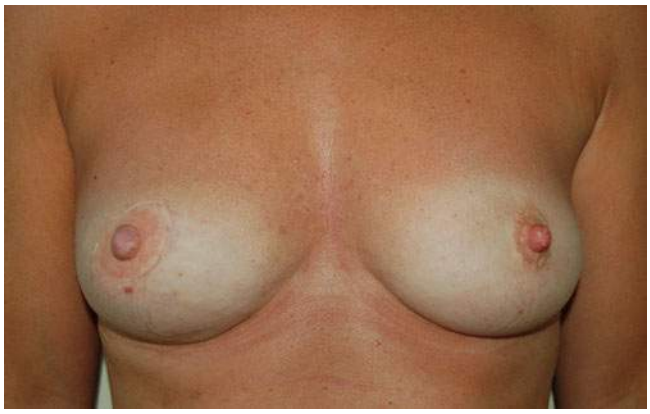

Fig. 10.1 Right mastectomy immediate reconstruction with LD flap, lipofilling and nipple graft. Post-radiotherapy result

[35]. One major reason patients get post-operative chest wall radiotherapy after mastectomy is having multiple axillary nodal involvement; thus an initial sentinel lymph node biopsy to assess the status of the axilla prior to mastectomy and consideration of reconstruction is a sensible approach. At the same time, as sentinel lymph node biopsy is performed, it is also possible to remove the central subareolar ducts, and this can assist in a decision about whether the patient is suitable for a nipple-sparing approach during the mastectomy operation [36]. Even in patients having an autologous reconstruction, it is useful because the nipple can be placed on any new skin island as a free nipple graft. The patient's own nipple is always the best match, it is underutilised, and there is a high success rate with this approach (Fig. 10.1).

10.8 Choosing Options (Refer to Table 10.3)

10.8.1 Implants and Expanders

Breast implants and expanders are best suited for breast reconstruction for women with smaller breasts with thick mastectomy flaps and minor degrees of ptosis [37]. For women who wish to avoid major surgery involving donor sites and scars on other parts of their body, breast reconstruction using implants may be the option of choice. When performed as a delayed procedure, a period of tissue expansion is usually required prior to the placement of the definitive implant. In the immediate setting however, a skin-sparing approach during mastectomy improves the quality of the final result [38]. Total submuscular implant placement can sometimes lead to upward displacement of the inframammary fold. To address this problem, the pectoralis major origin should be released or detached, and the inferior pole of the implant can be covered with an acellular dermal matrix to achieve enhanced projection [39]. Good candidates for the

ADM technique have small- to moderate-sized breasts and good-quality skin and show an absence of established glandular ptosis. Young patients requesting bilateral risk-reducing surgery are good candidates for ADM and implant-based reconstructions. In older age groups, the technique may still lead to very satisfactory results when combined with symmetrising surgery on the contralateral side. Irradiated tissues rarely do well with implant-based breast reconstructions [39]. Complication rates are high as are implant loss rates as reported above. Prior lipofilling of the mastectomy flaps can improve the state of the irradiated skin, and if either an implant-based or autologous reconstruction is being considered after radiation, then one or more episodes of lipofilling or lipomodelling are likely to improve cosmetic outcomes and reduce complication rates. During the reconstructive consultation, the limitations of this technique for unilateral reconstruction must be communicated and the patient advised that symmetry is possible usually only when clothed with the contralateral side supported in a bra.

10.8.2 Use of Tissue Matrices

A variety of tissues have been used to cover the lower pole of implants during breast reconstruction (Fig. 10.2). The problem with total muscular cover has been obtaining satisfactory inferior projection and reconstruction of a satisfactory inframammary fold. The tissue matrices in common use include those derived from human skin, pig skin, bovine pericardium and peritoneum [39, 40]. Both synthetic and absorbable meshes have also been utilised. De-epithelialised lower mastectomy flaps are another option to improve lower pole fullness and provide sufficient cover of the implant where it sits below the lower margin of the pectoralis major muscles. When using tissue matrices, meshes or de-epithelised skin, the pectoralis major is lifted from its site of origin, and the tissue matrix, mesh or de-epithelialised flap is stitched between the cut edge of the pectoralis major muscle and the new inframammary fold [40]. This provides a sling for the lower part of the implant alone, Becker implant/expander or tissue expander. The option of de-epithelialising the lower flap of the mastectomy and suturing this to the edge of the pectoralis major muscle is less good at creating an inframammary fold than acellular dermal matrix [41]. The two can be combined to good effect when carrying out a skin-sparing mastectomy (Fig. 10.3). Prepectoral implants with ADM or mesh covering is now being used by many in preference to subpectoral implants. Recovery is quicker and there are no problems with animation of the muscle. Most patients with prepectoral implants need either thick mastectomy flaps or multiple episodes of lipofilling or fat transfer to disguise the implant contour and give a natural breast shape. Many believe there is a lower rate of complications using this technique although there are no robust data to support this.

Complication rates with these various techniques can vary widely. Implant and tissue matrix loss rates can be as high as 17% [19, 40]. A recent report of 232 sheets of ADM in 147 patients reported a high rate of contralateral surgery (37.5%) in patients who had ADMs and implants for unilateral breast reconstruction [19]. The use of ADM is best considered in patients having bilateral procedures although patients need to understand that one or both implants may be lost in up to a quarter of patients in some series [19]. Particular care is needed when selecting the most appropriate incision especially if a nipple-sparing technique is to be used. Any wound edge necrosis particularly over the tissue matrix or mesh is associated with a high rate of implant loss. For this reason, we use an incision 1 cm below the inframammary fold in patients who are having a nipple-sparing mas-

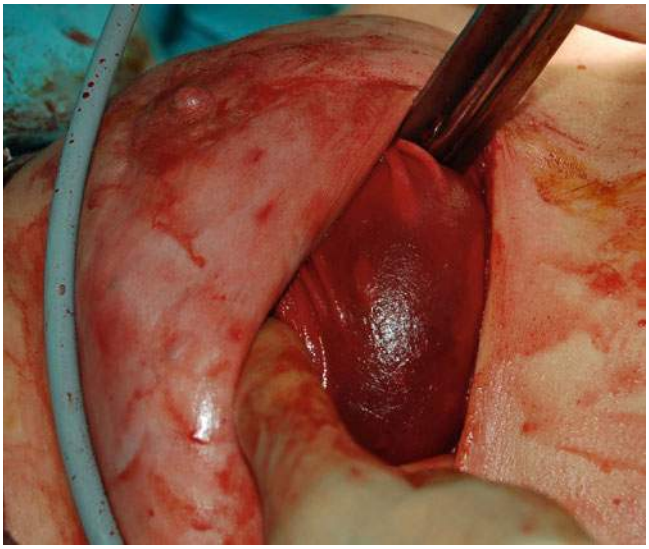

Fig. 10.2 Acellular dermal matrix being placed at surgery to cover the lower pole of an implant

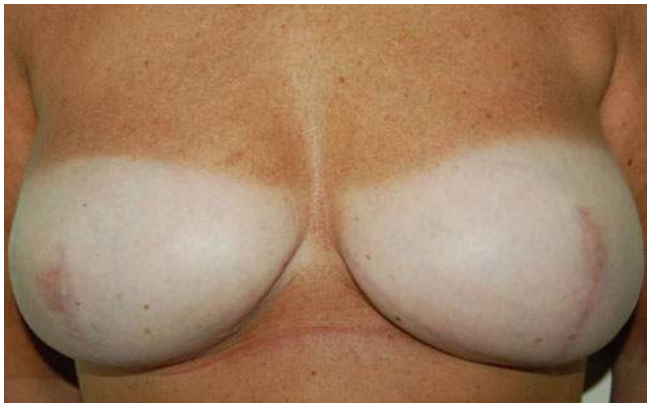

Fig. 10.3 Bilateral mastectomy with de-epithelialised lower flaps

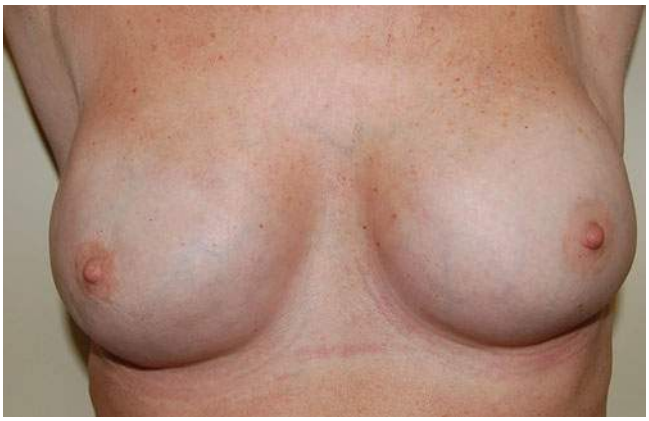

Fig. 10.4 Bilateral nipple-sparing mastectomies with implants and later lipofilling

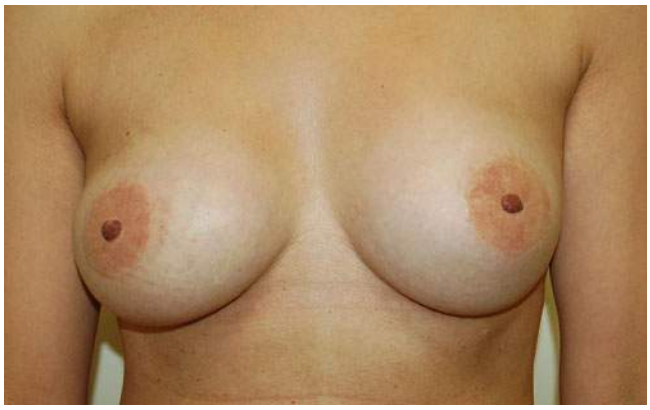

Fig. 10.5 Bilateral mastectomy with LD flap, lipofilling, small implants. Patient had small cancer with DCIS in the left breast and a right prophylactic mastectomy

tectomy. This avoids incisions around the nipple that interfere with nipple blood supply and lateral incisions that displace the nipple laterally (Fig. 10.4).

10.8.3 Latissimus Dorsi Flaps

Patients who are ideally suited for latissimus dorsi (LD) flaps include thin patients where the infraumbilical tissues are limited and patients who have undergone previous abdominoplasty or other abdominal operations through abdominal scars that may have compromised the blood supply to the abdominal flap. The latissimus dorsi appears more resistant to the effects of impaired wound healing in patients who smoke or who have diabetes [42]. Additionally the latissimus dorsi does not compromise the abdominal wall which may be an issue for patients considering future pregnancy. When considering patients for secondary reconstruction, the existing mastectomy scar may pose challenges to planning insertion of an LD flap. Compared to an oblique mastectomy scar, a vertical or horizontal scar can be difficult to conceal and may compromise projection of the reconstructed breast. If the flap is placed too high, then satisfactory ptosis and inferior pole projection cannot be obtained [43]. In patients with a very high scar, the flap can be inserted into a new incision placed in the inframammary fold. The main bulk of the muscle must be placed where it is required to create a breast mound which matches the opposite normal breast. One study comparing latissimus dorsi breast reconstruction with TRAM reconstruction found the LD flap was associated with fewer complications [44]. Patients who have undergone complex or multiple axillary surgery procedures or prior axillary radiotherapy both of which can compromise flow in the thoracodorsal vessels should be considered for CT angiography prior to performing a delayed reconstruction with an LD flap.

Until recently, it has been traditional to combine a latissimus dorsi flap in most patients with the insertion of a breast implant (Fig. 10.5). With the development of extended latissimus dorsi flaps, an increasing number of patients can have autologous breast reconstruction without the use of an implant [45]. The shape evolves over time, and it is important to inform women that the contour and shape will improve with time (Fig. 10.6). It is also possible to augment the volume of a latissimus dorsi flap by later lipofilling [46]. A new innovation is augmenting the volume of the LD flap by lipofilling the flap during the primary breast reconstruction (Fig. 10.1). This can be done under direct vision. It is important not to try this if the flap is not well vascularised. The volume injected should be such that the flap is not overfilled and the blood supply is not compromised. The results are impressive, and in patients who have subsequently had radiotherapy, the flaps have tolerated this treatment remarkably well (Fig. 10.7). A major drawback of latissimus flaps used to be the high rate of seroma formation on the back, although the rate has been reduced dramatically in our practice by the adoption of quilting sutures when closing the back wound [47].

10.8.4 TRAM and DIEP

Surplus tissue in the lower abdomen can represent an excellent source of material when considering breast reconstruction. Typically the reconstruction is performed without the need for breast implants, and the final result may be indistinguishable from the native breast when performed in ideal circumstances (Fig. 10.8). The transfer may be achieved as a pedicled muscle flap or as a free tissue transfer either incorporating part of the rectus abdominis muscle (TRAM) or based purely on the perforating branches of the deep inferior epigastric artery (DIEP) [40, 48, 49]. Prior abdominal operations require careful evaluation to ensure the axial vessels are likely to be intact and that pre-existing scars will not impact adversely on the abdominal closure or interfere with successful wound healing. A preoperative angiogram can ensure that sufficient good-quality vessels are present. A patient's

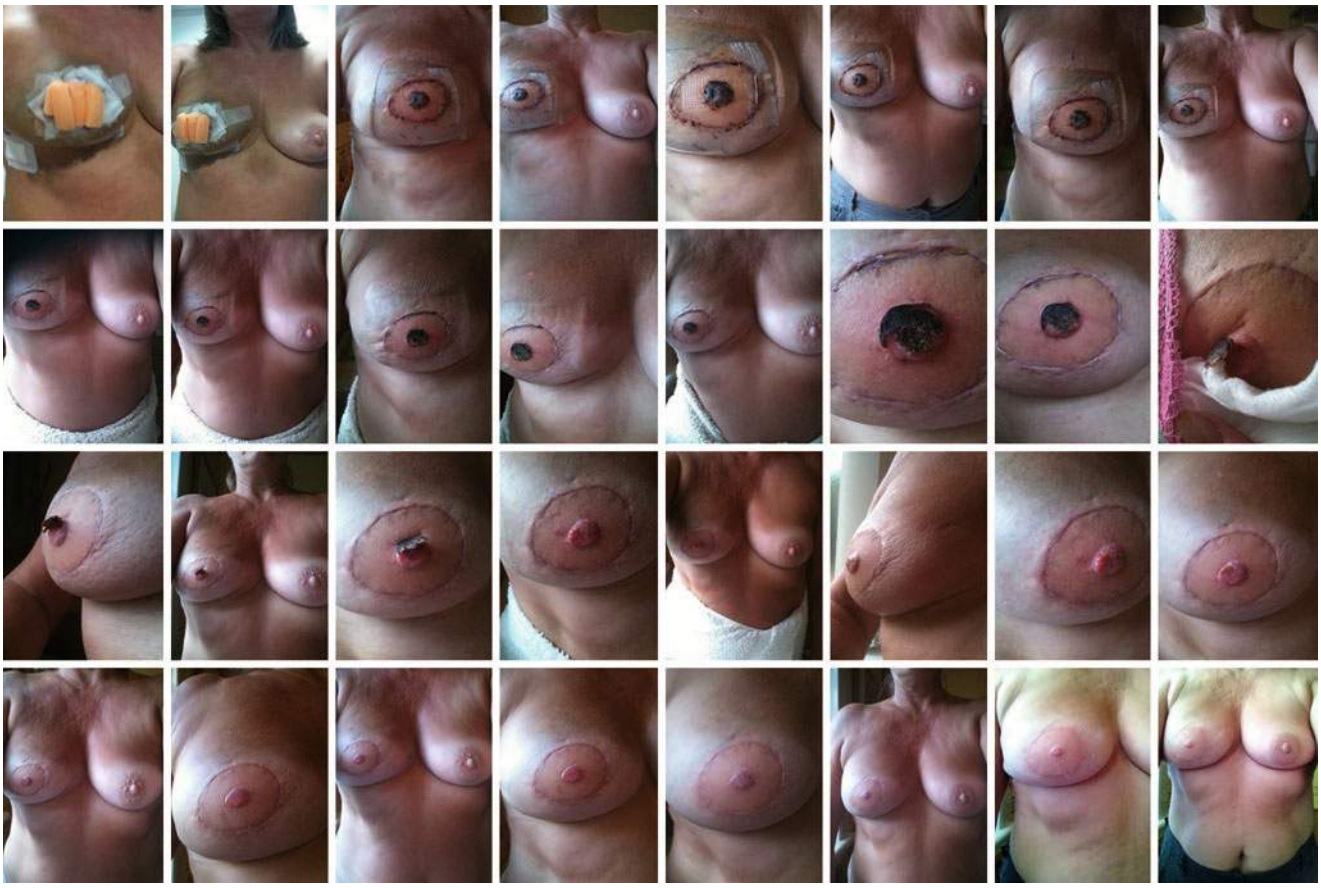

Fig. 10.6 Reconstruction in transition. A patient who underwent a right breast reconstruction with an excluded LD flap. Photography was taken regularly by the patient over a 3-month period after surgery

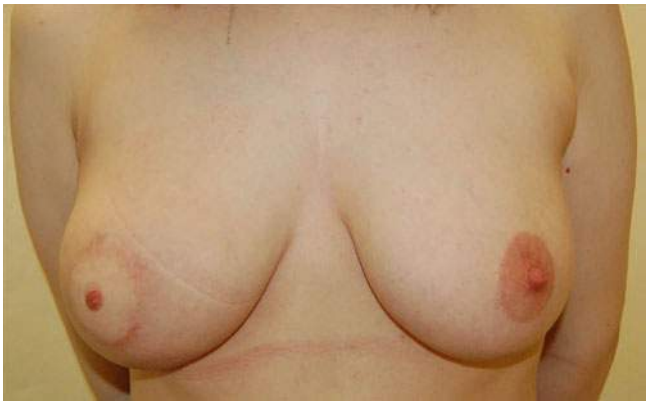

Fig. 10.7 Right mastectomy immediate reconstruction with LD flap lipofilling and nipple graft. Post-radiotherapy result

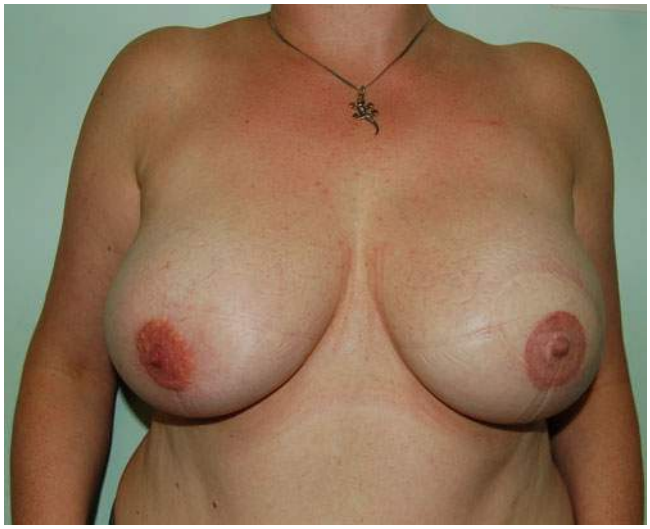

Fig. 10.8 Left mastectomy with De-Ep flap and nipple reconstruction

general health should be good, and cigarette smokers should be advised to stop for at least 3 months prior to surgery where circumstances allow [16]. Cigarette smoking increases significantly the risk of complications, and these patients may be served better by a procedure with a lower risk profile. There is also a well-recognised risk of total flap failure of around 3–5% which again is higher in smokers and of abdominal wall bulging or herniation, and these factors, when combined with a longer recovery period compared to other techniques, may significantly influence a patient's decision to proceed with this surgery. Where circumstances are favourable, however, fully autologous lower abdominal

breast reconstructions produce durable results with high levels of patient satisfaction in both the immediate and delayed settings [3].

10.8.5 Other Free Flaps

There are a range of other free flaps that have been described as options for breast reconstruction; these include superior and inferior gluteal artery perforator flaps (SGAP and IGAP flaps) and the transverse upper gracilis flap (TUG flap) [40].

These flaps are usually offered only by specialist plastic surgeons and are used mostly in patients who are not suitable for other options [40].

10.8.6 Lipofilling or Lipomodelling

Autologous fat transplantation also known as lipofilling or lipomodelling has been used to correct cosmetic deformities in almost every part of the body in recent years. The most common uses of lipofilling in the breast are to fill defects after breast-conserving surgery, to correct asymmetry after breast reconstruction, to correct congenital abnormalities and to prevent breast deformities in breast-conserving surgery. An important part of the preoperative assessment now involves inspection of possible donor sites—usually the abdomen, upper legs and thighs. Even in very slim women, sufficient volume of fat can be obtained to achieve satisfactory outcomes in asymmetry. In some instances with patient cooperation and sufficient fat available, whole breasts can be reconstructed with lipofilling alone although this usually involves many episodes.

There are some theoretical risks associated with the use of lipofilling in breast reconstruction in patients with cancer, but reviews and meta-analyses have been reassuring [50–55]. The technique and experience of the surgeon can influence outcome so it is important it is performed by a trained individual. There are concerns that the rate of absorption may be higher in smokers and in those who have previous radiotherapy.

Lipofilling has been used at the same time as breast-conserving surgery to stop deformity but needs to be injected into the breast parenchyma, subcutaneous fat, deep to the breast or into the pectoralis major not into the space (Fig. 10.9). For patients who have had prior mastectomy and radiotherapy, initial lipofilling improves the quality and thickness of the mastectomy flaps (Fig. 10.10a–c) and improves the final cosmetic result. We now use it in all such patients as an initial procedure. We also use lipofilling to thicken mastectomy flaps in patients having implant-based reconstructions. Lipofilling of the LD muscle can avoid the need for implants and is less affected by radiation than an implant under the LD muscle (Figs. 10.1 and 10.6). Volumes reaching many hundreds of millilitres can be injected under direct vision. For patients with volume asymmetry after prior breast reconstruction, lipofilling is often the only option that will achieve true symmetry.

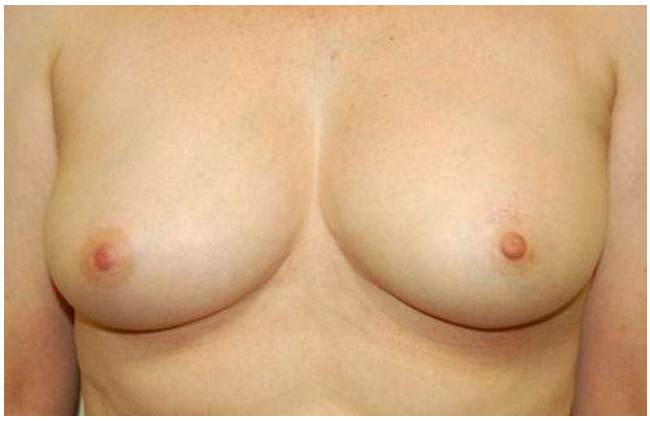

Fig. 10.9 Left wide local excision and lipofilling of a cancer high in the left breast. Result 2 years post-op

Patients need to be aware of the recovery time after this procedure and the complications the most common of which are pain, numbness and bruising. There are a number of patient information leaflets available on lipofilling, and all patients who are being considered for this procedure should be given one of these leaflets [56].

10.8.7 Skin-Sparing Mastectomy

The goal of breast reconstruction is to achieve an aesthetically pleasing breast resembling as closely as possible the native organ or at the very least achieving a result that can be matched by the minimum of additional surgery to the contralateral side. The preservation of as much native breast skin as possible at the time of mastectomy brings significant advantages both in terms of final breast shape and overall aesthetic appearance when combined with immediate breast reconstruction [57, 58]. A body of evidence now exists supporting the oncological safety of this technique [59–64]. These data show skin-sparing mastectomy (SSM) can be performed without compromising local disease control. Carlson et al. provide a 10-year retrospective review of 539 patients treated for 565 cases of breast cancer by SSM and immediate breast reconstruction. The local recurrence rate with an average 65-month follow-up was 5.5%; local recurrence rates increased as disease stage at presentation increased [65]. These rates of local recurrence are comparable to total mastectomy and nipple excision [66]. In an earlier publication, Medina-Franco reported a local recurrence rate of 4.5% with a median follow-up of 6 years in 173 consecutive patients undergoing SSM and breast

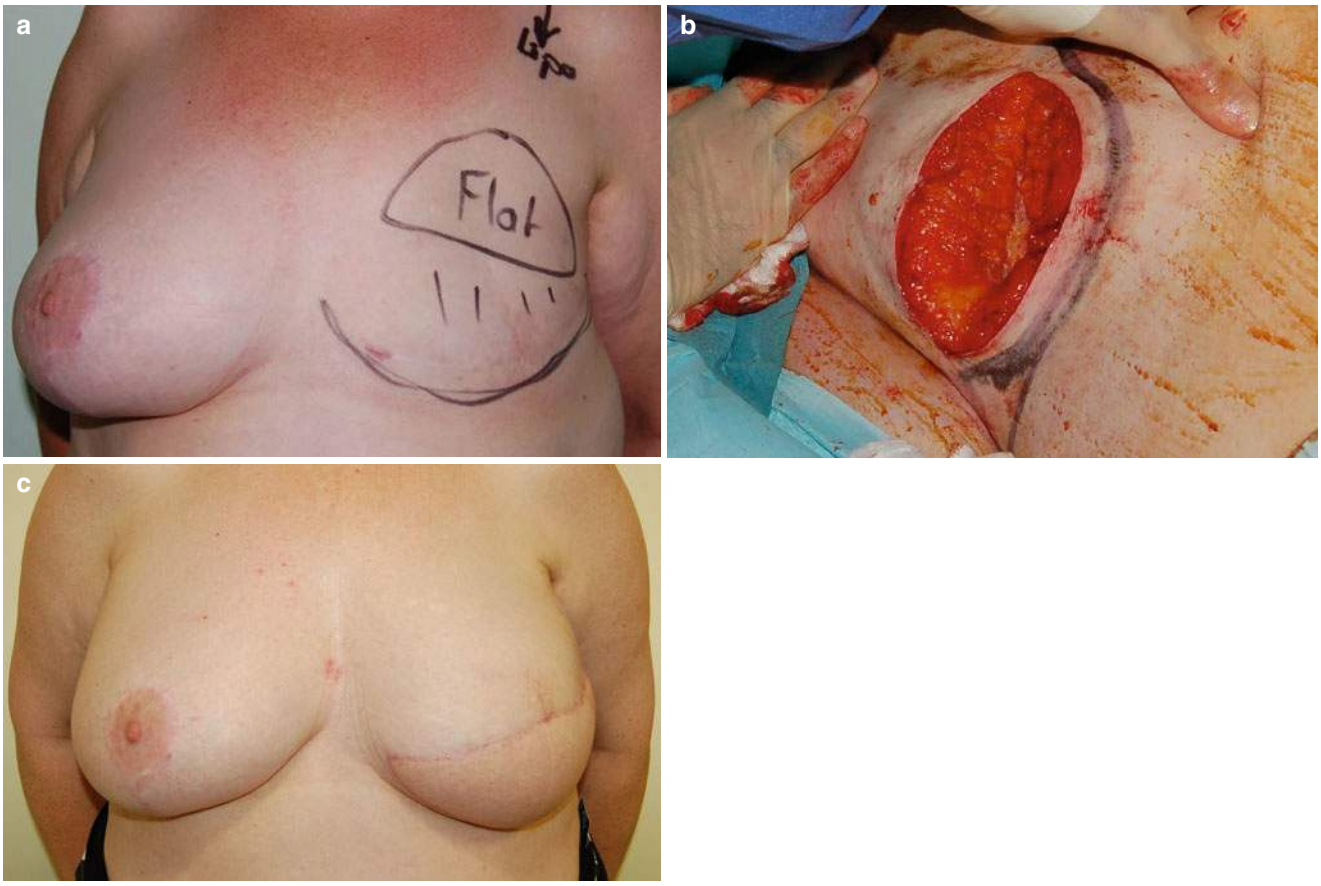

Fig. 10.10 (**a**) After mastectomy, before lipofilling. (**b**) Thickness of mastectomy flaps after lipofilling. (**c**) Delayed left LD flap with immediate lipofilling

reconstruction [61]. A skin-sparing approach to mastectomy is therefore both desirable and safe and should be considered whenever breast reconstruction is planned. Nipple-sparing mastectomy is also possible in patients with cancers and is discussed later.

10.8.8 Nipple-Sparing Mastectomy

Although nipple-sparing mastectomies are now widely used for prophylaxis, they can also be used in the treatment of women with invasive and in situ breast cancer. They have an acceptable risk of recurrence of less than 2% in T1 cancers [38, 67–70]. Selection of patients for nipple sparing has been based on distance of the cancer from the nipple; the greater the distance, the less likely nipple involvement by cancer is to be present. Where there are concerns that there may be nipple involvement, this can be checked prior to surgery either by using a mammotome to remove the subareolar ducts [69] or biopsying the ducts at the time of sentinel node biopsy prior to the mastectomy or during the operation by frozen section [70–73].

One problem with nipple-sparing mastectomies has been that it is not easy to get good results in patients with ptosis and the nipples are not always left in a satisfactory position. One solution is to perform an initial mastopexy and reposition the nipple [74]. This can be performed together with a cancer excision or as an initial procedure in patients having mastectomy for prophylaxis. The subsequent mastectomy and reconstruction are performed through the incision used for the reduction some 3–4 months later. The mastopexy and subsequent mastectomy can be combined with lipofilling to increase the thickness of the mastectomy flaps. With this technique, nipple loss at mastectomy is infrequent, and the cosmetic outcome can be excellent (Fig. 10.11). Thus in patients who are suitable candidates for nipple-sparing mastectomy, it is imperative to assess the nipple position and degree of ptosis prior to deciding the optimal approach.

10.8.9 The Opposite Breast

Symmetry is the primary focus of breast reconstruction. This is often difficult to achieve in many patients. Selection of one

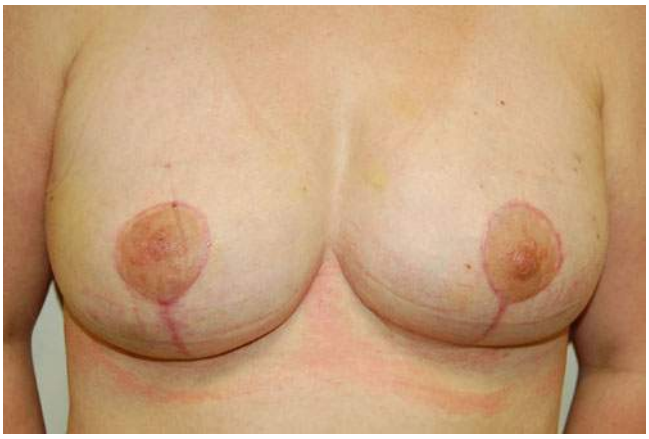

Fig. 10.11 Bilateral risk-reducing mastectomy with breast reconstruction using implants and lipofilling after an initial mastopexy

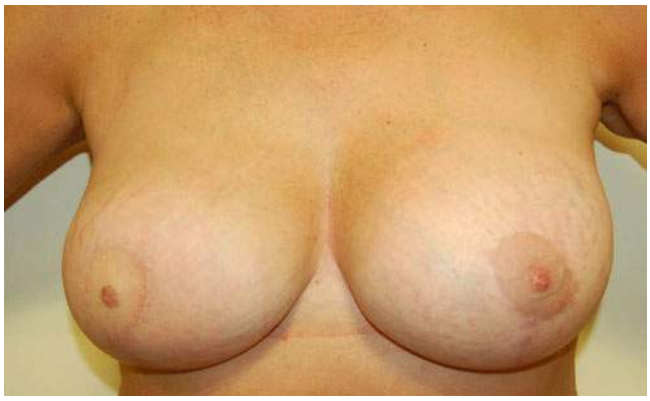

Fig. 10.12 Right mastectomy immediate LD flap reconstruction with lipofilling and immediate contralateral mastopexy

or other technique for breast reconstruction is influenced not only by the amount of skin that has been or very occasionally needs to be removed during the surgery to excise the breast cancer but by the appearance of the remaining breast including any possible procedures that may be advised on the opposite breast to achieve shape and/or volume symmetry (Table 10.3).

It is of upmost importance to consider the opposite breast in the initial breast reconstruction plan. For this reason, it is important to discuss with the patient, prior to any operation, what the options are for the opposite breast if symmetry is to be obtained. The reconstructive surgeon should, however, appreciate that most patients prefer to leave their opposite breast unscarred and untouched if possible. If the breast that is to be matched is well shaped without excessive ptosis, the goal of breast reconstruction should be to match it. If the opposite breast is large or small in relation to the patient's body habitus, then the options of enlarging or reducing the opposite breast should be considered and discussed. Even if the opposite breast is of adequate volume, it may be necessary to consider a mastopexy, if one is going to obtain symmetry of contour as well as symmetry of volume. Performing the breast reconstruction and contralateral procedure at a single operation has obvious advantages for the patient and is cost-effective (Fig. 10.12).

One option for the opposite breast is prophylactic mastectomy. Such an operation attempts to reduce the possibility of breast cancer developing in the opposite breast in women at high risk, and it can ease some patients' fears that they have about cancer development in their opposite breast (Fig. 10.5). The patient must however be guided in this by discussions and input from the multidisciplinary team before this approach is selected. Studies have shown a recent dramatic increase in the number of woman having prophylactic contralateral mastectomy [75]. Of note, a recent study identified the majority of women undergoing this surgery were not at heightened risk of developing contralateral breast cancer [76]. Significant risk factors for having a prophylactic contralateral mastectomy include having a breast MRI and having a breast reconstruction [77, 78]. Whilst it is true that it is easier to obtain symmetry when similar procedures are performed on both breasts, this in itself is not sufficient reason to remove a normal contralateral breast which is not at significant risk of breast cancer development. With adjuvant hormone therapy, the rate of contralateral breast cancer development is less than 4 per 1000 per year although that risk does persist over a 20–30-year period [76]. Even those patients who develop a contralateral breast cancer, mastectomy is not always necessary. Only in patients with a strong family history (with or without the knowledge that the patient is carrying a mutated BRCA1 or BRCA2 gene) and patients with atypical hyperplasia affecting a breast together with a significant family history should prophylactic mastectomy be considered as essentially a therapeutic procedure. There is some information that suggests patients who have a contralateral mastectomy at diagnosis have a better outcome than those who have a unilateral mastectomy [79]. This information is not from randomised studies and is inconsistent with the number of women who die from contralateral breast cancer [76]. Providing appropriate surveillance of the other breast is continued on a regular basis development, and treatment of a contralateral breast cancer does not appear to compromise outcome [76].

In summary there is no good-quality evidence to show that contralateral mastectomy improves outcome in women who are not BRCA1 or BRCA2 gene carriers and patients need to be informed of this. One study showed 69% of women having a prophylactic mastectomy experienced pain;

in 36%, this affected their sleep; and in 22%, it had an effect on daily activities with 75% reporting less enjoyment of sexual activity [80]. Prophylactic contralateral mastectomy should not thus be performed without a full and informed discussion of the pros and cons of the procedure.

10.9 Revisional Surgery Consultation

A number of patients who have had previous reconstruction and had an initially symmetrical and satisfactory result attend to discuss revisional reconstructive surgery, and others attend who have had a failed reconstruction. The untreated breast increases in size and develops increasing ptosis over time, whereas the reconstructed breast, with the exception of autologous reconstruction, tends to remain the same size or even shrink if the patient has had radiotherapy. The same range of reconstructive options is available to these patients as to patients who have had an immediate reconstruction. Options may be limited, depending on what procedures they have had previously and whether the patient has received prior radiotherapy. Revising and improving a patient's reconstruction can be more complex than a primary breast reconstruction, but good outcomes are possible (Fig. 10.13a, b). Considerable expertise in this area is required if an individual surgeon is to offer such an option. To obtain symmetry, it is usually necessary to consider surgery to both breasts and assess the need for reduction or mastopexy of the opposite breast together with revisional surgery on the previously reconstructed breast (Fig. 10.14a, b). Patients who have had previous implant surgery before the use of tissue matrices often do not have well-defined inframammary folds. If the

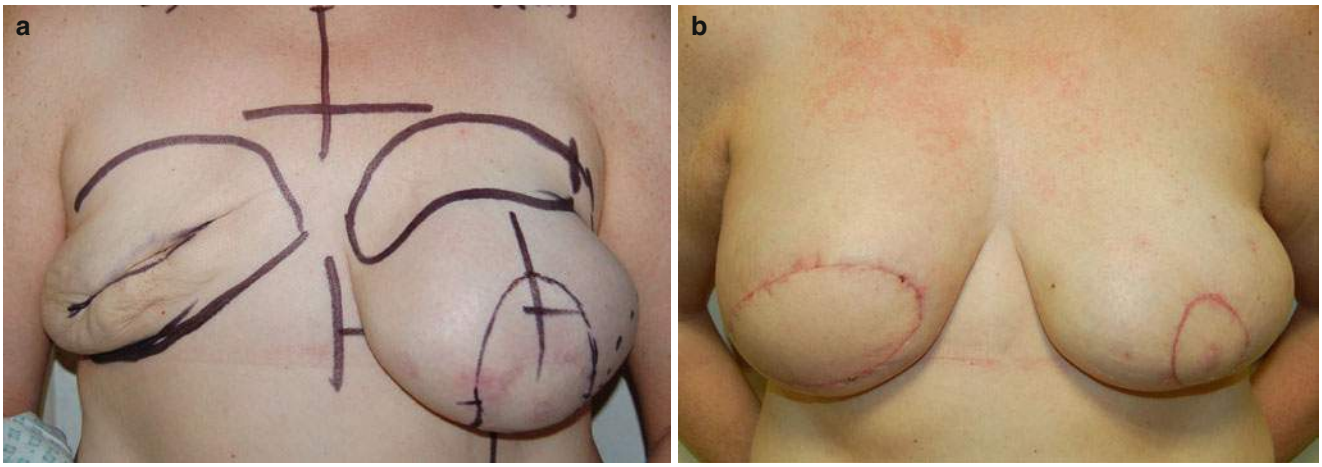

Fig. 10.13 (**a**) Patient with failed right De-Ep flap and poor result of right De-Ep flap prior to revisional surgery. (**b**) Result of revisional surgery

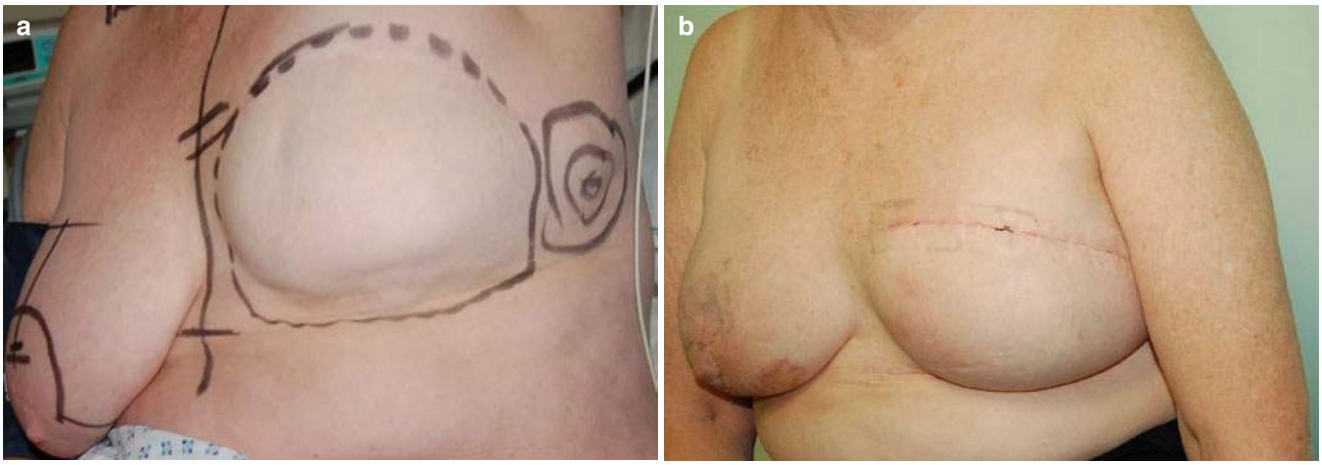

Fig. 10.14 (**a**) Patient who had a left breast mastectomy with implant 10 years earlier. Revision surgery involved placing Strattice® in the left breast replacing the prosthesis and doing a right mastopexy with a small reduction. (**b**) Result 2 weeks post-op

patient has sufficient skin inferiorly, then simply dividing the lower part of the capsule and placing a tissue matrix to define the inframammary fold and to provide a sling can provide much enhanced lower pole projection and allow placement of a shaped prosthesis and can produce satisfactory results in many patients. Advancement of lower abdominal skin using sutures to define and position the inframammary fold in the current position is another option. Alternatively autologous tissue transfer with or without lipofilling or lipomodelling can be offered. Lipomodelling has revolutionised revisional surgery and should be considered as part of the reconstructive options for most women having revisional surgery. Each patient requires careful assessment by the reconstructive team with sufficient time for the patient to consider all options.

10.9.1 Partial Breast Reconstruction

Breast distortion after breast-conserving surgery is not easy to correct. Better planning of the initial surgery, closing defects, limited resection volume and the use of immediate options to reconstruct the breast defects give the best outcome. Options that limit breast deformity include local flaps and immediate lipofilling. For patients who have significant degrees of asymmetry following breast-conserving surgery, there are a range of options. If the treated breast is small but of satisfactory contour, then the simplest option is to perform a contralateral breast reduction and mastopexy. The majority of patients however have distortion at the wide excision site often with displacement of the nipple. Lipofilling or lipomodelling can improve distortion and contour, but the problem of nipple displacement remains. Following two or three episodes of lipofilling, it is possible to mobilise the skin of the breast and recentralise the nipple on the residual larger volume of breast mound. Where there is distortion, lipofilling usually needs to be combined with either scar release or open scar revision excising the scar tissue at the wide excision site and reshaping the residual breast mound to get rid of the defect at the wide excision site. Despite multiple episodes of lipomodelling, some women still have deformity, but the breast is usually softer and more mobile. Placement of a prosthesis under the treated breast, or even in both breasts, has been used to good effect in carefully selected patients [81]. The implants can be placed underneath the breast or underneath the chest wall muscle. Although it was previously considered that implants in breasts treated by radiotherapy had a high rate of capsular contraction and unsatisfactory cosmetic outcomes, in selected patients, the results achieved have been excellent. However with the recent improvement in the volumes of fat that can be harvested and with the increasing use of lipofilling, the number of patients who are either suitable or require breast implants to gain satisfactory symmetry is small. In some patients, there is a need to replace skin and volume so the use of myocutaneous or even lipocutaneous flaps is the only option to obtain symmetry. The LD flap is the most widely used in this situation (Fig. 10.15a, b).

When patients are attending for consideration of procedures to achieve symmetry, then it is important to discuss all the appropriate and relevant options with the patient and give them time to come to an informed decision. Some patients with asymmetry attend for advice on the best way to achieve symmetry when clothed. This can be achieved very effectively by wearing a shell over the treated breast in the bra rather than more complex reconstructive surgical procedures. Provision of these external prosthetic shells increases women's confidence and their ability to wear a wider range of clothes. For many women, surgery to the opposite breast is the best option to achieve symmetry. Nonetheless surgery is not the only option for such women, and all such women should be given access to a properly trained prosthesis fitter as well as getting advice from an appropriately trained reconstructive surgeon.

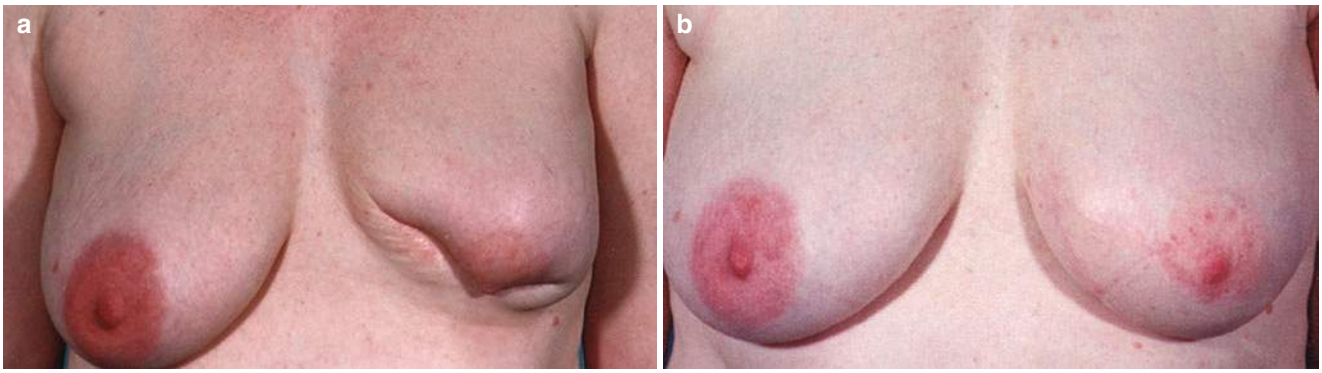

Fig. 10.15 (**a**) Patient with a poor cosmetic result pre- and post-LD flap partial breast reconstruction. (**b**) Post-op result

10.10 Reconstruction of One or Both Breasts

10.10.1 Bilateral Prophylactic Mastectomy in High-Risk Women

In the Mayo study of prophylactic mastectomy in high-risk women, 1065 women underwent prophylactic mastectomy over 32 years [82]. Two thirds were classified as having an increased breast cancer risk based on their family history. The remainder had a variety of conditions including breast pain, cystic disease and difficult mammograms. Ninety percent had a subcutaneous mastectomy which was skin sparing. In these patients, prophylactic mastectomy resulted in an over 90% reduction in subsequent breast cancer development. Eighty percent of the subcutaneous skin-sparing mastectomies were actually nipple sparing. In this study, of 425 low-risk women, 10 deaths would have been expected from breast cancer, but none were observed which is a 100% risk reduction. In the 214 high-risk women, between 11 and 31 deaths from breast cancer were expected, whereas 2 occurred which is an 81–94% reduction in death rate.

Candidates for prophylactic mastectomy should be seen at least twice by a breast surgeon and/or a plastic surgeon. It is important to allow the woman to assimilate all options and have the opportunity to discuss these with either a breast care nurse or a psychologist. This is an elective procedure, and the decision should not be rushed. The potential benefit of risk-reducing surgery must be balanced against the woman's age and risk. Either a genetic counsellor or a breast surgeon needs to advise the woman about how risk changes with age. Information on the risk over the next 5 years as well as lifetime risk is important in deciding the best age for surgery. Issues such as the level of anxiety and plans for having children and breast feeding need to be covered in discussions about risk-reducing surgery. A range of leaflets are available on the Macmillan website written and endorsed by the authors [83].

10.11 Timing of Breast Reconstruction

Immediate breast reconstruction is an increasingly appealing option offering women the option of waking up after their mastectomy with a reconstructed breast. This has obvious psychological advantages, and patients who request immediate reconstruction are usually pleased with this decision and their outcomes. Despite the psychological benefits of immediate reconstruction, there are some potential drawbacks including being uncertain of the need for post-operative radiotherapy, at the time the decision to choose the type of reconstruction is made. For patients having breast-conserving surgery in whom it is recognised, the surgery will remove a significant volume of tissue these women are best to either have reshaping to produce a smaller breast but of a satisfactory shape or to have immediate volume replacement by a local flap or by the use of immediate lipofilling.

Delayed reconstruction can be performed from several days to many years after mastectomy. Contrary to what some believe, many women do not become adjusted to breast loss. Some surgeons wait 3–6 months after mastectomy or 3–6 months after radiotherapy for the flaps to heal and for the skin reaction to settle. This allows time for seromas to resolve and for the patient to have time to consider the various options that may be suitable to reconstruct her breast. Results for both can be satisfying (Table 10.4; Figs. 10.10c and 10.16).

There is a third way. In patients where it is not clear whether they need radiotherapy or not, it is possible to place a tissue expander under the chest wall. The expander is inflated, and this maintains the residual skin [71, 72]. If the patient does not need radiotherapy, there is the option of continuing tissue expansion and replacing this with an implant later. For those who require radiotherapy, the expander can

Table 10.4 Patient's rating of the results of their surgery at 18 months post-operatively

Overall, how would you describe the results of your operation?	Mastectomy only	Immediate reconstruction	Delayed reconstruction
Excellent	1513 (36)	520 (34)	368 (47)
Very good	1565 (37)	505 (33)	242 (31)
Good	786 (19)	288 (19)	101 (13)
Fair	304 (7)	145 (9)	43 (5)
Poor	74 (2)	74 (5)	28 (4)

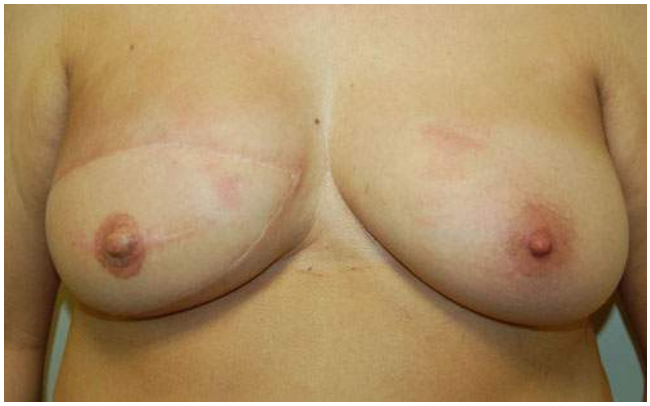

Fig. 10.16 Delayed right LD with flap lipofilling previous mastectomy with post-operative radiotherapy

be left in situ and if required reduced in volume to allow radiotherapy. A few weeks after completion of radiotherapy, the expander is reinflated, and 3 months later, the patient can then undergo a further procedure usually bringing in vascularised tissue such as a latissimus dorsi or abdominal flap. There is some evidence that the new tissue brought in rejuvenates skin which has been irradiated and results in an overall better result than performing a straightforward mastectomy, giving radiotherapy and then performing a standard delayed breast reconstruction.

10.12 Patient Preferences and Breast Reconstruction

There are a variety of studies which have looked at patient preferences in relation to breast reconstruction; 386 patients in one study were included of whom 309 had a therapeutic mastectomy and 79 underwent prophylactic mastectomy [73]. They were asked to express opinions in relation to a number of options including materials used for reconstruction, the number and duration of operations, short-term complication rate, long-term complication rate, aesthetic results and the time they might spend waiting for the operation. Two-hundred seventy-two patients (71%) agreed to participate in this study. Autologous tissue was preferred by these patients to implants, and shorter operations were preferred to longer operations. Patients preferred excellent results, with low rates of complications, but were willing to trade an excellent result for a good result with a lower rate of short-term complications. Based on what women thought was important, autologous LD flap with a good aesthetic result providing it only had a 10% complication rate was the highest ranked option. Second was an autologous DIEP flap with a 10% complication rate and a good result. Third was autologous DIEP flap with an excellent result but up to a 25% complication rate.

Patients select the reconstructive technique which suits their wishes after the initial discussion. Generally simpler techniques which produce acceptable aesthetic results are preferred by most women, but more complex procedures generally give better results [3, 84] (Table 10.4). Interestingly a study of female plastic surgeons exhibited a strong desire to pursue implant-based reconstructions with invasiveness of the procedure and recovery time cited as the most important reasons [85]. Patients' understanding of exactly what is involved in breast reconstructive surgery was investigated in one study where questions were asked in relation to the operation itself, the recognised complications and how breast reconstruction may influence the detection of recurrence. The study found that only 37.9% of patients answered the questions correctly [86]. Communicating options and providing informed choice are therefore a huge and ongoing problem [87].

Finally body image and the impact of breast reconstruction change over time (see Fig. 10.6). Body image may initially be worse in patients having reconstruction but improves over time, and by 2 years, it is as good as for patients having mastectomy or breast-conserving surgery [87]. Surgical issues even at 2 years may be still significantly greater in patients having reconstruction than for patients having breast-conserving surgery. Given the continued fall in local recurrence rates after breast-conserving surgery, the most important decision in breast reconstruction remains whether there are options to retain the patient's own breast safely. Data now suggests that not only are the outcomes as good with breast-conserving surgery as with mastectomy; they may even be better [88]. There is no subgroup who seem to benefit from mastectomy, and with modern oncoplastic techniques, there are few absolute contraindications to breast-conserving surgery [89]. There is also evidence the pain and discomfort [80] and lymphoedema rates [90] are all higher with mastectomy than breast-conserving surgery. Furthermore, however good a reconstruction is, it is rarely ever as good as a well-performed breast-conserving procedure.

10.12.1 Nipple Reconstruction

There are a variety of techniques, and examples of the results can be seen in Figs. 10.8 and 10.16. Nipple sharing (Fig. 10.5) and nipple grafting (Figs. 10.4, 10.7, 10.11 and 10.12) are options that should be discussed with patients at the first consultation. Some women are very clear that they are not concerned about nipple reconstruction, whereas others wish for nipple preservation providing that it is deemed feasible and safe.

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Aesthetic Principles for Breast Reconstruction: Breast Aesthetic Units and Evaluation of Late Aesthetic Results

11

Marcelo M. C. Sampaio and Murillo Fraga

11.1 Introduction

Aesthetics (aisthésis) is a branch of philosophy dealing with the study of nature and beauty. Several philosophers have encountered great difficulty when attempting to define beauty, or even ugliness, and even more when attempting to quantify this property. Kant, a respected philosopher whose aesthetic notions were quoted by his peers, asserted that it was impossible to establish theoretical rules to build beautiful things.

Upon attempting to establish aesthetic notions, physicians face difficulties in scientifically validating their results. Individual criteria are invariably attributed to judgment.

Because it is a subjective matter, aesthetic assessment imposes limitations on science's attempts to measure it. In breast reconstruction, a result is deemed good when it pleases most people, especially the patient. Questionnaires on quality of life can be applied as a scientific method to assess results, although quite often they were developed for other medical areas and later adapted for plastic surgery. Another possibility is to apply a statistically validated specific questionnaire to the assessment of results. Recently, one such questionnaire, the BREAST-Q, was validated [1]. After application to 817 women, it proved to be an efficient instrument to assess aesthetic or reconstructive surgery of the breast. The development of standardized questionnaires is important because these instruments allow comparisons among publications by different institutions and thus represent a powerful scientific tool. This questionnaire has been used in several clinical studies. Howes et al. [2] analyzed quality of life in women who were submitted to mastectomies, followed or not by immediate breast reconstruction, and compared to quality of life in women who had breast-conserving surgeries. In this study, the BREAST-Q was applied to 400 patients. Authors concluded that women who undergo total mastectomy and breast reconstruction achieve a quality of life outcome which is at least as good as the following breast-conserving surgery. Adding to that, the latter was associated with lower physical well-being in the chest area and poorer sexual well-being outcomes. Another group of researchers applied this same questionnaire to 1790 women who had breast reconstruction with autologous tissue: deep inferior epigastric artery perforator (DIEP) flap, muscle-sparing free transverse abdominis myocutaneous (TRAM) flap, free TRAM flap, or the pedicled TRAM flap. The authors concluded that the DIEP was associated with the highest abdominal well-being and the lowest abdominal morbidity compared to the pedicled TRAM flap; however it did not differ from muscle-sparing free TRAM or free TRAM flaps [3].

In recent years, there has been increasing concern with judging the effectiveness of plastic surgery procedures by means of questionnaires. Despite its biases, this method supports the consolidation of surgical procedures based on the improvement of the quality of life. The BREAST-Q might become an effective instrument for this purpose because it was developed specifically for plastic surgery and allows for the standardization of the assessment of results in future literature.

Are quality-of-life questionnaires able to assess aesthetic results? This question is the subject of long-standing debate, because even if it were proven that plastic surgery positively impacts quality of life, it is very difficult to quantify aesthetics. Despite these shortcomings, questionnaires represent an important tool for the validation of surgical techniques and may eventually compel health insurance companies to fund these procedures.

Owing to the difficulties in establishing a scientific method of assessing aesthetic results in plastic surgery, many of the notions discussed in this study are purely empirical and thus offer a low level of scientific evidence.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_11

11.2 Breast Reconstruction

Breasts are viewed by many as a fundamental indicator of femininity or as an element of sexual attraction, and they represent a very important factor in the psychosocial balance of women.

Since 1980, postmastectomy breast reconstruction has become an integral part of the therapeutic plan in breast cancer. Evidence of the oncologic safety of this procedure and developments and advancements in several surgical techniques allow satisfactory reconstruction of the shape and size of breasts.

The first decision to be made concerns the most appropriate time to perform the reconstruction, namely, whether during the same surgery as mastectomy or delayed by several months or years.

In ideal circumstances, immediate is preferred to delayed reconstruction. Patients are thus spared the trauma caused by breast amputation and have better odds of good aesthetic results because the anatomical elements are better preserved and less susceptible to the effects of late wound healing.

The choice of the reconstruction technique involves a complex assessment that must begin at the preoperative evaluation. The clinical history and physical examination allow not only the estimation of the anesthetic and surgical risks but also prediction of the viability of certain reconstruction techniques. Ideally, reconstruction must be individualized, and no priority should be attributed a priori to any of the several available possibilities.

There are several techniques for breast reconstruction. They differ as the amount of tissue to be removed in the mastectomy varies. Also, the location of the tumor and the possibility of autologous tissue donor sites are considered.

The anatomical elements that might require replacement include the skin, glandular tissue, and areolar–papillary complex. The extent and localization of the replaced tissue depend on the oncologic surgical treatment.

Breast reconstruction historically passed through several evolutionary phases as a function of its results. Initially, surgeons sought only to create a mammary volume. Next, the challenge was to give a proper shape to the reconstructed breast. Currently, it is possible to reconstruct symmetric breasts, aiming at attaining better balance between them. However, the search for perfection continues, and recently, an aesthetic concern arose regarding reconstruction. The challenge of applying aesthetic notions to reconstruction has become a trend, and the description of the anatomical units of the breasts and the chest wall motivates the discussions.

The assessment of the aesthetic results of reconstruction focuses on the attaining symmetric breasts in volume, shape, and position in the chest. This symmetry is a primordial, universally accepted notion, which is the goal of all patients. A new aesthetic criterion to consider was recently described and concerns the anatomical units of the breast. According to this principle, instead of repairing only the damage caused by the oncologic surgical treatment, the total reconstruction of these units might afford better aesthetic results [4, 5].

11.3 Breast Aesthetic Units

Burget and Menick [6] described the aesthetic subunits in nose reconstruction. The idea that the replacement of a full unit was better than partial reconstruction induced an extraordinary improvement in results. Similarly to nose reconstruction, the principle of aesthetic subunits in the planning of reconstructive breast surgery might result in better quality of the final results.

One of the objectives is to restore the tissue in the most similar and natural manner possible with minimal scarring trauma.

In aesthetic breast surgery, surgeons choose to perform the incisions on the skin folds and anatomical sulci (axillary fold, inframammary fold, and areolar margin), thus reducing the stigma of a surgical intervention. In reconstructive surgery, this principle might not be followed due to the oncologic priority of the treatment. The location and extent of the neoplasm determine the position of the scars. Nevertheless, the current approach still considers the aesthetic side without interfering in the local–regional treatment of disease [7, 8].

On these grounds, in recent years, the concept of breast oncoplastic surgery emerged, which might be defined as the balance between the maximal local–regional control of breast cancer and the minimal possible trauma. In the literature on breast cancer, the breasts were described as geometric circles divided into quadrants (“mammary mass”), without taking into account the natural and anatomical shape (of a drop) or the aesthetic demarcation lines. Surgical incisions on uncovered areas of the skin are aesthetically unpleasant. One of the main stigmas associated with the full process of breast reconstruction is the scar resulting from the catheter inserted to infuse chemotherapy agents, which remain visible on the upper chest area in the vast majority of patients [5].

In 1999, Restifo [9] applied the concept of breast aesthetic units in delayed reconstructions with a TRAM flap. In those cases where the lower flap was affected, the entire lower pole was replaced by the skin island derived from the abdominal flap (TRAM flap).

A similar principle was applied by Coutinho et al. [10], who observed that it is often preferable to sacrifice a part of the preserved tissue and replace the full anatomical unit to obtain more harmonious results. These same authors also reported their preference for single horizontal or

oblique scars that do not encroach on the upper medial quadrant.

In fact, the concept of anatomical subunits in surgical planning aiming to achieve better aesthetic results has been applied. In 2006, Song et al. [11] evaluated the results of 100 patients who had undergone reconstruction with TRAM flaps. When the breast reconstruction was divided into aesthetic subunits, there was a high degree of correlation between the overall score and the subunit scores ($r = 0.81$: $r > 0.6$ for good correlation).

11.4 Langer's Lines

Karl Langer, an Austrian anatomist, studied the skin of non-embalmed corpses and found that although the bundles of dermal collagen fibers are placed in all directions, thus resulting in a resistant tissue, in any particular location, most fibers follow the same direction. He noticed that boring wounds produced by an ice pick on the skin of a corpse are slit-shaped rather than rounded because the ice pick divides the dermis according to the prevailing direction of the collagen fibers and thus allows the wound to open. The prevailing pattern of the collagen fibers determines the characteristic tension and wrinkles of the skin. The cleavage lines (also known as lines of minimum tension or Langer's lines) tend to be longitudinal spirals in the limbs and transverse in the neck and trunk [12].

Whenever possible, surgeons choose to follow the cleavage lines because they afford better-looking scars (Fig. 11.1).

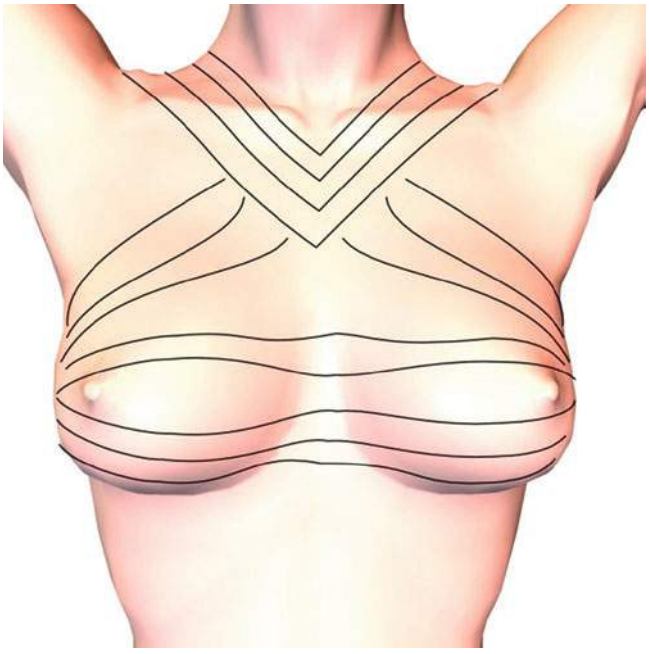

Fig. 11.1 Breast Langer's lines

11.5 The Subunit Principle

On the grounds of the breast subunit principle, two major approaches to reconstruction are described:

1. Reconstructions with flaps respecting the aesthetic subunits and thus producing good results
2. Reconstructions not respecting the aesthetic subunits and thus giving a patch-like appearance to the anterior chest area

The aesthetic subunits are characterized by the type of the skin, including its hue, texture, and thickness. These characteristics convey a uniform visual impression. The anatomical transitions between the breast and its boundaries, mainly the skin of the chest and the upper abdomen, demarcate clear transitional areas. Differences in the skin hue determine the characterization of the subunits and are crucial for the aesthetics of reconstruction.

Transitions are perceptible between the following locations:

- Breast skin and areola
- Areola and nipple
- Breast skin and sternum skin
- Breast skin and upper abdomen skin
- Breast skin and lateral chest wall skin

Spear and Davison [13], in a 2003 review covering 10 years, assessed 264 patients who underwent reconstruction with autologous tissue and concluded that the main breast subunits to be reconstructed and that delivered the best results in terms of appearance and scar camouflage were the areolar–papillary complex and the periareolar area. Once again, they emphasized the importance of taking these structures into account in surgical planning to achieve good results.

11.6 Reconstruction in Partial Mastectomies

The main goal of partial reconstruction is to preserve the cone shape of the breasts with the areolar–papillary complex centered on the breast projection apex. Scars must be linear or oblique and follow the lines of force (Langer's lines). Whenever possible, it is advisable to place the scars in the lower quadrants, inframammary fold, and periareolar area. The most difficult areas, which result in more visible scars, are the upper medial quadrants, which are not covered by the clothes.

The skin resection should be performed concentrically to the tumor, thus allowing the appropriate orientation of scars toward the better-camouflaged areas of the breasts (Fig. 11.2).

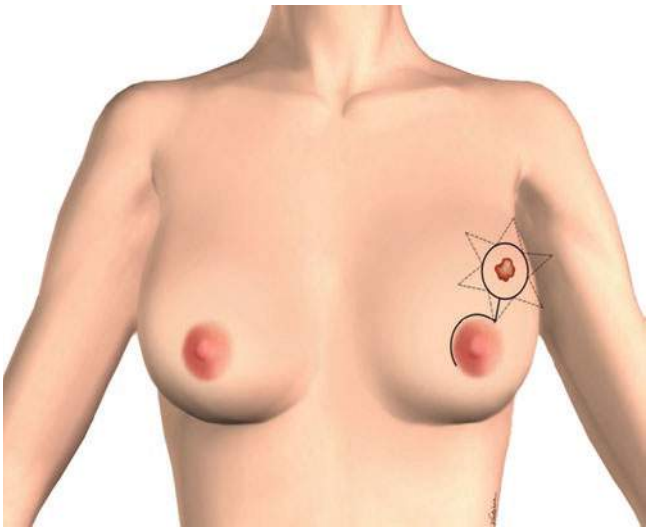

Fig. 11.2 The skin resection should be performed concentrically to the tumor, thus allowing the appropriate orientation of the scars toward the better-camouflage áreas of the breast

11.7 Classification of Aesthetic Results According to the Position of Scars (Sampaio and Fraga)

According to the principles of the position and quality of scars in breast reconstruction, the scars may be classified into five types in decreasing order as a function of the aesthetic results (Fig. 11.3):

1. Periareolar scar (most favorable)
2. Scar on the lower pole
3. Scar on the upper lateral quadrant
4. Scar on the upper medial quadrant
5. Scar crossing over quadrants (least favorable)

11.8 Reconstruction in Total Mastectomies

Attention to the breast subunits favors the aesthetic results of reconstruction. Scars on the inframammary fold and lateral wall of the chest have better quality than scars on the medial and upper pole.

The total reconstruction of one breast segment affords better results than the reconstruction of one quadrant because it avoids the patch-like appearance.

The approach to reconstruction that emphasizes the importance of the breast aesthetic units affords surgeons the possibility of choosing the best surgical technique and of offering patients differentiated and more attractive results.

Classification of Breast Reconstruction Results According to the Position of the Flap (Sampaio and Fraga)

According to the principles of flap position and scar quality in mastectomies, we may classify the reconstruction types from the aesthetic point of view into four types in decreasing order (Fig. 11.4):

1. Flap in the lower pole (most favorable)
2. Flap in the upper pole
3. Full breast reconstruction
4. Central flap crossing over quadrants (least favorable)

11.9 Long-Term Results of Breast Reconstructions

11.9.1 Psychological Aspects

A series of studies performed in the last 25 years considered the psychological aspects of patients who underwent mastectomy.

The earliest reports described a wide range of disorders, ranging from depression to the loss of the body image and eventually to suicide attempts.

Recently, more thorough studies have defined the psychosocial traumas related to mastectomies, which include loss of femininity and mood, interpersonal, and conjugal disorders [14]. In this context, the loss of the nipple–areola complex has great importance, considering that patients submitted to surgeries that preserve it have better self-image and sexuality [15].

Breast reconstruction acts as a “reverse mastectomy,” and it provides the most effective means of restoring biopsychosocial well-being.

The most frequently performed types of breast reconstruction are expanders, implants, expander prostheses, and autologous flaps (TRAM and latissimus dorsi flaps).

In 2000, Wilkins et al. [16] compared the psychological benefits of breast reconstruction on the basis of the time and type of procedure. They concluded that both immediate and delayed reconstructions promote substantial psychological benefits and that the type of reconstruction (expander/implants versus pedicled or free TRAM flap) in immediate reconstruction does not significantly affect the psychological status.

Recent data on breast cancer surgical treatment in 44,410 women in the United States revealed that since 2005, rates of immediate reconstruction and the use of implants have increased [17].

In delayed reconstruction, the use of expanders/implants promotes greater improvement of vitality and well-being, whereas the use of autologous flaps is associated with more remarkable improvement of the body image [16].

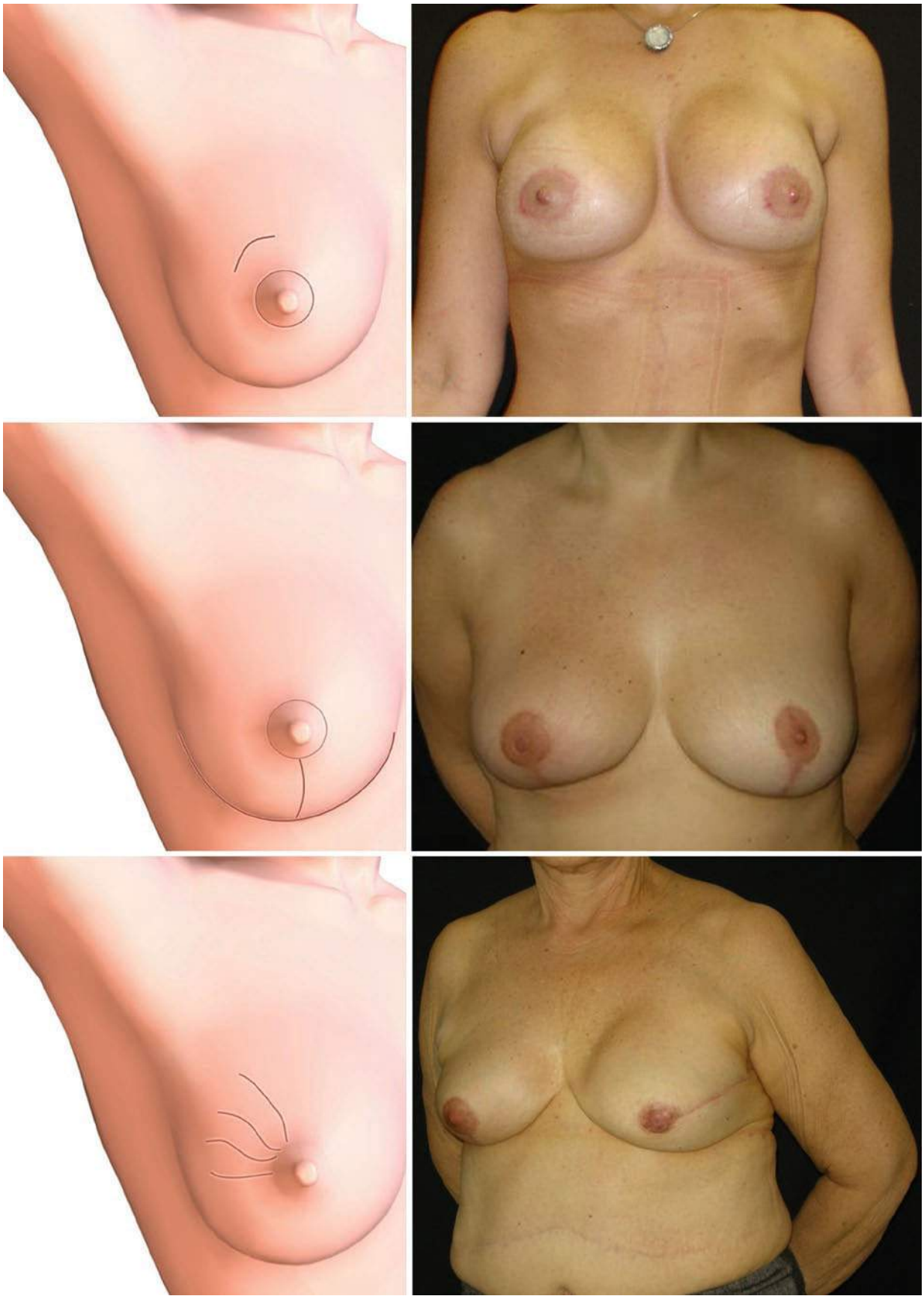

Fig. 11.3 (**a**) Type I—periareolar scar. (**b**) Type II—Scar on the lower pole. (**c**) Type III—Scar on the upper lateral quadrant. (**d**) Type IV—Scar on the upper medial quadrant. (**e**) Type V—Scar crossing over quadrants

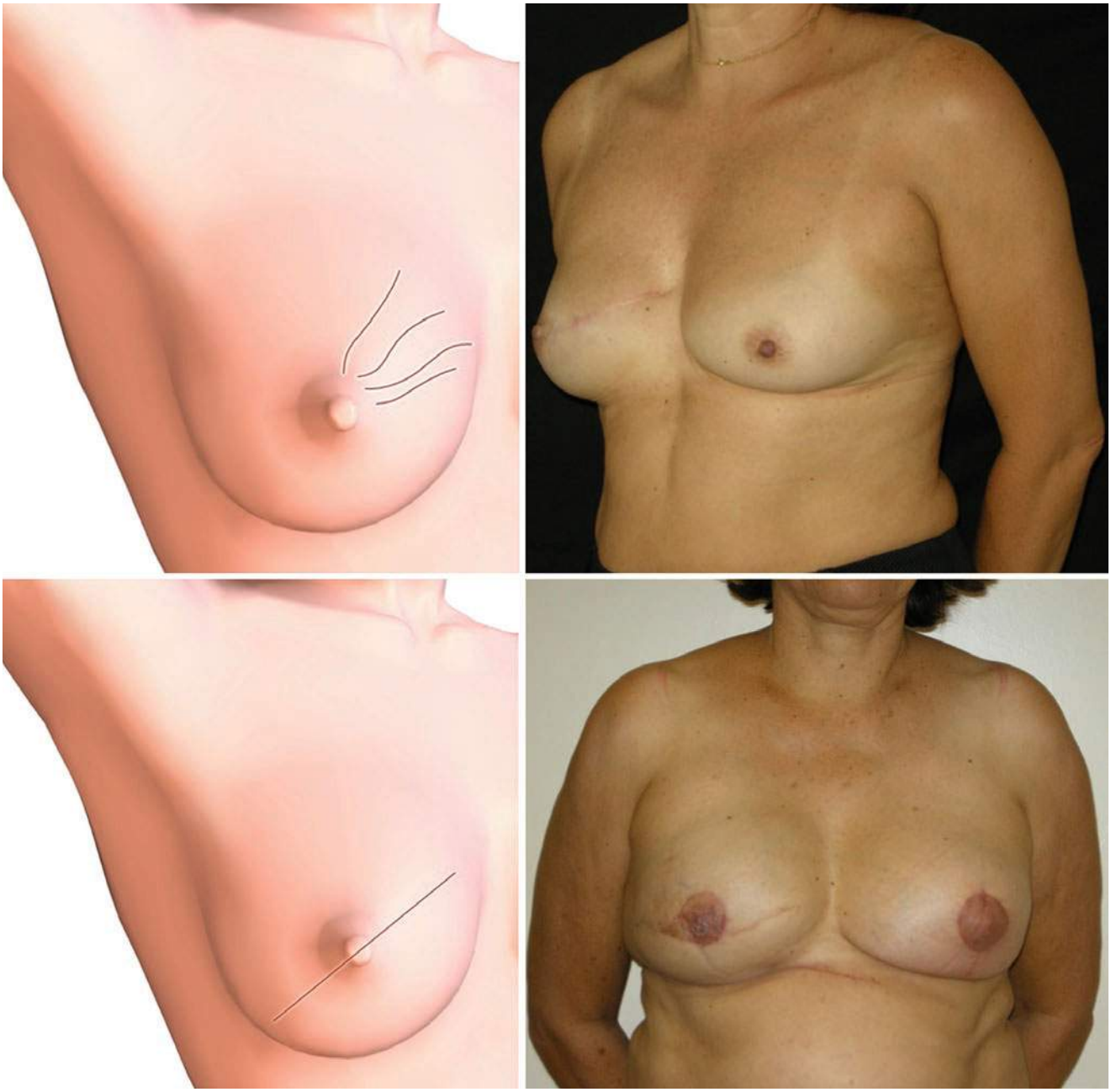

Fig. 11.3 (continued)

11.9.2 Complications of Postmastectomy Breast Reconstructions

In 2002, Alderman et al. [18] assessed the complications associated with the timing and type of reconstruction, as well as other variables, such as body mass index, radiotherapy, chemotherapy, age, and smoking. A total of 326 patients were analyzed, and the complications were classified as total or partial.

The results showed that immediate reconstructions are associated with a higher (statistically significant) rate of both total and partial complications compared with delayed reconstructions [18].

The body mass index is a variable associated with higher (statistically significant) rates of complications independently of the time and type of reconstruction [18].

No significant differences were observed in the rate of complications for the remaining variables or the type of procedure. However, certain evidence suggests higher rates of total and partial complications with the use of implants combined with radiotherapy and in patients who undergo reconstruction with a TRAM flap and have chemotherapy [18].

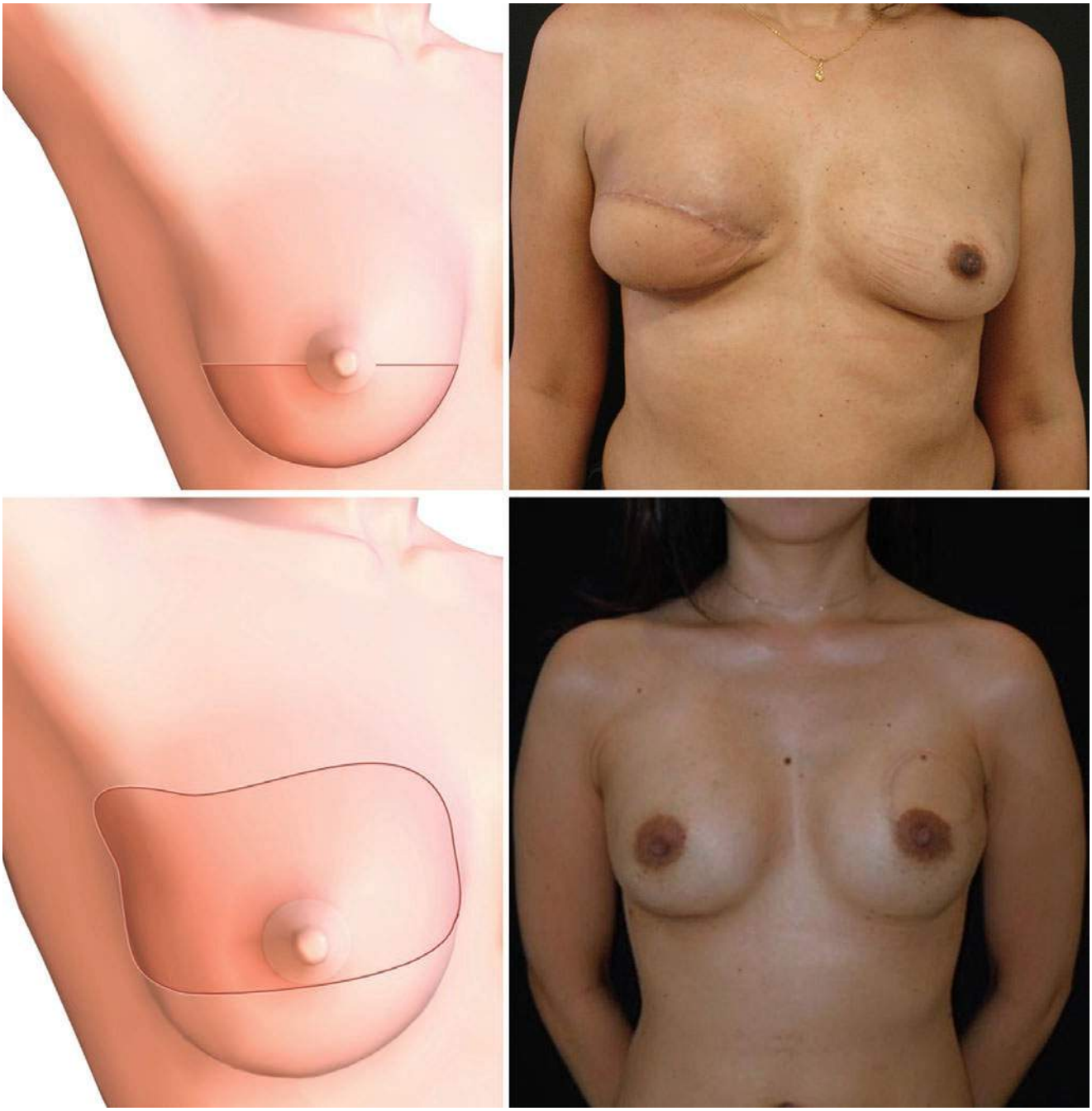

Fig. 11.4 (**a**) Type I—Flap in the lower pole. (**b**) Type II—flap in the upper pole. (**c**) Type III—Full breast reconstruction. (**d**) Type IV—Central flap crossing over quadrants

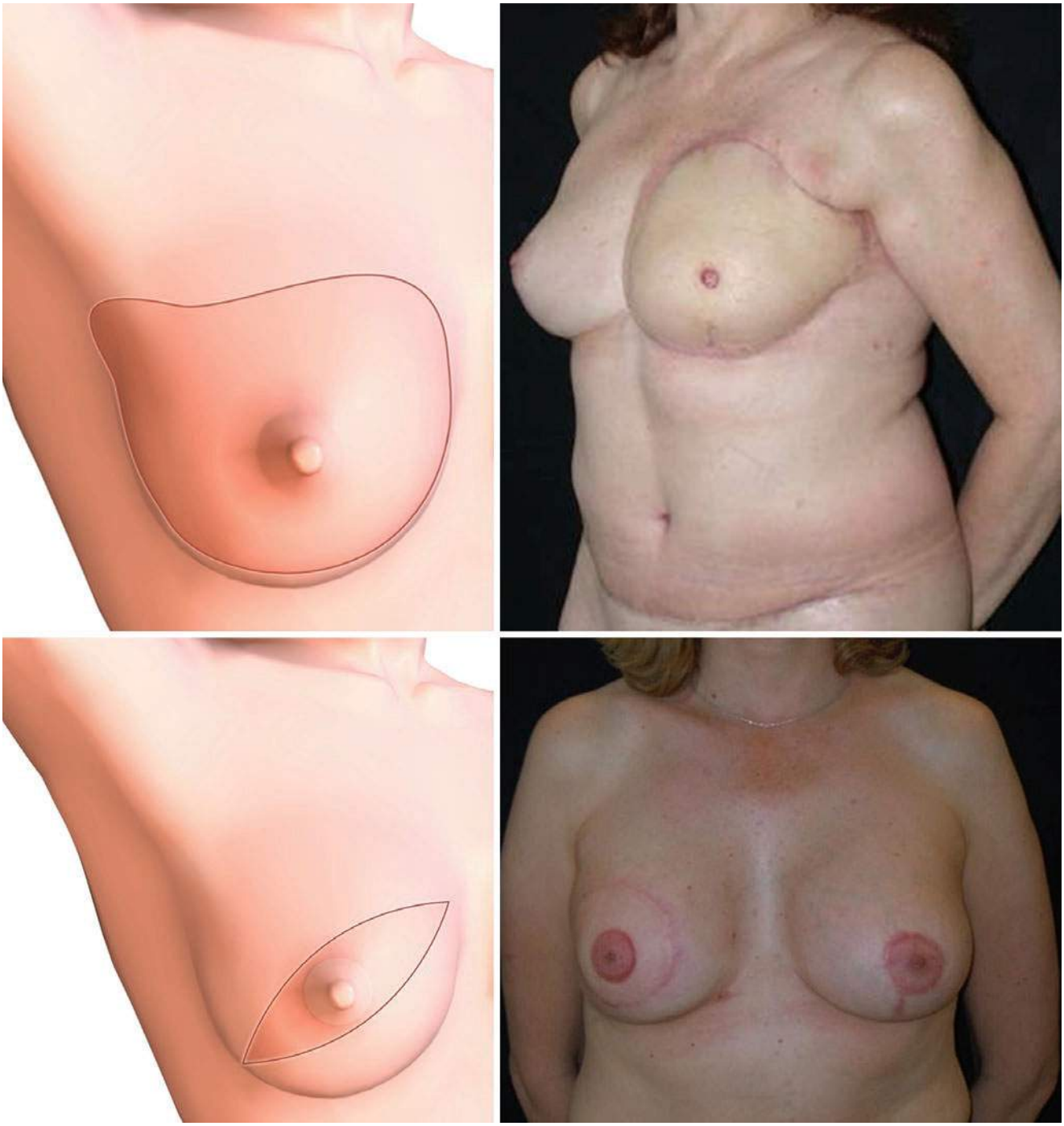

Fig. 11.4 (continued)

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Neoadjuvant Treatment in Breast Cancer

12

Rui Wang and Chau Dang

Abbreviation

BCS	Breast-conserving surgery
DFS	Disease-free survival
EFS	Event-free survival
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
HR	Hormonal receptor
HRD	Homologous recombination deficiency
OR	Odds ratios
OS	Overall survival
pCR	Pathologic complete response
RR	Clinical response rate

12.1 Introduction

Neoadjuvant therapy is defined as systemic therapy prior to definitive surgical treatment which includes chemotherapy, biologic therapy (i.e., HER2-targeted agents in HER2-positive disease), and hormonal therapy (in hormonal receptor-positive disease). Since the 1970s, neoadjuvant therapy has been routinely utilized as a standard treatment approach in patients with inoperable, locally advanced disease, or inflammatory breast cancer. It is administered to downstage the tumor, rendering an inoperable tumor to operable and to convert an indication for mastectomy to breast-conserving surgery, and to downstage the axilla. Other potential advantages include monitoring response to therapy and providing prognostic information such as attaining a pathological response rate (pCR), which can potentially serve as a short-term surrogate that may be predictive of favorable long-term outcomes [1–5]. It may also provide an ideal framework for biomarker studies utilizing breast tumor tissue, blood samples, and other clinical information that can be analyzed before, during, and after treatment, thus facilitating real-time clinical and biological assessment of the study regimen [6, 7]. However, neoadjuvant therapy has not been shown to improve long-term outcomes including disease-free survival (DFS) or overall survival (OS) compared with adjuvant chemotherapy [8, 9]. Of note, neoadjuvant chemotherapy may be associated with an increased risk of locoregional recurrence compared with adjuvant therapy, which could be due to the higher rates of breast conservation rates with NACT [8]. This is of limited concern given no effects on DFS and OS.

12.2 Pretreatment Evaluation

Prior to treatment, all patients will need a biopsy (preferably a core biopsy) of the primary tumor to confirm the presence of invasive tumor and evaluate receptor status [estrogen receptor (ER), progesterone receptor (PR), and HER2]. The preferred neoadjuvant therapy will depend on these characteristics. Radiopaque clips should be placed in the tumor prior to initiate neoadjuvant therapy to allow for the confirmation that the site of the tumor was removed and pathologic assessment of the surgical specimen, especially in the setting of pCR, is obtained. In addition, appropriate imaging, including mammography, ultrasound, or magnetic resonance imaging (MRI), can be used to assess the extent of the disease. For patients with clinical stage III disease and inflammatory breast cancer, further imaging to detect metastatic disease may be considered.

If axillary lymph nodes are palpable, an ultrasound-guided fine needle aspiration (FNA) or a core needle biopsy (CNB) will be required to confirm metastatic involvement. If axillary lymph nodes are not palpable, an axillary ultrasound is not required but can be considered to rule out pathological involvement prior to initiation of neoadjuvant therapy.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_12

12.3 Measurement of Response

During and following neoadjuvant therapy, regular clinical examination and proper imaging are necessary to document the response to therapy. Advances in ultrasound and MRI make these modalities good options for monitor treatment response. MRI may be the best currently available imaging to assess the extent of disease during and following neoadjuvant therapy.

12.3.1 Pathologic Complete Response (pCR) as an Evaluable Endpoint in Neoadjuvant Trials

In neoadjuvant studies, pCR has appropriately predictive long-term outcomes and, hence, has been considered as a potential surrogate marker for long-term benefits [3]. The pooled analysis from the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) involved 11,955 patients, and three definitions of pCR (ypT0 ypN0, ypT0/is ypN0, and ypT0/is) and the corresponding prognosis were analyzed [10]. Event-free survival (EFS) and OS were found to be significantly worse for the group with residual nodal involvement and similar in the groups (ypT0 ypN0 or ypT0/is ypN0). The likelihood of pCR in breast cancer was influenced by the biological subtype. For example, patients with tumors with luminal A features had the lowest pCR but better DFS and OS outcomes. Conversely, patients with TNBC had better pCR rates but poorer survival outcomes [11]. Furthermore, this pooled analysis demonstrated that pCR was a relevant surrogate endpoint in patients with the most aggressive tumor types (i.e., TNBC and HER2-positive and hormone receptor-negative). This was further confirmed in a pooled analysis in which pCR was a suitable surrogate for DFS in patients with HER2-positive/non-luminal, triple-negative, and luminal B/HER2-negative disease [12].

12.4 Neoadjuvant Treatment for Hormone Receptor-Positive, HER2-Negative Breast Cancer

12.4.1 Neoadjuvant Chemotherapy

Chemotherapy is the standard neoadjuvant treatment for patients with hormone receptor-positive disease. Chemotherapy can downstage the primary tumor and facilitate better surgical options but is less likely to achieve a pCR in HR-positive cancers [2, 10]. This was demonstrated in CTNeoBC in which 2616 patients had HR-positive, HER2-negative disease [10]. The frequency of pCR in this population was greater for high-grade tumors compared with low- to intermediate-grade tumors (16% vs. 8%). Patients with HR-positive disease who achieved a pCR also had improved survival outcomes relative to those who did not [2]. However, using pCR to predict outcomes in patients with HR-positive disease was limited given the low rate of pCR and the generally favorable survival outcomes, likely due to utilization of adjuvant endocrine therapy [13, 14].

Similar to chemotherapy in the adjuvant setting, most patients who receive neoadjuvant chemotherapy should receive anthracycline-based regimens such as dose-dense (every 2 weeks) doxorubicin and cyclophosphamide (AC) × 4 cycles followed by weekly or every 2-week paclitaxel or every 3-week docetaxel as the backbone of neoadjuvant therapy. The benefit of anthracycline-taxane regimens over anthracycline (without taxane) was demonstrated in the adjuvant setting [15] as well as directly in the neoadjuvant setting [16]. For example, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B27 trial randomized 2411 patients to either neoadjuvant AC (group 1) or AC followed by D (group 2) or AC followed by surgery and then followed by adjuvant D (group 3). With a median follow-up of 8 years, patients on AC followed by D in the neoadjuvant setting had higher rates of clinical response (91% vs. 86%) and pCR rate (26% vs. 13%) than those who had neoadjuvant AC. However, there was only a nonsignificant trend in DFS for patients who had D (5-year DFS, 71.1% and 70.0% for groups 2 and 3, respectively, 67.7% for group 1), and there was no difference in OS across all three groups [16]. For patients with a contraindication to a taxane or steroid, nab-paclitaxel can be used as an alternative based on the German Breast Group 69 (GeparSepto) trial which suggested nab-paclitaxel improves pCR rates compared to standard paclitaxel (38% vs. 29%, odds ratios (OR) 1.53, 95% CI 1.20–1.95), but with the cost of greater toxicity [17].

For patients with existing cardiac dysfunction, cardiac risk factors, advanced age, as well as unwillingness to accept anthracyclines, alternative non-anthracycline-based regimens can be considered. Options include docetaxel and cyclophosphamide or cyclophosphamide, methotrexate, and fluorouracil.

12.4.2 Neoadjuvant Endocrine Therapy

Although chemotherapy is the standard therapy for HR-positive, HER2-negative tumors, for those postmenopausal women with strong HR-positive tumors, neoadjuvant endocrine therapy is an acceptable alternative option, especially if the patient is unfit and may not tolerate chemotherapy. For postmenopausal women, neoadjuvant endocrine therapy confers a similar response and breast-conserving surgery (BCS) rates as neoadjuvant chemotherapy with lower toxicity. However, long-term survival data are not yet

available [18–21]. Recent meta-analysis including 20 studies with 3490 patients showed in HR-positive breast cancer, combination chemotherapy and endocrine therapy confer equal clinical response (RR) [odds ratios (OR) 1.08, 95%CI 0.50–2.35, $P = 0.85$], radiological response (OR 1.38, 95% CI 0.92–2.07, $P = 0.12$), pCR (OR 1.99, 95%CI 0.62–6.39, $P = 0.25$), and BCS rates (OR 0.65, 95% CI 0.41–1.03) [19]. The options for neoadjuvant hormonal therapy include an aromatase inhibitor (AI) and tamoxifen, but AI is preferred based on evidence suggesting better clinical outcomes with AIs across clinical trials and meta-analysis [19, 22, 23]. For example, in the meta-analysis discussed above, neoadjuvant monotherapy with AIs was associated with a higher clinical response (OR 1.69, 95% CI 1.36–2.10), radiologic response (OR 1.49, 95% CI 1.18–1.89), and BCS rates (OR 1.62, 95% CI 1.24–2.12) compared with tamoxifen [22]. The different AIs are comparably effective in trials, and each may be used in the neoadjuvant setting. In the American College of Surgeons Oncology Group (ACOSOG) Z1031 trial, 377 postmenopausal women with strongly HR-positive stage II or III breast cancer received 16–18 weeks of exemestane, letrozole, or anastrozole before surgery [24]. Treatment with any of the three agents resulted in similar clinical response and BCS rates. For women who are not tolerant of AIs (e.g., those with an osteoporotic fracture on AIs) or those who prefer to avoid the risk of osteoporosis associated with AIs, tamoxifen is a reasonable alternative.

For premenopausal woman, data of neoadjuvant endocrine therapy is limited. However, available phase II clinical trial suggests worse disease outcomes relative to chemotherapy. For example, subgroup analysis from the Grupo Español de Investigación del Cáncer de Mama (GEICAM) study showed inferior clinical outcomes with a 44% response rate who received neoadjuvant endocrine therapy (exemestane plus the luteinizing hormone-releasing hormone analog goserelin every 4 weeks for 24 weeks) vs. 75% who received neoadjuvant chemotherapy (four cycles of epirubicin and cyclophosphamide every 3 weeks followed by four cycles of docetaxel every 3 weeks) [18].

In terms of duration of endocrine therapy, response may not be seen until at least 3–4 months of treatment was delivered, and a few trials administered therapy over 6 months [25]. Thus, the duration of therapy is tailored according to the patient's response prior to definitive surgery.

12.5 HER2-Positive Breast Cancer

HER2 is a cell-surface receptor which signals cell growth and survival through the activation of downstream signaling pathways. The HER2 oncogene is amplified and/or overexpressed in 20–25% of breast cancers and is associated with an aggressive phenotype, including high-grade tumors, faster growth rates, and worse survival [26, 27]. Patients with HER2-positive breast cancer generally achieve a higher pCR rate to neoadjuvant therapy, even with chemotherapy alone, when compared to other types of breast cancer, especially if hormonal receptor is also negative.

Trastuzumab's role when adding to standard chemotherapy has been well demonstrated. The phase II NOAH (NeOAdjuvant Herceptin) study demonstrated that the addition of H to chemotherapy not only doubled the pCR rates (38% vs. 19%) but also improved the 3-year EFS from 56 to 71% (hazard ratio 0.59 [95% CI 0.38–0.90], $p = 0.013$) and 3-year OS from 79% (95% CI 70–86) to 87% (95% CI 79–92) [28]. Recently, the updated results of this study showed that at a longer follow-up of 5.4 years, there was a sustained benefit in EFS with the addition of H (hazard ratio 0.64, $p = 0.016$) [29]. This is consistent with the long-term follow-up data from the large adjuvant trials of H [30, 31]. Trastuzumab is continued after surgery to complete 12 months of treatment. Based on adjuvant clinical trials, 6 months is not non-inferior to 12 months of trastuzumab (PHARE) [32], and 24 months is equal to 12 months (HERA) [30]. Thus, 1 year of trastuzumab remains the standard.

Dual anti-HER2 therapy is also rational and has been evaluated in large clinical trials. Pertuzumab (P), a monoclonal antibody targeting HER2/HER3 dimerization, is approved by the FDA to use together with standard chemotherapy in the neoadjuvant setting. The NeoSphere was a randomized phase II study in which patients were randomized to one of four arms: DH, DHP, HP, and DP. Adding P to standard DH increased pCR rate from 29 to 45.8% (95% CI 36.1–55.7, $p = 0.0141$) [33]. Pertuzumab was well tolerated and its addition did not increase cardiac toxicity. The high pCR rate with adding P was confirmed in TRYPHAENA study, a multicenter randomized phase II study for patients with operable, locally advanced, or inflammatory breast cancer. In this study 225 patients were randomized to one of the three arms: Arm A, FEC (5-fluorouracil, epirubicin, cyclophosphamide) + HP × 3 → DHP × 3; Arm B, FEC × 3 → DHP × 3; and Arm C, DCbHP × 6. The study showed an approximately 60% pCR (ypT0/is) rate that was achieved with dual anti-HER2 therapy in each arm (Arm A, 61.6%; Arm B, 57.3%; and Arm C, 66.2%) with no increased cardiotoxicity [34]. The results of NeoSphere and TRYPHAENA led to FDA approval of pertuzumab in patients with stage II–III breast cancer. A study of ddAC followed by T + HP and FEC → DHP in neoadjuvant setting to evaluate cardiac safety was completed (BERENICE) and demonstrated a pCR rate of about 60% with both regimens with acceptable cardiac toxicity profile [35].

Although effective in metastatic setting, lapatinib (L), a small molecule tyrosine kinase inhibitor of HER1/HER2, was shown to be inferior to H in neoadjuvant setting in the

phase III GeparQuinto study [36]. Furthermore, the addition of L to H in neoadjuvant setting was also evaluated. In the phase III NeoAdjuvant Lapatinib and/or Trastuzumab Treatment Optimization (NeoALTTO) study, the combination therapy of HL with chemotherapy resulted in improved pCR compared to single-agent H with chemotherapy (51.3% vs. 29.5%, $p = 0.0001$) [37]. HL combination was also evaluated in other trials including CHERLOB, NSABP B-41, and CALGB 40601, with the latter two trials not demonstrating statistically significant improvement in pCR [7, 38, 39]. The survival outcome analysis of NeoALTTO study showed no benefit in event-free survival or overall survival when L was added to H and chemotherapy [40]. This is consistent with the outcomes reported from the large adjuvant ALTTO study which demonstrated no benefit with the addition of L to H and standard chemotherapy [41]. Notably, patients who achieve pCR have longer event-free and overall survival than do patients without pCR [40].

Several clinical trials evaluated the synergy between platinum drugs and H and the taxanes in the neoadjuvant setting based on preclinical data [42, 43]. The pCR rates reported in non-randomized phase II trials was reported to be 43–76% [43, 44]. In the randomized phase II GeparSixto study, in the cohort with HER2-positive tumors treated with HL with or without carboplatin, 45 (32.8%, 25.0–40.7) of 137 patients achieved a pCR with carboplatin compared with 50 (36.8%, 28.7–44.9) of 136 without ($p = 0.581$; test for interaction $p = 0.015$), suggesting no benefit with adding carboplatin [45].

Currently, the standard of care for neoadjuvant therapy of HER2-positive breast cancer is a combination of chemotherapy and HER2-targeted therapy with trastuzumab and pertuzumab based on results of two neoadjuvant studies (NeoSphere and TRYPHAENA). Pertuzumab should also be added to trastuzumab for the following indications: tumor size >2 cm, or nodal involvement, or inflammatory or locally advanced breast cancer [46, 47].

Standard Regimens

- AC-T (or D)+H (P): AC is given for four cycles (every 2 or 3 weeks) followed by weekly paclitaxel × 12 doses or docetaxel every 3 weeks x four cycles. Trastuzumab is administered during the taxane phase and will be continued after surgery to complete a 12-month treatment. If P is given, it is administered with H concurrently during the taxane phase, approved by FDA to be given for up to a total of six doses in the neoadjuvant setting.
- DCb+H (P): Docetaxel and carboplatin with concurrent H with or without P every 3 weeks for six cycles which is a standard option.
- Other acceptable regimens include FEC → THP, FEC → DHP, THP → FEC, or DHP → FEC.

12.6 Triple-Negative Breast Cancer (TNBC)

Patients with TNBC have worse survival than patients with non-TNBC [48]. Like HER2-positive breast cancer, patients with TNBC also experience a high pCR rate in the neoadjuvant setting. However, patients with extensive residual cancer after neoadjuvant chemotherapy remain at high risk of recurrence.

The chemotherapy regimens used in HR-positive, HER2-positive breast cancer as described above are also been used in TNBC. Two recent randomized phase II studies have demonstrated higher pCR rates with the addition of carboplatin to standard anthracycline and taxane-based regimen [45, 49]. In the GeparSixto study, in the cohort of TNBC, pCR rate was significantly higher in patients with carboplatin (36.9% vs. 53.2%, $p < 0.05$), with the cost of higher rates of grade 3/4 toxicities [45]. Furthermore, as an exploratory correlative study, increased levels of stromal tumor infiltrating lymphocytes (TILs) were found to predict for pCR in multivariable analysis ($p < 0.001$) [50]. The improved pCR with carboplatin in TNBC was later confirmed by CALGB 40603, a randomized phase II study which utilized a more conventional backbone chemotherapy regimen (weekly paclitaxel followed by dose-dense AC) and randomized 443 patients with TNBC to the addition of carboplatin AUC 6 concurrently with paclitaxel [49]. Carboplatin significantly increased pCR rate in breast/axilla (54% vs. 41%, OR 1.71, $p = 0.0029$), albeit more toxicities [49]. However, whether adding carboplatin will improve relapse-free or overall survival is still unknown. Currently, carboplatin added to standard chemotherapy is not routinely recommended as neoadjuvant therapy.

The I-SPY 2 trial (Investigation of Serial Studies to Predict Your Therapeutic Response through Imaging and Molecular Analysis 2) is a randomized phase II "platform" trial [51] in which patients with early-stage breast cancer receiving standard neoadjuvant therapy can undergo adaptive randomization for assignment to an experimental group with new agents/new combination. The trial is designed to rapidly identify which disease subtypes/signatures are sufficiently responsive to a given treatment regimen so that a small, focused, and successful phase III trial can start. The combination of a poly(ADP-ribose) polymerase (PARP) inhibitor, veliparib, in combination with carboplatin was recently reported [51]. In this ongoing trial, for HER2-negative breast cancer, a total of 72 patients were randomly assigned to receive veliparib-carboplatin, and 44 were randomized to control group. Three biomarker signatures including HER2-negative, HR-positive, and triple-negative were studied. The estimated rate of pCR was 33% (95% Bayesian probability interval [PI], 23–43%)

for veliparib-carboplatin group and 22% (95% PI, 10–35%) for control group [51]. Patients with TNBC were found to benefit from veliparib-carboplatin, with the estimated rate of pCR of 51% (95% PI, 36–66%) in veliparib-carboplatin vs. 26% (95% PI, 9–43% in control).

For patients with germline BRCA-mutated breast cancer, a clinical trial is ongoing to evaluate single-agent talazoparib for six cycles in the neoadjuvant setting prior to the treatment with physician's choice standard chemotherapy (clinicalTrials.gov identifier: NCT02282345). Other ongoing trials in the neoadjuvant TNBC include TBCRC 030, a phase II trial to evaluate preoperative cisplatin vs. paclitaxel without germline BRCA mutations and to assess if use of a research test homologous recombination deficiency (HRD) assay can predict response to preoperative treatment (clinicalTrials.gov identifier: NCT01982448). Another ongoing clinical trial is evaluating the role of implantable microdevice to predict in vivo chemotherapy sensitivity in neoadjuvant early-stage TNBC (clinicalTrials.gov identifier: NCT02521363). We eagerly await the results of these trials.

In summary:

- Indications for neoadjuvant therapy are to downstage the primary tumor and axilla.
- Standard chemotherapy regimens should be used in the neoadjuvant setting (the same as adjuvant treatment). Standard anthracycline-taxane combinations are recommended.
- In patients with hormone receptor-positive, HER2-negative breast cancer, standard chemotherapy options are recommended. Neoadjuvant endocrine therapy may be considered, but there are less data available when compared with neoadjuvant chemotherapy.
- In patients with HER2-positive breast cancer, trastuzumab with or without pertuzumab added to standard anthracycline-taxane combination (i.e., AC→TH+/−P or AC→DH+/−P) or non-anthracycline (i.e., DCbH+/−P) is recommended. Pertuzumab should be considered for those with the following findings: tumor size >2 cm, or nodal involvement, or inflammatory or locally advanced breast cancer.
- In patients with TNBC, standard chemotherapy options are recommended. Carboplatin, added to standard chemotherapy, is not routinely recommended.

Conflict of Interest Rui Wang has no conflict no interest.

Chau Dang has research funding through Roche/Genentech and GlaxoSmithKline.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Adjuvant Systemic Therapy in Breast Cancer

13

Shari GoldFarb and Wanqing Iris Zhi

13.1 Introduction

Patients with early-stage breast cancer are treated with curative intent. The goal of adjuvant therapy is to improve overall survival [1, 2]. After surgery, although there is no evidence of gross remaining disease, patients still have a risk of relapse from occult micrometastatic disease. The goal of adjuvant systemic therapy is to decrease risk of recurrence while minimizing toxicities and overtreatment. Therefore, it is important to identify patient populations that will benefit most from treatment in order to avoid unnecessary toxicities [3–5]. Patients require different adjuvant therapies based on their risk of recurrence, stage of disease, and tumor biology. In this chapter, we will discuss systemic adjuvant therapy including endocrine therapy, chemotherapy, and HER2-targeted therapy [6, 7].

13.2 Endocrine Therapy

The goal of endocrine therapy is to inhibit estrogen receptor (ER) and progesterone receptor (PR) signaling in hormone receptor-positive breast cancer. Downregulation of ER signaling, blockade of estrogen receptors, and depletion of estrogen pharmacologically or surgically (oophorectomy) can be utilized to achieve this goal.

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13.2.1 Tamoxifen

Tamoxifen is a selective estrogen receptor modulator (SERM), with both partial estrogen agonist and antagonist effects that work by interrupting cell growth. Tamoxifen was approved in 1986 for treating women with early-stage breast cancer after its initial approval in advanced breast cancer in 1977 [8]. Currently, tamoxifen 20 mg daily for 10 years is the standard care for premenopausal women with early-stage hormone receptor-positive breast cancer [9, 10]. In 2000, it was also approved for breast cancer prevention based on the results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) study, which showed 5 years of tamoxifen can reduce the risk of developing both invasive and noninvasive breast cancer by 50% in high-risk women [11].

Tamoxifen was studied in multiple clinical trials to determine the optimal duration of adjuvant therapy. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that 5 years of adjuvant tamoxifen treatment is significantly more effective than 1–2 years of tamoxifen therapy following surgery [12]. Five years of therapy with tamoxifen in both pre- and postmenopausal women significantly decreased breast cancer mortality (hazard ratio (HR), 0.66) and the risk of recurrence (HR 0.59). Moreover, women continued to benefit from adjuvant tamoxifen even after it was discontinued with carry-over benefits seen up to 15 years. Fifteen-year probabilities of mortality and recurrence were shown in 10,386 women of whom 80% were estrogen receptor positive, 20% had an unknown receptor status, and 30% were lymph node positive. There were a 9.2% 15-year improvement in mortality from 5 years of tamoxifen compared to placebo (tamoxifen arm 25.6% vs. placebo arm 34.8%, $2p < 0.00001$) and an 11.8% 15-year improvement in recurrence rate (tamoxifen arm 33.2% vs. placebo arm 45%, $2p < 0.00001$).

In subsequent NSABP B-14 study, 5 years of tamoxifen was compared to extended treatment with 10 years of tamoxifen [13]. After completing 5 years of therapy with tamoxifen,

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_13

1172 women were disease-free and re-randomized to receive either prolonged therapy with tamoxifen (n = 593) for an additional 5 years or placebo (n = 579). Seven-year follow-up after re-randomization showed no benefit from prolonged therapy with tamoxifen independent of age or other characteristics. Disease-free survival (DFS) was 82% in 5 years of tamoxifen arm versus 78% in extended tamoxifen arm (p = 0.03). Overall survival (OS) was 94% in 5 years of tamoxifen arm versus 91% in extended tamoxifen arm (p = 0.07). Both the DFS and OS were significantly better in women who took tamoxifen for 5 years compared to 10 years. When tamoxifen treatment was continued beyond 5 years in the NSABP B-14 trial, a significantly higher adverse event rate such as thrombosis and death was seen in the cohort of women who took tamoxifen for 10 years. As a result, the trial was terminated early due to the increased adverse events. The results from this study are contradictory to the results of the two larger multicenter studies discussed below. This may be secondary to a smaller sample size (n = 1172), early termination of the study, shorter follow-up, and the fact that only 25% of patients were pre- or perimenopausal at the time of randomization. It is well known that older patients have a higher rate of morbidity from tamoxifen.

More recently two large multicenter studies support the use of adjuvant tamoxifen for 10 years. The ATLAS trial addressed the question of extending adjuvant tamoxifen to 10 years by comparing the use of adjuvant tamoxifen for 5 years versus 10 years [9]. Both arms demonstrated that adjuvant tamoxifen decreased breast cancer relapse rate and associated mortality. The risk of disease recurrence after 10 years of tamoxifen was 21.4% versus 25.1% for women who took tamoxifen for 5 years. The absolute breast cancer mortality improved from 15% for women who took tamoxifen for 5 years to 12.2% in women who took extended tamoxifen for 10 years. Ten years of tamoxifen also reduced overall mortality (639 deaths in tamoxifen 10-year arm vs. 722 deaths in tamoxifen 5-year arm, p = 0.002). Patients taking tamoxifen 10 years (n = 3428) showed a continuous benefit from tamoxifen with a further risk reduction (HR 0.75, 95% confidence interval (CI) 0.62–0.90) after 10 years of therapy. In the ATLAS trial, serious adverse events such as pulmonary embolism and endometrial cancer were more frequent in women treated with 10 years of tamoxifen, but it did not impact breast cancer-specific mortality. Pulmonary embolism had a risk ratio (RR) of 1.87 (95% CI 1.13–3.07, p = 0.01) in the tamoxifen 10-year arm, but there was no difference in mortality between the two arms from pulmonary emboli (ten deaths in tamoxifen 10-year arm vs. eight deaths in tamoxifen 5-year arm, p = 0.69). Endometrial cancer during years 5–14 was found to have a 3.1% cumulative incidence and 0.4% mortality rate in patients treated with tamoxifen for 10 years. Both cumulative risk and mortality were significantly less in patients treated with 5 years of tamoxifen (cumulative risk of 1.6% with 0.2% mortality rate, p = 0.0002).

Similarly, the Adjuvant Tamoxifen-To Offer More (aTTom) trial randomized 6953 women who had completed at least 4 or more years of tamoxifen treatment to discontinue tamoxifen or to continue tamoxifen for an additional 5 years [10]. This was another well-powered, large, multicenter study. This study showed that extended tamoxifen treatment for 10 years was associated with reduced breast cancer recurrence (580 in tamoxifen 10-year arm vs. 672 in tamoxifen 5-year arm, p = 0.003) with a hazard ratio in favor of the extended treatment of 0.84 (95% CI 0.73–0.95) during years 7–9 and 0.75 (95% CI 0.66–0.86) beyond year 10. Breast cancer-specific mortality was reduced in the tamoxifen 10-year arm (HR 0.77, 95% CI 0.64–0.92) compared to the tamoxifen 5-year arm. Endometrial cancers were significantly higher in the tamoxifen 10-year arm (37 cases (1.1%) vs. 20 cases (0.6%), RR 2.20, 95% CI 1.31–2.34, $p < 0.0001$). The non-breast cancer mortality was similar (457 in tamoxifen 5-year arm vs. 467 in tamoxifen 10-year arm, RR 0.94). Both ATLAS and aTTom trials showed that extended tamoxifen for 10 years improved both overall and breast cancer-specific survival compared to 5 years of tamoxifen, making this the new standard for premenopausal women.

13.2.2 Aromatase Inhibitors

Aromatase inhibitors (AIs) decrease estrogen production by inhibiting aromatase, an enzyme of the cytochrome P450 family and the product of the CYP19 gene, which converts androgens to estrogen. In postmenopausal women, aromatase is the primary source of estrogen synthesis and is present in peripheral tissues including fat, muscle, breast cancer, normal breast, liver, and brain. The third-generation AIs can decrease estrogen production by >95%, resulting in subphysiologic levels of estrogen. However, AIs are not able to overcome ovarian aromatase activity. Therefore, only postmenopausal women or women with non-functioning ovaries, who have undergone either medical or surgical ovarian suppression, benefit from AIs. The most common side effects are hot flashes, arthralgias, musculoskeletal disorders, vaginal dryness, fatigue, nausea and vomiting, hair thinning, and loss of bone density.

Aromatase inhibitors are classified into two different types (1) steroidal or (2) nonsteroidal, which differ in their mechanism of interaction with the aromatase enzyme. Both steroidal and nonsteroidal third-generation aromatase inhibitors are potent and effective. There is no clinical evidence that demonstrates one mechanism of inhibition is superior to the other [14].

Adjuvant aromatase inhibitor use is the gold standard for postmenopausal women with hormone receptor-positive

breast cancer. However, the optimal duration of therapy remains unclear at present time. AIs have been studied when given after surgery instead of tamoxifen (ATAC, BIG 1-98 trials) [15–18], after 2–3 years of tamoxifen (IES, ABCSG-8, ARNO 95, ITA, BIG 1-98 trials) [18–21] or after 5 years of tamoxifen (MA.17, MA.17R trials) [22, 23]. All studies demonstrated that AIs consistently improve disease-free survival, decrease risk of distant recurrence and development of a contralateral breast cancer when compared to tamoxifen, and have replaced tamoxifen as first-line therapy for postmenopausal women with hormone receptor-positive breast cancer.

AI treatment has different side effects than tamoxifen therapy. The use of AIs results in less vaginal discharge, less irregular bleeding, fewer endometrial polyps and endometrial cancers, and fewer thromboembolic problems than seen with tamoxifen but more musculoskeletal events, pain, bone loss increasing risk of osteoporosis, skeletal events including bone fractures, hair thinning, vaginal dryness, and sexual dysfunction [24]. It should be acknowledged that there is still a role for tamoxifen in postmenopausal women with breast cancer who are intolerant of AIs. Postmenopausal women also benefit from tamoxifen followed by AIs.

Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial was the first reported study comparing efficacy and safety of AIs to tamoxifen for adjuvant therapy of early-stage breast cancer [15, 16, 25, 26]. The ATAC trial currently has the longest median follow-up (120 months) of any adjuvant AI trial. Nine thousand three hundred sixty-six postmenopausal women with early-stage breast cancer who were candidates for hormonal therapy were randomized in a double-blind fashion to tamoxifen (n = 3116), anastrozole (n = 3125), or combination of the two (n = 3125) for 5 years. At 120-month median follow-up, a total of 5216 patients with known hormone receptor-positive breast cancer were analyzed (anastrozole group n = 2618 and tamoxifen group n = 2598). The result showed that anastrozole significantly improved DFS (HR 0.86, 95% CI 0.78–0.95, p = 0.003) compared to the tamoxifen-alone arm [25]. Anastrozole was also superior to tamoxifen in terms of distant recurrence in both the intent-to-treat (HR 0.87, 95% CI 0.77–0.99, p = 0.03) and hormone receptor-positive groups (HR 0.85, 95% CI 0.73–0.98, p = 0.02). The lower recurrence rate in the anastrozole arm was maintained after completion of therapy and especially notable in the hormone receptor-positive subgroup. Anastrozole is also superior to tamoxifen in terms of incidence of new contralateral primary breast cancers (HR 0.60, p = 0.004). However, anastrozole did not show statistically significant reduction in overall survival compared to tamoxifen (HR 0.95, 95% CI 0.84–1.06, p = 0.4), but there were fewer deaths after recurrence in the anastrozole group (HR 0.87, 95% CI 0.74–1.02, p = 0.09) compared to the tamoxifen group. These results suggest that anastrozole in postmenopausal women improves disease-free survival and chemoprevention compared to tamoxifen.

Overall, anastrozole is well tolerated with fewer withdrawals from treatment compared to tamoxifen (odds ratio (OR) 0.80, 95% CI 0.71–0.90, p = 0.0002), including fewer withdrawal related to adverse events (OR 0.68, 95% CI 0.57–0.81, $p < 0.0001$) [15, 27]. It was associated with fewer serious adverse effects including hot flashes, vaginal discharge, venous thrombosis, and endometrial cancer (223 events in anastrozole group vs. 369 events in tamoxifen group, OR 0.57, 95% CI 0.48–0.69, $p < 0.0001$). There was no statistically significant difference in ischemic cardiovascular events between the different treatment arms (2.5% on anastrozole arm and 1.9% on tamoxifen arm, p = 0.14). However, anastrozole treatment was associated with a decrease in bone density, an increased rate of skeletal events such as fractures (incidence rate ratio (IRR) 1.55, $p < 0.0001$), and arthritis. In the posttreatment follow-up period, the increased yearly fracture rate did not continue (IRR 1.03, p = 0.72). Therefore, the benefits of anastrozole were maintained posttreatment, but the risks were not.

13.3 Sequential Therapy

BIG 1-98 was a large upfront trial evaluating aromatase inhibitors in the adjuvant setting for early-stage breast cancer [17, 18]. The study randomized 8010 postmenopausal women with hormone receptor-positive, early-stage breast cancer to four arms (tamoxifen × 5 years, letrozole × 5 years, tamoxifen × 2 years → letrozole × 3 years, and letrozole × 2 years → tamoxifen × 3 years). At a median follow-up of 71 months after randomization in the BIG 1-98 study [18], the letrozole monotherapy arm was compared to the sequential therapy arms (tamoxifen × 2 years → letrozole × 3 years and letrozole × 2 years → tamoxifen × 3 years). A total of 6182 postmenopausal women were included in the evaluation. No significant improvement in disease-free survival was seen in either sequencing arms compared to the letrozole monotherapy arm (HR for tamoxifen followed by letrozole 1.05, 99% CI 0.84–1.32; HR for letrozole followed by tamoxifen 0.96, 99% CI 0.76–1.21). Women who received tamoxifen followed by letrozole had a nonsignificant increase in the rate of early relapse compared to women who received letrozole alone (HR for letrozole 0.87, 95% CI 0.75–1.02, p = 0.08). DFS at 5 years after randomization is 87.9% (99% CI 85.5–89.8) in letrozole monotherapy arm, 87.6% (99% CI 85.2–89.6) in letrozole followed by tamoxifen arm, 86.2% (99% CI 83.8–88.3) in tamoxifen followed by letrozole arm, and 84.6% (99% CI 82.1–86.8) in tamoxifen monotherapy arm. In terms of disease-free survival, there was no statistically significant difference between the letrozole monotherapy, tamoxifen sequenced to letrozole,

letrozole followed by tamoxifen arms, or tamoxifen monotherapy arms. However, 39.5% of patients crossed over to letrozole after 5 years of tamoxifen, which may explain the nonsignificant results.

A combined analysis of the Austrian Breast and Colorectal Cancer Study Group (ABCSG)-8 trial and German Adjuvant Breast Cancer Study Group (ARNO)-95 trial was performed to investigate the benefits from AIs after initial 2–3 years of tamoxifen [21]. Three thousand two hundred twenty-four postmenopausal women received tamoxifen for 2 years and then received either 3 additional years of tamoxifen or 3 years of anastrozole. In the ABCSG-8 study, patients were randomized to a treatment arm prior to the initiation of any hormonal therapy. However, in the ARNO-95 study, patients were randomized after the completion of their first 2 years of tamoxifen therapy. At a median follow-up of 28 months, there was an improved DFS in the anastrozole group (HR 0.60, 95% CI 0.44–0.81, $p = 0.0009$) compared to tamoxifen group. In the anastrozole arm, there was a 40% event risk reduction compared to the tamoxifen arm. Anastrozole-treated patients also had a lower rate of distant recurrence (HR 0.61, 95% CI 0.42–0.87, $p = 0.0067$). However, there was no difference in survival between the two groups. Both anastrozole and tamoxifen were well tolerated. In patients receiving anastrozole, there was a significantly higher rate of fractures ($p = 0.015$) and fewer thrombosis ($p = 0.034$). The results of this analysis support the benefit of switching to anastrozole after 2 years of initial treatment with tamoxifen instead of remaining on tamoxifen for 5 years.

Similarly, a meta-analysis of three clinical trials ABCSG-8, ARNO 95, and the Italian Tamoxifen Anastrozole (ITA) was performed [28]. ITA was a small open-label trial of 426 lymph node-positive patients who either received tamoxifen for 5 years or were switched to anastrozole after 2–3 years of tamoxifen [29]. The meta-analysis showed fewer disease recurrences and deaths in the anastrozole-treated patients. Switching treatment from tamoxifen to anastrozole resulted in a significant improvement in disease-free survival (HR 0.59, 95% CI 0.48–0.74, $p < 0.0001$) and OS (HR 0.71, 95% CI 0.52–0.98, $p = 0.04$). Toxicities found in these trials were similar to other adjuvant AI trials. Based on the results of this analysis, it appears treatment of early-stage breast cancer with anastrozole improves event-free survival, which translated into an overall survival benefit in this meta-analysis.

13.3.1 Optimal Duration

The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) MA.17 trial evaluated the benefit of 5 years of letrozole after the completion 5 years of adjuvant tamoxifen [22, 23]. This study randomized 5187 postmenopausal patients who completed 5 years of tamoxifen to receive either letrozole or placebo. At an interim planned analysis with a median follow-up of 2.4 years (total 207 events), the addition of letrozole showed a statistically significant improvement in 4-year disease-free survival over placebo (93% vs. 87%, respectively, $p < 0.001$). A 43% reduction in relapse was seen with extended letrozole therapy (HR 0.57, 95% CI 0.43–0.75, $p = 0.00008$).

At a median follow-up of 30 months, an updated analysis of the MA.17 was performed. It confirmed the results of the first interim analysis. There continued to be an improvement in both disease-free survival (HR 0.58, 95% CI 0.45–0.76, $2p < 0.001$) and distant disease-free survival seen with letrozole (HR 0.60, 95% CI 0.43–0.84, $p = 0.002$) compared to placebo. The improvement in recurrence rate did not translate into a statistically significant difference in overall survival. However, in a preplanned subset analysis of lymph node-positive patients, there was a statistically significant improvement in overall survival (HR 0.61, 95% CI 0.38–0.98, $p = 0.04$). This shows that higher-risk patients derive the most benefit from prolonged adjuvant therapy.

After the unblinding of the MA.17 study, patients who received placebo were offered letrozole [22]. Eight hundred nine (809) women declined letrozole, and 1579 opted to take letrozole at a median of 2.8 years after the completion of 5 years of tamoxifen. The women who elected to receive letrozole were younger, had higher-risk disease, were more likely to have received adjuvant chemotherapy, and had a better performance status. At a median follow-up of 6.3 years, there was a statistically significant improvement in both disease-free survival (HR 0.66, 95% CI 0.23–0.61, $p < 0.0001$) and distant recurrence (HR 0.39, 95% CI 0.20–0.74, $p = 0.004$) in the placebo → letrozole group compared to the placebo → placebo group. The placebo → letrozole arm had a higher rate of osteoporosis (5.3% in the placebo → letrozole arm vs. 1.6% in the placebo → placebo arm, $p < 0.0001$) and fractures (5.2% in the placebo → letrozole arm vs. 3.1% in the placebo → placebo, $p < 0.0001$). This analysis supports the importance of aromatase inhibitors in the adjuvant treatment of postmenopausal women with hormone receptor-positive breast cancer. A significant benefit was seen with letrozole after the completion of tamoxifen even after a prolonged delay since the completion of 5 years of tamoxifen. Thus, letrozole therapy should be considered for appropriate high-risk patients even if there is a delay after the completion of tamoxifen.

The MA.17R trial addressed the question of the benefit from an additional 5 years of AI after completing 5 years of adjuvant AI therapy [30]. It was a phase III, randomized, double-blinded, placebo-controlled trial. One thousand nine hundred eighteen postmenopausal women who had received 5 years of adjuvant AI were enrolled and randomized to letrozole or placebo for an additional 5 years. 68.5% of the

women had received tamoxifen prior to the 5 years of AI therapy. The primary endpoint is disease-free survival, which is defined as breast recurrence or contralateral new breast cancers. At a median of 6.3 years of follow-up, there were a total of 165 events (67 in the letrozole arm and 98 in placebo arm). The 5-year DFS was 95% (95% CI 93–96%) in the letrozole arm and 91% (95% CI 89–93%) in the placebo arm. The hazard ratio was 0.66 (95% CI 0.48–0.91, $p = 0.01$), indicating significant lower risk (by 34%) of recurrence and contralateral breast cancer in extended letrozole arm. There was no difference in the 5-year OS between the extended letrozole and placebo arm (93% in letrozole arm vs. 94% in control arm, HR 0.97, $p = 0.83$). The study showed that extended letrozole lowers contralateral breast cancer rate compared with the placebo group (0.21% vs. 0.49%, respectively, HR 0.42, $p = 0.007$). AI-associated bone-related toxicities such as bone fractures and new-onset osteoporosis were more frequently seen in the extended letrozole group. No difference in quality of life was seen between the two arms.

Recently, three studies with conflicting results were presented at the 2016 San Antonio Breast Cancer Symposium [31–33]. NSABP B42 trial studied the benefit of extended 5-year letrozole therapy in 3966 women after an initial 5 years of endocrine therapy (either tamoxifen followed by AI or AI) [31]. At a median of 6.9 years follow-up, disease-free survival with extended letrozole arm was 84.7% compared with 81.3% in placebo arm (HR 0.85, $p = 0.048$). The overall survival was 91.8% with extended letrozole arm and 92.3% in placebo arm (HR = 1.15, $p = 0.22$). B42 trial showed breast cancer-free interval events, which include breast cancer recurrence and contralateral breast cancer incidence which were significantly less in women treated with extended 5 years of letrozole arm (6.7% in extended letrozole arm vs. 10.0% in placebo arm, $p = 0.003$) and similarly less distant recurrence in women treated with extended 5 years of letrozole arm (3.9% in extended letrozole arm vs. 5.8% in placebo arm, $p = 0.03$). There was no significant difference in fractures from osteoporosis and thrombotic events in extended letrozole arm. Of note, the definition of primary endpoint in B42 trial is different from MA.17R trial. In B42 trial, disease-free survival included breast or non-breast cancers and deaths as first events, while in MA.17R, disease-free survival only included breast cancer recurrence and contralateral breast cancers. When adding non-breast cancers and deaths as first events in MA.17R trial, the hazard ratio becomes similar to B42 trial (MA.17R, HR 0.80, $p = 0.06$; B42, HR 0.85, $p = 0.048$). It reflected the importance of using standard outcome definitions to compare clinical trials and facilitate data interpretation [34].

The phase III DATA study compared 1912 women after initial 2–3 years of tamoxifen to either 3 or 6 years of anastrozole [32]. The study was designed to detect an increase in the adapted disease-free survival, which is disease-free survival after 3 years of anastrozole and includes recurrence and contralateral breast cancers and deaths. Five-year adapted disease-free survival was 83.1% for women who received 6 years of anastrozole and 79.4% for women who received 3 years of anastrozole (HR 0.79, $p = 0.07$).

Similarly, IDEAL trial compared a total of 7.5 years versus 10 years of endocrine therapy [33]. One thousand eight hundred twenty-four women who completed an initial 5 years of adjuvant endocrine therapy (10% tamoxifen alone, 30% AIs, 60% tamoxifen followed by AI) were randomized to receive either 2.5 years or 5 years of AIs. The primary endpoint of this study is disease-free survival. The 5-year disease-free survival was 88.4% in women with extended 2.5 years of AI and 87.9% in women with extended 5 years of AI (HR =0.95, $p = 0.70$). The overall survival was 93.5% in women with extended 2.5 years of AI and 92.6% in women with extended 5 years of AI (HR =1.08, $p = 0.59$). Even though both DATA and IDEAL trials were not able to demonstrate survival benefits in extended endocrine therapy, the data was based on a short follow-up at this time, and longer follow-up is warranted. Extended AI therapy in postmenopausal women should be considered for patients with younger age, high risk, and node involvement, but it is unknown what the best duration is. Patient's tolerability and comorbidities particularly underlying bone disease should also be considered.

13.3.2 Ovarian Suppression

Ovarian ablation was one of the first systemic treatments for breast cancer and can be performed via oophorectomy or medical suppression. Surgical castration via bilateral oophorectomy immediately reduces estrogen levels to the postmenopausal range in all women, while medical suppression may take several weeks to take full effect. Medical suppression can be performed using luteinizing hormone-releasing hormone (LHRH) analogues, which are administered as either monthly or every 3 months intramuscular injections. LHRH analogues include goserelin, buserelin, triptorelin, and leuprolide. LHRH analogues act on the hypothalamic-pituitary-ovarian axis and suppress circulating estrogen levels. Approximately 2–3 weeks after the administration of LHRH analogues, estrogen levels decline, creating a postmenopausal state. However, the postmenopausal state is reversible after therapy is discontinued.

Ovarian suppression in the adjuvant setting has been studied for decades with conflicting results. Fifteen-year follow-up of the Early Breast Cancer Trialists' Collaborative Group study demonstrated that in the adjuvant setting, ovarian suppression in combination with tamoxifen was found to be at least as effective as adjuvant chemotherapy with CMF not

followed by tamoxifen [12, 35]. Recently, three large phase III randomized clinical trials addressed the question of ovarian suppression in addition to tamoxifen or AI in adjuvant therapy.

Eastern Cooperative Oncology Group trial E3193 compared adjuvant tamoxifen versus tamoxifen in combination with ovarian suppression, which could be achieved with surgical oophorectomy, radio-frequency ablation, or LHRH analogues [36]. The trial enrolled premenopausal women who either had a menstrual cycle within 6 months or serum estradiol level in the premenopausal range. All women had node-negative disease with tumors <3 cm in size and hormone receptor-positive breast cancer. Women enrolled on the study were not allowed to receive chemotherapy. In women treated with tamoxifen plus ovarian suppression, the DFS at 5 years was 90% compared to 88% in women treated with tamoxifen alone (HR 0.85, 95% CI 0.47–1.56). The OS at 5 years was 98% in the tamoxifen plus ovarian suppression arm versus 95% in tamoxifen-alone arm (HR 0.84, 95% CI 0.38–1.89). After a median follow-up of 9.9 years, there was no difference in DFS or OS between the two arms.

The Suppression of Ovarian Function Trial (SOFT) randomizes premenopausal women with hormone receptor-positive breast cancer to receive either 5 years of tamoxifen, ovarian suppression with tamoxifen (Tam/OS), or ovarian suppression with exemestane (AI/OS) [37]. Women receiving chemotherapy were eligible if they remained premenopausal 8 months after completion of adjuvant chemotherapy as determined by either serum estradiol range or resumption of menses. Fifty-three percent of women enrolled in the SOFT trial received chemotherapy.

The Tamoxifen and Exemestane Trial (TEXT) randomized premenopausal women with hormone receptor-positive breast cancer to receive either 5 years of triptorelin with tamoxifen or 5 years of triptorelin with exemestane. Adjuvant chemotherapy was allowed. The SOFT Tam/OS and AI/OS arms were added to the TEXT for a combined primary analysis. In addition, the SOFT study results were reported separately.

The combined TEXT and SOFT analysis showed that AI/OS is superior to Tam/OS in terms of the 5-year DFS (91% in AI/OS arm vs. 87% in Tam/OS arm, HR 0.72, 95% CI 0.60–0.85, $p < 0.001$). However, the overall survival was the same in both groups (96% in AI/OS arm vs. 97% in Tam/OS arm, HR 1.14, 95% CI 0.86–1.51) [38].

The SOFT primary analysis showed that DFS at 5 years is 86.6% in the Tam/OS arm versus 84.7% in the Tam-alone arm (HR 0.83, 95% CI 0.66–1.04, $p = 0.1$). In women who received adjuvant chemotherapy, the 5-year DFS is 84% in the AI/OS arm (HR 0.70, 95% CI 0.53–0.92) and 81% in the Tam/OS arm (HR 0.82, 95% CI 0.64–1.07) compared with 77% in the Tam-alone arm. In women who did not receive chemotherapy, the Tam/OS and Tam-alone arms have the same 5-year DFS of 93%. In summary, for premenopausal women with hormonal-positive breast cancer, ovarian suppression in combination with aromatase inhibitor for 5 years should be considered for patients at high risk of relapse such as women who are young in age, have lymph node involvement, have high-grade tumors, and received chemotherapy.

13.3.3 New Agents Under Investigation

Novel agents such as everolimus and palbociclib have specific targets in breast cancer cells and demonstrate survival benefit in the metastatic setting. These agents are actively being studied in early breast cancer.

Palbociclib is a CDK 4/6 inhibitor and approved by the FDA for treatment of metastatic hormone receptor-positive breast cancer. In PALOMA-2 study, palbociclib in combination with letrozole demonstrated superior PFS and OS than letrozole alone in treatment-naïve patients with HR-positive breast cancer (PFS 24.8 months in palbociclib plus letrozole arm vs. 14.5 months in letrozole-alone arm, HR 0.58, 95% CI 0.319–0.748, $p < 0.01$) [39]. The main toxicities were neutropenia, anemia, and leukopenia. Currently, palbociclib is being evaluated in the adjuvant setting. The PALLAS trial (NCT02513394) is a randomized phase III trial of palbociclib for 2 years in combination with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for hormone receptor-positive, HER2-negative breast cancers. The primary endpoint is 5-year DFS.

13.4 Bone-Modifying Agents

Women with early-stage breast cancer have higher risk of osteoporosis and fractures secondary to adjuvant therapy. Bisphosphonates and denosumab have shown improvement of bone density, reduction of skeletal events, and possible survival benefit in women receiving adjuvant therapy for breast cancer.

Bisphosphonates inhibit osteoclast reabsorption of the bone and promote osteoclast apoptosis. Adjuvant bisphosphonates such as zoledronic acid and clodronate have been studied in multiple clinical trials showing consistent benefit in reducing skeletal-related adverse events and improving bone density but have conflicting results in terms of breast cancer outcome. The AZURE trial included 3360 women with early-stage breast cancer receiving standard adjuvant endocrine therapy [40]. The results from the entire study showed that the addition of zoledronic acid did not improve DFS, OS, invasive disease-free survival (IDFS), or distant recurrence. However, zoledronic acid delayed the time until development of bone metastases. In postmenopausal women,

zoledronic acid improved IDFS (n = 1041, HR 0.77, 95% CI 0.63–0.96), but this was not seen in premenopausal women. The side effects of bisphosphonates include renal insufficiency, osteonecrosis of the jaw (ONJ), and uveitis. Dental surveillance is recommended before and during bisphosphonate therapy. Serum creatinine and calcium levels should be routinely monitored. Optimal vitamin D and calcium intake, exercise, and lifestyle modification are recommended during bisphosphonate therapy.

The ABCSG-12 trial investigated the benefit of adding zoledronic acid in 1803 women receiving endocrine therapy with ovarian suppression [41]. At a median follow-up of 47.8 months, there was no difference in DFS between anastrozole and tamoxifen. Addition of zoledronic acid resulted in 3.2% absolute reduction and 36% relative reduction in risk of disease progression (HR 0.64, 95% CI 0.46–0.91, p = 0.01), but no reduction of risk of death was observed (HR 0.60, 95% CI 0.32–1.11, p = 0.11). A recent meta-analysis suggested that bisphosphonates in postmenopausal women may reduce the rate of disease recurrence in the bone and improve breast cancer survival [42].

Denosumab is a novel anti-RANK ligand monoclonal antibody. RANK ligand plays an important role in regulating osteoclast activity and bone reabsorption. ABCSG-18 is a large randomized phase III trial to investigate the effects of denosumab in postmenopausal women with early-stage breast cancer receiving AIs [43]. Three thousand four hundred twenty-five women were enrolled and randomized 1:1 to receive denosumab 60 mg every 6 months or placebo. Denosumab significantly delayed time to first clinical fracture (HR 0.50, 95% CI 0.39–0.65, $p < 0.0001$) and fewer incidents of fractures (92 vs. 176 in control groups). At median 4-year follow-up, denosumab arm had an 18% reduced risk of disease recurrence compared with those assigned to placebo (HR 0.816, p = 0.051). The long-term survival data of this trial is pending. The main toxicities were arthralgia and other AI-related symptoms. ONJ was not seen in this study with vigorous dental surveillance during the study.

13.4.1 Biomarkers

The decision of adjuvant chemotherapy is based on patient comorbidities, risk of disease recurrence, magnitude of benefits of adjuvant chemotherapy, and toxicity [4]. Both prognostic and predictive information are helpful for decision-making. Adjuvant! Online is one of the earliest tools that was used to help determine risk. It has algorithms estimating 5- and 10-year risk of death based on patient age, tumor size, tumor grade, number of involved lymph nodes, receptor status, and type of chemotherapy [44]. This computer-based validated algorithm may be useful for clinician and patients when estimating risk of disease relapse, overall survival, and benefit from different chemotherapy regimens. However, early websites like Adjuvant! Online that help to predict risk of recurrence have largely been replaced by more individualized tumor-based genomic risk prediction.

Onco*type* Dx® is a 21-gene recurrence score (RS), using reverse transcription polymerase chain reaction (RT-PCR) on primary breast tumor to determine risk of recurrence and benefit from chemotherapy. It guides adjuvant chemotherapy decision-making in patients with ER-/PR-positive, HER2-negative, node-negative breast cancer [45]. Onco*type* Dx® was developed based on the NSABP B-20 trial, which compared tamoxifen versus chemotherapy with tamoxifen alone in a node-negative patient population [46]. The RS provides both prognostic and predictive information. A high RS indicates benefit from adjuvant chemotherapy. Patients with low RS do not benefit from chemotherapy compared to endocrine therapy.

Trial Assigning Individualized Options for Treatment (TAILORx, NCT00310180) is a prospective randomized study to determine the benefits of chemotherapy in patients with intermediate RS [47]. TAILORx defined a low risk score as 0–10, an intermediate risk score as 11–25, and a high risk score as ≥26. This is different from the original study, which considered a low risk score as 0 to <18, an intermediate risk score as 18–30, and a high risk score as ≥31 [45]. The study enrolled 10,253 women with breast cancers ranging in size from 1.1 to 5.0 cm that were ER and/or PR positive, HER2 negative, and without lymph node involvement. Onco*type* Dx® was used to determine the recurrence score. Patients were assigned to receive endocrine therapy alone if they had low recurrence scores, and a total of 1626 women (15.9%) received endocrine therapy alone. At 5 years, DFS was 93.8% (95% CI 92.4–94.9) with OS 98% (95% CI 97.1–98.6) in the low-risk cohort. Approximately 67% of patients had an intermediate risk score of 11–25 and were randomly assigned chemotherapy followed by endocrine therapy or endocrine therapy alone. We are still awaiting the results from this randomization. Currently, adjuvant chemotherapy in patients with intermediate RS requires a team-based decision-making process. However, it is important to remember that the standard-of-care arm in this study for women with intermediate RS is chemotherapy followed by endocrine therapy and the experimental arm withholds chemotherapy to see if patients do as well without the chemotherapy.

In patients with early-stage breast cancer who had one to three positive lymph nodes from two randomized trials, the Southwest Oncology Group (SWOG) S8814 and ATAC [48, 49], the Onco*type* Dx® recurrence scores were retrospectively determined. In patients with low RS, there was no benefit from chemotherapy (HR 1.02, 95% CI 0.54–1.93). However, patients who have positive lymph nodes

and low RS carry worse prognosis (HR 2.64, 95% CI 1.33–5.27, $p = 0.006$) compared with those patients who have low RS and negative lymph nodes. There is lack of consensus regarding whether Onco*type* Dx RS predicts chemotherapy benefit in patients with node-positive disease since it has not been validated for this purpose yet. We know that a patient's prognosis is worse with increasing number of lymph nodes, but we do not know if chemotherapy benefits patients with lymph node-positive disease and low recurrence scores. The Rx for Positive Node, Endocrine-Responsive Breast Cancer (RxPONDER) NCT01272037 is a prospective clinical trial in patients with one to three involved axillary lymph nodes that will answer this question. This study is completely accrued with 4000 patients, and at this time, we are awaiting results. The result of this trial will help determine if there is a subset of patients with lymph node-positive disease that can avoid chemotherapy based on their recurrence score [50].

MammaPrint is a 70-gene assay to analyze gene expression profile from breast tumor tissue and identify patients with high-risk disease in early-stage breast cancer [51, 52]. This is a FDA-approved assay to determine recurrence for both ER-positive and ER-negative early-stage breast cancers. Microarray in Node-Negative and 1–3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT, NCT000433589) study is a large, phase III, prospective, randomized clinical trial to determine whether the MammaPrint assay can predict benefit from chemotherapy in certain subset patient populations [52]. In this phase III trial, 6693 women with early-stage breast cancer were enrolled, and their breast cancers were stratified based on genomic risk using the MammaPrint assay and clinical risk based on biologic criteria. Women with both low genomic and clinical risk did not receive adjuvant chemotherapy, and those with both high genomic and clinical risk received chemotherapy. Women with discordant genomic and clinical risk were randomized to either receive chemotherapy or no chemotherapy. The hypothesis was that distant metastasis-free survival at 5 years in the low genomic risk/high clinical risk group was not inferior in patients who did not receive chemotherapy compared to patients who received chemotherapy. The results of this study showed at the 5-year intent-to-treat analysis, the distant metastasis-free survival in the groups that did not receive chemotherapy was 94.7% (95% CI 92.5–96.2). The distant metastasis-free survival was 95.9% with chemotherapy and 94.4% without chemotherapy (HR 0.78, $p = 0.267$) in the subgroup of women with low genomic risk and high clinical risk. In women with high genomic risk and low clinical risk, the distant metastasis-free survival was 95.8% with chemotherapy and 95.0% without chemotherapy (HR 1.17, $p = 0.657$). The study was not powered to detect the significance of benefit from chemotherapy in the discordant groups.

13.4.2 Chemotherapy

Adjuvant chemotherapy improves overall survival in breast cancer patients with early-stage disease. The absolute benefit derived from each therapy is dependent of the individual patient's risk of recurrence. The Early Breast Cancer Trialists' Collaborative Group provided data that supports the use of adjuvant polychemotherapy. It shows an overall survival advantage to polychemotherapy compared to no chemotherapy [2]. In women younger than 50 years old, there were a 12.3% 15-year gain in disease-free survival and a 10% 15-year gain in breast cancer-specific mortality. In women between the age of 50 and 69, there were a 4.1% 15-year gain in disease-free survival and a 3.0% 15-year gain in breast cancer-specific mortality. The consideration of regimen efficacy, toxicity, and comorbidities is all taken into account when making treatment decisions.

13.4.3 Anthracycline- and Taxane-Based Regimens

Anthracyclines (doxorubicin, epirubicin) inhibit topoisomerase II, which is an essential enzyme for DNA replication. Anthracycline-containing regimens are dose-dense doxorubicin with cyclophosphamide (ddAC); epirubicin and cyclophosphamide (EC); AC with sequential weekly or every 2 weeks of paclitaxel (AC-T); AC with sequential docetaxel every 3 weeks; fluorouracil, epirubicin, and cyclophosphamide (FEC/CEF) followed by docetaxel; fluorouracil, doxorubicin, and cyclophosphamide (FAC); and docetaxel, doxorubicin, and cyclophosphamide (TAC).

Taxanes (paclitaxel, docetaxel, and nanoparticle albumin-bound (nab)-paclitaxel) are a type of chemotherapy that acts as microtubule stabilizers, which promote formation and inhibit disassembly of stable microtubules, inhibiting mitosis. Dose-dense doxorubicin and cyclophosphamide with sequential paclitaxel chemotherapy were studied in two randomized trials, and both trials showed addition of paclitaxel improved PFS and OS in women with node-positive breast cancer compared to AC alone. The Cancer and Leukemia Group B (CALGB) trial 9741 explored the concepts of sequential chemotherapy and dose density of adjuvant chemotherapy based on the Norton modeling in an attempt to improve effectiveness and overall survival [53]. Two thousand five (2005) women were randomized to four arms: (1) sequential doxorubicin (A), paclitaxel (T), and cyclophosphamide (C) every 3 weeks; (2) sequential A and T, followed by C every 2 weeks with granulocyte colony-stimulating factor (GCSF) support; (3) concurrent AC and then T every 3 weeks; and (4) concurrent AC and then T every 2 weeks with GCSF support. At a median follow-up of 36 months, the concurrent and sequential treatment schedules were

equivalent in terms of disease-free and overall survival. However, dose-dense treatment significantly improved both overall survival (risk ratio (RR) = 0.69, $p = 0.013$) and disease-free survival (RR = 0.74, $p = 0.010$). The disease-free survival at 4 years for the dose-dense regimens was 82% and 75% for other every-3-week regimens. With granulocyte colony-stimulating factor (GCSF) support, severe neutropenia was less frequent in patients who received the dose-dense treatments. Therefore, the trial demonstrated that administering chemotherapy sequentially is as effective as concurrent administration but dose-dense treatment significantly improves OS compared with every-3-week regimens.

A study was performed evaluating four versus eight cycles of taxanes and anthracyclines as adjuvant therapy for lymph node-positive primary breast cancer [54]. There was no benefit from extended taxane therapy. However, there was an improvement in both disease-free and overall survival when four cycles of paclitaxel were administered after four cycles of doxorubicin and cyclophosphamide. The paclitaxel arms had a decrease in the hazard of recurrence by 17% (HR 0.83, adjusted Wald $\chi^2 P = 0.002$) and the hazard of death by 18% (HR 0.82, adjusted $p = 0.006$) when compared to the non-paclitaxel arms.

ECOG E1199 trial evaluated the efficacy of weekly versus every-3-week paclitaxel and docetaxel as adjuvant treatment for early-stage breast cancer [55, 56]. Four thousand nine hundred fifty (4950) women with either high-risk or lymph node-positive disease were enrolled after surgery. Patients all received four cycles of doxorubicin and cyclophosphamide every 3 weeks and then were randomized to receive either (1) four cycles of docetaxel or paclitaxel administered every 3 weeks or (2) weekly docetaxel or paclitaxel for 12 weeks. The standard arm for comparison is paclitaxel administered every 3 weeks. The odds ratio (OR) for disease-free survival with every-3-week docetaxel is 1.23 ($p = 0.02$) and 1.09 ($p = 0.29$) for weekly docetaxel group. Weekly paclitaxel significantly improves both overall survival (OR 1.32, $P = 0.01$) and disease-free survival (OR1.27, $P = 0.006$). Women with triple-negative breast cancer particularly benefit from weekly paclitaxel with 10-year DFS of 59% ($p = 0.032$) and OS of 66% ($p = 0.094$). However, weekly paclitaxel was associated with increased grade 2, 3, and 4 neuropathy compared to every-3-week paclitaxel (27% in weekly paclitaxel arm vs. 20% in every-3-week paclitaxel arm). Every-3-week docetaxel was associated with a higher rate of myelosuppression (incidence rate of 46%, all other groups' incidence rate $\leq 4\%$).

Docetaxel and cyclophosphamide (TC) was compared with dose-dense AC × 4 in 1016 women with stage I–III breast cancer (US Oncology 7535 trial) [57]. TC showed a significant improvement in disease-free survival (DFS) and overall survival when compared to AC (DFS 81% in TC arm vs. 75% in AC arm, HR 0.74, $p = 0.33$; OS 87% vs. 82%, respectively, HR 0.69, $p = 0.032$). Based on this result, both NCCN and ASCO guidelines recommend TC × 4 as an alternative to AC × 4. However, TC has not been formally compared with dose-dense AC-T either in combination or sequential. Three ongoing clinical trials are addressing this question: Phase III Trial of TC Versus Anthracycline and Taxane-Containing Regimen (TAC) in HER2-Negative Early-Stage Breast Cancer Patients (US Oncology USOR 06/090, NCT00493870); NSABP49 TC Compared with Anthracycline-Based Chemotherapy in Treating Women with HER2-Negative Breast Cancer (NCT01547741); and NASBP46 TC Plus Bevacizumab Versus TC Alone Versus TAC (NCT00887536).

Recently, a preplanned joint efficacy analysis of these three trials was performed [58]. Patients who received bevacizumab were excluded from this analysis. The primary aim of this preplanned analysis is non-inferiority of TC × 6 compared to TAC × 6 with the primary endpoint as invasive disease-free survival (IDFS). At a median follow-up of 3.3 years, a total of 2125 patients received TC × 6, and 2117 patients received TAC × 6, and there were a total of 338 events. The HR for TC versus TAC was 1.202 (95% CI 0.97–1.49), and in the intent-to-treat (ITT) group, the HR was 1.23 (95% CI 1.01–1.50, $p = 0.04$). Neither HR met the primary endpoint, which was a non-inferiority HR ≤ 1.18 based on modified Cox model. The exploratory, unplanned analysis suggests that anthracycline-containing regimens are more effective in women with hormone receptor-negative breast cancer or hormone receptor-positive breast cancer with axillary lymph node involvement. Long-term follow-up is underway to determine the impact on overall survival.

The 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) × 6 cycles were compared with AC × 4 in women with node-negative breast cancer [59]. The NSABP B-36 trial showed non-superior survival benefits at 8-year follow-up between FEC and AC. However, more significant side effects were experienced in women treated with FEC than AC. In the FEC cohort, there were more grade 3 and 4 toxicities including fatigue, febrile neutropenia, thrombocytopenia, and death.

The FEC regimen was studied in women with high-risk, node-positive breast cancer in two prospective randomized clinical trials [60, 61]. The MA.5 trial studied classic CMF versus high-dose epirubicin-containing FEC in premenopausal women with node-positive breast cancer. Both 10-year relapse-free survival (RFS) and overall survival favored FEC (RFS 52%, $p = 0.007$; OS 62%, $p = 0.085$). FEC with epirubicin at two dose levels (50 mg/m^2 vs. 100 mg/m^2) was studied in women with node-positive breast cancer, and results showed improved 5-year DFS and OS in the high-dose epirubicin arm (100 mg/m^2).

The addition of a taxane to FEC was studied in three clinical trials [62–64]. One study showed in women with

node-positive breast cancer, FEC × 3 followed by docetaxel ×3 was superior to FEC × 6 in terms of both 5-year DFS (78.4% vs. 73.2%, respectively, $p = 0.12$) and OS (90.7% vs. 86.7%, respectively, $p = 0.017$). Another large randomized trial showed FEC × 4 followed by docetaxel × 4 every 3 weeks had no difference in 5-year DFS when compared with other anthracycline-containing regimens (FEC or epirubicin followed by CMF) in women with early-stage breast cancer including node-negative, node-positive, and high-risk status. FEC followed by weekly paclitaxel showed 23% risk reduction in relapse when compared with FEC alone (HR 0.77, 95% CI 0.62–0.95, $p = 0.022$), but there was no significant difference in OS between the two regimens after 66 months of follow-up.

Fluorouracil, doxorubicin, and cyclophosphamide (FAC) and docetaxel, doxorubicin, and cyclophosphamide (TAC) were studied in women with node-positive breast cancer [65, 66]. TAC showed superiority to FAC in both 5-year DFS (75% in TAC arm vs. 68% in FAC arm, HR 0.72, 95% CI 0.59–0.88, $p = 0.001$) and OS (87% in TAC arm vs. 81% in FAC arm, HR 0.70, 95% CI 0.53–0.91, $p = 0.008$). In NSABP B-30 trial, TAC was compared with AC followed by T (docetaxel) and AT (doxorubicin and docetaxel). The result demonstrated that TAC had similar OS but inferior DFS when compared with AC followed by T; AT was non-inferior with TAC in terms of DFS and OS.

13.4.4 CMF Regimen

Cyclophosphamide-methotrexate-fluorouracil (CMF) is a first generation adjuvant chemotherapy regimen that was developed in the 1970s for patients with node-positive breast cancer. NASBP B-20 and other studies showed that CMF significantly improved DFS and OS compared with no chemotherapy in women with early-stage breast cancer in both ER-positive and ER-negative subtypes [1, 67]. CMF regimens with different schedules, dosages, and administration routes have been used in clinic based on the presumption of similar efficacy and better compliance; however, there is lacking of direct comparison between these classic and modified CMF regimens. Anthracycline and cyclophosphamide (AC) were compared with CMF in eight clinical trials with mixed results. Three of them showed anthracycline-based regimens have better OS and DFS, while others showed no difference [68]. In NSABP B-28 and CALGB 9344 trials [69, 70], taxane in addition to anthracycline was compared with AC regimen, thus indirectly compared with CMF. The results showed that anthracycline-taxane regimens were superior to CMF in PFS but not OS. CMF can also be considered in adjuvant setting for both hormonal-positive breast cancer and TNBC with small tumor size.

13.4.5 Capecitabine

Capecitabine has been studied in adjuvant setting with conflicting results. One randomized clinical study showed that in elderly women, AC and CMF are superior to capecitabine and the decision needs to individualize with consideration of comorbidities [71]. ICE trial studied capecitabine as adjuvant monotherapy in women greater than 65 years of age [72]. There was no difference in 3-year and 5-year invasive disease-free survival (IDFS) between capecitabine and control arm (85.4% vs. 84.3% at 3 years, 78.8% vs. 75% at 5 years, respectively). Recently CREATE-X trial by Japan and Korean oncology group addressed the role of capecitabine in adjuvant setting in patients who received chemotherapy before surgery and did not achieve completely pathological response (pCR) in surgical specimen [73]. The study enrolled 910 women with HER2-negative breast cancer and residue disease after neoadjuvant anthracycline- or taxane-based regimen. About 60% patients received 5-FU during preoperative systemic therapy. At 2-year follow-up, capecitabine group improved DFS to 74.1% versus 67.7% in control group (HR 0.70, $p = 0.0524$). The OS was 89.2% in capecitabine arm and 83.9% in control group, respectively (HR 0.60, $p < 0.01$). The benefit in triple-negative breast cancer (TNBC) subgroup showed a 42% reduction in risk of recurrence with capecitabine. The above result was presented in abstract and not yet published in peer-reviewed journal. Further study is needed to clarify the benefit of capecitabine as adjuvant therapy in patients did not achieve pCR.

13.4.6 Carboplatin

In tumor cells with DNA repair defects, carboplatin can induce DNA damage and lead to apoptosis. TNBC has similar DNA repair defect feature as in germ line BRCA1 (BReast CAncer gene 1) mutation-associated cancers. In neoadjuvant setting, carboplatin has been studied in women with TNBC when using alone or in combination. The GEICAM 2006–2003 showed the same pathological complete response (pCR) rate when adding carboplatin to epirubicin and cyclophosphamide × 4 [74]. However, CALGB 40603 trial showed that carboplatin improved pCR significantly (54% in carboplatin arm vs. 41% in control arm, $p = 0.0029$) when combined with weekly paclitaxel × 12 followed by AC × 4 [75]. A median 3-year follow-up demonstrated that addition of carboplatin to AC-T regimen improved OS (85.5% vs. 76.1%; HR = 0.56; 95% CI, 0.33–0.96) in TNBC population but not in other breast cancer subtypes. The GeparSixto study explored the role of carboplatin when added to weekly paclitaxel, weekly liposomal doxorubicin, and bevacizumab every 3 weeks [76]. The pCR rate was significantly higher in the arm with addition of carboplatin (53% in carboplatin arm

vs. 37% in control arm, $p = 0.005$) and improved DFS at 3-year follow-up. None of the above studies was powered to evaluate survival; however, there was a trend of association among platinum, higher pCR rates, and improved survival in TNBC patients [77]. Currently, carboplatin is being investigated in adjuvant setting: NRG-BR003 (NCT02488967) is evaluating the benefit of addition of carboplatin to anthracycline- or taxane-containing regimen. Another study is evaluating carboplatin versus observation in women with TNBC residue disease after preoperative chemotherapy: the Eastern Cooperative Oncology Group—American College of Radiology Imaging Network trial EA1131 (NCT02445391). Before these studies result, carboplatin should not be used in adjuvant therapy outside clinical study setting.

13.5 Anti-HER2 Therapy

In postoperative setting, HER2-specific target therapy has improved survival and prognosis in patients with HER2-overexpressed breast cancer. The definition of HER2 amplification is based on ASCO HER2 immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) testing guideline [78]. IHC copy number ≥ 6 and/or FISH HER2/CEP17 ratio ≥ 2.0 is considered as HER2-positive tumor.

13.5.1 Trastuzumab

Trastuzumab is a humanized monoclonal antibody that selectively binds to the extracellular domain of HER2 receptor. Several randomized clinical trials demonstrated that trastuzumab combined with chemotherapy improves DFS and OS in women with surgically resected breast cancers that overexpress HER2.

NSABP B-31 studied AC × 4 followed by paclitaxel weekly with and without trastuzumab every 3 weeks for a total of 52 weeks [79]. NCCTG N9831 has similar design except trastuzumab was delayed after completion of paclitaxel. Combined analysis of NSABP B-31 and NCCTG N9831 showed that after median 3.9-year follow-up, addition of trastuzumab provided a 48% reduction of recurrence (HR 0.52 95% CI 0.45–0.60, $p < 0.001$) and 39% reduction risk of death (HR 0.61 95% CI 0.50–0.75, log-rank $p = 0.001$). Cardiac toxicity is a potential side effect of trastuzumab therapy and is more prevalent in patients who were previously treated with doxorubicin. Trastuzumab should not be administered concurrently with doxorubicin because of an increased risk of cardiac toxicity. There are 4.1% of patients treated with doxorubicin and trastuzumab in B-31 trial and 2.9% of patients in the N9831 trial who developed New York Heart Association Class III or IV congestive heart failure or death from cardiac causes at 3-year follow-up [80].

The Herceptin Adjuvant (HERA) trial enrolled 5081 women with early-stage HER2-positive breast cancer and tested the efficacy of 1 or 2 years of trastuzumab in addition to standard adjuvant chemotherapy [81]. After 1-year follow-up, there was a 46% reduction of recurrence with addition of trastuzumab (HR 0.54, 95% CI 0.43–0.67, $p < 0.0001$). There was no difference in OS between two arms, but initial analysis suggested 34% reduction of risk of death (HR 0.66, 95% CI 0.47–0.91, $p = 0.115$) in trastuzumab arm. After this analysis, patients in control arm were allowed to cross over to trastuzumab arm. After 4-year follow-up, the intent-to-treat (ITT) group showed PFS was significantly higher than the control arm (78.6% in trastuzumab arm vs. 72.2% in control arm, HR 0.76, 95% CI 0.66–0.87, $p < 0.0001$). At median 8-year follow-up, there was no survival benefit seen between 1 and 2 years of trastuzumab. Based on this result, 1-year trastuzumab becomes the standard treatment in adjuvant setting.

BCIRG 006 randomized women with high-risk node-negative or node-positive HER2-positive breast cancer into (1) AC followed by docetaxel (AC-T); (2) AC followed by docetaxel plus trastuzumab for 1 year (AC-TH); or (3) carboplatin, docetaxel, and trastuzumab for 1 year (TCH) [82]. The result of this trial showed superior DFS in trastuzumab arms compared with standard chemotherapy arm (HR 0.64, $p < 0.0001$). Two trastuzumab-containing regimens had no DFS difference between them. There was a significant improvement of OS in both trastuzumab-containing arms compared with the control arm (HR for AC-TH 0.63, $p = 0.001$; HR for TCH 0.77, $p = 0.04$). TCH regimen had significantly lower incidents of cardiac toxicity compared with AC-TH (9.4% in TCH arm vs. 18.6% in AC-TH arm, $p < 0.0001$).

The Finland Herceptin (FinHer) trial studied the addition of trastuzumab to adjuvant chemotherapies: (1) vinorelbine followed by FEC × 3 and (2) docetaxel followed by FEC × 3 [83]. Among 1010 women, 232 women with HER2-positive cancer were randomized to 9 weeks of trastuzumab or none with vinorelbine or docetaxel during the treatment. At median 3-year follow-up, trastuzumab decreased risk of recurrence (HR 0.42, 95% CI 0.21–0.83, $p = 0.01$). No differences in OS or cardiac toxicity were seen with the addition of trastuzumab. At 5-year follow-up, addition of trastuzumab to both adjuvant chemotherapy regimens showed significant improvement in both distant DFS (HR 0.65, 95% CI 0.38–1.12, $p = 0.12$) and OS (HR 0.55, 95% CI 0.27–1.11, $p = 0.094$).

Based on the above clinical trial findings, ASCO and NCCN guidelines recommend 12 months of trastuzumab with standard chemotherapy as postoperative therapy in HER2-positive breast cancer women.

A phase II single-arm clinical trial investigated the combination of paclitaxel and trastuzumab in women with

low-risk, node-negative, stage I, HER2-positive breast cancer [84]. The result showed that in 406 women, 3-year DFS was 98.7% (95% CI 97.6–99.8) with less than 0.5% heart failure reported. Based on this result, paclitaxel and trastuzumab are an option for patients with stage I HER2 disease.

13.5.2 Pertuzumab

Pertuzumab is a monoclonal HER2 antibody, which has a different binding site from trastuzumab. Pertuzumab, in combination with trastuzumab and neoadjuvant chemotherapy, showed significantly improved pCR rate than trastuzumab regimen in women with HER2-positive, early-stage, or locally advanced breast cancer (39.3% in combination arm vs. 21.5% in trastuzumab-alone arm, $p = 0.0063$) [85]. The addition of pertuzumab to trastuzumab also improves 5-year PFS (86% in combination arm vs. 81% in trastuzumab-alone arm, HR =0.69, 95% CI 0.34–1.00) and DFS (84% in combination arm vs. 81% in trastuzumab-alone arm, HR =0.60, 95% CI 0.28–1.27) [86]. In a meta-analysis, higher pCR was correlated with improved OS and PFS at patient level, but not at trial level [77]. In metastatic setting, pertuzumab in combination with trastuzumab showed significantly improved PFS (HR = 0.68, 95% CI 0.58–0.80, $P < 0.001$) and OS (HR = 0.68, 95% CI 0.56–0.84, $P < 0.001$) [87]. Both NCCN and ASCO guideline consider "it is reasonable" to incorporate pertuzumab into adjuvant setting, particularly in women did not receive pertuzumab in preoperative setting. The most common regimens are dose-dense AC × 4, followed by weekly paclitaxel and trastuzumab and pertuzumab every 3 weeks, and carboplatin, docetaxel, trastuzumab, and pertuzumab every 3 weeks. The Adjuvant Pertuzumab and Herceptin in Initial Therapy in Breast Cancer (APHINITY, NCT01358877) is a large phase III randomized clinical trial in 4800 women with early-stage HER2-positive breast cancer. The initial report by Genentech in March 2017 states the addition of pertuzumab to trastuzumab improved DFS, and full result will be reported later in 2017.

13.5.3 Ado-trastuzumab Emtansine (T-DM1)

T-DM1 is a novel agent in which a cytotoxic agent (maytansine, DM1) is conjugated with HER2-specific monoclonal antibody trastuzumab. T-DM1 is approved in metastatic HER2-positive breast cancer as first- and second-line settings [88]. In a phase III study, T-DM1 with and without pertuzumab was compared with trastuzumab and taxane (TH). The PFS for T-DM1 with pertuzumab was non-inferior to trastuzumab with taxane (15.3 months in T-DM1 with pertuzumab arm vs. 13.7 months in TH arm, respectively, HR 0.87, 95% CI 0.69–10.8, $p = 0.14$). The PFS for T-DM1 alone was non-inferior to trastuzumab with taxane (14.1 months in T-DM1-alone arm vs. 13.7 months in TH arm, respectively, HR 0.91, 95% CI 0.73–11.3, $p = 0.31$) [89].

T-DM1 versus Paclitaxel/Trastuzumab for Breast (ATEMPT Trial, NCT01853748) is a phase II trial comparing T-DM1 versus paclitaxel and trastuzumab in early-stage HER2-positive breast cancer after surgery. The study has completed 500 patient enrollments, and the primary endpoint is DFS at 2 years. Secondary endpoints include OS, DFS in patients with different tumor size, and T-DM1 toxicities.

13.6 Conclusions

Adjuvant systemic therapy improves survival for women with early-stage breast cancer after surgery. Therapy is tailored to the individual based on risk of recurrence and receptor status. In patients with ER- and/or PR-positive and HER2-negative breast cancer, Onco*type* Dx® among other biomarkers can further identify patients who will benefit the most from chemotherapy. Endocrine therapy should be offered to every woman with ER- and/or PR-positive breast cancer. The type of endocrine therapy depends on menopausal status. The gold standard for postmenopausal women is an aromatase inhibitor. However, women have options such as tamoxifen, nonsteroidal AIs, and steroidal AIs. Ovarian suppression should be considered in young women with high-risk disease. In patients with triple-negative breast cancer, polychemotherapy remains the mainstay of adjuvant therapy. Platinum-based adjuvant therapy is promising, and further study is underway. Women with HER2-positive breast cancer should receive anti-HER2 therapy including trastuzumab and/or pertuzumab in combination with chemotherapy. Many novel agents are currently under study in the adjuvant setting in order to advance the treatment of early-stage breast cancer.

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Whole-Breast Radiotherapy After Breast-Conserving Surgery

14

Lior Z. Braunstein

14.1 Introduction

The management of breast cancer has advanced considerably since the historical dependence on increasingly aggressive forms of mastectomy. With advances in technology, including enhanced imaging, pathologic margin assessment, systemic agents, and radiotherapy techniques, breast conservation has become increasingly feasible and now heralds outcomes that are at least as favorable as mastectomy in the majority of cases [1, 2].

The combination of breast-conserving surgery (BCS) and adjuvant radiotherapy (RT) is known as breast-conserving therapy (BCT). This approach has been evaluated over several decades by a number of landmark studies that have established BCT as a standard of care for localized breast cancer. A meta-analysis further analyzed these studies in aggregate, establishing a clear survival benefit for adjuvant radiotherapy following BCS, with outcomes approximating those of mastectomy [1].

Breast cancer awareness and screening initiatives have increased the number of those presenting with early-stage disease who are eligible for BCT [3–5]; despite this, there has been a paradoxical increase in the rate of both therapeutic and prophylactic mastectomies that runs counter to the general oncologic trend of organ preservation [6]. In this chapter, we discuss the principles of BCT, the rationale for adjuvant radiotherapy, and the recent advances with practice-changing implications.

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14.2 Selecting Candidates for Breast-Conserving Therapy

As with any organ-sparing treatment, the predominant factor in determining appropriateness relates to optimizing post-treatment cosmesis and function. If the underlying tumor involves a large proportion of the overall breast volume, breast conservation is less likely to yield a cosmetically adequate result, possibly favoring mastectomy. Thus, a relatively small tumor might require mastectomy if arising in a small-volume breast, while a large tumor could potentially be managed with lumpectomy if arising in a larger-volume breast. The traditional threshold for consideration of BCT has been a maximal tumor dimension of ≤5 cm, although expected cosmesis and patient motivation should predominate in clinical decision-making [7].

BCT is contraindicated in the following settings where safety or efficacy may be compromised:

- Diffuse disease that cannot be adequately excised with negative margins or with an acceptable cosmetic result.
- Presence of multiple areas of suspicious or malignant-appearing calcifications.
- Breast cancer detected early in a pregnancy that would necessitate RT prior to delivery. Radiation is a robust teratogen and should be avoided during pregnancy if at all possible.
- Prior breast or chest wall radiotherapy increases the risk of RT-induced toxicity, typically favoring mastectomy. While prior RT was previously an absolute contraindication to breast conservation, repeat BCT is now being investigated in prospective fashion [8], with a number of retrospective reports demonstrating feasibility with marginally increased toxicity [9–11]. Previous RT may now represent a relative contraindication.
- A number of connective tissue disorders and collagen vascular diseases have been reported to increase the toxicity of RT. Among these, the presence of systemic lupus

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_14

erythematosus, discoid lupus, Sjogren's syndrome, and scleroderma have prompted avoidance of RT [12–17].
– The presence of an underlying predisposing breast cancer syndrome (e.g., the hereditary breast and ovarian cancer syndrome among *BRCA1* or *BRCA2* mutation carriers) should favor mastectomy given that the residual breast tissue remains at high risk of developing a metachronous cancer [7].

14.3 Adjuvant Breast Radiation Following Breast-Conserving Surgery

Since the era predominated exclusively by mastectomy, a series of landmark studies has established the role for adjuvant radiation as a standard component of breast conservation [18, 19]. Radiation to the ipsilateral whole breast has been shown in a number of setting to reduce the risk of local recurrence (LR) following lumpectomy. Moreover, large scale meta-analyses by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) collected sufficient data to demonstrate a survival benefit to adjuvant radiotherapy in addition to this improvement in local control. The initial report by the EBCTCG exhibited a 4:1 relationship between the reduction in LR at 5 years and the survival improvement at 15 years [1]. Another important finding of this study was that radiotherapy reduced LR by approximately 70% in either the lumpectomy or the mastectomy setting. Following a number of subsequent radiation trials, the meta-analysis was updated in 2011 to include 17 prospective randomized studies comprising over 10,000 women with a median follow-up of nearly 10 years [20]. In this report, radiation reduced the risk of any first recurrence at 10 years from 35.0% with lumpectomy alone to 19.3% with lumpectomy + radiation. Breast cancer death was concomitantly reduced at 15 years from 25.2% to 21.4% with the addition of RT to lumpectomy, further cementing the role of adjuvant radiotherapy in the BCT setting. Of note, RT appeared to reduce the risk of any first recurrence by about half in most subgroups, suggesting the greatest absolute benefit among subgroups at the highest risk. Conversely, the most favorable subgroups, such as those with smaller tumors that were estrogen receptor (ER) positive, of older age, and node-negative, benefitted only modestly from the addition of radiotherapy to surgery.

Overall, outcomes for BCT appeared excellent in the early trials and have only improved since. The EBCTCG reported a 5-year ipsilateral breast recurrence rate of 6.7% for node-negative patients and 11% for node-positive cases. At 10 years, these rates increased marginally to 10 and 13.1%.

Whereas whole-breast radiotherapy was traditionally administered in daily fractions of 180–200 cGy requiring 5–6 weeks to deliver a full course, studies in recent years have revealed that larger daily fraction sizes, termed "hypofractionation," can safely and effectively reduce the duration of a treatment course to 3–4 weeks. In 2010, Whelan et al. reported the results of a Canadian trial in which 1234 patients were randomized to either the standard dose of 50 Gy in 25 fractions or the hypofractionated regimen of 42.5 Gy in 16 fractions [21]. At 10 years, no significant differences were noted between the groups with regard to local recurrence (6.7% for the standard arm versus 6.2% for the hypofractionated arm) and those reporting good-to-excellent cosmesis (71.3% vs. 69.8%, respectively). On subgroup analysis, patients with high-grade disease were initially reported to have higher local recurrence rates, although this finding was not borne out in subsequent studies. A pair of similarly directed studies from the United Kingdom also aimed to assess the feasibility of hypofractionation [22, 23]. Much like the Canadian study, the UK START B trial enrolled 2215 women who were randomized to either the standard regimen of 50 Gy in 25 fractions as above or a hypofractionated regimen of 40 Gy in 15 fractions (one fraction fewer than the Canadian trial). At a median follow-up of 9.0 years, the proportion of patients with local or regional recurrence did not differ between the standard and hypofractionated arms (5.5% vs. 4.3%, respectively). Of note, there appeared to be less breast shrinkage, telangiectasia, and edema in the hypofractionated arm.

Given these largely favorable outcomes, significant resources have been devoted in recent years to identifying those patients at highest risk for recurrence in an effort to tailor therapy. Several institutional reports have identified young patient age as an independent risk factor for adverse outcomes including both recurrence and survival [24–27]. Along these lines, the European Organisation for Research and Treatment of Cancer (EORTC) conducted an evaluation of boost radiation following whole-breast radiotherapy and determined that younger patients had both the highest rates of local recurrence and were also most likely to benefit from boost radiation (5-year LR rate for those <40 years of age was 15% vs. 7% for those 41–50, 4% for those 51–60, and 3% for those older than 60 years of age) [24].

Of particular interest is that the influence of age on LR may be diminishing with advances in the overall management of breast cancer. For example, Van der Sangen et al. demonstrated that among women younger than 40, the 5-year rate of LR following BCT declined from 11% to 3.8% from the mid-1990s to the early 2000s [28]. Similar observations have been made among other cohorts and are likely attributable to improvements in breast cancer detection and continued advances in the efficacy of systemic therapies.

In addition, it is now largely recognized that breast cancer is not a single disease entity but rather is a heterogeneous class comprising at least four biologic subtypes, including luminal A, luminal B, HER2-enriched, and basal-like, each of which has its own natural history and is both prognostic and predictive [29–31].

There also appear to be at least 30 histologic subtypes of breast cancer, among which invasive ductal carcinoma (IDC) is the most common and represents 60–70% of cases; invasive lobular carcinoma (ILC) accounts for another 5–15% [32, 33]. ILC exhibits several clinical and pathologic features that distinguish it from IDC, including a loss of E-cadherin, a cell-cell adhesion molecule [34], a tendency toward multifocality, and a predominance of the luminal A biologic subtype in contrast to IDC, which is broadly distributed among other subtypes (i.e., luminal A/B/HER2-, HER2-, and triple-negative) [35]. Furthermore, in contrast to IDC, ILC more often requires re-excision or mastectomy following breast-conserving surgery due to challenges detecting its diffuse growth both radiographically and operatively, thereby leading to mastectomy more frequently than IDC [36–40].

14.4 Omitting Adjuvant Breast Radiation

Although well-tolerated and effective, RT poses an inconvenience to patients and confers a small, yet real, risk of long-term adverse effects, such as cardio-/pulmonary toxicity and secondary malignancies. As described above, large meta-analyses [41] and institutional reports have suggested that not all patients stand to benefit equally from RT, with certain disease features portending an excellent prognosis regardless of the adjuvant treatment approach [42]. As a result, several attempts have been made to identify those low-risk patients who might be safely spared the cost and morbidity of RT.

From 1986 to 1992, several Harvard centers prospectively accrued a cohort of 87 women with T1N0 invasive breast cancer who were treated with BCS alone [43, 44]. Despite selecting for favorable features such as unicentric disease, margins ≥1 cm, and no lymphovascular invasion, the (LR) rate was 23% at a median follow-up of 86 months. This outcome was worse than anticipated for a low-risk sample, supporting the continued use of adjuvant RT among such favorable patients. Importantly, this trial included several patients <50 years of age, and estrogen receptor (ER) status was unknown in 50% of cases.

In a similarly minded study, the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-21 trial sought to determine whether the reduction in LR afforded by tamoxifen could supplant the need for adjuvant RT [45]. In that trial, 1009 women who had undergone BCS for tumors ≤1 cm were randomized to adjuvant tamoxifen, RT, or both. At 8 years, the cumulative incidence of local recurrence (LR) was 16.5% for patients who received tamoxifen alone, 9.3% for RT, and 2.8% for those who received both ($p = 0.01$). The authors concluded that despite careful selection, this population remained at sufficient risk of LR to merit adjuvant RT. Of note, despite the implications of hormonal therapy in this trial, ER status was unknown in nearly 30% of patients, and about 20% were <50 years of age.

Since older age at diagnosis has long yielded favorable breast cancer outcomes (including reduced LRR even when adjusted for biologic subtype), a Canadian trial included only women ≥50 years of age [46]. Between 1992 and 2000, 769 women with T1 or T2 breast cancers were randomized to tamoxifen alone or in combination with RT. The 5-year rate of LR was 7.7% for women who received tamoxifen alone versus 0.6% for those who received the combination ($p < 0.001$), again demonstrating the local benefit of RT. In further subgroup analyses of the most favorable patients with T1 ER+ tumors, the local recurrence rate at 8 years remained elevated at 15.2%.

A number of smaller historical studies have also attempted to omit radiotherapy for select subgroups of breast cancer patients. A Finnish study accrued 264 segmentectomy patients with small, unifocal tumors and randomized them to receive RT or not [47]. After a median follow-up of 12 years, LR was noted in 12% of those who received RT versus 27% in those who did not. An analogous German trial employed a 2 × 2 factorial design to evaluate the influence of both RT and tamoxifen on LR [48]. Though not powered to detect an interaction between RT and tamoxifen, 10-year LR was 34% among patients receiving BCS alone versus 10% among those who also received adjuvant RT. Of note, the addition of tamoxifen reduced these rates to 7% without RT and 5% with RT, although the sample was insufficient to make definitive conclusions. Milan 3 was an Italian study of 579 quadrantectomy patients with tumors <2.5 cm, randomized to the receipt of RT or no RT [49]. The 10-year cumulative incidence of LR was 5.8% among patients treated with RT versus 23.5% among those who were not ($p < 0.001$). This difference was reported to be especially large among women ≤45 years of age, with no apparent difference among those >65 years old ($p = 0.326$). Notably, these studies were unable to rigorously evaluate tumor ER status or other molecular signatures which were more recently discovered. As described below, the modern use of robust biomarkers has significantly improved our ability to risk-stratify patients prior to enrollment in such trials.

Thus far, the Cancer and Leukemia Group B (CALGB) has conducted the main study to date showing the feasibility of omitting RT in the setting of breast conservation [42, 50]. The CALGB 9343 accrued 636 women from 1994 to 1999. All patients were ≥70 years old, had T1 ER+ breast carcinoma, and were treated with BCS. Patients were

randomized to adjuvant therapy including tamoxifen with RT or tamoxifen alone. The 10-year rate of local and regional recurrence (LRR) was significantly different between the two groups: 2% for those receiving tamoxifen with RT versus 10% for tamoxifen alone. However, no significant differences were noted with regard to DM or OS between treatment arms. While the difference in LRR was statistically significant, the small absolute benefit of RT along with the absence of a survival benefit has been deemed sufficient evidence to reasonably offer women over 70 the option of omitting RT should they plan to pursue antiestrogen therapy. To date, there are limited data to inform the omission of RT in women younger than 70 years of age, and, moreover, this population has not been studied in the modern treatment era.

Modern advances in imaging, systemic therapy, margin assessment, and molecular analysis have changed the BCT landscape, now reducing LRR rates for early breast cancer to below 5–10% in many reports [27, 51, 52]. In contrast, the studies cited above that attempted to identify low-risk subgroups were largely conducted with now outdated approaches, yielding higher-than-expected LRR rates even among the most favorable patients. Standard treatment approaches and risk-stratification techniques have since been refined considerably, with efforts to de-escalate treatment for the lowest-risk patients [53].

Molecular profiling studies have also since revealed that breast cancer is not a single disease entity, but rather a class of distinct biological subtypes. These subtypes carry prognostic and predictive significance with a discrete natural history characterizing each [30, 54–56]. Given the costs and complexity associated with comprehensive transcriptional profiling, surrogate methods using widespread immunohistochemical (IHC) and histologic techniques have been correlated with the relevant transcriptional profiles; these have been largely based on staining for the estrogen receptor (ER), progesterone receptor (PR), Her2neu overexpression (HER2), and the Ki-67 proliferation marker, along with an assessment of histologic grade. Among the intrinsic biologic subtypes distinguished by these markers, the most favorable is luminal A, typically defined by immunohistochemistry showing ER+, PR+, and Her2-, along with a low histologic grade and/or low Ki-67 proliferation rate [27, 31, 57]. Accordingly, luminal A tumors appear to confer the lowest risk of LRR among all breast cancers. This recent biologic insight may be the key factor in identifying patients of sufficiently low risk that RT might be reasonably omitted following BCS.

However, with the widespread clinical adoption of IHC-based subtyping, concerns have been raised regarding the fidelity of this technique in capturing the underlying molecular profile and predicting intrinsic tumor biology. As a result, researchers have sought to develop more comprehensive and standardized assays to reliably and reproducibly characterize biologic subtype. Two large ongoing studies seek to robustly identify subpopulations of patients who may be able to safely omit radiotherapy following lumpectomy. The Individualized Decisions for Endocrine Therapy Alone (IDEA; ClinicalTrials.gov NCT02400190) study uses a 21-gene recurrence score (Oncotype DX, Genomic Health) to risk-stratify eligible patients, whereas the Profiling Early Breast Cancers for Radiotherapy Omission (PRECISION, ClinicalTrials.gov NCT02653755) trial is employing the prediction analysis of microarray 50 (PAM-50) gene expression profile which was initially used to describe the intrinsic breast cancer subtypes and is now available as a validated prognostic and predictive clinical assay [58–60] (ProSigna, NanoString). Molecular assays such as these gene expression profiles have begun to play an increasingly prominent role as adjuncts to traditional clinicopathologic features [61].

14.5 Toxicity of Whole-Breast Radiotherapy

Whole-breast radiotherapy has benefited from recent advances in radiation technology and is now a safe and well-tolerated approach. Treatments are typically administered daily, in less than 30 min per fraction, without significant decrement in day-to-day quality of life. The most common adverse effects associated with whole-breast radiation are cumulative and typically arise after several weeks of treatment; these include radiation-associated fatigue and a cutaneous reaction typical of radiation dermatitis. The extent of fatigue reported by patients is highly variable, including some who report no fatigue through the end of treatment, while others report feeling generalized weakness and resort to daily naps or modified sleep schedules. Regardless of the degree of reported fatigue, the majority of patients revert to their baseline activity level within 1–2 months of treatment completion, while a minority will report residual fatigue even after several months of follow-up.

Radiation dermatitis is a phenomenon noted among many radiation-treated disease sites and shares clinical features with the common sunburn. Contemporary approaches that employ megavoltage photons can promote “skin-sparing” along with algorithms to optimize dose homogeneity which have generally improved the expected cutaneous toxicities that were previously commonplace with breast radiotherapy. Skin reactions with contemporary whole-breast radiation techniques are typically mild, consisting of warmth, mild tenderness, mild-to-moderate erythema, and occasional

pruritus. As with fatigue, the degree of reaction varies considerably among patients, likely to owing to both anatomic and genetic contributors. Rare patients will exhibit more severe skin reactions that range from dry to moist desquamation, and skin necrosis has been reported in rare circumstances or unusual scenarios such as re-irradiation or concurrent surgical manipulation. The majority of mild-to-moderate skin effects typically resolve within 1–2 months following the completion of radiotherapy, although mild hyperpigmentation or breast edema/heaviness may persist in the long term [7].

Contemporary treatment planning allows for the estimation of radiation dose to normal structures, making permanent tissue injury exceedingly rare in modern settings. A noted long-term complication following lumpectomy and breast radiation is a subcutaneous fibrosis of the manipulated breast tissue [62, 63]. However, with typical whole-breast treatment courses ranging from 40 to 50 Gy, excellent cosmesis is noted by the majority of patients.

Secondary radiation-induced malignancies can be a devastating complication following any form of radiotherapy. Following whole-breast radiation, lung cancers, angiosarcomas, and metachronous breast cancers have been reported, although each is fortunately exceedingly rare [64–67]. Contralateral breast cancers are of particular concern given a number of data to suggest that whole-breast radiation may increase the risk of a metachronous contralateral cancer [68–70]. As a result, breast radiation techniques have been continually refined to limit the amount of contralateral scatter radiation. Indeed, techniques for reducing hotspots, which were historically dependent largely on the use of physical wedges which increased scatter dose [71], now exploit advanced technologies such as intensity modulation, multiple subfields, and tangents designed to limit direct contralateral breast dose. In one analysis, contralateral breast dose was decreased by up to 82% using intensity modulation [72].

As the long-term outcomes for breast cancer have become increasingly favorable, focus has appropriately been placed on the long-term toxicities of treatment. Perhaps most notably, the cardiac consequences of breast radiation have received considerable attention given historical techniques and long-term data. The landmark EBCTCG analyses described above revealed that among patients treated with radiation for breast cancer, there was a relative risk of 1.27 for cardiac death in comparison to patients who did not receive radiotherapy [1, 20]. Of note, this effect was most notable among older subgroups that were treated comprehensively with post-mastectomy radiation, using techniques that are now outdated. Fortunately, improved treatment approaches have since been developed to minimize cardiac dose, and contemporary patients likely face far less cardiac risk than their predecessors. A SEER analysis demonstrated that radiation no longer increased the risk of cardiac death as early as the 1980s, whereas cardiac toxicity was still elevated in the 1970s [73]. Another SEER-Medicare study revealed no increase in cardiac events among older patients who underwent radiation for left-sided breast lesions [74]. Conversely, a contemporary series demonstrated that patients who received radiation for left-sided cancers exhibited an increased risk of coronary events in comparison to their right-sided counterparts [75]. Along similar lines, a landmark study by Darby et al. evaluated the dosimetric relationship between breast radiotherapy and cardiac toxicity, reporting that for each 1 Gy increase in mean cardiac dose, baseline cardiac events rose by a relative 7.4% [76]. Of particular note is that cardiac toxicity following breast radiation can have a latency in excess of 10 years, making the avoidance of cardiac radiation particularly important.

As a result of these and other findings, a number of techniques have been developed to minimize cardiac exposure when administering whole-breast radiotherapy. For example, a heart block can be used when the tumor cavity is some distance from the cardiac silhouette. This small block typically comes at the expense of complete coverage of the lateral and medial edges of the inferior breast/chest wall, although for tumors in the upper quadrants of the breast, this tradeoff may be considered acceptable [77]. The deep inspiration breath-hold (DIBH) technique is another approach to mitigating heart dose, whereby radiation is delivered during a prolonged breath hold that inflates the lungs, depresses the diaphragm, and typically displaces the heard inferomedially away from the targeted chest wall (Fig. 14.1). The use of this technique depends on the employment of motion management devices, such as surface anatomy monitoring (e.g., AlignRT) or spirometric gating [78–81]. Additionally, if treating the whole breast and not the regional lymph nodes, prone or lateral recumbent positioning may allow sparing of the heart by exploiting gravity to displace breast tissue away from the chest wall (Fig. 14.2) [82–84].

Occasionally, pulmonary toxicity manifests as radiation pneumonitis—a syndrome variably consisting of cough, dyspnea, fever, and malaise that is typically self-limited, arising within 4–12 weeks following radiation. A late, fibrotic radiation pneumonitis has also been described, developing 6–12 months following RT and comprising similar clinical manifestations. While the optimal management for radiation-associated lung injury is unknown, a common regimen for those with progressive symptoms involves a moderate course of glucocorticoid therapy (often prednisone 60 mg daily for 2 weeks, followed by a gradual taper of 3–12 weeks).

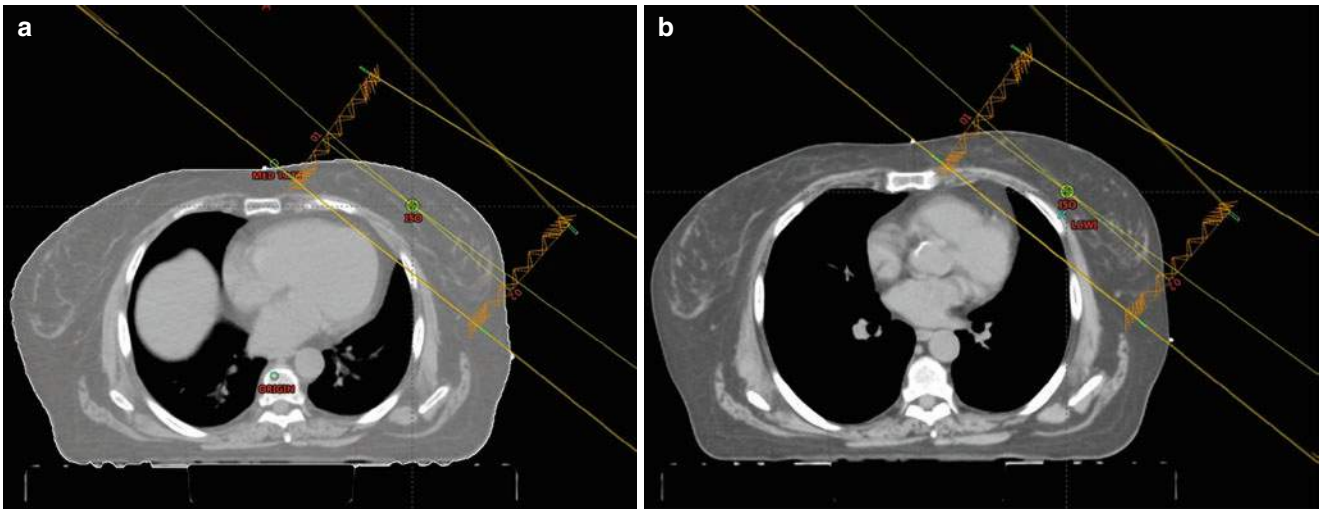

Fig. 14.1 The deep inspiration breath-hold (DIBH) technique uses spirometric gating or surface monitoring technologies to allow delivery of radiation during a reproducible inspiration. Favorable anatomic dynamics are noted in most patients when comparing a free-breathing simulation (Panel **A**) to DIBH (Panel **B**). These images represent the same index location in the same patient. Note the proximity of the left ventricle to the targeted breast/chest wall

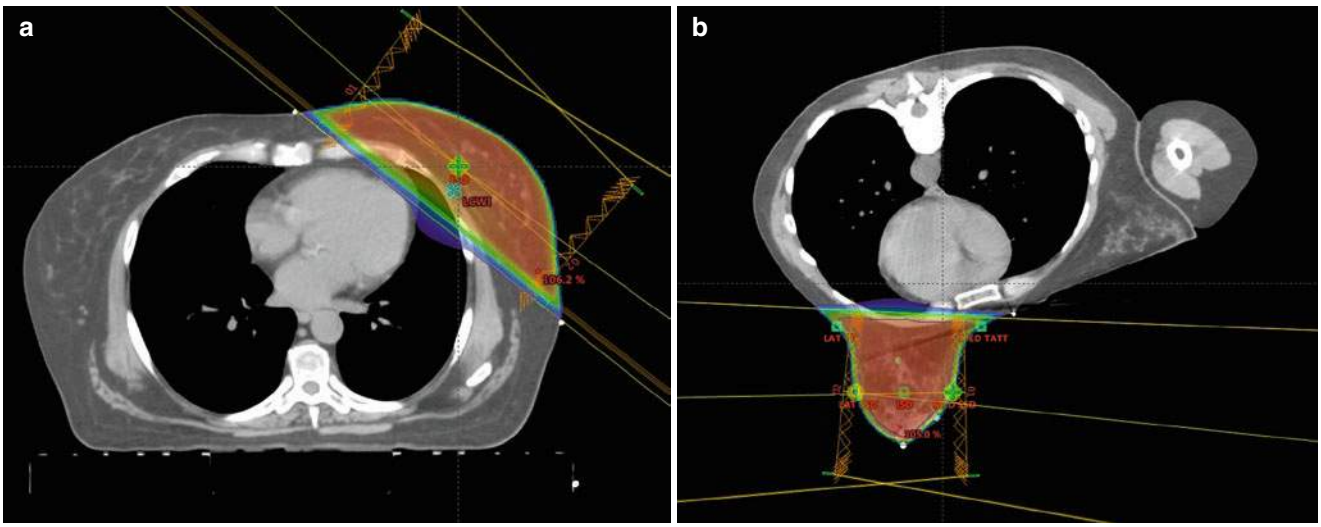

Fig. 14.2 In comparison to supine positioning (panel **A**), select patients benefit from prone simulation (panel **B**) which exploits gravity to displace targeted breast tissue away from the chest wall, yielding improved geometry and a concomitant reduction in radiation dose to the ipsilateral lung and heart

14.6 Follow-Up After Radiotherapy

Acute radiation-associated toxicities such as fatigue and erythema are typically short-lived and resolve within weeks following treatment. In a minority of cases, symptoms persist for months and require close monitoring to mitigate the risk of longer-term sequelae. The longer-term risks of breast radiotherapy, as described above, include poor cosmesis, radiation pneumonitis, cardiac toxicity, and secondary malignancy. Brachial plexopathy has been rarely reported with treatment of the lymph nodes, as targeting of the supraclavicular fossa necessitates delivery of full treatment dose to the brachial plexus. Given these late effects, posttreatment monitoring is an important component following definitive therapy.

Overall long-term management is beyond the scope of this chapter and may include follow-up with multidisciplinary oncologic providers, in addition to physical therapists, sexual health providers, mental health practitioners, and others. Current guidelines recommend annual posttreatment mammography and physical examination 1–4 times per year [85], based on the generally favorable outcomes following breast-conserving therapy. Several groups have demonstrated the value of a multidisciplinary approach to the

evaluation, management, and follow-up of breast cancer, and, while resource-intensive, patient satisfaction appears to benefit from this comprehensive design [86].

14.7 Conclusions

With increasing emphasis on organ preservation among oncologic disciplines, there is considerable evidence to support the use of breast conservation in the management of breast cancer. Indeed, contemporary series demonstrate results in most cases that are at least equivalent to those of mastectomy yet improve quality of life for treated patients. In appropriately selected patients, the conserved breast following lumpectomy and radiation maintains excellent cosmesis with limited risk. These considerations remain particularly relevant with advances in systemic therapy and radiation techniques, which are being applied with increasing precision based on individual risk. Further research will continue to refine our understanding of breast cancer biology and of the optimal multidisciplinary approach for individual patients.

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15 Radiotherapy: Principles and Consequences for Breast Reconstruction

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15.1 Postmastectomy Radiotherapy Indications

A clear evidence of survival advantage by adding radiotherapy (RT) to high-risk patients after mastectomy emerged toward the end of the 1990s, and the number of patients who require postmastectomy radiotherapy (PMRT) has increased over time. There is a worldwide recommendation that chest wall and supraclavicular RT is administered to locally advanced (pT3/pT4) tumors and to any tumor size with four or more positive axillary lymph nodes [1]. For women at an intermediate risk of recurrence, the role of PMRT is more controversial, but it is increasingly used, mainly when some aggressive features are present, such as young age 40 years or less, negative estrogen receptors, and grade III, vascular, or lymphatic invasion [2]. Several specifically addressed trials broadening the indications for PMRT are still ongoing, and the percentage of patients who require adjuvant RT following mastectomy is expected to further increase. On the other side, the benefits of breast reconstruction (BR) after partial or total mastectomy are well-established, including psychological health and aesthetic outcome, and most women are choosing to have a BR. The optimal integration of breast reconstruction and PMRT is still under investigation. The best strategy is each case be discussed within the context of a multidisciplinary team in order to offer the best management option according to the doctors and patients' points of view [3]. The choice of type of reconstruction (allogeneic versus autologous), and the timing (immediate versus delayed), depends on several variables, such as comorbidity, tumor stage, need for adjuvant therapies, body habits, breast size and shape, and personal preference, and all these aspects have to be considered.

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15.2 Physiopathology of Radiation

Radiation side effects are classified as acute and chronic, according to the time at which they occur. Acute effects manifest within days to weeks and usually involve cellular death in rapidly proliferating cells. The most typical acute reactions consist of erythema, dry desquamation, edema, and epilation. Later, skin hyperpigmentation due to stimulation of epidermal melanocytes can be also observed. These initial reactions can progress into more severe side effects such as moist desquamation, characterized by exposure of the dermis, secreting exudates, which results from eradication of stem cells from the basal layer. Chronic side effects may occur after several months or years and usually manifest as atrophy and fibrosis. Clinically, fibrosis causes hardening and thickening of the dermis. Dyschromic changes consist of either hyperpigmentation or hypopigmentation, due to abnormal stimulation or depletion of melanocytes, respectively. Telangiectasia consists of superficial vessel dilatation. The mechanisms of radiation-induced damage include either the microvascular occlusion theory or the chromosomal alteration theory [4]. Recent evidence supports the latter theory, showing permanent damage to fibroblasts and to stem cells, which are inhibited from replicating and providing new vessels [5]. In case of BR, fibrosis and shrinkage can lead to an increased incidence of revision surgery, following autologous reconstruction. In prosthetic-based reconstruction, these radiation-induced changes can be associated with higher rate of infection, capsular contraction, and revision surgery.

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_15

15.3 Delayed Versus Immediate Breast Reconstruction

Recommendations range from delaying BR until after PMRT to using a delayed-immediate approach, placing a temporary tissue expander (TE) before definitive reconstruction, to performing immediate BR followed by PMRT. BR is considered safe by the oncological point of view in terms of local control or in any survival endpoint compared to patients who only received RT following mastectomy without reconstruction [6, 7]. The use of immediate BR has markedly increased in recent years, due to the positive psychological impact, the ease of operating with non-irradiated tissues, and the great cost-effectiveness [8, 9]. The potential drawbacks consist in a more complicated RT technique and in an increased postoperative complication rate with adverse cosmetic outcome [10–12]. Immediate BR can be adversely affected by PMRT and may compromise the radiation field design leading to a suboptimal radiation delivery [11]. On the other hand, delayed BR after PMRT may be technically challenging because of chronic inflammation that increases the risk of perioperative complications, delayed healing, wound infection, and anastomotic failure [13]. The main points emerging from a comprehensive review including 11 studies are that immediate BR and PMRT are more likely to cause morbidity when compared to immediate BR alone, and autologous tissue is the superior reconstruction technique in terms of postoperative morbidity in case of PMRT after BR, and delaying BR until the completion of PMRT had no significant effect on outcome [14]. Most of studies addressing the issue of sequencing do not find any increase in overall complication rates between immediate BR and delayed BR [15, 16] but point out the different nature of complications [17]. Early complications (vessel thrombosis, partial or total flap loss, infection, no healing open wounds) tend to develop in patients having PMRT first, whereas patients having BR first have a higher risk of late complications (fat necrosis, flap volume loss, and flap contracture) [18, 19]. Javaid et al. conducted a systematic review including ten studies on the optimum timing of RT in relation to autologous BR [20]. All studies but one described an increased complication rate when BR is combined with PMRT compared to BR alone, from 0–21% to 16–33%. The general recommendation is to delay the BR with autologous tissue until after the end of RT in order to avoid adverse cosmetic outcome [21, 22]. Regarding the appropriate timing of delayed BR after PMRT, there is no consensus in the literature. In one dedicated study, an interval of 12 months between the completion of PMRT and delayed abdominal free flap BR was shown to minimize complications and optimize outcomes [23]. The most frequent complication of BR using a prosthesis is capsular contracture (CC). Although both previous and postoperative RT are strongly involved in capsule formation [24], for patients irradiated after immediate BR, the risk increases a lot [25]. In the study conducted by Behranwala et al., capsule formation is three times more likely to occur after immediate BR in association with a RT field [26]. Regarding the appropriate timing of PMRT after BR with TE/PI, Tallet et al. found that the complication rate was not influenced by the RT delivered either 1 or 5 months after BR with an expander [27]. However, using an animal model, Goodman et al. demonstrated that a time interval of 2–3 weeks after complete filling of the expander increased tissue tolerance to radiation [28]. In previously irradiated patients, delaying BR for at least 12 months after the completion of RT seems to reduce the incidence of CC [29, 30]. Kronowitz et al. reported on a two-stage approach delayed-immediate BR as to optimize outcomes in those patients for whom the need for PMRT is unknown at the time of mastectomy [31]. The first stage consists in placing a saline-filled tissue expander, followed by immediate BR if RT is not required, according to the final histopathology report. Conversely, if RT is required, the expander is deflated, and patients undergo delayed BR after the completion of RT using an autologous tissue flap. This approach appears to be both technically feasible and safe. A systematic review of the literature published from 2000 to 2015 on the surgical outcomes after BR and adjuvant therapy has been quite recently published [32]. This included 56 manuscripts (5437 patients) evaluating patients treated with PMRT and 11 manuscripts (820 patients) evaluating patients treated with chemotherapy. Pooled analysis of the PMRT cohort reported a total complication rate of 35%. A significantly higher weighted incidence of reoperation ($P < 0.0001$), total complication ($P < 0.0001$), and reconstructive failure ($P < 0.0001$) was observed on prosthetic reconstruction compared to autologous. Reconstructive failure had a weighted incidence of 16.8% in device-based reconstruction and 1.6% in autologous reconstruction. A subgroup analysis of reconstructive failure based on the timing of PMRT demonstrated a significant increase when PMRT preceded definitive implant reconstruction (irradiation to the TE) when compared to PMRT following definitive permanent implant (18.8% versus 14.7%; $P = 0.006$). Only a trend toward PMRT preceding autologous reconstruction versus delaying PMRT was observed. As opposite, there was a little evidence that adjuvant chemotherapy is associated with poorer cosmetic outcomes.

15.4 Type of Reconstruction

For women receiving BR, there are a variety of reconstructive options available, each with its own pros and cons. The four most common types of BR performed today are expander/implant (TE/PI), latissimus dorsi (LD), transverse rectus

abdominis myocutaneous flap (TRAM), and deep inferior epigastric perforator flap (DIEP). The decision regarding which type of BR should be used is determined by a number of variables related to disease, patients' characteristics, and doctors' expertise [33]. Autologous BR is always the preferential choice when a patient is a candidate for RT. In a study conducted by Jhaveri et al., the impact on cosmesis, functional outcome, and daily life activity was significantly heavier for TE/PI compared with autologous BR [34]. The group from Massachusetts General Hospital reported complication rates of 53% and 12%, respectively, with TE/PI and autologous BR, with none of autologous BR requiring corrective surgery [21]. A retrospective review of patients who underwent mastectomy plus autologous or TE/PI BR at Cleveland Clinic was performed by Berry et al. [35]. In the TE/PI population, there were a total complication rate of 31.8% and overall major complication rate of 24.8%. RT increased major complication rate from 21.2% to 45.4%. The most common complications were implant extrusion and CC. However, TE/PI BR was successful in 70.1% of patients receiving RT. In the autologous BR group, there was a total complication rate of 31.5%, and 19.7% had major complications. There was no statistically significant difference between the irradiated and non-irradiated autologous tissue BR, with major complication rates of 17.9% and 20.5%, respectively. Different autologous flap types provided similar complication rates. Berry found that preoperative and postoperative RT led to higher major complication rates compared with no RT ($P < 0.001$), and autologous BR had significantly fewer major complications compared with TE/I BR in both preoperative ($P < 0.005$, odds ratio 0.22) and postoperative RT ($P < 0.05$, odds ratio 0.35). Conversely, in the study conducted by Anderson et al., the type of BR irradiated did not predict for complications, and both BR with TRAM and TE/PI experienced a very low rate of major complications (0–5%), probably due to a more sophisticated RT technique [36].

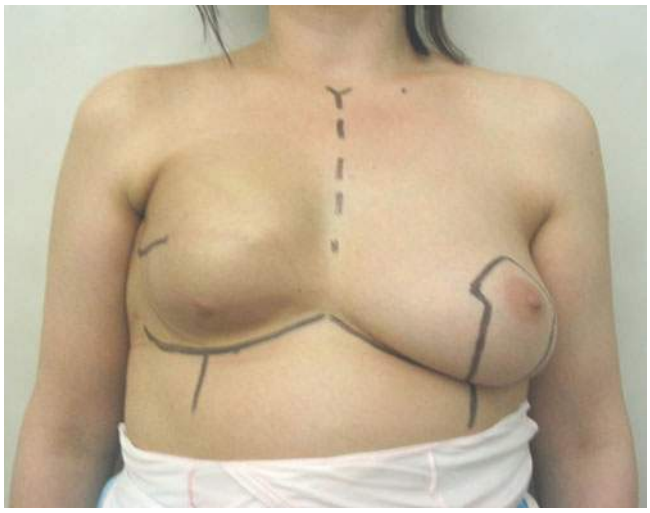

Fig. 15.1 Photograph of a patient with radiation-induced deformity of the tissue expander after immediate breast reconstruction

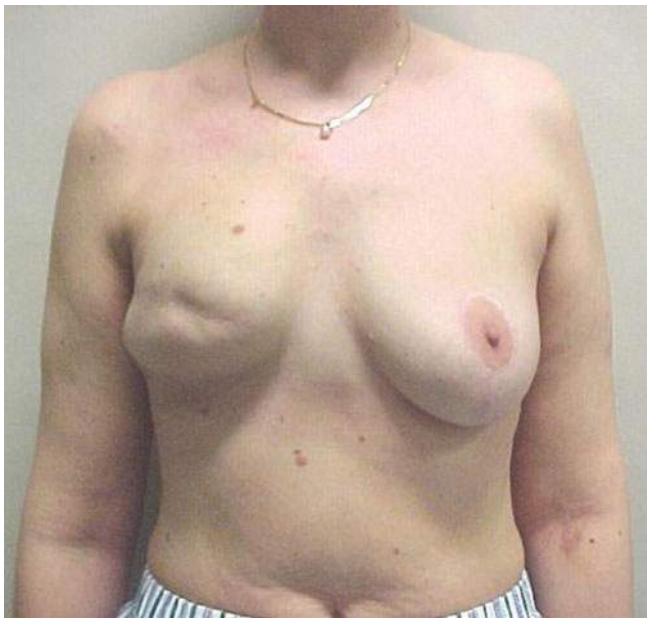

Fig. 15.2 Photograph taken after completion of radiotherapy showing capsular contracture of the permanent implant of the right breast

15.4.1 Allogeneic Reconstruction

The reconstructive technique with TE/PI represents a faster and less complex operative procedure as compared to autologous tissue BR, in spite of its having a greater bearing on complication rates [14]. Long-term complications include CC, infection, pain, skin necrosis or inadequate healing, fibrosis and progressive asymmetry, implant rupture, extrusion, or malpositioning (Figs. 15.1 and 15.2). CC is by far the most complication: the etiology of CC is probably multifactorial, where subclinical infections, patient sensitivity to the inflammatory response, and hematomas may also play a role [37]. Some authors have hypothesized that RT may activate the wingless signaling pathway implicated in regulating fibro-proliferation in capsular tissue around the allogeneic reconstructions. Abnormal levels of proteins involved in the fibro-proliferative processes have been described in irradiated capsules compared with non-irradiated capsules [38]. Clinically, examining patients with bilateral TE/PI reconstruction and unilateral RT, a clear difference in CC between irradiated and non-irradiated breasts was observed in 60% of the cases [39]. The rate of complications and unfavorable aesthetic results ranges from 3% to 40% in the absence of RT [40] and might raise to 17–80% by adding RT [41]. Tallet et al. reported a three times higher complication rate (14% versus 51%) and prosthesis loss rate (9% versus 24%) when

RT was applied [27], whereas a sixfold higher odds of complications (OR, 6.4; 95% CI, 1.6–25.0) was observed in the Michigan Breast Reconstruction Outcomes prospective study [42]. In that series, the use of RT was significantly associated with BR failure, and complications occurred in 68% of the irradiated group compared with 31% in the no RT group ($P < 0.006$). The overall complication rate in the irradiated group was 52.5% with 32.5% of CC, as compared with 10% in a non-irradiated control group in a study including 40 patients [15]. Ascherman et al. reported on 27 patients reconstructed with TE/PI that the irradiated group had a higher overall complication rate compared with the control group (40.7% versus 16.7%) requiring a more frequent removal of the implant (18.5% versus 4.2%) [16]. In the study by Drucker-Zertuche et al., the irradiated group, facing a greater complication rate (45.9% versus 11.6%), also underwent a higher percentage (54%) of major or minor correction surgeries as compared to 5% in the non-RT group and experienced a greater BR failure rate (16.2% versus 0%) [43]. Despite the fact that RT increases the rate of complications, TE/PI remains for many investigators an acceptable option for reconstruction. The group from the Memorial Sloan Kettering Cancer Center continues to use immediate BR with TE/PI for women who are not ideal candidates for autologous tissue reconstruction despite finding in their series 68% of CC after RT, which was significantly higher than that for non-irradiated patients (40%, $P < 0.025$) [41]. Complications aside, the overall success rate for implant BR was 90% among the irradiated patients compared with 99% among the non-irradiated patients, and 80% of the irradiated women demonstrated acceptable aesthetic results versus 88% of non-irradiated women. Hazard et al. reached the same conclusions in a small retrospective study, with an acceptable rate of CC and good or excellent cosmetic outcomes in 85% of cases [7]. Modern RT with the alternate use of customized bolus and intensity-modulated radiotherapy (IMRT) in one-third of cases allows the achievement of a very low incidence of complications as observed in the series conducted by Anderson, which might be promising for future studies [36]. The combined use of an autologous flap and an implant did not offer protection from experiencing higher complication rates when BR was performed before PMRT (67%) as compared with PMRT being administered first (30%) which was of borderline significance ($P < 0.093$) [18]. However, immediate BR with implant in conjunction with a flap shows a rate of CC which is threefold lower than that with implant alone (6.8% versus 25%) [27]. With regard to patients who have previously undergone PMRT, BR with TE/PI alone is considered a relative contraindication because of the risk of bone deformity and rib fractures [44]. However, in a selected group of women who did not develop severe skin changes nor induration with initial PMRT, delayed TE/PI reconstructions have been considered as an option, as shown in one study [46].

15.4.2 Autologous Reconstruction

The two most commonly used autologous tissue flaps for BR are the latissimus dorsi (LD) and transverse rectus abdominus myocutaneous (TRAM) flaps. Recent studies report on the use of the deep inferior epigastric perforator flap (DIEP), whereas with regard to the superficial inferior epigastric artery flap (SIEA) and others based on gluteal and thigh regions, the ability to withstand RT is still unknown. The free flap version of the TRAM appears to be more resistant to RT changes than a pedicled TRAM, because of the different blood supply [47]. However, the fewer complications and flap losses after irradiation of free TRAMs as compared to pedicled TRAMs observed in several studies are not confirmed by others [48]. The most common complications after autologous BR are fat necrosis, flap and mastectomy skin loss, fibrosis, and contracture. Even in the absence of RT, complication rates range from 5% to 41%. The addition of RT increases this incidence, and current literature reports complication rates in the range of 7% to 87.5% [19, 47–55, 58]. Complications occur irrespectively of whether an immediate or delayed BR is performed [49], but a trend toward an increase in complications (overall aesthetic appearance, symmetry, flap contracture, and hyperpigmentation) was evident for immediate BR and PMRT [50]. The TRAM flap is one of the most commonly studied flaps in the literature for BR. When the need for PMRT is unknown at the time of surgery, the TRAM flap is a good option to provide good tolerance and aesthetically acceptable results (Fig. 15.3). Apart

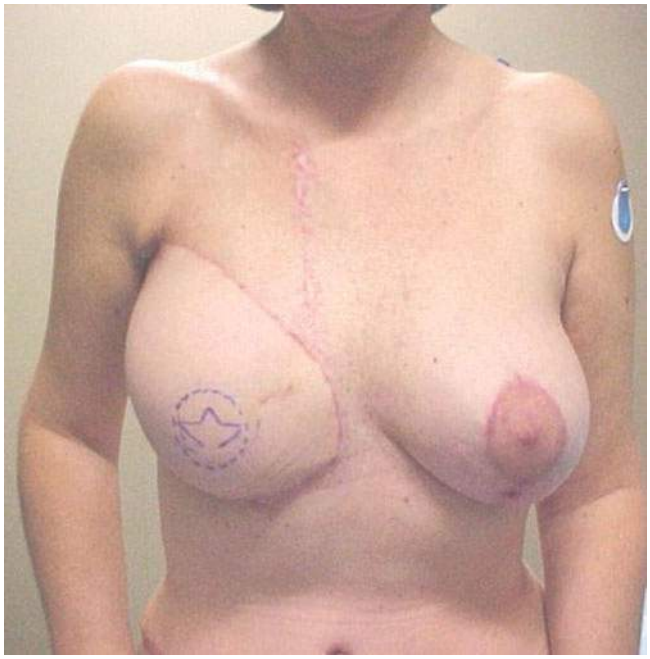

Fig. 15.3 Cosmetic results after postmastectomy radiotherapy to the right side and delayed breast reconstruction with TRAM flap

from fat necrosis, a recent study from Emory University did not find any difference either in complication rate or in the need for surgery revision among patients with immediate BR alone as compared with patients receiving PMRT, although cosmesis was worse [48]. On the other hand, studies from the MD Anderson Cancer Center indicate that RT after autologous BR clearly increased morbidity and worsened the cosmetic results, supporting the delay of BR until after RT [24]. In their experience, no flap loss was reported, but fat necrosis was observed in 34%, atrophy and loss of symmetry in 78%, and hyperpigmentation in 37% of cases. These changes required multiple revisions and additional flaps to correct deformities. Williams et al. compared the outcomes of patients who had preoperative RT and then TRAM flap BR with those of patients who did not undergo preoperative RT [23]. Overall complication rates were comparable between the two groups with exception of fat necrosis which was seen in 17% of the irradiated group versus 10% of the non-irradiated patients. Jacobsen et al., reporting on a series from the Mayo Clinic, confirmed no increase in complication rates in patients who received preoperative RT compared to patients who received BR alone [52]. In the study conducted by Albino et al. among 76 women who underwent autologous BR, complications occurred in 70% of cases after RT, and 47% of these required surgery for postoperative RT effects [53]. Fat necrosis or fibrosis was noted in 19.7%, skin complications (retraction or hypertrophic scarring) were recorded in 30.3%, and general dissatisfaction arose in 27.6% of patients. Previous published series of LD BR have shown a capsular contracture rate affecting between 0% and 56% of cases [26, 54, 57, 58]. This great variability can be attributed to the variation in sample size, follow-up, technique, and population involved. The LD muscle is considered a useful flap in the previously irradiated chest, and no increase in flap loss has been documented, although prior RT negatively affects the aesthetic results [56]. Nevertheless, patient satisfaction was similar between patients undergoing immediate and delayed BR with PMRT [57]. Apffelstaedt et al. showed no significant difference in complication rate between preoperative RT and non-irradiated women [58]. More recently, some studies are focused on the DIEP flap BR. The general recommendation remains that of delaying BR until after the completion of PMRT. A case-control study from the Memorial Medical Center in New Orleans, comparing a small series of patients receiving PMRT after BR with patients having DIEP flap BR alone, found substantially higher rates of fat necrosis (23% versus 0%), fibrosis or shrinkage (57% versus 0%), and contracture (17% versus 0%) in the irradiated cases, but no difference in the rate of flap revisions or dehiscence [62]. However, a recent study from Dundee found that postoperative RT did not significantly affect breast volume after immediate DIEP flap BR and that there was no difference in other complications between irradiated and non-irradiated cases [63].

15.5 Impact of Reconstruction on Delivery and Quality of PMRT

Conventional RT doses in the literature are around 50 Gy in 1.8–2 Gy daily (five times a week) fractions using tangential beams with a variable proportion of patients receiving boost doses to the scar of typically around 10–16 Gy. Altered fractionated schemes, such as hypofractionaction, are less used due to concern it may be associated with a higher risk of late side effects. However, Whitfield et al. reported that the rates of severe CC in patients receiving the common UK fractionation of 40 Gy in 15 fractions over 3 weeks appeared comparable to the conventional 5-week schedule, achieving a crude rate of 19.5% [64]. Modern RT modalities using an immobilization device and computed tomography to plan RT delivery are bound to minimize complications [61, 66]. In older series in which the RT technique was not optimal, patients experienced higher complication rates [67]. An important issue in BR is whether the immediate reconstruction impairs the delivery of PMRT. In fact, the reconstructed breast is different in size, shape, and firmness compared with the natural one and may cause technical problems with the design of the radiation fields. The thickness of the chest wall (CW) in a reconstructed breast may be not uniform, causing dosimetric inhomogeneities of dose within the treatment field, which might translate into higher risk of complications [68]. Because of the steep contour caused by the expander or prosthesis, the junction between the radiation fields can be less precise leading to regions of under- and overdosage (Fig. 15.4). In two follow-up studies from the MD Anderson Cancer Center, the authors examine the impact of an imme-

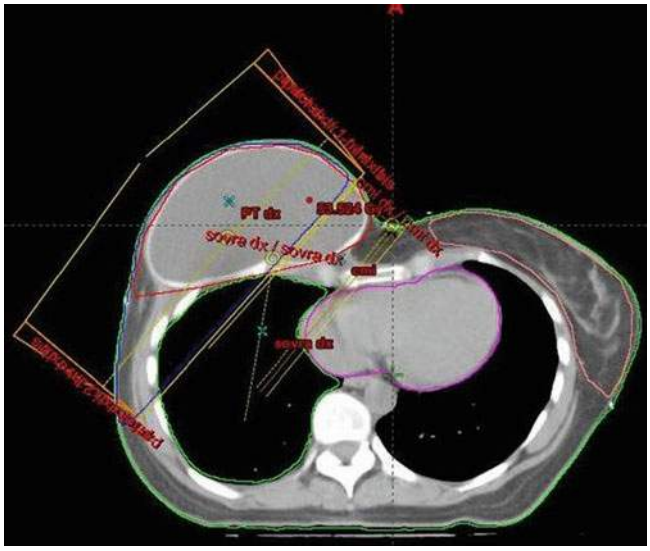

Fig. 15.4 Axial computed tomography slice showing the geometrical match between the medial electron beam field and the lateral photon tangential fields occurring over the steeply sloping contour of the reconstructed breast with permanent implant

diate BR on optimal coverage of the targeted areas including CW and internal mammary nodes (IMN) and avoidance of the lung and heart. In the first report published in 2005, only 4 of the 18 plans met the criteria for optimal treatment [69]. In 2006, a further report on 110 patients with immediate BR who were compared with a group of 108 patients without BR was published. The treatment plan was compromised in 52% of the patients with immediate BR compared with just 7% in the control group, 20% of them having a major compromise [11]. The largest compromises were observed in those with left-sided cancers. Delaying BR makes it easy to deliver RT and to spare the organs at risk, allowing the use of electrons [70]. By using the more sophisticated approach of intensity-modulated RT (IMRT), patients with immediate BR can achieve excellent local control with acceptable heart and lung doses, even when IMN are being treated, although doses to heart and lung will be higher (Fig. 15.5). IMRT allow to adequately cover the target volume in almost three quarters of patients [71]. The overall complication rate was extremely low in a group of patients, where IMRT was used in one-third of the cases, due to the improved dose homogeneity [37]. Regarding the compatibility of radiation and TE/PI reconstructions, prostheses do not interfere with dosimetric distribution as they are essentially tissue equivalent [72, 73]. Similarly, no dosimetric effects of saline-filling in the expanders with consecutively relevant changes in the prescribed dose were seen in dedicated studies [67]. TE should be kept at a constant volume during RT to avoid treatment setup changes and deviation from the prescribed radiation dose. With repeated dosimetric evaluations during the course of treatment, the expanders appear to go through minimal anatomical changes without any interference with the prescribed dose distribution [74]. The quantification of the radiation dose distribution in the vicinity of the metallic port of the TE and the determination of its potential contribution of the high complication rate are controversial and debated (Fig. 15.6). Two studies measuring the dosimetric changes around the metallic port showed an increased dose in the immediate vicinity of the metallic port due to the scattering of secondary electrons. As this increased dose does not reach the surface of the expander, it can hardly contribute to increase complication rate [75, 76]. On the other hand, the metallic port can attenuate the radiation beam and decrease the dose to the tissue, which lies in its direct shadow. However, in clinical situations, both the small size of the metallic port and the use of tangential opposed beams make underdosage quite small and acceptable [77]. Risk factors for increased complications related to radiation treatment have been identified throughout the studies. The use of a bolus is associated with more severe intensity of acute side effects and impaired cosmesis [78]. The choice of a customized bolus rather than a standard one may lead to a significantly better outcome. The subpectoral placement of the implant may be preferable over a subcutaneous placement because of the lower propensity for capsular contracture due to radiotherapy [79]. Textured implants are less likely to develop CC than smooth ones, since they allow minimal abnormal collagen deposition on their surface [80]. Using modern techniques and practice, the impact of BR reconstruction on timing of PMRT, target coverage, and dose at organs at risk has been recently investigated in a specialized breast multidisciplinary center [81]. The results were that reconstruction did not significantly increase the mean time to PMRT initiation (51 days reconstructed versus 45 days non-reconstructed) or the number of patients who initiated PMRT

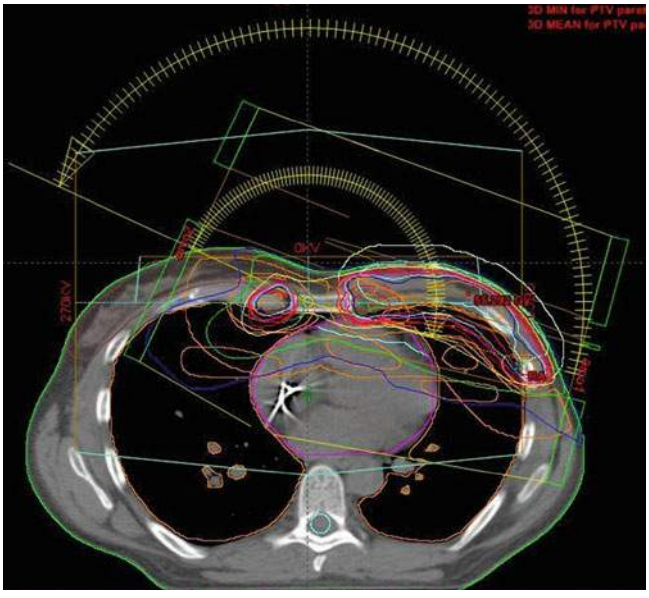

Fig. 15.5 Intensity-modulated radiotherapy plan on axial computed tomography image using inverse-planned multisegmental technique to treat left chest wall and bilateral internal mammary nodes

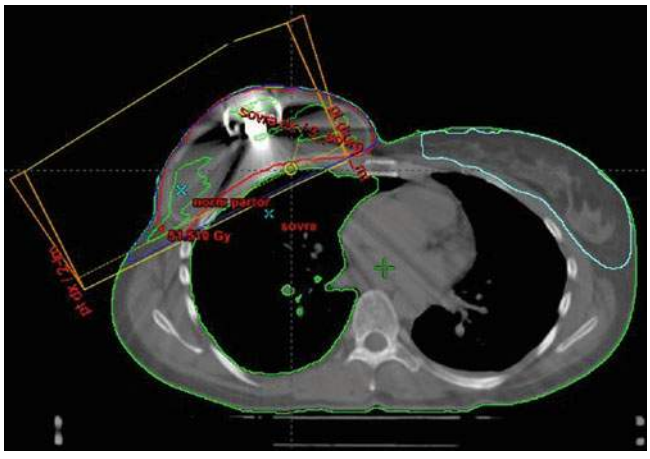

Fig. 15.6 Axial computed tomography slice showing the interference of high-Z metallic port with photon tangent beams of radiation fields in the tissue expander reconstruction

12 weeks, as usually recommended, of the last therapeutic intervention (96.0% versus 92.4%). There was no significant difference in the percentage of internal mammary node target coverage and on the mean ipsilateral lung V20 or the mean heart dose.

15.6 Reconstruction in Previously Irradiated Fields

BR in case of salvage mastectomy for local recurrence after breast conservative surgery and RT (QUART) faces the difficulty of being performed on previously irradiated and manipulated tissue. Prior RT to the chest may have a negative impact on the recipient vessels and predispose to vascular complications. In a study reviewing the outcome of flaps placed into an irradiated field, there is a significantly higher rate of intraoperative vascular complications (7.6% vs. 14.2%, $P < 0.003$) in the irradiated group (9.5% versus 17.3%, $P < 0.001$) and a trend toward higher anastomotic revision rates [82]. More recent studies show that the combination of flaps alongside breast prosthesis offers greater advantages in previously irradiated patients. In fact, several studies demonstrated that when an autologous flap is used with an implant for reconstruction of previously irradiated breast, the flap may protect the implant from the negative effects of RT. An interesting study by Michy et al. reported a series of patients treated with neoadjuvant RT in which immediate BR accomplished by LD with prosthesis showed a lower complication rate and fewer additional surgical revisions than either TRAM alone or a simple prosthetic implant [83]. Similar results are recorded in small series of patients undergoing salvage mastectomy plus LD-based immediate BR, where the incidence of CC was acceptable, being as high as 12–17% [84]. The use of TE alone is generally considered a contraindication in the case where previous RT has been administered. Few reports of abnormal concave and painful deformity of the CW were reported using a TE after QUART [85]. Conversely, the feasibility of implant reconstruction after QUART was described by Persichetti [86]. No significant difference in the total number of capsular contractures was observed between previously irradiated patients undergoing immediate BR with two-stage TE/PI and the non-irradiated group, but major complications occurred more frequently if RT had been delivered.

15.7 Aesthetic and Satisfaction Consideration

The cosmetic outcome of all BR deteriorated over time even though RT is not performed [87]. In fact, the irradiated reconstructed breasts show the worst aesthetic outcome that can be evident even after long periods of time. A worsened aesthetic result is observed with increasing tumor stage, bolus application, and earlier delivery of RT after the reconstructive procedure [88], even if the sequencing of PMRT did not affect the level of satisfaction, with sometimes a trend toward improved cosmetic outcomes when BR is delayed. Recent evidence demonstrated that autologous tissue flaps provide greater levels of aesthetic satisfaction relative to TE/PI reconstruction. Excellent/good cosmetic outcome is generally reported in more than 80% of patients undergoing PMRT and autologous BR, although aesthetic appearance and satisfaction are generally lower compared to non-irradiated cases [54]. A very recent review tried to evaluate the current available data regarding aesthetic outcomes, patient satisfaction, and BREAST-Q scores to better understand both the impact of PMRT and its timing relative to reconstruction on patient-centered outcomes to facilitate the informed consent and shared decision-making process [23, 53].

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Postmastectomy Radiation

16

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Postmastectomy radiation is a well-established component of breast cancer treatment in patients with advanced disease. Its role in patients with early disease continues to be the subject of much scientific inquiry and debate. Current consensus guidelines recommend administration of postmastectomy radiation in women with four or more positive axillary nodes or tumors greater than 5 cm [1–3]. It is not routinely recommended for patients with tumors ≤ 5 cm and node-negative disease. However, in the group of women with one to three positive lymph nodes and T1–2 breast cancers, the recently published Postmastectomy Radiation: An American Society of Clinical Oncology (ASCO), American Society for Radiation Oncology (ASTRO), and Society of Surgical Oncology (SSO) Focused Guideline Update has endorsed that while postmastectomy radiation reduces locoregional failure in this group, there are certain subsets who are likely to have a low risk of locoregional failure, and, therefore, the absolute benefit of postmastectomy radiation may be outweighed by the risks in this group [4]. In these cases, decisions regarding the administration of postmastectomy radiation require a multidisciplinary approach and are largely based on an individualized assessment of risk versus benefit. Factors to consider that impact risk recurrence are age 40–45 years, limited life expectancy due to older age or comorbidities, co-existing conditions that might increase the risk of complications, pathologic findings associated with a lower tumor burden (T1 tumor size, absence of lymphovascular invasion, presence of only a single positive node and/or small size of nodal metastases, or substantial response to neoadjuvant systemic therapy), and biologic characteristics of the cancer associated with better outcomes and survival, and/or greater effectiveness of systemic therapy. Beyond its use in advanced disease, postmastectomy radiation is also considered in cases where there is concern for local control as in positive margins after mastectomy.

16.1 The Basis for Postmastectomy Radiation

The utilization of postmastectomy radiation has evolved considerably over the past decades, in large part due to advances in technology as well as technique. Early trials of postmastectomy radiation included patients treated with antiquated techniques which lead to increased radiation doses to normal structures, including the heart and lung. Radiation exposure to these vital structures resulted in a greater than expected number of cardiovascular-related deaths [5, 6]. Cuzick et al. performed a meta-analysis involving 7941 women participating in trials of mastectomy with and without postmastectomy radiation initiated prior to 1975 [6, 7]. A greater than expected number of cardiovascular-related deaths were observed in the irradiated group. Although there was an overall improvement in breast cancer mortality in those patients who received postmastectomy radiation at 10 years, this effect was diminished by the excess number of cardiovascular-related deaths. The question of safety and efficacy of postmastectomy radiation led to a short-lived decline in its use in breast cancer treatment prior to the 1990s. However, with the advent of 3D conformal techniques, breath-hold techniques that limit the dose delivered to the heart, as well as the application of sophisticated technologies such as intensity-modulated radiation therapy and proton beam therapy to the treatment of breast cancer over the past decade, there has been a resurgence in the use of postmastectomy radiation, particularly in patients with 1–3 positive nodes.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_16

16.2 Evidence Supporting Postmastectomy Radiation

The advent of systemic therapy and emerging data showing a benefit in terms of systemic and local recurrence resulted in a rethinking of the potential role of postmastectomy radiation in the treatment of breast cancer. This led to the initiation of trials geared toward evaluating the potential benefits of postmastectomy radiation in the presence of systemic therapy. Two landmark randomized controlled trials were published in the late 1990s: the Danish trial and the British Columbia trial [8, 9]. In Danish Breast Cancer Cooperative Group Protocol 82b, premenopausal women with breast cancer were randomized to modified radical mastectomy and cyclophosphamide-methotrexate-fluorouracil (CMF) with or without postmastectomy radiation. A total of 1708 patients were enrolled from 1982 to 1989. The British Columbia trial enrolled premenopausal women with breast cancer undergoing modified radical mastectomy and receiving adjuvant CMF, and randomized them to postmastectomy radiation versus no radiation. A total of 318 node-positive women were enrolled. Both trials demonstrated an improvement in locoregional control as well as overall survival in the group of women treated with both chemotherapy and postmastectomy radiation. A 20-year follow-up of the British Columbia trial demonstrated a statistically significant reduction in the rate of locoregional and systemic breast cancer recurrence in the postmastectomy radiation group compared to chemotherapy alone [10]. Locoregional recurrence-free survival rates between the irradiated and non-irradiated group were 90% and 74%, respectively (risk ratio [RR] 0.36, 95% confidence interval [CI] 0.18–0.71, $p = 0.002$). Breast cancer-specific survival was 38% in the chemotherapy-alone group versus 53% in the postmastectomy radiation group (RR 0.67, 95% CI 0.49–0.90, $p = 0.008$). There was also an improvement in overall survival in the postmastectomy radiation group compared to chemotherapy-alone group, 47% versus 37% (RR 0.73, 95% CI 0.55–0.98, $p = 0.03$). All in all, survival outcomes were substantially improved. There were also low rates of cardiovascular-related deaths in both groups, 1.8% in the postmastectomy radiation group versus 0.8% in the chemotherapy-alone group ($p = 0.62$). Similarly, the Danish trial demonstrated a decrease in locoregional failure with chemotherapy and postmastectomy radiation versus chemotherapy alone, 9% versus 32% ($p < 0.001$), respectively. There was also an increase in disease-free survival as well as overall survival in the postmastectomy radiation group compared to chemotherapy alone—48% versus 35% ($p = 0.001$) and 54% versus 45% ($p < 0.001$) [8]. The Danish group also established these findings in postmenopausal women treated with tamoxifen alone versus tamoxifen and postmastectomy radiation. They found a decrease in locoregional failure—35% versus 8% ($p < 0.001$)—and an increase in disease-free survival at 10 years—24% versus 36% ($p < 0.001$) [11]. The Danish trial also aimed to identify groups with particular risk factors, which improved with the addition of postmastectomy radiation. High-risk groups identified were women with tumors greater than 5 cm (34% to 10%) and pectoral fascia invasion (45% to 6%) or skin invasion (34% to 8%). Altogether, these studies established postmastectomy radiation as an essential component of locoregional control in breast cancer. However, there remained questions as to specific subgroups within these trials that might have limited benefit from postmastectomy radiation, such as those with 1–3 positive nodes.

16.3 Effect of Nodal Status on Locoregional Recurrence

Several studies have investigated the influence of nodal status on locoregional recurrence. Among older "historical" trials of patients treated with mastectomy and no radiation, a study by Recht et al. including 2016 patients enrolled in randomized trials at 10 years found a 12.9% risk of locoregional recurrence in the group of patients with 1–3 positive nodes compared to 28.7% for patients with 4 more positive lymph nodes [12]. Katz et al. examined rates of locoregional recurrence in 1031 patients who had undergone mastectomy and adjuvant anthracycline-based chemotherapy [13]. Investigators found that 10-year rates of locoregional recurrence increased as the number of positive lymph nodes increased. Locoregional recurrence rates were 4%, 10%, 21%, and 22% for patients with 0, 1–3, 4–9, and ≥10 positive lymph nodes, respectively. Furthermore a tumor size greater than 4 cm or extranodal extension ≥ 2 mm predicted an increase in locoregional recurrence rate in excess of 20% ($p < 0.01$). These studies supported hypotheses that a greater locoregional recurrence risk was associated with increasing nodal involvement.

Current guidelines recommend postmastectomy radiation for locoregional control in patients with advanced primary tumors (T3/T4) or four or more positive axillary lymph nodes. In women with earlier-stage tumors (T1/T2) and 1–3 positive lymph nodes, the guidelines are less clear. The National Comprehensive Cancer Network (NCCN) guidelines recommend strongly considering postmastectomy radiation in this group [14].

16.4 Postmastectomy Radiation in Patients with T1-2 Tumors and 1-3 Positive Lymph Nodes

The most recent meta-analysis by the Early Breast Cancer Trialists' Collaborative Group provides convincing evidence that postmastectomy radiation reduces both recurrence and breast cancer mortality in women with 1–3 positive lymph nodes. This meta-analysis included individual data for 8135

women assigned to modified radical mastectomy with and without postmastectomy radiation [15]. In an effort to address previous concerns regarding the adequacy of axillary lymph node dissection in these trials, they further stratified the groups into patients having greater than or equal to 10 lymph nodes removed as having an axillary dissection, and those with less-extensive axillary surgery as having axillary sampling. There were 1314 women with axillary dissection and 1–3 positive lymph nodes. Of these, 1133 women were enrolled in trials in which systemic therapy was given. In this group, the administration of radiotherapy reduced locoregional recurrence. At 10 years, locoregional recurrence in the postmastectomy radiation group was 4.3% compared to 21% in the no-radiation group ($p < 0.0001$). Overall recurrence was significantly reduced (RR 0.68, 95% CI 0.57–0.82, $p = 0.00006$), as was breast cancer mortality at 20 years (RR 0.80, 95% CI 0.67–0.95, $p = 0.01$). These data provide strong evidence for the use of postmastectomy radiation in patients with 1–3 positive lymph nodes. However, with modern adjuvant hormonal, anthracycline-containing, and HER2 directed therapies, locoregional recurrence rates have decreased, making the risk reduction that would be observed in patients treated today likely much less than that seen in these trials. Recurrence rates reported in the group of patients with 1–3 positive lymph nodes in more modern retrospective series are below 5%. We looked at 1331 women with breast cancer treated at Memorial Sloan Kettering Cancer Center between 1995 and 2006. All patients had T1–2 tumors and 1–3 positive axillary lymph nodes. At 5 years, the locoregional recurrence rate was 3.2% in the postmastectomy radiation group versus 4.3% in the no-radiation group ($p = 0.57$). Risk factors for recurrence were age < 50 years and lymphovascular invasion [16]. This group, however, represents a selected group of patients in which those who were at higher risk were given postmastectomy radiation. That being said, these data illustrate that with adequate selection criteria, a low local recurrence rate can be achieved in patients with T1–2 tumors and 1–3 positive axillary lymph nodes, and that postmastectomy radiation may not be indicated for all patients in this group. A similar study by Buchholz et al. looked at locoregional recurrence rates in 1027 patients with T1–2 breast cancer and 1–3 positive lymph nodes treated in two different eras. The early era spanned from 1978 to 1997, the later era from 2000 to 2007. In the earlier cohort, postmastectomy radiation significantly reduced the rate of local recurrence at 5 years. Those patients receiving postmastectomy radiation had a recurrence rate of 3.4% compared to 9.5% in those without postmastectomy radiation ($p = 0.02$). This benefit in locoregional recurrence was not seen in patients treated in the later cohort. Five-year locoregional recurrence rates in the cohort treated between 2000 and 2007 were 2.8% without postmastectomy radiation and 4.2% with postmastectomy radiation ($p = 0.48$). Overall, the most significant factor predicting locoregional recurrence was the era in which the patient was treated [17].

16.5 Identification of a High-Risk Subgroup Among Patients with T1–2 Tumors and 1–3 Positive Lymph Nodes

Several studies have sought to identify a subgroup of patients among those with 1–3 positive lymph nodes who may benefit from postmastectomy radiation. Truong et al. looked at 821 women with T1–2 tumors and 1–3 positive lymph nodes who did not receive postmastectomy radiation and found that age less than 45 years, more than 25% positive lymph nodes, medial tumor location, and estrogen receptor negative status predicted for a higher risk of locoregional recurrence [18]. Wallgren et al. reviewed over 5000 patients enrolled in the International Breast Cancer Study Group trials and found that among patients with 1–3 positive lymph nodes, those with lymphovascular invasion, grade 3 tumors, and premenopausal status were at an increased risk for locoregional recurrence. These studies propose high-risk criteria that may be used to select women from the group of patients with 1-3 positive lymph nodes for postmastectomy radiation. Young age and the presence of lymphovascular invasion appear to be consistently reported as negative prognostic indicators across several studies [19–21]. Strong consideration of postmastectomy radiation in these subgroups may be warranted. The recommendation for postmastectomy radiation in high-risk women with 1-3 positive lymph nodes, as defined by the presence of young age and lymphovascular invasion, has been supported by the 2016 Postmastectomy Radiation ASCO/ASTRO/SSO Focused Guideline Update [22].

The management of the axilla and how this impacts postmastectomy radiation decision making in patients with 1-3 positive lymph nodes is also an issue of active debate. Several trials have addressed the management of the axilla in node-positive early-stage breast cancer; however, none of them have been able to be extrapolated to the 1–3 node-positive mastectomy population to answer the question of whether postmastectomy radiation is necessary after sentinel node biopsy alone. The American College of Surgeons Oncology Group Z0011 study demonstrated similarly favorable disease outcomes among patients having breast conservation with 1–2 positive sentinel nodes as those who received axillary dissection. These results are not applicable to mastectomy patients, leading to the question of whether or not postmastectomy radiation is indicated in women with T1–2 tumors and a positive sentinel node biopsy who do not undergo completion axillary lymph node dissection [23]. The International Breast Cancer Study Group 23–01 trial examined the use of completion axillary dissection vs. observation in women with T1–2 breast cancer and sentinel lymph node micrometastases, and demonstrated no difference in outcome [24]. A minority (9%) of the study population included patients treated with mastectomy. Whole-breast radiation was administered to those treated with breast-con-

serving surgery, but not to those treated with mastectomy. Finally, the European Organization for Research and Treatment of Cancer AMAROS trial compared axillary dissection versus axillary radiation in women with T1–2 breast cancer and 1–2 positive nodes. Investigators found comparable recurrence rates with a significantly lower incidence of lymphedema in the group undergoing axillary radiation. However, only 18% of the study population included women treated with mastectomy [25]. In view of the differences in patient populations between trials and the low representation of women treated with mastectomy, the question of whether or not postmastectomy radiation is indicated in all patients with few positive nodes who receive SLNB alone for axillary management remains unresolved. The ASCO/ASTRO/SSO Focused Guideline Update specifically highlighted this question as a current clinical dilemma and concluded that "clinicians may offer ALND for women with early-stage breast cancer with nodal metastases found on SLNB who will undergo mastectomy," although the quality of the evidence supporting this recommendation was "low" [4].

It is clear that a randomized controlled trial incorporating contemporary therapy is required to clarify the indications for postmastectomy radiation in early breast cancer. The SUPREMO (Selective Use of Postoperative Radiotherapy After Mastectomy) trial is a phase III randomized trial evaluating the role of postmastectomy chest wall radiation in intermediate-risk breast cancer that closed to recruitment in 2013. The study aimed to recruit 1600 women with stage II breast cancer following mastectomy and receipt of appropriate adjuvant systemic therapy to postmastectomy radiation versus no radiation. Results will likely shed more light on the benefit of postmastectomy radiation in the coming years. Investigators in Canada are also conducting a randomized trial of nodal radiation therapy/postmastectomy radiation in women with 1–3 positive nodes who have been treated with breast-conserving surgery or mastectomy (Tailor RT).

16.6 Postmastectomy Radiation for Positive Margins

Positive margins after mastectomy for breast cancer are often viewed as a risk factor for locoregional recurrence. However, there are limited supporting data for this view, as positive margins after mastectomy are relatively uncommon. Truong et al. examined outcomes among 94 patients with T1–2 tumors and negative lymph nodes who had positive margins after mastectomy. Forty-one patients received postmastectomy radiation, and 53 did not. At a median follow-up of 7.7 years, there was a non-significant trend toward an increase in locoregional recurrence among those patients who had not received postmastectomy radiation, 11.3% vs. 4.9% ($p > 0.1$). Locoregional failure rates approached 20% in women with positive margins and at least one of the following risk factors: age $\leq$ 50 years, T2 tumor size, grade 3 histology, or lymphovascular invasion [26]. Similarly Freedman et al. examined local recurrence in 34 patients with close or positive margins after mastectomy for a tumor smaller than 5 cm. All patients had 0–3 positive axillary lymph nodes and no postoperative radiation. The 8-year local recurrence rate was 18% and increased to 28% in those patients who were age $\leq$ 50 years [27]. Given the rarity of this finding and the scarcity of data on outcomes, the decision for postmastectomy radiation in patients with positive margins should be made in the multidisciplinary setting, with consideration given to the presence of the additional risk factors.

16.7 Postmastectomy Radiation After Neoadjuvant Chemotherapy

As the delivery of neoadjuvant chemotherapy (NAC) in patients with operable disease has increased, the administration of postmastectomy radiation poses a significant challenge. Particular areas of controversy include cases where NAC results in downstaging of axillary disease (ypN0) or a pathologic complete response (pCR) in the breast and axilla. It is unclear whether or not postmastectomy radiation may be withheld without increasing the risk of locoregional recurrence, and there are no prospective trials to date that might be used to guide decision-making. Studies looking at retrospective data have demonstrated that women at the highest risk of locoregional recurrence after NAC followed by mastectomy are those who have residual lymph node involvement at surgery and those who present with advanced clinical disease (stage III) [28, 29]. There may be a role for omission of postmastectomy radiation in patients achieving a pCR or complete nodal response (ypN0). Mamounas et al. looked at predictors of locoregional recurrence after NAC in a combined analysis of the National Surgical Adjuvant Breast and Bowel (NSABP) B-18 and B-27 neoadjuvant trials consisting of 3088 patients. In these trials, mastectomy patients (n = 1071) were not permitted to receive postmastectomy radiation, and so these data provided an opportunity to study predictors of locoregional recurrence. Chemotherapy regimen consisted of doxorubicin/cyclophosphamide alone or in combination with docetaxel. Independent predictors of locoregional recurrence among the mastectomy group were increasing clinical tumor size ($p = 0.009$) and positive clinical nodal status prior to NAC ($p = 0.001$) that converted to negative pathological nodal status with breast pCR ($p = 0.001$) [30]. These findings suggest that age, clinical/pathologic tumor features prior to NAC, and tumor response in the breast and axilla may be used to select patients who would benefit from adjuvant radiation following NAC. Nevertheless, prospective, randomized studies are

needed to optimize patient selection for postmastectomy radiation after NAC. NSABP B51/Radiation Therapy Oncology Group (RTOG) 1304 is a phase III clinical trial designed to evaluate the effect of chest wall and regional nodal irradiation on recurrence-free survival after mastectomy or breast conservation in patients who present with N1 disease and convert to N0 after NAC. Women in the mastectomy group will be randomized to observation vs. chest wall and regional nodal irradiation, and those undergoing lumpectomy will be randomized to whole-breast radiation vs. whole-breast and regional nodal irradiation. The anticipated completion date of this trial is 2028.

16.8 Complications of Postmastectomy Radiation

Chest wall radiation poses a risk of toxicity to the skin, underlying skeletal structures, heart, and lung. Radiation to the nodal fields also adds the risk of injury to the brachial plexus and axillary lymphatics, which may result in brachial plexopathy and lymphedema. Skin reactions and fatigue are the most commonly observed acute toxicities, and are usually self-limited, resolving within 4–6 weeks of treatment. The use of contemporary radiation techniques with 3D conformal radiation, intensity-modulated radiation therapy, and proton therapy has minimized high doses of radiation exposure to the heart and lungs, and subsequently reduced associated toxicities such as radiation pneumonitis, and late cardiac morbidity such as ischemic heart disease and myocardial infarction. Although excess cardiac morbidity was reported in earlier trials [7], more recent data demonstrate comparable cardiac morbidity among patients treated with and without chest wall radiation [31, 32]. The Danish Breast Cancer Cooperative Group 82b and 82c postmastectomy radiation protocols showed no excess cardiac mortality between radiated and non-irradiated groups with a median follow-up of 12 years [32].

Postmastectomy radiation can result in a number of complications after both autologous and implant-based reconstructions. These complications range from poor cosmesis to fat necrosis, fibrosis, and capsular contracture. Cordiero et al. examined 2133 implant reconstructions with 319 undergoing postmastectomy radiation and found that grade 4 capsular contracture occurred in 6.9% of irradiated implants compared to 0.5% of those not irradiated ($p < 0.01$). Furthermore, predicted implant loss rates at 12 years were 17.5% and 2% in the irradiated versus non-irradiated implants, respectively ($p < 0.01$) [33]. Despite these complications, 92% of patients in this study had good to excellent cosmetic results, and 94% would choose implant reconstruction again. In the setting of postmastectomy radiation, autologous reconstruction has been demonstrated to be an oncologically safe option with improved cosmesis [34]. Consideration should be given to performing autologous reconstruction as a staged procedure with tissue expanders being placed at the time of mastectomy and flap reconstruction after delivery of postmastectomy radiation. Garvey et al. examined complications in 625 autologous reconstructions and found 6.4% irradiated compared to 93.6% non-irradiated. Investigators found that while overall complication rates were similar for both irradiated and non-irradiated flaps, rates of fat necrosis were significantly higher in the irradiated group: 22.5% versus 9.2% ($p = 0.009$) [35].

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Part II

Oncologic Surgery

Oncologic Principles for Breast Reconstruction: Indications and Limits

17

Patricia A. Cronin, Virgilio S. Sacchini, and Jennifer L. Marti

17.1 Introduction

Breast cancer occurs in one of eight women in the United States [1]. Although many patients are candidates for breast-conservation therapy, the rates of mastectomy and of contralateral risk-reducing mastectomy have risen in recent years in the United States [2–9]. The vast majority of patients undergoing mastectomy are candidates for breast reconstruction. Accordingly, the number of breast reconstruction operations has also increased [5, 10]. Extensive literature clearly supports the advantages and oncologic safety of reconstruction after mastectomy. Reconstruction after mastectomy has been shown to be effective in restoring body image, improving quality of life, and reducing the psychological distress of mastectomy [11–15]. At the same time, immediate reconstruction has been found to be oncologically safe after mastectomy, even in cases of advanced breast cancer [16–18]. This has been conclusively demonstrated in multiple studies, including a meta-analysis by Gieni et al. [19], which confirmed no increased risk of local recurrence with immediate breast reconstruction (IBR) after mastectomy. Historically, fewer than 25% of U.S. patients underwent reconstruction after mastectomy [20, 21]. This rate has been increasing in recent years (37.8–63%), but there are persistent concerns with respect to access, as there can be many geographic variations [10, 22]. The overall increased pool of reconstructive patients may come from a number of sources. There is expanded insurance coverage as a result of enactment of the U.S. Women's Health and Cancer Rights Act and increased awareness of IBR following mastectomy due to state legislation that mandates surgeons inform patients about reconstruction [23].

Options for breast reconstruction include reconstruction with autologous tissue or with a tissue expander and implant. Autologous flap options include latissimus dorsi myocutaneous flaps, transverse rectus abdominus myocutaneous (TRAM) flaps, deep inferior epigastric perforator flaps, and gluteal artery perforator flaps. Implants contain either saline or silicone. An immediate one-stage reconstruction with an implant may be feasible; however, most patients undergo a staged procedure with a tissue expander to allow for interval expansion, followed by an exchange to a permanent implant. Autologous reconstruction may be difficult or complicated in patients who have undergone prior surgery at potential donor sites; who have medical comorbidities such as hypertension, diabetes, and chronic obstructive pulmonary disease; who are smokers; or who are at the extremes of body mass index.

17.2 Mastectomy Options

17.2.1 Skin-Sparing Mastectomy

Skin-sparing mastectomy (SSM) is the surgical approach to mastectomy that is most commonly utilized in conjunction with IBR. SSM followed by IBR has been shown to be superior to standard mastectomy and breast reconstruction in terms of aesthetic outcomes [24]. Acceptance of SSM, though initially hesitant due to concerns about local recurrence, has rapidly become routine practice. It involves excision of all breast tissue, including the nipple-areola complex (NAC) while preserving the breast skin envelope. Nipple-sparing mastectomy (NSM), in contrast, includes the preservation of the NAC. Of note in the literature, some authors have used the term SSM interchangeably with NSM to reference to a nipple-sparing technique.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_17

Concerns with regard to the oncologic safety of SSM arose from the possibility of residual breast tissue following this technique, leading to an increase in the risk of local recurrence. Residual breast tissue was found in 59.5% of SSM skin flaps in a study by Torresan et al. [25], which tried to address this question. However, three-quarters of mastectomy specimens in a population of predominately standard mastectomy have an anterior margin that is positive for breast tissue [26]. There are no randomized data comparing SSM to standard mastectomy with or without IBR. A meta-analysis of seven observational studies [27] that compared local recurrence rates in patients who had SSM and IBR with standard mastectomy with no reconstruction found no significant difference in the local recurrence rates between SSM and standard mastectomy (odds ratio [OR] 1.22, 95% confidence interval [CI] 0.85–1.74). A recent series with 10 years of follow-up demonstrated local and locoregional recurrence rates of 2.9% and 8.2%, respectively, in an oncologically unselected population of women undergoing SSM and IBR [28].

As SSM involves near maximal preservation of the skin of the breast, any tumor involvement of that skin (such as ulceration, fungation) in locally advanced breast cancer may limit the usage of this technique, but may not necessarily preclude it. Discrete areas of skin tethering do not necessarily translate to involvement of skin and are not a contraindication to SSM. Eighty-seven patients who had more-advanced tumors with stage IIB (T3 N0) or stage III disease who had SSM (n = 73) or NSM (n = 14) with IBR had no difference in 5-year local recurrence, disease-free survival, or overall survival compared to similar staged disease that had standard mastectomy [29]. Inflammatory breast cancer is a contraindication to SSM.

17.2.2 Nipple-Sparing Mastectomy

After SSM, patients may subsequently undergo nipple reconstruction. This requires an additional surgical procedure and tattooing, and, ultimately, many patients may never pursue this. Furthermore, results may be disappointing. Jabor et al. [30] reported a 14% rate of patient dissatisfaction after NAC reconstruction owing to loss of nipple projection, and the overall appearance and texture of the reconstructed NAC. Therefore, preservation of the NAC with a nipple-sparing mastectomy (NSM) may be desirable in some patients. Preservation of the NAC may enhance cosmetic outcome and offer psychological benefit, as the NAC plays an important role in the identification of a woman's body image [31]. NSM has higher reported rates of patient cosmetic satisfaction in patients [32, 33], and improved psychosocial and sexual well-being as compared to SSM [34].

When selecting a candidate for NSM, one must consider the risk of cancer involvement of the NAC, and the size and degree of ptosis of the breast [35]. Candidates for NSM include patients undergoing risk-reducing mastectomy and selected patients with ductal carcinoma in situ (DCIS) or invasive breast cancer [36]. In appropriately selected patients, only 12% will have tumor involvement at the NAC, precluding preservation [37, 38]. The factors associated with nipple involvement include tumors larger than 2–4 cm, a tumor-nipple distance of less than 2 cm, breast tumors overlapping more than one quadrant, grade 3 or undifferentiated cancers, stage III disease, human epidermal growth factor receptor 2 (HER2)/neu positivity, and an extensive intraductal component of greater than 25% [39–41]. With increasing adoption of the NSM technique, the boundaries of the criteria initially suggested for patient selection are being pushed, with some centers offering the technique to those with more advanced disease [42–45]. A study utilizing the National Cancer Institute's Surveillance, Epidemiology, and End Results database demonstrated a 202% increase in the use of NSM between 2005 and 2009 in the United States [46].

Patients with invasive cancer, with small tumors located in the periphery of the breast, have the lowest risk of NAC involvement. The lowest risk of NAC involvement occurs in tumors smaller than 2 cm, located at least 2.5 cm from the NAC. Tumors located within 2 cm of the NAC, or larger than 4 cm, were found in one report to have occult tumor present at the nipple in 50% of cases [47]. A pathologic analysis of 140 mastectomy specimens reported a 16% rate of NAC involvement with cancer. In all cases, the primary tumor was located within 2.5 cm of the NAC [48]. Many series of carefully selected patients have reported low rates of NAC involvement, ranging from 6% to 10% [35, 49, 50].

Identification of NAC tumor involvement precludes NAC preservation. Intraoperative pathologic assessment with frozen section of the retroareolar ducts can be useful to identify the presence of NAC tumor involvement at the initial surgery [37, 40, 51]. Dissection of the retroareolar ducts should be done sharply, as cautery can cause thermal damage to the NAC [51]. Coring of the nipple ducts may be facilitated by everting the nipple [51].

Multiple series with less than 3 years of follow-up have reported recurrence rates of 5% or less after NSM, comparable to rates of recurrence after SSM [32, 38, 52, 53]. Voltura et al. [53] reported a 5% recurrence rate at 24 months in patients with aggressive triple-negative tumors. Sacchini et al. [52] reported recurrences in only 2 of 123 patients undergoing NSM, with a median follow-up of 25 months. Recurrences did not occur at the NAC. Breast cancer occurred in two patients who underwent risk-reducing mastectomies, located in peripheral locations. In a review of 112 patients who underwent NSM and had tumors

located at least 2 cm from the nipple, 5% of patients had recurrence at a mean follow-up of 59 months [40]. Recurrences occurred in the chest wall, upper breast, and inframammary fold, with only one recurrence in the NAC [40].The location of these recurrences highlights the importance of considering the potential for elevated risk at the periphery of the breast after NSM, as access to the peripheral breast may be more difficult if a small periareolar incision is used.

Four thousand six hundred and sixty-three patients who had therapeutic NSM from eight studies that had comparative arms were included in a meta-analysis that looked at overall survival, disease-free survival, and local recurrence [54]. Seven of the eight studies had information on overall survival, and the weighted average risk difference was 3.4% in favor of NSM; this was not statistically significant. Similarly, five of the studies with data on disease-free survival and all eight studies with data on local recurrence also showed weighted average risk differences in favor of NSM—9.6% and 0.4%, respectively—which were also not statistically significant. The results of a subset analysis of studies with longer than 5 years of follow-up were similar to the overall group. A systematic review was also performed and reported in the same publication [54] to include studies that did not have a comparative arm. They divided the studies into their reported length of follow-up, <3 years, 3–5 years, and >5 years, and found weighted averages for local recurrence of 5.4%, 1.4%, and 11.4%, respectively.

The oncologic safety of NSM in *BRCA* mutation carriers is controversial, as breast tissue connects with the nipple and cannot be completely resected with NAC preservation. One pathologic analysis of mastectomy specimens of *BRCA* patients revealed that terminal ductal lobular units were present in 24% of the NACs and 8% of nipples [55]. In this study, occult NAC tumor involvement was 0% in risk-reducing specimens and 10% in therapeutic specimens. These rates are similar to those for non-*BRCA* mutation carriers. In a recent study of 177 NSM with IBR performed in 89 *BRCA* mutation carriers, there was no evidence of compromise to oncological safety at short-term follow-up [56]. Twenty-six patients had NSM for early-stage breast cancer and a contralateral prophylactic mastectomy. There were no local or regional recurrences in the 26 patients with breast cancer at a median follow-up of 28 months. Sixty-three patients had prophylactic NSM, eight of whom had an incidental diagnosis of DCIS. There were no newly diagnosed breast cancers in the 63 patients undergoing prophylactic NSM at a median follow-up of 26 months. Five patients (6%) required subsequent excision of the nipple-areola complex for oncological or other reasons. Studies with longer follow-up are needed before we can say with absolute certainty that NSM is an oncologically sound procedure in *BRCA* patients.

17.3 Reconstruction Options

17.3.1 Immediate Versus Delayed Reconstruction

Most patients undergoing mastectomy are candidates for immediate reconstruction. Immediate reconstruction offers multiple advantages, including one-stage surgery, better cosmetic outcome, and improved psychological state. In the only randomized controlled trial to date comparing immediate and delayed breast reconstruction, Dean et al. [57] reported increased psychological well-being with immediate reconstruction. Immediate reconstruction is associated with reduced psychiatric morbidity at 3 months [12]. Immediate reconstruction often achieves a better aesthetic result than delayed reconstruction, owing to preservation of the skin envelope and inframammary fold [58]. For patients who undergo delayed reconstruction, use of an autologous flap is preferable to use of an implant, as the process of tissue expansion required for an implant is difficult owing to skin stiffness, resulting in a suboptimal cosmetic result [59]. A combination of a tissue expander and an implant with a latissimus dorsi flap is another option for breast reconstruction.

17.3.2 Prosthetic Versus Autologous Reconstruction

Reconstructive options can be divided into two types, prosthetic and autologous [60, 61]. Prosthetic reconstruction is a simpler operative procedure and associated with a shorter postoperative recovery. The downside is that prosthetic devices have a shelf life and may need replacement at some point in time. Autologous reconstruction is a broad category that encompasses any technique where the breast is reconstructed from the patient's own tissue. This includes both pedicled techniques and more technically demanding free flap techniques. The length of stay is typically longer (3–7 days) after an autologous reconstruction than it is after a prosthetic reconstruction (1 day) [62, 63]. The advantage of autologous reconstruction is that when successful, the result is durable. The decision as to which to choose will be based on patient factors, surgeon factors, and oncologic factors.

17.4 Adjuvant Therapies

17.4.1 Radiation Treatment

Immediate reconstruction in patients who will undergo anticipated postmastectomy radiotherapy (PMRT) is controversial. The two main issues that raise concern are compromised

delivery of radiotherapy in the face of a reconstructed breast and the impact of radiotherapy on the long-term cosmetic result of the reconstruction [64].

Historically, delayed reconstruction has been recommended when PMRT is planned. Some still advocate this approach, owing to concerns of compromised delivery of radiotherapy in the presence of a reconstructed breast, whether a tissue flap or an implant [65–68]. Concerns include compromised delivery to the internal mammary lymph nodes, non-uniform radiotherapy delivery, underdosing of the chest wall, and increased radiotherapy dose to normal tissues with a breast reconstruction in place [64]. The evidence is conflicting. On the one hand, Motwani et al. [67] reported compromised delivery of radiotherapy in 52% of patients who had undergone immediate reconstruction, compared with 7% of controls. However, Koutcher et al. [69] found no compromised delivery of radiotherapy to the chest wall in most patients, with an excellent 30-month actuarial locoregional control rate of 97%. Owing to concerns of compromised radiotherapy delivery attributable to the reconstructed breast, a "delayed-immediate" reconstruction algorithm is advocated at The University of Texas MD Anderson Cancer Center for patients who will receive PMRT [70]. With this approach, a tissue expander is placed at the time of mastectomy and is deflated during adjuvant radiotherapy. Tissue expansion is performed after the completion of radiotherapy, and reconstruction with an autologous flap is performed 4–6 months thereafter [71]. In this series, the approach resulted in low complication rates, with tissue expander loss in 14% of patients. The recurrence rate at 32 months of follow-up was low, at 3% [72]. The complication rate with a "delayed-immediate" approach with subsequent flap reconstruction may be lower than that for a standard delayed flap reconstruction (26% vs. 38%, $p = 0.40$) [71]. Despite the concerns about radiation delivery that prompted development of the "delayed-immediate approach," many authors have reported acceptable recurrence rates and cosmetic outcomes with immediate reconstruction followed by PMRT [69]. In one retrospective review of 191 patients requiring PMRT who underwent TRAM flap reconstruction in either an immediate or a delayed fashion, the risk of locoregional recurrence was not significantly increased in the group undergoing immediate reconstruction (3.7% vs. 1.8%, $p = 0.65$) at 40 months of follow-up [73]. In a similar, more recent study by the same authors, 492 patients with stage II or III breast cancer who underwent modified radical mastectomy and chemotherapy followed by PMRT, and who underwent immediate or delayed TRAM reconstruction, showed no difference in local recurrence, disease-free survival, or overall survival, with a mean follow-up of 7.2 years [74]. Similarly, Wright et al. [75] retrospectively reviewed 104 patients who underwent exchange for a permanent implant prior to PMRT. Local control rates were excellent—0% at 5 years—and immediate reconstruction was not associated with an elevated risk of distant metastases or death. In contrast to these data, others have reported higher rates of locoregional recurrence among patients undergoing immediate reconstruction. Nahabedian et al. [76] retrospectively analyzed 146 patients who underwent immediate or delayed reconstruction after PMRT. Locoregional recurrence rates were higher in patients who underwent immediate versus delayed reconstruction (27% vs. 15%, $p = 0.04$). These data should be interpreted with caution because of the higher-than-expected rates of recurrence [76, 77]. As a result of these conflicting data, the safety of immediate reconstruction prior to PMRT remains controversial.

In addition to conflicting data about oncologic safety, there is also debate about the impact of reconstruction prior to PMRT on cosmetic outcomes. The main complications caused by radiation on the reconstructed breast include fat necrosis, impaired wound healing, contracture, fibrosis, volume loss, and architectural distortion [78]. There are data to support superior cosmetic results with delayed reconstruction compared with immediate reconstruction. Javaid et al. [78], in a systematic review of ten published reports of patients undergoing immediate and delayed reconstruction and PMRT, found a higher incidence of breast fibrosis and contracture with immediate reconstruction. Other groups have also reported lower rates of complications after delayed reconstruction. Adesiyun et al. [79], in a review of 113 patients who underwent immediate or delayed breast reconstruction with PMRT, reported a lower rate of complications in the delayed reconstruction group (32% vs. 44%, $p = 0.18$), although this difference was not statistically significant. The patients' general satisfaction with their cosmetic outcome was similar in the two groups (68%) [79]. Another group found no significant difference in complication rates with immediate or delayed reconstruction with TRAM flaps in patients who received PMRT, but the authors ultimately recommended delayed reconstruction because of the possible low power of the study [80]. Compared with the aforementioned studies, other groups have reported acceptable cosmetic results and complication rates with immediate reconstruction. A meta-analysis of 11 studies by Barry et al. [81] concluded that postoperative outcomes did not differ depending on whether reconstruction was performed before or after PMRT. Autologous flaps appeared to have superior outcomes. Postoperative complications such as fibrosis, contracture, infection, fat necrosis, and reoperation were lower with autologous flap reconstruction than with implant reconstruction [82]. Thus, if immediate reconstruction is pursued, many authors advocate reconstruction with an autologous flap over a tissue expander/implant to enhance cosmetic results [17]. Although many authors have reported superior outcomes with flap reconstruction compared with implant

reconstruction prior to PMRT, this does not necessarily imply that successful outcomes cannot be achieved with implant reconstruction. For example, Cordeiro et al. [83, 84] reported satisfactory aesthetic results with immediate tissue expander placement, followed by exchange for a permanent implant prior to radiotherapy. Aesthetic results were categorized as "good to excellent" in 90% of patients, with an implant loss rate of 9.1% [83].

17.4.2 Systemic Therapy

Adjuvant chemotherapy is frequently required for the systemic management of breast cancer. One concern often voiced is that IBR increases the time to adjuvant chemotherapy, which may have a negative impact on recurrence and survival rates. Xavier Harmeling et al. [85] in a systematic review of 14 studies of women who underwent mastectomy with and without IBR followed by adjuvant chemotherapy found what they classified as significant delays after IBR averaging 6.6–16.8 days in four studies. It is unclear whether a delay of this magnitude is of any clinical significance. The IBR in these studies was a mixture of prosthetic and autologous. One could hypothesize that free flap reconstruction could lead to the greatest delay in adjuvant therapy. Kontos et al. [86] examined 27 women who underwent free flap reconstruction in comparison to a control group that did not undergo any reconstruction. The mean time to initiation of chemotherapy was 15 days longer in the flap group than in the control group (55 days vs. 40 days). The initiation of chemotherapy was delayed past 6 weeks in 28.8% of the control group vs. 67% of the flap group and past 12 weeks in 3.6% of the control group vs. 7% of the flap group. The most common reasons for delay were flap and donor site complications. The optimal time of chemotherapy administration for patients with breast cancer is not precisely defined. Current guidelines recommend the initiation of adjuvant chemotherapy 4–12 weeks postmastectomy [87, 88].

17.5 Special Issues

17.5.1 Inflammatory Breast Cancer

In patients with inflammatory breast carcinoma, delayed reconstruction is recommended because of extensive skin involvement and a high risk of local recurrence [89]. The required resection of skin precludes an SSM. Furthermore, timely administration of radiotherapy is imperative, making the delay for healing after reconstruction undesirable. Therefore, reconstruction should be delayed in patients undergoing mastectomy for inflammatory breast cancer. This recommendation is reflected in the 2016 National Comprehensive Cancer Network guidelines [90].

There is a published series of 59 patients with inflammatory breast cancer who underwent a mixture of immediate (n = 7) and delayed reconstruction (n = 52). Complications occurred in 21 patients (35.6%), with one total flap loss (1.7%). Of note, the authors noted a survival benefit in those patients who underwent breast reconstruction compared to those with inflammatory breast cancer who did not, and this suggests a selection bias in those who underwent reconstruction, which is not surprising. Forty-nine patients (83.1%) were alive without evidence of recurrent disease at a median follow-up of 44 months. The immediate reconstructions in this cohort were performed for five patients who had an inflammatory breast recurrence previously treated with lumpectomy and radiation, and in two patients who required free flap insertion for chest wall coverage.

There are some small series that have reported success with immediate reconstruction. Chin et al. [91] performed a retrospective analysis of 23 patients with inflammatory breast cancer who underwent immediate (n = 14) or delayed reconstruction (n = 9). They reported similar rates of locoregional recurrence (29% vs. 33%, p not significant), suggesting no compromised oncologic outcome with immediate reconstruction. Importantly, these small studies do not offer sufficient statistical power to conclusively demonstrate the safety of IBR for patients with inflammatory breast cancer, and therefore it is not recommended.

17.5.2 Lipofilling

Lipofilling is a technique where the patient's own fat is harvested using a liposuction technique and then transplanted into the breast. The technique has been used for many years in aesthetic surgery, and it has been increasingly used for postmastectomy and postlumpectomy breast reconstruction. It can allow optimization of the aesthetic outcome and to help manage complications such as volume deficit, asymmetry, surface deformities, and scar retraction [92, 93]. Many studies have reported high surgeon and patient satisfaction with the aesthetic and functional outcome [94].

Two case-controlled series demonstrated no statistical difference between those who had lipofilling and matched controls. With mean follow-up post primary breast cancer surgery of 88 months and 32 months post lipofilling, Gale et al. found a 5.2% ipsilateral disease-related event rate compared to 4.5% in the control arm (p = 0.95) [95]. An earlier similar study by Petit et al. [96] showed similar results, but a subset analysis of those with ductal (DCIS) (n = 35) or lobular (LCIS) carcinoma in situ (n = 2) demonstrated increased local recurrence in the lipofilling patients and prompted further investigation. In a follow-up

retrospective case-control cohort study from the same authors [97] of 59 patients with DCIS or LCIS, the median follow-up was 63 and 66 months from surgery and 38 and 42 months from baseline, for the lipofilling and control groups, respectively; the 5-year cumulative incidence of local events was 18% and 3% ($p = 0.02$). Therefore, caution may be needed in offering this technique to those with DCIS or LCIS.

There have also been concerns with the effect that lipofilling may have on radiologic surveillance. In a meta-analysis of 1979 patients [94] who had lipofilling and had radiological follow-up, 323 (14.5%) had radiological abnormalities, of which 263 needed an interval radiologic exam and follow-up. Of those with radiological abnormalities, 60 proceeded to biopsy, representing 2.7% of the total sample reporting radiological outcomes. Biopsy results were not reported.

17.5.3 Partial Breast Reconstruction

Oncoplastic surgery represents the most recent option in the reconstructive armamentarium of breast and plastic surgeons. This option is frequently considered in women with a large tumor-to-breast ratio in order to complete their breast cancer resection rather than total mastectomy. The primary limitation of breast conservation is that 20–30% of women will have a contour abnormality, especially following the radiation therapy [98–100]. The ability to replace breast volume with autologous tissue for effective correction of volume loss has allowed breast-conserving surgery to be performed with good cosmetic outcomes [101, 102]. Mastopexy and reduction techniques can also be used to achieve this, sometimes combined with a similar contralateral procedure for symmetry [103]. It can be performed immediately or as staged procedures. The local rearrangement of breast tissue or insertion of a flap can interfere with subsequent interpretation of the margins if they need to be re-excised. The staged approach can assist in ensuring that the surgeon has achieved clear margins and is usually performed 1–2 weeks later and before radiation therapy.

17.6 Conclusions

Most patients are candidates for SSM and IBR after mastectomy. For patients who will require postmastectomy radiation, immediate reconstruction is controversial, but many authors have reported acceptable cosmetic results and locoregional recurrence rates with immediate reconstruction. Nipple-sparing mastectomy with IBR may be an attractive option for women for risk reduction or in selected patients with early-stage breast cancer.

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Surgical Margins in Breast-Conserving Surgery

18

Anita Mamtani, Adriana D. Corben, and Monica Morrow

18.1 Surgical Margins in Breast-Conserving Surgery

Breast-conserving therapy (BCT), consisting of removal of the primary tumor and whole-breast irradiation, is a well-accepted method for breast cancer management. Six prospective randomized trials, some with follow-up of 20 years or more [1, 2], have established without a doubt that there is no survival advantage for mastectomy compared to more limited surgery and radiotherapy (RT). Over time, rates of local recurrence after BCT have declined steadily and are now considerably less than 10% at 10 years of follow-up [3, 4]. However, the appropriate extent of surgical resection needed to maintain local control remains a matter of debate, and the lack of consensus regarding what constitutes an adequate negative margin results in multiple trips to the operating room for margin re-excision in a significant number of patients, and in unnecessary mastectomies in others [5]. The perception that a more widely clear margin enhances local control has been a major factor in the development of oncoplastic surgery.

The demonstration in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview that differences in local control between treatments of 10–20% at 5 years are associated with significant differences in breast cancer-specific survival at 15 years [6] has focused new attention on the importance of local control. For many years, disease burden as defined by margin status was felt to be the primary determinant of local control. Over time, it has become increasingly clear that both the underlying genetics of the tumor and the availability of effective systemic therapy are also critical components of local control. In this chapter, we will discuss techniques of margin evaluation, review the available data on the relationship between margin status and local control for invasive and intraductal cancer, and discuss the impact of molecular subtype of breast cancer and targeted therapy on local control outcomes.

18.2 Methods of Margin Evaluation

The term "margin" is often used without specifying the pathologic method used to determine the margin status. Unfortunately, there is no standard method of margin evaluation, nor are there a standard number of histologic sections which are examined from each margin surface. Margins can be evaluated using a radial method or a shaved method, or by shaving the walls of the lumpectomy cavity. These techniques are described below. Variations in pathology protocols take on considerable potential significance when clinicians assert that differences of 1–2 mm separate an adequate from an inadequate resection. This variability in margin processing is documented in a study which examined 91 consecutive excisional breast biopsies submitted from 50 different hospitals to a single university pathology department over a 2-year period [7]. Only 18% of reports described the technique (shaved or radial) used to evaluate the margins. Only 30% of the specimens were submitted in total; an unknown amount of tissue was submitted in 1%; and representative sections averaging 13 blocks per specimen were submitted in 69%.

18.2.1 Radial Margin Approach

The most common method of margin assessment is the perpendicular (or radial) margin technique, which allows for precise measurement of the distance separating the tumor from the inked margin. With this method, the specimen is received with at least two of the margins marked with clips or sutures to indicate specimen orientation. The six margins

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_18

of the specimen are inked in six different colors by the prosector. The ink should be applied gently to prevent artificial disruption. Excess ink should be carefully removed by pressing with gauze to reduce the problem of "running" ink. A brief application of acetone on the inked surface helps stain enhancement and reduces the problem of running ink. The inked specimen is sequentially cut into 0.2–0.3 cm slices perpendicular to its long axis so that the perimeter of each tissue slice contains few (two to four) margins identified by the different ink colors. Margins within 0.5 cm from the index lesion are best evaluated in their entirety, and the more distant margins can be representatively sampled (Fig. 18.1a). With this method, the pathologist can report the exact microscopic distance from the tumor to each individual margin and distinguish between a truly positive margin (tumor at ink) and a close margin. The extent of tumor at the margin or in close proximity to it can also be assessed.

The disadvantages of this method include running ink, imprecise margin orientation, and surface complexity. Running of the ink from the irregular fatty specimen surface to the inside of the specimen (Fig. 18.2a) and different color inks running into each other (Fig. 18.2b) occur frequently, leading to possible overinterpretation and false-positive margins. In addition, breast tissue is soft and may be artificially disrupted when the specimen is compressed to obtain a specimen radiograph or during gross examination. Flattening of the specimen in the gross room may distort the margin orientation. In one study, surgeons and pathologists disagreed on margin designation in 31% of cases when two marking sutures for orientation were placed in the operating room. The presence of the skin or muscle on the specimen did not reduce the disorientation rate, but the specimen size was highly correlated with this problem. Specimens less than 20 cm in size had a disorientation rate of 78% compared to only 20% for larger specimens ($p < 0.001$) [8]. In addition, it has been estimated that complete examination of a spherical 2 cm specimen would require in excess of 3000 sections [9]. Taking into account that the surfaces of breast excisions are highly complex and irregular, and that the surface area of some specimens is quite large, margin assessment using the inked radial margin method is highly subject to a sampling error.

18.2.2 Shaved Margin Approach

The use of shaved (en face) margins allows the oriented specimen to be inked entirely in one color as long as the prosector is able to maintain the proper orientation. This eliminates the problem of different colored inks running together. The margins are shaved off parallel to the outer surface of the specimen, similar to the process of peeling an orange, at a tissue depth of 0.2–0.3 cm (Fig. 18.1b). The shaved margins closest to the index lesion are submitted

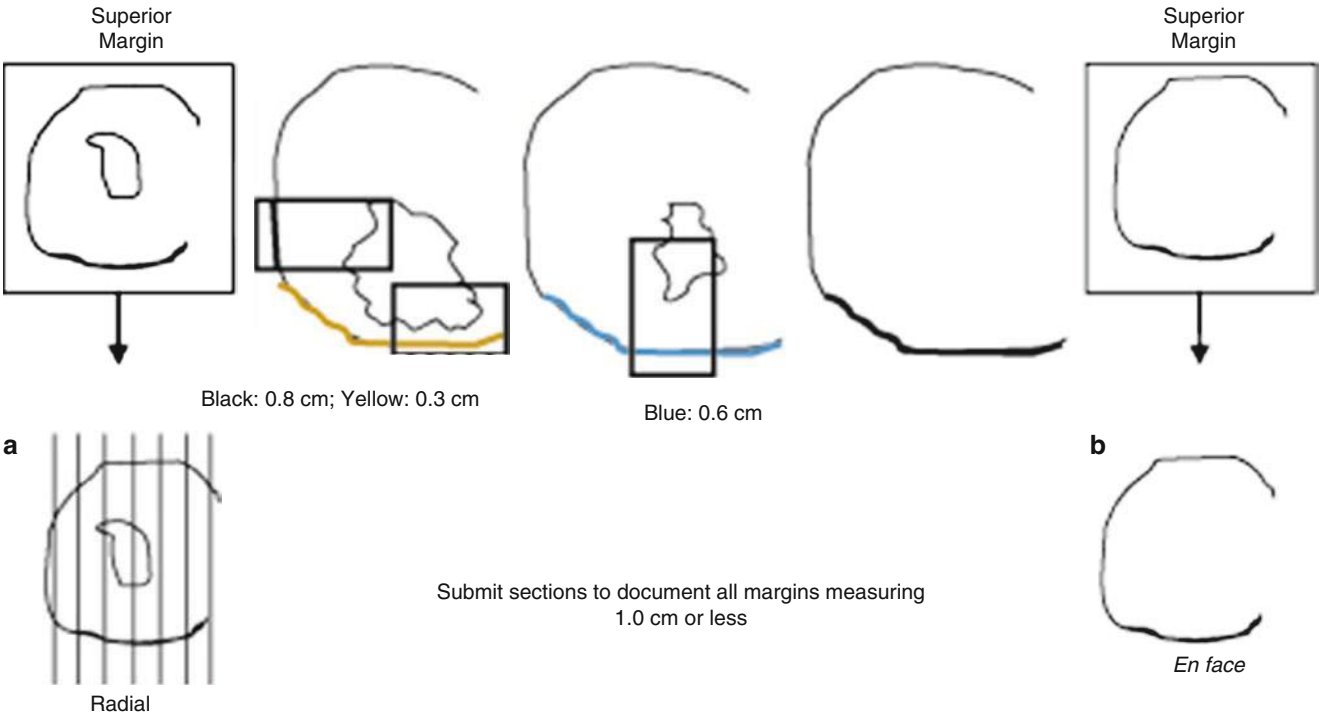

Fig. 18.1 (**a**) Radial (perpendicular) margin evaluation; (**b**) shaved (en face) margin evaluation. With the radial margin technique (**a**), each margin surface is inked a different color, and the distance from the tumor to the ink is reported for each margin. With the en face method (**b**), the entire surface is shaved, and no inking is needed

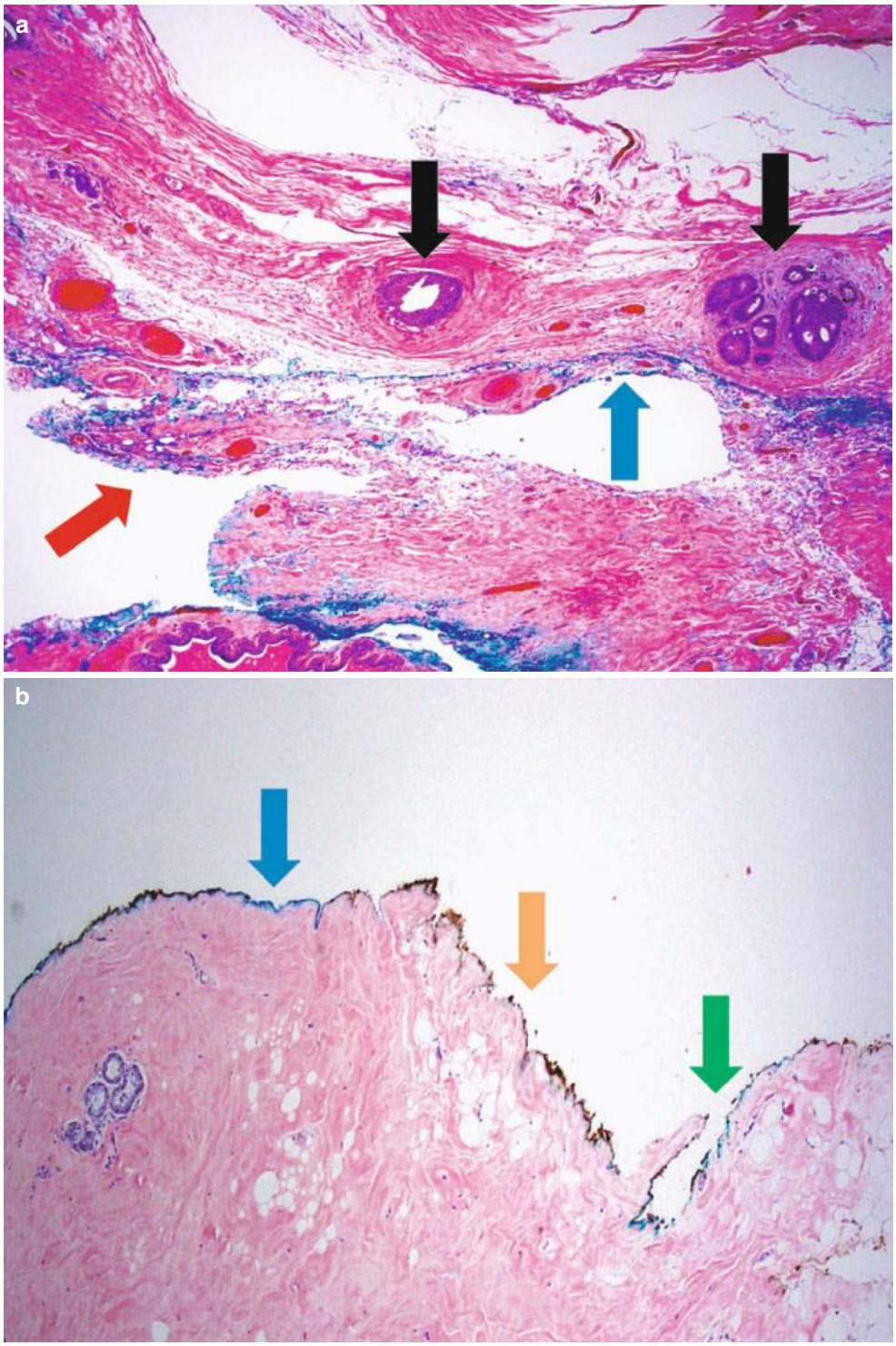

Fig. 18.2 Problems with radial margin assessment and inking. (**a**) "Running" of ink (blue arrow) inside a specimen challenges the interpretation of the distance of the ductal carcinoma in situ (black arrows) from the true inked resection margin (red arrow); (**b**) different color inks (orange, blue, and green arrows) "running" into each other create false interpretations of margin designation

entirely. The sections are embedded en face with the inked surface facing down so that the microscopic examination starts from the inner aspect of the tissue. With this method, a margin is reported as positive when tumor is present anywhere in the section. This means that malignant cells may be present within a 0.2–0.3 cm radius from the surgical margin or at the margin itself, but the exact distance of the tumor to margin cannot be assessed. If no tumor is identified, the margin is reported as negative. The advantages of this method include straightforward microscopic examination, no occurrence of ink problems, and the examination of a large proportion of the specimen's surface with relatively few sections. Although advantageous to the pathologist, this technique is extremely problematic for surgeons since it

substantially increases the number of margins which are called positive.

Guidi and colleagues [10] compared the shaved margin technique with the conventional radial margin method by evaluating 22 surgical specimens using both methods. The specimens were inked, and the margins were shaved and microscopically examined. The tissue was then extracted from the block, cut perpendicular to the inked surface, and re-embedded to assess the radial inked margin status. The study demonstrated that a negative shaved margin was highly predictive of a negative inked margin (98% concordance) but that the positive predictive value was much lower, with only 61% of the positive shaved margins being called positive (tumor at ink) by the radial margin technique. In a study at Memorial Sloan Kettering Cancer Center, Wright et al. reported that when the Department of Pathology switched from radial margin assessment to the shaved method, the positive margin rate increased from 16–49% even though surgical technique did not change [11].

18.2.3 Cavity Shave Approach

Evaluation of separate cavity shaves obtained by the surgeon provides a solution to margin assessment which combines the advantages of both the radial and the shaved margins. With this approach (Fig. 18.3), the surgeon resects the index lesion and then takes separate shaved margins from the surgical cavity. A separate anterior margin may or may not be submitted. The main specimen containing the tumor is received unoriented and does not necessarily need to be inked. The tumor is entirely sampled, including any prior biopsy site, and one or two representative sections of any grossly uninvolved breast tissue present are also submitted. Each shave specimen represents a margin (medial, lateral, inferior, superior, and posterior walls of the surgical cavity) and is received oriented with a suture or metal clip designating the final margin surface. Sometimes one specimen may consist of two adjacent margins. Each margin is inked on the side designated by the suture or clip, perpendicularly sectioned, and submitted either entirely or representatively in ten blocks (Fig. 18.3). In our institution, after an internal review, only six blocks are now being submitted per shave specimen unless any epithelial atypia or carcinoma is microscopically identified; the remaining margin is then entirely submitted. This technique allows for precise margin designation and accurate measurement of the margin width. These specimens are more easily handled by the prosector with limited manipulation of the tissue, and the use of a single color of ink contributes to a reduction of problematic artifacts of the prior described techniques. A significant increase in the number of blocks and slides is the main disadvantage of this method. A number of investigators have reported that this method significantly reduces the rate of re-excision for close margins [12–18]. These results are summarized in Table 18.1 [13–20]. Chagpar et al. recently conducted a prospective randomized trial comparing the cavity shave technique to standard perpendicular margin assessment of the lumpectomy. Two hundred thirty-five patients were intraoperatively randomized to cavity shave or no shave. A significantly lower rate of positive margins was observed in the cavity shave group compared to the no-shave group, 19% vs. 34%, respectively ($p = 0.01$), as well as a lower rate of second surgery for margin clearance (10% vs. 21%, $p = 0.02$) [19]. While this study clearly demonstrates a benefit for the shave technique, the 34% rate of positive margins in the control group is rather high, and the 19% positive margin rate after shaving is also high. In comparison, Moo et al. [20] reported a 15% rate of margin positivity with perpendicular margin assessment and an 11% positive margin rate with shaved margins in a study of 431 lumpectomies. A non-statistically significant trend toward a benefit of the cavity shave technique was seen for larger tumors and those with an

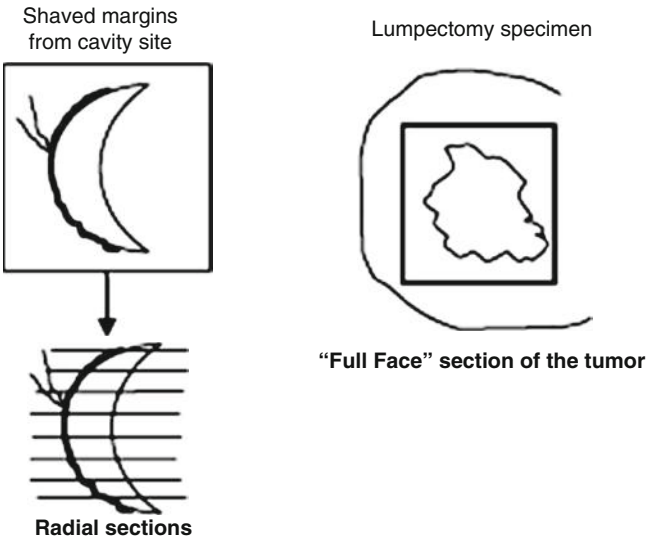

Fig. 18.3 Cavity shaved margin evaluation (one out of five shown). With the cavity margin evaluation method, the primary lumpectomy specimen is not inked. The outer surface of each of the individual margins is inked, and the distance to any tumor measured

Table 18.1 Impact of tumor cavity sampling on re-excision rates

		% positive margin		
Author	# cases	Cavity margins	Routine	*P*-value
Huston TL [13]	171	18	39	
Jacobson AF [14]	125	18	66	
Tengher-Barna I [18]	107	13	33	
Marudanaygam R [16]	786	5.6	12.5	<0.01
Rizzo M [17]	320	15	43	< 0.05
Kobberman A [15]	138	22	42	0.01
Chagpar A [19]	235	19	34	0.01
Moo TA [20]	555	11	33	<0.0001

extensive intraductal component. These findings suggest that the utility of the cavity shave technique may vary based on the rate of positive margins seen using the perpendicular technique. One issue with the routine use of cavity shave margins is the potential removal of larger amounts of breast tissue, resulting in a worsening of cosmetic outcome. Huston et al. compared rates of margin positivity and volume of tissue excised among patients undergoing lumpectomy with shaving of all margins ($n = 45$), lumpectomy with selective shaving of margins thought by the surgeon to be suspicious ($n = 77$), and lumpectomy alone ($n = 49$). The routine resection of additional margins resulted in the lowest reoperation rate, 17.7%, compared to 32.5% and 38.7% for selective re-excision and lumpectomy, respectively. The mean total specimen volumes were 129 cm^3, 46 cm^3, and 37 cm^3 for the three groups [13]. In contrast, Moo et al. [20] recently reviewed the institutional experience at Memorial Sloan Kettering Cancer Center with different margin evaluation techniques over time among a sample of six surgeons. Of 555 patients, 140 had radial margin evaluation, 124 had shaved margin evaluation, and 291 had cavity shave evaluation. Median volume of tissue excised was similar (55, 64, and 62 ml; $p = 0.24$), and four of six surgeons had lowest rates of positive margins when using the cavity shave method. Similarly, Rizzo et al. [17] found no difference in the volume removed with or without additional shaved margins if negative margins were achieved with the initial excision. However, in patients requiring re-excision, a smaller total volume of breast tissue was removed if the cavity shave technique was used initially ($p < 0.005$).

18.2.4 Other Issues Related to Margin Assessment

In addition to the method of margin assessment, other factors related to specimen processing may influence the margin width or whether or not tumor is identified at the margin. Graham et al. compared the measurement of the mean height of the lumpectomy specimen in the operating room by the surgeon to the measurement in the pathology lab in 100 consecutive specimens [21] and found a 46% decrease from a mean of 2.6 cm as measured by the surgeon to 1.4 cm as measured in pathology. This was independent of patient age, lesion type (mass vs. calcifications), or breast density. When compression devices were used for specimen radiography, the decrease was 54% compared to 41% when these devices were not used ($p = 0.0003$). These findings indicate that measurements of anterior and posterior margin distances on the primary tumor specimen are subject to significant variation depending upon how the specimen is handled.

There has been great interest in the development of adjunctive devices for intraoperative margin assessment, such as the MarginProbe™ (Dune Medical Devices, Framingham, MA), to guide the extent of resection. This device utilizes radio-frequency spectroscopy to detect the electromagnetic response of tissue, a property impacted by cell membrane potential, nuclear morphology, vascularity, and cellular integrity. These factors may differ between normal and malignant tissues, and allow the MarginProbe to provide the surgeon with "positive" or "negative" readings. A randomized prospective study of this device in a cohort of 298 patients with non-palpable malignancies compared to a control arm of 298 similar patients revealed a false-negative rate of 25% vs. 66% and a false-positive rate of 54% vs. 17%. Sensitivity of the device was 75%, and specificity was 46%. Re-excision rates were 19.8% vs. 25.8%, a 23% overall reduction in re-excision in the device arm. There was no significant difference in overall volume of tissue removed [22]. Similarly, a 62% reduction in re-excision with use of the MarginProbe was reported by Sebastian et al. [23] in a multicenter retrospective review of 165 consecutive cases using the device compared to 186 control cases.

Zysk et al. [24] performed a multicenter, prospective, blinded study of another handheld device employing optical coherence tomography (OCT) and interferometric synthetic aperture microscopy (ISAM) image processing to identify positive margins ex vivo in the operating room. Of 46 patients with 229 shave margin specimens, 8 patients had positive margins, among which 5 were correctly identified by the handheld OCT probe and potentially could have avoided re-excision. The false-negative rate was 38%, and the false-positive rate was 63%. An estimated mean additional tissue volume of 10.7 ml would have been removed due to false-positive readings. These studies emphasize that device cost, optimizing intraoperative efficiency and minimizing time under anesthesia, and baseline positive margin rates must all be considered in determining the utility of these devices in individual practices.

18.3 Margin Width and Local Recurrence: Invasive Cancer

Given the lack of standardization in pathology methods, it is not surprising that there has historically been little consensus regarding what constitutes an adequate negative margin. Azu et al. [25] surveyed a population-based sample of 318 surgeons identified from patients in the Surveillance, Epidemiology, and End Results (SEER) registry. Surgeons were asked "What negative margin width precludes the need for re-excision in a 60 year old with a 0.8 cm invasive cancer which is estrogen receptor (ER), progesterone receptor (PR), and HER2 negative?" and offered the options of tumor not touching ink, >1–2 mm, >5 mm, or >10 mm. No answer was endorsed by more than 50% of respondents. Only 11%

selected tumor not touching ink, 42% selected >1–2 mm, and 19% selected >10 mm. Similar variation exists among radiation oncologists. In a survey of 1133 North American and European radiation oncologists, 45% of those from North America endorsed a margin of tumor not touching ink, while those in Europe favored more widely clear margins, with greater than 5 mm being the most common answer, selected by 29% [26]. The net result of the lack of consensus on what constitutes an adequate negative margin is the frequent performance of re-excision to obtain more widely clear margins. Morrow et al. [5], reporting on a population-based sample from the SEER registry of 800 women attempting BCT, observed that although the procedure was successful in 88%, 22% underwent a re-excision. Other studies report a wide variation in re-excision rates ranging from 6% [16] to 49% [27], with the majority noting re-excision in 15–30% of patients [13, 28, 29].

The prospective randomized trials that established the safety and efficacy of BCT [1, 2, 30–33] do not provide much guidance on the margin question since only the NSABP B06 trial used a microscopic definition of a negative margin, which was tumor not touching ink [1]. Although the other trials are often perceived as requiring more widely clear margins, they relied upon gross margin definitions, making the actual margin width impossible to assess. Similarly, although a trial by Veronesi et al. which randomized patients to quadrantectomy or a more limited tumorectomy demonstrated a lower rate of local recurrence in the quadrantectomy group (2.2% vs. 7.0%), this study also relied on gross margin assessment. The tumorectomy was performed with a gross margin of 1 cm, but in a subset of patients who had microscopic margin evaluation, 16% of those in the tumorectomy group had positive margins [34]. The uncertainty over margin status in this trial makes it impossible to conclude that a larger quadrantectomy type procedure is associated with a lower rate of local recurrence than a more limited resection with negative inked margins. The authors have been unable to identify any prospective randomized trials which directly compare outcomes between microscopically verified margins of differing widths.

Recently, Houssami et al. updated results of a methodologically rigorous meta-analysis of the relationship between local recurrence and margin distance. The meta-analysis included 33 studies with 28,162 patients and 1506 local recurrences with a median follow-up of 79.2 months. The relationship between positive margin status and local recurrences was verified, with an odds ratio (OR) for local recurrence of 2.44 for positive or unknown vs. negative margins. No relationship between margin width, defined as 1 mm vs. 2 mm vs. 5 mm, and local recurrence was identified [35]. Although a non-statistically significant numeric trend for a benefit of more widely clear margins was seen in some models, this did not persist after adjustment for other factors such as the use of a radiation boost or receipt of endocrine therapy. This review included information on a large number of factors relevant to local recurrences, such as the date of study enrollment, patient age, use of radiation including a boost, and pathologic tumor features such as lymphovascular invasion (LVI), extensive intraductal component (EIC), and tumor grade, and provides the most convincing evidence to date that margins more widely clear than tumor not touching ink do not have a major impact upon local control in the era of modern multidisciplinary therapy.

Table 18.2 Local recurrence in randomized trials of mastectomy versus breast-conserving surgery

		% local recurrence	
Trial	Follow-up (years)	Breast-conserving surgery	Mastectomy
Institut Gustave-Roussy [30]	15	9	14
Milan 1 [2]	20	9	2*
NSABP B06 [1]	20	14	10
Danish [31]	6	3	4

NSABP National Surgical Adjuvant Breast and Bowel Project
*$P < 0.0001$

Although this may seem counterintuitive, it becomes much more logical if one considers that even mastectomy does not entirely eliminate the problem of local recurrence. In the initial randomized trials comparing BCT to mastectomy in which at least grossly negative margins were required, only the Milan study [2], which included T1 cancers treated with radical mastectomy, showed a statistically significant reduction in local recurrence for mastectomy compared to BCT (Table 18.2) [1, 2, 30, 31]. This, coupled with the observation from the EBCTCG overview [6] that even with the addition of postmastectomy RT, the incidence of local recurrence is higher in node-positive women than it is in node-negative women, indicates that local recurrence may be due to either excessive tumor burden or aggressive biology. The failure to observe a decrease in local recurrence with surgical margins more widely clear than tumor on ink suggests that once disease burden is reduced to this level (i.e., no clinically detectable cancer), tumor biology is the main determinant of local control.

18.4 The Influence of Histology on Margin Width

Variations in the growth patterns of different histologic types of cancers raise the possibility that the same margin width may not be appropriate for all histologic tumor types. Infiltrating lobular cancers are frequently multifocal and grow as single cells in linear strands separated by normal stroma [36], raising the possibility that margins negative only by tumor not touching ink might be associated with a

significant residual tumor burden. However, clinical studies do not document a higher rate of local recurrence after BCT for lobular cancers when compared to ductal cancers [37–39], suggesting that if negative margins are obtained, the growth pattern is irrelevant. Galimberti et al. [40] analyzed 382 patients with pure infiltrating lobular carcinoma treated with BCT to determine if rates of local control differed among those with margins less than 1 cm compared to 1 cm or greater. The local failure rate was 4.6% for the less than 1 cm margin group compared to 3.7% in the 1 cm or greater group, leading the authors to conclude that more widely negative margins were not necessary for patients with infiltrating lobular carcinoma.

The other group of concern is patients with an EIC in association with their invasive cancer. Early studies performed prior to the routine inking of margins suggested that an EIC was associated with a higher rate of local recurrence in patients undergoing BCT [41]. Holland et al. documented that approximately 30% of patients with EIC-positive cancers had prominent intraductal carcinoma more than 2 cm beyond the primary tumor, compared to only 2% of patients with EIC-negative tumors [42], indicating that a substantial number of patients with an EIC treated by excision to grossly negative margins have a heavy residual tumor burden. When patients with an EIC are excised to negative inked margins, rates of local recurrence are not increased compared to patients without an EIC [43, 44]. However, Faverly et al. have demonstrated that low- and intermediate-grade ductal carcinoma in situ (DCIS) often grows with gaps between the DCIS lesions, although these gaps are usually less than 5 mm in size [45], suggesting that margins negative by only tumor not touching ink could be associated with a significant residual tumor burden. The issue of margins and DCIS is discussed in detail later in this chapter. The presence of an EIC in association with invasive cancer indicates it may be prudent to obtain a margin of at least 2 mm if large amounts of DCIS are in proximity to the margin. In the case of both infiltrating lobular carcinoma and an EIC, clinical judgment remains important. A single duct of DCIS or microscopic focus of lobular carcinoma in close proximity to the margin is unlikely to be associated with a heavy residual tumor burden, while a large area of tumor immediately adjacent to a margin is associated with a greater risk of residual disease [46] and should prompt re-excision.

18.5 Other Factors Influencing Local Control in Invasive Cancer

It is important to recognize that a "negative" margin does not indicate that there is no residual tumor in the breast. Holland et al. [47], in a landmark study using serial subgross sectioning to evaluate the remaining breast tissue in 264 mastectomy specimens from patients with clinically unifocal cancers 4 cm or less in size, showed that only 39% of cases had no additional tumor beyond the index cancer. In 20% of cases, the tumor foci were within 2 cm of the index tumor, and in 41% of cases, the tumor foci were more than 2 cm from the primary tumor (Fig. 18.4). From a practical point of view, a negative margin indicates that the residual tumor burden in the breast is low enough that it is likely to be controlled by RT. The role of RT in maintaining local control is well documented in the EBCTCG overview [6]. At 5 years, the absolute incidence of local recurrence in node-negative women receiving RT was 16% lower than in those not receiving RT, while for node-positive women, a 30% reduction in isolated local recurrence was seen. These reductions in local recurrence at 5 years translate to 15-year survival gains of 5% and 7% in node-negative and node-positive women, respectively. Bartelink et al., in a prospective randomized trial examining the benefits of a boost dose of RT on local control, demonstrated statistically significant reductions in local recurrence with the addition of a boost in women of all ages [48]. While the role of RT in local control has long been recognized, the impact on local control of both improvements in systemic therapy and its widespread use are less well recognized.

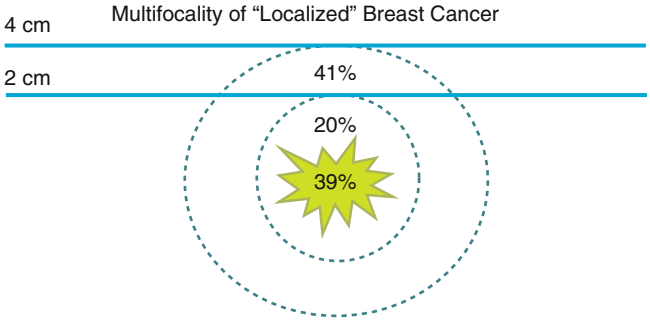

Fig. 18.4 Distribution of cancer identified on serial subgross sectioning of 264 mastectomy specimens with clinically localized tumors less than 4 cm in size. Only 39% of clinically localized cancers had all malignant cells confined to the tumor mass. In 20%, the residual cancer was within 2 cm of the primary, and within 4 cm in the remainder. Data from Holland R et al. [47]

The majority of women with invasive breast cancer now receive some form of adjuvant systemic therapy in addition to surgery and RT. Both endocrine therapy and chemotherapy significantly reduce the likelihood of local recurrence after BCT. In the NSABP B14 trial, in which node-negative, ER positive women were randomized to tamoxifen citrate or placebo, the 10-year rate of in-breast recurrence was reduced from 14.7% in the placebo group to 4.3% in the tamoxifen group [49]. In the NSABP B13 trial, node-negative ER negative women were randomized to chemotherapy or a no-treatment control group [49]. At 8 years, local recurrence was seen in only 2.6% of those receiving chemotherapy

compared to 13.4% of controls. In a report of 3799 node-negative women participating in 5 NSABP trials of adjuvant systemic therapy, the cumulative incidence of in-breast recurrence at 12 years for those receiving adjuvant therapy was only 6.6% [3]. Since the time that these trials were conducted, our ability to target therapy has improved, and this will undoubtedly result in a further decrease in local recurrence rates. For example, in the randomized trials that established the efficacy of adjuvant trastuzumab, the addition of trastuzumab to chemotherapy resulted in a 50% decrease in locoregional recurrence (LRR) compared to treatment with chemotherapy alone [50]. Similar results have been reported in ER positive, node-negative patients when systemic treatment is selected on the basis of the Oncotype DX (Genomic Health, Redwood City, CA) score. Although this score was developed to predict the risk of systemic recurrence, Mamounas et al. [51] demonstrated that in the absence of systemic treatment, patients with high-risk Oncotype DX scores had an 18.4% risk of LRR compared to those with low-risk scores who had a 10.8% risk. The addition of tamoxifen, appropriate treatment for those with low-risk scores, reduced the incidence of LRR by more than 50% to 4.3% in the low-risk group. In contrast, a much more modest reduction in LRR from 18.4% to 15.8% was seen in the high-risk group. However, when chemotherapy was added, the LRR rate in the high-risk group decreased to 7.8%.

The importance of biology and targeted therapy is further supported by the emerging literature on the impact of tumor subtype on local recurrence after BCT or mastectomy. Both Millar et al. [52] and Nguyen et al. [53] have demonstrated that the rate of local recurrence after BCT varies among the intrinsic subtypes of breast cancer as approximated by ER, PR, and HER2 status. In both studies, the lowest rates of local recurrence at 5 years were seen among the ER positive, PR positive, HER2 negative (luminal A-like) group, and the highest rates were among the triple-negative (basal-like) and ER negative, HER2 positive patients in the absence of adjuvant trastuzumab. However, ER, PR, and HER2 status are not indicators of the need for more widely clear margins since the same pattern of an increased risk of chest wall recurrence among ER negative patients, regardless of HER2 status, was observed in a retrospective analysis of the Danish Breast Cancer Group randomized trials of mastectomy with or without RT [54]. A meta-analysis by Lowery et al. [55] evaluated 12,592 patients from 15 studies, of whom 7174 were treated with BCT and 5418 with mastectomy. Patients with ER and/or PR positive tumors had a lower risk of local recurrence than HER2 positive tumors (relative risk 0.34) and triple-negative tumors (relative risk 0.38). Patients with HER2 positive tumors had a higher risk of local recurrence than triple-negative tumors (relative risk 1.44). As previously noted, the addition of trastuzumab to chemotherapy has been shown to reduce the risk of local recurrence in HER2 positive patients [50], indicating that targeted therapy is a major contributor to local control. Kiess et al. [56] validated a significant decrease in LRR in patients treated with BCT by the addition of adjuvant trastuzumab. Among 197 patients who were treated with BCT immediately before and after adjuvant trastuzumab became available, 3-year rates of LRR fell from 10% to 1%. Pilewskie et al. [57] addressed the question of whether local recurrence varied with margin width in triple-negative breast cancer. Among 535 triple-negative cancers treated with BCT, 71 had negative margins ≤2 mm, and 464 had negative margins >2 mm. A cumulative incidence of local recurrence at 5 years of 4.7% with margins ≤2 mm and of 3.7% with margins >2 mm was observed, a difference which was not significant after controlling for use of chemotherapy and tumor size. In aggregate, this information validates the importance of systemic therapy in local control, indicates that factors other than disease burden are key determinants of local control, and provides evidence that margins more widely clear than no tumor on ink are not indicated even for high-risk tumor subtypes.

18.6 Margins After Neoadjuvant Chemotherapy

Prospective randomized trials have demonstrated that the use of preoperative (neoadjuvant) chemotherapy allows for BCT in patients who would have required a mastectomy if surgery was performed initially [58, 59]. A meta-analysis of randomized trials of neoadjuvant vs. adjuvant chemotherapy demonstrated no increase in the risk of LRR after neoadjuvant therapy as long as surgery was performed (hazard ratio 1.12, 95% confidence interval (CI) 0.92–1.37, $p = 0.25$) [60]. However, in the NSABP B18 trial, after 9 years of follow-up, the patients who required chemotherapy to downstage to lumpectomy ($n = 65$) had a 15.9% rate of in-breast recurrence compared to 9.9% for those who were lumpectomy candidates at presentation ($p = 0.04$) [61]. This finding raises the possibility that margins need to be considered somewhat differently in the setting of neoadjuvant therapy.

The purpose of neoadjuvant therapy is to allow the removal of a smaller amount of breast tissue than would be necessary if initial surgery was performed. Breast cancer shrinkage in response to neoadjuvant therapy has been shown to occur in two different ways: concentrically, and in a honeycomb or buckshot pattern. Magnetic resonance imaging (MRI) is the most reliable means of assessing both the amount of residual tumor and the pattern of shrinkage [62]. This was validated in a recent retrospective review by Jochelson et al. [63] of 111 consecutive patients receiving neoadjuvant therapy. MRI alone correctly predicted suitability for BCT in 88% of cases, with the addition of mam-

mography increasing accuracy to 92% due to identification of malignant-appearing calcifications in cases with no residual enhancement on MRI. In patients with a pathologic complete response or concentric tumor shrinkage, consideration of margin width does not differ from that in the primary surgical setting. In patients with the honeycomb pattern, determination of the appropriate extent of resection is more difficult. Investigators from The University of Texas MD Anderson Cancer Center have shown that on multivariate analysis, a honeycomb pattern of response, residual disease >2 cm, and clinical N2 or N3 disease were statistically significant predictors of local recurrence after BCT [64]. However, whether the higher rate of local recurrence observed with the honeycomb pattern of shrinkage can be reduced with more widely clear margins is uncertain, as this pattern of shrinkage may be a reflection of biologic properties of the tumor which influence local recurrence just as they do in the primary surgical setting. Evidence supporting this concept comes from a study of 149 patients examining the impact of ER, PR, and HER2 status on local recurrence after neoadjuvant therapy [65]. The highest rate of local recurrence was seen in the ER-, PR-, and HER2-negative group, just as was seen in studies examining the significance of these markers in the primary surgical setting [52, 53]. A recent update from the multicenter randomized phase 3 GeparTrio, GeparQuattro, and GeparQuinto trials from 2002 to 2010 of 6134 women provides continued evidence for the feasibility of BCT for patients with initially multifocal/multicentric tumors who receive neoadjuvant therapy, if a pathologic complete response or tumor-free margins are obtained. BCT was performed in 3834 of these cases after neoadjuvant therapy, with local recurrence seen in 5.6% at 3-year follow-up [66]. In the absence of definitive information on the benefit of more widely clear margins after neoadjuvant therapy, it seems prudent to follow the current joint guideline of the American College of Surgeons, American College of Radiology, and College of American Pathologists, which suggests that if viable tumor is present scattered throughout the lumpectomy specimen, even if it is not actually on the margin, re-excision should be considered [67].

18.7 Summary and Conclusion on Invasive Cancer: Consensus Guidelines

The failure of mastectomy, the most widely clear margin which can be obtained in the breast to achieve rates of local control approaching 100%, is clear evidence that disease burden is not the only factor determining local control. Evidence that margins more widely clear than tumor not touching ink decrease local recurrence in patients receiving whole-breast RT is lacking, and the underlying biology of the tumor and the availability of targeted therapy appear to be major determinants of local control.

In recognition of the many factors impacting local control, a multidisciplinary panel was convened in 2013 by the Society of Surgical Oncology (SSO) and American Society for Radiation Oncology (ASTRO) to establish consensus guidelines on margin width for patients with invasive cancer undergoing BCT. The meta-analysis of Houssami et al., discussed previously, as well as other published literature, formed the basis for the group's deliberations. The group concluded that while positive margins, defined as ink on invasive tumor or DCIS, were associated with an increased rate of local recurrence, evidence that margins more widely clear than no ink on tumor reduce the risk of local recurrence is lacking, and that the routine use of re-excision to more widely clear margins is not indicated. This conclusion applies independent of age, histology, biologic subtype, the presence of an EIC, or the now-uncommon scenario of no planned adjuvant systemic therapy. The consensus statements are summarized in Table 18.3 [68]. These guidelines have been endorsed by the American Society of Clinical Oncology (ASCO) and the American Society of Breast Surgeons (ASBrS) in addition to the SSO and ASTRO. It is hoped that their adoption will decrease re-excision rates and lower healthcare costs [68]. This does not mean that in some circumstances a more widely clear margin is not appropriate; it does mean that the routine use of unnecessarily large surgical resections or mandatory re-excisions to obtain a more widely clear margin in all patients should be abandoned.

18.8 Margin Width and Local Recurrence: DCIS

All of the caveats regarding the lack of a standardized approach to margin assessment apply to DCIS as well as invasive cancer. In addition, because DCIS is not clinically detectable in the overwhelming majority of cases, limited sampling of margin specimens is particularly likely to underestimate the extent of DCIS. A potential discontinuous or multifocal morphology seen with DCIS further complicates this assessment. Due to these variations and the limited use of adjuvant endocrine therapy in DCIS, the conclusions of the 2013 consensus guidelines for invasive cancer cannot be immediately extrapolated to pure DCIS [68]. Three of the randomized trials evaluating the benefit of RT in DCIS used a margin definition of tumor not touching ink [69–71], while 20% patients in the SweDCIS study [70] had positive or unknown margins. Just as in the case of invasive cancer, level 1 evidence from randomized trials on the effect of increasing margin width on local recurrence is lacking. Low rates of local recurrence are seen with long-term follow-up in studies

Table 18.3 Society of Surgical Oncology and American Society for Radiation Oncology consensus guidelines on margins for BCS with RT in stage I and II breast cancer

Positive margin: ink on invasive cancer or DCIS A positive margin confers a twofold increase in risk of IBTR		
Clinical question	Recommendation	Level of evidence
Can the use of **radiation boost, systemic therapy, or favorable tumor biology** mitigate the two-fold increased risk of IBTR with a **positive** margin?	This increased risk in IBTR is **not nullified** by delivery of a boost, delivery of systemic therapy (endocrine therapy, chemotherapy, biologic therapy), or favorable biology	Meta-analysis; secondary data from prospective trials and retrospective studies
Do margin widths **wider** than no ink on tumor cells reduce the risk of IBTR?	Negative margins (no ink on tumor) optimize IBTR; **wider margin widths do not significantly lower this risk**; the routine practice to obtain wider negative margin widths than ink on tumor is not indicated	Meta-analysis and retrospective studies
What are the effects of endocrine or biologically targeted therapy or systemic chemotherapy on IBTR? Should a patient who is not receiving any systemic treatment have wider margin widths?	Rates of IBTR are **reduced** with the use of systemic therapy; in the uncommon circumstance of a patient not receiving adjuvant systemic therapy, there is **no evidence suggesting that margins wider than no ink on tumor are needed**	Multiple randomized trials and meta-analysis
Should unfavorable biologic subtypes (such as triple-negative breast cancers) require wider margins (than no ink on tumor)?	Margins wider than no ink on tumor are **not indicated** based on biologic subtype	Multiple retrospective studies
Should margin width be taken into consideration when determining WBRT delivery techniques?	Choice of whole-breast radiation delivery technique, fractionation, and boost dose should **not be dependent on margin** width	Retrospective studies
Is the presence of LCIS at the margin an indication for re-excision? Do invasive lobular carcinomas require a wider margin (than no ink on tumor)? What is the significance of pleomorphic LCIS at the margin?	Wider negative margins than no ink on tumor are **not indicated** for invasive lobular cancer; **classic LCIS at the margin is not an indication** for re-excision; the significance of pleomorphic LCIS at the margin is **uncertain**	Retrospective studies
Should increased margin widths (wider than no ink on tumor) be considered for young patients (age < 40 years)?	Young age (< 40 years) is associated with both increased IBTR after BCT and increased local relapse on the chest wall after mastectomy, and is also more frequently associated with adverse biologic and pathologic features; there is **no evidence that increased margin width nullifies** the increased risk of IBTR in young patients	Secondary data from prospective randomized trials and retrospective studies
What is the significance of an EIC in the tumor specimen, and how does this pertain to margin width?	EIC identifies patients who may have a large residual DCIS burden after lumpectomy; there is **no evidence of an association** between increased risk of IBTR when margins are negative	Retrospective studies

BCS breast-conserving surgery, *RT* radiation therapy, *DCIS* ductal carcinoma in situ, *IBTR* ipsilateral breast tumor recurrence, *LCIS* lobular carcinoma in situ
Data from Moran et al. [68]

using the tumor-not-touching-ink definition of a negative margin. In spite of the lack of a boost dose of RT in NSABP B17 [71], the incidence of in-breast recurrence at a median follow-up of 17.3 years was 20%. In NSABP B24, this was reduced to 13.2% with the addition of tamoxifen, even though positive margins were allowed in this study [71]. In the United Kingdom-Australia-New Zealand DCIS study (UK-ANZ), after a median follow-up of 12.7 years, the incidence of in-breast recurrences was 10% [69].

Dunne et al. performed a meta-analysis of 4600 patients with DCIS treated with BCT to examine the question of margin width. Patients with negative margins were significantly less likely than those with positive margins to experience local recurrence (OR 0.36, 95% CI 0.27–0.47%). When specific margin widths were examined, patients with margins of 1 mm or less had a higher rate of local recurrence than those with more widely clear margins, but once a margin of 2 mm was obtained, no benefit for a more widely clear margin was seen (Table 18.4) [72]. Of note, local recurrence was infrequent in all of the negative margin groups. In a study of 994 women with DCIS treated between 1985 and 2000 and identified through tumor registries in Monroe County, New York, and the Henry Ford Health System, Detroit,

Table 18.4 Impact of margin width on local recurrence in ductal carcinoma in situ

Negative margin width	Number	% in-breast recurrence	Odds ratio (95% confidence interval)
Tumor not touching ink	914	9.4	2.6 (1.1–7.3)
1 mm	1239	10.4	2.9 (1.3–8.1)
2 mm	207	5.8	1.5 (0.5–5.0)
≥5 mm	154	3.9	1.0

Data from Dunne et al. [72]

Michigan, the multivariate relative risk of ipsilateral event-free survival for patients with margins less than 2 mm was 1.39 (95% CI 0.71–2.73) compared to those with more widely clear margins [73]. This translates to an absolute difference of 1.6% at 5 years (95.6% vs. 94.0%) and 3.2% at 10 years (90.5% vs. 87.3%). Van Zee et al. [74] examined 2996 prospectively accrued cases of DCIS patients managed with BCT from 1978 to 2010. It was found that margin width was significantly associated with local recurrence in those who did not receive RT, but not in those who did receive RT. At a median follow-up of 75 months, in patients not receiving RT, the recurrence rates were 27% vs. 23% and 16% for patients with margins ≤2 mm, 2–10 mm, and >10 mm, respectively ($p = 0.0001$). In those receiving RT, the corresponding figures were 12%, 13%, and 10% for margins <2 mm, 2–10 mm, and >10 mm in size ($p = 0.95$). These findings persist on multivariable analysis adjusting for patient and tumor factors, and suggest that wider margins may be important in reducing recurrence risk in women who choose to forego RT.

As was previously discussed, DCIS may grow discontinuously in the ducts. In a study of 60 mastectomy specimens with DCIS, Faverly et al. [45] demonstrated that 50% had a discontinuous growth pattern. This was seen in only 10% of high-grade DCIS lesions compared to 70% of well-differentiated lesions and 55% of intermediate-grade lesions. These findings suggest that margins more widely clear than tumor not touching ink are particularly relevant for patients with low- and intermediate-grade DCIS. The presence of residual calcifications at the lumpectomy site is a powerful predictor of the presence of residual DCIS, and even when margins are negative, residual suspicious calcifications are an indication for re-excision [75, 76]. Thus, margin width and the findings of postexcision mammography are complimentary methods of assessing the completeness of an excision. As in the case of invasive cancer, the extent of DCIS approaching the margin and which margin is approached by DCIS warrant consideration as well.

A great deal of confusion regarding appropriate margin width in DCIS seems to have been engendered by the report of Silverstein et al. [77] that any DCIS lesion, regardless of size or grade that could be excised with a margin of 1 cm in all directions, did not require RT or tamoxifen. Many extrapolated these findings to indicate the need for a margin of 1 cm even when RT is used, an issue not addressed in that study. Efforts to duplicate these findings in a multi-institutional setting have been unsuccessful to date. In the prospective, single-arm, multi-institutional, intergroup Eastern Cooperative Oncology Group trial 5194 study examining the role of excision alone in DCIS, margins of at least 3 mm and a negative postexcision mammogram were required. Patients with low- or intermediate-grade DCIS 2.5 cm or smaller in size and high-grade DCIS <1 cm in size were eligible. Approximately 50% of patients had negative margins of 1 cm or more. The 7-year rate of in-breast recurrence was 10.5% for the low- and intermediate-grade group compared to 19.0% for the high-grade group, but no significant impact of margins greater or less than 1 cm was noted for high-grade or non-high-grade lesions [78]. Thus, it is not even clear that margins of 1 cm or more are important when DCIS is treated with excision alone.

18.9 DCIS: Summary and Conclusions

In 2016 an SSO-ASTRO-ASCO consensus conference examined the relationship between margins in DCIS and local recurrence after treatment with whole breast RT [79]. A metaanalysis performed as part of this process found no benefit to margins greater than 2 mm in reducing LR, while margins of 2 mm reduced LR compared to smaller negative margin widths [80]. A negative postexcision mammogram for calcification cases is a complimentary method of assessing the completeness of excision. The panelists concluded that while a margin of 2 mm minimized local recurrence, caution should be exercised before subjecting a patient to mastectomy or nipple removal to obtain an arbitrary predetermined margin width based on the excellent outcomes in the clinical trials of DCIS which used the definition of no ink on tumor for a negative margin. As with invasive cancer, the extent of DCIS and other factors which impact upon the risk of local recurrence, such as patient age and willingness to take tamoxifen, are important in the decision-making process.

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Axillary Surgery

19

Farin Amersi and Armando E. Giuliano

19.1 Introduction

Over the last 25 years, outcomes from randomized clinical trials have brought about major changes in the surgical management of the axilla in patients with breast cancer. Axillary sentinel node biopsy (SNB) has substantially changed management and has become accepted as a staging procedure in patients with early-stage breast cancer.

The role of axillary lymph node dissection (ALND) has been an area of controversy for the last decade as it became accepted as a procedure for axillary staging and improving local control; however, there was no survival benefit [1, 2]. In addition, the decision to initiate either neoadjuvant or adjuvant chemotherapy is no longer limited to patients with nodal involvement but also depends upon characteristics of the primary tumor including tumor size, histologic grade, lymphovascular invasion, and receptor status.

It is well known that SNB has less morbidity and fewer complications than traditional axillary lymph node dissection (ALND) [3–5]. The ability to perform a less invasive procedure with significantly less morbidity and complications, without compromising prognostic information, has always been appealing.

Three prospective randomized clinical trials in patients with a clinically node-negative axilla comparing SNB to ALND have been published [6–8]. In NSABP-B32, which was the largest randomized sentinel node trial, 5611 patients with clinically T1 and T2 tumors who were clinically node-negative were randomized to either SNB followed by ALND or SNB alone with ALND only performed if the sentinel lymph node (SLN) contained metastases [6]. There were 80 participating centers and 233 surgeons. This study used frozen section analysis of SLN and both radioisotope and isosulfan blue to identify the SLN. The technical success rate for identifying the sentinel nodes was reported at 96.9% and a false-negative rate of 9.5%. At mean follow-up of 8 years, the axillary recurrence rate for sentinel node-negative patients was 0.7%. Interestingly, the axillary recurrence is far less than the false-negative rate.

The false-negative rate in the other two randomized trials of SLN-negative patients was also reported to be between 6.7% and 8.8% with an axillary recurrence rate between 0.2% and 0.8%, also far less than expected from the false-negative rate [7, 8].

19.2 Axillary Surgery with Sentinel Node Biopsy: Indications

SNB has become the standard of care for axillary staging in clinically node-negative patients with breast cancer. As the indications for adjuvant therapy continue to involve, SNB provides a basis for identifying high-risk patients who may benefit from the use of adjuvant systemic therapy, hormonal therapy, or radiation. SNB also provides local control if metastasis is limited to the SLN. For patients with early-stage breast cancer, the status of the axilla may help decide for or against adjuvant therapy.

Consensus conferences such as ASCO Guidelines and Recommendations for Sentinel Lymph Node Biopsy in Early-stage Breast Cancer and the 2005 International Consensus Conference on Image-Detected Breast Cancer: State of the Art Diagnosis and Treatment have endorsed SNB as the preferred method for axillary staging of clinically node-negative patients with breast cancer [9–11]. The indications for SNB indication and our understanding of the significance of the findings continue to evolve. This chapter reviews the latest developments of SNB and future directions.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_19

19.3 Indications for SNB

SNB has become well accepted in the staging and management of early-stage breast cancer patients, in the management of patients with DCIS who undergo mastectomy, patients with a clinically node-negative axilla who undergo neoadjuvant treatment, and patients with previous breast and axillary surgery; however, its role for patients with clinically palpable axillary disease and patients with clinically node-positive disease who undergo neoadjuvant treatment and are rendered node-negative, inflammatory breast cancer, and pregnancy-associated breast cancer continues to be debated (Table 19.1).

19.4 Prophylactic Mastectomy

Prophylactic mastectomy is accepted as an option for patients who are BRCA-1 and BRCA-2 gene mutation carriers, patients with a strong family history of breast cancer, history of mantle radiation, and lobular carcinoma in situ, and for cosmesis or phobia of developing breast cancer in patients undergoing a contralateral mastectomy for breast cancer. In patients who have undergone a prophylactic mastectomy, the risk of finding an occult cancer has been reported to be about 5%; in addition, in patients with a history of breast cancer, the risk of developing a contralateral breast cancer is as high as 1% per year [12, 13]. The feasibility of performing SNB is jeopardized in patients who choose to have a prophylactic mastectomy without SNB and are subsequently found to have invasive cancer in the specimen; an ALND is then required to stage the axilla. If SNB is performed at the time of prophylactic mastectomy, and the patient is found to have an invasive cancer with histologically negative SLNs, the morbidity associated with an ALND can be avoided. Dupont et al. reported a series of 57 patients who underwent prophylactic mastectomy and SNB for LCIS or were gene carriers of the BRCA-1 and BRCA-2 mutation, of whom 2 patients (3.5%) were found to have positive SLNs by IHC, in the absence of cancer in the mastectomy specimen [14]. In addition, invasive breast cancer was found in two other patients with negative SLNs. Based on these findings, 7% of the patients subsequently had a change in their surgical management. SNB may be offered to high-risk patients who choose to undergo prophylactic mastectomies. Those most likely to benefit from SNB are patients with imaging or other undiagnosed findings but without an abnormality; SNB is usually of no value.

Table 19.1 Indications for sentinel lymph node biopsy

Approved guidelines	Unapproved indications
Prophylactic mastectomy	Inflammatory breast cancer
T1–T2 breast cancer	Pregnancy
Multicentric disease	T3–T4 lesions
Male breast cancer	
DCIS with mastectomy	
Before or after neoadjuvant treatment	
Prior axillary or breast surgery	

Adapted from American Society of Clinical Oncology Guidelines for SLNB in breast cancer [9]

19.5 Previous Breast or Axillary Surgery

No large studies have reported success in identifying SLNs in patients who present with previous breast or axillary surgery. Many of the large trials excluded patients who had previous breast biopsies or previous axillary surgery [15–17]. Of the limited studies available on SNB in patients who have had previous breast surgery, the data suggests that identifying the SLN can be achieved after previous breast biopsies, regardless of the size, location, or the length of time between the initial biopsy and the SLN procedure [18, 19]. In a retrospective review at the European Institute of Oncology, Luini et al. determined the accuracy of SNB in 543 patients who had previous breast biopsies [20]. The SLN was identified in 99% of the patients. Based on these findings and other studies in the literature, a prior breast biopsy is not considered a contraindication to SNB.

The accuracy of SNB in patients who have undergone previous axillary surgery has also not been studied in large clinical trials. Controversy involves the ability to successfully identify the SLN due to disruption of lymphatic channels during surgery that can lead to aberrant lymphatic drainage patterns. A recent study was reported on the feasibility of performing a second SNB in a series of 18 patients who developed recurrences after breast conservation and SNB for early-stage breast cancer, who had negative SLNs at the time of their initial surgery [21]. All patients underwent preoperative lymphoscintigraphy which demonstrated a SLN, and all patients had successful identification of the SLN intraoperatively with an average of 1.3 SLNs removed. Two patients were found to have positive SLNs, requiring ALND. Of the 16 patients with negative SLNs, no recurrences were observed. In patients with prior axillary surgery, SNB can be offered but should be performed with both preoperative lymphoscintigraphy and blue dye for localization.

19.6 Ductal Carcinoma In Situ

Ductal carcinoma in situ (DCIS) is a noninvasive lesion and does not have the ability to metastasize to regional lymph nodes. In theory, DCIS should not require SNB staging. However, due to sampling errors in about 20% of cases in which a core biopsy shows DCIS, invasive cancer can be

found in the final excised specimen. Because of this some surgeons will perform SNB for patients who have a core biopsy showing DCIS. Positive sentinel nodes have been reported in 0–13% of DCIS patients [22–24]. A recent study of 398 patients diagnosed with DCIS on core biopsy found that 20% had invasive disease found when the excised specimen was examined on final pathology [25]. On multivariate analysis, risk factors for invasive disease included age <55 (odds ratio (OR) 2.19, $p = 0.024$), diagnosis on a core biopsy (OR 3.76, $p = 0.006$), mammographic size of DCIS >4 cm (OR 2.92, $p = 0.001$), and high-grade DCIS (OR 3.06, $p = 0.002$). Of these patients, 141 had SNB done at the time of their initial operation. Seventy-three percent were diagnosed on core biopsy, 30% had invasive disease on final pathology, and 10% (14/141) had SLN metastases. Of the 14 patients with positive nodes, 11 (79%) had invasive cancer found on their final pathology. SNB should not be done after an excisional biopsy that shows only DCIS. If microinvasion is found, then SNB is reasonable.

ASCO guidelines recommend that SNB should not be done routinely for patients with DCIS who undergo breast conservation; however, exceptions include when a mastectomy is being performed or when the DCIS is large and high grade. In patients who have DCIS extensive enough to require mastectomy, SNB may be indicated because if invasive cancer is found on the final specimen, then sentinel node biopsy could not be performed and the patient would require an axillary dissection.

19.7 Multicentric Lesions

Multicentric cancers occur in approximately 10–15% of patients and have been considered a contraindication to SNB; however, there is evidence that the entire breast may drain through the same afferent lymphatic channels to the same axillary sentinel node (Table 19.2). In multiple small non-randomized studies, SNB was performed with accuracy rates similar to patients with unifocal lesions [26, 33]. Goyal et al. demonstrated an identification rate of 94% in 75 patients with multicentric disease [27]. These studies reflect similar identification rates to patients with unifocal disease. Most investigators report greater success using a combination of radiolabeled colloid and blue dye. Moreover, Bauer et al. demonstrated that regardless of the injection of radiolabeled colloid and blue dye into the same location or different locations in the breast, they both resulted in localization of the same sentinel nodes with an identification rate of 95% and 97%, respectively [34].

Table 19.2 Sentinel lymph node biopsy for multicentric disease

Study (year)	Patients	# SLN	% SLN ID rate	% FN rate
Tousimis (2003) [26]	70	2.1	96	8
Goyal (2004) [27]	842	2.4	94	8.8
Gentilini (2006) [28]	42	1.36	100	2.3
Knauer (2006) [29]	142	1.67	91	4
Holwitt (2008) [30]	93	–	100	7
Fearmonti (2009) [31]	23	1.3	100	15
Lo (2009) [32]	23	1.1	100	0

19.8 Male Breast Cancer

Breast cancer in men is rare and accounts for less than 1% of all breast cancers, and decisions regarding management have usually been made based on evidence from studies on female breast cancer. Although male patients usually present with larger tumors because of a delay in diagnosis, survival rates parallel women stage for stage [35]. Men who develop breast cancer who undergo ALND are at similar risk of developing complications associated with this procedure. It seems logical that SNB could be used for men with breast cancer. In a study of 16 male patients with T1 tumors, the SLN was successfully identified in 93% of patients [36]. Although data on management of men with breast cancer is limited, the treatment and outcomes appear to be similar to women with breast cancer, and SNB may be offered to men with early breast cancer.

19.9 Micrometastatic Disease and SNB

The recent publication of three large randomized controlled trials has changed the perspective on occult metastases detected by immunochemistry and the management of the axilla after a positive SNB in early-stage breast cancer. The American College of Surgeons Oncology Group Z0010 trial was designed to determine the association between survival and metastases detected by immunochemical staining (IHC) of SLNs and bone marrow specimens from patients with early-stage breast cancer [37]. The study enrolled 5538 patients who underwent lumpectomy and SNB with bilateral iliac crest bone marrow aspiration. Both the bone marrow and histologically negative sentinel nodes were evaluated with IHC in a central laboratory for the presence of micrometastases. The SLN was successfully identified in 5485 (99%) women, and histologic SN metastases were found in 1239 (23.9%). IHC identified an additional 350 patients with sentinel node metastases. Bone marrow metastases were identified by IHC in 105 of 3491 specimens examined (3.0%). At 5 years, overall survival was 92.8% among women with SLN IHC-detected metastasis and 95.6% with negative histology. Overall survival was 95.1% with IHC-detected metastasis and 95.8% for those patients with a negative sentinel node. This study demonstrated that the detection of occult micrometastases for T1–T2 N0M0 disease does not help predict

overall survival. Interestingly, bone marrow micrometastasis detected by IHC predicted decreased 5-year overall survival, 90.2% for positive status and 95.1% for negative. However, the rate of bone marrow metastasis was so low, and the results did not achieve statistical significance.

Similarly, the NSABP B-32 trial randomly assigned 5611 women with breast cancer to SNB with immediate ALND (2807 patients) or SNB alone (2804 patients) [38]. In the SNB with immediate ALND group, 1978 patients were found to be SLN negative. Of these patients, 316 demonstrated occult metastases on further IHC staining. In the SN-only group, 2011 patients were SLN negative. Of these patients, 300 demonstrated occult metastases on further IHC staining. Five-year Kaplan–Meier estimates of overall survival among patients in whom occult metastases were detected and those without detectable metastases were 94.6% and 95.8%, respectively. While occult metastases were a statistically significant independent prognostic variable for overall survival in patients with sentinel nodes that were negative on initial examination, the difference in outcome at 5 years was clinically insignificant. With the information obtained from ACOSOG Z0010 and NSABP B-32, micrometastases do not appear to be clinically significant. The authors of both studies concluded that the additional evaluation of a SLN with IHC analysis and serial sectioning of negative sentinel nodes on routine H&E staining in patients with early-stage breast cancer is of no value and treatment recommendations should not be made based solely on IHC nodal status.

19.10 Macrometastatic Disease and SNB

Although SNB has been well established as a means of identifying axillary node metastasis, the management of breast cancer continues to evolve. Radiation, adjuvant chemotherapy, hormonal therapy, and other targeted therapies have allowed for better locoregional control as well as improvements in survival. For patients treated with breast conservation standard whole breast opposing tangential fields results in radiation to part of the axilla which may contribute to regional control.

The recently reported American College of Surgeons Oncology Group (ACOSOG) Z0011 randomized trial was designed to address the question of whether women with a positive SLN treated with whole-breast irradiation (WBI) and adjuvant treatment could avoid a completion ALND [39]. Women with T1–T2 breast cancers, who were clinically node-negative and found to have less than three positive SLNs detected on H&E staining, were randomized to either completion ALND or no further axillary surgery (Fig. 19.1). All patients were to receive WBI and systemic treatment. Of the women enrolled in the study, 446 evaluable women were assigned to no ALND, and 445 women were randomized to

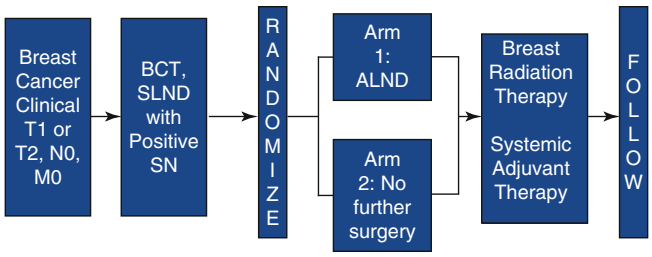

Fig. 19.1 ACOSOG Z011 study design schema

Table 19.3 Indications for axillary lymph node dissection after a positive sentinel lymph node biopsy

Clinically palpable nodal disease preoperatively
Patients undergoing mastectomy
Patients undergoing treatment with partial breast irradiation
Patients undergoing neoadjuvant chemotherapy
≥3 SLN with metastatic disease
SLN with extranodal involvement
Matted axillary lymph nodes

ALND with removal of 10 or more additional axillary nodes. At a median follow-up of 6.3 years, four patients (0.9%) had a regional nodal recurrence in the sentinel node-only group compared to two patients (0.5%) in the ALND group. Despite the fact that 27.4% of patients in the ALND group had additional positive lymph nodes removed, there were no statistically significant differences seen in locoregional recurrences. The study reported a 5-year overall survival of 91.8% for women who underwent ALND vs. 92.5% for those that had SNB alone who had one or two positive SLNs, demonstrating no survival advantage to having additional lymph nodes removed.

On multivariate analysis, no clinical or pathological factors including younger age, estrogen receptor status, and tumor size were found to significantly affect locoregional recurrences when comparing both groups. This data clearly demonstrates that patients with a positive SLN who meet ACOSOG Z011 eligibility criteria can safely avoid undergoing a completion ALND; however, the authors did emphasize that there are many patients with a positive SLN who should still undergo completion ALND (Table 19.3). These findings were also supported by the IBCSG multicenter phase III randomized clinical trial of 934 patients with stage I–II breast cancer, who after a SNB which demonstrated one or more micrometastatic SLNs were randomized to ALND versus no further axillary surgery demonstrated no significant differences in overall survival or regional recurrences [40].

19.11 Clinically Positive Axilla

Management of patients with suspicious axillary lymph nodes based on clinical exam is unreliable. The results of several series show a positive predictive value of 64–82%, a

negative predictive value of 50–63%, and an overall accuracy of 63–68% [41–43]. Specht et al. published a study of SNB in patients with clinically suspicious axillary nodes. Two experienced surgeons documented clinically suspicious axillary nodes in 106 patients preoperatively [44]. The patients were classified into two groups. The first group which consisted of 62 patients was believed to have nodes that were moderately suspicious and was described as "firm, shotty, and more prominent that those on the contralateral side." The second group of 44 patients had nodes which were thought to be "highly suspicious or unequivocally positive." All patients then underwent SNB. The PPVs of physical examination were 47% in the moderately suspicious group, 77% in the highly suspicious group, and 59% overall. The patients in the highly suspicious group had larger tumors (2.2 cm vs. 1.6 cm) and more lymphovascular invasion (41% vs. 32%). Both larger tumor size and lymphovascular invasion are known to correlate with a higher rate of axillary metastases. Overall 41% of these patients with clinically involved nodes were node-negative and could be treated with SNB alone and spared ALND. The more suspicious the axillary involvement is, the more likely that the lymph nodes are truly involved. SNB is not recommended in patients with palpable axillary disease. When performing SNB any lymph node that is clinically suspicious for metastatic disease because of firm texture or enlarged size must be removed. These nodes are to be considered and evaluated as sentinel nodes even if they are not radioactive or blue. ASCO guidelines recommended against performing SNB in patients with clinically positive nodes. The clinical problem that often occurs is the management of a patient with a non-palpable but imaging-detected, even biopsy-proven axillary nodal metastasis. These patients are often subjected to ALND. However, ACOSOG Z011 and the AMAROS trial used only palpation to exclude patients. Those women with imaging-detected metastasis may still undergo SNB with removal of the biopsy-proven involved node, and they may be spared ALND.

19.12 Neoadjuvant Chemotherapy and Management of the Axilla

The use of neoadjuvant chemotherapy for patients with locally advanced breast cancer has received considerable attention over the last several years. The rationale for treating patients early with large operable tumors is reflected in many studies that demonstrate that systemic treatment downsized these large lesions, providing the alternative of breast conservation instead of mastectomy. Although there is increasing data to support the use of SNB after neoadjuvant chemotherapy in patients who are clinically node-negative at initial presentation, its value and effect on long-term outcomes are unproven. Recent studies have shown that SNB may be an accurate means of staging the axilla after completion of NAC in patients who were clinically node-negative prior to NAC [45–47].

Table 19.4 Studies of sentinel node biopsy after neoadjuvant chemotherapy

Study	Tumor stage	# Pts	% SLN ID rate	% False negative
Tausch (2008) [48]	1–3	144	85	8
Menard (2009) [49]	1–3	20	100	0
Hunt (2009) [45]	1–3	575	97	6
Schwartz (2010) [50]	1–3	79	98	4
Pecha (2011) [51]	2–3	343	81	19
Aquiar (2012) [52]	1–2	34	92	12
Zhang (2013) [53]	1–3	57	98	8

Several studies have shown an acceptable identification rate and a low false-negative rate after neoadjuvant therapy in clinically node-negative patients (Table 19.4). The largest multicenter trial demonstrating the feasibility and accuracy of SNB after neoadjuvant chemotherapy was conducted as part of the NSABP-B27 study in which 784 patients underwent neoadjuvant chemotherapy followed by surgery [54]. The authors reported that the SLN was successfully identified in 84.8% of patients with a false-negative rate (FNR) of 10.7%, suggesting that the SNB technique was technically feasible after neoadjuvant chemotherapy. The identification rate increased significantly with the use of radioisotope and blue dye (88.9%) compared to the use of blue dye alone (78.1%, $p = 0.03$).

Neoadjuvant chemotherapeutic regimens have led to axillary downstaging with a significant decrease in the number of palpable nodes after treatment [55, 56]. Controversy continues to exist with regard to the reliability and sensitivity of SNB after NAC for patients who were clinically node-positive prior to NAC and demonstrate a complete clinical response.

Axillary ultrasound with needle biopsy of suspicious lymph nodes is often used in the initial diagnostic workup of breast cancer patients for whom NAC is planned in order to document nodal status and staging prior to initiating treatment. For patients with metastases detected by needle biopsy who are then treated with NAC, it has been standard to perform an ALND at the time of breast surgery. This is because prior studies have shown lower identification rates and higher false-negative rates of SNB after NAC in patients with clinically positive nodes at presentation [57, 58]. Furthermore, the outcome of node-positive patients who become node-negative after NAC and do not undergo ALND is currently unknown.

The benefits of NAC for patients with clinically positive axillary lymph nodes were confirmed by the NSABP B-18 trial [59]. Wolmark et al. evaluated the effect of preoperative

doxorubicin and cyclophosphamide on downstaging the primary breast tumor as well as the involved axillary lymph nodes. They reported a clinical nodal response rate of 89% in node-positive patients: 73% had a complete clinical response and 44% had a pathologically complete response. Furthermore, there was a 37% increase in the occurrence of pathologically negative nodes. Similarly, Dominici et al. from MD Anderson, demonstrated the efficacy of NAC in treating axillary metastases [60]. In this study, 109 patients with documented axillary LN metastases were treated with preoperative trastuzumab and chemotherapy and then underwent a level I and II ALND. Eighty-one of the 109 patients (74%) had a complete pathologic nodal response with a higher disease-free survival seen in patients who had an axillary pathological complete response than those who had residual axillary disease. The use of Her-2-targeted therapy has further increased nodal complete pathological response rates.

The role of SNB with clinically node-positive disease who underwent neoadjuvant chemotherapy was investigated in ACOSOG Z1071 [61]. In this study, 687 patients underwent sentinel lymph node biopsy followed by an ALND. The authors reported successful identification of the sentinel node in 92.9% of patients, and 41% of node-positive patients had a complete pathological response following NAC. However, the false-negative rate was 12.6% when two LNs were identified by SNB which was more than the accepted 10% false-negative rate than the authors' pre-specified threshold. The authors concluded that SNB alone after NAC for biopsy-proven node-positive patients who have a complete clinical response could not be recommended. The unreliability of SNB after NAC has been attributed to disruption and obstruction of lymphatic channels as well as nonuniform chemotherapy delivery to the axillary lymph nodes. However, in this study when three or more LNs were removed by SNB, the false-negative rate was under 10%. In addition, the authors recently reported on clinical and surgical factors such as patient age, BMI, tumor size, the use of dual tracer for identification of the sentinel node, site of injection of the tracer, and the type of breast surgery and found that the only factor that was statistically significant in influencing identification of the SLN was the use of blue dye alone versus the use of dual tracer. The rate of identification of the SLN was significantly higher when radiolabeled colloid was used in combination with blue dye (93.8%) versus blue dye alone (89.3%) [62]. This may be a reflection of the number of nodes removed during SNB.

The controversy regarding the optimal timing and reliability in staging the axilla after NAC in patients with node-negative or node-positive disease was also recently addressed in the SENTINA (SENTinel NeoAdjuvant) trial, which was designed as a prospective, multicenter trial in Germany and Austria of patients who received NAC [63]. This was a four-arm prospective study where in the first arm, patients who were clinically node-negative underwent SNB prior to NAC induction, and if they were found to have sentinel node metastases, they were selected to undergo a second SNB once NAC was completed (arm B). Women who were clinically node-positive received NAC and either underwent SNB followed by mandatory ALND if they had a complete clinical nodal response (arm C) or ALND alone if their nodal status remained positive despite NAC (arm D). The sentinel node detection rate for clinically node-negative patients prior to NAC induction was 99.1%; however, 35% of these clinically node-negative patients were found to have nodal metastases on SNB. For these patients found to have nodal metastases, their second SNB after NAC was only successful in identifying the sentinel node 60.8% of the time with a high false-negative rate of 51.6%. Patients whose axillary nodal status converted from clinically positive to clinically negative after NAC had a sentinel node detection rate of 80.1% and a false-negative rate of 14.2%. The authors also reported that false-negative rate decreased with increasing number of lymph nodes removed. This data suggests that SNB is more accurate and reliable prior to NAC in clinically node-negative patients but in patients who are node-positive prior to NAC induction, SNB alone without ALND is not adequate to accurately stage the patient.

Although further studies with long-term follow-up are needed to fully evaluate the role of SNB after neoadjuvant treatment for clinically node-positive patients who undergo NAC, there is supporting evidence that this technique is applicable in patients who demonstrate a complete clinical response. ASCO guidelines state that currently available data is not sufficient to recommend SNB in patients with clinically node-positive disease who undergo NAC and become clinically node-negative and that SNB should only be performed in patients with clinically negative axillary lymph nodes.

19.13 Recurrent Disease/New Primary Breast Cancers

The dilemma of optimal treatment for new breast cancers or in-breast recurrences after previous ipsilateral SNB or ALND will often arise. Although SNB has been successful in patients who have had previous biopsies, its role in patients who have had previous axillary surgery continues to evolve. In patients who present with recurrent disease or a new primary, some investigators advocate a combination of both lymphatic mapping with radiocolloid, preoperative lymphoscintigraphy and intraoperative blue dye in identifying alternate lymphatic pathways such as internal

mammary nodes or the contralateral axilla [21, 64]. Port et al. reported their experience of 32 patients with in-breast recurrences who had prior axillary surgery for breast cancer [65]. In this group of patients, the SLN was successfully identified in 75% of patients, and there was a significant difference in the SLN identification rate if less than ten nodes had been removed during the previous axillary surgery compared to patients who had more than ten nodes removed (87% vs. 44%, respectively). The role of SNB in this group of patients remains to be established, and more data with larger numbers of patients are necessary to develop guidelines. Further identification of nodal metastasis may be of limited clinical value for patients with recurrent disease.

19.14 Contraindications to SNB: Inflammatory Breast Cancer

Inflammatory breast cancer represents one of the most rare but aggressive forms of locally advanced breast cancer with a poor prognosis. The diagnosis is based on the clinical presentation of diffuse inflammatory skin changes, with skin thickening, as well as histological confirmation of dermal lymphatic invasion. The current management of inflammatory breast cancer includes neoadjuvant chemotherapy as first-line treatment followed by modified radical mastectomy and postoperative radiation therapy. SNB is not recommended for patients with inflammatory breast cancer due to invasion and obstruction of dermal lymphatics by tumor cells. ASCO guidelines list inflammatory breast cancer as a contraindication to SNB

19.15 Conclusion

Since the early 1990s, the development and wide acceptance of SNB have profoundly affected the management of breast cancer. The technique reliably stages the axilla with more accuracy and less morbidity than traditional ALND. SNB initially was used to identify women with node-negative disease and spare them an ALND. Over the last decade with large multicenter randomized phase III clinical trials, we have now been able to avoid ALND even in SLN-positive patients who undergo breast conservation and are treated with adjuvant therapy and whole-breast radiation. SNB continues to be an invaluable tool for clinicians to guide decisions regarding treatment, and with the continuing advancements in neoadjuvant treatments, patients who have a positive SLN will not have to undergo extensive axillary surgery, will have the same local outcomes that are less invasive, and have better functional outcomes than those undergoing ALND.

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Skin-Sparing Mastectomy

20

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20.1 Introduction

The term skin-sparing mastectomy was designated by Toth and Lappert in 1991 to describe mastectomy incisions that maximized skin preservation in an attempt to facilitate immediate breast reconstruction [1]. Skin-sparing mastectomy removes the breast and nipple-areola complex, and can incorporate the skin over superficial tumors, previous excisional biopsy, or lumpectomy sites. The technique builds on previous descriptions of subcutaneous mastectomy and immediate implant-based reconstruction from the 1980s [2, 3].

Skin-sparing mastectomy is now routinely utilized as the mastectomy technique for patients selected as suitable for immediate breast reconstruction. Preservation of the native skin and in the inframammary fold enhances the cosmetic outcome for patients undergoing implant or, indeed, autologous immediate reconstruction. Multiple studies over the last 15 years have demonstrated low locoregional recurrence rates following skin-sparing mastectomy, comparable to those for women undergoing modified radical mastectomy.

The indications for mastectomy in the surgical management of breast cancer including ductal carcinoma in situ will depend on a variety of patient and tumor factors. Established tumor factors such as multicentric disease, T4 disease, and large or central tumors in a small breast are all elements that would exclude breast-conserving surgery as a management option, therefore necessitating a mastectomy.

Inflammatory breast cancer is an absolute contraindication to skin-sparing mastectomy. Authors have advocated its use in some locally advanced cases with limited skin involvement that is amenable to inclusion in the area of the skin removed. However, there is a paucity of data to provide definitive support. Rigorous evaluation of preoperative breast imaging is required when evaluating suitability for skin-sparing mastectomy. In certain cases of ductal carcinoma in situ, calcifications can encroach close to the skin, and, if identified, consideration should be given to inclusion of this area in the skin component being resected (Fig. 20.1).

As the indications for neoadjuvant chemotherapy expand, mirrored by improvements in both clinical and pathological response rates, more patients who may have been deemed not suitable for a skin-sparing mastectomy may be in a position to consider this approach with successful completion of neoadjuvant therapy. There are no trials with sufficient follow-up of comparative patients after skin-sparing mastectomy with or without the use of neoadjuvant chemotherapy. However, data from the American College of Surgeons National Surgical Quality Improvement Program actually found that after mastectomy, morbidity rates were lower in patients who had received neoadjuvant chemotherapy [4]. The findings were applicable to patients who did not have and who did undergo an immediate breast reconstruction. The mechanisms underlying this reduction in morbidity have yet to be elucidated, but the findings do support the safety of neoadjuvant chemotherapy in patients scheduled for a mastectomy and immediate reconstruction.

The predicted need for adjuvant chest wall radiotherapy following mastectomy may impact the reconstruction decision process. It has been shown that radiotherapy has a negative effect on health-related quality of life and breast satisfaction metrics in patients with implant-based reconstructions [5].

20.2 Surgical Technique

20.2.1 Incisions and Carlson Classification

The classification system for skin-sparing mastectomy defined by Carlson in 1997 has prevailed for describing skin-sparing mastectomy based upon the type of incision used and

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_20

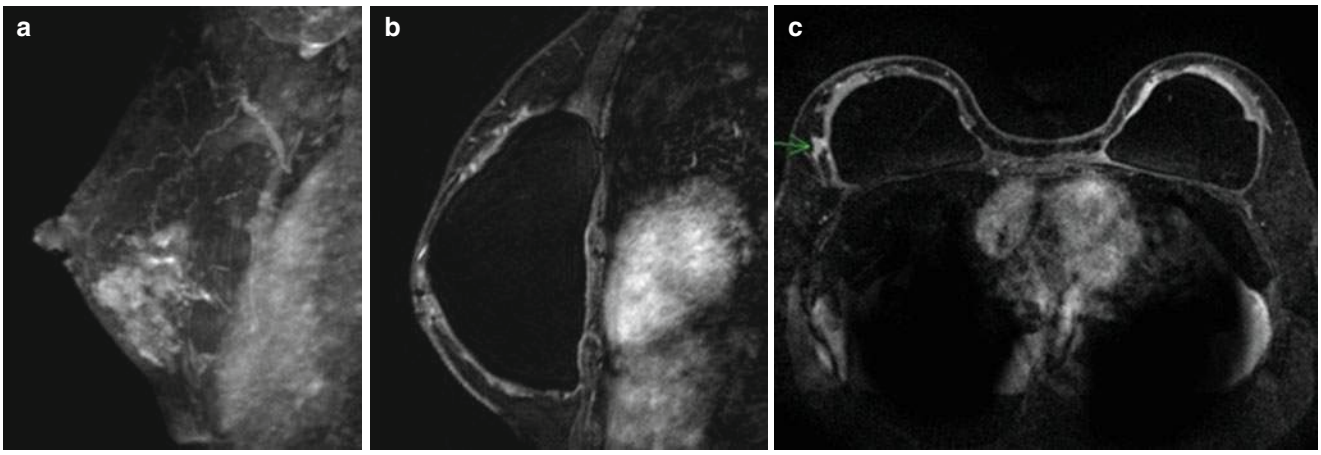

Fig. 20.1 Use of MRI in patient selection for skin-sparing mastectomy. (**a**) MRI showing extensive mass enhancement in close proximity to the skin in the lower pole of the breast. (**b**, **c**) MRI post-skin-sparing mastectomy for ductal carcinoma in situ with implant reconstruction demonstrating evidence of residual areas of calcifications and enhancement

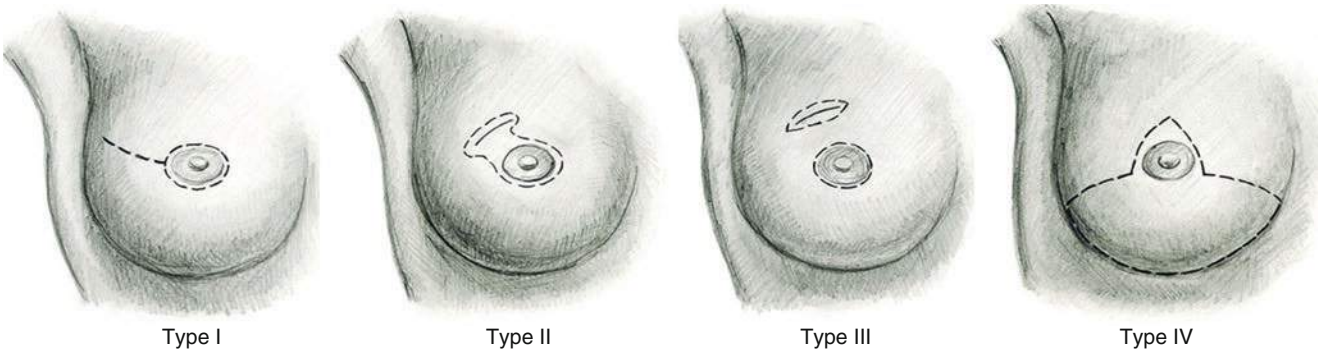

Fig. 20.2 Types of incision for skin-sparing mastectomy based on Carlson classification (Reproduced with permission from Chapter 2: Oncoplastic Breast Surgery: A Guide to Clinical Practice Edition 1: 2010. Pages 134 -135. Editors: Florian Fitzal and Peter Schrenk. Published by Springer Wien New York (ISBN: 978-3-211-99316-3.)

the amount of skin removed [6]. The four types of skin-sparing mastectomy incisions (Fig. 20.2) described are:

- *Type I*: Removal of the nipple and areola only. This approach is frequently used in prophylactic cases. In patients with a small-diameter areola, a lateral extension to the incision is sometimes required to improve access to the axillary tail and upper outer quadrant. In cases where the planned immediate reconstruction is with a tissue expander, we revert to an elliptical rather than a circum-areolar incision, as these circular incisions are often revised to an ellipse to allow a flat skin closure.
- *Type II*: Removal of the nipple and areola complex as well as the skin overlying superficial tumors and/or previous biopsy incisions. These incisions are suitable if the biopsy incisions or superficial tumors are in close proximity to the areola allowing removal in continuity with the nipple-areola complex.
- *Type III*: Removal of the nipple-areola complex as well as skin overlying superficial tumors and/or previous biopsy incisions (without resecting intervening skin). The bridge of intervening skin is vulnerable to ischemia, and care must be taken to ensure viability.
- *Type IV*: Removal of the nipple-areola complex with an inverted or reduction pattern skin incision, suitable for large or ptotic breasts. This reduction of an excessive skin envelope is referred to as a skin-reducing mastectomy in contemporary terms. The degree of skin reduction must be carefully measured and marked preoperatively.

20.2.2 Mastectomy

The patient should be positioned supine on the operating table with arms at 90° on arm boards. The prepped operative field should include both breasts from above the sternal notch to the just below the costal margins. We include both arms prepped to the level of the wrist and then enclosed in a sterile sleeve to the mid-humerus level and secured with a circumferential wrap. After incision of the skin and dermis, electrocautery can be used to elevate the skin flaps. We use the pinpoint coagulation mode. Some surgeons prefer to use

a scalpel or scissors due to concern over the risk of "burn" injury to the mastectomy skin flap.

Much debate and agonizing have taken place over the optimal mastectomy skin flap thickness that would minimize the risk of leaving residual breast tissue while not denuding the skin flap of its blood supply. The skin flap thickness is dependent on the patient body habitus and breast size, and, simply put, a single specific universal thickness for mastectomy skin flaps cannot be recommended [7]. However, in a skin-sparing mastectomy, the skin flaps are longer than in a non-skin-sparing mastectomy. Maintaining flap viability is therefore important to reduce the risk of a poorer cosmetic outcome that may result from scarring after necrosis, and due to the risk of implant loss, which is increased with the development of flap necrosis. Breast tissue does extend closer to the skin in the lower pole of the breast. In most cases, there is an identifiable plane between the breast and subcutaneous fat delineated by a distinct layer of superficial fascia. The thickness of this layer is variable and difficult to predict preoperatively.

Elevation of the skin flaps initially with sharp hooks allows counter traction to be applied to the underlying breast that reveals the surgical plane of dissection. Encountering excessive bleeding indicates that the dissection is not in the correct anatomical plane. The plane of dissection extends from the sternal edge medially to the latissimus dorsi laterally, and from the clavicle to the inframammary fold in the cranio-caudal direction. In contrast to a traditional simple mastectomy where dissection proceeds logically, from the upper flap to the lower flap, in a skin-sparing mastectomy, the smaller incision requires progressive rising of the skin flaps in a circumferential manner. At the sternal edge, it is common to encounter perforating vessels from the internal mammary artery, the largest in the second or third intercostal spaces. If injured, these vessels should be ligated or clipped due to their size; however, they represent an important part of the blood supply to the mastectomy skin flaps, and every effort should be made to preserve these perforators. When circumferential elevation of the skin flaps has been completed, the breast and pectoral fascia are dissected off the pectoralis muscle fibers from superior to inferior.

20.2.3 Reconstruction

A variety of both implant-based and autologous reconstructive options are available for immediate reconstruction after a skin-sparing mastectomy. The choice of reconstruction will be based on a range of both patient and surgeon factors.

20.2.3.1 Two-Stage Expander-Implant-Based Reconstruction

Placement of a submuscular tissue expander underneath the pectoralis major muscle reinforced laterally with a pocket created in serratus anterior allows for a gradual expansion of the implant pocket prior to the definitive placement of a permanent implant at a second operation.

20.2.3.2 One-Stage Implant Reconstruction with Acellular Dermal Matrix

In suitable patients, a one-stage or direct-to-implant strategy may be used. This incorporates the use of a commercially available acellular dermal matrix to provide coverage of the permanent implant. After creation of the submuscular pocket to accommodate the implant, the lower divided edge of pectoralis major is approximated to the acellular dermal matrix, and the lower, free edge of this is then used to refashion the inframammary fold. The benefit of this approach is that it negates the need for a second procedure. Multiple studies have found the risk of complications with a one-stage approach comparable to those with a two-stage strategy [8].

20.2.3.3 Implant Reconstruction with a De-Epithelialized Dermal Flap

This represents a skin-reducing mastectomy whereby the excess skin of the lower pole is de-epithelialized and then fashioned as a dermal sling to provide implant coverage. The upper edge of this de-epithelialized skin flap is then sutured to the lower divided edge of pectoralis major. These patients usually require a symmetrizing contralateral procedure, the timing of which can be adjusted based on the predicted need for adjuvant radiotherapy [9].

20.2.3.4 Autologous Breast Reconstruction

A pedicled flap, such as a TRAM or LD, or a free flap, such as a DIEP, can be utilized for reconstruction. In these cases, we elect to perform the mastectomy through a circumareolar incision.

These concepts and techniques are discussed in more detail in Sect. 20.4.

20.3 Complications

Aside from the instinctive complications associated with simple mastectomy, most attention on complications following skin-sparing mastectomy is directed toward the risk of skin flap necrosis. In the 1997 paper that classified the incision types for skin-sparing mastectomy, Carlson et al. noted epidermolysis or skin loss requiring debridement and local wound care in 10.7% of 327 skin-sparing mastectomies, a rate that was the same as that seen in patients undergoing non-skin-sparing mastectomy [6]. The subsequent literature assessing the risk of skin flap necrosis is somewhat inconsistent due to differing definitions of mastectomy skin flap necrosis. Contemporary studies still report rates in

excess of 10% for any degree of skin flap necrosis, with somewhere in the range of 2–10% of patients requiring a return to the operating room for surgical debridement [10–12]. The implications of mastectomy skin flap necrosis can be considerable, requiring additional operations, prolonged wound management, reconstruction failure, and implant loss as well as causing delays in beginning adjuvant systemic therapy if indicated.

A variety of both patient factors (smoking, older age, obesity, smoking, hypertension) and surgeon factors (type of incision: higher rates of skin flap necrosis are seen with a Wise-type incision and volume of tissue expander) have been identified as risks for the development of mastectomy skin flap necrosis [11–16]. The native breast size is an important factor in determining the type of reconstruction selected, but also affects the complication rate. In patients undergoing an implant-based reconstruction, surrogates of breast size including BMI [17], cup size [18], weight of excised specimen, increased size of expander, and increased sternal notch to nipple [12, 14] length all reflect the presence of a longer mastectomy skin flap that has been shown to be associated with an increased risk of skin flap necrosis. Rates of implant loss following immediate reconstruction range from 0.8% in multi-institutional datasets [19] to anywhere between 0.7% [12] and 12% [20, 21] in single-institutional studies.

20.4 Cosmetic Outcome

Mastectomy and reconstruction, irrespective of the type, can exert a profound impact on a woman's sense of self and body image. A variety of measurement tools have been used to assess patient-reported outcomes after mastectomy and reconstruction, ranging from ad hoc questionnaires to general breast cancer quality-of-life questionnaires to some breast surgery-specific instruments [22]. The Breast-Q measurement tool [23], first described in 2009, provides a useful and validated framework to assess the impact and effectiveness of breast surgery from the patient's perspective. It is administered both preoperatively and postoperatively, and assesses both quality-of-life and patient satisfaction domains.

Studies have consistently shown that patients who have mastectomy without reconstruction report the lowest score for breast satisfaction postoperatively [24]. The 2010 meta-analysis of skin-sparing mastectomy acknowledged the problems in reporting differences that have made study comparisons between quality-of-life and cosmetic satisfaction outcomes difficult [25]. A number of studies have demonstrated excellent cosmetic outcomes following skin-sparing mastectomy. The degree of satisfaction is heavily influenced by the type of reconstruction employed [26–28].

20.5 Oncologic Safety

When performing a skin-sparing mastectomy, most surgeons remove all the breast tissue that they would have removed with a non-skin-sparing mastectomy. This premise would suggest that skin-sparing mastectomy should be as safe from an oncologic perspective as a non-skin-sparing mastectomy. It has long been acknowledged that even a traditional total mastectomy does not remove all breast tissue. A number of studies incorporating varying methodologies, from cadaveric analysis to intraductal dye injection of mastectomy specimens and biopsy of residual skin flaps following mastectomy, have demonstrated the presence of residual breast tissue in anywhere between 6% and 60% of cases [29–32]. These studies do support the hypothesis that the risk of superficial mastectomy margin positivity is increased with thicker skin flaps, but do not provide a reliable quantification of what constitutes an ideal skin flap thickness. As our understanding of the molecular basis for breast cancer expands, it is appreciable that biological subtype is not only a predictor of distant disease recurrence, but also of local recurrence [33].

No randomized study of skin-sparing versus non-skin-sparing mastectomy has been performed. The adoption of the technique into routine practice has been on the basis of a number of comparative and non-comparative studies. Comparative studies up until 2009 were synthesized in a meta-analysis by Lanitis et al. [25]. There is considerable heterogeneity between the studies in terms of duration of follow-up, inclusion criteria, and patient populations studied. Table 20.1 [6, 28, 34–38] and Table 20.2 [39–48] provide an overview of some of the larger comparative and non-comparative trials that have examined locoregional recurrence, in patients with breast cancer, following skin-sparing mastectomy.

The majority of comparative studies recruited patients in the 1990s, and considerable advances have been made in adjuvant systemic therapies since that period, which may have further influence on local recurrence rates. This may partly explain the lower rate of recurrence at 4.1% seen in the series of non-comparative studies that were performed in a more contemporary period. Taken in conjunction, at a follow-up of around 5 years, a local recurrence rate of <6.0% should be expected for a properly selected patient with breast cancer electing to undergo a skin-sparing mastectomy. A Cochrane review of skin-sparing mastectomy is underway, but is unlikely to be in a position to draw further conclusions than previous reviews in the absence of either contemporary comparative studies or reports on already-studied cohorts that review longer term (10- or 15-year) local recurrence rates. One study with 10-year follow-up

Table 20.1 Comparative studies of local recurrence following skin-sparing mastectomy and non-skin-sparing mastectomy

			No. of patients		Duration of follow-up (mos)		% of local recurrence	
Author and year	Country	Study period	SSM	Mx	SSM	Mx	SSM	Mx
Horiguchi (2001) [34]	Japan	1993–1999	133	910	66	81	3.8%	1.3%
Carlson (1997) [6]	USA	1989–1994	187	84	38	48	4.8%	9.5%
Greenway (2005) [35]	USA	1989–2004	225	1022	49	49	7.1%	5.4%
Gerber (2009) [36]	Germany	1994–2000	48	130	101	101	10.4%	11.5%
Simmons (1999) [37]	USA	1990–1998	77	154	16	32	3.9%	3.2%
Ueda (2008) [28]	Japan	2000–2004	41	178	47	54	2.4%	1.7%
Kroll (1999) [38]	USA	1986–1990	114	40	>60	>60	7.0%	7.5%
Total			**825**	**2518**	**Mean: 51 mos**	**Mean: 63 mos**	**5.7%** (95% CI 4.2–7.5%)	**4.0%** (95% CI 3.3–4.9%)

These studies have all been cited in the 2010 meta-analysis by Lanitis et al. [25]
SSM skin-sparing mastectomy, *Mx* non-skin-sparing mastectomy, *mos* months, *CI* confidence interval

Table 20.2 Single-institution non-comparative studies of local recurrence following skin-sparing mastectomy

Author and year	Country	Study period	No. of patients	Duration of follow-up (mos)	% of local recurrence
Yoo (2014) [39]	South Korea	2001–2010	581	31	2.1%
Missana (2013) [40]	Monaco	1992–2002	400	88	3.5%
Carlson (2003) [41]	USA	1989–1998	375	65	8.1%
Newman (1998) [42]	USA	1986–1993	372	50	6.2%
Liang (2013) [43]	Taiwan	1995–2010	249	53	1.2%
Boneti (2011) [44]	USA	1998–2010	227	38	5.0%
Medina-Franco (2002) [45]	USA	1988–1999	173	73	4.5%
van Mierlo (2013) [46]	The Netherlands	2004–2011	157	39	2.9%
Romics (2012) [47]	UK	1995–2000	153	119	3.9%
Doddi (2011) [48]	UK	1999–2005	108	58	2.8%
Totals			**2849**	**Mean: 59 mos**	**4.1%** (95% CI 3.4–4.9%)

Minimum 100 cases per series. Data extracted only for cases of breast cancer if studies included patients who underwent a skin-sparing mastectomy as prophylactic surgery or for treatment of ductal carcinoma in situ only
mos months, *CI* confidence interval

identified an average time to locoregional recurrence of 24 months, with 13% of locoregional recurrences occurring after 5 years of follow-up [47]. The already published non-randomized studies with average follow-up periods of around 5 years are likely to have captured the majority of local recurrence events; there is scope for further reporting of long-term recurrence rates given the paucity of randomized control trials.

20.6 Conclusion

Skin-sparing mastectomy has been accepted as an oncologically safe procedure for appropriately selected patients proceeding to either therapeutic or risk-reducing mastectomy. Preservation of the skin envelope and inframammary fold considerably enhances the cosmetic outcome with immediate breast reconstruction.

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Nipple-Sparing Mastectomy

21

Damian McCartan and Virgilio S. Sacchini

21.1 Introduction

Nipple-sparing mastectomy, also referred to as total skin-sparing mastectomy, involves the removal of all glandular breast tissue with conservation of the skin of the breast, the nipple-areolar complex (NAC), and the inframammary fold. It represents advancement on skin-sparing mastectomy in an attempt to maximize the cosmetic outcome following mastectomy. A variety of factors underlie the recent increase in mastectomy rates for women with early breast cancer [1, 2]. Increasing use of MRI [3], patient factors such as family history [4], and improved access to testing for deleterious BRCA1/2 mutations are only some of the factors that have contributed to an increase in the utilization of mastectomy. Evaluation of nipple-sparing mastectomy focuses attention on the risk of occult tumor involvement of the NAC in patients undergoing therapeutic mastectomy, the risk of NAC necrosis and loss in the early postoperative period, and the long-term risk of tumor recurrence in therapeutic cases or the development of tumor in the preserved NAC in patients who undergo the procedure prophylactically.

21.2 Indications and Selection Criteria

The estimated risk of the development of breast cancer by the age of 70 years is 55–65% for women with a deleterious BRCA1 mutation and 45% with a BRCA2 mutation [5]. Four prospective studies have demonstrated that bilateral risk-reducing mastectomy leads to a highly significant reduction in the risk of breast cancer in these women [6]. While alternative risk-reduction strategies, such as chemoprevention and regular surveillance, do exist, approximately half of these women will elect for risk-reducing surgery [7]. When evaluating these patients for suitability for a nipple-sparing mastectomy, only patient factors need to be assessed given the absence of a known breast cancer. Relative contraindications to nipple-sparing mastectomy include smoking history, larger breast size, and grade 3/4 ptosis.

The estimated risk of identifying an occult cancer at the time of prophylactic mastectomy is approximately 5%. Most high-risk, known mutation carriers will have undergone an MRI in the 1-year period prior to surgery. MRI has a high negative predictive value for excluding invasive breast cancer. If a patient has had a recent diagnostic breast MRI that has not shown any evidence of concern, we do not perform sentinel node biopsy at the time of mastectomy [8]. However, in patients who proceed to surgery and have not had an MRI, it is justifiable to include a sentinel lymph node biopsy due to the risk of finding an occult breast cancer on final pathology, similar to the rationale for sentinel lymph node biopsy for cases of ductal carcinoma in situ treated with mastectomy.

In patients with a known breast cancer who are considering nipple-sparing mastectomy, a number of tumor factors should be considered in the preoperative phase. Cases with clinical evidence of skin or nipple involvement, including symptoms of bloody nipple discharge, are not suitable for nipple-sparing mastectomy. As experience with nipple-sparing mastectomy has grown, the eligibility criteria have expanded in terms of tumor proximity to the nipple [9]. Early reports had a threshold requiring a minimum 2 cm distance of tumor from the NAC based on ultrasound and mammographic assessment [10]. Many institutions now selectively use MRI if the tumor or calcifications appear close to the NAC on clinical or radiological assessment. Routine MRI is not necessary for all cases of nipple-sparing mastectomy. Tumor-to-NAC distance as measured by MRI is an important predictor of occult NAC on final pathology [10]. Our current threshold is that patients with tumor or microcalcifications less than 1 cm from the NAC are excluded. These criteria are based on non-randomized data and surgeon experience.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_21

Most authors report that both erectile function and the sensitivity of the nipple are reduced following nipple-sparing mastectomy, an outcome that is important to stress to patients when counseling them with regard to postoperative expectations.

21.3 Surgical Technique

A variety of skin incisions have been adopted through which to perform a nipple-sparing mastectomy. The most commonly described are (1) inframammary, (2) periareolar (inferior or superior) with radial extension if required, (3) radial incision, or (4) lateral incision (Fig. 21.1). In our experience, the most commonly used approach is a periareolar incision with a short lateral extension. When closing the skin incision, great care is taken to avoid deviation and lateralization of the NAC, which has been cited as a problem with the periareolar approach. Prior to incision, we use focused tumescence by injecting 10 mL of saline into the retroareolar tissue saline to help develop the plane of dissection between the breast tissue and the NAC. Care is taken to include only 25–30% of the circumference of the areola in the incision, as more extensive periareolar incisions increase the potential of NAC necrosis [11]. Initial elevation of the skin flaps with sharp, hooked retractors allows the commencement of the dissection in the mastectomy plane through the lateral extension to improve access to the retroareolar tissue.

In common with most authors who have reported their technique, we strictly use sharp dissection, in our case,

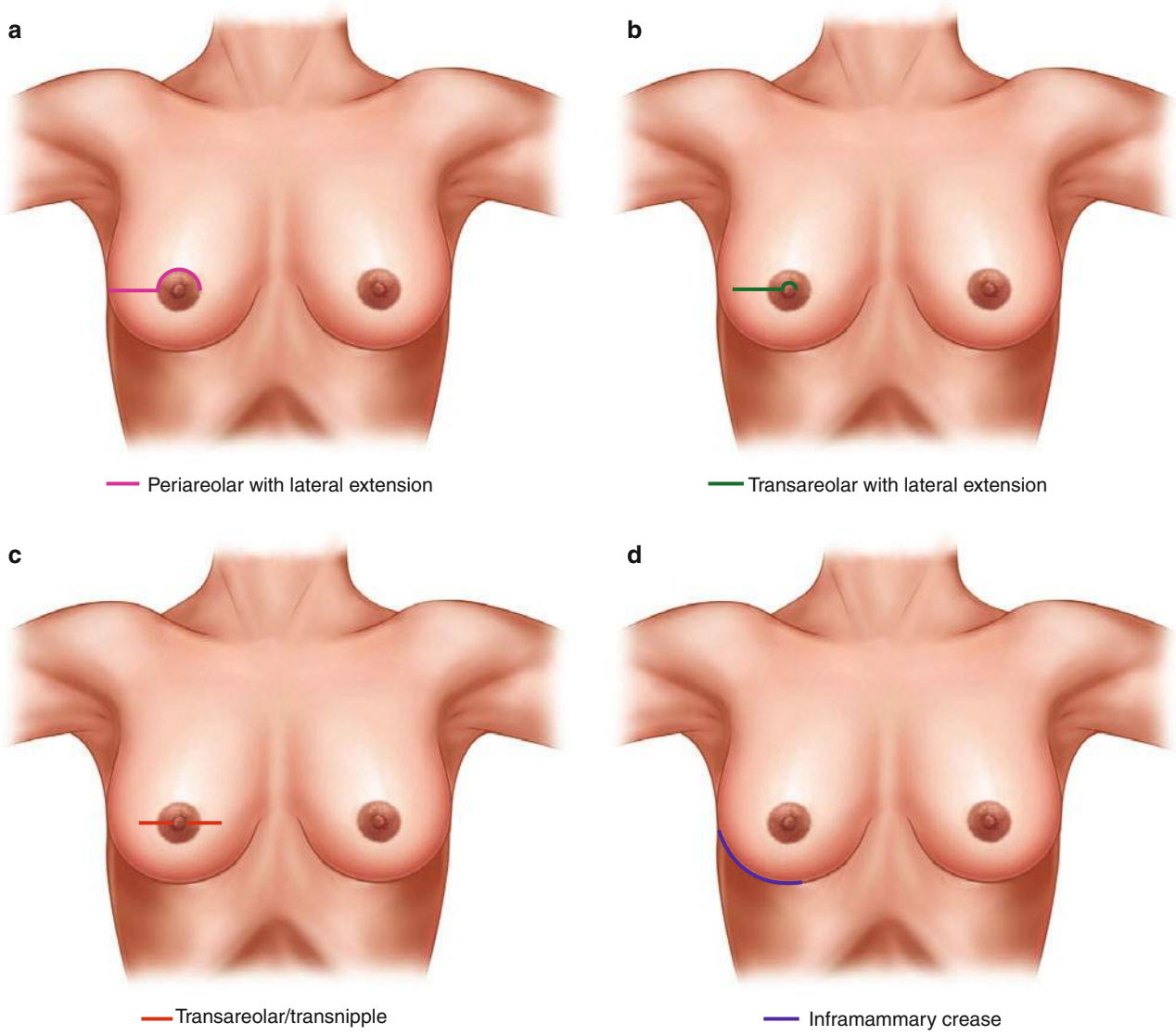

Fig. 21.1 Possible skin incisions through which to perform a nipple-sparing mastectomy

with scissors, when dissecting the retroareolar ducts. The lactiferous ducts are dissected out of the nipple, and care is taken not to fully expose the dermal plane at this level. We aim to preserve a 3 mm rim of nipple tissue to prevent NAC necrosis. It is mandatory to carry out a histological assessment of the retroareolar margin in these cases. In therapeutic cases, we use a frozen section, while in prophylactic cases, the separately submitted retroareolar margin is sent for routine histological analysis. The presence of either in situ or invasive cancer in the separately submitted retroareolar margin requires excision of the NAC. Areola-sparing mastectomy, where in cases of retroareolar margin positivity, the nipple is removed but the areola spared followed by a purse-string closure of the nipple defect, has been described. However, there are no data to justify this approach, and the concept does not appear oncologically sound.

When the subareolar tissue has been completely dissected, it is safe to revert to electrocautery for the remainder of the mastectomy, acknowledging that some surgeons prefer to use sharp dissection—sometimes coupled with tumescence—for the entire elevation of the skin flaps. Neither approach seems superior in terms of reducing postoperative morbidity [12].

Proponents of an inframammary approach point to the hidden scar as the main benefit. Dissection in these cases proceeds retro-glandular, initially taking care not to enter a retropectoral plane of dissection at the lower border of pectoralis major. Access to the upper outer quadrant and accurate transection of the axillary tail can prove taxing with this approach. A lighted retractor and an extended electrocautery tip are useful in completing the elevation of the mastectomy skin flaps at the periphery of the breast, irrespective of the incision chosen. A judicious use of gentle traction of the skin flaps during the mastectomy may prevent small capillaries from breaking and help to preserve the blood supply to the mastectomy skin flap.

The reconstructive options following nipple-sparing mastectomy are similar to those following skin-sparing mastectomy. In the majority of cases, we adopt a tissue expander as the reconstruction of choice. The use of a direct-to-implant or autologous reconstruction involves the use of a higher volume when compared to a tissue expander, increasing pressure on the NAC and mastectomy skin flap, and increasing the possibility of necrosis.

The most common factors that have been associated with pathological involvement of the nipple include the size and location of the tumor, and the distance of the tumor from the nipple as well as the presence of axillary nodal metastasis [13–15]. One recent series identified that the rate of pathological nipple involvement with either ductal carcinoma in situ or invasive cancer was 5.1% in over 600 therapeutic cases of nipple-sparing mastectomy, comparable to the 6.4% rate in a 2013 meta-analysis [9, 16].

21.4 Complications

The same concern over mastectomy skin flap necrosis and implant loss seen with skin-sparing mastectomy exists with nipple-sparing mastectomy, with the added concern over NAC necrosis. A recent prospective study found that the use of a nipple-sparing technique was an independent risk factor for mastectomy skin flap necrosis in a series of 606 mastectomies with immediate reconstruction [17]. Overall, the early postoperative risks following nipple-sparing mastectomy are higher than those for skin-sparing mastectomy [18]. In larger series, rates of major skin flap necrosis requiring operative debridement of 3–7% have been described [9, 19, 20]. The estimated rate of implant loss following nipple-sparing mastectomy in 16 studies involving a total of 2343 breast reconstructions was 3.9%, similar to our own recent experience [16, 20].

Necrosis of the NAC can range from a mild, temporary epidermiolysis that resolves with no long-term sequelae, to complete necrosis mandating return to the operating room for debridement with loss of the NAC (Fig. 21.2). Reported rates of NAC necrosis range from 1% to 41%. A recent estimate of a 2.0% rate of NAC loss was provided by a systemic review of outcomes following nipple-sparing mastectomy in 21 studies [21]. Table 21.1 [9, 20, 22–25] outlines the early postoperative outcome in selected studies that have specifically reported short-term outcomes with regard to postoperative complication. The average rate of early implant loss in these studies was 8%, a risk that is important to outline to patients preoperatively.

A technique does exist to allow intraoperative skin perfusion assessment using laser-assisted indocyanine green angiography (SPY Elite®) (Novadaq, Bonita Springs, FL) [26]. A specialized infrared camera-computer system is used to identify patterns of perfusion of the NAC, three of which have been described. The highest rates of ischemic complications were seen when perfusion appeared to originate predominantly from the underlying breast tissue. However, the clinical utility of this technology has yet to be clearly defined; further studies are required to determine if subgroups of patients in whom its use may be beneficial, in terms of aiding intraoperative decisions in a cost-effective manner, can be characterized (Fig. 21.3).

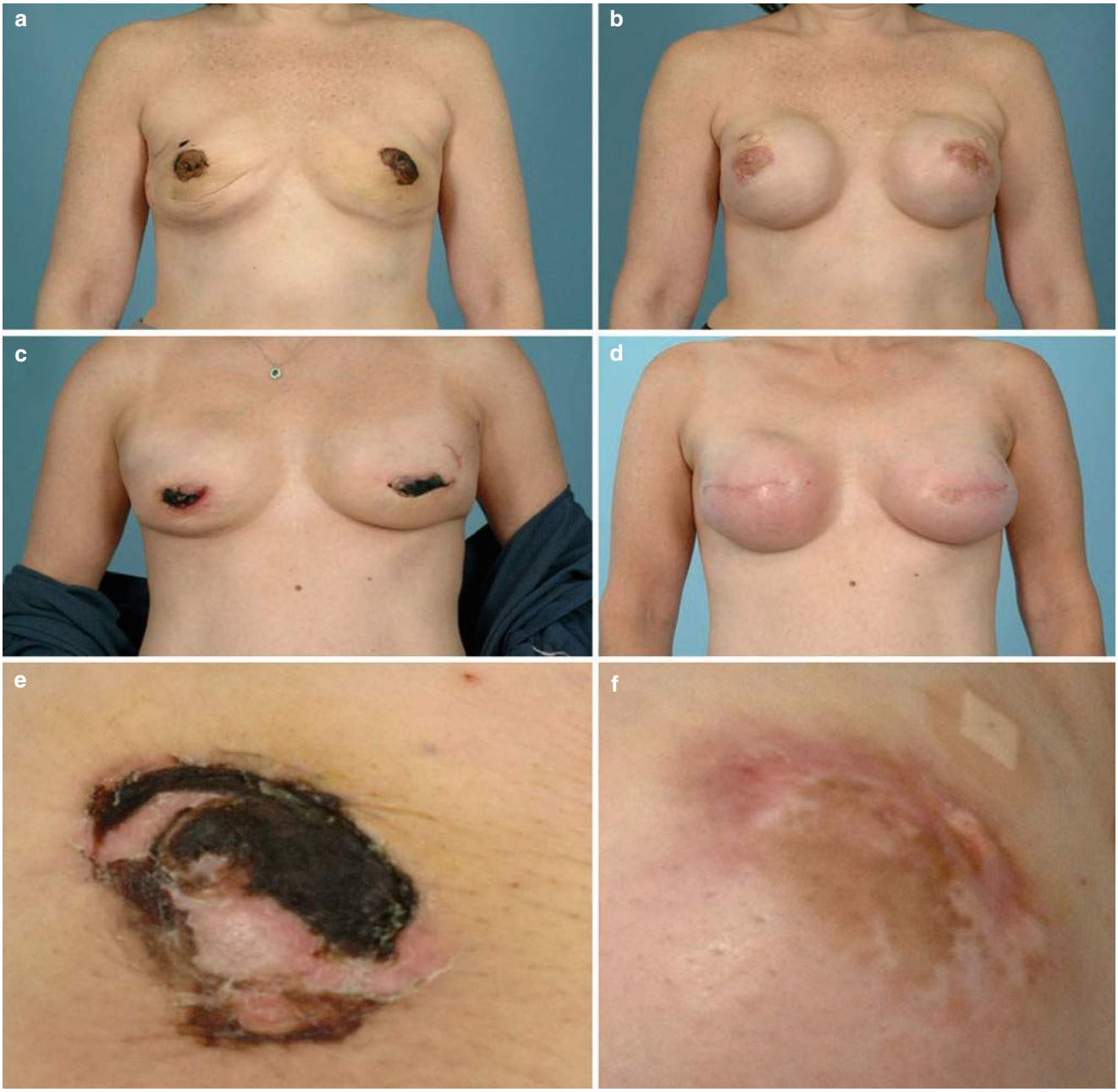

Fig. 21.2 Complications of nipple-areola necrosis following nipple-sparing mastectomy. (**a**) Partial nipple necrosis resulting in loss of a portion of the NAC. (**b**) The resulting poor cosmetic outcome of the NAC following final implant exchange. (**c**) Complete nipple necrosis leading to loss of the entire NAC. (**d**) The final result, after removal of the complete nipple necrosis in (**c**) following implant exchange. (**e**) Close-up image of partial nipple necrosis. (**f**) Appearances of partial nipple necrosis at 4 months postoperatively (Courtesy of Dr. Virgilio S. Sacchini, Memorial Sloan Kettering Cancer Center, New York, NY, USA)

Table 21.1 Nipple-areola necrosis and implant loss following nipple-sparing mastectomy

Study/year	Country	Study period	No. of procedures	Partial NAC necrosis (%)	NAC loss (%)	Implant loss (%)
Crowe (2008) [22]	USA	2001–2007	149	2.6	1.3	–
Kim (2010) [23]	Korea	2001–2006	115	13.0	9.6	
Radovanovic (2010) [24]	Serbia	2004–2008	214	–	2.5	5.6
Manning (2015) [20]	USA	2005–2013	177	7.3	4.5	3.5
Wang (2014) [9]	USA	2005–2012	981	5.0	2.1	8.2
Warren Peled (2012) [25]	USA	2001–2010	657	2.0	1.5	9.9
Total			**2293**	**4.5**	**2.5**	**8.1**

NAC nipple-areolar complex

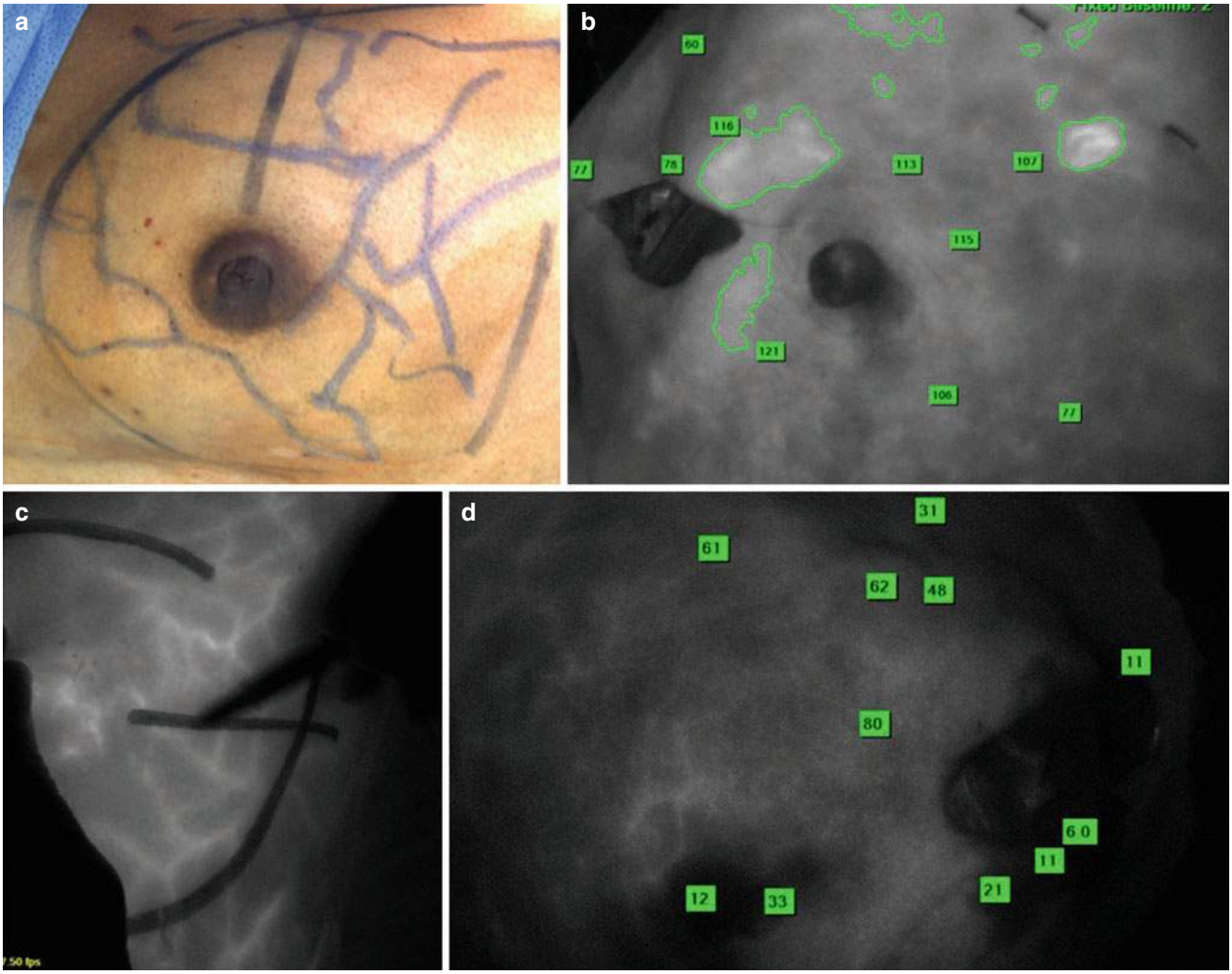

Fig. 21.3 Application of intraoperative skin perfusion assessment. (**a**) Skin flap vessels marked preoperatively following indocyanine green angiography. (**b**) Example of good perfusion values following nipple-sparing mastectomy via lateral incision prior to implant placement. (**c**) Skin incisions can be adjusted to avoid larger skin flap vessels identified on pre-incision angiography. (**d**) Poor perfusion of nipple areola complex following nipple-sparing mastectomy after indocyanine green angiography (SPY Elite®) (Courtesy of Dr. Virgilio S. Sacchini, Memorial Sloan Kettering Cancer Center, New York, NY, USA)

21.5 Cosmetic Outcome

One of the theories underpinning nipple-sparing mastectomy is that among women, NAC preservation results in higher psychological satisfaction and the perception of less mutilation. There are few studies that have used validated patient outcome instruments to compare aesthetic outcomes between nipple-sparing and skin-sparing mastectomy. Survey-reported outcomes do suggest that preservation of the NAC is associated with improved patient satisfaction, body image, and psychological adjustment when compared to patients who had completed nipple-areolar reconstruction following mastectomy [27]. After a follow-up period of over 2 years, both "satisfaction with breasts" and "satisfaction with outcome" scores as assessed by the Breast-Q Patient Reported Outcomes Instrument were similar between 40 patients undergoing either skin-sparing mastectomy or nipple-sparing mastectomy as a risk-reducing procedure [28]. A range of disease (more-advanced stage), patient (BMI, socioeconomic status), and surgical variables (implant versus autologous reconstruction) are known to effect ensuing patient-reported outcomes after mastectomy. Following nipple-sparing mastectomy, the majority of patients do report satisfaction with nipple appearance and relatively low levels of body image-related distress [28, 29]. Studies that have assessed NAC sensitivity following nipple-sparing mastectomy have confirmed that most women have objectively minimal or absent sensation following surgery [28, 30]. Other areas of dissatisfaction that

are reported following nipple-sparing mastectomy include disappointment with the position of the NAC, a reduction in sexual pleasure, hypersensitivity of the preserved NAC when touched, and loss of erection of the nipple. These grievances stress the importance of thorough preoperative counseling when appraising the motivations and preferences of patients (Fig. 21.4).

As with skin-sparing mastectomy, the use of postmastectomy radiotherapy does negatively impact the longer-term cosmetic outcome following nipple-sparing mastectomy; this is discussed further in Chap. 59 [31].

21.6 Oncologic Safety

As with skin-sparing mastectomy, the long-term oncologic outcomes for nipple-sparing mastectomy are not yet well established. There are, to date, no randomized trials examining rates of local recurrence, and, based on the low event rates in published retrospective cohorts to date, it is unlikely that such a trial will ever take place. Many of the cohorts on which oncologic outcomes have been reported to date have yet to reach the maturity of 5 years of follow-up that we have come to expect in breast

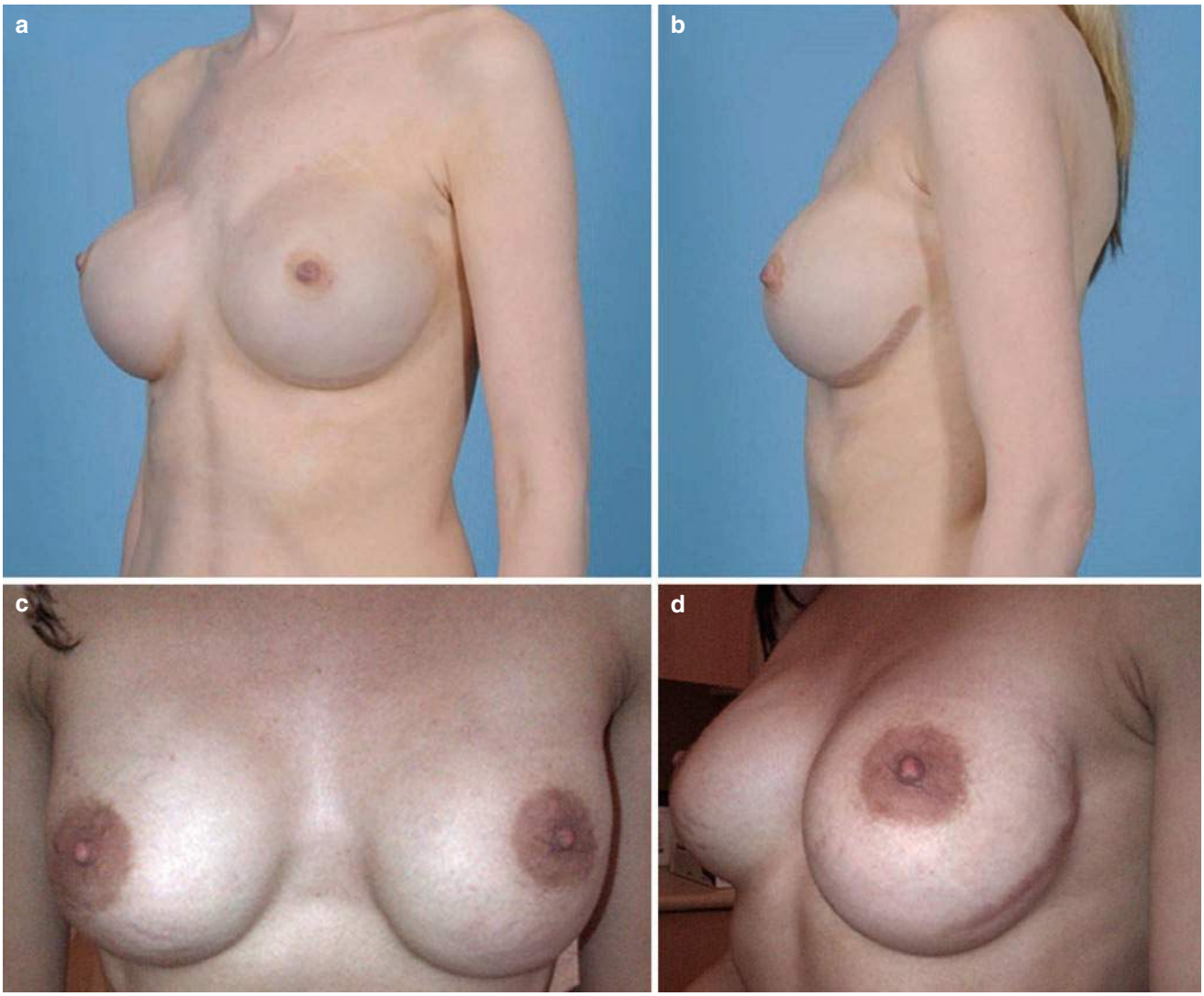

Fig. 21.4 Examples of final cosmetic outcomes following nipple-sparing mastectomy. (**a**, **b**) Anterior and lateral views at 2 years following nipple-sparing mastectomy via inframammary crease incision. (**c**, **d**) Anterior and lateral views 3 years following nipple-sparing mastectomy via inframammary crease incision (Courtesy of Dr. Virgilio S. Sacchini, Memorial Sloan Kettering Cancer Center, New York, NY, USA)

Table 21.2 Studies of local recurrence following nipple-sparing mastectomy with ≥4 years median follow-up

Author and year	Country	Study period	No. of patients	Duration of follow-up (months)	% Local recurrence
Caruso (2006) [10]	Italy	1994–2004	50	66	2.0%
Benediktsson (2008) [32]	Sweden	1988–1994	216	156	24%
Gerber (2009) [31]	Germany	1994–2000	60	101	11.7%
Kim (2010) [23]	Korea	2001–2006	152	60	2.0%
Jensen (2011) [33]	USA	1997–2008	99	60	3.0%
Petit (2012) [21]	Italy	2002–2007	934	50	5.1%
Shi (2012) [34]	China	2000–2008	35	68	5.7%
Sakurai (2013) [35]	Japan	1985–2004	788	87	8.2%
Stanec (2014) [36]	Croatia	1997–2012	252	63	3.7%
Shimo (2015) [37]	Japan	2000–2013	413	47	5.8%
Seki (2015) [38]	Japan	2003–2013	121	60	7.6%
Sakamoto (2015) [39]	Japan	2003–2011	404	61	2.6%
Totals			**3524**	**Mean: 69 months**	**6.6%** (95% CI 5.8–7.5%)

CI confidence interval

surgical oncology. Well-defined reporting of the oncologic outcomes will need to continue through either cancer registry data or thorough, updated reports from single institutions to confirm that the low rates of local recurrence are consistent through future years of follow-up. Table 21.2 [10, 21, 23, 31–39] contains details of 12 studies of therapeutic (including both invasive cancer and ductal carcinoma in situ) nipple-sparing mastectomy that have accrued an average follow-up of 4 years or more. The average local-regional recurrence rate reported is 6.6%, comparable to the 5.7% rate seen with skin-sparing mastectomy as mentioned in the previous chapter. These account for recurrences both in the preserved NAC and in the residual skin envelope. There are considerably more reports of outcomes less than 4 years, and as these cohorts mature, ongoing reporting of the longer-term local recurrence outcomes will be required to allow continued evaluation of the oncologic safety of nipple-sparing mastectomy.

The employment of electron intraoperative radiotherapy as an adjunct with the aim of reducing local recurrence is described in Chap. 15.

21.7 Conclusion

Nipple-sparing mastectomy has entered the realm of everyday breast surgical oncology. The technique, applied to properly selected patients, can provide excellent cosmetic outcomes and greatly enhance overall patient satisfaction postmastectomy. Patients need to be thoroughly counseled through preoperative planning to cover the risks of NAC loss either on the basis of a positive retroareolar margin assessment or due to ischemic complications. It is important to ensure patients understand that, while promising, data pertaining to oncologic outcome both for therapeutic and prophylactic procedures do not yet cover long-term outcomes and that the absolute reduction in risk is not 100%.

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Part III

Partial Breast Reconstruction

Preoperative Planning for Oncoplastic Surgery

22

Cicero Urban, Mario Rietjens, and Mahmoud El-Tamer

22.1 Introduction

Oncoplastic surgery (OP) represents an important evolution in breast cancer treatment. It allows better aesthetic-functional outcomes and an improvement of the psychological aspects of patients with breast cancer, broadening indications for breast-conserving treatment (BCT). The various techniques for immediate partial breast reconstruction must be dealt with case by case so the best results concerning the aesthetic-functional binomial and symmetry can be achieved. Considering delayed reconstructions, results are generally inferior to those obtained in immediate ones, and in many cases major surgical procedures are required. Therefore, the emphasis of this new phase in breast surgery must be on immediate reconstruction associated with the transversal integration between oncologic and aesthetic concepts [1–17].

However, the risk of local recurrence after a BCT is hard to be completely discharged. A local failure might reflect a disease with more aggressive biology, as well as a new primary tumor or even a failure in the treatment. These failures may occur as a consequence of selection of patients or inadequate treatment, but they tend to lower after the use of high-quality image testing, adjuvant radiotherapy and systemic treatment, and surgical excisions with negative margins [18, 19]. Concerning this last point, the surgeon daily faces the dilemma of performing resections with wide margins, aiming to reach ideal oncologic control and, at the same time, not remove too much breast tissue, which could result in major deformities or asymmetry between the breasts. If locoregional control represents the main target of oncologic surgeries, aesthetical outcomes are the basic principle in BCT.

A way to reduce this conflict is to apply plastic surgery techniques to oncology breast surgery. This concept, which has been tailored in some centers in Europe, the USA, and Brazil in the 1980s, is based on three fundamental points: ideal oncology surgery, ipsilateral reconstruction, and immediate contralateral symmetry applying plastic surgery techniques [1–17]. Therefore, it allows for more extensive resections in BCT, and it does not cause severe damage to final aesthetic outcomes [20, 21]. The focus of OP, as well of other techniques, like sentinel node biopsy, is to improve patients' quality of life through treatments that can be more effective and less aggressive.

Then, this chapter will deal with OP planning in early breast cancer, which is as important as operative time for this surgery. Both are fundamental to achieve the best oncological and aesthetical outcomes and reduce/avoid decision and technical errors in this kind of surgery.

22.2 Patient Selection

OP is more complex and time-consuming than lumpectomy and quadrantectomy. Thus, selection of patients from oncological, aesthetical, and psychological point of view is critical. All attempts should be made to minimize the risk of positive margins, which are difficult and sometimes impossible to reassess in a second surgery, and to reduce and prevent complications that may delay adjuvant treatments. In addition, patients strongly motivated to preserve their breasts better tolerate this kind of surgery. Therefore, there are some established indications for OP in BCT, the main ones are for patients with more than 20% of volume of mammary resection, and specially in the cases of macromastia, where results

Electronic Supplementary Material The online version of this chapter (doi:10.1007/978-3-319-62927-8_22) contains supplementary material, which is available to authorized users.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_22

Table 22.1 Indications and relative contraindications for oncoplastic surgery in breast-conserving surgery

Indications
• Resections over 20% of breast volume
• Macromastia
• Severe ptosis and asymmetry
• Need for large skin resections inside mammoplasty area
• Central, medial, and inferior tumors
• Previous plastic surgeries in the breast
Relative contraindications
• Extensive tumors located in medial regions
• Low-volume breasts without ptosis
• Previously irradiated breasts
• Large skin resections beyond the mammoplasty area
• Tobacco addiction and uncontrolled diabetes
• Exaggerated patient's expectations with aesthetic results

from skin-sparing or nipple-sparing mastectomy are usually unsatisfactory and OP approach may also favor radiotherapy planning [22]. Current indications and limits of OP in BCT are in Table 22.1.

22.3 Preoperative Planning

It is essential that the choice of OP techniques in BCS depends on elements related to the tumor location, size and multifocality/multicentricity, characteristics of the breast, and clinical evaluation of the patient. Although the only significant element referred as an aesthetical risk in BCS in Cochrane evaluation was the volume of breast resection over 20%, in clinical practice there are other individualized risk factors that should be observed [22]:

- Tumor size
- Multicentricity and multifocality
- Location of tumor and proximity with skin
- Distance between tumor and nipple areola complex (NAC)
- Previous and future radiotherapy
- Previous mammoplasty
- Volume and shape of the breast
- Level of mammary ptosis and breast asymmetry
- Liposubstitution level

In some circumstances, associated clinical conditions may influence on the choice of the most appropriate technique. Diabetic patients, tobacco addicts, those with collagen diseases, and those above 70 years old are subject to risks concerning unsatisfactory aesthetic results and higher skin healing complication risks. Major resections and wide NAC dislocations may bring risks of fat necrosis and of partial or total NAC losses [22].

The ideal location for a tumor is within the wise resection area or inside the mammoplasty area. When the tumor is close to the skin and out of this area, the OP procedure may be more complex, and it may require combined or non-conventional techniques, whose results are not always satisfactory. In such cases skin-sparing or nipple-sparing mastectomy should be considered as an option, as well as in the cases that a major resection of the skin is needed. Flaps as the one from the *latissimus dorsi*, which has a different color and texture from the breast, usually bring unsatisfactory results and therefore should be considered as an exception [22].

High-volume breasts, with severe ptosis, allow for surgeries with wider margins and usually bring more satisfactory results. Patients with macromastias present a formal indication for OP due to better radiotherapy planning. In cases of previous breast augmentation surgeries, it is necessary to take into consideration that the breast volume is not the real one, and consequently some considerable deformities may result. The biggest problem concerning OP is dealing with young patients, with conic breasts, without mammary ptosis, and with low- or medium-volume ones. In such cases, according to the location or tumor size, local flaps offer a little chance of good results, so skin-sparing or nipple-sparing mastectomy with immediate reconstruction may be the best choice [22].

OP decision is based on oncological and aesthetic concepts and principles, so a structured guideline is not possible to assist all cases with all involved variables, but it can help the decision-making process. Basically, the flowchart for OP planning should be taken according to the features of the patient's breast and the tumor size and location (Figs. 22.1 and 22.2) [22].

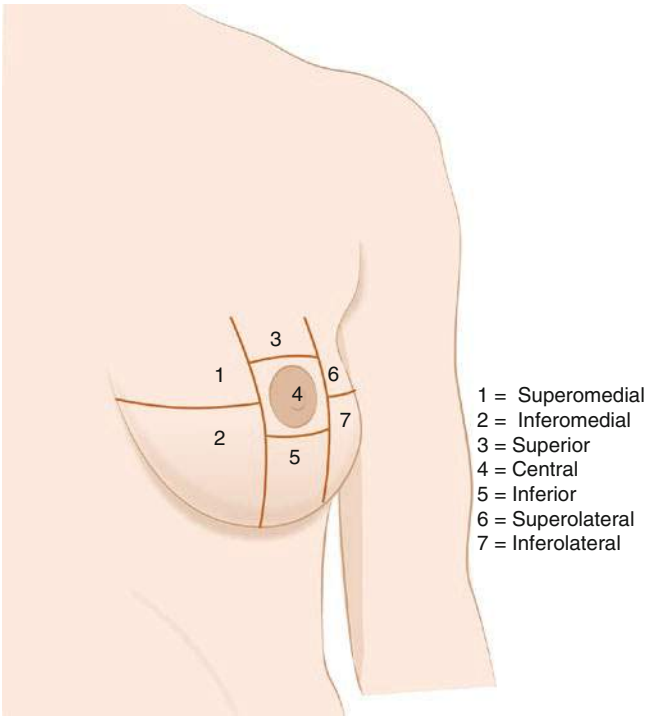

Fig. 22.1 Breast quadrants in oncoplastic surgery

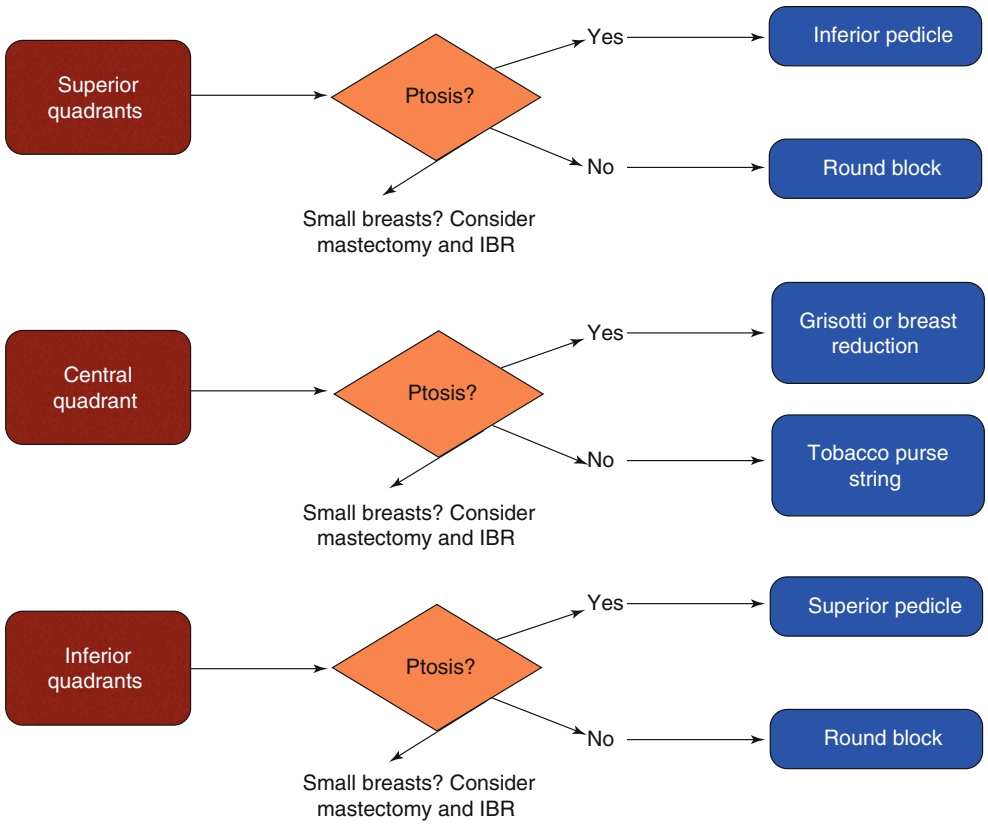

Fig. 22.2 Decision planning flowchart in oncoplastic surgery. *IBR* immediate breast reconstruction

22.4 Immediate Partial Breast Reconstruction Techniques

22.4.1 Class I Techniques

22.4.1.1 Planning for Glandular Flaps

Class I techniques consist of moving glandular flaps around the defect caused by classical quadrantectomy or lumpectomy resections, in an attempt to cover it. It is preferentially indicated for premenopausal patients, when the glandular component of the breast is higher, therefore reducing the risks of liponecrosis in the postoperative period. These techniques are also more indicated in cases of tumors located in the upper quadrants, where mammary gland is less thick. Even if there is a small filling defect, such a defect is not so visible. The opposite effect happens in the lower quadrants, where the mammary gland thickness is more important, and if some specific techniques are not applied, the resulting aesthetic defect may be disastrous. Glandular reshaping in lower portions of the breast is possible for small tumors, in vertical or oblique ways. Planning for the position of the incisions should consider the quadrant of tumor location and proximity to skin (Figs. 22.3 and 22.4).

22.4.1.2 Planning for Central Quadrant Techniques

This represented a great innovation in early days of BCT, as up to some years ago having a retroareolar neoplasia was synonymous of mastectomy. Immediate breast reconstruction techniques for central quadrant resections may vary according to breast volume, level of ptosis, and shape of ptosis (either vertical or lateral). Considering breasts without ptosis or with slight ptosis, it is possible to use the glandular suture in tobacco purse string. Two or three layers of glandular suture allow for obtaining the central projection of the mammary cone, and the intradermal suture also in tobacco pouch would produce a residual scar within the area where the future nipple and areola complex would be reconstructed, therefore causing the scar to disappear almost completely (Fig. 22.5). The only disadvantage of this technique is that there isn't good confrontation of the coetaneous edge and consequently there might be some delay in the healing process.

Considering large breasts with oblique ptosis, it is possible to use a technique, originally described by Grisotti, derived from the reductive mammoplasty techniques based on rotation of infero-lateral glandular pedicle, preserving a dermal island that replaces NAC (Fig. 22.6). This might be the first OP technique described in the literature, as it was a direct adaptation of plastic surgery techniques to BCT [23].

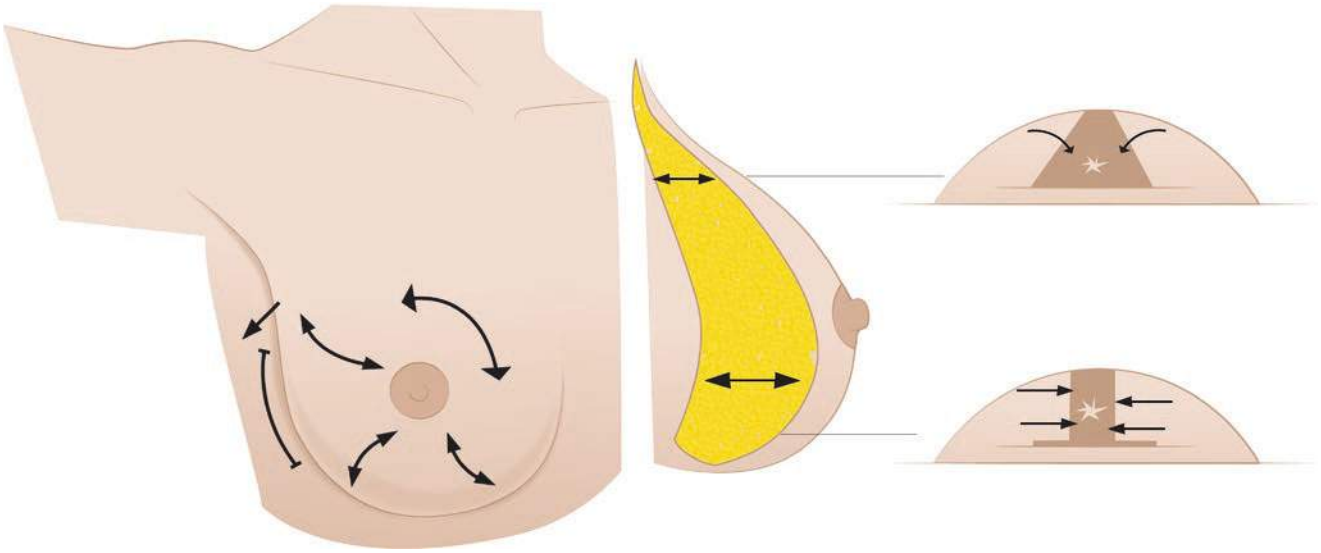

Fig. 22.3 Class I glandular flaps: skin incisions and glandular reshaping

Fig. 22.4 Class I glandular reshaping for superior quadrants tumors

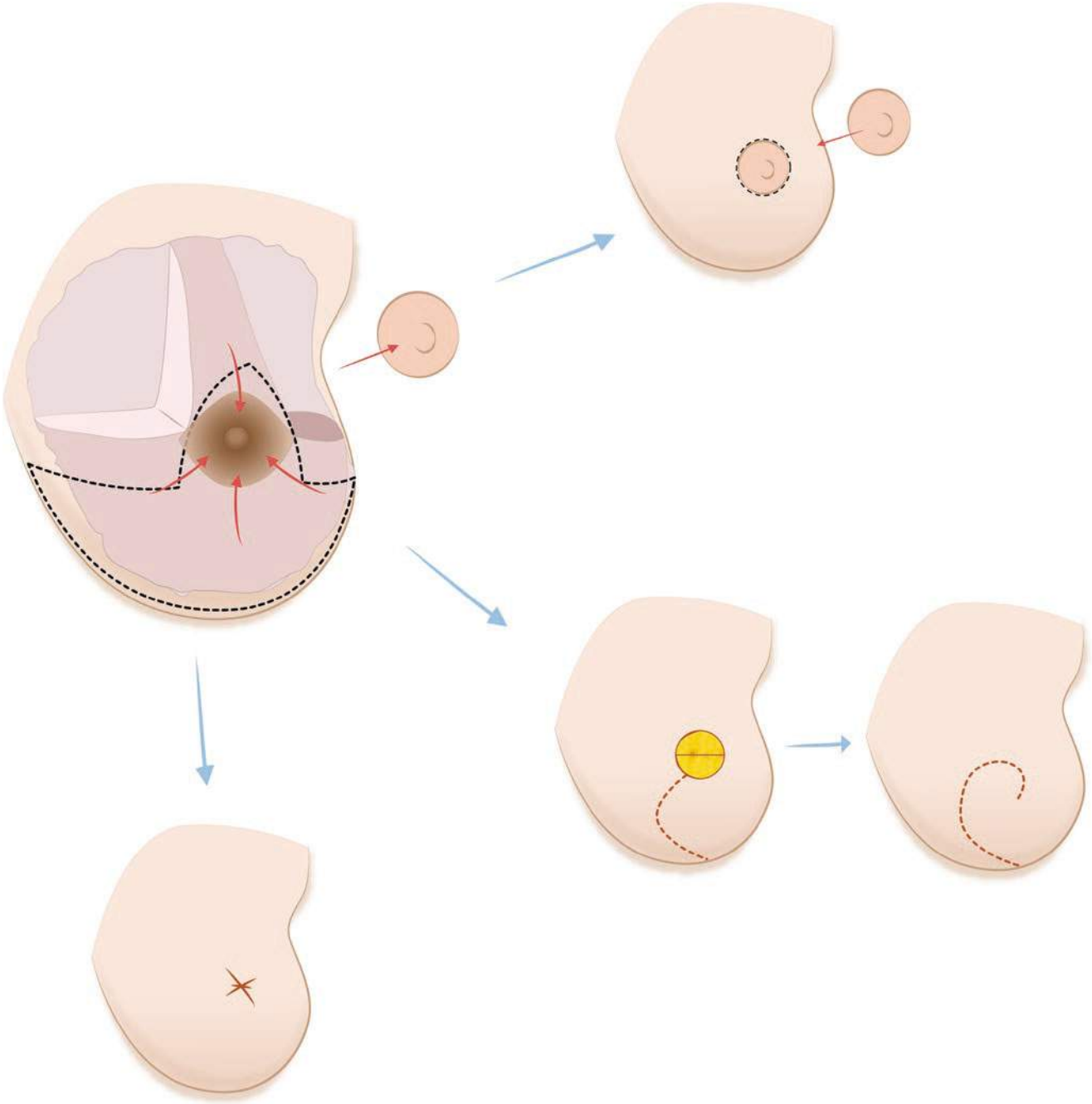

Fig. 22.5 Central quadrant planning for tobacco purse string suture and for dermoglandular flaps

22.4.2 Class II Techniques

22.4.2.1 Planning for Periareolar Techniques

These class II techniques are inspired by reductive mammoplasty techniques proposed by Sampaio-Góes [24] and Benelli [25], in which a major glandular coetaneous undermining procedure for remodeling through a periareolar scar is performed. It is indicated for cases of small- or medium-volume breasts and with slight or medium ptosis. The great advantage of these techniques is that it allows for a tumorectomies in any part of the breast.

The preoperative drawing is done with the patient standing up, and basically it is necessary to calculate only two points (A and B). Point A represents the position of the upper edge of the areola, which can be calculated by different methods. The simplest method is that this point corresponds to the transition from the superior 2/3 of the arm to the inferior 1/3. Another method, proposed by Pitanguy [26], would be to calculate initially the future position of the nipple, which would be the projection of the tip of a finger placed in the level of the inframammary sulcus. Bearing in mind that the diameter of a normal are-

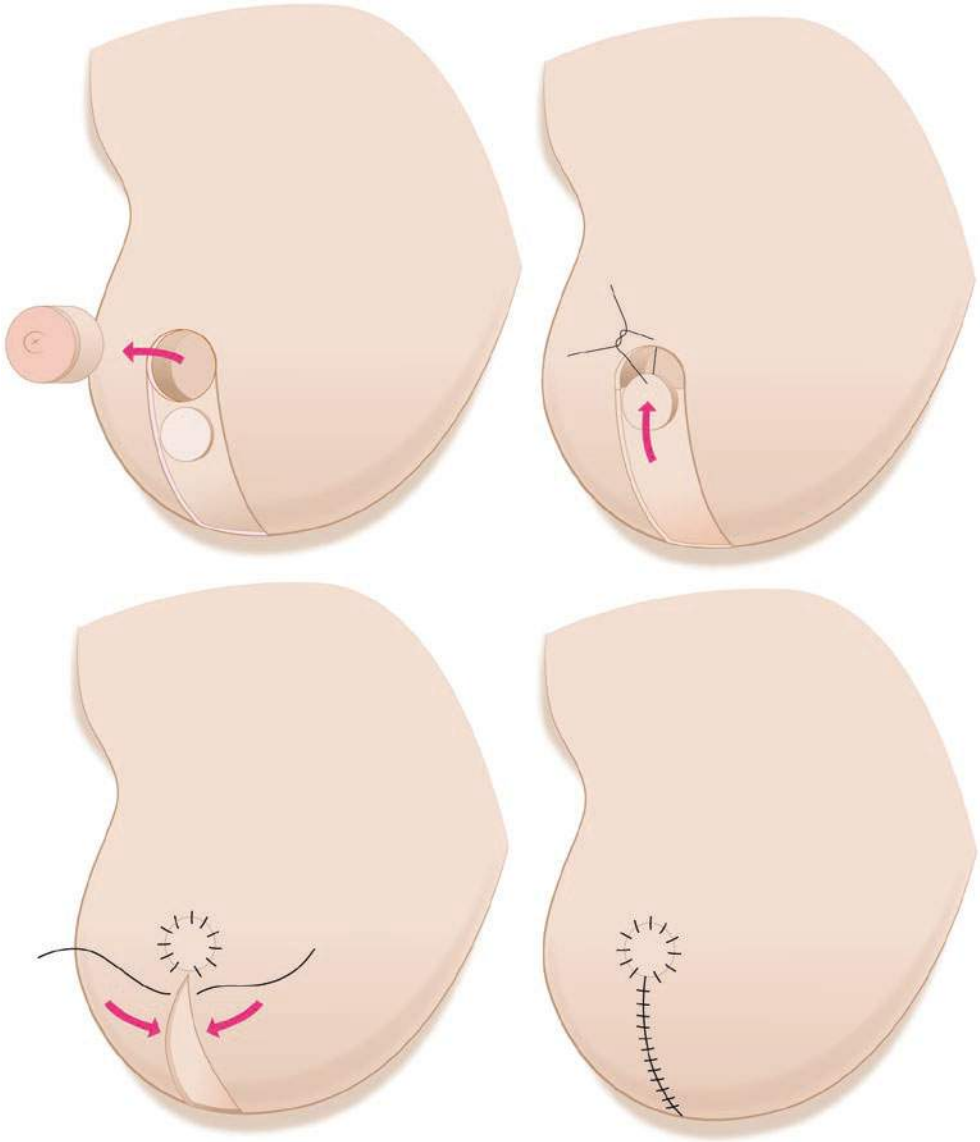

Fig. 22.6 Grisotti's flap planning for central quadrant reconstruction

ola is about 45 mm, one can calculate the radius of 23 mm superiorly to mark point A. Point B would be the inferior point of the areola, whose calculation is based on the distance between the lower point of the areola and the inframammary sulcus, around 40 mm for a small breast and about 60 mm for a large breast, without ptosis (Fig. 22.7). Once these two points are obtained, it is necessary to trace an ellipsis, which will indicate the coetaneous removal.

22.4.2.2 Planning for Superior Pedicle Techniques

These techniques are based on superior vascular pedicles as those proposed by Pitanguy [26] or Lejour [27]. They may be useful in cases of tumors situated in the lower quadrants and are appropriate for large breasts or medium-volume ones with minimal to big ptosis. These techniques are similar to the ones used in aesthetic surgeries. The upper point of the areola (point A) is calculated as in the preceding technique. Point B can be obtained by drawing an inverted "T" of 5-4-4 cm, which originates an areola whose diameter is approximately 45 mm. The superior drawing is made in a "mosque roof" shape in order to reduce the tension in point B. Vertical pillar design is made through superior-internal and superior-external mobilization of the breast as described in the technique by Lejour [27]. Decision on whether to perform only a vertical scar or an inverted "T" scar will depend on the level of hypertrophy and the level of ptosis. Considering smaller breasts and those with less ptosis, it is possible to perform only a vertical scar, and considering cases of larger breasts with a major ptosis, an inverted "T" scar will avoid the coetaneous excess as the skin fold produced in the vertical scar. The format of the scar as vertical or inverted "T" can be central (more frequent), medial, or lateral, according to the location of the tumor and the need for skin removal on the nodule aiming to obtain a better surgical radicalization (Fig. 22.8).

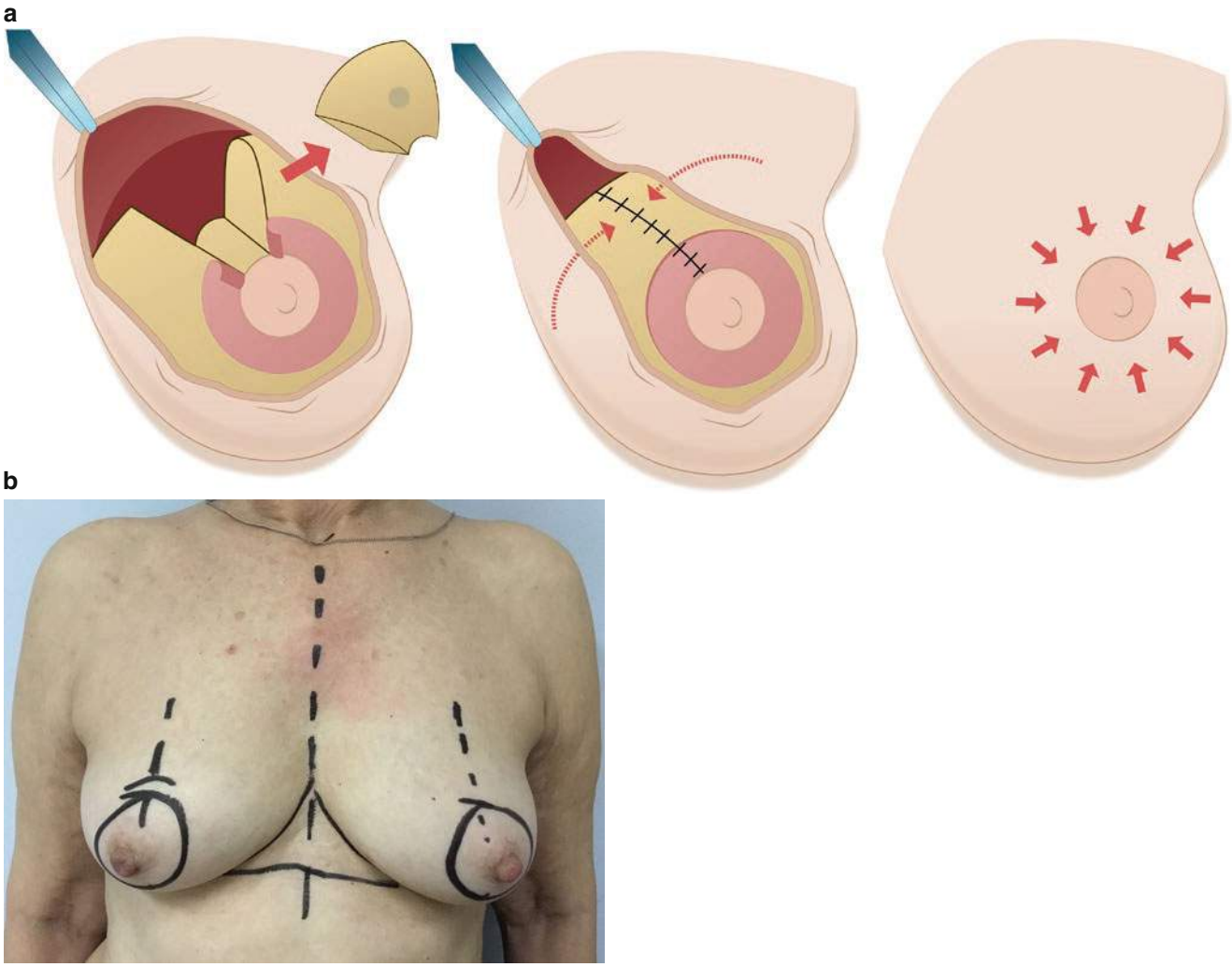

Fig. 22.7 Round-block technique planning

22.4.2.3 Planning for Inferior Pedicle Techniques

These techniques are based on inferior and posterior vascular pedicles, as described by Ribeiro and Robbins. They may be applied in cases of tumors situated in the upper quadrants of the breast [28, 29]. Preoperative drawings can be made in the same way and measurements of Pitanguy's and Lejour's techniques, with a periareolar scar and inverted "T" or vertical/oblique inferior line. The areolar pedicle is in the inferior-posterior pedicle and should be drawn at least with a 6–8 cm of inferior base. This measurement is important to preserve the posterior vessels located in the lateral edge of the pectoralis major muscle, which penetrate in the pedicle (Fig. 22.9).

22.5 Conclusions

Preoperative planning is the most important time in OP surgery. It implies in two fundamental aims: organization of surgical steps to follow in the theater and to reduce surgical risks. In OP planning is essential to anticipate the size and location of future glandular and skin defects and NAC relations to them. Symmetry is the big challenge, and it is clear that with a good preoperative planning it is possible to achieve better oncological and aesthetical-functional outcomes. It is the time to plan how to correct previous asymmetries and combine it to oncological approach. And it is the last time for the surgeon to detect some patient's misconceptions about this kind of surgery and its limitations, which are bigger than aesthetic surgeries (Figs. 22.7, 22.8, and 22.9).

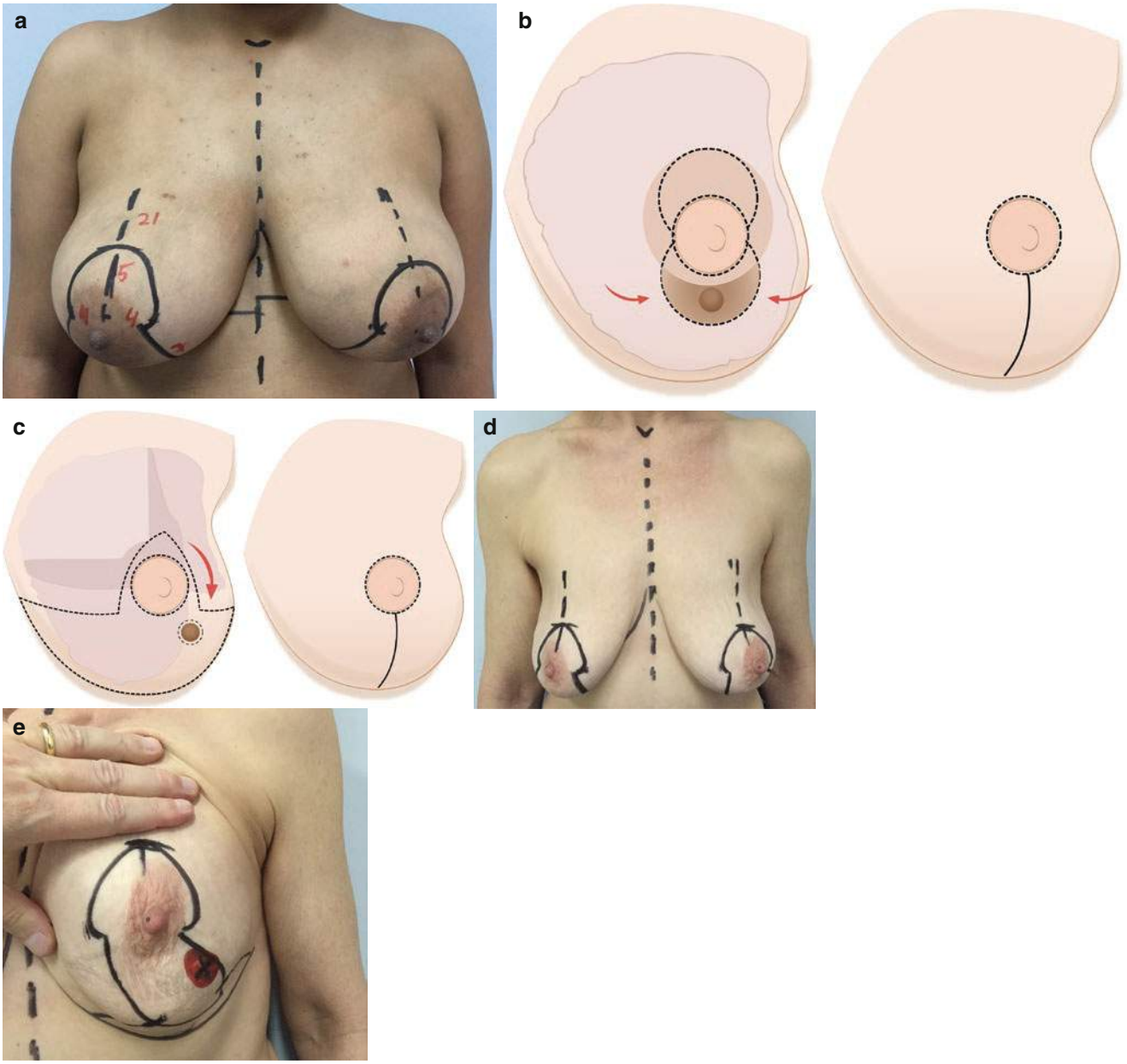

Fig. 22.8 Superior pedicle technique planning (tumors in inferior quadrants), with example of measurements

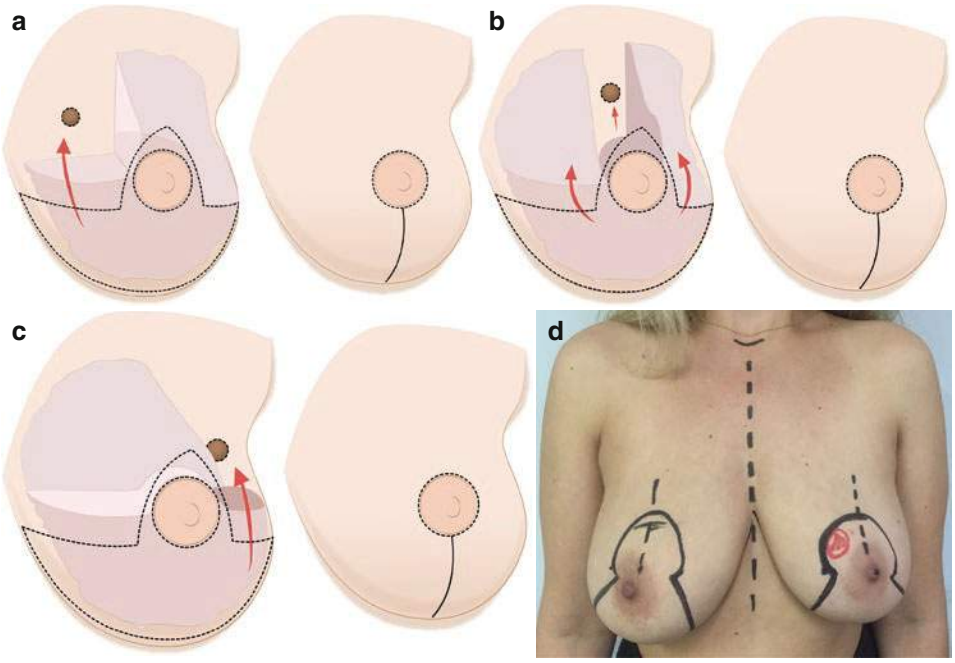

Fig. 22.9 Inferior pedicle technique planning (tumors in superior quadrants)

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Improving Breast Cancer Surgery: A Classification and Quadrant-per-Quadrant Atlas for Oncoplastic Surgery

23

Raquel F. D. van la Parra, Claude Nos, Isabelle Sarfati, and Krishna B. Clough

23.1 Introduction

23.1.1 Breast Conservation Limitations

Breast conservation surgery (BCS) combined with postoperative radiotherapy has become the preferred locoregional treatment for the majority of patients with early-stage breast cancer, with equivalent survival to that of mastectomy and improved body image and lifestyle scores. The success of BCS for breast cancer is based on the tenet of complete removal of the cancer with adequate surgical margins, while preserving the natural shape and appearance of the breast. Achieving both goals together in the same operation can be challenging, and BCS has not always produced good cosmetic results in all patients. One of the limiting factors is the amount of tissue removed, not only in terms of absolute volume but also in relation to tumour location and relative size of the breast. If either of these two goals is not obtainable, mastectomy is often proposed to the patient. An alternative is to downsize the tumour preoperatively with either chemotherapy or hormone therapy. However, not all tumours respond to neoadjuvant treatment. The failure of classical BCS techniques to offer solutions for challenging scenarios has stimulated the growth and advancement of new techniques in breast surgery during the past decade.

23.1.2 Oncoplastic Surgery Defined

Oncoplastic surgery (OPS) has emerged as a new approach to allow wide excision for BCS without compromising the natural shape of the breast. It is based upon integration of plastic surgery techniques for immediate breast reshaping after wide excision for breast cancer. The conceptual idea of OPS is not new, and its oncologic efficacy in terms of margin status and recurrence compares favourably with traditional BCS [1–4].

Oncoplastic techniques for breast conservation range from simple reshaping and mobilization of breast tissue to more advanced mammoplasty techniques that allow resection of up to 50% of the breast volume. Our goal is to develop a clear classification system of oncoplastic techniques and outline a systematic approach for all breast surgeons to follow when undertaking BCS.

23.2 Oncoplastic Principles: Selection Criteria

23.2.1 Elements for Selection

We identify three elements to select patients who would benefit from an oncoplastic approach for BCS. The two factors already recognized as major indications for OPS are excision volume and tumour location [5]. The third additional element we evaluate is glandular density. When taken into consideration together, these three elements comprise a sound guideline for determining when and what type of OPS to perform and, more importantly, to reduce the guesswork in performing BCS.

23.2.2 Excision Volume

The first element, excision volume, is the single most predictive factor of surgical outcome and potential for breast deformity. Studies have suggested that, once 15–20% of the breast volume is excised, there is a clear risk of deformity [6]. Excision volume compared to the total breast volume is estimated preoperatively. Through systematic determination of specimen weights, accurate preoperative estimation of excision volume can be achieved. The average specimen from BCS weighs 20–40 g; as a general rule, 80 g of breast tissue is the maximum weight that can be removed from a medium-sized breast without resulting in deformity.

OPS techniques allow for significantly greater excision volumes while preserving natural breast shape. All OPS studies

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_23

have demonstrated that an average of 120 g up to 1000 g or more can be removed from a medium- to large-sized breast during BCS with no cosmetic compromise [7]. Reshaping of the breast is based upon the rearrangement of breast parenchyma to create a homogenous redistribution of volume loss. This redistribution can be achieved easily through either advancement or rotation of breast tissue into the lumpectomy cavity. Others advocate the harvesting of a latissimus dorsi "miniflap" to fill in the defect. This volume replacement technique has been recently described by Rainsbury [5]. In general, this approach is reserved for small-sized breasts and will not be discussed here.

23.2.3 Tumour Location

The location of the tumour is the second factor in planning OPS. There are zones that are at high risk of deformity during BCS when compared with more forgiving locations. The upper outer quadrant of the breast is a favourable location for large-volume excisions. In this location, defects can readily be corrected by mobilization of adjacent tissue. Excision from less favourable locations, such as the lower pole or upper inner quadrants of the breast, often creates a major risk for deformity. For example, a "bird's beak" deformity is classically seen on excision of tumours from the lower pole of the breast [1]. Therefore, a key tool used in planning the appropriate surgical approach is evaluating the tumour location and the associated risk of deformity. For extensive resections, we have developed an oncoplastic Atlas of surgical techniques based on tumour location. This Atlas provides a specific mammoplasty technique for each segment of the breast.

23.2.4 Glandular Density

Glandular density is the final component of a complete OPS evaluation before surgery and is evaluated both clinically and radiographically. Although the clinical exam is reliable, mammographic evaluation is a more reproducible approach for breast density determination. Breast density predicts the fatty composition of the breast and determines the ability to perform extensive breast undermining and reshaping without complications. Breast density can be classified into four categories based on the Breast Imaging Reporting and Data System (BIRADS): fatty (1), scattered fibroglandular (2), heterogeneously dense (3) or extremely dense breast tissue (4) [8].

Undermining the breast from both the skin and pectoralis muscle (dual-plane undermining) is a major requirement to perform level I OPS. A dense glandular breast (BIRADS 3/4) can easily be mobilized by dual-plane undermining without risk of necrosis. Low-density breast tissue with a major fatty composition (BIRADS 1/2) has a higher risk of fat necrosis after extensive undermining. Low breast density should provoke the decision to either limit the amount of undermining during level I OPS or proceed to a level II OPS that requires only posterior undermining, leaving the skin attached.

23.2.5 Oncoplastic Classification System

We propose a new classification of OPS techniques into two levels based upon the amount of tissue excised and the relative level of surgical difficulty. A level I approach is based on dual-plane undermining, including the nipple-areola complex (NAC), and NAC recentralization if nipple deviation is anticipated. No skin excision is required. Level II techniques allow major volume resection. They encompass more complex procedures derived from breast reduction techniques. These "therapeutic mammoplasties" involve extensive skin excision and breast reshaping [9]. They result in a significantly smaller, rounder breast.

23.2.6 Bi-Level Classification

Our bi-level classification system leads to a practical guide of OPS techniques (Table 23.1). This guide allows for selection of the most appropriate OPS procedure during surgical planning.

1. If less than 15% of the breast volume is excised, a level I procedure is often adequate. These procedures can be performed by all breast surgeons without specific training in plastic surgery.
2. Anticipation of 15–50% breast volume excision will require a level II procedure with excision of excess skin to reshape the breast. They are based upon mammoplasty techniques and require specific training in OPS.

Another major consideration in the patient selection criteria is glandular density. If the breast parenchyma is fatty in composition, it may be risky to use a level I technique. Therefore, when planning a large resection in a fatty breast, employing a level II procedure will result in a safer outcome and better cosmetic result.

23.2.7 General Considerations for All OPS Techniques and Patient Counselling

Although oncoplastic procedures can provide high satisfaction with the final breast shape and in some situations may avoid the need for mastectomy, OPS may result in longer and multiple scars. The patient should be aware of the possible asymmetry caused by level II OPS. Because of the extensive resection, an asymmetry in volume is expected compared with the contralateral breast. This asymmetry may require

Table 23.1 Oncoplastic decision guide

Criteria	Level I	Level II
Maximum excision volume ratio	15%	15–50%
Requirement of skin excision for reshaping	No	Yes
Mammoplasty	No	Yes
Glandular characteristics	Dense	Dense or fatty

immediate symmetrization of the contralateral side if desired by the patient or can be performed as a second-stage procedure.

All oncoplastic procedures begin with the preoperative marking of the patient sitting in the upright position prior to induction of anaesthesia. Once marked, both breasts are draped into the operative field for comparison. The patient is centred on the operating room table to accommodate both the supine and upright position, as she will be transitioned between these positions to allow optimal reshaping and symmetry. The patient is then secured into place with either arms extended, for access to the axilla, or both arms at the sides if no axillary surgery is needed.

23.3 Step-by-Step Approach for Level I OPS

There are six steps for level I OPS (Table 23.2; Figs. 23.1 and 23.2). They begin with skin incision (1) followed by undermining of the skin (2) and NAC (3). After completion of undermining, a full-thickness glandular excision is performed

Table 23.2 Level I OPS: step-by-step surgical approach

Procedure	Result
Skin incision	Allows wide access for excision and reshaping
Skin undermining	Facilitates wide excision and glandular mobilization for reshaping
NAC undermining	Avoids displacement of nipple towards excision defect
Full-thickness excision	Prevents anterior and posterior margin involvement
Glandular reapproximation	Late-occurring deformity is avoided
Deepithelialization and NAC repositioning	Recentres NAC on new breast mound

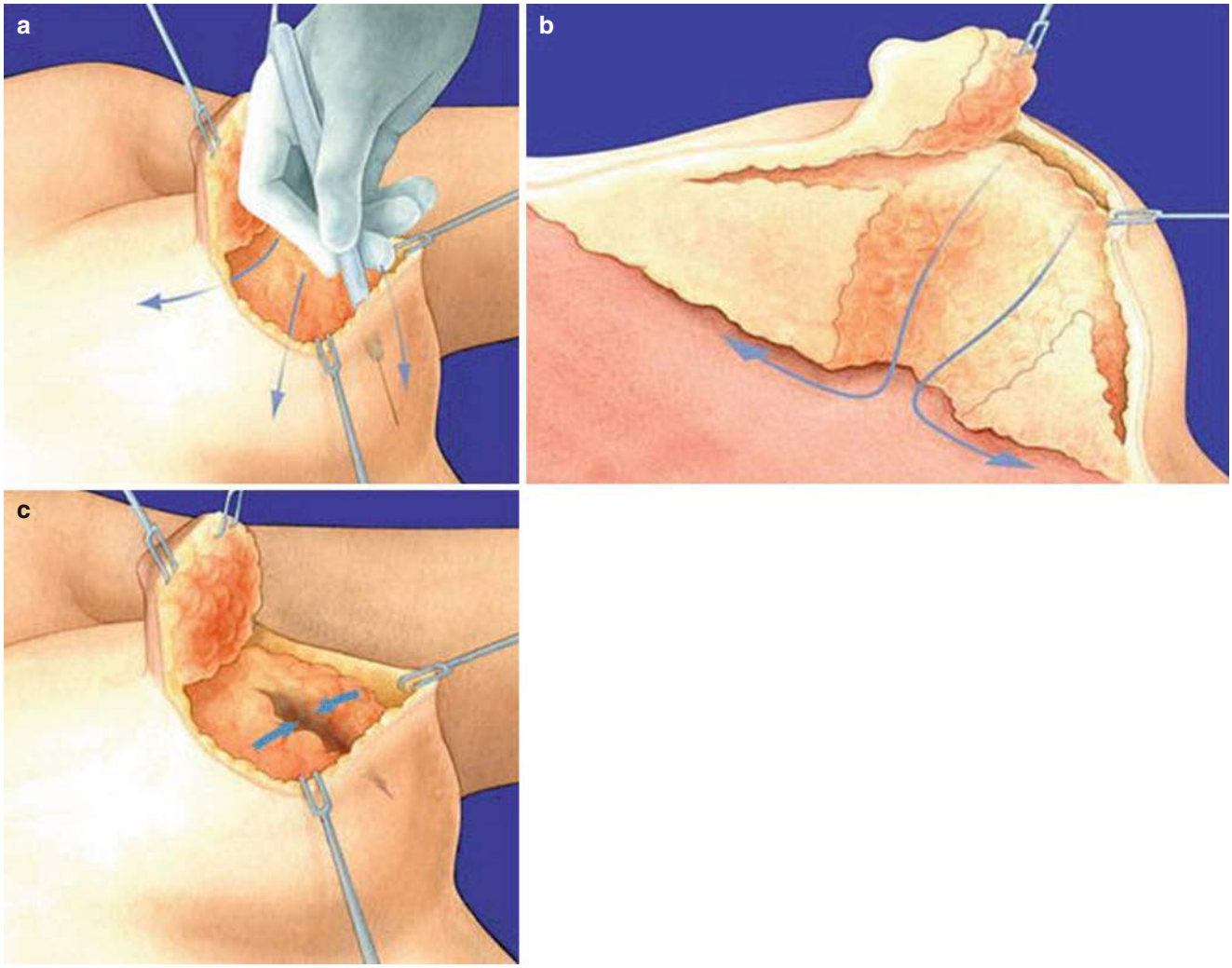

Fig. 23.1 Level I OPS: surgical concept. (**1**) Initial extensive skin undermining. (**2**) Excision of the lesion from subcutaneous tissue to pectoralis fascia. (**3**) Reapproximation and suturing of the gland

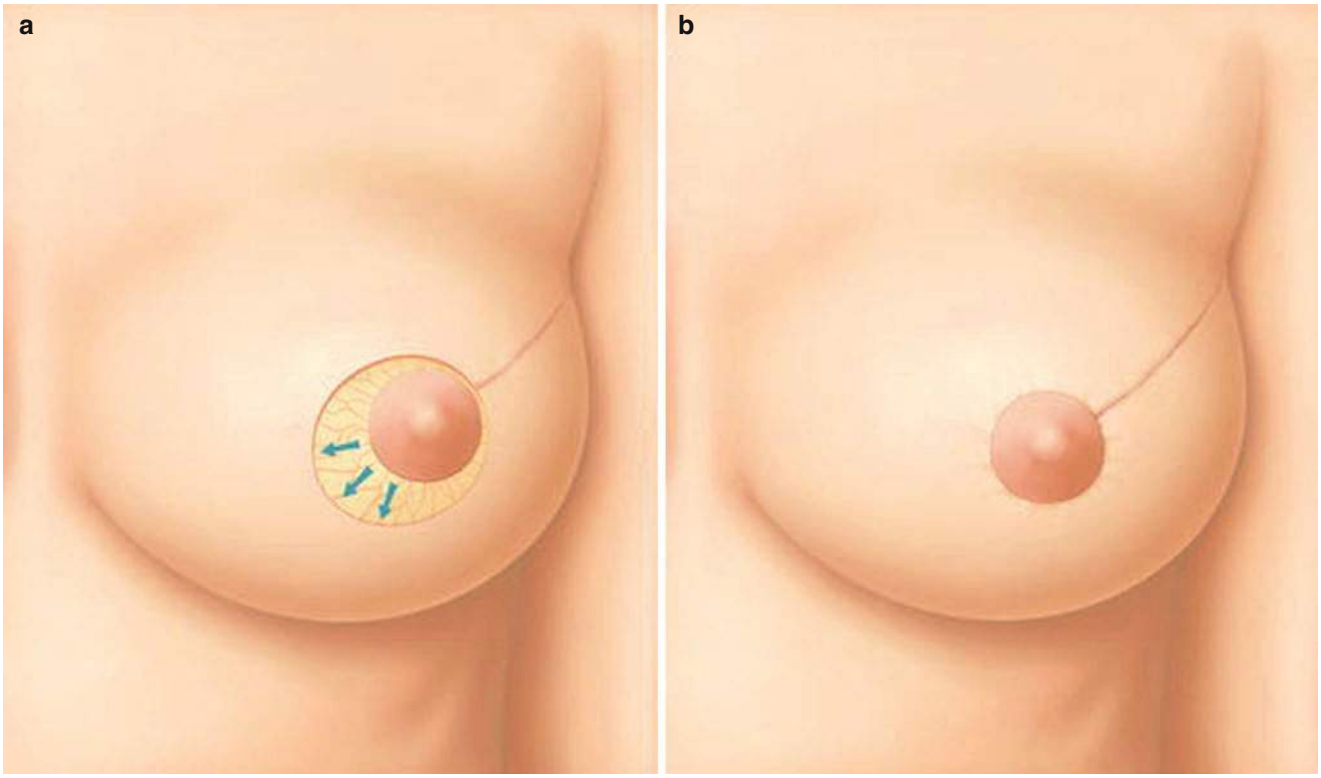

Fig. 23.2 Level I OPS: nipple recentralization. (**1**) A skin crescent is deepithelialized opposite to the lumpectomy bed in the upper outer quadrant. (**2**) NAC is recentralized to avoid NAC deviation post lumpectomy

from the subcutaneous fat to the pectoralis fascia (4). The glandular defect is closed with tissue reapproximation (5). If required, an area in the shape of a crescent bordering the areola is deepithelialized and the NAC is repositioned (6).

Oncoplastic surgery is based upon allowing wide excisions with free margins, not on minimizing incision length. Short incisions limit mobilization of the gland and do not permit creation of adequate glandular flaps to fill in excision defects. This effective mobilization of the gland is a key component of breast reshaping after wide excisions.

The location of the incision is at the discretion of the operating surgeon. All incisions should allow for both en bloc excision of the cancer, without causing fragmentation of the specimen, and extensive undermining to facilitate reshaping. For level I procedures, if a direct incision over the tumour is chosen, the general principle is to follow Kraissl's lines of tension to limit visible scaring [10]. However, in many cases an indirect incision along the areola border is possible and can be extended by a radial extension towards the tumour.

23.3.1 Skin Undermining

One of the key factors of level I OPS techniques is extensive subcutaneous undermining. It is easier to undermine the skin before excising the lesion. The undermining follows the mastectomy plane and extends anywhere from one-fourth to two-thirds of the surface area of the breast envelope. Extensive skin undermining facilitates both tumour resection and glandular redistribution after removal of the tumour. The area of undermining should be reduced if risk factors for fat necrosis are present. The two main risk factors are smoking history and fatty composition of the breast.

23.3.2 NAC Undermining

Extensive resections lead to NAC deviation towards the excision area. NAC repositioning is easily performed with simple undermining: this is a key component of both level I and II OPS. The first step is to completely transect the terminal ducts and separate the NAC from the underlying breast tissue. A width of 0.5–1 cm of attached glandular tissue is maintained to ensure the integrity of the vascular supply. This appropriate amount of subareolar tissue prevents NAC necrosis and avoids venous congestion. Ultimately, the level of NAC sensitivity may be reduced after extensive mobilization and undermining [11].

23.3.3 Glandular Resection

Our standard approach is to perform full-thickness excisions from the subcutaneous fat underlying the skin down to the pectoralis fascia. A full-thickness excision ensures free ante-

rior and posterior margins, leaving only the lateral margins in question. The breast parenchyma itself is excised in a fusiform pattern oriented towards the NAC. This shape facilitates reapproximation of the remaining gland. Before closing the defect, metal clips are placed on the pectoralis muscle and lateral edges of the resection bed to guide future radiotherapy.

23.3.4 Defect Closure: Glandular Flaps

During standard BCS, breast tissue is either reapproximated or left open, allowing for the eventual formation of a hematoma or seroma. Seroma formation, however, does not always result in predictable long-term cosmetic results for larger-volume excisions. Once reabsorption of the seroma occurs, the excision cavity becomes prominent due to fibrosis and retraction of the surrounding tissue, creating a noticeable defect and causing NAC displacement towards the previous excision cavity. Extensive resections require closing the cavity and redistribution of the volume loss.

Advancement flap: The most common breast reshaping technique is based on advancing the surrounding breast tissue into the cavity. In most cases, tissue can be mobilized from lateral positions of the remaining gland or recruited from the central portion of the breast. This allows creation of glandular flaps immediately adjacent to the cavity that are sutured together to close the defect.

Rotation glandular flap: Simple advancement flaps are not suitable in all cases. Rotation of a wide-based glandular flap into the excision cavity could reshape the breast. This technique was originally developed for upper inner quadrant tumours; however it can be used for all quadrants. It is indicated when simple closure of the defect by approximating the resection margins is not possible or would leave a deformity. This technique involves extensive undermining of the gland, and therefore it should be reserved for patients with glandular breasts (BIRADS 3 or 4) in order to minimize the risk of postoperative fat necrosis. Rotation flaps are not appropriate for patients who are at risk of glandular necrosis, i.e. patients with fatty breasts and diabetes and those who smoke or who smoke or had previous radiotherapy.

The preferred incision is periareolar, either with or without a small radial extension, to avoid a visible scar in the cleavage area. The first four steps are identical to those described for level I OPS (Table 23.2). Wide undermining of the skin is undertaken, to release the gland from its dermal attachments. This involves detaching the whole upper inner and central skin from the breast in the same plane as that used for a nipple sparing mastectomy. This will allow wide tumour excision. In order to mobilize the central gland towards the defect, the nipple areolar complex (NAC) is completely elevated. All the terminal ducts are transected on 5–10 mm thickness of breast tissue to allow safe vascularization. The tumour resection is performed from the subcutaneous fat to the muscle with wide lateral margins (Fig. 23.3). Clips are placed in the cavity to mark the tumour bed.

A wide V-shape glandular flap is then created by releasing the central gland from its pectoral attachments with posterior undermining. The glandular incision starts medially at the inferior part of the lumpectomy cavity, closest to the NAC, and extends laterally. This elevates a full-thickness glandular flap with a wide lateral base, ensuring its vascular integrity (Fig. 23.4). The flap is rotated medially into the defect (Fig. 23.5) and sutured into the cavity. The cavity is completely closed by this method. No drainage is required (Fig. 23.6). Once the skin edges are approximated, the patient is placed in the sitting position in order to check the symmetry of the breasts, including the relative NAC position. If the NAC is displaced, it should be recentralized by de-epithelializing a crescent of the skin diametrically opposite from the original tumour bed [12, 13].

This rotation glandular flap allows the safe transfer of the central gland into the defect of a wide local excision in the upper inner quadrant. It extends the scope of level I OPS, allowing larger defects to be repaired safely and cosmetically [14].

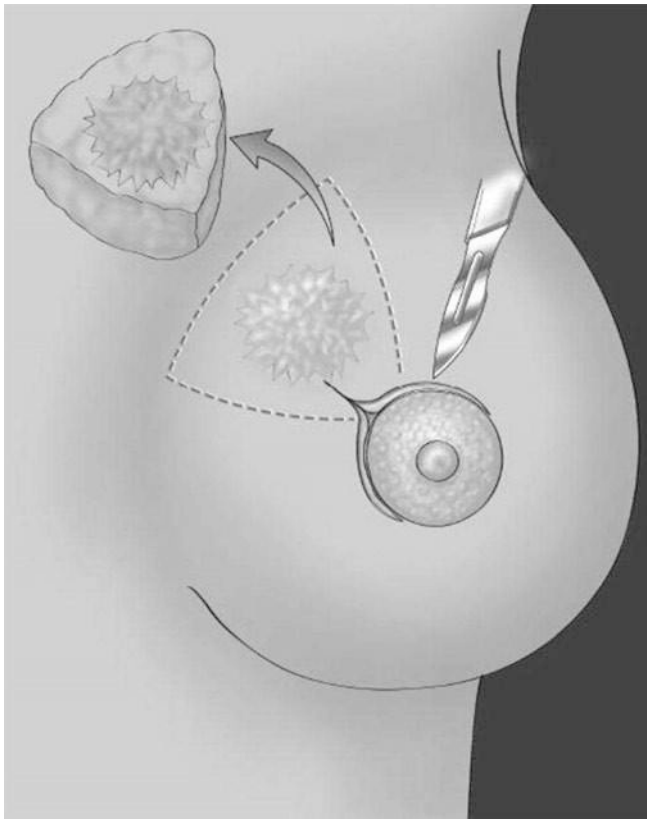

Fig. 23.3 Periareolar skin incision with a radial extension. Full-thickness glandular excision

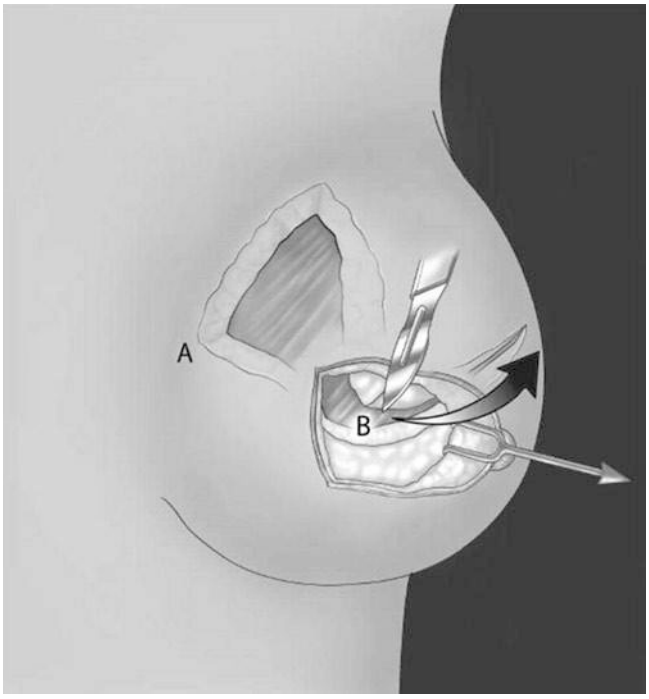

Fig. 23.4 The nipple areolar complex is undermined on 5–10 mm of gland. A wide centro-lateral glandular flap is harvested by double plane undermining. The glandular incision is extended laterally

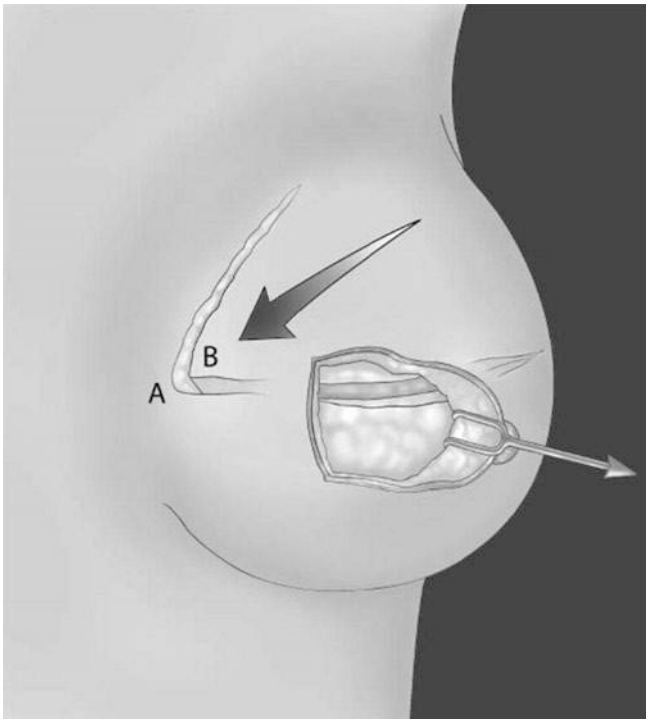

Fig. 23.5 The glandular flap is rotated into the cavity

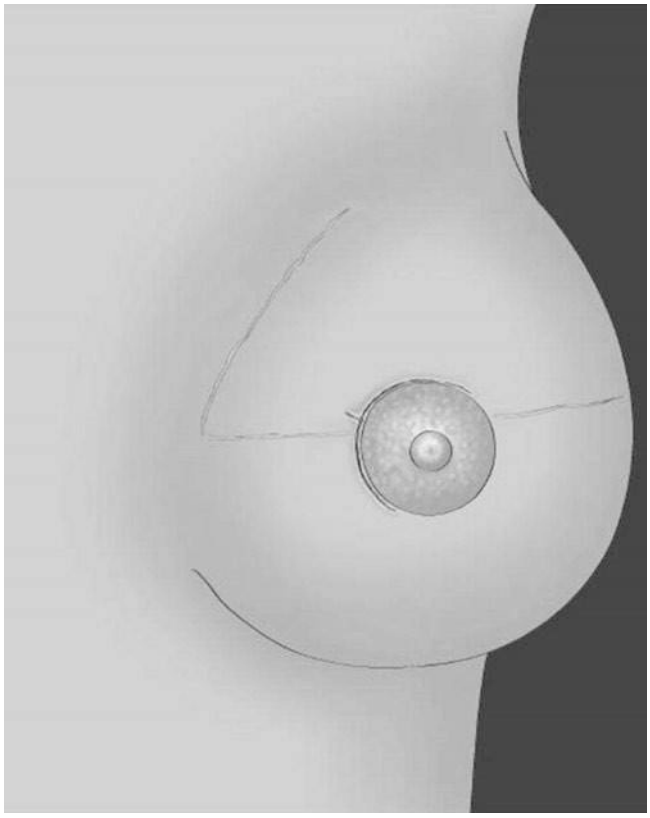

Fig. 23.6 The cavity is completely closed by the rotation glandular flap

23.3.5 NAC Repositioning

Avoiding NAC displacement is a key element for both levels I and II OPS. An unnatural position of the NAC deviated towards the excision site can be one of the major sources of patient dissatisfaction after BCS. This result should be expected after all extensive volume resections. NAC repositioning is difficult to attempt after radiotherapy; therefore, immediate recentralization is preferred and should be anticipated during initial resection [13]. An area of periareolar skin opposite the excision defect is deepithelialized in the shape of a crescent. For level I procedures, the width of deepithelialization can measure up to 6 cm. Deepithelization should be achieved sharply, using a scalpel blade or fine scissors. This technique is simple and safe and is used systematically in aesthetic surgery of the breast. The vascular supply of the NAC after its separation from the gland and deepithelialization is based on the dermal vasculature [15].

23.4 Level II Oncoplastic Surgery

A major consideration when choosing between OPS levels is the extent of excision volume. A level I approach is suitable for excision volumes less than 20% of the entire gland. In most quadrants, the resulting glandular defect can usually be filled by advancement of adjacent tissue. Level II techniques are reserved for situations that require major volume excisions of 20–50%. They are based upon different mammoplasty techniques. To simplify the selection of the appropriate technique, we devised an Atlas based on tumour location. This Atlas does not contain an exhaustive list of options, but provides one or two surgical techniques for each tumour location. Existing mammoplasty techniques were initially adapted for OPS for specific tumour locations such as lower-pole cancers [1, 16, 17]. In other locations, such as the lower inner and upper outer quadrants, a series of new mammoplasty techniques were created to serve for breast cancer treatment [18].

The superior pedicle reduction mammoplasty will serve as a model for the technical description of all mammoplasty techniques. Schematically rotating the NAC pedicle opposite the site of tumour excision allows the application of this technique for a variety of tumour locations. These procedures are listed in a clockwise direction and described for the left breast (Table 23.3).

Because of the volume excised, level II OPS will generally result in a breast that is smaller, rounder and higher than the contralateral breast. Thus, the need for contralateral symmetrization should be discussed in the preoperative setting. Either immediate or delayed symmetrization can be performed depending on the amount of tissue resection and the desire of the patient.

Table 23.3 Level II OPS: quadrant-per-quadrant Atlas (orientation for the left breast)

Clock position	Procedures
5–7 o'clock	Superior pedicle mammoplasty/inverted T or vertical scar
Lower pole	
7–8 o'clock	Superior pedicle mammoplasty/V scar
Lower inner quadrant	
9–11 o'clock	Batwing
Upper inner quadrant	
12 o'clock	Inferior pedicle mammoplasty or round block mammoplasty
Upper pole	
1–2 o'clock	Racquet mammoplasty/radial scar
Upper outer quadrant	
4–5 o'clock	Superior pedicle mammoplasty/J scar
Lower outer quadrant	
Central subareolar	Inverted T or vertical-scar mammoplasty with NAC resection

23.4.1 Lower-Pole Location (5–7 O'Clock)

23.4.1.1 General Principles

The lower pole of the breast was the first recognized high-risk location for deformity (Fig. 23.7) [1, 16, 19]. Retraction of the skin and downward deviation of the NAC resulting from excision of tissue from the 6 o'clock position became known as the "bird's beak" deformity. A superior pedicle mammoplasty can allow for large-volume excision at the lower pole without causing NAC deviation with the added benefit of breast reshaping.

23.4.1.2 Technique: Superior Pedicle Mammoplasty with Inverted T Scar/ Vertical Scar

The superior pedicle mammoplasty technique that we routinely use results in inverted T and periareolar scars as seen in most breast reduction patients. The procedure has been described in detail in a previous paper (Fig. 23.8) [20]. It begins with deepithelialization of the area surrounding the NAC. The NAC is then dissected away from the underlying breast tissue on a superior dermoglandular pedicle. The inframammary incision is then completed, followed by wide undermining of the breast tissue off the pectoralis fascia. The undermining starts inferiorly and then proceeds superiorly beneath the tumour while encompassing the medial and lateral aspects of the breast as well as the NAC. The tumour is removed en bloc with a large margin of normal breast tissue and overlying skin as determined by the preoperative drawings.

Mobilization of the breast tissue from the pectoralis muscle allows for palpation of both the deep and superficial surfaces of the tumour, improving the ability to obtain adequate lateral margins. Once the resection is completed, the breast is reshaped by reapproximation of the medial and lateral glandular columns towards the midline to fill in the defect, followed by NAC recentralization (Fig. 23.9).

One possible modification to this technique is the vertical-scar mammoplasty described by Lejour and Lassus [21, 22]. The site and volume of excision are identical to the inverted T scar, but this approach avoids the submammary scar.

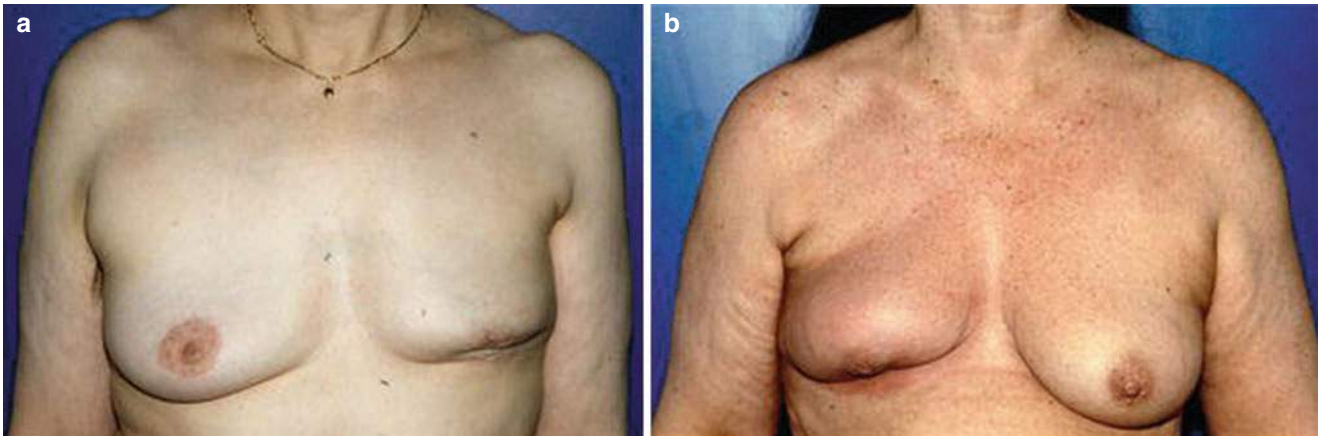

Fig. 23.7 (**1**, **2**) "Birds beak" deformity of the lower pole

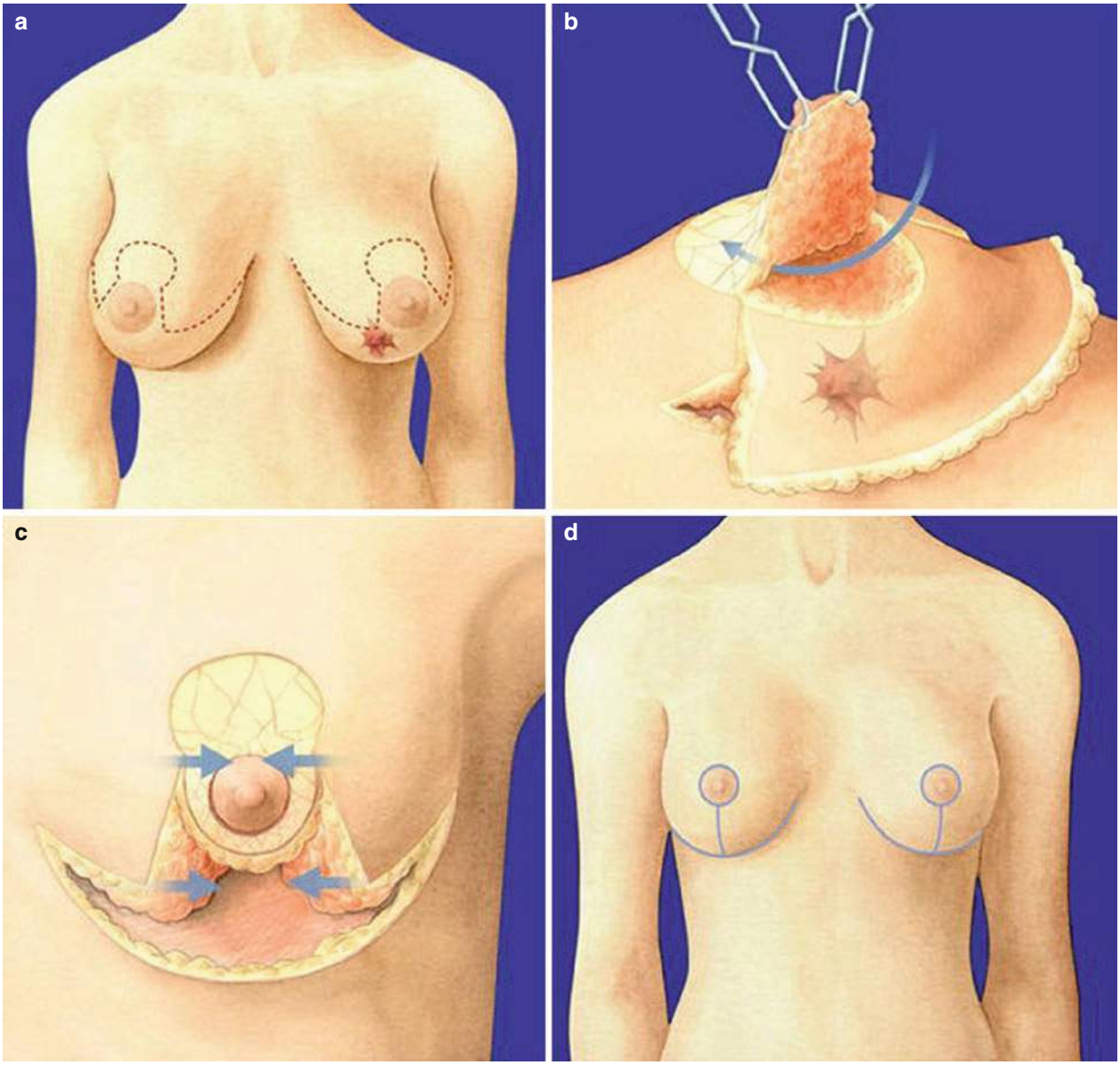

Fig. 23.8 Level II OPS: superior pedicle mammoplasty for lower-pole lesion (6 o'clock). (**1**) Preoperative drawings. (**2**) Superior pedicle deepithelialized and elevated. (**3**) Reapproximation of medial and lateral glandular flaps after wide excision. (**4**) Final result after reshaping and contralateral symmetrization

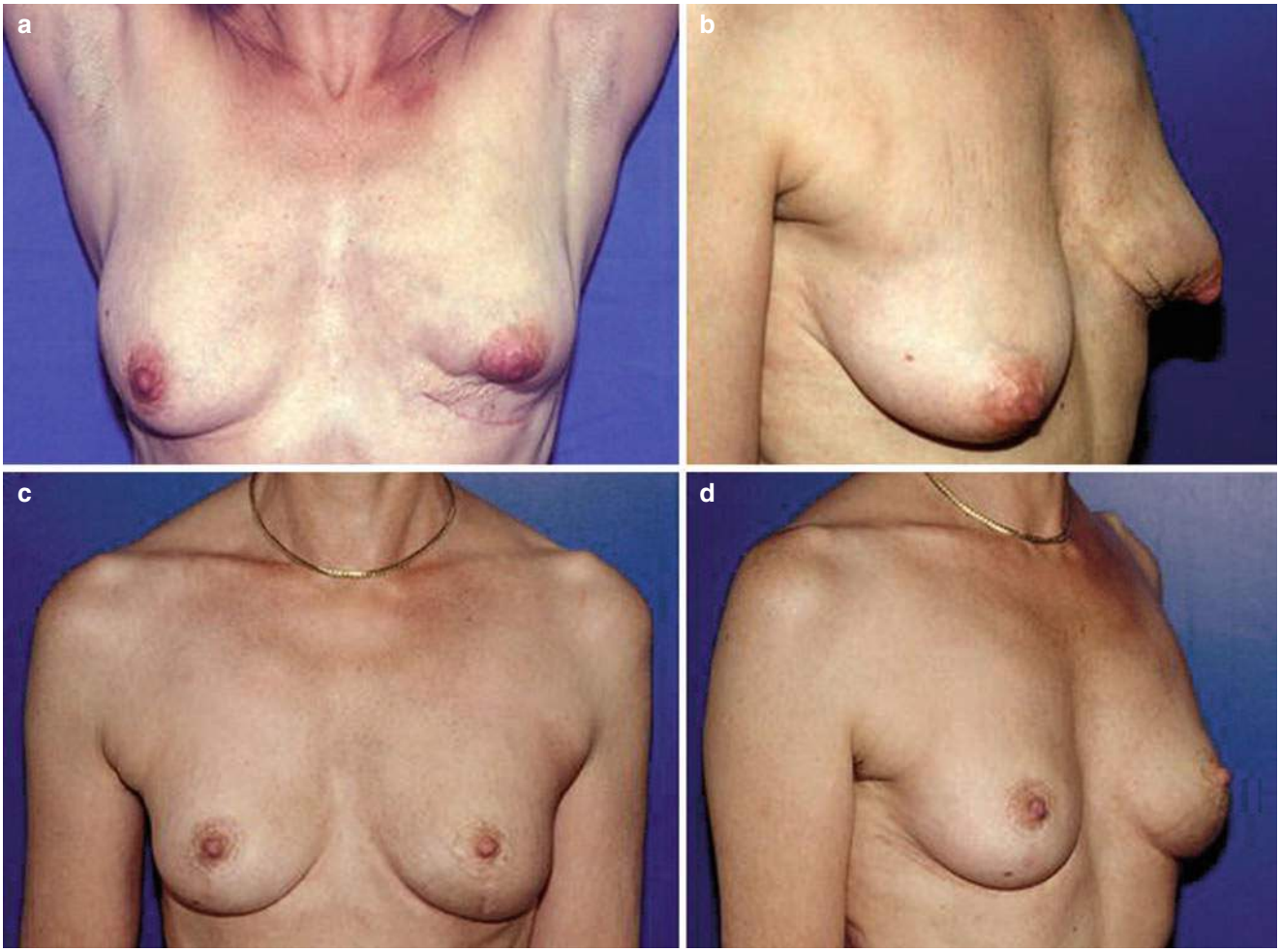

Fig. 23.9 Re-excision of lower-pole lesion for positive margins. The patient was offered mastectomy prior to consultation; however, utilizing a level II OPS technique, both negative margins and a natural shape of the breast were achieved. (**1**) After first resection patient has both deformity and positive margins. (**2**) Deformity of lower pole. (**3**, **4**) Results after mammoplasty and left breast radiotherapy

A new approach for patients with moderate- to small-sized breasts who present with lower-pole tumours near the inframammary fold has recently been described by Nos. This technique is based on the creation of a fascio-cutaneous flap and harvesting of underlying fatty tissue below the inframammary fold. The flap is then rotated to fill in the area of defect created by the segmental excision of the cancer [23].

23.4.2 Lower Inner Quadrant (7–9 O'Clock)

23.4.2.1 General Principles

Superior pedicle mammoplasty can be used for tumours located from 5 to 7 o'clock. However, adaptation for tumours located more medially, between 7 and 9 o'clock, is more difficult and requires a novel level II technique (Fig. 23.10) [24].

23.4.2.2 Technique: V-Mammoplasty

This procedure involves excising a pyramidal section of gland, with its base located in the submammary fold and apex at the border of the areola. The section is removed en bloc, including the skin attached to the gland down to the pectoralis fascia. The submammary fold is then incised, from the resection site to the anterior axillary line. The incision is taken laterally as far as necessary to perform adequate rotation of the remaining gland into the defect. The lower pole of the breast is then entirely undermined off the pectoralis muscle and is transferred medially to fill the defect. The NAC is then recentralized on a deepithelialized superior-lateral pedicle (Figs. 23.11 and 23.12).

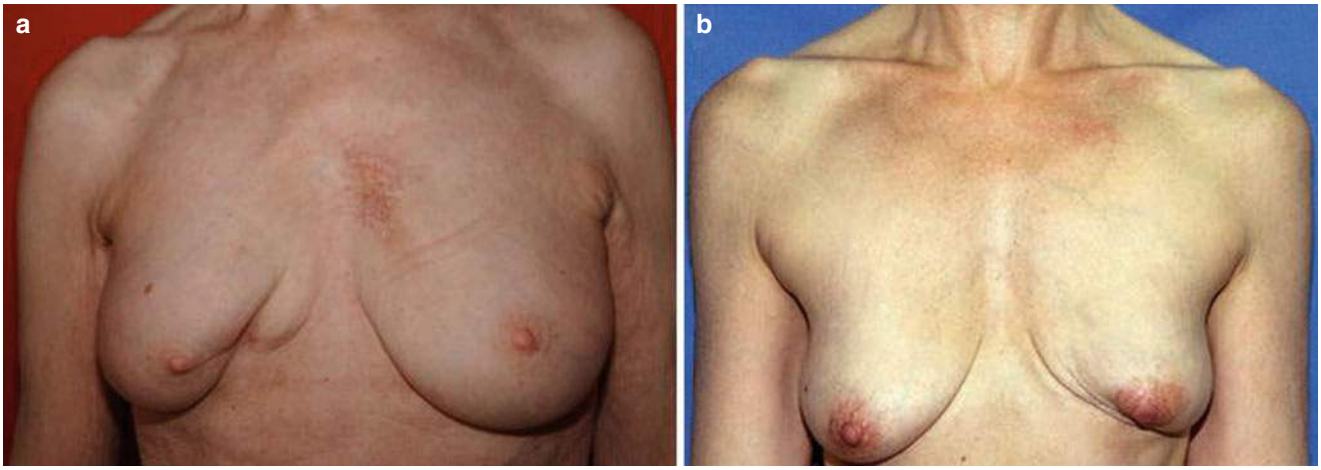

Fig. 23.10 (**1**, **2**) Lower inner quadrant deformity

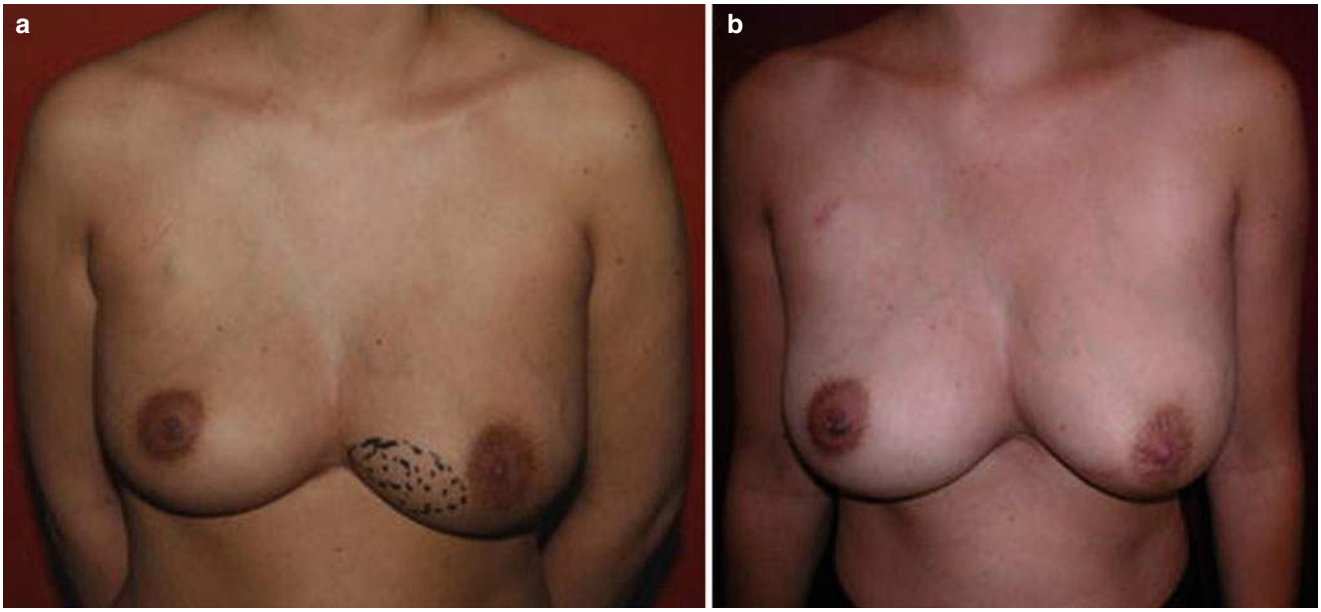

Fig. 23.11 V-mammoplasty. (**1**) Patient underwent neoadjuvant treatment; however, extensive microcalcifications required wide excision of lesion. (**2**) Natural shape of breast maintained after excision

23.4.3 Upper Inner Quadrant (10–11 O'Clock)

Special caution is needed when considering BCS for lesions in the upper inner quadrant of the breast. A wide excision in this location can have a significant impact on the overall quality of the breast shape by distorting the visible breast line known as the "décolleté" (Fig. 23.13).

For moderate resections, level I techniques can be utilized safely. For more extensive excisions, we currently have not developed a standard level II oncoplastic procedure that reliably addresses the limitations of BCS at this troublesome location. Silverstein has described an effective OPS procedure to address the upper inner quadrant. His approach utilizes a batwing excision pattern [25]. Silverstein's OPS solution is innovative and reproducible; however, more research is needed when performing large excisions exceeding 20% of the breast volume in this area.

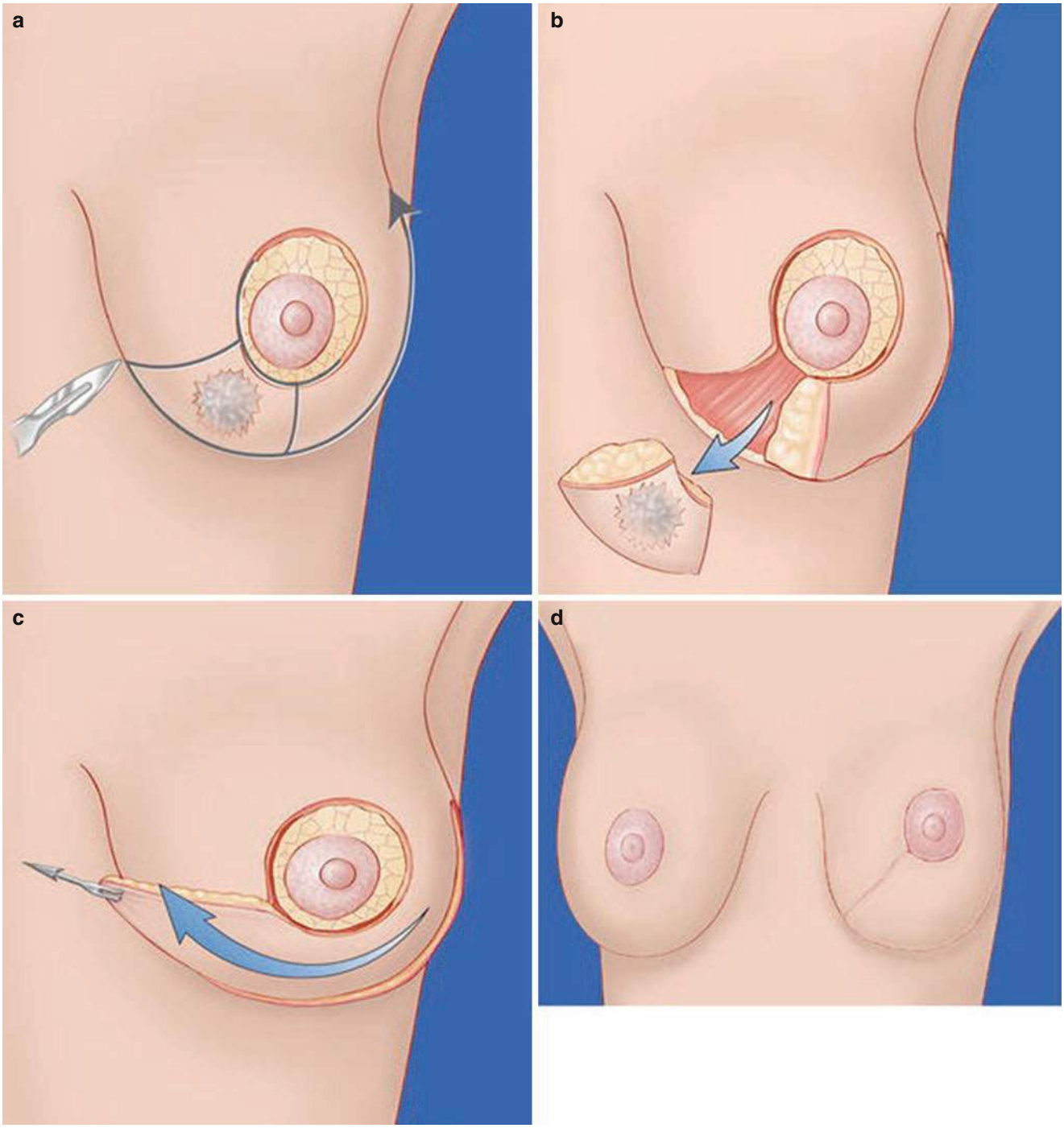

Fig. 23.12 Level II OPS: V-mammoplasty for lower inner quadrant (7–8 o'clock). (**1**) Preoperative drawings. (**2**) Full-thickness excision and inframammary incision. (**3**) Medial rotation of lateral glandular flap to fill in the defect and reshape the breast. (**4**) Resulting scars

23.4.4 Upper Pole (11–1 O'Clock)

23.4.4.1 General Principles

Excision of lesions located at the 12 o'clock position rarely causes a deformity (Fig. 23.14), as they can be excised widely followed by volume redistribution with tissue from the central location. For large excision volumes (Fig. 23.14), repair of upper-pole resections can be accomplished through an inferior pedicle mammoplasty. This mammoplasty is commonly performed in the United States as a breast reduc-

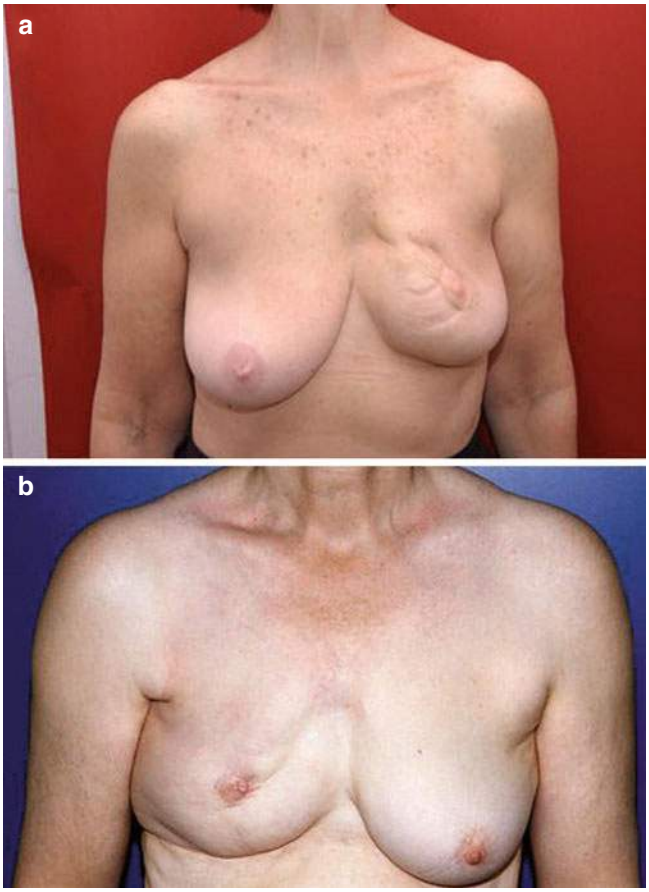

Fig. 23.13 (**1**, **2**) Upper inner quadrant deformity

tion technique and utilizes an inverted T-scar pattern [4]. Another possible approach is a round block mammoplasty with a periareolar scar.

23.4.4.2 Techniques: Inferior Pedicle Mammoplasty

The skin markings are identical to those described for the superior pedicle. The resection, however, is located in the upper pole; hence, the vascular supply of the NAC is based on its inferior and posterior glandular attachments. The inferior pedicle is deepithelialized and advanced upwards towards the excision defect to achieve volume redistribution. Complementary resection is performed in the inner and outer lower quadrants to optimize the breast shape (Fig. 23.15).

23.4.4.3 Round Block Mammoplasty

The round block mammoplasty utilizes a periareolar incision and was originally described by Benelli [26, 27]. The procedure starts by making two concentric periareolar incisions, followed by deepithelialization of the intervening skin. The outer edge of deepithelialization is incised, and the entire skin envelope is undermined in a similar manner to performing a mastectomy. The NAC remains vascularized by its posterior glandular base. Wide excision of the tumour and surrounding tissue is performed from the subcutaneous plane down to the pectoralis fascia. The medial and lateral glandular flaps are then mobilized off the pectoralis muscle and sutured together. The periareolar incisions are then approxi-

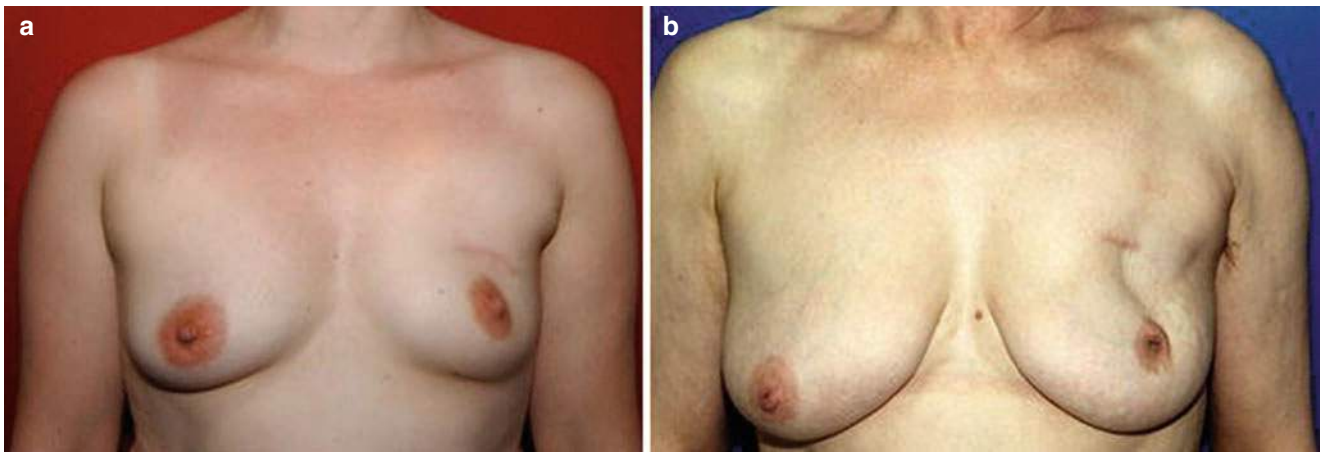

Fig. 23.14 (**1**, **2**) Upper-pole deformity

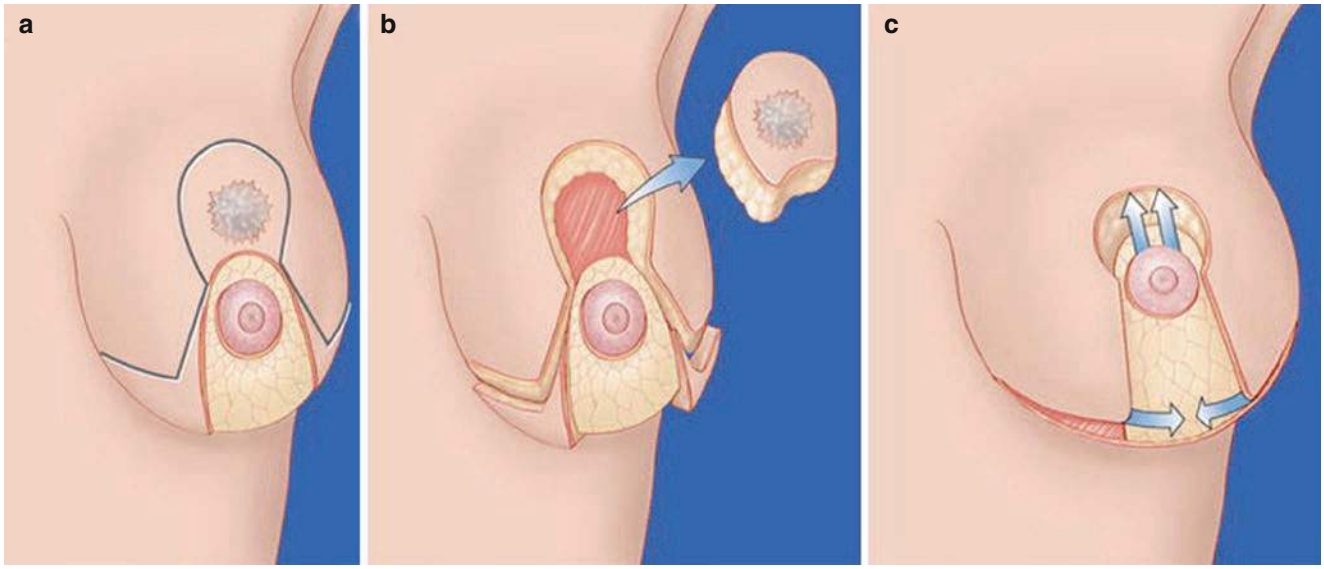

Fig. 23.15 Level II OPS: inferior pedicle mammoplasty for 12 o'clock tumours. (**1**) Preoperative drawings. Inferior pedicle deepithelialized. (**2**) Tumour resection. Complementary resection of medial and lateral pillars. (**3**) Advancement of inferior pedicle into the defect and skin closure

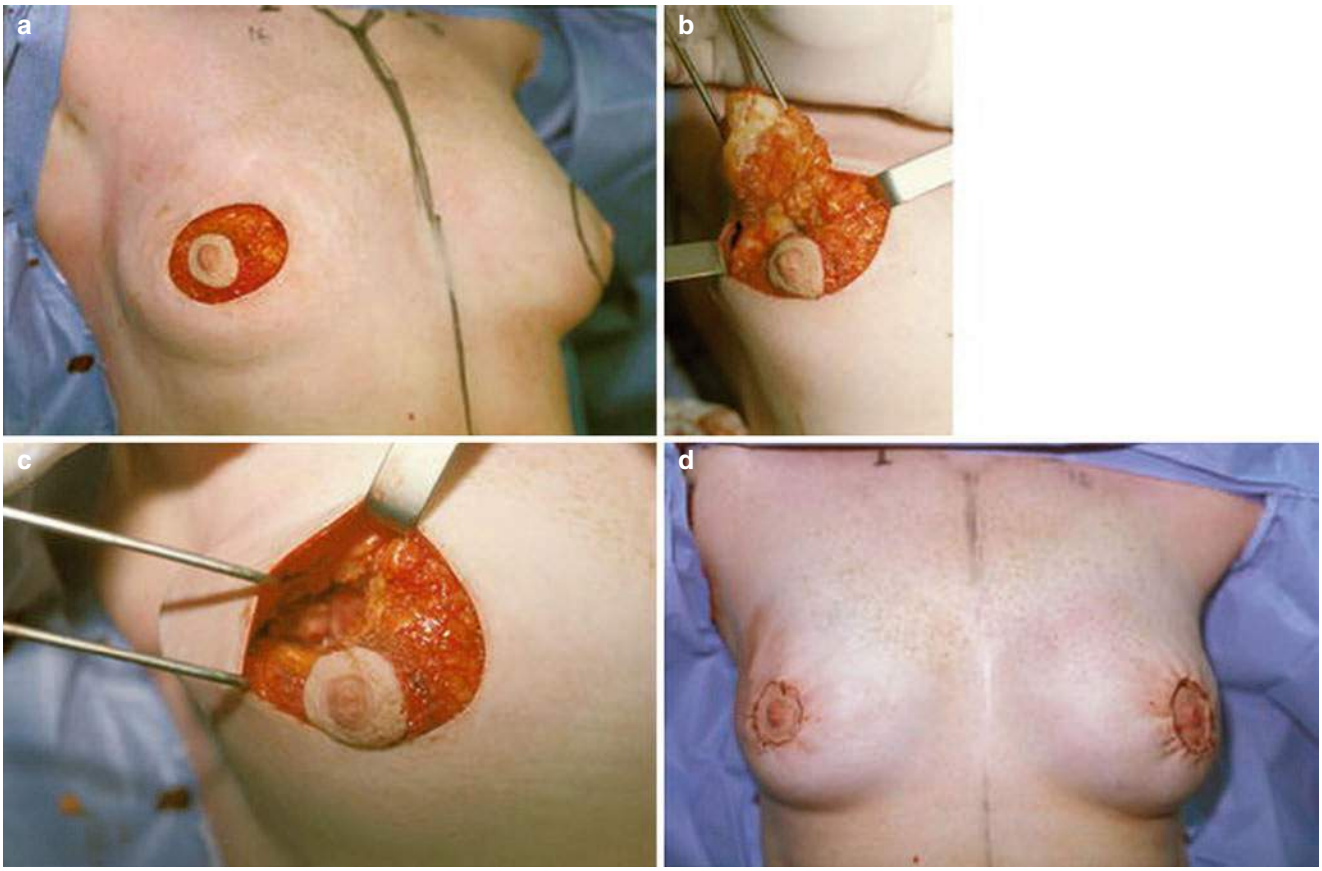

Fig. 23.16 Round block: 3 cm invasive lobular cancer in the upper pole, patient undergoing round block. (**1**) Incision. (**2**) Tumour removal. (**3**) Excision cavity. (**4**) Final result

mated, resulting only in a periareolar scar. Although we have used the round block mammoplasty initially for upper-pole tumours, it is a versatile technique that can be easily adapted for tumours in any location of the breast. It is a challenging technique as the reduced skin excision mandates sophisticated glandular reshaping (Figs. 23.16 and 23.17).

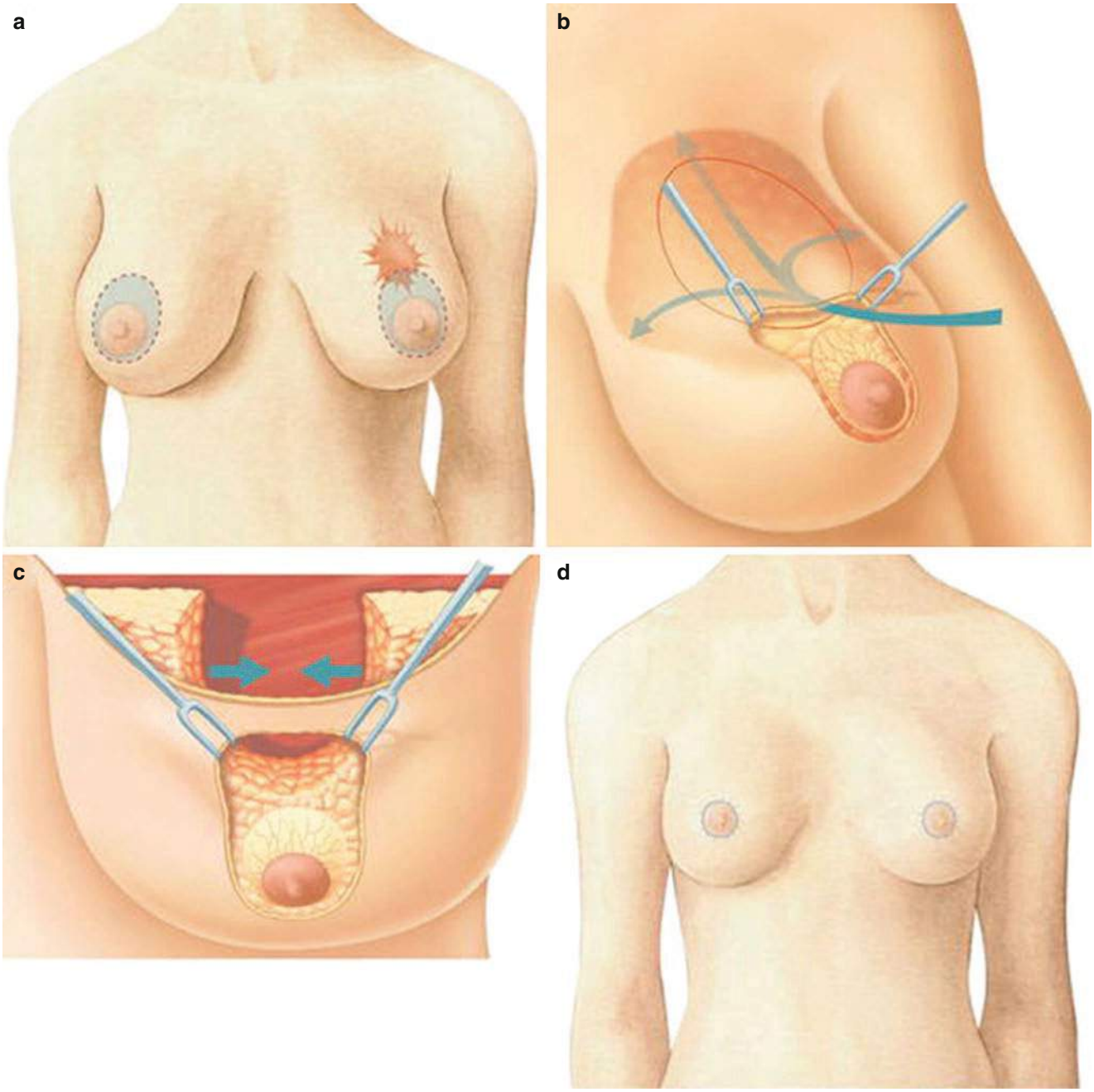

Fig. 23.17 Level II OPS: round block technique for upper-pole lesion (11–1 o'clock). (**1**) Skin drawing and concentric periareolar incisions. (**2**) Circumferential skin undermining. (**3**) Reapproximation of the glandular flaps. (**4**) Resulting scars

23.4.5 Upper Outer Quadrant (1–3 O'Clock)

23.4.5.1 General Principles

This is the most "forgiving" of all quadrants. In this quadrant, large lesions can often be excised with standard BCS without causing deformity. However, resection of greater than 20% of the breast volume will result in retraction of the overlying skin with NAC displacement towards the excision site (Fig. 23.18). Level II OPS can be utilized to increase resection possibilities while limiting the risk of postoperative deformities.

23.4.5.2 Technique: Racquet Mammoplasty

A large portion of the upper outer quadrant can be excised utilizing a direct incision over the tumour, from the NAC towards the axilla, similar to a quadrantectomy [28, 29].

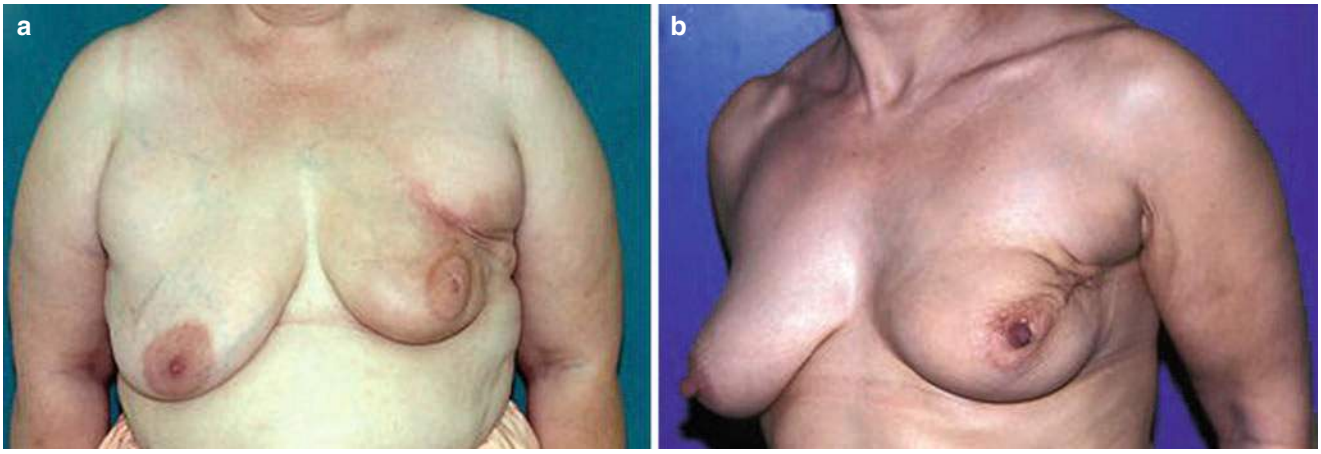

Fig. 23.18 (**1**, **2**) Upper outer quadrant deformity

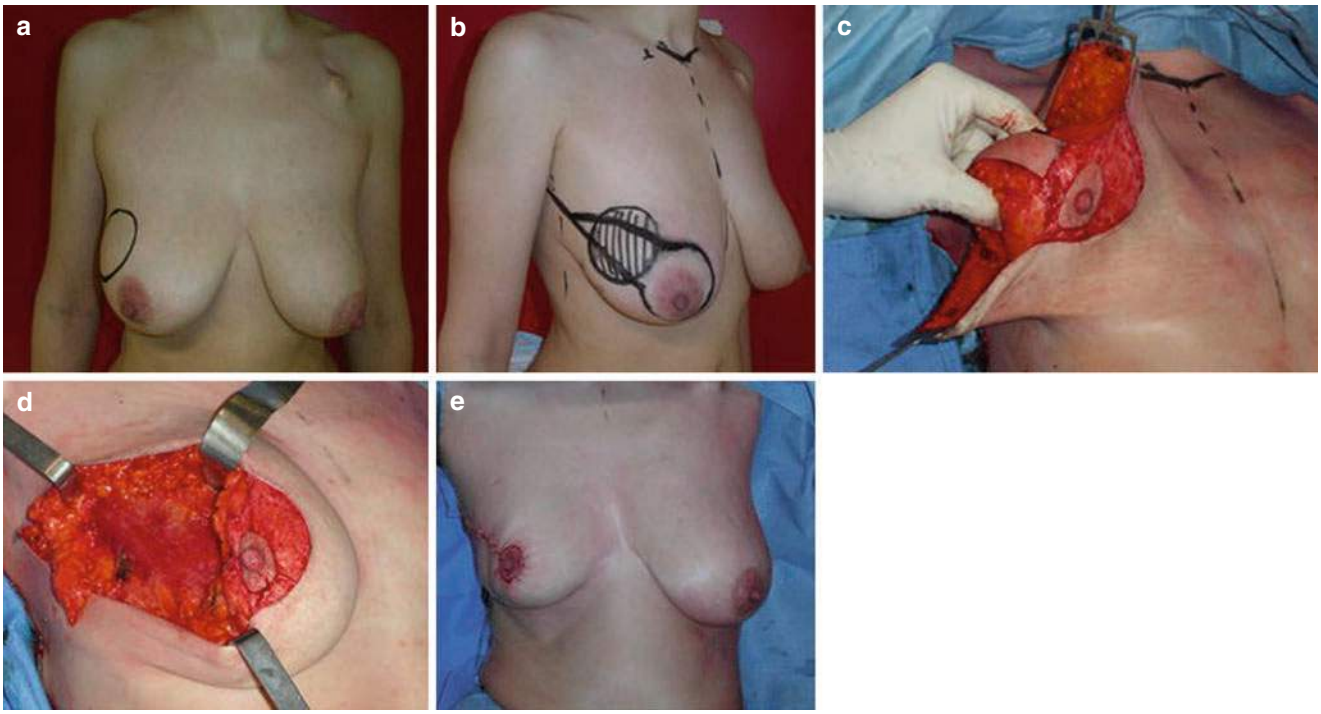

Fig. 23.19 Racquet mammoplasty. Patient underwent neoadjuvant treatment with poor response and large residual tumour. (**1**) Upper outer quadrant tumour. (**2**) Skin markings. (**3**) Excision of tumour. (**4**) Excision cavity. (**5**) Final result prior to contralateral symmetrization

After wide excision, the reshaping is performed by mobilizing lateral and central gland into the cavity and suturing it together. Central gland advancement is easily accomplished through NAC undermining. Complete detachment of the retroareolar gland from the NAC enables maximal mobility of the central gland for volume redistribution. Once the defect is eliminated, the NAC is placed in its optimal position, at the centre of the new breast mound. This mammoplasty results in a long radial scar over the original tumour site with a periareolar extension (Figs. 23.19 and 23.20).

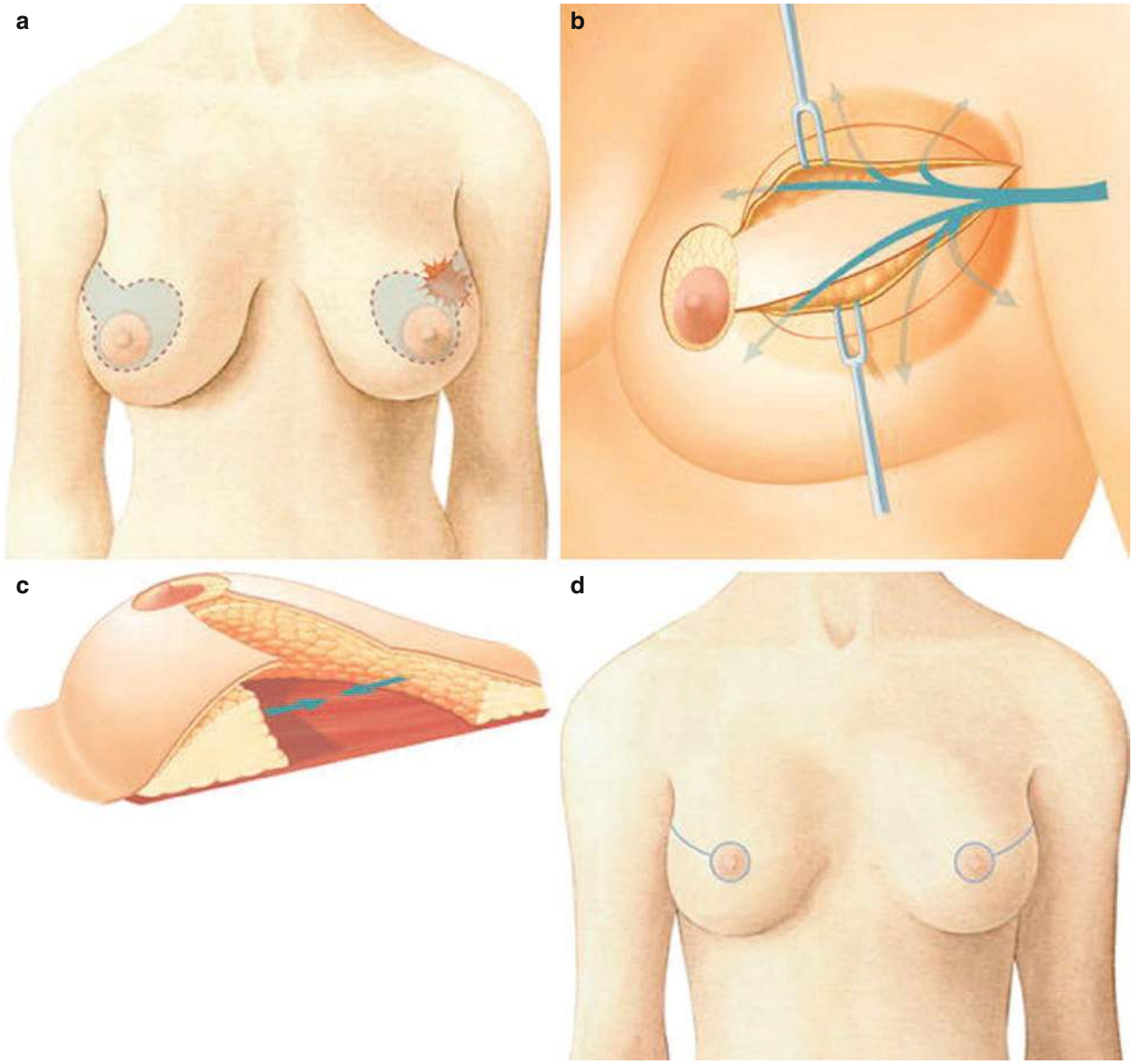

Fig. 23.20 Level II OPS: racquet technique for upper outer quadrant (1–3 o'clock). (**1**) Racquet technique preoperative drawings. (**2**) Skin excision and quadrant undermining. (**3**) Reapproximation and NAC recentralization. (**4**) Final result with periareolar and lateral scars

23.4.6 Lower Outer Quadrant (4–5 O'Clock)

23.4.6.1 General Principles

Like for the lower inner pole, the inverted T mammoplasty does not "fit" well for this quadrant. The optimal procedure to avoid lateral retraction of the breast and deviation of the NAC is a J-type mammoplasty (Fig. 23.21) [30].

23.4.6.2 Technique: J-Mammoplasty

Like for all lower-pole excisions, the NAC is carried on a deepithelialized superior pedicle. The first incision begins at the medial edge of the deepithelialized periareolar area and then gently curves downwards with a concavity to the inframammary crease. The second incision starts at the lateral border of the deepithelialized zone and follows a similar pattern. The parenchymal excision then follows the skin pattern in the shape of the letter J. Lateral and central gland can then be recruited into the excision defect to achieve an equitable redistribution of remaining breast volume. The NAC is recentralized in its optimal position (Fig. 23.22).

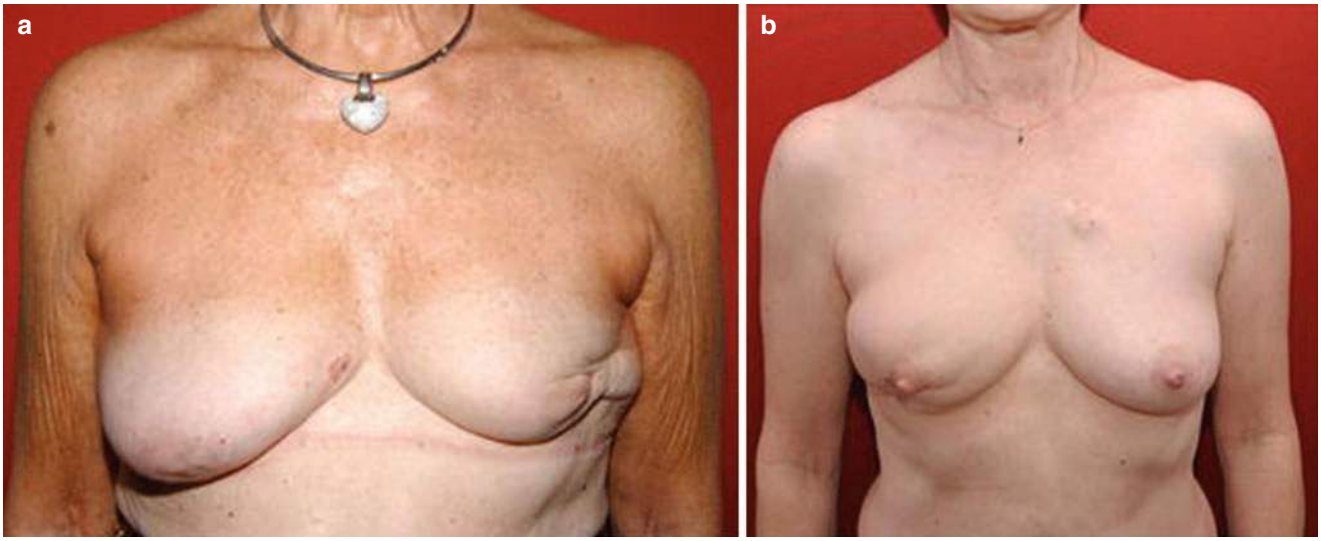

Fig. 23.21 (**1**, **2**) Lower outer deformity

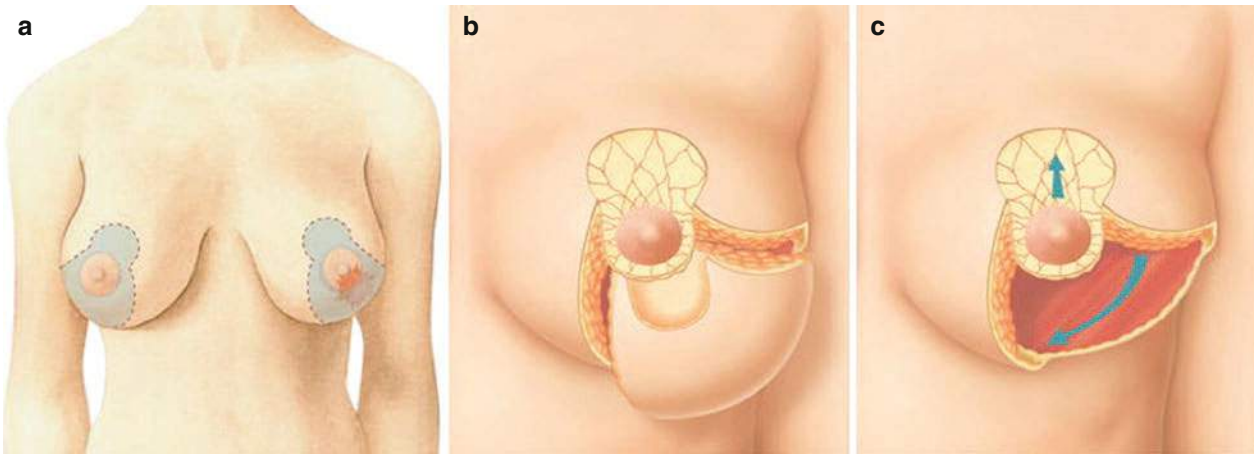

Fig. 23.22 Level II OPS: J-mammoplasty for lower outer quadrant (4–5 o'clock). (**1**) Preoperative drawings. (**2**) Excision specimen and deepithelialization of NAC pedicle. (**3**) Breast reshaping and NAC recentralization

23.4.7 Retroareolar Location

23.4.7.1 General Principles

Subareolar breast cancers are candidates for BCS. However, superficial subareolar tumours are associated with a risk of NAC involvement approaching 50% [31]. In such cases en bloc removal of the NAC with the tumour may be required. This often results in a poor cosmetic outcome with a flat breast**.** If the patient has a glandular breast allowing wide undermining for reshaping, a level I OPS is a reasonable option. As in other locations, level II mammoplasty techniques are reserved for patients with fatty breasts or for patients for whom excision of more than 20% of the breast volume is required. There are a number of mammoplasty approaches that can be chosen for the centrally located lesion. They include the inverted T mammoplasty with resection of the NAC, a modified Lejour or J pattern with NAC excision or Grisotti's technique [32]. The latter offers the advantage of

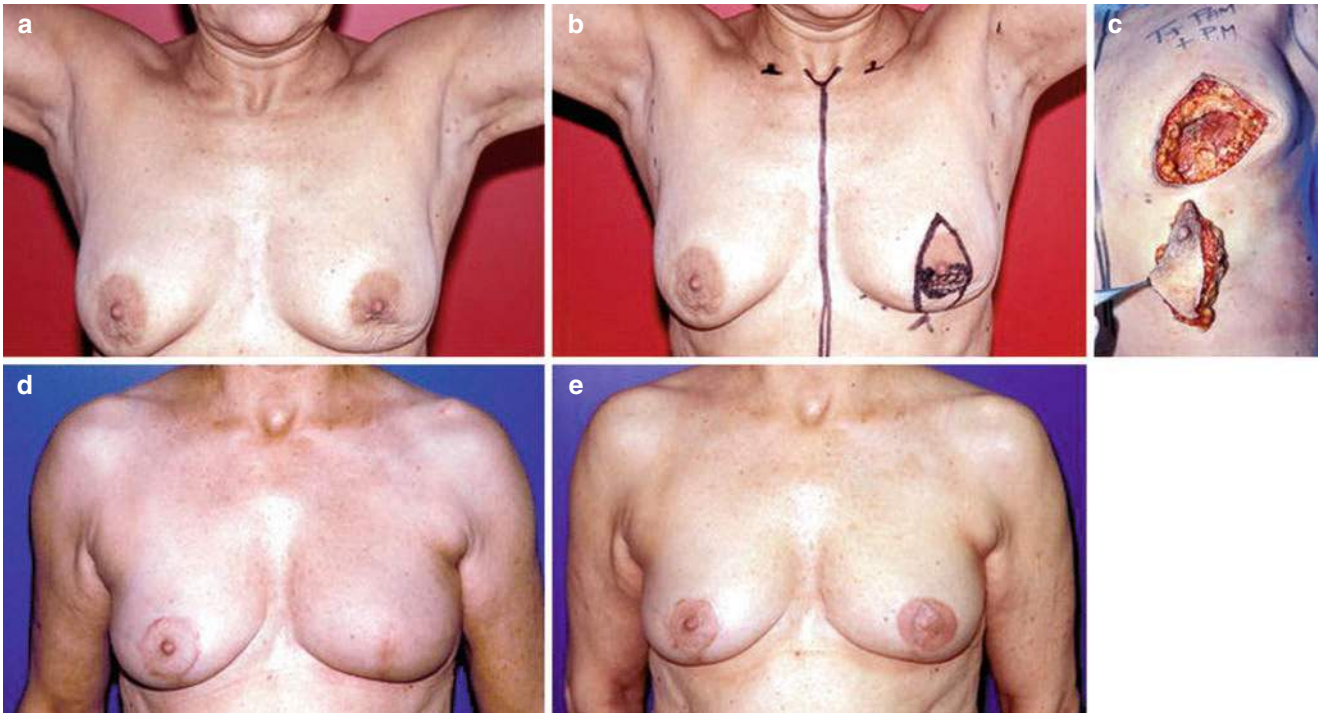

Fig. 23.23 Lejour/vertical mammoplasty. (**1**) Centrally located tumour with involvement of the NAC. (**2**) Skin marking. (**3**) Excision of tumour and NAC. (**4**) Postoperative result. (**5**) NAC tattoo

allowing for immediate NAC reconstruction through preservation of a skin island on an advancement flap [33].

23.4.7.2 Technique: Modified Inverted T Mammoplasty

Oncoplastic techniques for centrally located tumours have been outlined by Huemer et al. [34]. Preferentially we utilize an inverted T or vertical incision, similar to the superior pedicle mammoplasty. The only modification is that the two vertical incisions encompass the NAC, which is removed together with the tumour. The NAC is usually reconstructed at a later stage, after completion of radiotherapy, but can also be reconstructed during the same procedure (Fig. 23.23).

23.5 Discussion

23.5.1 Advantages of Oncoplastic Surgery

Until recently, the breast surgeon could provide only two options for patients with breast cancer: either a modified radical mastectomy or a segmental excision followed by radiation. Integration of plastic surgery techniques at time of tumour excision has delivered a third pathway, enabling surgeons to perform major resections involving more than 20% of breast volume without causing deformity. This new combination of oncologic and reconstructive surgery is commonly referred to as oncoplastic surgery. This "third pathway" allows surgeons to extend the indications for BCS without compromise of oncologic goals or the aesthetic outcome. It is a logical extension of the quadrantectomy technique described by Veronesi [35]. With immediate reshaping employed through OPS, major resections can now be achieved with enhanced cosmetic outcomes [36–38].

Another advantage of OPS is avoiding the need for secondary reconstruction by preventing breast deformities [39]. Prior to the development of OPS, patients with major deformities were secondarily referred to plastic surgeons. Despite continued efforts to treat these deformities, the results of postoperative repair of BCS defects in irradiated tissue were found to be poor, regardless of the surgical procedure or team [40–43]. Immediate reshaping of the breast eliminates the need for complex delayed reconstruction of deformities after BCS.

23.5.2 Indications for Oncoplastic Surgery

The main indication for OPS is large lesions for which a standard excision with safe margins would either seem impossible or lead to a major deformity. Extensive ductal carcinoma in situ (DCIS), lobular carcinoma, multifocality and partial or poor responses to neoadjuvant treatment (Figs. 23.11 and 23.19) are all potential indications for OPS intervention. Standard BCS that results in positive margins

constitutes an additional category of patients (Fig. 23.9) [44].

23.5.3 Oncoplastic Validation

Oncoplastic surgery is fully integrated into a multidisciplinary environment. Pre- and postoperative treatments are not modified. During surgery, the original tumour bed is clipped, allowing precise localization for postoperative radiotherapy.

23.5.4 Margin Status

In our extended series of 350 level II oncoplastic cases, margins were involved in 44 cases (12.6%) [45]. These involved 25 of the 239 invasive ductal cases (10.5%), 10 of the 68 DCIS cases (14.7%) and 9 of the 34 invasive lobular cases (20.9%). Of the 44 patients with an involved margin, 12 underwent conservative re-excision, 28 underwent mastectomy and 4 were treated with radiotherapy alone because they had minimal margin involvement and refused further surgery. The overall breast conservation rate was 92%. The average reoperation rate after standard breast-conserving surgery in four national databases, which included predominantly small cancers (less than 3 cm), ranges from 20% to 24% [46–49]. The analysis of the US national database [49] showed a significant linear trend between increasing tumour size and reoperation rates. For tumours smaller than 1.5 cm, the repeat surgery rate was 20.8% compared with a repeat surgery rate of 48.2% for tumours larger than 5 cm.

23.5.5 Survival Rates

Our recent review of an extended series of 350 patients treated with OPS demonstrated 5-year disease-free and overall survival rates of 84.4% and 95.1%, respectively [45]. The 5-year local recurrence rate was 2.2% [45]. Rietjens reported on the long-term results of 454 OPS cases from the European Institute of Oncology and found a 5-year local recurrence rate of 3.2% [50]. The 5-year disease-free and overall survival rates were 83.7% and 95.9% for their oncoplastic cases and 88.1% and 95.4% for their matched cohort of standard breast-conserving surgery cases [50]. Both studies confirm the initial equivalent comparison of OPS and standard BCS.

23.5.6 Complications of Oncoplastic Surgery

Surgeons embarking in OPS should be aware of the risk of complications and the factors that increase this risk. Glandular necrosis is the most challenging complication. Aggressive undermining of both the skin envelope and gland from the pectoralis muscle can lead to glandular necrosis if the breast is fatty. Areas of fat necrosis can become infected and cause wound dehiscence resulting in postoperative treatment delay. Our prospective evaluation of complications in our initial series demonstrated a high incidence of delayed wound healing (9%) [20]. This rate has been considerably reduced since we began incorporating the third key element, breast density, into our decision-making process. In our recent prospective review, the early complication rate (less than 2 months) was 8.9% over the last 350 procedures [45]. There were 24 cases of fat necrosis, with secondary infection requiring antibiotic treatment in 21 cases, 5 hematomas and 3 seromas. A reoperation was required in 5 cases (2 wound infections, 2 hematomas and 1 seroma). This induced a delay in postoperative treatment in 4.6% of patients [45]. The more extensive level II techniques and the remodelling process have not affected continued screening and radiographic follow-up of patients [51].

23.5.7 Growth of Oncoplastic Surgery Field

Oncoplastic surgery level II techniques are numerous and are generating increased attention in the surgical literature. Most authors describe the utilization of the inverted T mammoplasty for all quadrants of the breast [52–54]. Thus, for upper-pole tumours, the excision defect is filled by extensive mobilization of the lower gland. In our experience the implementation of the same reduction mammoplasty pattern for tumours in all locations of the breast has significant limitations. Advancement of distant breast tissue to fill the defect is at high risk of complications due to tissue necrosis. Kronowitz reports a 26% complication rate in a series of 50 patients. Our Atlas is based upon a direct excision of the skin over the tumour that allows reshaping and avoids complications due to extensive glandular mobilization. Because almost all cosmetic mammoplasties rely on inverted T-incisions, we had to develop new mammoplasty patterns specifically for breast cancer treatment. These include the V- and racquet mammoplasty techniques. We also adapted old techniques, such as the J-mammoplasty, that had been abandoned by most plastic surgeons. Thus, we developed almost one technique for each quadrant of the breast.

23.5.8 Integration into Current Surgical Practice

Difficulty in performing advanced level II techniques might constitute a limitation for the implementation of the Atlas. However, training for OPS can be acquired gradually, and level I techniques do not require any advanced training. One solution for the more complex cases is to incorporate a dual-team approach with the plastic surgeon. However, we would

favour OPS training for all future breast surgeons for a long-term solution [55, 56].

23.6 Conclusion

Oncoplastic surgery allows for wide resections with favourable cosmesis and integrates into a standard multidisciplinary approach for BCS. The ultimate goal is to allow large-volume resections with free margins and fewer re-excisions and mastectomies that is obtainable with standard BCS. We propose to stratify OPS into two levels. We define three key factors for technique selection: excision volume, tumour location and glandular density. Even though we are aware that there is no clear-cut division between standard BCS and oncoplasty, and that a crossover between levels I and II exists, we strongly advocate the adoption of a standardized OPS classification system. This classification should help training in OPS. Surgeons will be able to select appropriate courses and training experiences based on the distinct levels. The OPS classification and Atlas is intended to assist surgeons to choose the optimal approach for each individual patient to avoid complications and obtain the best oncologic and cosmetic results.

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Glandular Displacement Techniques

24

Siun M. Walsh and Mahmoud El-Tamer

Oncoplastic techniques have been developed in recent years for the surgical management of breast cancer, as they allow the resection of large volumes of breast tissue, while facilitating cosmesis and the avoidance of mastectomy [1]. Oncoplastic breast surgery has been shown to reduce rates of positive margins, and to increase patient satisfaction and psychosexual well-being [1–3]. Oncologic outcomes have been shown to be comparable with breast-conservation surgery [3–5]. Oncoplastic techniques can be broadly classified into two categories, simple and advanced, as was first suggested by Clough in 2010 [6]. Advanced oncoplastic techniques are employed in the treatment of tumors where > 25% of total breast volume is expected to be lost in the resection, and may also be extended to patients with macromastia or ptosis irrespective of the resected volume of the breast, particularly in patients who were contemplating such cosmetic procedures. These patients are often better served with a mastopexy or breast reduction as part of the oncologic procedure, irrespective of the volume of tissue loss, as breast reduction or mastopexy may be associated with higher complication rates after breast irradiation.

In contrast, simple oncoplastic techniques are generally used in the management of tumors, which require resection of < 25% of the total breast volume. These techniques involve primary closure of the breast defect using glandular displacement. Occasionally, these techniques can be used for larger proportions of tissue loss, depending on the overall breast size and the availability of surrounding glandular tissue.

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24.1 Anatomy

24.1.1 The Planes of the Breast

The breast is entirely surrounded by a pseudo-fascial plane—the superficial fascia of the anterior thoracic wall. This enveloping fascia divides into two distinct layers: anterior and posterior. The superficial or anterior layer merges with the cervical fascia superiorly and Campers fascia inferiorly. The posterior or deep layer is found immediately deep to the breast, and anterior to the retromammary bursa and the pectoralis fascia; this bursa is a potential space between the two layers of fascia, which allows the breast tissue to move freely against the chest wall.

Running between the fascial layers of the breast are a network of fibrous bands, known as Cooper's ligaments [7]. These extend from the pectoralis fascia to the skin and attach the breast tissue to the chest wall. The strength and laxity of these suspensory ligaments dictate the degree of ptosis of the breast. Cadaveric studies have also revealed a thin mesentery-like fibrous septum reaching from the pectoral fascia to the nipple-areola complex [8]. At its edges, it curves into a medial ligament, which attaches to the sternum, and a lateral ligament, which attaches to the lateral border of pectoralis minor. This fibrous septum and its associated ligaments serve as scaffolding, maintaining shape and movement in the breast.

One of the most crucial steps in oncoplastic surgery is the mobilization of glandular tissue, which involves the elevation of skin flaps. It is essential to identify the appropriate plane in order to create a flap. Below the dermis of the skin of the breast lies a layer of subcutaneous fat, of variable thickness. Fibrous bands connect this fatty subcutaneous layer to the adjacent breast parenchyma. There are minimal blood vessels accompanying the fibrous bands, and, therefore, dissection between the parenchyma and the subcutaneous fat tends to precipitate minimal bleeding (Fig. 24.1). This is the mastectomy plane. In cases with superficial tumors, the overlying skin may be elevated at the level of the superficial fascia plane or preferably excised en bloc with the tumor. This plane is dissected in cases of superficial tumors. For deeper

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_24

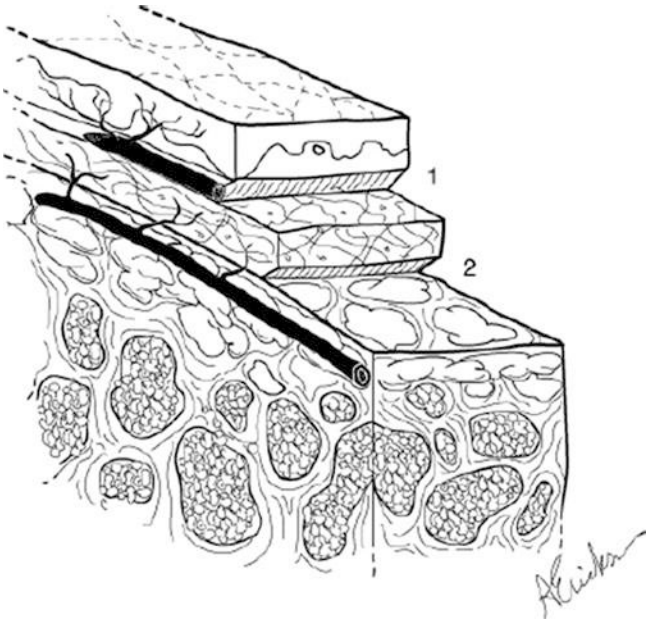

Fig. 24.1 Planes of the breast. (Reproduced with permission from: *Principles and Techniques in Oncoplastic Breast Cancer Surgery*. El-Tamer M, ed. 2013; World Scientific Publishing: Singapore)

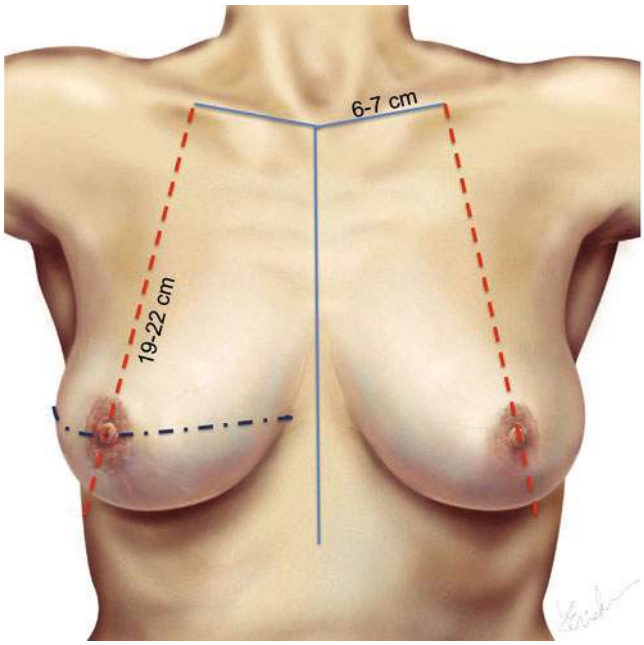

Fig. 24.2 Nipple meridian. Ideally, the nipple is positioned along the intersection of the nipple line and the inframammary line when transposed to the anterior aspect of the breast. The transposition of the inframammary line is estimated by placing the index and middle finger behind the breast and locating that point with the thumb on the anterior surface of the breast (Reproduced with permission from: *Principles and Techniques in Oncoplastic Breast Cancer Surgery*. El-Tamer M, ed. 2013; World Scientific Publishing: Singapore)

tumors, a deeper plane is dissected, as illustrated (Fig. 24.1). This is known as the lumpectomy plane and is located just above the glandular tissue. Utilization of this plane is cosmetically superior to utilization of the mastectomy plane.

24.1.2 Surface Markings of the Breast

There are several features of the surface anatomy of the breast that the surgeon should take care in defining before undertaking oncoplastic surgery. Breast markings should be carefully examined, with the patient standing normally with relaxed shoulders, facing straight ahead, with arms by the sides. After identification of the sternal notch, the clavicle, the midline, and the nipple, the nipple meridian can be drawn. This is achieved by extending a vertical line from a point on the clavicle that is 6–7 cm lateral to the midpoint of the sternal notch, down through the midpoint of the nipple. This can be extended in the same line to reach the inframammary fold. When planning oncoplastic surgery, the final position of the nipple should sit on the meridian line (Fig. 24.2). With breast reductions and mastopexies, the inframammary fold is transposed anteriorly on the breast along the nipple meridian to mark the new position for the nipple. We strongly recommend that surgeons who are not well versed in oncoplastic techniques, and whose patients may not be interested in future contralateral symmetrizing procedures, limit the elevation of the nipple to 19–22 cm from the midclavicular line (a vertical line dropped from the midpoint of the clavicle). The ideal distance from the nipple to the clavicle varies between patients and has been recommended to be at the level of the inframammary line or at the same level as the mid humerus.

24.1.2.1 Blood Supply of Nipple

Many oncoplastic procedures employ periareolar incisions and/or de-epithelialization of the periareolar area. It is therefore imperative to be aware of the blood supply of the nipple. The majority of the blood supply of the nipple is derived from the internal mammary artery, but branches of the anterior intercostal arteries and the lateral thoracic artery have also been shown to provide blood supply [9]. Venous drainage is to the internal mammary veins. Periareolar incisions involving > 50% of the total areolar circumference are not advisable due to the high risk of nipple necrosis.

24.2 Factors to Be Considered

24.2.1 Size of the Breast

The size of both breasts should be taken into consideration when planning oncoplastic surgery. It is important to note that 80% of women wear the incorrect cup-size. Cup-sizes vary according to country and brand. It is therefore imperative

to assess cup-size objectively, to avoid error. Asymmetry should be noted and documented. Breast size asymmetry is reported in approximately 65% of women [10]. This can be advantageous to the surgeon in cases where the tumor has arisen in the larger breast. In contrast, in cases where the smaller breast will now lose further volume, contralateral reduction mammoplasty may be required in the future to achieve acceptable symmetry.

24.2.2 Ptosis

Ptosis of the breast should be assessed and documented. Ptosis is generally described as grade 1–3, with grade 1 implying mild sagging and grade 3 describing significant sag. The degree of ptosis correlates with the amount of breast tissue available inferiorly. Patients with significant ptosis may benefit from mastopexy-style resections (Fig. 24.3).

24.2.3 Tumor Characteristics

The size of the tumor should be assessed using mammogram and ultrasound. MRI, while not always necessary, may be useful in estimating the extent of disease of lobular carcinomas and in assessing response to treatment in cases where neoadjuvant chemotherapy has been given to facilitate breast conservation [11, 12]. Tumor size, in relation to breast size, will help to select the appropriate oncoplastic technique.

24.2.4 Localization of the Tumor

The use of modern imaging techniques to accurately localize the tumor preoperatively facilitates precise planning of the surgery and minimizes the volume of tissue that is excised. At Memorial Sloan Kettering Cancer Center, we routinely use radioactive seed for localization of a single lesion or even

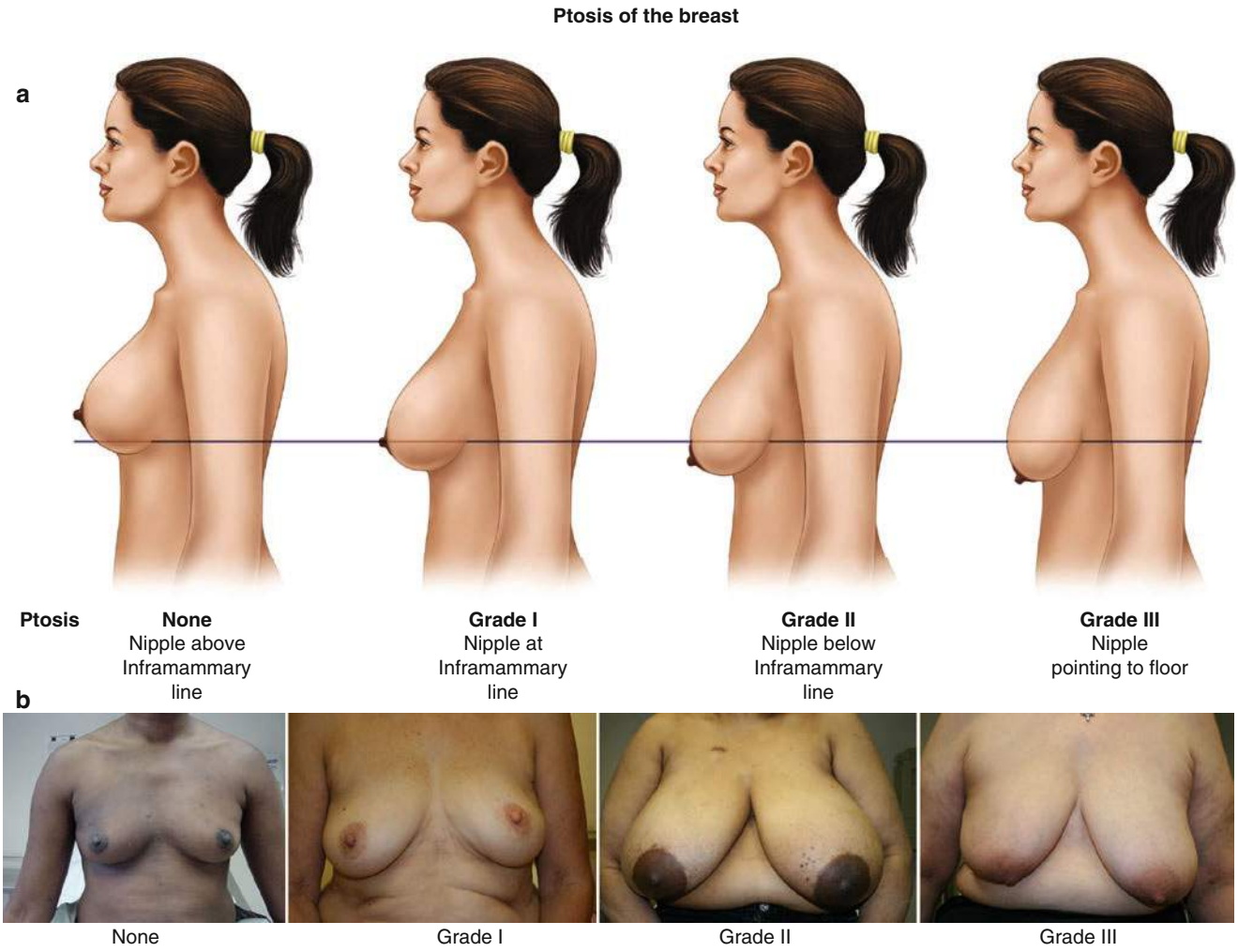

Fig. 24.3 (**a**) Ptosis of the breast. (**b**) Examples of grades of ptosis of the breast (Courtesy of Dr. Mahmoud El-Tamer, Memorial Sloan Kettering Cancer Center, New York, NY)

for bracketing. The safety and efficacy of this usage have been demonstrated previously [13]. Advantages include smaller excision volumes, shorter operative time, and increased patient comfort and satisfaction [14–16]. We recommend for each surgeon to use the localization technique they are most familiar with.

24.2.5 Margins

It is important to clarify that the main purpose of an oncoplastic procedure is to repair the defect created in order to maintain or enhance the final cosmetic result, rather than to achieve the widest possible margin. New guidelines for appropriate margins have been recently published and adopted by many breast and oncologic societies. A margin of 2 mm is now acceptable for ductal carcinoma in situ (DCIS) [17], and no ink on tumor is sufficient for invasive carcinoma [18]. Wider margins have not been associated with a lower rate of local recurrence. The adoption of these guidelines into practice has resulted in decreased re-excision rates [19, 20]. For further details on margins, please refer to the chapter in this book on the subject of surgical margins in breast-conserving surgery.

24.3 Skin Incisions

24.3.1 Principles of Breast Incision Planning

Complete and adequate surgical excision of the tumor, with the achievement of clear margins, remains the pillar-stone of breast cancer treatment. The first step in surgical excision is the creation of a skin incision. There are several considerations. Firstly, the incision must be placed and sized to allow sufficient access for complete resection of the tumor. Secondly, the incision should allow adequate exposure to mobilize surrounding tissue and repair the defect. In addition, the incision should be placed in an aesthetic position. The ideal skin incisions are those placed around the areola, inframammary line, or axilla.

24.3.2 Periareolar Incisions

The periareolar incision is generally accepted as the most cosmetic incision. With proper flap dissection, periareolar incisions allow access to all quadrants of the breast. We strongly recommend the use of a headlight or a lighted retractor with these incisions, as standard overhead lights may not be adequate. Furthermore, we cannot overemphasize the importance of adequate hemotasis, as such wide flap dissections are associated with a higher rate of postoperative hematomas. When placed at the junction of the areola and skin, scarring is minimal and the incision usually can fade considerably. The position of a periareolar incision can be placed to access any quadrant of the breast. The incision should not involve more than 50% of the circumference of the areola, as further disruption can lead to compromise of the blood supply of the nipple and necrosis. Preoperative planning is essential, as the demarcation of this junction can be difficult to identify, after application of antiseptic solution. This incision also may not be suitable for patients with small areolae, relative to their breast and tumor size. Furthermore, this incision may not provide adequate access to tumors distant from the nipple, particularly in patients with poor circulation or with large and/or pendulous breasts. However, the incision can be extended laterally or medially (Fig. 24.4), to improve access. The areola should be retracted gently, and pressure should be intermittently released, to minimize vascular injury. Electrocautery, although not contraindicated, should be used with caution in this area, due to risk of neurovascular injury. To avoid scar widening, the incision has to be properly closed with approximation of the deep dermis, which usually retracts after completing the resection.

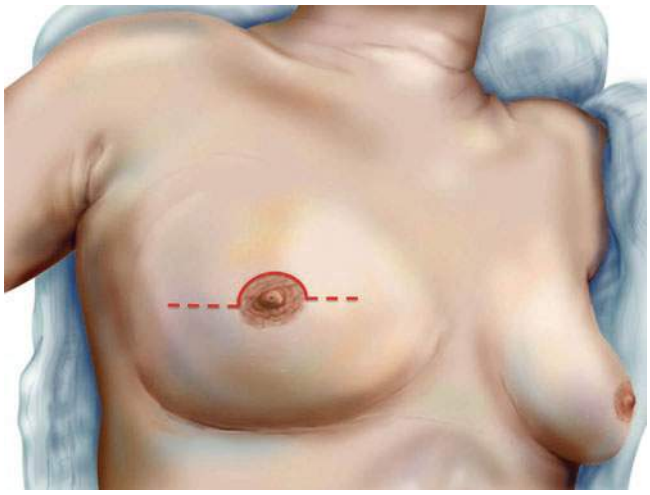

Fig. 24.4 Periareolar incision and extensions (Courtesy of Dr. Mahmoud El-Tamer, Memorial Sloan Kettering Cancer Center, New York, NY)

Finally, in cases where there is a high possibility of completion mastectomy, the potential incision for mastectomy should be taken into consideration. The incision should either align with or be within the area of the skin, which would potentially be excised if a mastectomy is needed.

Although the majority of patients report normal nipple sensation 6 months after surgery, it is important to warn patients of the risk of short-term numbness if planning to use a periareolar incision.

We recommend that surgeons who are new to these oncoplastic techniques perform the incision that allows them the most direct access. With experience, surgeons can become

more comfortable with accessing distant tumors through periareolar incisions.

24.3.3 Curvilinear Incisions

These incisions are often utilized for resection of tumors in the upper aspect of the breast. Numerous lines, such as the lines of Langer, Kraissl, and Borges [21], have been used as guidance for the optimal placement of curvilinear incisions. The authors favor incisions in the lines of Kraissl, which are lines perpendicular to the action of the underlying muscle. When excising skin in the upper quadrants, it is important to realize that the nipple will be lifted and to ensure that the nipple is not displaced medially or laterally. The final position of the nipple-areola complex should lie on the nipple meridian line. Curvilinear incisions crossing the 3 o'clock axis or 9 o'clock axis should be avoided, as they may cause distortion of the nipple-areola complex. In the lower quadrants, curvilinear incisions are acceptable when the excision of skin is not necessary and when excising small tumors only. Resection of skin or a large volume of tissue via a lower quadrant curvilinear excision may result in an inferior displacement and downward pointing of the nipple, known as "bird's beak" deformity.

24.3.4 Radial Incisions

Radial incisions are convenient and facilitate the removal of the skin and large volumes of tissue in the upper outer quadrants (Fig. 24.5). They can begin as far medially as the areola and may be extended into the axilla to allow access for a sentinel lymph node biopsy or axillary lymph node dissection. These incisions should be avoided in the upper inner quadrants, as the scars in this area prove difficult for the patient to conceal. In the 3 o'clock axis and 9 o'clock axis, we exclusively use radial incisions. We also exclusively use radial incisions in the lower quadrants when an en bloc resection that includes the overlying skin is planned. Such incisions will avoid downward displacement of the nipple-areola complex.

24.3.5 Inframammary Incisions

Incisions placed in the inframammary fold are cosmetically pleasing and easy to conceal. However, if completion mastectomy with standard central elliptical incisions is expected, these incisions may cause cosmetic problems and may compromise the blood supply of the lower flap. Following an inframammary incision if a mastectomy is planned, we recommend using the inverted-T incision used for breast reduction to complete the mastectomy. We try to limit the extent of the inframammary incision while performing the mastectomy to maintain an adequate blood supply to the cutaneous flaps.

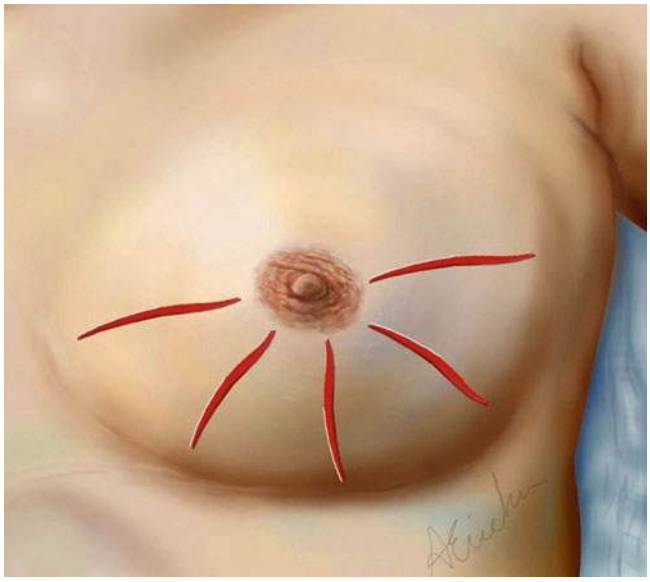

Fig. 24.5 Radial incisions (Courtesy of Dr. Mahmoud El-Tamer, Memorial Sloan Kettering Cancer Center, New York, NY)

24.4 Raising the Skin Flap

After incising the skin, flaps are raised around the area of the tumor. The purpose of this is to allow access to the tumor and to mobilize skin to repair the defect. We recommend elevating the flaps at the glandular level as seen in Fig. 24.1. We have labeled this plane as the lumpectomy plane; it is easily identified in young women with glandular breast tissue. In older patients with fatty replacement of the breast, identifying the lumpectomy plane may require experience. The breast skin and subcutaneous tissue are raised as one unit while transecting Cooper's ligaments. For deeply located tumors, using the lumpectomy plane is oncologically safe. In superficially located lesions, particularly when there is skin tethering, we strongly recommend excising the overlying skin en bloc with the tumor to maintain the oncologic appropriateness of the resection.

24.5 Resection of the Tumor and Shave Cavity Margins, Clipping of the Cavity

The optimal surgical management of breast carcinoma has changed dramatically in recent years. Breast surgery reached its peak of invasiveness in the 1940s with the advent of the super-radical mastectomy. In the mid-1980s breast-conservation surgery was shown to have equal survival rates when compared with mastectomy. It also became clear that a histologically negative margin of resection achieves the lowest local recur-

rence rate after breast conservation. For some time, there was a significant debate regarding what constitutes a negative margin. Some continued to routinely apply the Halstedian principle of resection to lumpectomies with en bloc resection of the overlying skin, the breast, and underlying muscle fascia with resection of the totality of the quadrant of breast tissue where the tumor is located, in a form of quadrantectomy [22, 23]. Some surgeons also used oncoplastic techniques for the main purpose of achieving wider negative margins. We have not adopted that philosophy. We have always recommended a sound oncologic procedure followed by an oncoplastic repair to restore, maintain, or enhance the physical appearance of the breast. We limit en bloc resection of the overlying skin and underlying fascia to select cases in which the skin is close or involved and in which the tumor extends to the deep layers of the breast. Furthermore, recent guidelines developed and adopted by the Society of Surgical Oncology (SSO), American Society of Radiation Oncology (ASTRO), American Society of Breast Surgeons (ASBrS), and the American Society of Clinical Oncology (ASCO) have established that "no ink on tumor" is sufficient to call a margin negative [18, 24, 25].

We utilize a relatively new strategy to achieve clear margins, which has been reported to decrease re-excision rates significantly [26, 27]. The tumor is narrowly excised, and then the lumpectomy cavity is circumferentially re-excised. The re-excised margins are oriented and submitted separately.

At this point, after meticulous hemostasis is achieved, the walls and base of the cavity are clipped. This is important to assist the radiation oncologists in identifying the tumor bed for irradiation, as the tumor site may not necessarily underlie the incision site. These clips are also useful in identifying cavity edges when re-excision of margins is needed. The cavity edges can prove difficult to identify after complex oncoplastic closure of the cavity.

Some have routinely used intraoperative ultrasound to guide the resection; we have not adopted such a tool, as the vast majority of our positive margins has been limited to DCIS.

24.6 Preparation for Glandular Displacement; Elevation of Breast Off the Underlying Muscle

In larger breasts, where the resection of breast tissue down to the pectoral fascia has not been necessary, elevation of the breast off the underlying muscle may not be necessary. In patients with cup-sizes A or B or in cases where the resection extends down to the muscle, elevation of the glandular tissue posteriorly allows mobilization of the breast tissue to close the defect, while helping to minimize distortion of breast shape. This is performed after resection of the tumor by entering the aforementioned retromammary bursa. When both a skin flap is raised and breast tissue is elevated from the pectoral fascia, this is known as a biplanar mobilization. In elderly patients, smokers, and patients with peripheral vascular disease, one has to be considerate of the vascularity of the tissue. In such patients, we frequently avoid oncoplastic procedures altogether or limit the extent of mobilization to avoid the risk of necrosis of the fat and glandular tissue.

Table 24.1 Summary of glandular displacement techniques

	Optimal area for use	Areas not to use	Cautions
Transverse	Upper hemisphere and central breast	Lower breast	Displacement of nipple
Radial	All quadrants		If used horizontally at 9 or 3 o'clock, nipple displacement
Triangular	Upper hemisphere	None	Skin puckering
Purse-string	Central		Nipple-areola complex wrinkling
Mobilization of surrounding subcutaneous tissue	Lateral and inferior quadrants	Central or medial	Excess fatty subcutaneous or axillary tissue needed

24.7 Techniques of Glandular Displacement

For simplicity, we have categorized this type of repair into five categories. Occasionally, however, one can combine types of repair for the same defect. We have routinely used absorbable sutures of 2-0 or 3-0 caliber with a round or cutting needle, depending on the thickness of the breast tissue. We routinely describe our technique of repair in the operative report; we find that reporting is very helpful in cases where we need to re-excise positive margins. See Table 24.1 for a summary of these glandular displacement techniques.

24.7.1 Transverse Closure

Transverse closure describes the advancement of the upper edge and lower edge of breast tissue, to a point at which they meet, resulting in a transverse line of closure of the glandular tissue (Fig. 24.6). This technique is ideal for repairs in the upper hemisphere and central breast. Transverse closure of the breast with upper quadrant defects invariably results in elevation of the nipple-areola complex. Such elevation is welcomed in most patients with some degree of ptosis. In patients without any ptosis, elevation of the nipple-areola complex will result in significant deformity that is quite challenging to fix. Hence we stress the importance of preoperative evaluation of the grade of ptosis preoperatively to plan the type of repair.

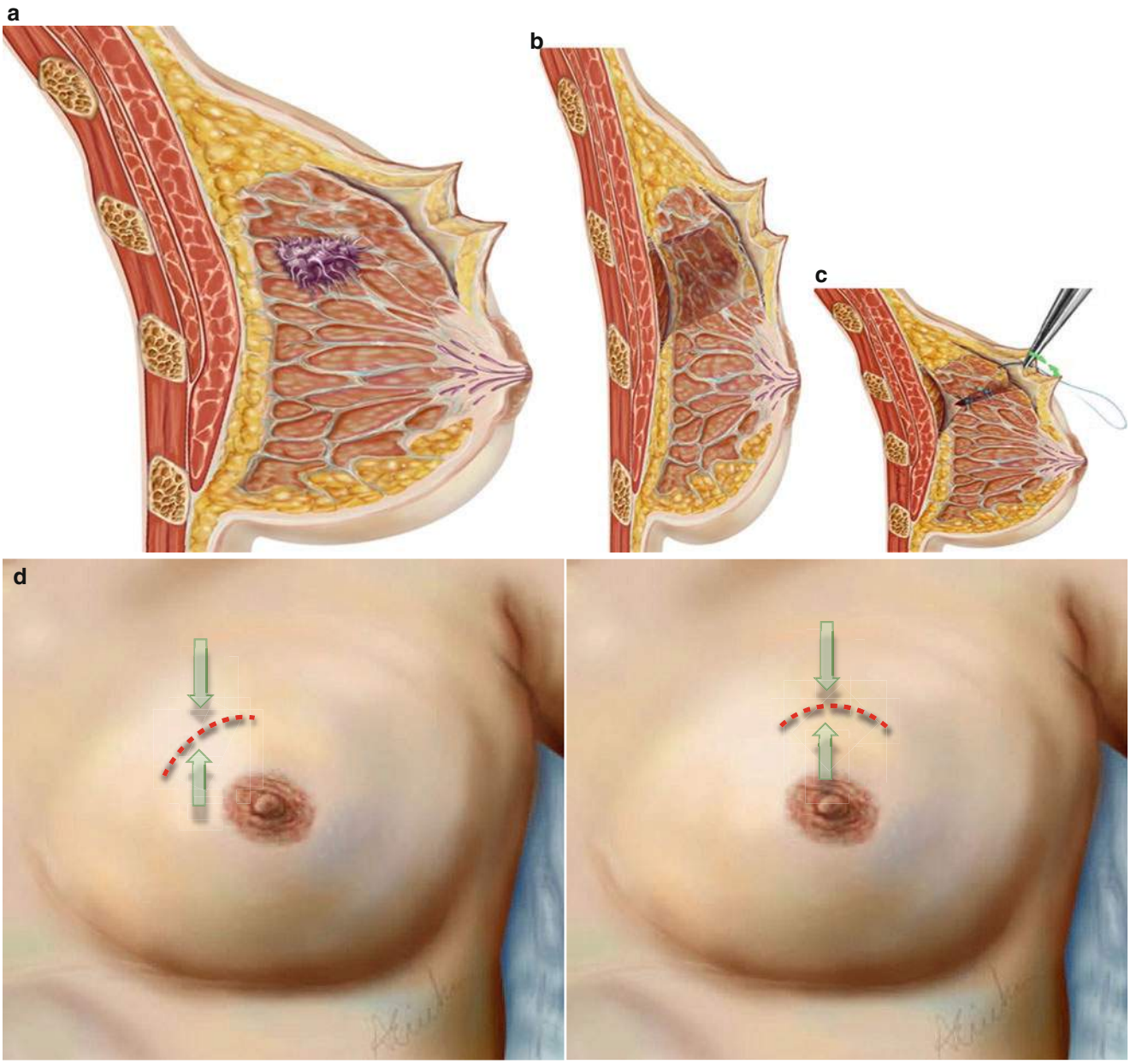

Fig. 24.6 Transverse closure. (**a**) The skin flaps are raised. (**b**) The tumor is excised with appropriate margins. (**c**) The breast is elevated off the underlying muscles; the skin flaps are further elevated as needed. The breast tissue is approximated along a transverse plane. (**d**) Transverse closures in the upper quadrants. The arrows show the direction of the mobilization of the breast tissue and closure pattern (**a–c**: Reproduced with permission from: *Principles and Techniques in Oncoplastic Breast Cancer Surgery*. El-Tamer M, ed. 2013; World Scientific Publishing: Singapore; **d**: Courtesy of Dr. Mahmoud El-Tamer, Memorial Sloan Kettering Cancer Center, New York, NY)

We have avoided transverse repairs in the lower quadrants of the breast due to the high probability of inferior displacement of the nipple-areola complex, particularly with tumors located in the 6 o'clock axis and the lower inner quadrant. In such quadrants, we have routinely resorted to radial closures.

24.7.2 Radial Closure

After resection of the lesion and adequate mobilization from the underlying fascia and overlying skin, the breast tissue is approximated along a radial line (Fig. 24.7). This technique can be used in any quadrant, but is most cosmetically effective in the lower aspect of the breast, particularly in cases requiring resection of the overlying skin. The closure is facilitated when the specimen is excised in an elliptical shape. The area containing the larger amount of breast tissue, which is to be used to fill the defect, should be mobilized more extensively. For example, in the lower inner quadrant, there is more available tissue in the lateral flap, so this flap should be mobilized more expansively. Radial closure of the defect can be performed through any type of skin incision, radial, transverse, circum-

areolar, or inframammary incisions. In the upper quadrants, such closures are particularly useful in patients with minimal ptosis. Radial closure of the breast may also be used in the upper inner quadrant; we do not, however, recommend using a radial skin incision for access in the upper inner quadrant, as it may result in a scar that is difficult to conceal.

24.7.3 Triangular (Mercedes Closure)

This procedure combines the principles of the transverse and radial repair techniques. It is commonly used in the upper hemisphere, as it allows better control of the upward displacement of the nipple-areola complex. Following resection of the lesion, a triangular or three-point suture is placed at the center of the defect, to transform the circular defect into a three-pointed star-shaped wound (Fig. 24.8). The limbs of the star are then approximated with separate sutures. The final result of the repair is a three-pointed star shape similar to a Mercedes-Benz® logo. The placement of the base of triangular sutures allows control of the extent of the elevation of the nipple-areola complex as illustrated (Fig. 24.9a). Furthermore, one can fine-tune the medial and lateral deviation of the nipple-areola complex by changing the position of the apical suture (Fig. 24.9b). Such fine-tuning is quite helpful in defects that are in the upper or inner quadrants of the breast. We have infrequently used this technique to repair defects in the lower quadrants of the breast, as it may result in an unsightly downward pointing of the nipple-areola complex. After repair of the defect has been completed, the skin flaps may need to be further elevated to avoid puckering.

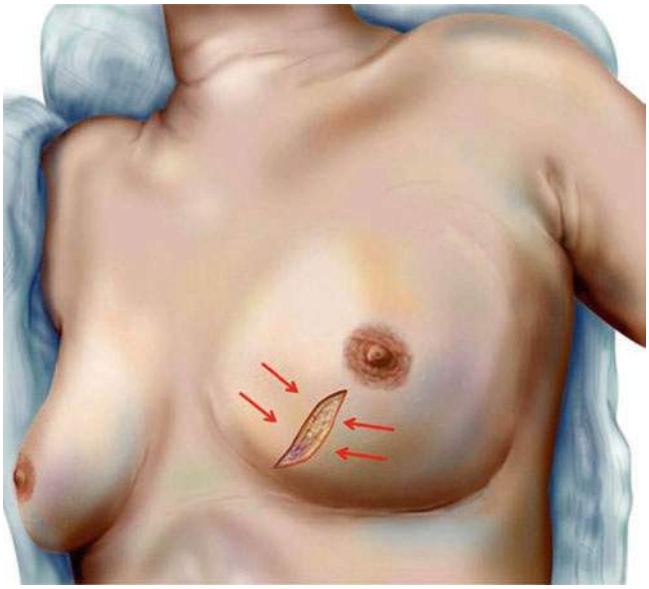

Fig. 24.7 Radial closure. Radial closure can be performed irrespective of the style of the skin incision. For ease, we have chosen a radial skin incision. The breast tissue is mobilized along the arrows and approximated along a radial plane (Courtesy of Dr. Mahmoud El-Tamer, Memorial Sloan Kettering Cancer Center, New York, NY)

24.7.4 Purse-String Repair

The purse-string repair follows the basic principle of tightening the opening of a coin purse. It is particularly useful for the repair of central defects. The nipple-areola complex is mobilized from the underlying tissue. The thickness of the nipple-areola complex flap depends on the distance between the tumor and the nipple-areola complex. Following completion of the resection, the repair is carried out by placing a series of purse-string sutures in the walls of the defect. The defect is closed in layers, working from deep to superficial (Fig. 24.10). This obliteration of the lumpectomy cavity creates a scaffold on which the nipple-areola complex will rest, thus preventing its posterior retraction. The surgeon must have an adequate understanding of the vascularity of the nip-

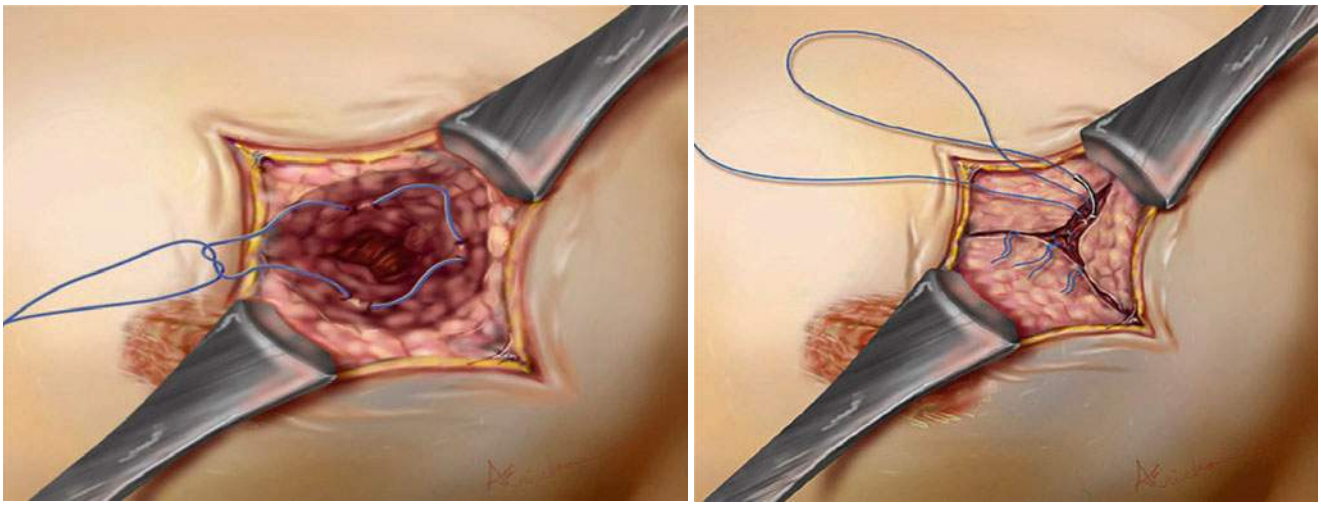

Fig. 24.8 Triangular closure: Mercedes repair. The defect is approximated with a triangular suture (Reproduced with permission from: *Principles and Techniques in Oncoplastic Breast Cancer Surgery*. El-Tamer M, ed. 2013; World Scientific Publishing: Singapore)

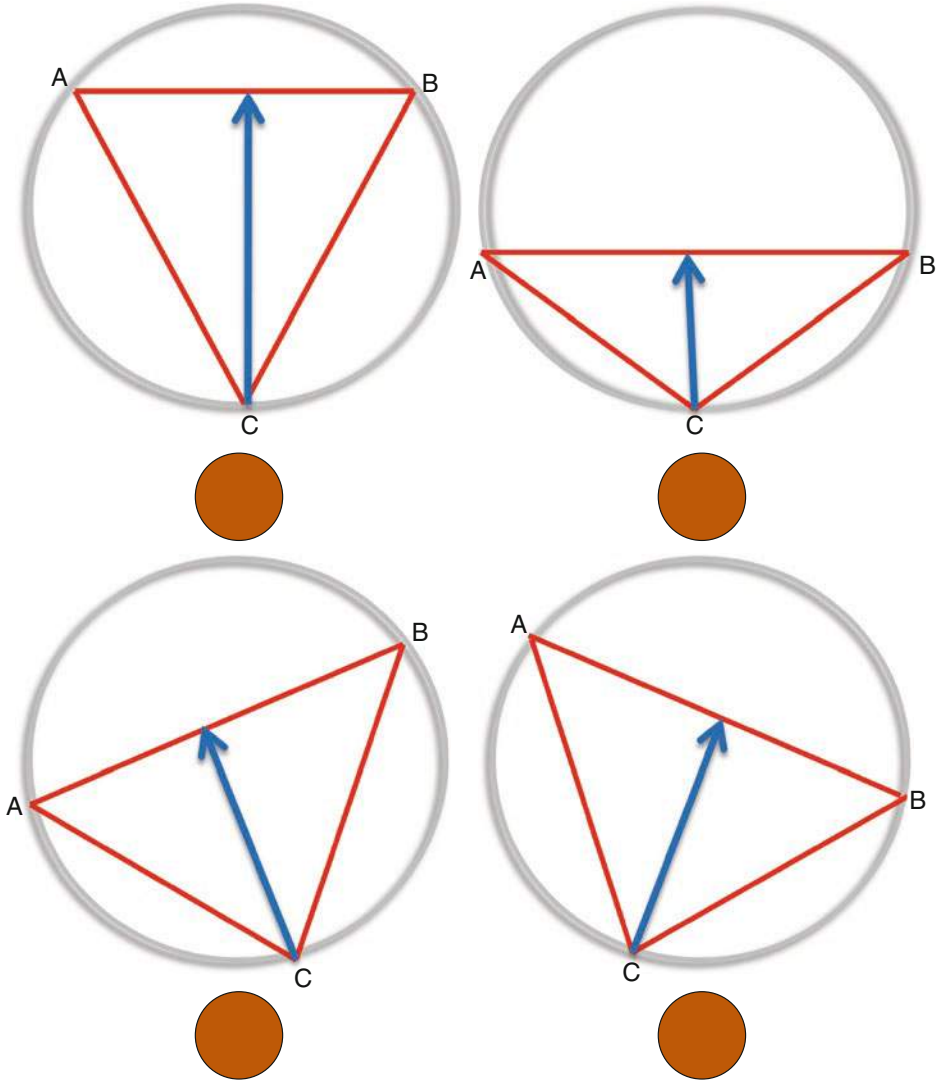

Fig. 24.9 Triangular closures—control of the extent of the elevation of the nipple-areola complex. The brown circles represent the nipple. The placement of the sutures A and B will dictate the extent of the elevation of the nipple-areola complex. Furthermore, the location of the A, B, and C sutures also allow for pulling the nipple medially or laterally in order to keep its position along the nipple line (Reproduced with permission from: *Principles and Techniques in Oncoplastic Breast Cancer Surgery*. El-Tamer M, ed. 2013; World Scientific Publishing: Singapore)

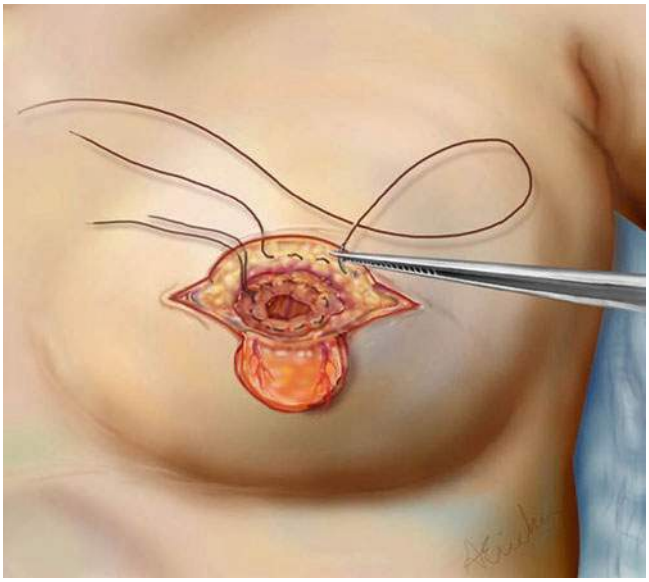

Fig. 24.10 Purse-string closure (Reproduced with permission from: *Principles and Techniques in Oncoplastic Breast Cancer Surgery*. El-Tamer M, ed. 2013; World Scientific Publishing: Singapore)

ple-areola complex to avoid compromise. The surrounding skin should be adequately mobilized to prevent puckering of the nipple-areola complex. For cases that require resection of a large volume of tissue, we have usually resorted to a dome mastopexy procedure as described in Chap. 27.

24.7.5 Mobilization of Surrounding Subcutaneous Tissue

This method is reserved for peripherally located tumors (Fig. 24.11). The most commonly used tissues used for this repair are the lateral axillary fat pad and, occasionally, the subcutaneous tissue of the upper abdomen, just inferior to the inframammary fold. The subcutaneous tissue is released from the overlying skin and detached from the underlying musculature, and then advanced to fill the defect, where it is then sutured to the surrounding breast tissue. It is important to note that sufficient fatty subcutaneous tissue is needed to perform this type of repair.

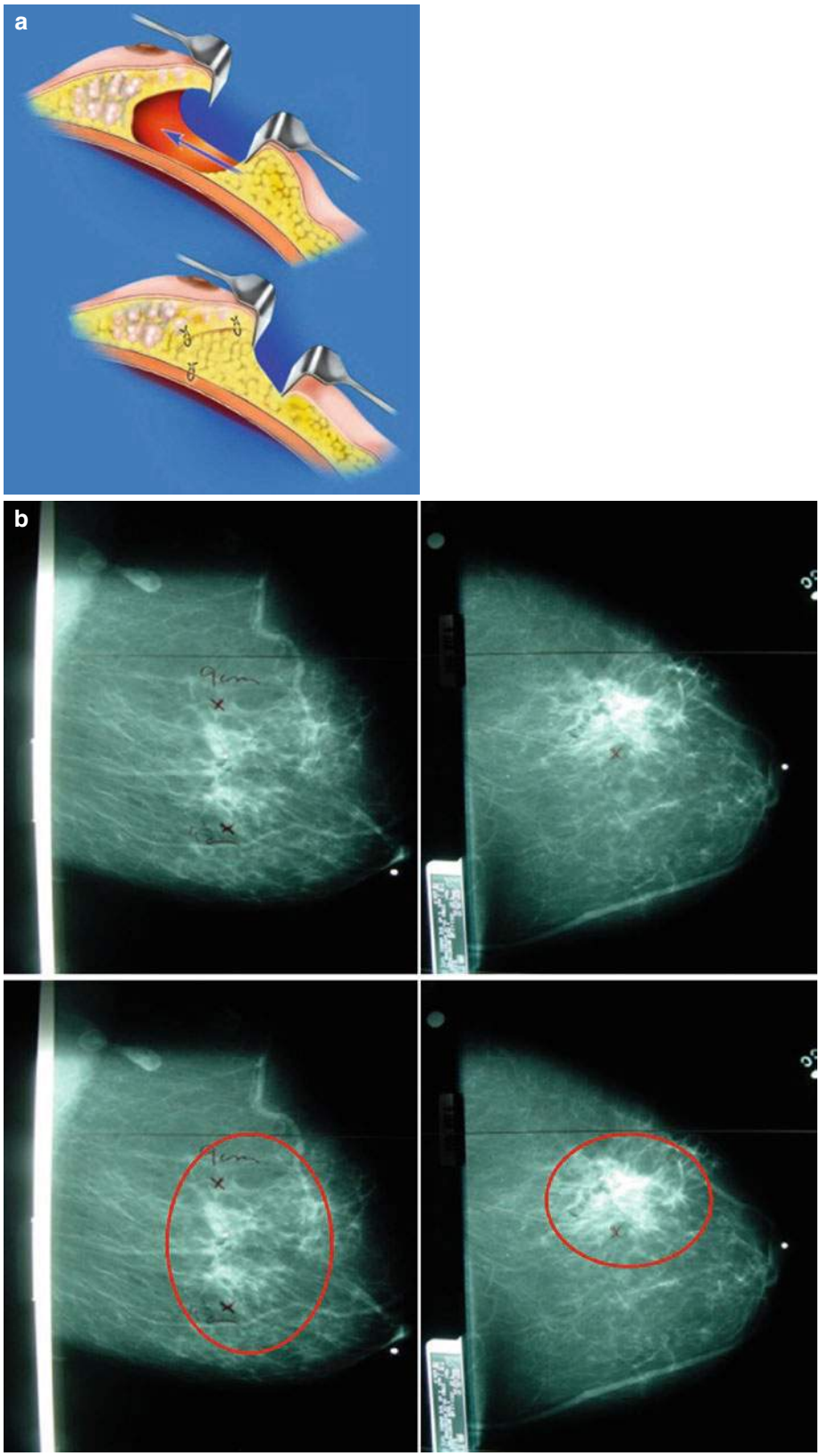

Fig. 24.11 (**a**) Mobilization of surrounding subcutaneous tissue. (**b**) Case images: 68 year old with comorbidities presents with new contralateral breast cancer. (**c**) Case images: resection. (**d**) Case images: post-resection without breast repair; post-resection with repair using axillary fat pad. (**e**) Case images: post-reconstruction. (**f**) Case images: 2 weeks postoperatively. *Left*: status post left lumpectomy and sentinel node biopsy. The patient had a prior right breast cancer treated 2 years before the left breast cancer (Reproduced with permission from: *Principles and Techniques in Oncoplastic Breast Cancer Surgery*. El-Tamer M, ed. 2013; World Scientific Publishing: Singapore)

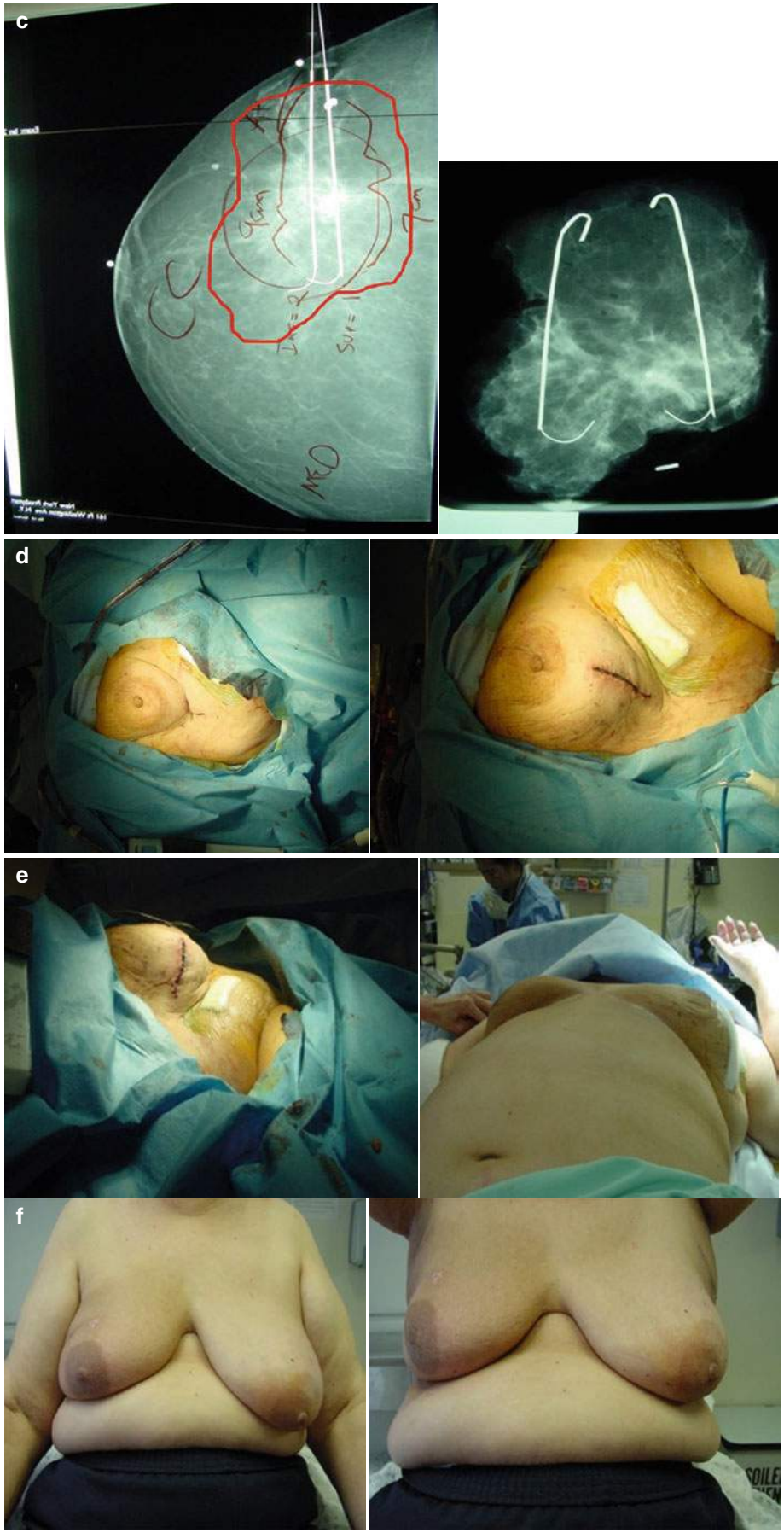

Fig. 24.11 (continued)

24.8 Conclusion

Glandular displacement is a simple technique within the reach of any general surgeon. However, it requires a good understanding of anatomy and some level of training. This technique is very helpful in closing breast defects following lumpectomies that require resection of less than 25% of a patient's breast volume.

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Glandular Displacement: The Swiss Experience

25

Christoph J. Rageth and Christoph Tausch

The most common methods of oncoplastic breast surgery used by nonplastic surgeons are described below. We intentionally did not include breast reduction techniques in this list.

All diagrams are made from the perspective above the patient's left shoulder.

Two important questions must be asked before selecting the incision and two before selecting the reconstruction technique.

The two important questions *before* the incision (Fig. 25.1):

1. How much tissue must be removed?
   (a) *Little*: Incision in the Langer's lines or semicircular incision without a spindle-shaped excision
   (b) *Much*: Radial incision with excision of an island of the skin (spindle shaped or triangular for a dermoglandular rotation reconstruction) or round block technique with excision of a donut-shaped portion of periareolar skin

   In the two lower quadrants, "much" tissue must usually be excised in relation to the existing tissue, which is why a radial incision is more often made there.
2. Is the tumor close to the skin?
   (a) *Yes*: Incision over or near the tumor.
   (b) *No*: The incision can also be made at a distance from the tumor (usually near the areola or in the submammary fold or further in lateral direction).

   Intraoperative sonography is very helpful for measuring the distance from the skin to the tumor.

   If *intraoperative radiation* will be given, the incision must usually be placed over the tumor even if the distance to the skin is large because otherwise the distance of 1 cm from the skin is not ensured.

If there is *ptosis or macromasty* and much tissue must be excised, a reduction mammoplasty technique is often selected. However, this technique is not described here.

The two important questions *after* excision and before reconstruction:

1. Does the tissue adapt sufficiently without an oncoplasty technique, or does an oncoplasty technique have to be used?
   (a) *Yes*: This is the case in around half of segmental excisions, and after local mobilization, adaptation can be achieved with a few (usually 1–2) sutures placed as deep as possible.
   (b) *No*: A glandular displacement or glandular replacement technique or reduction of the contralateral side must be selected.

   If a glandular displacement or glandular replacement technique must be selected, the second question must be asked:
2. Is there enough breast tissue after excision of the tumor (or tumors) for reconstruction that results in adequate breast size?
   (a) *Yes*: A glandular displacement technique can be used.

   We generally use one of the following three methods:
   - Intramammarian flap reconstruction [1]
   - Dermoglandular rotation flap
   - Round block technique (a) with complete de-epithelialization of skin around the nipple-areola complex or (b) with partial de-epithelialization of skin around the nipple-areola complex

   Two other methods are used here relatively rarely and are not described in detail here:
   - Primarily for central tumors – the Grisotti flap [2]
   - Nipple displacement if the nipple-areola complex would be too far lateral

   (b)*No*: Either a *glandular replacement* technique or reduction mammoplasty to achieve symmetry with the contralateral breast must be performed.

   We use the following three methods, only the first of which is explained here:

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_25

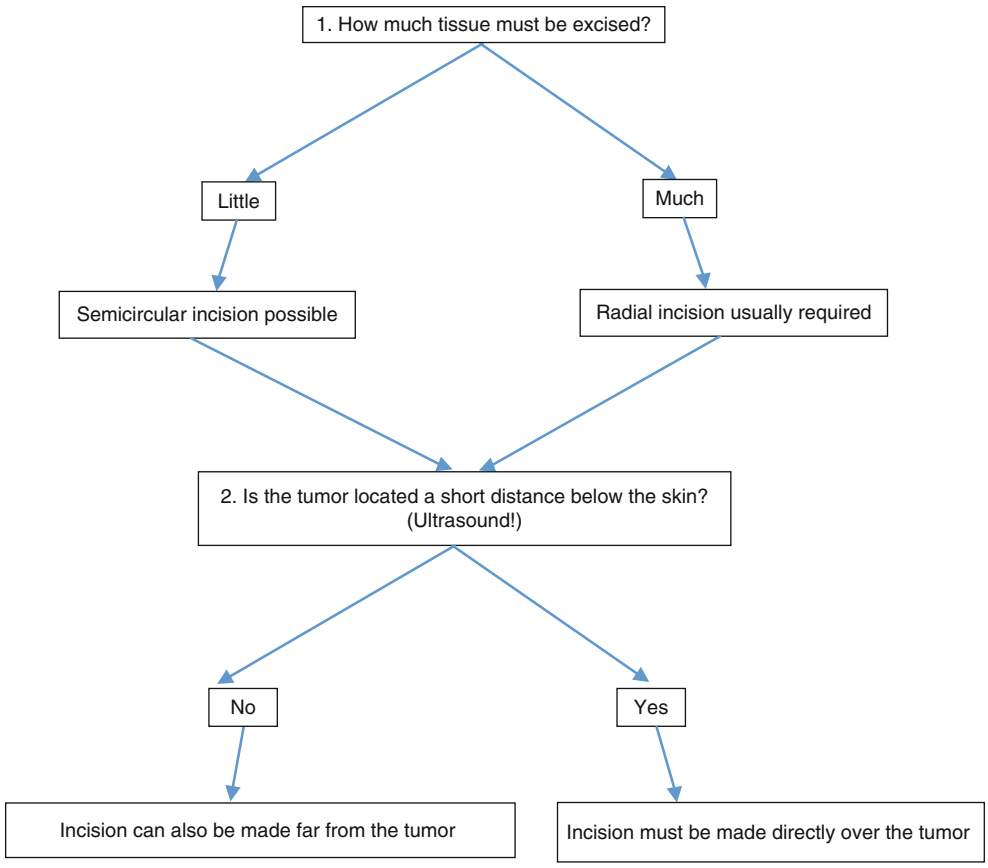

Fig. 25.1 Algorithm for selecting the incision

- Lateral advancement (the latissimus dorsi muscle is attached to the pectoralis major muscle, which shifts the subcutaneous tissue lying over the latissimus dorsi muscle toward the breast).
- Defect filing using a free or pedicled latissimus dorsi flap.
- Reduction mammoplasty on the affected side and reduction mammoplasty of the contralateral side to achieve symmetry.

Description of the three *glandular displacement techniques* most often used here:

1. *Intramammarian flap reconstruction* (Fig. 25.2)
   This technique can be used in every quadrant and was described by Rageth and Tausch [1].
   Prerequisite: Non-fatty breast tissue (otherwise there is a high risk of fat necrosis).
   Technique: The residual breast is split horizontally to form a tissue flap from the pectoral segment of the breast that can be placed in the defect. A temporary adaptation of the wound cavity before the horizontal split is made can be used to identify the region from where the major portion of the flap should be taken. It is generally necessary to make a wide sharp split, especially behind the nipple, so the nipple is not displaced when the flap is moved.
2. *Dermoglandular rotation flap* (Fig. 25.3)
   This technique is used in the caudal area of the mammary gland.
   Prerequisite: The breast may not be too large or too small.
   Technique: A triangular section shaped like a slice of pie containing the tumor is excised from the breast. The excision must be made at a right angle to the surface of the skin, and the skin may not be undermined because otherwise the mammary gland cannot adapt without tension. In the submammary fold, the incision is extended in lateral direction toward the axilla until the caudal wound margin is about twice as long as the cranial wound margin. Generally, no deep sutures are required; skin adaptation is sufficient.
3. *Round block technique* (Fig. 25.4)
   With complete de-epithelialization the skin around the nipple-areola complex or with partial de-epithelialization of the nipple-areola complex. The round block technique was first described in 1990 by Benelli [3] as a reduction technique. For oncoplastic surgeries Clough described it in 2012 [4]. It did not initially become an established reduction mammoplasty technique but is today increasingly used in oncoplastic surgery.
   This technique is especially suited for fatty breasts that are unsuitable for an intramammarian flap reconstruction

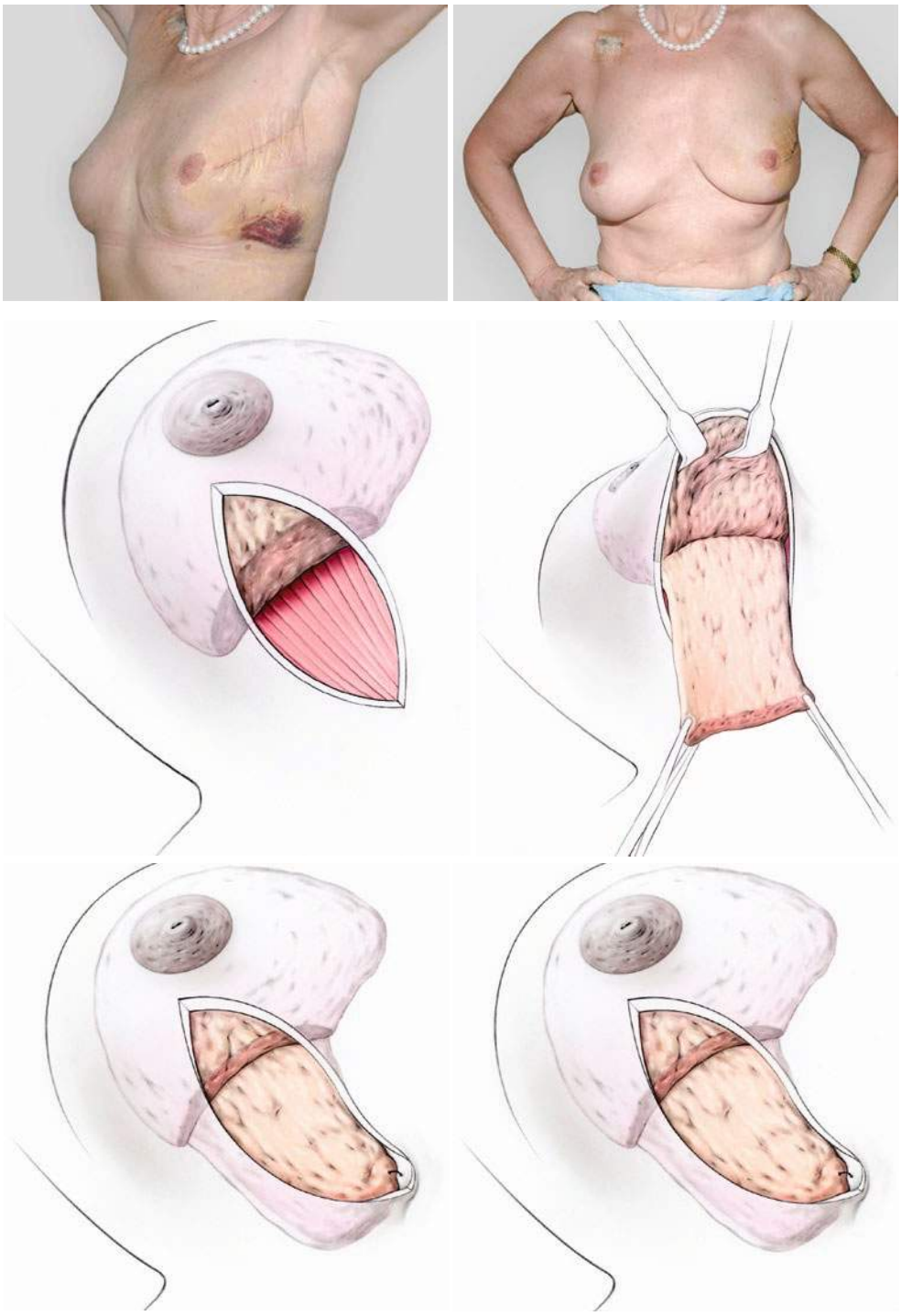

Fig. 25.2 Intramammarian flap technique [1]. After the segmental excision, a wide horizontal split is made in the residual breast tissue (high in glandular, low in fatty tissue), and the pectoral section is moved toward the tumor cavity as a pedicled flap to cover the defect. This method is not suitable for fatty breasts because flap necrosis with large defects can occur

and can be used in all quadrants. A periareolar or semicircular incision is made near the tumor. In the first phase, a wide area with the tumor must be exposed by separating a wide section of the skin from the mammary gland. After the excision of the breast segment, the residual breast tissue must be separated from the pectoralis major muscle, so the wound bed can be readapted without tension.

Whether an incision is made around the entire areola or only part of it, or whether a ring of skin is excised around the areola to perform a central mastopexy (possibly to achieve symmetry with the contralateral side), must be decided on a case-by-case basis. However, the classical form of the round block technique involves de-epithelialization of the donut-shaped area of the skin.

We occasionally use the Grisotti flap [2] for central tumors and nipple displacement techniques when the nipple-areola complex would be positioned too far lateral. These methods are not described separately here.

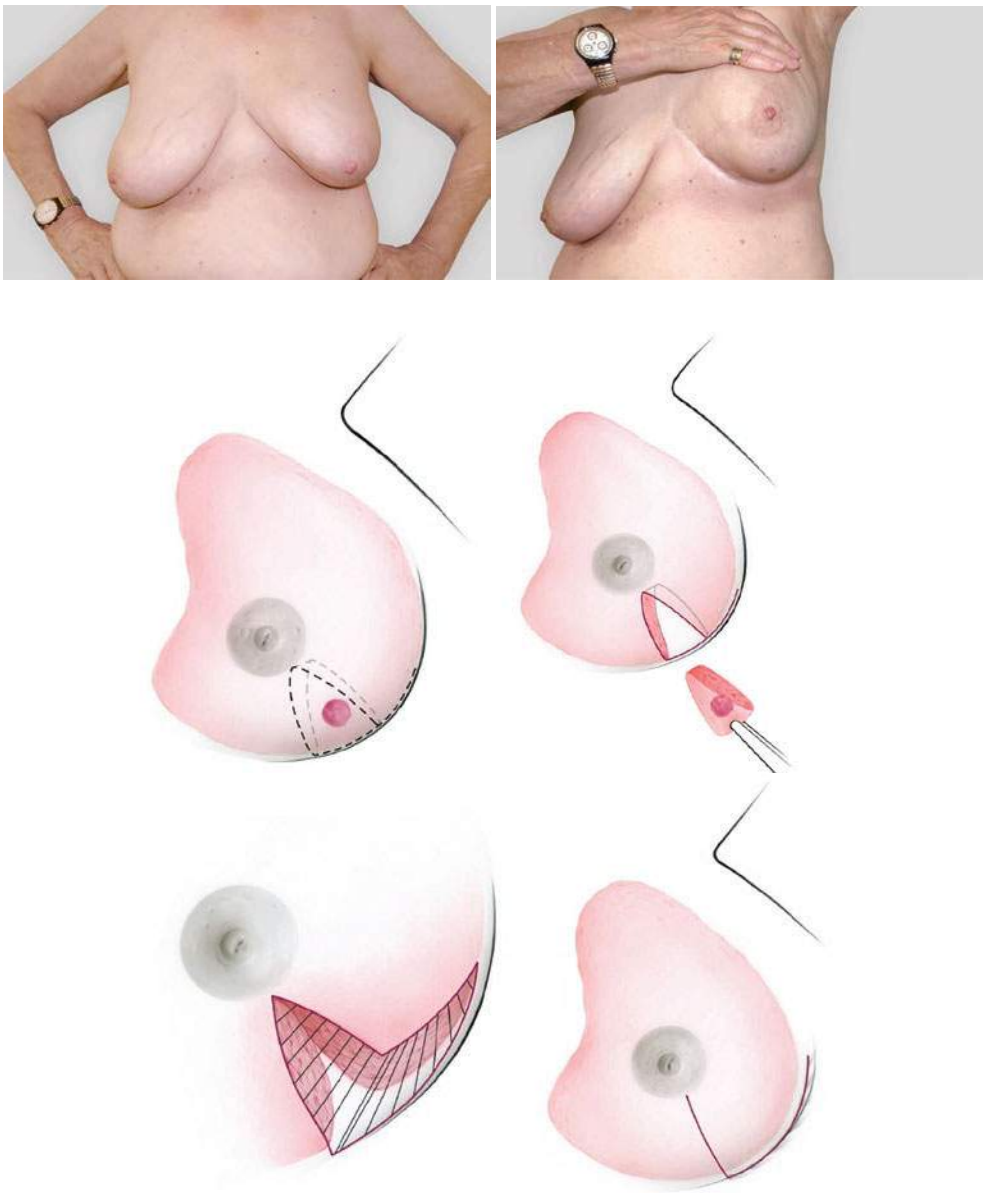

Fig. 25.3 Dermoglandular rotation flap. In a dermoglandular rotation flap, which can be used only in the caudal section of the breast, a triangular piece is removed. The incision must be made at a 90° angle to the skin, and it must be possible to adapt the residual breast tissue without tension. To relieve skin tension, the subdermal cutaneous sutures are placed as in the diagram

Description of the *glandular replacement technique* most frequently used here:

4. *Lateral advancement* (Fig. 25.5)
   This technique is used for replacing volume for lateral defects [5]. There is often a subcutaneous fat pad in the posterior axillary fold that can be moved forward toward the breast by dissecting the latissimus dorsi muscle at the anterior edge, not separating the skin and fatty tissue located over it from the muscle, and suturing the edge of the latissimus dorsi muscle to the edge of the pectoralis major muscle. Care must be taken to ensure that no intercostobrachial nerve is sutured, so the edge of the muscle must be clearly visualized.

Other glandular replacement techniques are, in addition to the large flap reconstructions, pedicled or free flap reconstructions from the area of the latissimus dorsi, which are sufficient for partial breast reconstruction. These methods are also not described separately here.

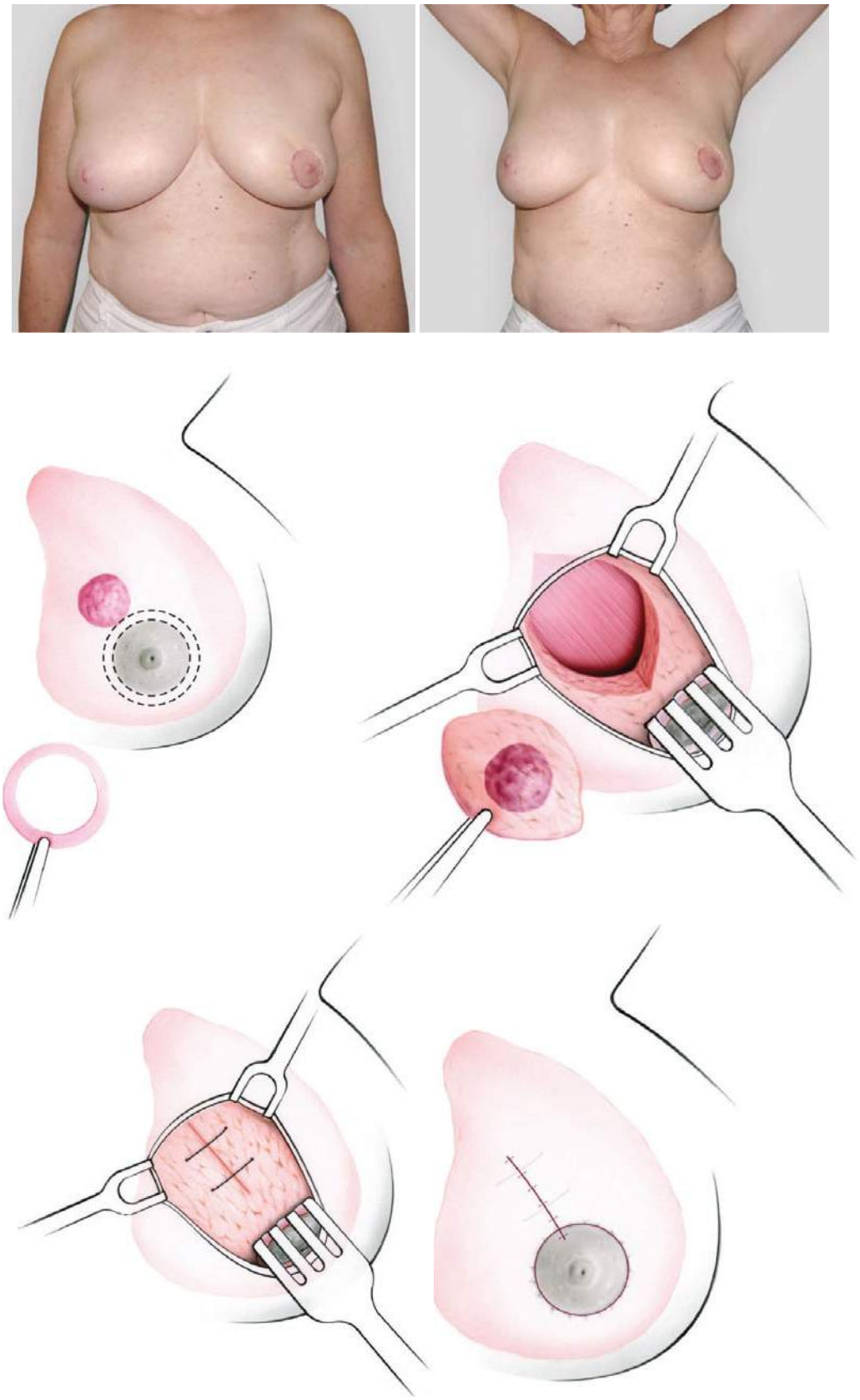

Fig. 25.4 Round block technique. The round block technique is especially suited for central, cranial, and upper medial tumors and fatty breasts. It allows good exposure of the tumor area, and sentinel lymphonodectomy can usually also be performed through the generous access. Altough 2 deep sutures are marked here, usually no deep sutures are required. The remaining tissue fills the cavity without sutures because the skin envelope is reduced

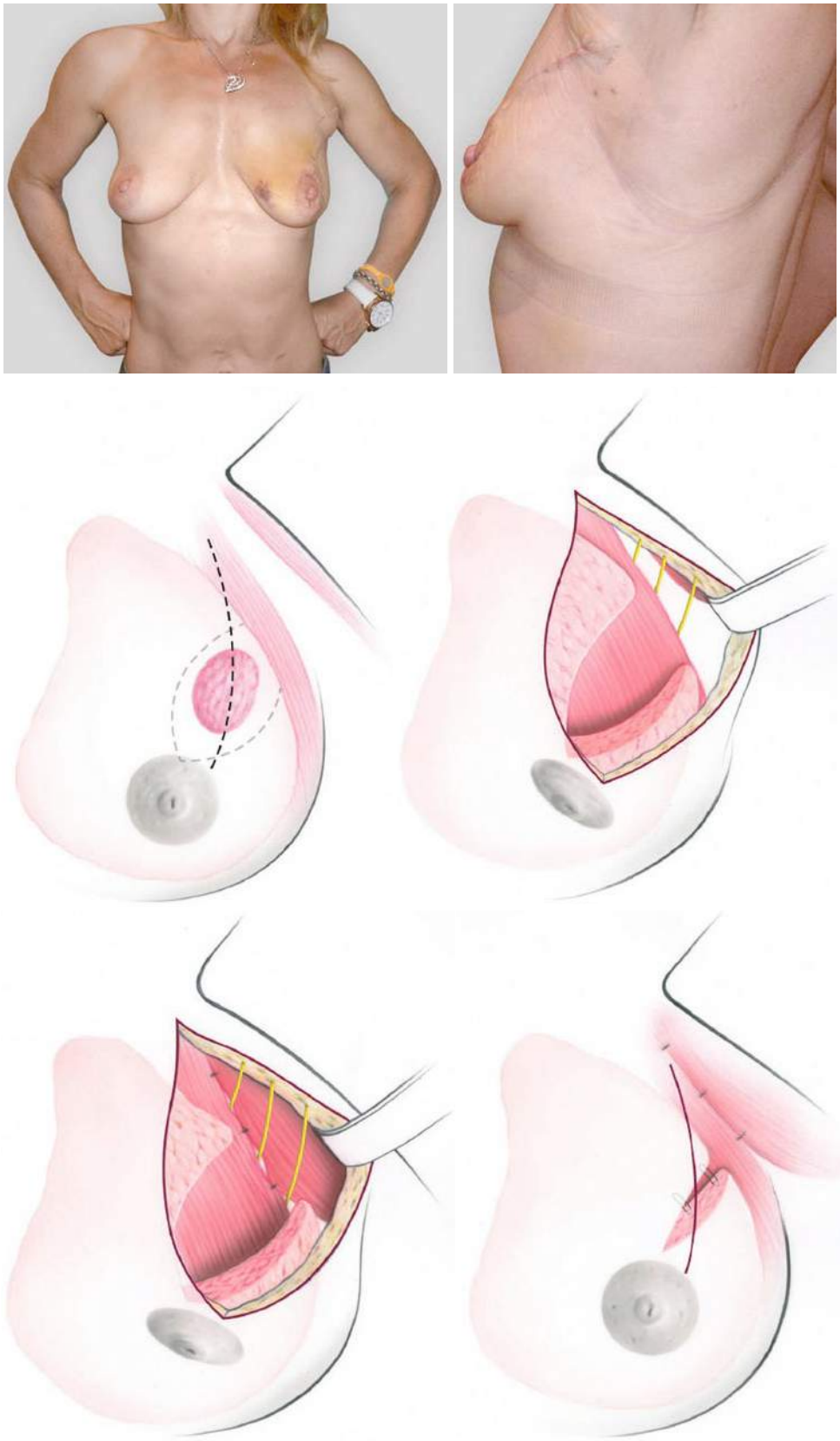

Fig. 25.5 Lateral advancement. This glandular replacement technique replaces part of the defect by moving the axillary fat pad forward. This is done by suturing the dissected latissimus dorsi muscle to the pectoralis major muscle. Intercostobrachial nerves must be spared

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Oncoplastic Surgery: Central Quadrant Techniques

26

Kristine E. Calhoun and Benjamin O. Anderson

26.1 Introduction

Breast-conserving therapy was introduced as an alternative to whole breast removal for women affected by breast cancer beginning in the 1970s and became established as standard therapy once randomized clinical trials demonstrated equivalent overall survival rates comparing lumpectomy plus radiation versus mastectomy [1, 2]. For appropriately selected patients, breast-conserving therapy offers both effective treatment and the psychological benefit of retention of the breast. For breast conservation to be effective, the primary tumor must be resected with adequate surgical margins while simultaneously maintaining the breast's shape and appearance, goals which may prove challenging and in some settings seem to be conflicting [3].

In a traditional lumpectomy, no specific efforts are made to obliterate the internal resection cavity. The simple "scoop and run" approach to lumpectomy may work well for small tumors, but declivity of the skin and/or displacement of the nipple-areolar complex (NAC) can occur when the target lesion is sizable and can create especially troubling defects for centrally located lesions. Some type of central closure of the breast is commonly required when larger areas of breast tissue are removed.

While it might seem appealing to simply close the resection cavity by suturing the middle-depth fibroglandular tissues together, this can result in unsightly defects when tissue alignment is suboptimal. A primary breast closure might look well when the patient is supine on the operating table but nonetheless will acquire a dimpled, irregular appearance once the patient stands up and the breast becomes pendulous. Given this potential for positional deformity, many surgeons choose to only close the skin of a lumpectomy cavity without approximation of the underlying tissue. For larger resections of segmentally distributed disease, more advanced closure techniques are required. The use of "volume-displacement" techniques for advancing fibroglandular tissue sections along the chest wall to close large resection cavities has become a fundamental tool for cosmetically optimized breast conservation surgery.

In 1994, Werner P. Audretsch was one of the first to advocate the use of "oncoplastic surgery" for repair of partial mastectomy defects by combining the techniques of volume reduction with immediate flap reconstruction [4]. Although initially used to describe the partial mastectomy combined with myocutaneous flap reconstruction using the latissimus dorsi or the rectus abdominis muscles, oncoplastic surgery now more commonly describes numerous surgical techniques that utilize partial mastectomy and breast flap advancement to address tissue defects following wide resection. Compared to breast reconstruction using a myocutaneous flap, breast flap advancements are easily learned and implemented by breast surgeons, even those lacking formal plastic surgery training [5].

A comprehensive understanding of normal ductal anatomy is valuable for planning an oncoplastic partial mastectomy [6]. Analysis of segmental ductal anatomy suggests that the number of major ductal systems is probably fewer than 10 [7]. The size of ductal segments is variable, and while some ducts pass radially from the nipple to the periphery of the breast, others travel directly back from the nipple toward the chest wall. In contrast, well-defined breast vasculature allows the surgeon to remove and remodel large amounts of fibroglandular tissue without major risk of breast devascularization and/or tissue necrosis. The most common sources of arterial blood supply in the human breast arise from the axillary and internal mammary arteries. By maintaining communication with one of these two arterial connections, an adequate blood supply for the breast parenchyma is maintained during tissue advancement and mastopexy closure.

Electronic Supplementary Material The online version of this chapter (doi:10.1007/978-3-319-62927-8_26) contains supplementary material, which is available to authorized users.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_26

The use of oncoplastic surgical techniques for breast conservation allows for larger resections without subsequent tissue deformity and thereby allows surgeons to achieve wide surgical margins while preserving the shape and appearance of the breast [8]. Such techniques can be especially useful for more centrally located lesions, which when resected with standard surgical techniques may result in suboptimal cosmetic outcomes [9]. While specific oncoplastic techniques are variable, all of the approaches involve fashioning the tissue resection to the anatomic shape of the cancer while decreasing the likelihood of having positive surgical margins requiring re-excision [10]. The indications and contraindications of oncoplastic surgery are the same as those of traditional breast-conserving surgery, and such techniques should only be offered to those otherwise believed to be breast preservation candidates based on size and centricity [11, 12].

The techniques described in this chapter include those used for central segmental resections that utilize volume-displacement techniques in which local parenchymal tissue flaps are advanced for glandular remodeling [13] and include the central lumpectomy, batwing mastopexy lumpectomy, donut mastopexy lumpectomy, and variations on the reduction mastopexy lumpectomy which utilize a pedicle flap to restore the nipple-areolar complex.

26.2 Preoperative Planning

Patients undergoing central quadrant resections should undergo standard preoperative history and physical, with the elements of gynecologic, family, and social history including smoking emphasized. Special attention should be given to any prior breast surgical history, including the placement of breast implants, as scar patterns on the breast may need to be incorporated into subsequent resections. Core needle sampling should be performed to document malignancy, with mandatory internal review of all external pathology slides required at our institution.

Those being considered for oncoplastic resections should undergo a standard preoperative breast imaging workup, which typically includes some combination of mammography, ultrasound, and in some circumstances breast MRI. Although mammography may underestimate the extent of DCIS by as much as 1–2 cm, it is still warranted and is often the initial diagnostic study [14].

Although controversial, the use of MRI may contribute to the surgeon's ability to preoperatively determine the extent of disease, especially for mammographically subtle and/or occult cancers, and to conceptualize the location of the tumor more three-dimensionally than allowed on mammography. Compared with mammographic and ultrasound images, the extent of disease seen on MRI may correlate best with the extent of tumor found at pathologic evaluation. In addition, MRI has the lowest false negative rate in detecting invasive lobular carcinoma [15]. While its sensitivity for detection of invasive breast cancer is high, MRI unfortunately has a low specificity of 67.7% in the diagnosis of breast cancer before biopsy [16]. Meaning that up to one-third of MRI studies will show some area of enhancement that needs further assessment that ultimately proves to be histologically benign breast tissue. For cancers containing both invasive and noninvasive components, a combination of imaging methods may yield the best estimate of overall tumor size [17].

26.3 Perioperative Planning

Once a patient commits to a central oncoplastic approach, decisions regarding the use of preoperative wire localization for nonpalpable malignancies must be made. In planning oncoplastic resections, the surgeon needs to accurately identify the area requiring removal. Silverstein and colleagues previously suggested the preoperative placement of 2–4 bracketing wires to delineate the boundaries of a single lesion [18]. In a study by Liberman and colleagues, wire bracketing of 42 lesions allowed for complete removal of suspicious calcifications in 34 (81.0%) [19]. It has been suggested that single wire localization of large breast lesions is more likely to result in positive margins, because the surgeon lacks landmarks to determine where the true boundaries of nonpalpable disease are located. For such scenarios, multiple bracketing wires may assist the surgeon in achieving complete excision at the initial intervention. Alternatives to wire localization are increasingly being identified and utilized. Radioactive seed localizations [20] and the SAVI SCOUT [21], the latter of which relies on infrared technology to triangulate the location of the biopsied abnormality, permit intraoperative localization and resection, techniques which likely will gain wider acceptance and utilization. For more palpable lesions, surgeons often implement intraoperative ultrasound to augment their palpation-driven resection.

Skin landmarks should be identified and drawn with the patient sitting up in the preoperative area, including the inframammary crease, the anterior axillary fold at the pectoralis major muscle, the posterior axillary fold of the latissimus dorsi muscle, the sternal border of the breast, and the periareolar circle. Identifying these entities with the patient in the upright position is very important to the final cosmetic outcome, because these anatomic sites may prove challenging to accurately locate once the patient is anesthetized and lying supine on the operating room table. Generally, for reduction-type procedures, markings will be placed on both breasts.

For all oncoplastic techniques, the patient should be supine on the operating room table and with both arms abducted on arm boards and secured. It is preferable to have both breasts prepped and draped into the field so that visual comparison with the patient in a beach chair position is possible as the wound is closed. Such an approach allows the surgeon to identify any areas of unnecessary tugging or dimpling which are inadvertently created so that they can be corrected.

26.4 Central Quadrant Techniques

26.4.1 Central Lumpectomy (Fig. 26.1a–f)

For those cancers involving the NAC, including Paget's disease of the nipple, the cosmetic impact of nipple removal with central lumpectomy typically accounts for the common use of mastectomy in this situation. In recent years, with improved NAC reconstructive capabilities, central lumpectomies have been utilized more. While a central lumpectomy removes the NAC and underlying central tissues, it typically leaves behind a significant breast mound, especially for those with larger breasts at baseline. The cosmetic outcome with central lumpectomy can range from good to outstanding, depending on the woman's body habitus, and is likely to be better tolerated than reconstruction of an entire breast [3]. The central lumpectomy can be particularly valuable in women with large, ptotic breasts where loss of the entire breast with mastectomy may create prominent asymmetry. Surgical issues of NAC reconstruction in an irradiated field, including wound healing issues and NAC loss, must be considered, so early referral to plastic surgery is warranted.

In central lumpectomy, the incision can be made in the pattern of a large parallelogram that encompasses the entire NAC or more circular in nature. After excision of the skin island/NAC, short-distance mastectomy-type skin flaps are raised along both sides of the wound. The dissection is carried down to the chest wall, and the breast gland is lifted off the pectoralis muscle. After full-thickness excision of the tumor, 4–6 marking clips are typically placed at the base of the defect within the surrounding fibroglandular tissue for future imaging and radiation oncology purposes. A small drain may also be placed in the lumpectomy wound in cases where the dissection is more extensive and risk of seroma formation increased. For adequate evaluation of margin status by the pathologist, sharp rather than cautery dissection should be considered, as sharp dissection will not alter the histological margins of the resected tissues with so-called cautery effect. Larger intraparenchymal vessels can be ligated or coagulated during the dissection, and cautery can then be used on the exposed fibroglandular tissue faces to control bleeding.

Once tissue specimens have been resected and hemostasis obtained, the fibroglandular tissue at the level of the pectoralis fascia is undermined so that breast-tissue advancement can be performed over the muscle. Once the fibroglandular tissues are sufficiently mobilized and hemostasis confirmed, the margins of the residual cavity are shifted together by the advancement of breast tissue over muscle, and the defect is sutured at the deepest edges using 3-0 absorbable suture. The direction of tissue advancement can be adjusted depending upon the location of the fibroglandular defect and the excess tissue that can be shifted to close it. The goal of the mastopexy is to perform as complete a closure over the pectoralis muscle as possible to discourage communication between the anterior skin and the deeper tissues. Side-to-side comparisons with the patient in an upright position are warranted to ensure that no unusual retractions of the tissues or unsightly cosmetic results have occurred.

The superficial tissue layer is next closed with interrupted subdermal 3-0 absorbable suture, while the skin is closed by 4-0 absorbable subcuticular sutures in routine fashion. Two variations on closure exist. The first, which is more typical, involves closure in a manner which results in a scar that is a horizontal, straight line, while other surgeons choose instead to close the wound utilizing a purse-string closure to facilitate areolar tattooing.

26.4.2 Batwing Mastopexy Lumpectomy (Fig. 26.2a–f)

For cancers adjacent to or deep to the NAC, but without direct nipple involvement, lumpectomy can successfully be performed without sacrifice of the nipple itself. The batwing approach preserves the viability of the NAC while preserving the breast mound by using mastopexy closure to close the resulting fibroglandular defect of the full-thickness resection. This procedure may result in lifting of the nipple into the upper breast, and a contralateral lift often needs to be performed to achieve symmetry, especially when the native breast is large and pendulous.

Two similar semicircle incisions are made with angled "wings" on each side of the areola. The two half-circles are positioned, so they can be re-approximated to each other at wound closure. Removal of these skin wings allows the two semicircles to be shifted together without creating redundant skin folds at closure. Fibroglandular tissue dissection is carried down deep to the known cancer, with the depth in relation to the chest wall dictated by the position of the lesion within the breast. In most situations, the dissection is carried down to the chest wall, and the breast gland is lifted off the pectoralis muscle in a fashion similar to that for the central

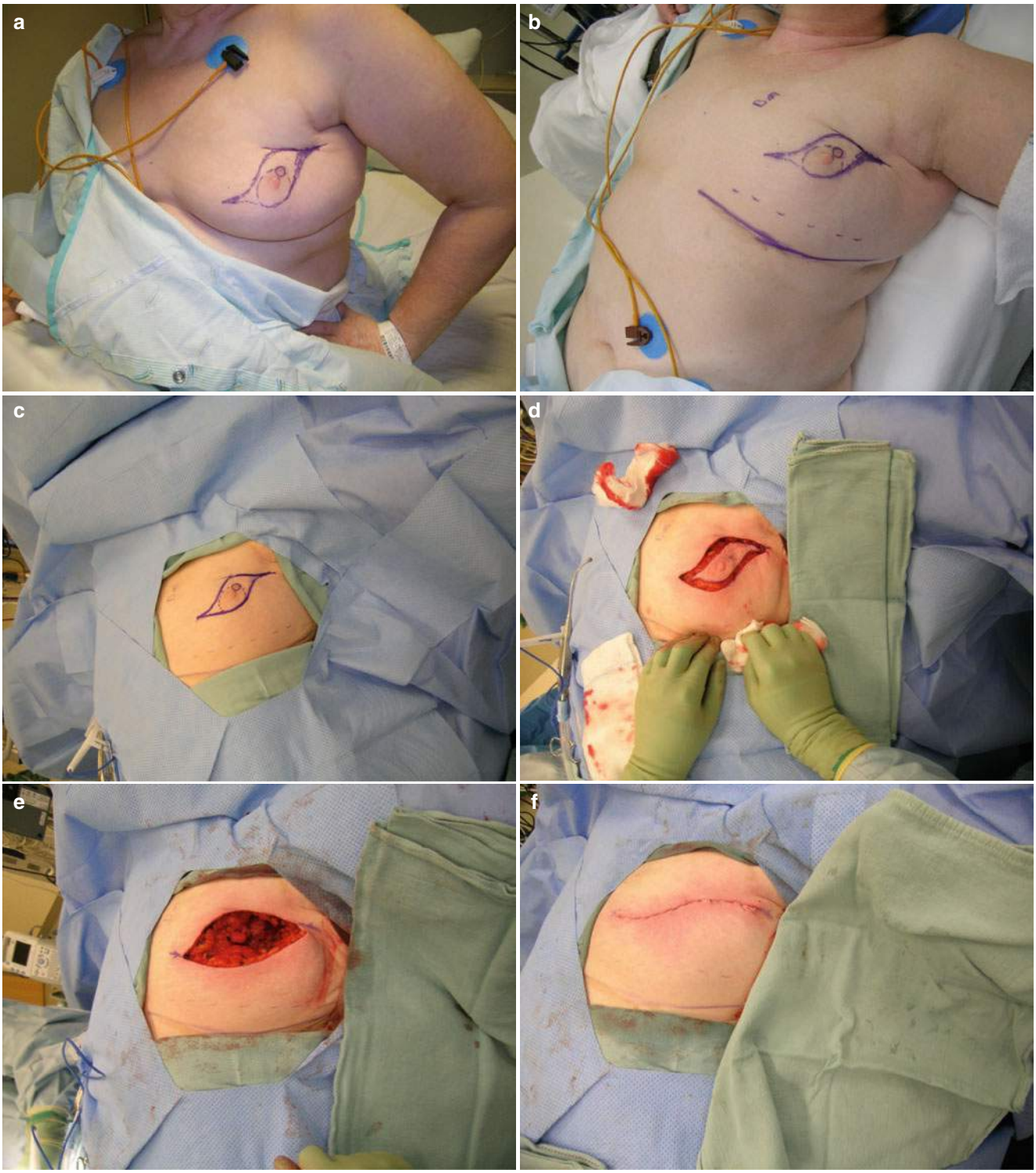

Fig. 26.1 (**a**–**f**) Central lumpectomy. (**a**) Preoperative marking with patient in upright position. (**b**) Intraoperative marking with patient in supine position illustrating positional shift of the breast landmarks. (**c**) Rounding of parallelogram incisions. (**d**) Central resection. (**e**) Post-excision cavity. (**f**) Final closure

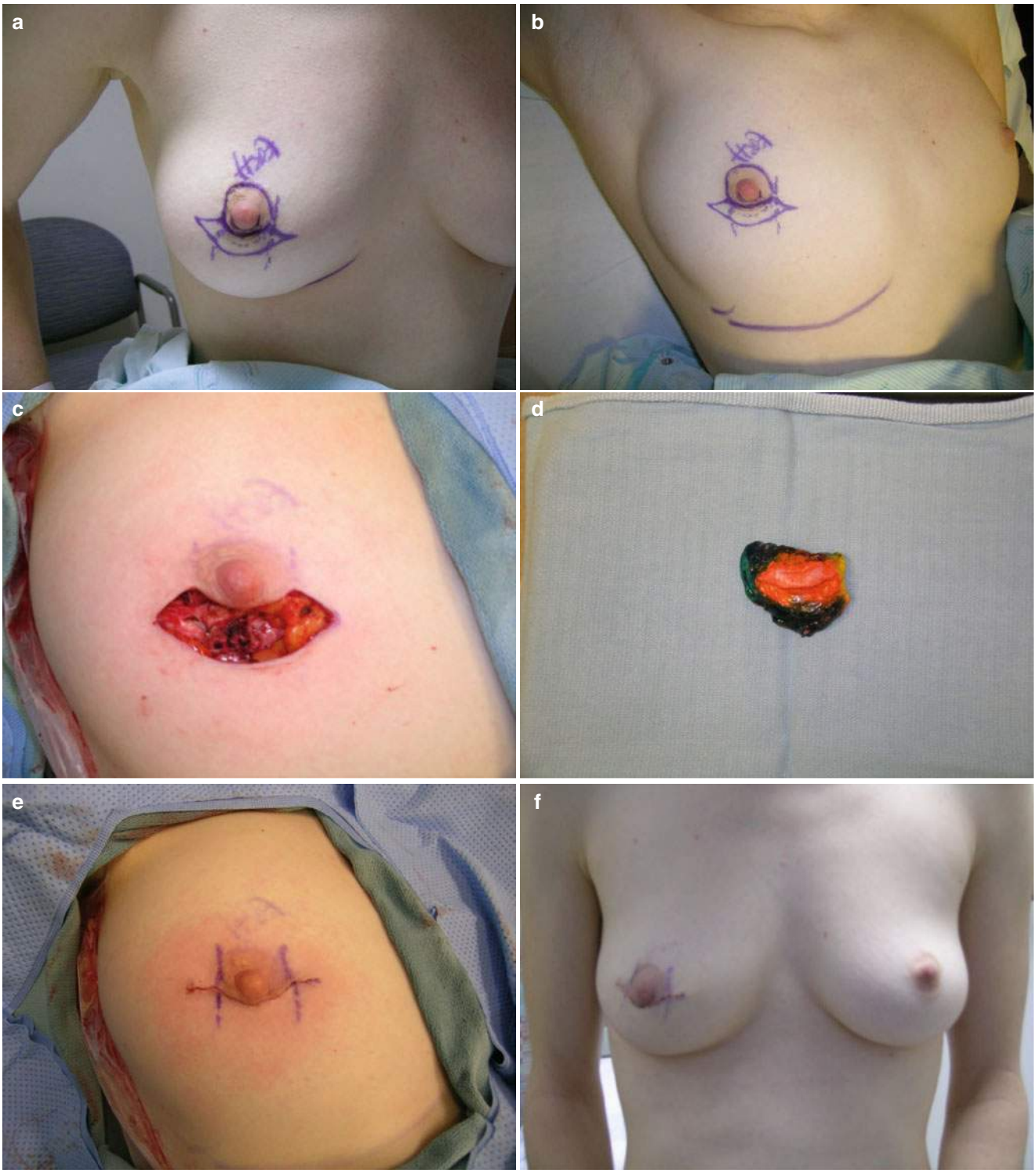

Fig. 26.2 (**a**–**f**) Batwing mastopexy lumpectomy. (**a**) Preoperative marking with patient in upright position. (**b**) Intraoperative marking with patient in supine position. (**c**) Resection cavity. (**d**) Resection specimen. (**e**) Final closure. (**f**) Post-op result with patient in upright position

lumpectomy. The principles of sharp dissection and the placement of marking clips are also similar to those utilized in central lumpectomy.

Following full-thickness resection of the target, mobilization of the fibroglandular tissue for mastopexy closure will likely be required. The breast tissue is elevated off of the chest wall at the plane between the pectoralis muscle and breast gland and the fibroglandular tissue advanced to close the resulting defect. The deepest parts are approximated by interrupted sutures. We typically secure the fibroglandular tissue to fibroglandular tissue and do not place anchoring stitches into the chest wall, thereby allowing the approximated breast tissues to move along the chest wall. The superficial layer is closed in the same fashion as the central lumpectomy. As this procedure can cause some lifting of the nipple, it may create asymmetry compared to the non-cancerous breast. A contralateral lift can be performed afterward adjuvant radiation has been completed and the treated breast has "declared" its new size and shape to achieve symmetry, although some plastic surgeons may choose to perform this symmetry procedure concurrent with the oncologic surgery.

26.4.3 Donut Mastopexy Lumpectomy (Fig. 26.3a–f)

For segmentally distributed cancers located in the upper or lateral breast that approach the NAC, the donut mastopexy lumpectomy can be used to achieve effective resection of long, narrow segments of breast tissue. The donut mastopexy avoids a visible long radial scar which is against the Kraissl's line or Langer's line. In this procedure, two concentric lines are placed around the areola and a periareolar "donut" skin island is excised, with only a periareolar scar visible after this operation. Deepithelialization by separating this skin island from the underlying tissues is done, taking care to avoid full devascularization of the areolar skin. The width of the "donut" skin island should be approximately 1 cm but is somewhat dependant on the size of areola and expected extent of excision. Removal of this tissue ring is required, to allow for both adequate access and exposure to the breast tissue and closure of the skin envelope around the remaining fibroglandular tissue that will reduce tissue volume overall.

A skin envelope is created in all directions around the nipple-areolar complex. The quadrant of breast tissue containing the target lesion is fully exposed utilizing the same dissection used for a skin-sparing mastectomy. The full-thickness breast gland is then separated from the underlying pectoralis muscle and delivered through the circumareolar incision. The segment of breast tissue with the tumor is resected in a wedge-shaped fashion, with the width of tissue excision required to achieve adequate surgical margins balanced against the difficulty that will be created by virtue of an oversized segmental defect.

The remaining fibroglandular tissue is returned to the skin envelope, and the peripheral apical corners of the fibroglandular tissue are secured to each other and then anchored to the chest wall. This anchoring step maintains proper orientation of the mobilized fibroglandular tissue within the skin envelope during the initial phases of healing. A purse string using absorbable 3-0 suture is placed around the areola opening and is clamped at a size that re-approximates the original nipple-areolar complex. Interrupted inverted 3-0 absorbable sutures are placed subdermally around the NAC, at which time the purse-string suture is tied and then 4-0 subcuticular sutures are used to close the wound. Uplifting of the NAC may create mild asymmetry in comparison to the untreated breast. If desired, a contralateral lift can be performed to achieve symmetry, either at the time of the initial lumpectomy or later after radiation changes have resolved.

26.4.4 Reduction Mastopexy Lumpectomy Modifications (Fig. 26.4a–f)

Initially used in women with macromastia and excessive breast ptosis, this procedure is currently used for resection of lesions in the lower hemisphere of the breast between the 4 o'clock to 8 o'clock positions, where "scoop and run" lumpectomy using circumareolar incision would result in unacceptable downturning of the nipple due to scar contracture after radiotherapy. This unpleasant cosmetic outcome can be prevented by using the technique of reduction mastopexy lumpectomy. Recently, the indications for using reduction techniques have been expanded to include women with centrally located tumors faced with NAC loss. In these situations, the reduction is coupled with a de-epithelialized pedicle flap with an overlying skin island to recreate the NAC, ultimately resulting in a wise-type scar and a neo-nipple [22].

In traditional reduction mammoplasty, a keyhole pattern incision is made, and the skin above the areola is de-epithelialized in preparation for skin closure. A superior pedicle flap is created by inframammary incision and undermining of the breast tissue off the pectoral fascia to mobilize the NAC and underlying tissues. Mobilization of the breast tissue allows palpation of both the deep and superficial surfaces of the tumor, which can aid the surgeon in determining the lateral margins of excision around the target lesion. When used for a central lesion, the primary tumor and overlaying NAC are resected down to the chest wall. The principle of sharp dissection and the placement of marking clips are the same as those of parallelogram mastopexy lumpectomy. A caudally located inferior flap is

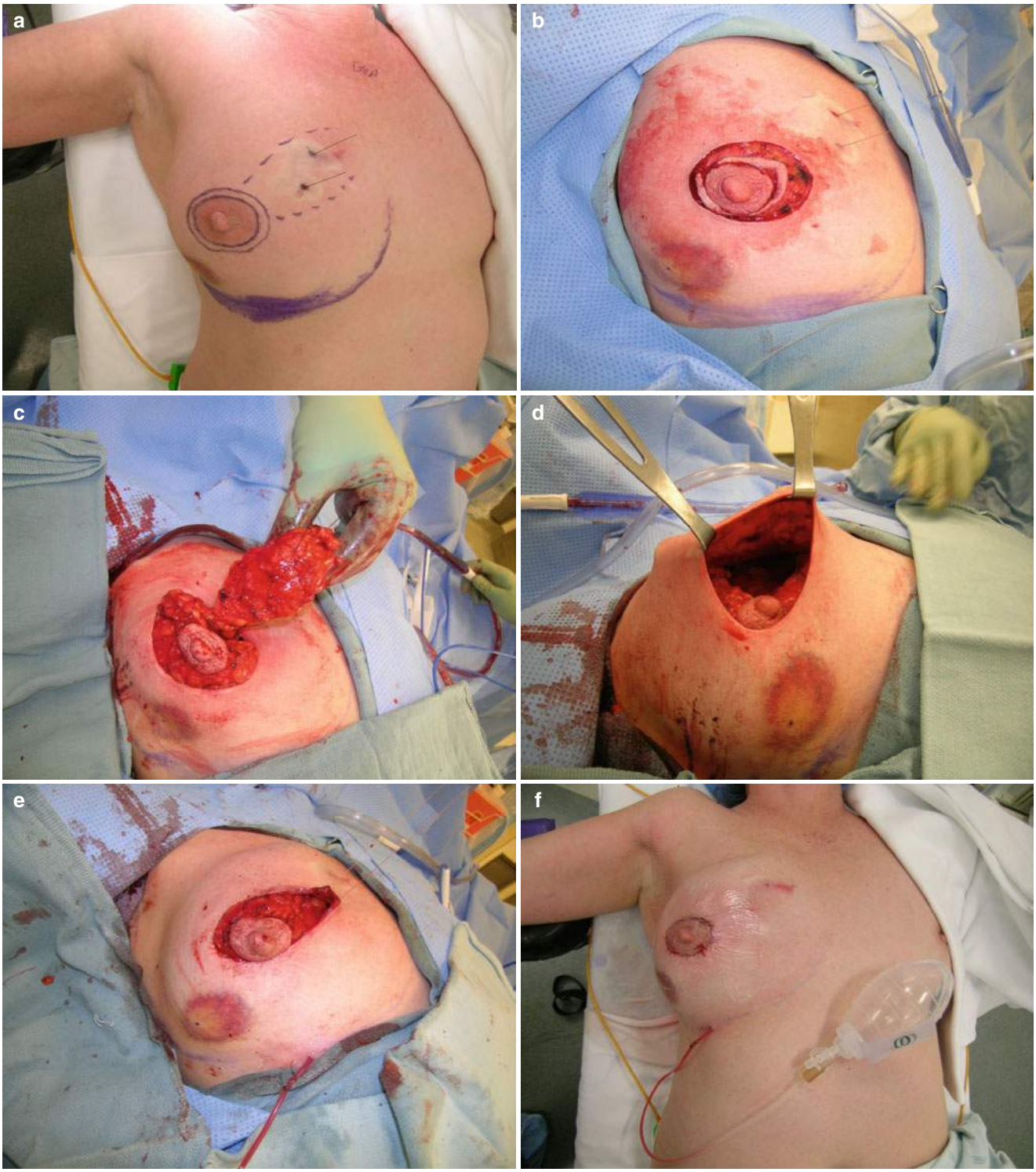

Fig. 26.3 (**a**–**f**) Donut mastopexy lumpectomy. (**a**) Preoperative marking including marking of region to be removed based on preoperative bracketing wires and concentric circles for skin donut excision. (**b**) Initial skin incision. (**c**) Delivery of tissue segment through periareolar incision. (**d**) Remaining cavity after resection. (**e**) Purse-string closure. (**f**) Final operative result

then de-epithelialized, except for an appropriately sized skin island that will function as the neo-nipple. Following this, redundant medial, lateral, and superior tissues are then resected while preserving the pedicle tissue. An incision at the inframammary crease facilitates mobilization and assists in restoration of normal breast shape and contour.

Once all tissues have been resected, the central, inferior pedicle is mobilized, brought cephalad, and utilized to

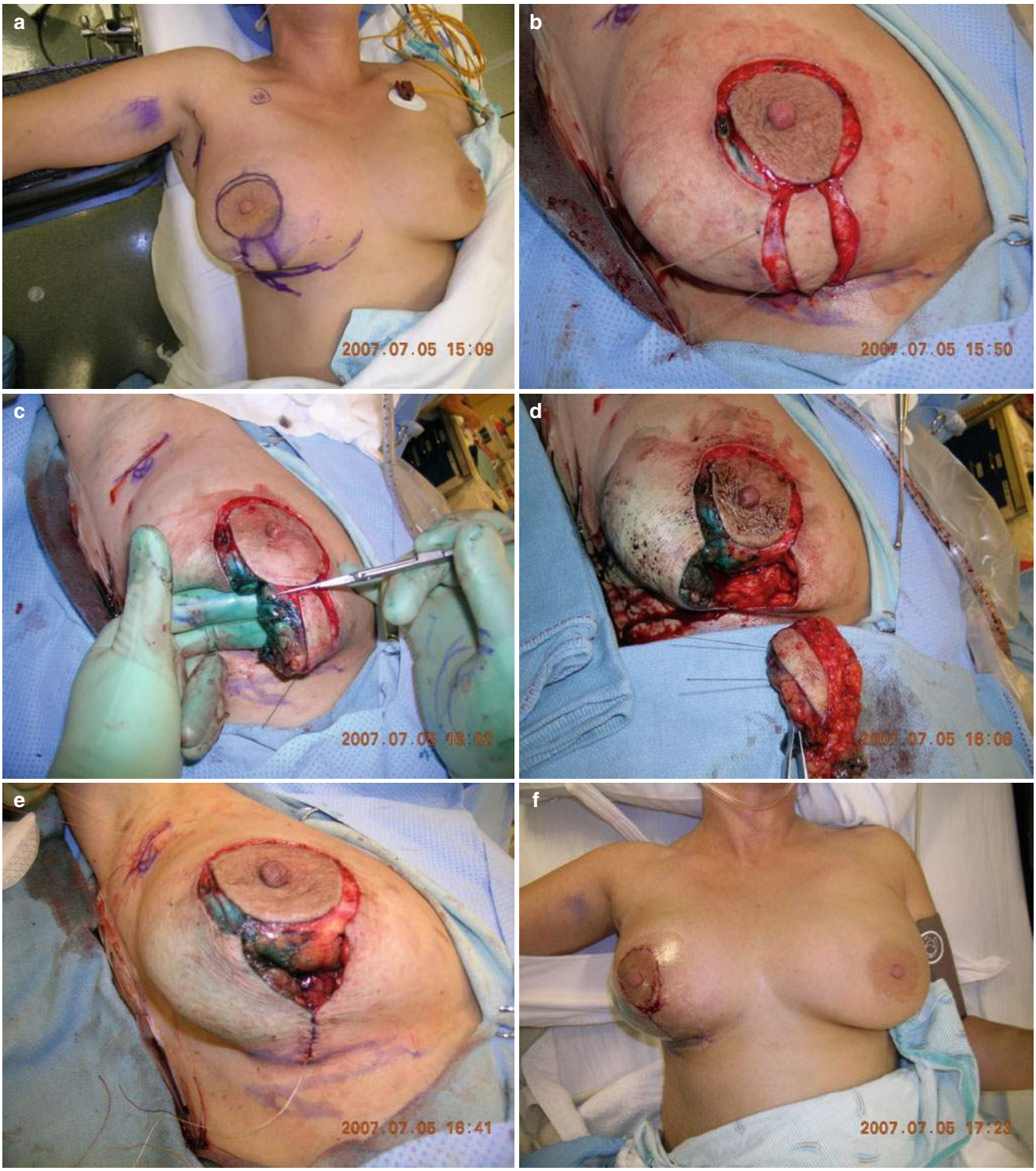

Fig. 26.4 (**a**–**f**) Reduction mastopexy lumpectomy. (**a**) Preoperative skin markings showing keyhole incision pattern. (**b**) Initial skin incision. (**c**) Full-thickness resection. (**d**) Excised specimen and residual cavity. (**e**) Closure. (**f**) Final result

occupy the defect created by removal of the prior NAC. The neo-nipple is sutured to the margins of NAC resection. The medial and lateral breast flaps are undermined and sutured together to fill the excision defect, leaving a typical inverted T scar. Variations of this technique have been reported, including the Grisotti flap which extends the pedicle laterally and results in an inferior and laterally sweeping incision [23] and free nipple graft from the skin of the contralateral

reduction tissue [24]. Finally, some choose to utilize the reduction flap without creation of a neo-nipple, leaving the patient with a wise-type incision and the choice of NAC in a delayed fashion [22].

26.5 Postoperative Management

While drains are rarely required in standard partial mastectomy cases, with more extensive dissections, such as the donut mastopexy lumpectomy and the reduction mastopexy approaches, fluid accumulation can become more pronounced and require postoperative aspiration. In recent years, we have started to place small, 15 drains at least overnight to avoid excessive fluid accumulation in the dissected breast that might distort the oncoplastic closure. These drains are typically removed either prior to discharge or on postoperative day 1 in the clinic.

26.6 Complications

When using central oncoplastic approaches, surgeons without formal plastic surgery training must determine which procedures they are comfortable performing without plastic surgery consultation or intraoperative collaboration [3]. While these techniques appear to be relatively safe in the immediate postoperative period, issues such as wound infection, fat necrosis, and delayed healing in the more advanced techniques are all potential, reported complications [25–27]. Despite more extensive resections, hematomas requiring reoperation appear to be infrequent, occurring roughly 2–3% of the time in two recent studies [26, 27]. The blood supply of the external nipple arises from underlying fibroglandular tissue using major lactiferous sinuses rather than the collateral circulation from surrounding areolar skin, so nipple necrosis may occur if dissection extends high up behind the nipple but is also fortunately rare. Finally, in a review of 84 women who underwent partial mastectomy and radiation therapy, Kronowitz and colleagues showed that immediate repair of partial mastectomy defects with local tissues results in fewer complications (23% vs. 67%) and better aesthetic outcomes (57% vs. 33%) than that with a latissimus dorsi flap, which some surgeons used for delayed reconstructions [28].

26.7 Results

The main goal of oncoplastic lumpectomy remains negative surgical margin resection. Complete excision of calcified lesions and masses should be confirmed with specimen radiography during surgery. Additional oriented margins can be resected prior to mastopexy closure when the radiograph suggests inadequate resection may have occurred, hopefully eliminating the need for a delayed re-excision. While some centers utilize intraoperative analysis with frozen section to aid in decisions regarding the resection of additional segments of tissue, it is not our policy.

Multicolored inking performed by the surgeon in the operating helps to improve margin identification. Inking kits are now available with six colors (black, blue, yellow, green, orange, and red), which are very useful for labeling all of the surgical margins (superior, inferior, medial, lateral, superficial, and deep). Clear uniformity between surgeon and pathologist in terms of what color means what margin is required, especially when inadequate margins are identified that require reoperation.

Although the historic gold standard for negative surgical margin has been 10 mm, margins have now been defined in a joint consensus statement from the Society of Surgical Oncology and the American Society of Radiation Oncology as negative when tumor is not at ink for invasive disease and 2 mm or greater for ductal carcinoma in situ [29, 30]. A recent review article of all oncoplastic techniques, not just central procedures, reported a positive margin rate of 11.9%, despite a mean tumor size of 26 mm and a range up to 160 mm when oncoplastic resections are utilized [31].

If re-excision is needed for inadequate surgical margins following the initial resection, both the surgical approach and timing of the operation must be considered. When the positive margin involves a minority of the specimen, the entire biopsy cavity does not need to be re-excised and instead can be directed toward the inadequate region. If re-excision is delayed for 3–4 weeks, the previous seroma cavity may be nearly reabsorbed, which leaves a fibrous biopsy cavity that can be easily located by intraoperative palpation. With noninvasive cancer, Dr. Silverstein has suggested that it is feasible to delay re-excision for up to 3 months, at which point the seroma cavity has been fully reabsorbed [32].

When all the margins of resection are positive, mastectomy may be needed to attain satisfactory surgical clearance. In this instance, it may be technically challenging to include both the initial oncoplastic incision and the NAC in a subsequent total mastectomy, and consultation with the plastic surgeon in the event of immediate postmastectomy reconstruction is mandatory. Despite a clear ability to resect widely with these central oncoplastic techniques, inadequate margins remain an issue. Although reports remain sparse, reported rates of inadequate margins following initial resection range from 8% up to 22% [26, 27, 33, 34]. The decision between a re-excision and a mastectomy must be based on the operating surgeon's ability to appropriately localize the involved region, and with more advanced resections, this may only be possible with breast sacrifice.

In a recent review of the available oncoplastic data, conversion to mastectomy was only necessary in 9%, with 55% of those mastectomy specimens revealing residual disease [31].

Although large studies of long-term outcomes specifically addressing oncoplastic approaches in breast conservation are sparse, the limited available results continue to look promising. One investigation from Europe followed 148 women for a median of 74 months (range 10–108 months), and only two were lost to follow-up. Among the 146 individuals available for analysis, there were only 5 (3%) women who suffered an ipsilateral in-breast cancer recurrence after 5 years, and all had either T2 or T3 tumors at presentation. These authors argued that recurrence rates for women with oncoplastic resections and concurrent radiation therapy were comparable to the in-breast recurrence rates reported with standard breast conservation techniques [35]. Studies of more limited follow-up recently reported no in-breast local recurrences at 26 months [26], 38 months [27], and 34 months [24], although there were some distant recurrences reported. More recently, a meta-analysis comparing BCS alone to all oncoplastic approaches found that patients with oncoplastic resections had lower rates of positive margins (12.3% vs. 20.6%) and lower rates of re-excisions (4% vs. 14.6%) but higher rates of completion mastectomies (6.5% vs. 3.8%) when compared to their traditional BCS counterparts [36]. This was accomplished with lower complication rates (15.5% oncoplastic vs. 25.9% traditional) and achieved lower rates of local recurrence (4.2% vs. 7% in BCS alone) over variable follow-up times [36], thus demonstrating the safety of these oncoplastic procedures. This growing body of literature should serve to allay any fears of cosmesis being favored over cancer control.

26.8 Conclusions

Although shown to be a reasonable alternative to mastectomy for the appropriately selected breast cancer patient, traditional "scoop and run" lumpectomy may result in poor cosmesis. Central oncoplastic techniques, including the central lumpectomy, batwing mastopexy lumpectomy, donut mastopexy lumpectomy, and variations of reduction mastopexy lumpectomy, have been developed to address this issue. By combining large-volume tumor removal with breast flap advancements, the oncoplastic approaches allow for wider margins of resection and better breast shape and contour preservation. Candidates are those felt to be standard lumpectomy candidates and include those with no evidence of multicentric disease.

Standard preoperative workup, including dedicated breast imaging, and tumor localization via any number of techniques are necessary to aid the surgeon in successful resection. Complications of tissue necrosis are fortunately rare, despite sometimes significant remodeling of the fibroglandular tissues due to the breast's rich blood supply. Outcomes appear at least equivalent to standard breast conservation techniques with generally lower rates of re-excision and higher rates of negative margin clearance. Oncoplastic lumpectomy can be learned by individuals familiar with breast surgical techniques and generally results in better cosmesis and equivalent oncologic outcomes.

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Dome Mastopexy

27

Mahmoud El-Tamer

As its name indicates, dome mastopexy is a simple procedure in which a sliver of skin, in a shape of a dome or crescent, is excised to lift a ptotic breast (Fig. 27.1). Some authors describe this technique as a crescent mastopexy; "dome" and "crescent" terms are interchangeable, however. This procedure is simple and easy to learn. It is applicable to tumors in the central or upper quadrants of the breast, particularly for lesions located in the 12:00 o'clock axis. I have not applied this technique to resect lower quadrant breast lesions. The dome mastopexy procedure may be performed with different extensions either for extended exposures or to excise laterally or medially located tumors.

The dome of skin excised above the upper edge of the areola has multiple purposes:

1. As part of an en bloc resection of the tumor
2. Exposure
3. Resection of redundant skin to accommodate for the loss in breast volume
4. Elevation of the nipple areola complex.

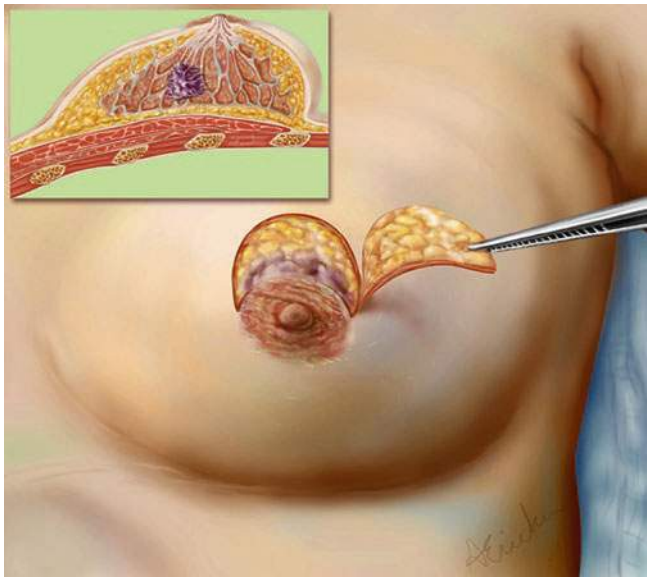

Fig. 27.1 Dome incision (Used with permission from El-Tamer M, ed. *Principles and Techniques in Oncoplastic Breast Cancer Surgery*. World Scientific Publishing 2013; Singapore)

In preparation for such a procedure, surgeons must familiarize themselves with the nipple line. This is a line that connects the mid clavicle to the nipple (Fig. 27.2). Ideally, this line is drawn with the patient in the upright position. The nipple should be mobilized upward along that line. Positioning of the nipple off that line may result in an unsatisfactory cosmetic outcome. The lower part of the dome is the upper edge of the areola and extends from 9:00 to 3:00 o'clock. The upper incision is a semicircular ellipse centered at the nipple line (Fig. 27.3). The height of the ellipse will dictate the extent of elevation of the nipple areola complex. We have avoided large resection of the skin above the nipple areola and limited it to a maximum height of 3.0 cm. Significant elevation of the nipple areola complex without adjustment of the distance between the lower edge of the areola and the inframammary line may result in malpositioning of the nipple areola complex. In patients with significant ptoses of the breast that necessitate a larger ellipse or dome, we would recommend using a different type of mastopexy technique.

Depending on the location of the tumor, the ellipse of skin may be resected en bloc with the underlying tumor or simply de-epithelialized and used for access. For periareolar lesions, particularly those that are close to the skin, we favor the en bloc excision of the skin (see Case 1). In cases where the lesion is at a distance from the nipple, we have favored de-epithelializing the epidermal layer of the dome (Fig. 27.4). The skin incision is performed at the upper edge of the dome. We do not recommend using the dome mastopexy in cases where the tumor is very superficial and at distance from the nipple, where the resection would necessitate inclusion of the overlying subcutaneous tissue and/or skin.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_27

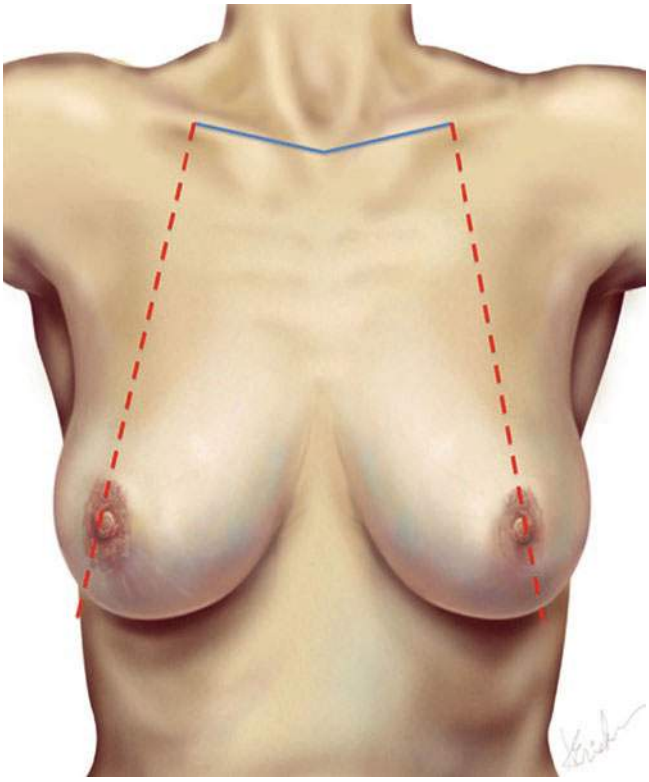


Fig. 27.2 Nipple line. The nipple line starts at the mid clavicle (6–7 cm from the sternal notch) and extends through the nipple (Used with permission from El-Tamer M, ed. *Principles and Techniques in Oncoplastic Breast Cancer Surgery*. World Scientific Publishing 2013; Singapore)

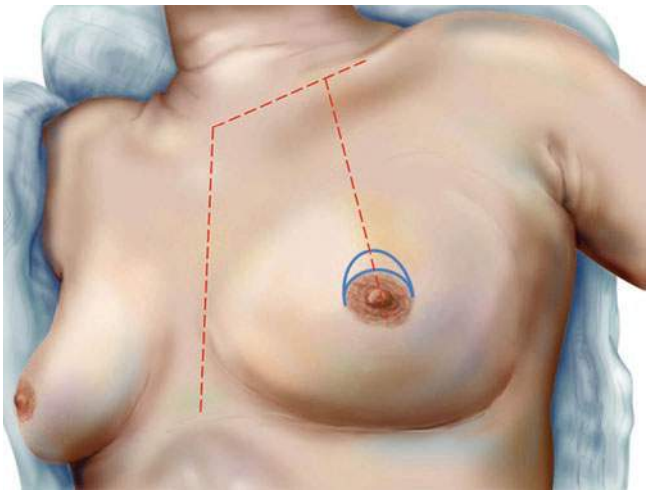


Fig. 27.3 The dome design with the patient on the table (Notice the highest point of the ellipse is centered along the nipple line) (Courtesy of Dr. Mahmoud El-Tamer, Memorial Sloan Kettering Cancer Center, New York, NY)

Regardless of which approach is used for the dome, en bloc resection or de-epithelialization, the skin flaps are raised to expose the underlying the breast. The tumor is resected while using sound oncologic techniques and maintaining adequate perfusion to the nipple areola complex (Fig. 27.5).

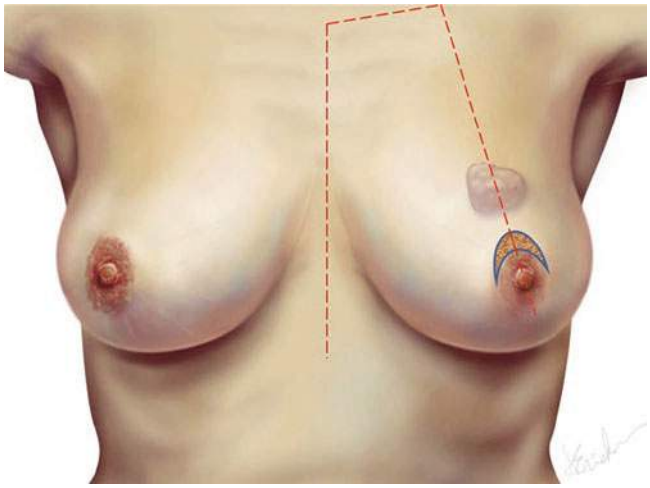


Fig. 27.4 The epidermal layer of the dome is de-epithelialized. The incision starts close to the upper level of the dome, the flaps are raised, the breast is exposed, and the resection is conducted (Courtesy of Dr. Mahmoud El-Tamer, Memorial Sloan Kettering Cancer Center, New York, NY)

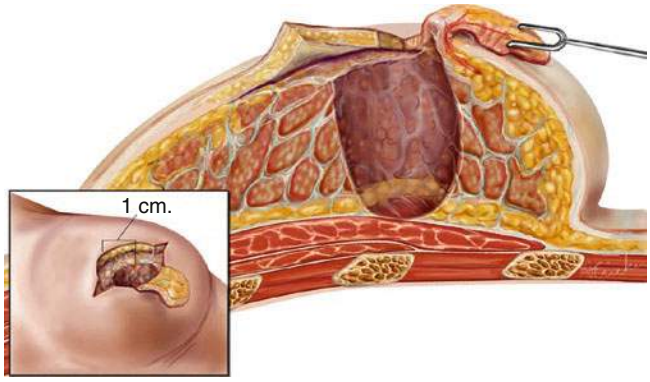


Fig. 27.5 The breast tumor is resected with the best attempt at achieving negative margins. The vascularity of the nipple areola complex should be maintained. In this drawing, we set the height of the dome at 1 cm. The height of the dome is usually determined by the extent of desired elevation of the nipple areola complex and the extent of the volume of tissue resection (Used with permission from El-Tamer M, ed. *Principles and Techniques in Oncoplastic Breast Cancer Surgery*. World Scientific Publishing 2013; Singapore)

After completion of the resection, the breast is elevated off the underlying pectoralis fascia as needed. We have routinely used hemoclips to mark the edges of the defect, to help guide further radiation therapy. The breast tissue is mobilized and approximated using one of the glandular displacement techniques as described in the chapter entitled Glandular Displacement Techniques. We have usually selected a repair that achieves the best final position of the nipple areola complex.

Following the repair of the defect, the superior and inferior edges of the dome are approximated with triangular sutures (Fig. 27.6) to accommodate for their length discrepancy. The triangular sutures are placed subdermally, while using 3-0 or 4-0 Vicryl. The suture is placed in a vertical

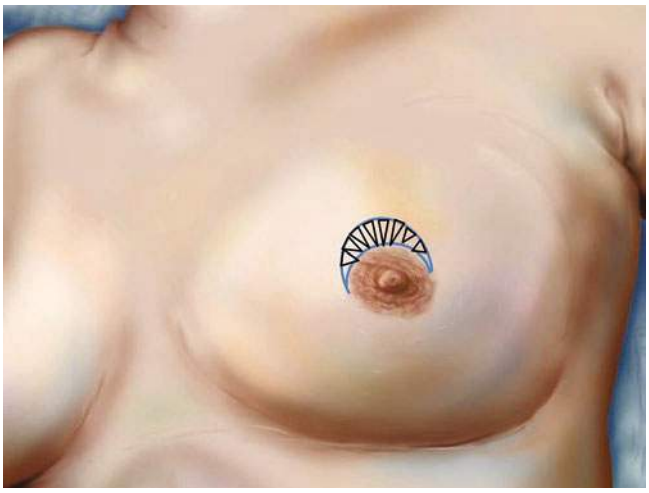


Fig. 27.6 The superior edge of the dome is obviously longer than the inferior. To correct for this difference in length, the subdermal sutures are placed in a triangular fashion, vertically at the inferior edge, and transversely at the superior part (Courtesy of Dr. Mahmoud El-Tamer, Memorial Sloan Kettering Cancer Center, New York, NY)

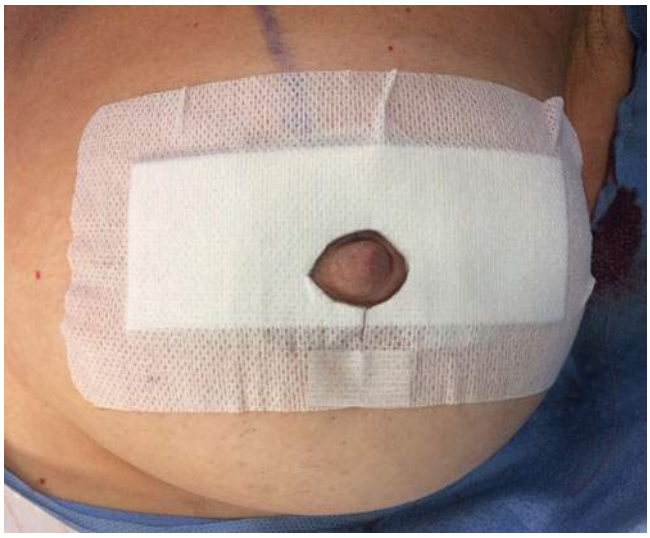


Fig. 27.7 The final dressing covers the surgical incision while keeping the nipple exposed to avoid any compromise of its blood supply (Courtesy of Dr. Mahmoud El-Tamer, Memorial Sloan Kettering Cancer Center, New York, NY)

fashion at the lower edge of the dome and transversely at the upper edge. The discrepancy of the length ought to be spread equally between the multiple triangular sutures. The epidermal layer is usually approximated with a running absorbable 4-0 monofilament suture. At the completion of the skin closure, the skin will show some wrinkling at the upper edge; this effect will resolve over time (see Case 1).

We have applied this technique to retroareolar lesion with great success; in such cases, the nipple areola complex is elevated as a dermal flap with particular attention to maintaining its vascularity.

We have avoided placing surgical drains following this procedure. We cover the wound with a light occlusive dressing while keeping the nipple exposed (Fig. 27.7). We frequently use a postoperative supportive brassiere to hold the breast repair and minimize the feeling of heaviness.

27.1 Dome Mastopexy Extensions

The dome mastopexy technique is very versatile. Extensions may be added to accommodate different clinical scenarios. Small areolas may significantly limit access to the breast. To cope with such a limitation, the dome can be extended laterally, medially, or in both directions. The bilateral triangular extensions have been described by Anderson et al. as the "Batwings" [1], and the group at the Institut Curie in Paris has named the procedure the omega plasty [2].

The planning of such a procedure follows the same principle described for the dome mastopexy with some important nuances. The lower incision surrounds the upper edge of the areola (Fig. 27.8a). The upper incision, however, is a parallel semicircle placed above the areola at the desired extent of elevation of the nipple areola complex (Fig. 27.8b). The center of elevation must remain along the nipple line. The upper and lower semicircles are connected laterally and medially by triangular extensions as shown in (Fig. 27.8c). In our practice, we have limited the bilateral triangular extensions to patients with very small areolas that limit the exposure.

Dome mastopexy can be extended to include tumors that are medial or lateral to the nipple areola complex. These extensions allow complex en bloc resection of skin and underlying breast for tumors located at the 3:00 and 9:00 o'clock axes (Fig. 27.9a–c). To maintain proper vascularity and sensation to the nipple, we only de-epithelialize the skin of the dome as seen in Case 1.

27.2 Cases

(All images courtesy of Dr. Mahmoud El-Tamer, Memorial Sloan Kettering Cancer Center, New York, NY)

27.2.1 Case 1

A 36-year-old woman who noticed a palpable left subareolar thickening. A mammogram showed a 3 cm mass with obscured borders in the retroareolar area that corresponded on ultrasound to a ×2.8 2.2 cm hypoechoic mass. An ultrasound-guided core needle breast biopsy yielded an estrogen and progesterone receptor positive infiltrating ductal carcinoma; the HER2/neu oncogene was not amplified. Clinically, the mass was vague. No axillary nodes were palpable.

A radioactive seed was placed next to the clip to localize the mass.

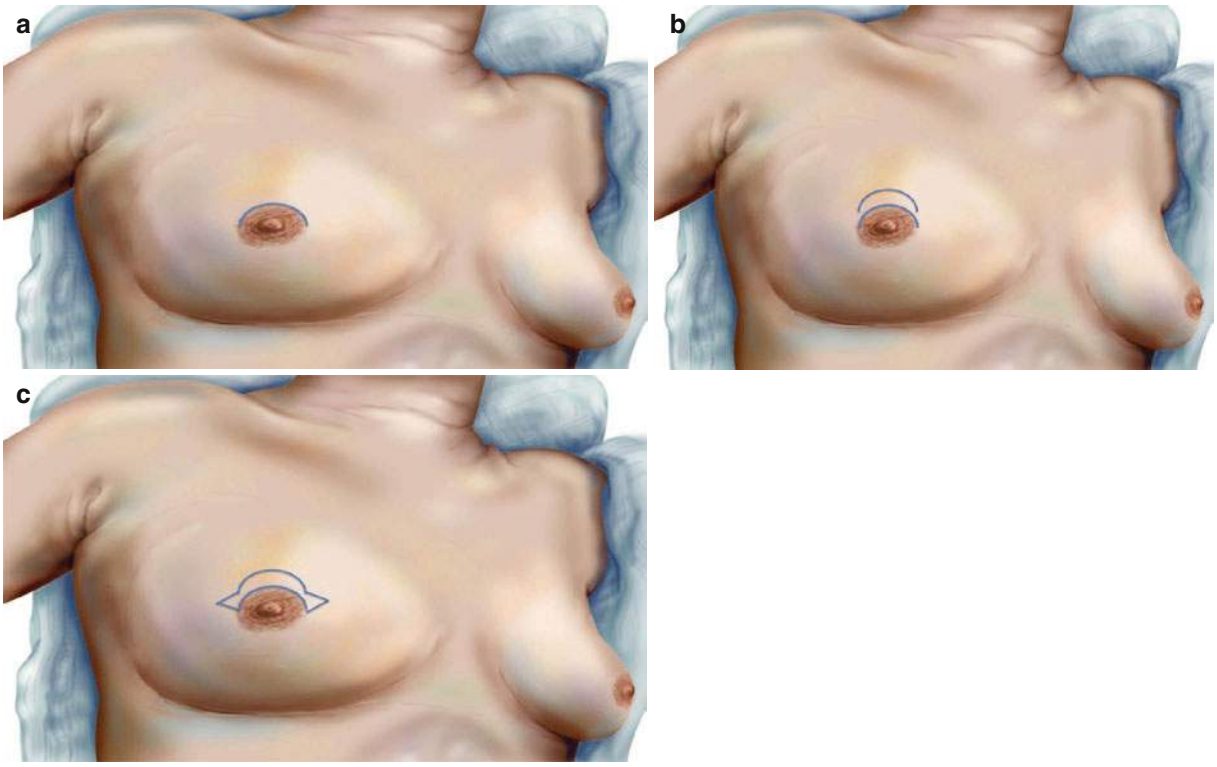


Fig. 27.8 Dome mastopexy extensions. (**a**) The lower incision surrounds the upper edge of the areola. (**b**) The upper incision is a parallel semicircle placed above the areola at the desired extent of elevation of the nipple areola complex. (**c**) The upper and lower semicircles are connected laterally and medially by triangular extensions (Used with permission from El-Tamer M, ed. *Principles and Techniques in Oncoplastic Breast Cancer Surgery*. World Scientific Publishing 2013; Singapore)

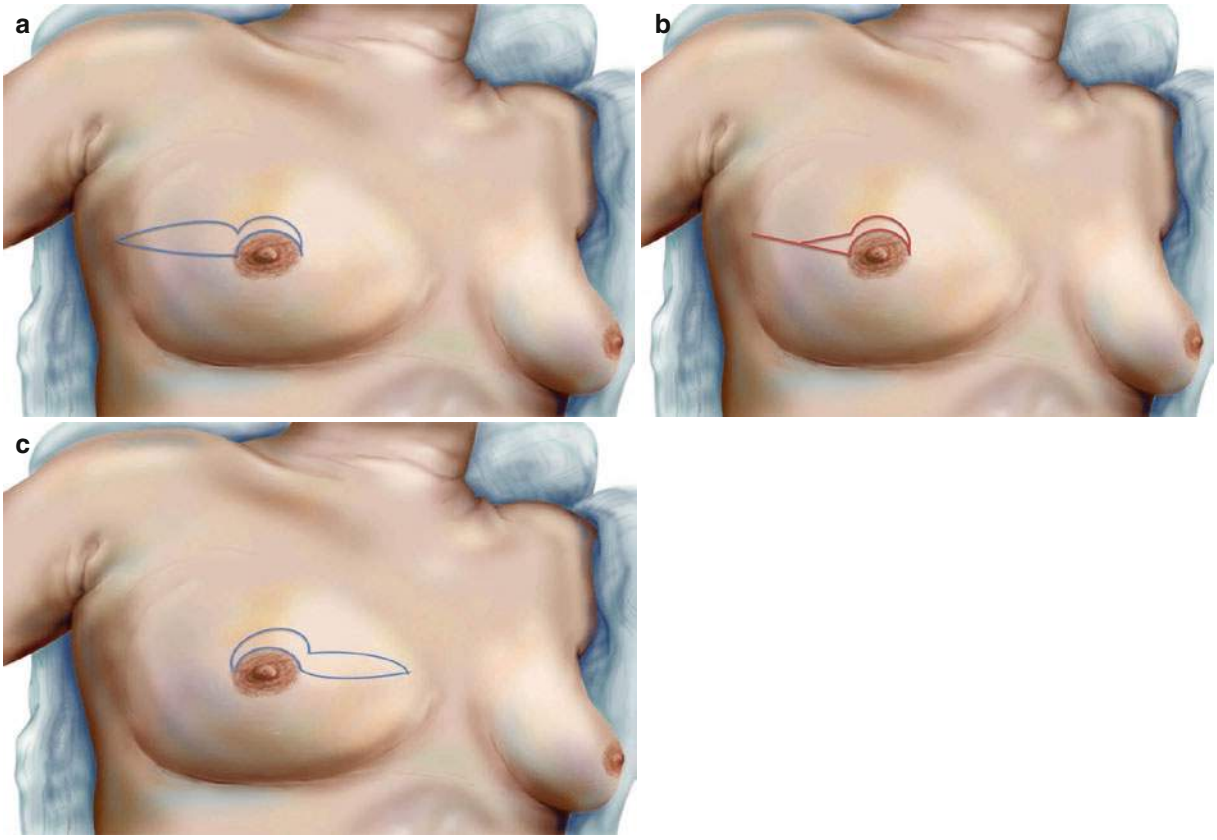
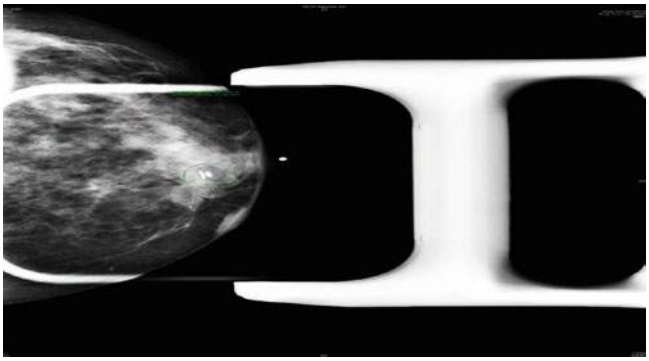


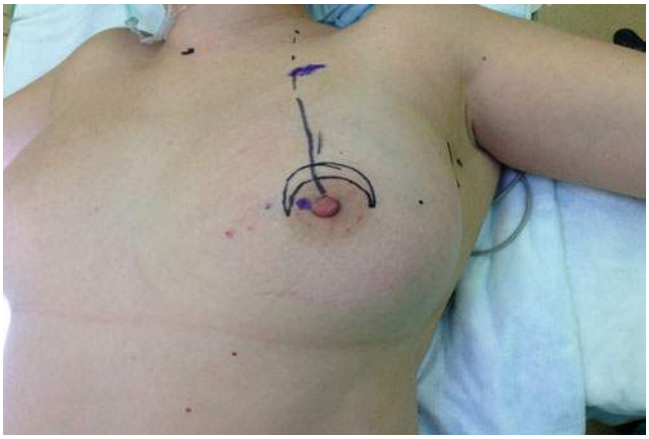
Fig. 27.9 Complex en bloc resection of skin and underlying breast for tumors located at the 3:00 and 9:00 o'clock axes (Used with permission from El-Tamer M, ed. *Principles and Techniques in Oncoplastic Breast Cancer Surgery*. World Scientific Publishing 2013; Singapore)

Case 1 Image 1



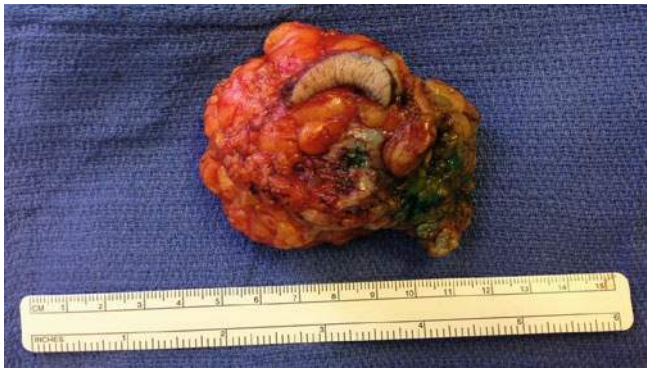
Case 1 Image 1. Tumor Localization. The patient had a seed localization *to facilitate resection* by way of a dome mastopexy

Case 1 Image 2



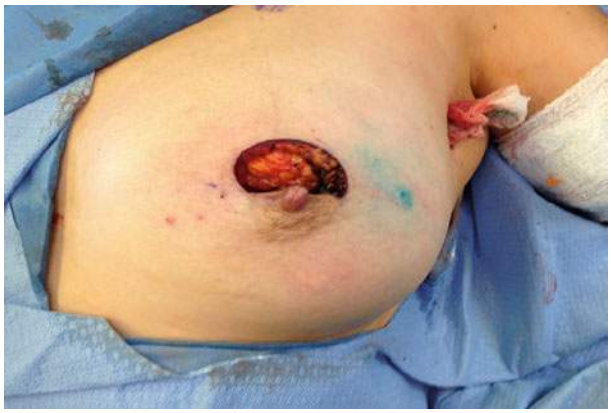
Case 1 Image 2. Patient on the Operating Room Table for a Planned Dome Mastopexy. This image shows the patient on the OR table for the planned dome

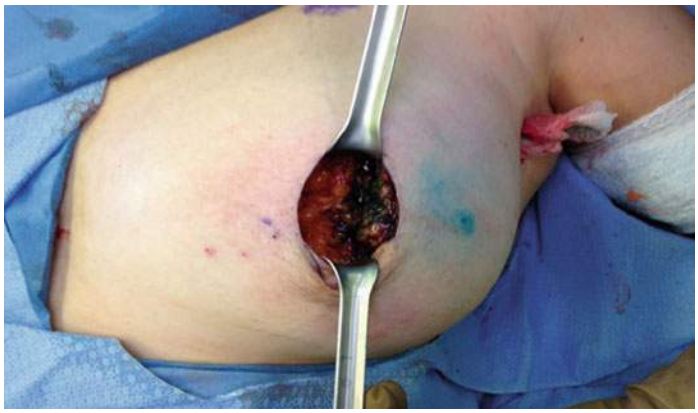
Case 1 Image 3



Case 1 Image 3. Resected Specimen. The specimen and the margins measured 10.5 × 7.0 × 4.0 cm. It is our practice to shave the cavity and submit separate margins; all were reported as negative

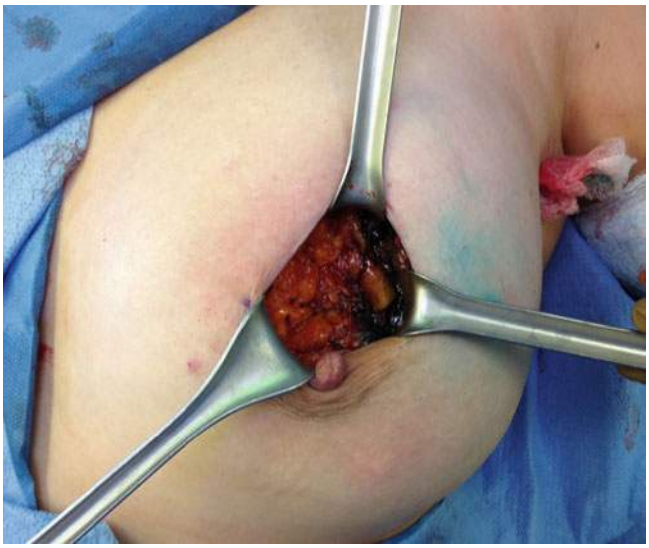
Case 1 Images 4 and 5





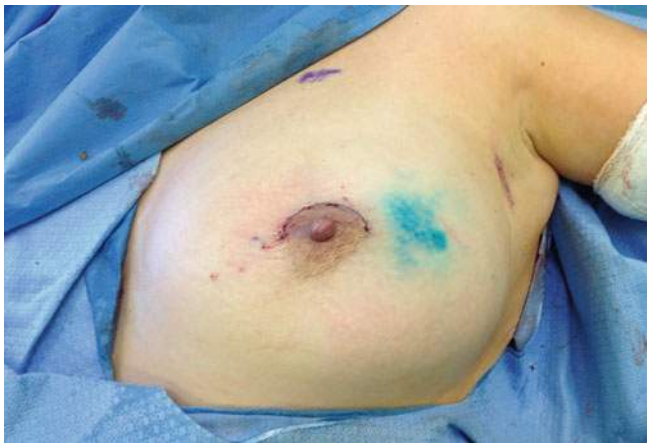
Case 1 Images 4 and 5. Intraoperative Image After Completing the Excision of the Tumor. The nipple areola complex was elevated as a dermal flap, and the totality of the underlying tissue was resected. These images show the defect of the breast and the nipple areola dermal flap

Case 1 Image 6



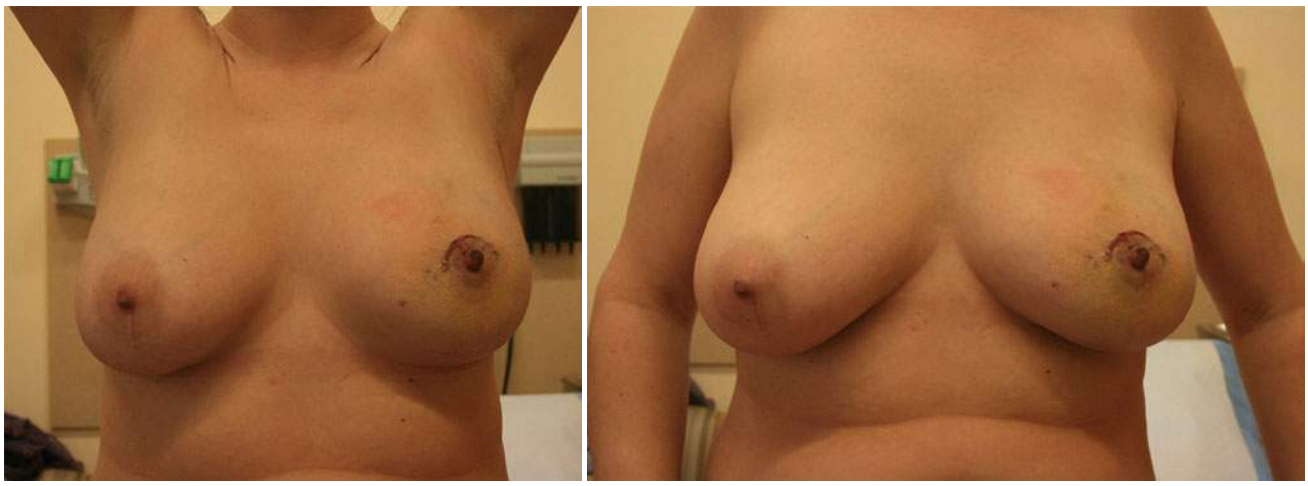
Case 1 Image 6. Defect Repair with Purse-String Suture. Due to the location of the defect, the extent of resection and the grade 1 ptosis of the breast, we have used a purse-string technique to approximate the defect as seen in Image 6

Case 1 Image 7



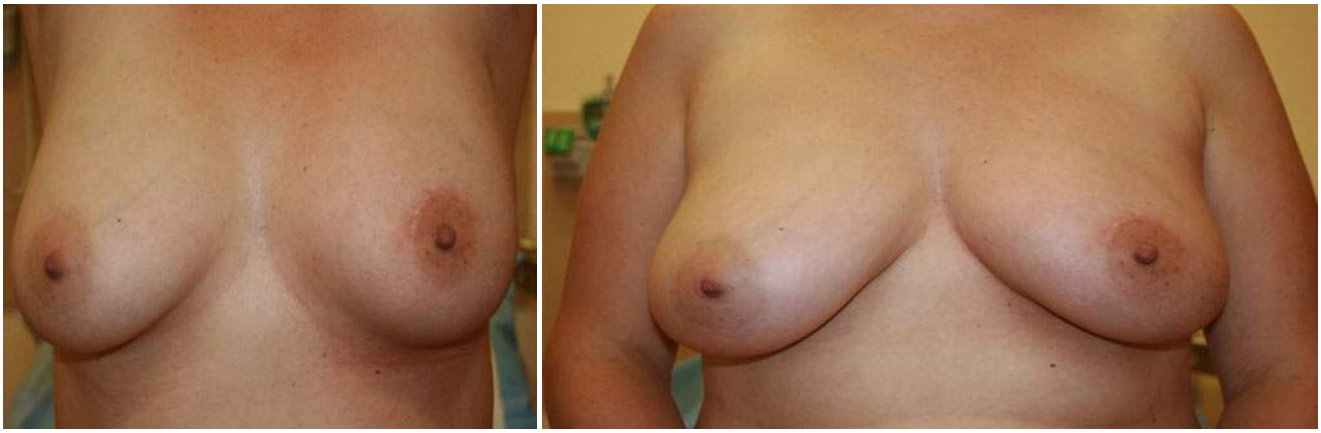
Case 1 Image 7. Intraoperative View of Closed Wound. The dome cutaneous defect was closed primarily with triangular sutures, as previously described. The discrepancy in the length of the skin edges was distributed over the length of the incision. The subtle wrinkling of the upper edge remains noticeable, however

Case 1 Images 8 and 9



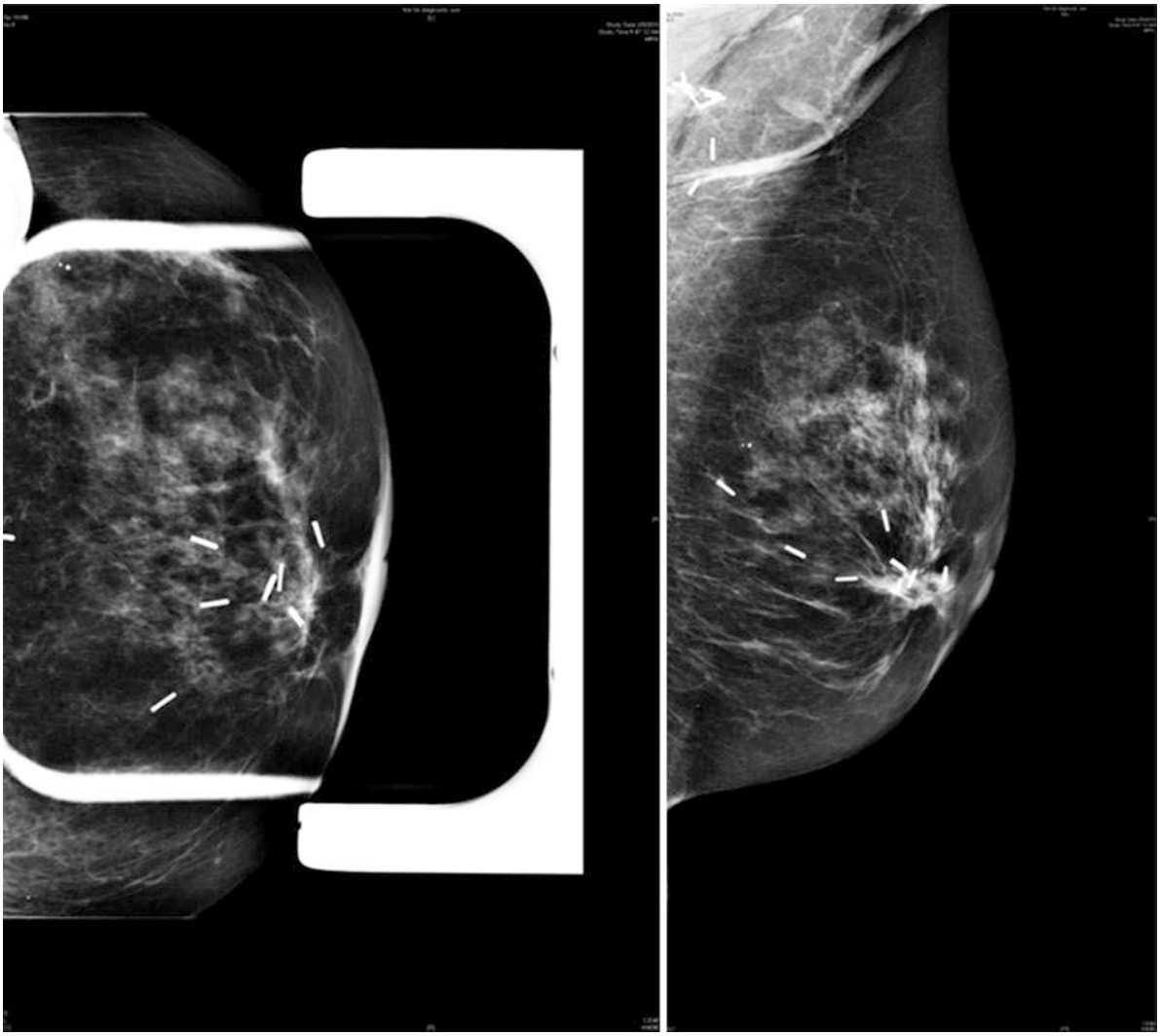
Case 1 Images 8 and 9. Two Weeks Postoperatively. Due to the extent of resection and shaving the base of the nipple as an anterior margin, the nipple showed some subtle ischemia at her postoperative visit. The operated left breast is clearly less ptotic than the right

Case 1 Images 10 and 11



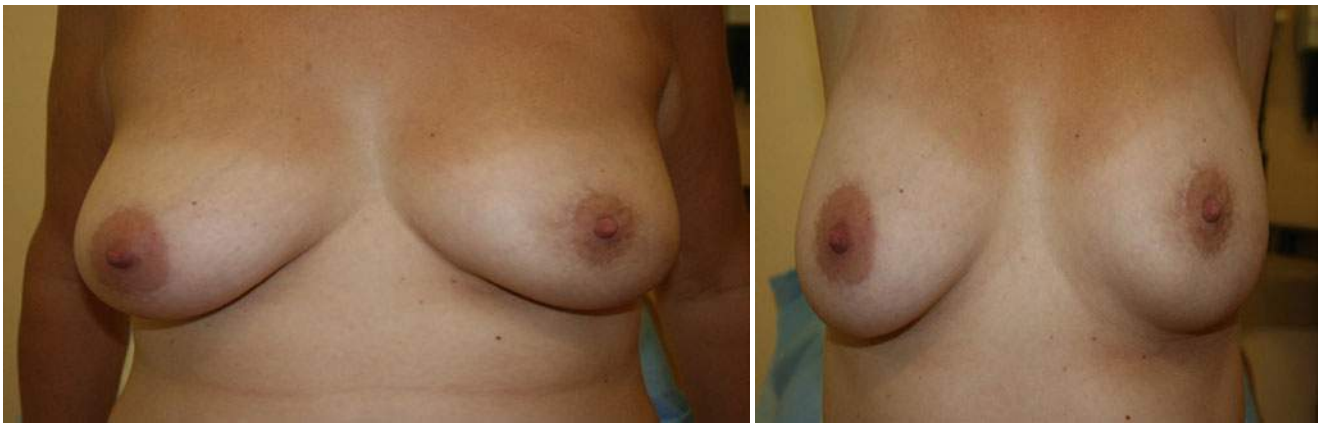
Case 1 Images 10 and 11. Seven Months Postoperatively. The patient completed the radiation treatment course. The subtle nipple compromise has completely recovered and the skin wrinkling faded. The patient has an excellent cosmetic result

Case 1 Images 12 and 13



Case 1 Images 12 and 13. Yearly mammogram. A mammogram was performed 1 year after the surgical intervention. The hemoclips are clearly seen. There is minimal postoperative scarring, as the lumpectomy cavity was closed. There was no evidence of any recurrence

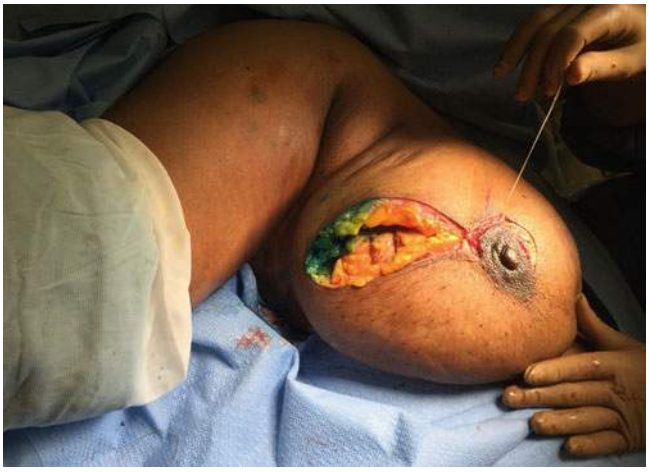
Case 1 Images 14 and 15



Case 1 Images 14 and 15. Two-and-a-Half Year Follow-Up. At 2.5 years follow-up, the patient is pleased with her cosmetic result. She did report significant recovery of nipple sensation. The left breast is slightly asymmetric from the right side; however, the patient is satisfied due to the lack of ptosis. She did not want any symmetrizing procedures

27.2.2 Case 2

Case 2 Image 1



Case 2 Image 1. Dome with Lateral Extension. The patient received neoadjuvant chemotherapy with 7 cm calcifications. The tumor was laterally located. The dome was de-epithelialized, and the tumor was excised en bloc with the overlying skin

References

1. Anderson BO, Masetti R, Silverstein MJ (2005) Oncoplastic approaches to partial mastectomy: an overview of volume-displacement techniques. Lancet Oncol 6(3):145–157
2. Berry MG, Fitoussi AD, Curnier A, Couturaud B, Salmon RJ (2010) Oncoplastic breast surgery: a review and systematic approach. J Plast Reconstr Aesthet Surg 63(8):1233–1243

Round Block Technique

28

Fábio Bagnoli, Guilherme Novita, Vicente Renato Bagnoli, and Vilmar Marques Oliveira

28.1 Introduction

Conservative surgery followed by radiation therapy is considered the method of choice for the treatment of breast cancer, based on evidences of numerous studies and mainly on randomized clinical trials conducted by Umberto Veronesi in Italy and Bernard Fisher in the United States with results published in the late 1970s and early 1980s and updates of over 20 years. The results of these clinical trials have shown that the overall patient survival was the same when they were treated by mastectomy or quadrantectomy followed by radiation therapy (41.2%/41.7%; $p = 1.0$) [1], and therefore if there is no contraindication to conservative treatment and if this is the patient's choice, it has become the surgical treatment of choice [1, 2].

In addition to oncological safety, studies have shown that breast sparing and good postsurgical esthetic outcomes have a positive psychosocial impact on patients [3, 4].

In some cases, even though conservative surgery adequately treats cancer, it results in breast mutilation levels whose deleterious esthetic effects are very important, and thus, the partial reconstruction of the breast, also called oncoplasty gains space [5, 8]. Waljee et al. [9] compared the degree of asymmetry after conservative breast surgery and quality of life, concluding that the more marked the asymmetry, the greater are the depression symptoms, fear of dying, and fear of recurrence in addition to the unfavorable effect of quality of life.

The concept of breast oncoplasty was developed in large Europeans centers and represents a major advance in the surgical treatment of breast cancer, integrating classic concepts of breast plastic surgery to oncological treatment.

Oncoplastic surgery is aimed at providing optimal surgical outcomes in the treatment of the disease as well as providing a good quality of life to these patients [6–10]. It is based on the displacement principle, where the correction of the defect promoted by the removed tissue volume is enabled by the use of residual breast tissue.

Depending on the tumor location, the best technique is individualized, chosen, and indicated on a case-by-case basis. It is essential to resect the area involved by the tumor with free surgical margins, maintain irrigation of the nipple-areola complex (NAC), adequately correct hypertrophy and breast ptosis whenever present, and with the remaining breast tissue, remodel providing a natural aspect to the breast cone [7].

Well-established mammoplasty techniques were incorporated in partial breast reconstruction after oncological surgery, including the superior pedicle technique reported by Pitanguy (1961) [11, 12], the inferior pedicle technique reported by Lyacir Ribeiro [13], the periareolar technique reported by Andrews [14], and the periareolar round block reported by Benelli [15].

28.2 Periareolar Mammoplasties

28.2.1 Round Block Technique

The Round Block periareolar technique was reported in 1988 by Benelli [15] and differed from the periareolar mammoplasty techniques used until then, since with certain details of the new technique, the indications for periareolar mammoplasty were no longer limited to small volume breasts and those with a small degree of ptosis. Another advantage of the

Electronic Supplementary Material The online version of this chapter (doi:10.1007/978-3-319-62927-8_28) contains supplementary material, which is available to authorized users.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_28

new technique was the lower incidence of enlargement and distortion of the scar caused by suture tension [16–22].

The surgery is based on the use of an inverted T internal mastopexy and sparing of breast tissues in the upper quadrants where the pedicles irrigating the NAC are located. On the other hand, the skin, as opposed to the inverted T technique, is only incised around the areola. To guarantee maintenance of breast format, most of the times the author reports breast gland fixation to the pectoralis major muscle as an important aspect. One of the main elements of the technique is to treat ptosis and hypertrophy by using a blocked circular dermal suture passed in a purse-string fashion. The round block constitutes a cerclage, fixing a solid circular dermodermal scar block around the areola [23, 24].

The periareolar approach may be used in different surgeries, such as mastopexy, reduction or augmentation mastopexy, tumorectomy, quadrantectomy, and nipple-sparing mastectomy.

With the development of oncoplastic surgery, periareolar techniques gained space in breast oncologic and repair treatment. Among them, in addition to the round block, we highlight a technique reported by Góes in 1989 [25], where as opposed to the round block, irrigation of the nipple–areolar complex does not come from the superior pedicles, but from the posterior deep perforating vessels, since this technique includes an incision and 360° dissection around the areola [26]. A combination of techniques enabled access to tumors in different topographies in addition to breast remodeling, correction of ptosis, and breast hypertrophy.

Therefore, with adequate planning, periareolar round block and other techniques may be used in the oncoplastic treatment of breast cancer.

28.2.2 Patient Selection

Before proposing any surgical technique, it is essential to carefully evaluate patient's expectations regarding treatment outcomes. In most cases, sectorectomy or quadrantectomy will adequately treat patients without leading to unsatisfactory esthetic results. However, there are situations such as resections of 20% or more of breast tissue in any quadrant, 10% or more of medial and inferior quadrants and central quadrant resections or superior quadrant junctions, where surgical treatment may cause significant anatomic defects [8, 27, 28].

With a careful assessment of breast size, degree of ptosis, tumor location, tumor–breast relationship, comorbidities, and patient's expectations we can determine indications and absolute and relative contraindications for the use of round block periareolar techniques which will be detailed in Table 28.1 [1, 2, 6, 8, 15, 22, 27–29].

Table 28.1 Indications and absolute and relative contraindications for periareolar round block oncoplastic surgery in breast-sparing surgery

Indications	Absolute contraindications	Relative contraindications
Tumor–breast relationship suitable for conservative surgery	Contraindications to conservative surgery	Marked degree of breast ptosis
Tumors in any breast quadrant	Breast–tumor relationship does not allow adequate breast remodeling	Overly fatty-replaced breasts
Small- and medium-sized breasts	Need to resect a large amount of skin	Very large breasts
Medium, small, or no degree of ptosis		Some comorbidities and habits (decompensated diabetes, active collagen disease, obesity, vascular diseases, and smoking)
Resection of 20% of breast tissue in any quadrant		
Resection of 10% of breast tissue in medial or inferior quadrants		

28.3 Surgical Technique

28.3.1 Patient Marking

With patient in standing or sitting position, trace a line dividing the breast in half to maintain symmetry and correction of very lateralized or medialized areolas. The new topography of the papilla will be the projection of the tip of a finger placed at the level of the inframammary sulcus, which depending on the patient's biotype will have a distance of 18–22 cm from the sternal furcula and should not be located above the midline of the patient's arm. Point A (superior edge of the areola) will be marked 2 cm from the new topography of the papilla. Point B (the inferior edge of the areola) must be at a distance of 4–7 cm from the inframammary sulcus depending on breast volume, but most of the times it will be 5–6 cm. Once points A and B are determined, an ellipse is traced checking points C and D, where C is the lateral limit and D is the medial limit which will be at a distance of

8–12 cm from the midsternal line. In breasts without ptosis where there will not be a repositioning of the nipple–areolar complex (NAC), only a circle should be marked around the NAC to resect eventual excess skin and guarantee good surgical access. It is important to double check markings using the pinching maneuver, joining points A and B together and then C and D to make sure the remaining skin is enough to cover the mammary gland without any tension. In the contralateral breast, the same marking steps should be followed (Fig. 28.1) [6, 22, 25, 26, 29].

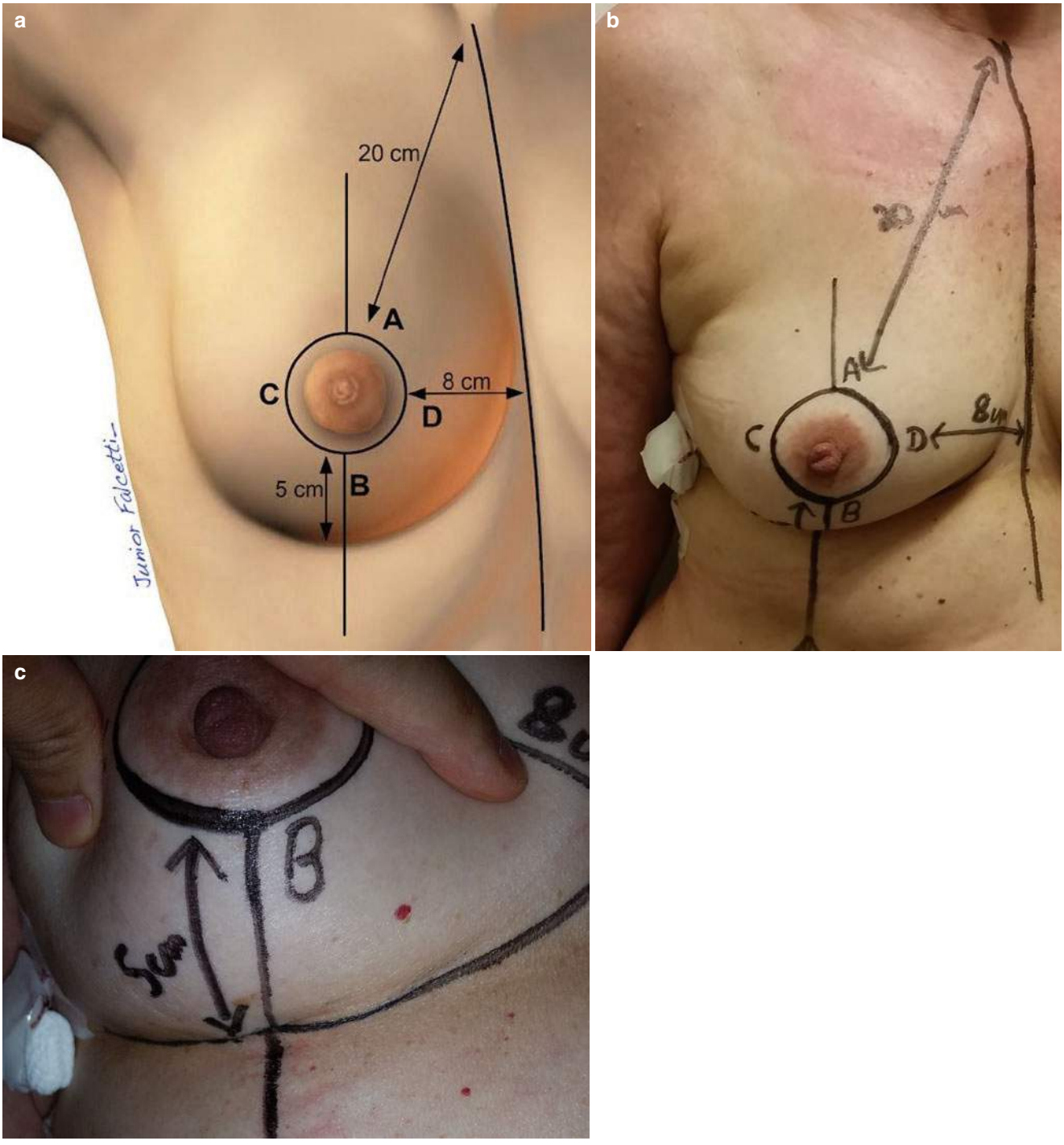

Fig. 28.1 Skin marking. For descriptions of points *A*, *B*, *C,* and *D* see text

28.3.2 Breast Incision, Dissection, and Remodeling

Mark the areola with the areolotome and make an incision using the cold scalpel until the dermis is visualized. De-epithelize between the skin incision and the previous marking. Depending on tumor location and the degree of ptosis, perform an incision throughout the dermis around the areola (360°) or choose a main pedicle whose dermis should not be incised. If you have chosen to use a main pedicle, do not detach the gland in its topography (Figs. 28.2 and 28.3). However, if you have chosen to maintain NAC irrigation using the posterior branches, dissect the mammary gland all the way to its deep limits, maintaining a skin and subcutaneous cell tissue flap with a thickness of 0.5–1 cm.

Define the tumor resection area by performing a sectorectomy. Perform gland remodeling by detaching the gland flaps surrounding the resection area and approximating them to cover the sectorectomy resection defect (Fig. 28.4). Sentinel lymph node biopsy or axillary lymphadenectomy may be performed through the same incision or separately.

Suture is performed in three planes: (1) purse-string suture more deeply in the dermis (nonabsorbable suture: prolene 2-0, mononylon 2-0) to decrease the circumference and decrease the probability of enlarging the scar (Fig. 28.5). The same areolotome used in the beginning should be used to determine the diameter of the new areola; (2) dermal suture with inverted separate stitches on cardinal points for an adequate distribution of the areola (preferably absorbable suture: monocryl 3-0); (3) intradermal occlusive suture (preferably absorbable suture: monocryl 3-0 or 4-0) (Fig. 28.6).

In the contralateral breast, perform the same surgical times, and in case of symmetric breasts, use a mirror image

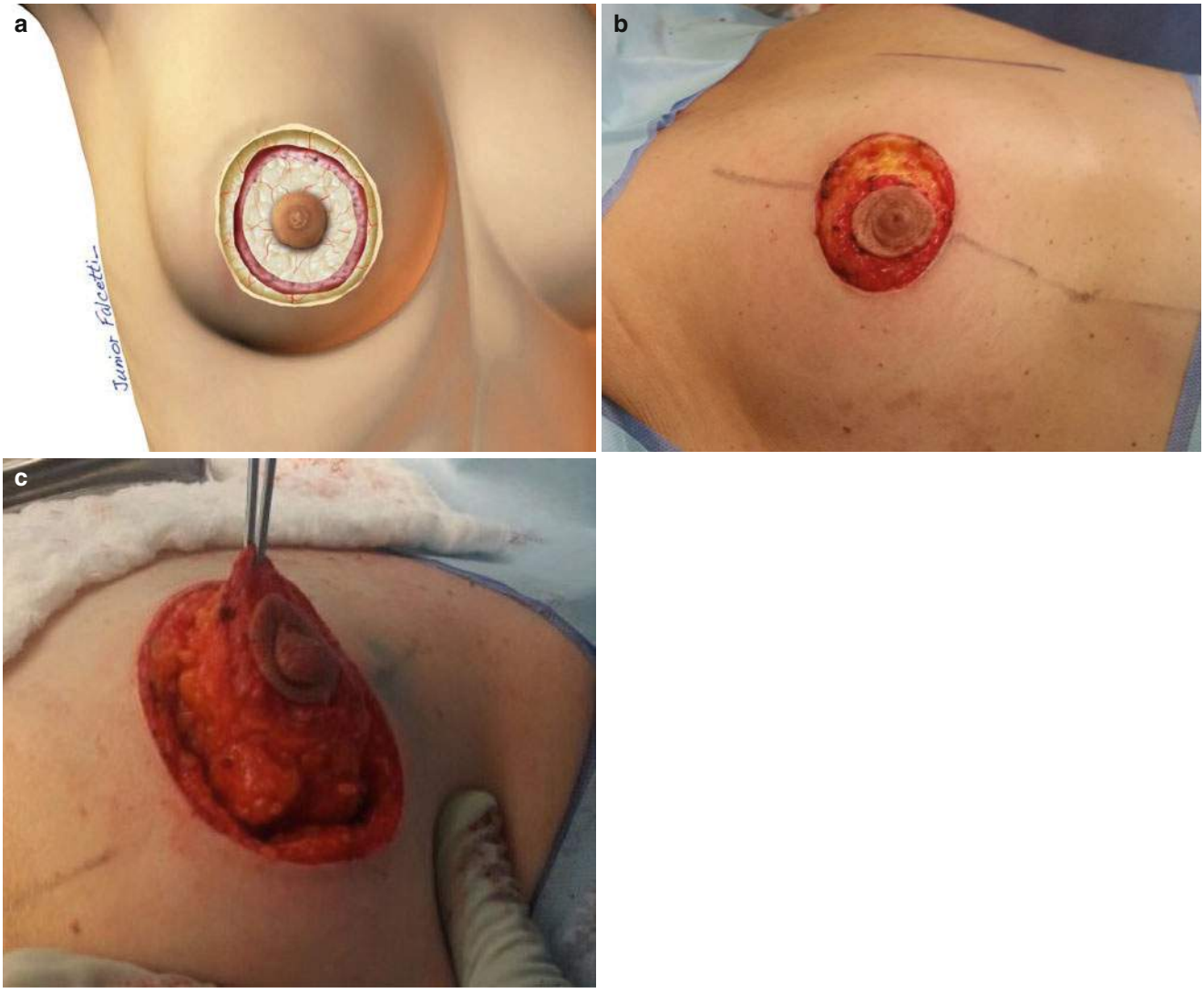

Fig. 28.2 Incision throughout the dermis around the areola (360°) until glandular limits

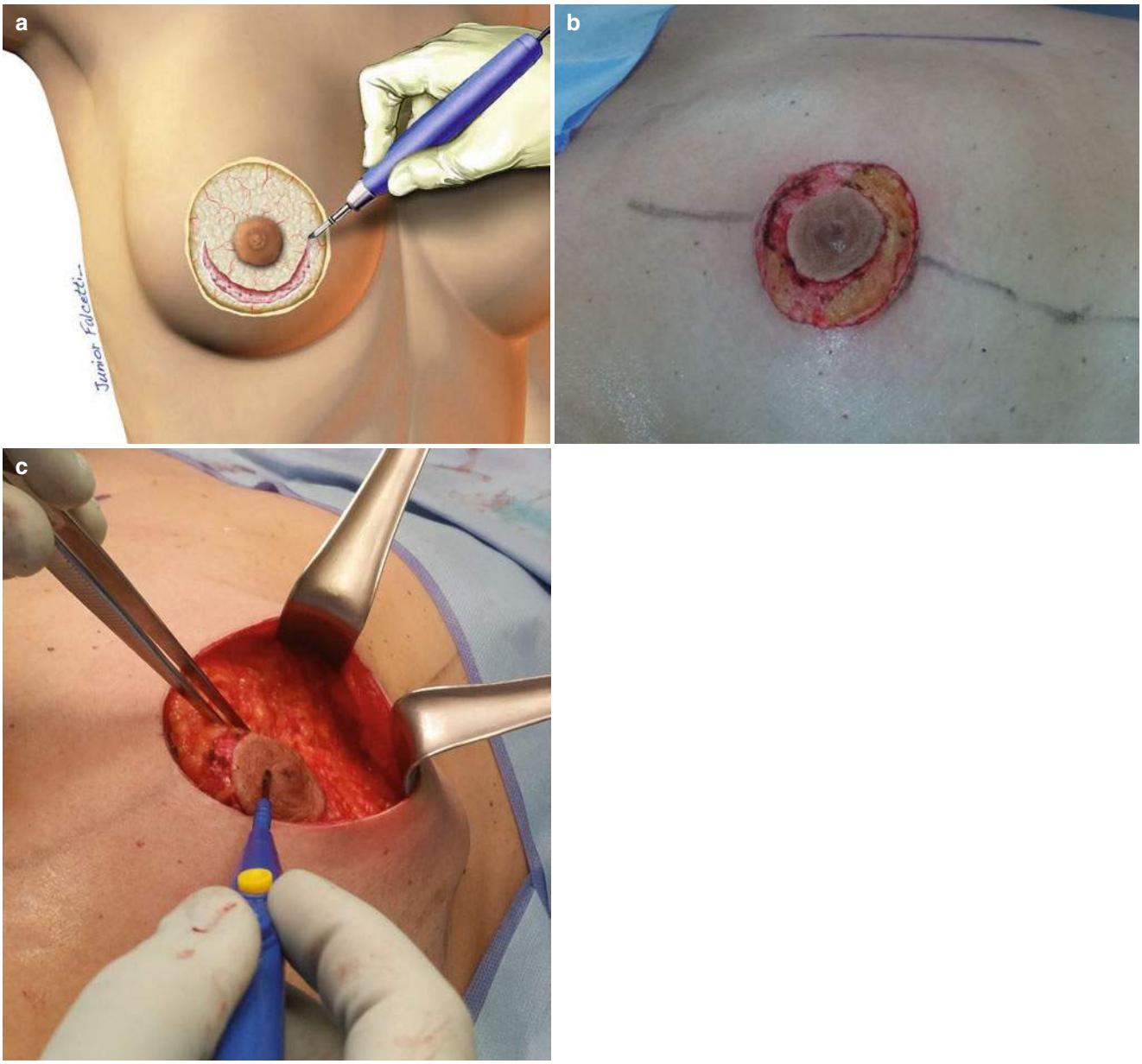

Fig. 28.3 Incision throughout the dermis around the areola (approximately 180°)

resection of the same amount of breast tissue [6, 22, 25, 26, 29] (Figs. 28.7 and 28.8).

28.4 Discussion/Conclusion

Oncoplastic surgery has gained more space in the treatment of breast cancer, bearing in mind that its efficacy in oncologic treatment enables the repair and reduction of eventual unsatisfactory esthetic results. Numerous studies have evaluated the safety of the oncologic and plastic surgery combination. Among them, we highlight the meta-analysis by Losken et al. [30] demonstrating that conservative surgery combined to mammoplasty techniques have guaranteed longer disease-free survival ($p < 0.0001$) in addition to greater satisfaction with the esthetic outcomes ($p > 0.001$) when compared to patients undergoing conservative surgery without mammoplasty techniques. Lorenzi et al. in a cohort study [31] where 454 patients were evaluated with a follow-up of 7.2 years observed similar overall survival among patients undergoing conservative surgery whether combined or not to mammoplasty techniques (91.4%/91.3%) and lower local recurrence rates, without significant statistical difference, in the group combining mammoplasty techniques (69%/71.3%). As major complications of mastopexies and esthetic periareolar mammoplasties when compared to other

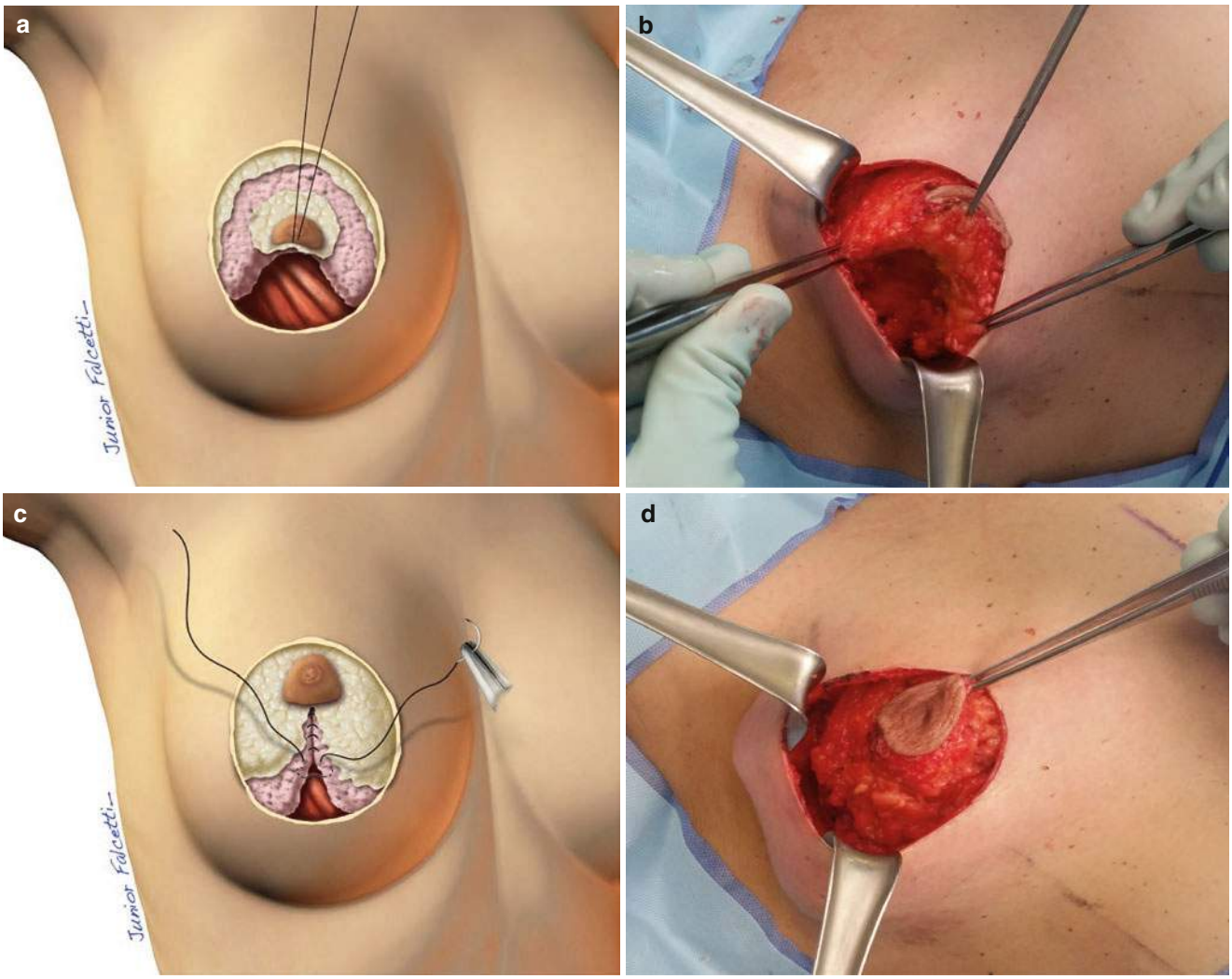

Fig. 28.4 Perform gland remodeling by detaching the gland flaps surrounding the resection area and approximating them to cover the sectorectomy resection defect

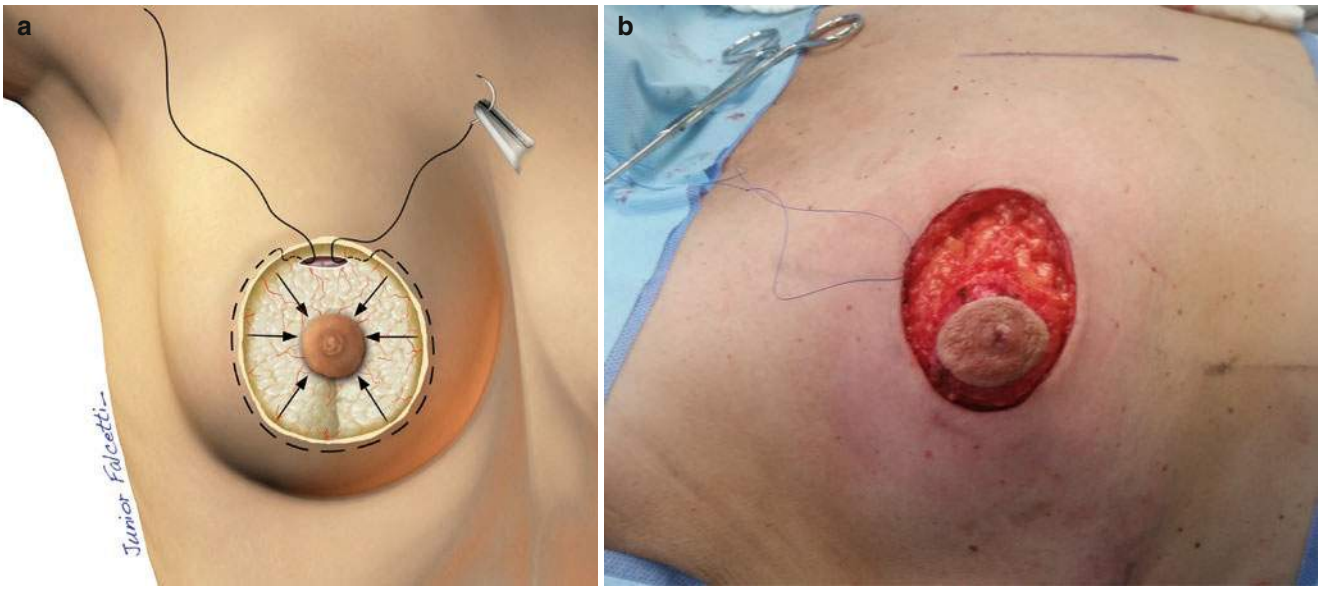

Fig. 28.5 Purse-string suture more deeply in the dermis to decrease the circumference and decrease the probability of enlarging the scar

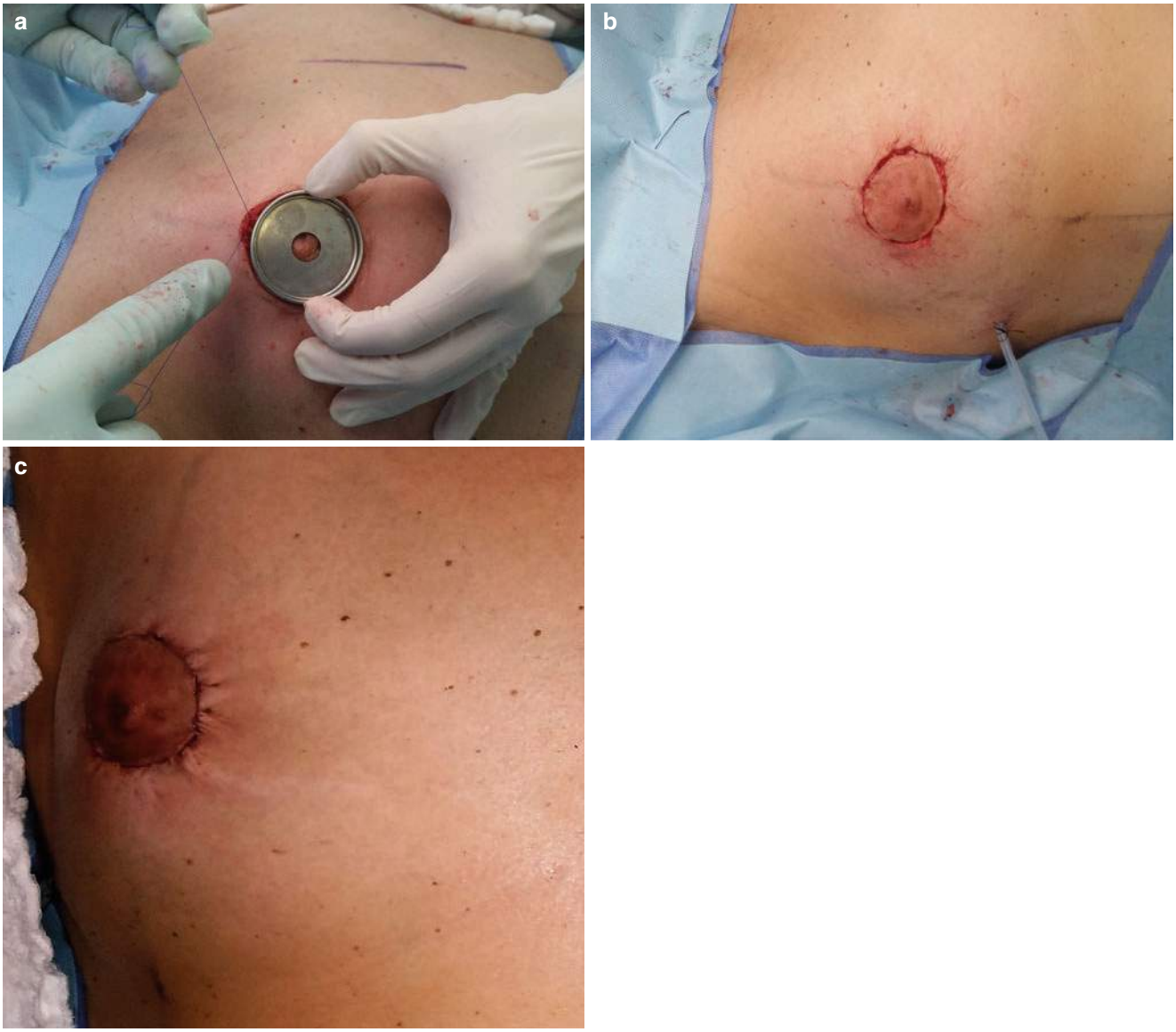

Fig. 28.6 (**a**) The areolotome used to determine the diameter of the new areola; (**b**) dermal suture with inverted separate stitches on cardinal points for an adequate distribution of the areola; and (**c**) intradermal occlusive suture

techniques are evaluated. Rohrich [32] observed that the periareolar group reported suture spitting (61.8%), excess scarring (50%), and the need for revision (50%) as the most frequent complications. And this compared to other techniques had significant statistical difference ($p = 0.002$). In this scenario, we highlight periareolar techniques, and more specifically the Round Block technique, which tend to provide satisfactory results when used appropriately in cases of small- and medium-sized breasts with no ptosis or with mild ptosis and not accentuated ptosis.

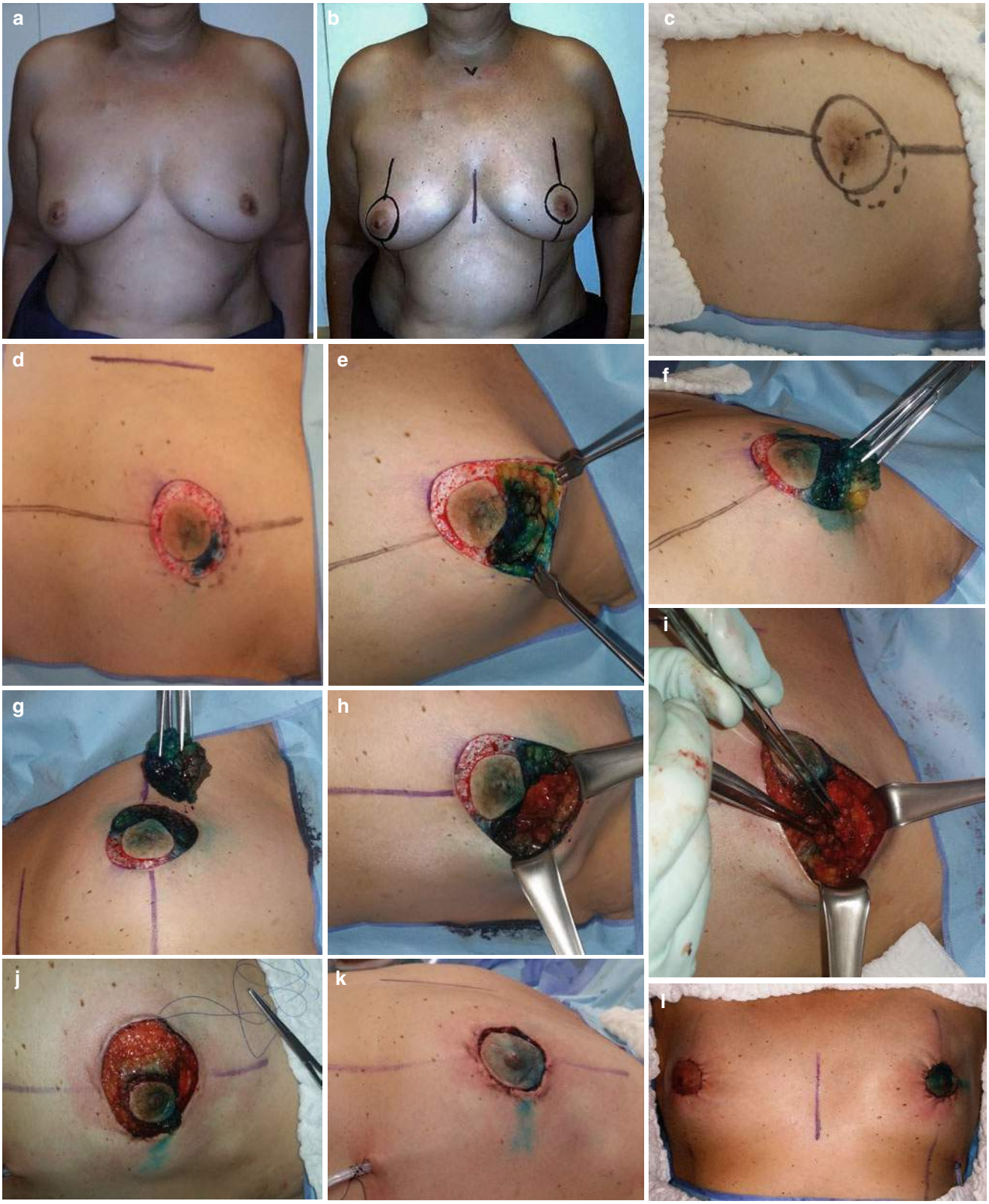

Fig. 28.7 Patient with invasive carcinoma on the upper external quadrant on the left breast underwent immediate reconstruction with local glandular flaps periareolar "round-block" technique (**a**, **b**, **c**, **d**, **e**, **f**, **g**, **h**, **i**, **j**, **k**, **l**). Postoperative appearance at 3 weeks with a hematoma involution (**m**, **n**, **o**)

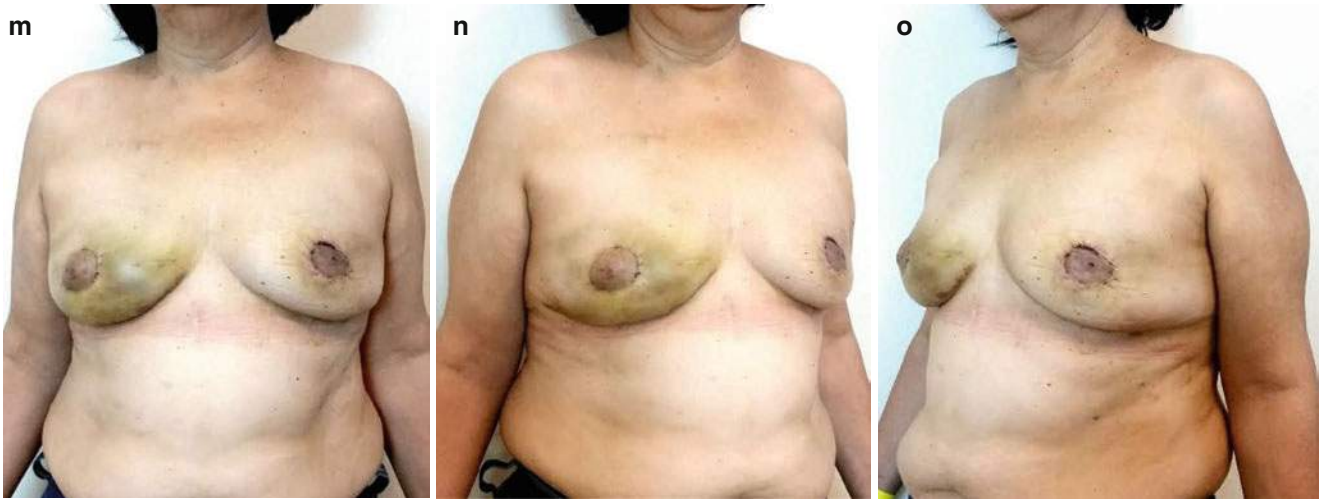

Fig. 28.7 (continued)

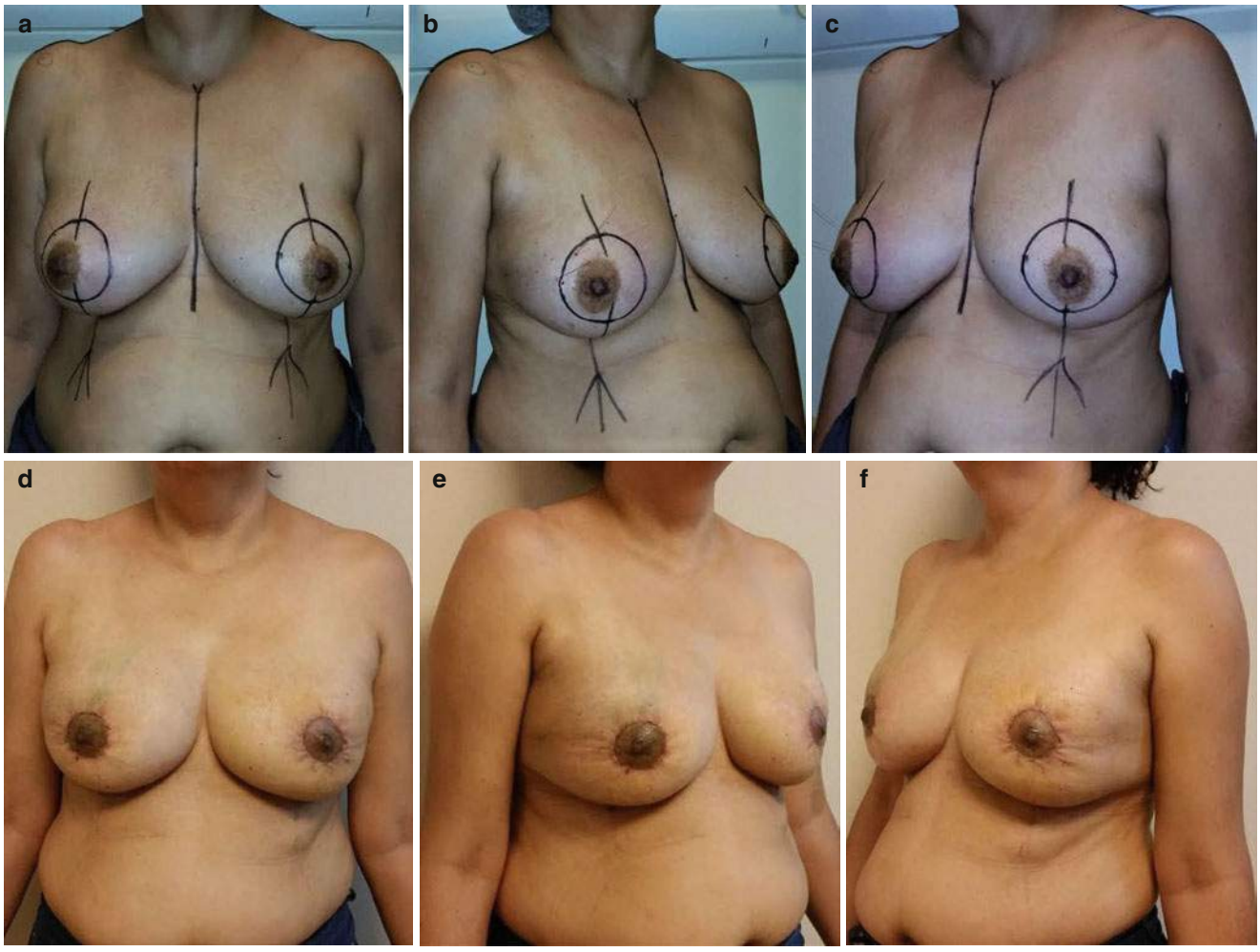

Fig. 28.8 Pre- and post-operatory of quadrantectomy and periareolar round block technique

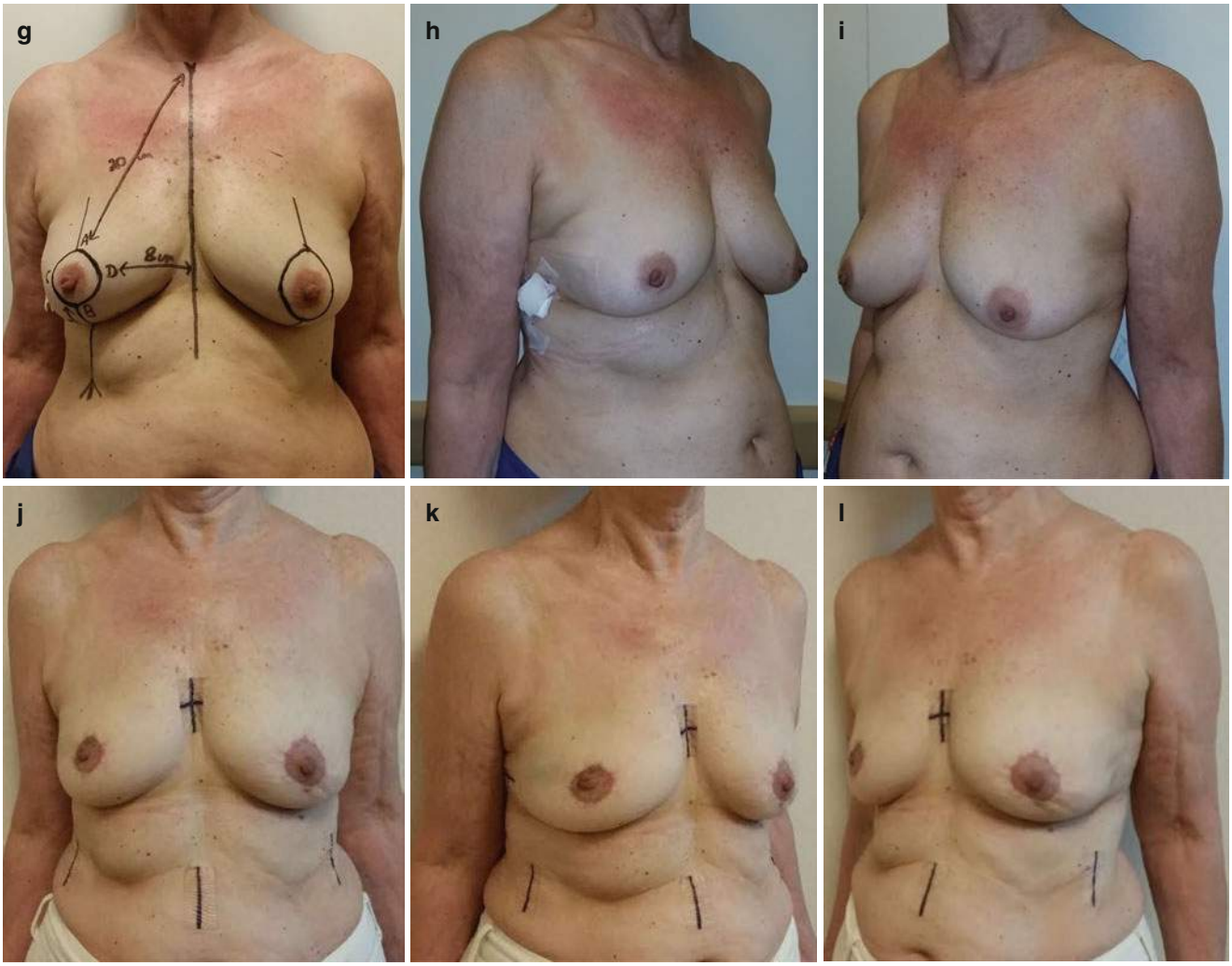

Fig. 28.8 (continued)

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Superior Pedicle Techniques

29

Flavia Kuroda, Cicero Urban, and Mario Rietjens

29.1 Introduction

Breast conservation therapy (BCT) has become an increasingly popular treatment option for women with breast cancer. In select patients, the lumpectomy defect and adjuvant radiation therapy can cause substantial breast deformity in shape, size, and nipple-areola complex (NAP) position [1]. Poor cosmetic results of BCT have been reported in 5–40% of patients [2–4]. This occurs more often when tumor/breast size ratio is unfavorable.

Several oncoplastic surgery (OP) techniques have been incorporated in BCT in an attempt to optimize the balance between the risk of local recurrence and cosmetic outcomes [2, 5]. These techniques include local tissue rearrangement, reconstruction thought reduction mammoplasty or mastopexy approaches, and transfer of local-regional flaps. The combined plastic surgery techniques of tissue replacement or rearrangement provide a wider local excision while achieving better shape and symmetry [6].

The combination of a tumor resection in a mammoplasty pattern with a contralateral breast reduction for symmetry was introduced in the late of 1980s. Positive results in terms of margins and cosmetic outcomes have been reported by many authors. In addition to reducing reoperations in BCT, OP can improve the effectiveness of radiation therapy, alleviate somatic symptoms that may accompany large pendulous breasts, and enhance the patient's perceptions of their bodies after surgery [5, 7, 8].

There are many algorithms and approaches for mastopexy and reduction patterns in OP, including different skin reduction patterns, NAC pedicles, and breast tissue rearrangement. Superior pedicle breast technique is one of the most popular and useful in practice. So, in this chapter it will be discussed their indications, surgical techniques, and outcomes.

29.2 Patient Selection

The choice of the pedicle in OP is related to tumor location and some breast characteristics. Good knowledge of the breast blood supply is essential for designing different potential pedicles to carry the NAC and reconstruct the defect [9]. Superior pedicle technique is useful for treatment of tumors in inferior quadrants, from 4 o'clock to the 8 o'clock position, and is appropriate for large and ptotic breasts or medium-volume breasts with minimal ptosis.

NAC is plicated higher on the thoracic wall with this technique. Therefore, it is reliable and able to preserve nipple sensation. However, some caution arises from difficulty in moving NAC, especially in patients with significant hypertrophy and high degree of ptosis. Use of this pedicle may be particularly difficult when it is necessary to do large reductions [5].

The pattern of incisions used in superior pedicle includes wise pattern and vertical ones. Traditional wise pattern incision (or inverted "T") is the most commonly used because offers more opportunities for breast reshaping. This incision travels along the inframammary fold (IMF), up to the NAC [5], as described by Pitanguy in 1960 [10]. It Combines wider excision of the lower outer, central, and lower inner quadrants, with excess of gland resection resulting in an improved aesthetic for large and ptotic breasts [11]. Skin overlying the tumor can be removed en bloc. Wise pattern also has the advantage that axillary surgery could be

Electronic Supplementary Material The online version of this chapter (doi:10.1007/978-3-319-62927-8_29) contains supplementary material, which is available to authorized users.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_29

Table 29.1 Comparison between different superior pedicle techniques in oncoplastic surgery

	Pitanguy (1960)	Lejour (1994)	Lassus (1969)
Skin markings	Wise pattern	Vertical pattern	Elliptical pattern
Breast characteristics	Moderate to big hypertrophy and ptosis and large amount of skin	Mild to moderate hypertrophy and ptosis and moderate amount of skin	Mild to moderate hypertrophy and ptosis and moderate amount of skin
Pedicle thickness	2–3 cm	2–3 cm	5 mm
Skin undermining	Limited	Extensive	No
Liposuction	No	Yes (if it is necessary)	Yes (if it is necessary)
Breast reshaping	Skin and parenchyma of medial and lateral pillars sutured together with the inframammary fold	Skin and parenchyma of medial and lateral pillars sutured together	Only skin of medial and lateral pillars sutured together

performed through the tail of the incision [12], although many surgeons opt for axillary incisions.

Vertical scar technique was first described by Arie in 1957, but did not gain popularity because the scar often extended below IMF. Lassus in 1969 [11] and Lejour in 1994 [13] renewed the interest in this technique. Hall-Findlay described a modification of Lejour's technique in 1999 [14], with a medial pedicle, very popular in aesthetic surgery. In vertical incision mammoplasty, the incision is made around the nipple-areola complex and extended down to the IMF. It is ideal for inferior pole tumors, which can be widely excised within the boundaries of the standard markings. Tumors lying just outside the design can be approached with a parenchymal flap from the opposite breast pillar [11]. The advantages of this technique include shorter skin incisions, straightforward glandular resection, and shorter pedicle which offers reliable blood supply to the NAC for a variety of breast sizes [14].

Comparison between different superior pedicle techniques in OP, regarding to patient selection is shown in Table 29.1.

29.3 Preoperative Planning

Patients were seen preoperatively by a multidisciplinary team that discusses the case and reviews all the exams. Surgeon plans the tumor removal with or without radiographic/ultrasound/MRI guidance. The team approach is critical in defining areas of excision and in designing reduction techniques. Preoperative photographs are taken in front view, three-quarter view right and left, and lateral view right and left.

Drawings are done with the patient in a standing position. Landmarks are boldly indicated, as they provide orientation for intraoperative tailoring, guiding to prevent unnecessary resections. Landmarks include the midline of the chest, extending from the sternal notch to superior part of abdominal wall. The anterior axillary fold and existing IMFs are also marked. The axis of each breast is determined and typically runs from the midclavicular line to the NAC. Tumor location was marked on the breast skin. The site of the future superior border of NAC is determined by projecting the inframammary fold onto the anterior breast skin. The superior NAC (point A) is marked 2 cm above this point, so the distance of the future NAC to suprasternal notch ranged between 19 and 25 cm. Point B can be obtained by drawing an inverted "T" of 5-4-4 cm, which creates NAC whose diameter is approximately 45 mm. The superior drawing is made in a mosque dome pattern, in order to reduce the tension at point B. A vertical pillar design is made through superior-internal and superior-external mobilization of the breast, as described by Lejour [15]. The decision on whether to perform only a vertical scar or an inverted "T" scar will depend on the tumor location, the level of hypertrophy, and the level of ptosis. For midline tumors, small breasts, and those with less ptosis, it is possible to perform only a vertical scar, but for large breasts and further lateral tumor with major ptosis, an inverted "T" scar will avoid the cutaneous excess such as the skin fold produced in the vertical scar. The position of the scar as vertical or an inverted "T" can be central (more frequent), medial, or lateral, according to the location of the tumor and the need for skin removal on the nodule aiming to obtain better surgical radicalization [16].

29.4 Surgical Technique

Superior pedicle mammoplasty is performed by making two semicircular periareolar incisions, one along the border of the areola and other one superior and parallel to this. Skin between these incisions is subsequently deepithelialized. The NAC is dissected free from the breast tissue on a superior dermoglandular pedicle. An inframammary incision is then created, and the breast tissue is widely undermined and freed from the fascia of the pectoralis muscle. The tumor and surrounding margins are removed en bloc with the overlying skin, down to the pectoralis fascia [8, 17]. Weight of the lumpectomy specimen should be recorded to determine the amount of additional breast tissue to be removed on the ipsilateral side and the total amount to be removed on the contralateral side. All tissue removed is routinely marked and prepared for histopathological analysis. Surgical clips are placed in the tumor bed to allow targeted postoperative radiotherapy [18] (Fig. 29.1).

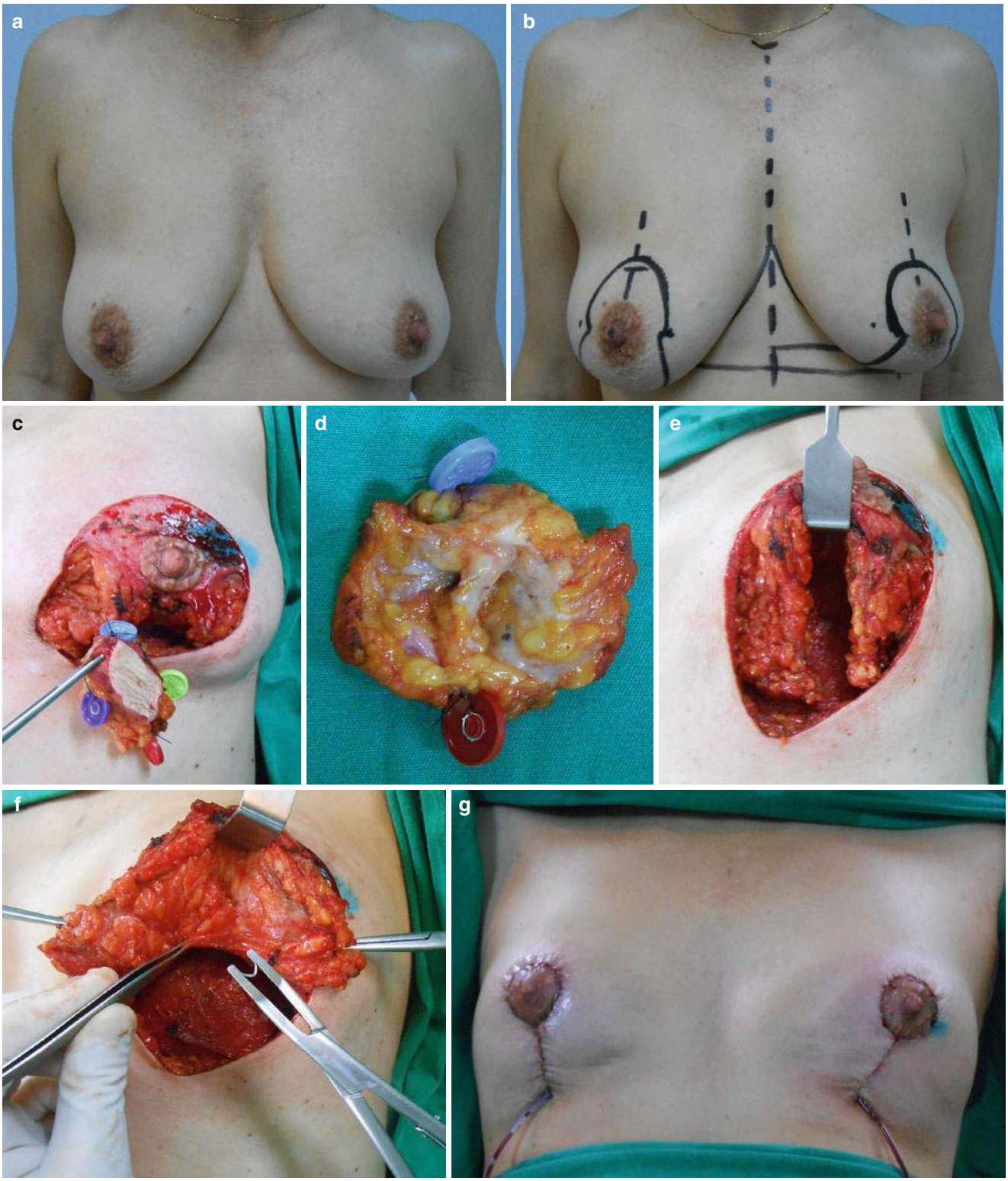

Fig. 29.1 Superior pedicle technique step by step in a 50-year-old patient with a mild hypertrophy and ptosis and 19 mm invasive ductal carcinoma in the inferior quadrants of the left breast. (**a**) Patient in stand position before draws. (**b**) Preoperatory draws for a vertical superior pedicle oncoplastic surgery (Lejour's technique). (**c**) Resection of the inferior quadrant of the left breast. (**d**) Demarcation of the margins with colored buttons to guide the pathologist in margins evaluation. (**e**) Two pillars preserved after tumor resection. (**f**) Insertion of the clips to guide the boost. (**g**) Final result after symmetrization

Once the tumor has been removed, its location dictated the reduction pattern, resection and insetting. Reshaping of the breast is performed by approximating the medial and lateral pillars to fill the lumpectomy defect. The NAC is recentralized by re-approximation of the semicircular periareolar incisions [17, 19]. A single drain is placed and the incisions are closed with interrupted dermal and running subcuticular sutures with absorbable monofilament material.

29.5 Contralateral Breast

Patients who undergo a breast reconstructive procedure may require surgery of the contralateral breast in order to obtain a better breast symmetry or to improve the aesthetic appearance of both breasts. The same procedure is performed in a mirror image fashion during the same operation time for the contralateral breast. The reduction of the contralateral breast offers tissue sampling [20]. The rate of occult breast cancer found in contralateral symmetrizing reduction specimens in patients undergoing breast reconstruction ranges from 4.6 to 11% [21, 22].

29.6 Oncologic Outcomes

Although current OP data is based in series of patients and some cohorts, it supports its use in BCT. Clough reported a prospective analysis of a 100-patient series undergoing more complex type of oncoplastic breast surgery, with 5-year overall and disease-free survival rates of 95.7% and 82.8%, respectively [23]. Rietjens reported an overall local recurrence rate of 3% in their series involving similar surgical techniques [4]. In addition, there is an increasing evidence that OP reduces reoperations in BCT, including some meta-analysis [5, 7, 8].

29.7 Aesthetic Outcomes

The rates of satisfactory aesthetic results are encouraging with OP as they range between 84 and 89% compared with lumpectomy, ranging from 60 to 80% [24]. A meta-analysis showed significantly higher satisfaction with aesthetic results in OP group (89.5 vs. 82.9% in lumpectomy) [20]. Santos, using three different tools—BCCT.core software, specialists, and patients evaluation—for comparing aesthetic outcomes found higher proportion of excellent aesthetic results in OP group [25]. Other series comparing specifically patients with lower pole tumors using superior or superior medial pedicle found good or very good cosmetic outcomes too [26–28].

29.8 Complications

Superior pedicle techniques are safe and effective in OP. However, complications can occur. Careful patient selection will minimize its incidence. Overall OP complication rate ranges from 15 to 30% [5]. Some specific complications of this type of surgery include skin/flap necrosis, NAC necrosis, seroma, hematoma, infection, wound dehiscence, and fat necrosis. The most common complication in wise pattern/inverted "T" techniques is delayed healing of the "T" junction (the areas where perpendicular pillars are sutured. This is due to reduced vascular perfusion. While wound-healing complication may delay time to adjuvant radiotherapy, this is a rare occurrence in all series reported to date [6]. Obesity, diabetes, and tobacco-addicted patients have higher complication rates. If adjuvant chemotherapy is planned, it may begin even if it is not completely healed. However, for radiotherapy everything should be healed before its beginning [5].

29.9 Conclusions

OP, using superior pedicle techniques, is an extremely valuable tool in comprehensive oncologic treatment. This is relatively simple, reliable, and highly versatile technique and leaves patients with minimal breast deformities following proper treatment, without compromising oncologic safety. Careful patient selection, coordinated team planning, and meticulous intraoperative management are the keys to favorable surgical outcomes.

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Partial Breast Reconstruction: Inferior Pedicle Techniques

30

Albert Losken

30.1 Introduction

Partial breast reconstruction is occasionally required after tumor resection in women who choose breast conservation therapy (BCT) [1]. Various options exist including rearranging breast tissue and flap transfer. The oncoplastic reduction or mastopexy technique is very beneficial and seems to be one of the more commonly used approaches [2, 3]. Plastic surgeons are familiar with different breast reduction techniques and pedicles and will often have preferences in terms of which technique they perform most of the time. The same applies for oncoplastic reduction techniques; however, location of the tumor defect in addition to breast size and shape will influence the decision.

The inferior pedicle is still one of the most commonly performed breast reduction techniques since it is easy to perform, reliable, and versatile [4]. It makes sense for it to be a commonly used technique in oncoplastic reduction for defects as well and can essentially be used to reconstruct a partial mastectomy defect in any location except purely inferior [5].

30.2 The Benefits of the Inferior Technique

The inferior pedicle can reliably keep the nipple areolar complex well perfused in almost any breast size and shape. It is a technique that is easy to learn and is reproducible. The complications are comparable to other approaches [6]. Although it does require some flap undermining and the Wise pattern in the majority of cases, it can be performed in 2–3 h. Some feel that the inferior pedicle has a lower complication rate since its inferior location obliterates dead space in the dependent region of the breast. In a recent publication of oncoplastic techniques in 353 patients, the complication rate was 16%, and at over 1 year postoperatively, women reported increased self-confidence ($p = 0.020$), feelings of attractiveness ($p = 0.085$), emotional health ($p = 0.037$), and satisfaction with sex life (0.092) [12]. The positive margin rate was 6%, and at a mean follow-up of 2 years, the recurrence rate was 6.25%.

30.3 Indications

The indications for an inferior pedicle oncoplastic reduction are women with breast cancer who wish to preserve their breasts and have moderate- to large-sized breasts with ptosis. A reduced breast will tolerate radiation therapy better than a large breast, and aesthetic results have been shown to be superior. If the tumor is in the upper or medial pole and there is a concern about creating an unfavorable result from a cosmetic standpoint with lumpectomy alone, then this oncoplastic approach would be preferable: if medial, superior, or lateral tumors where the respective surgeons are concerned about being able to obtain negative margins and anticipate a large resection of if the tumor to breast ratio is greater than 20%, then this is another indication for an inferior pedicle oncoplastic procedure. The ideal patient is one where the tumor can be excised within the expected breast reduction specimen where sufficient breast parenchyma remains following resection to reshape the mound (Fig. 30.1).

30.4 Contraindications

The inferior oncoplastic pedicle technique typically cannot be used if the tumor defect is in the midline lower pole. If the tumor defect is slightly off midline and the inferior pedicle

Electronic Supplementary Material The online version of this chapter (doi:10.1007/978-3-319-62927-8_30) contains supplementary material, which is available to authorized users.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_30

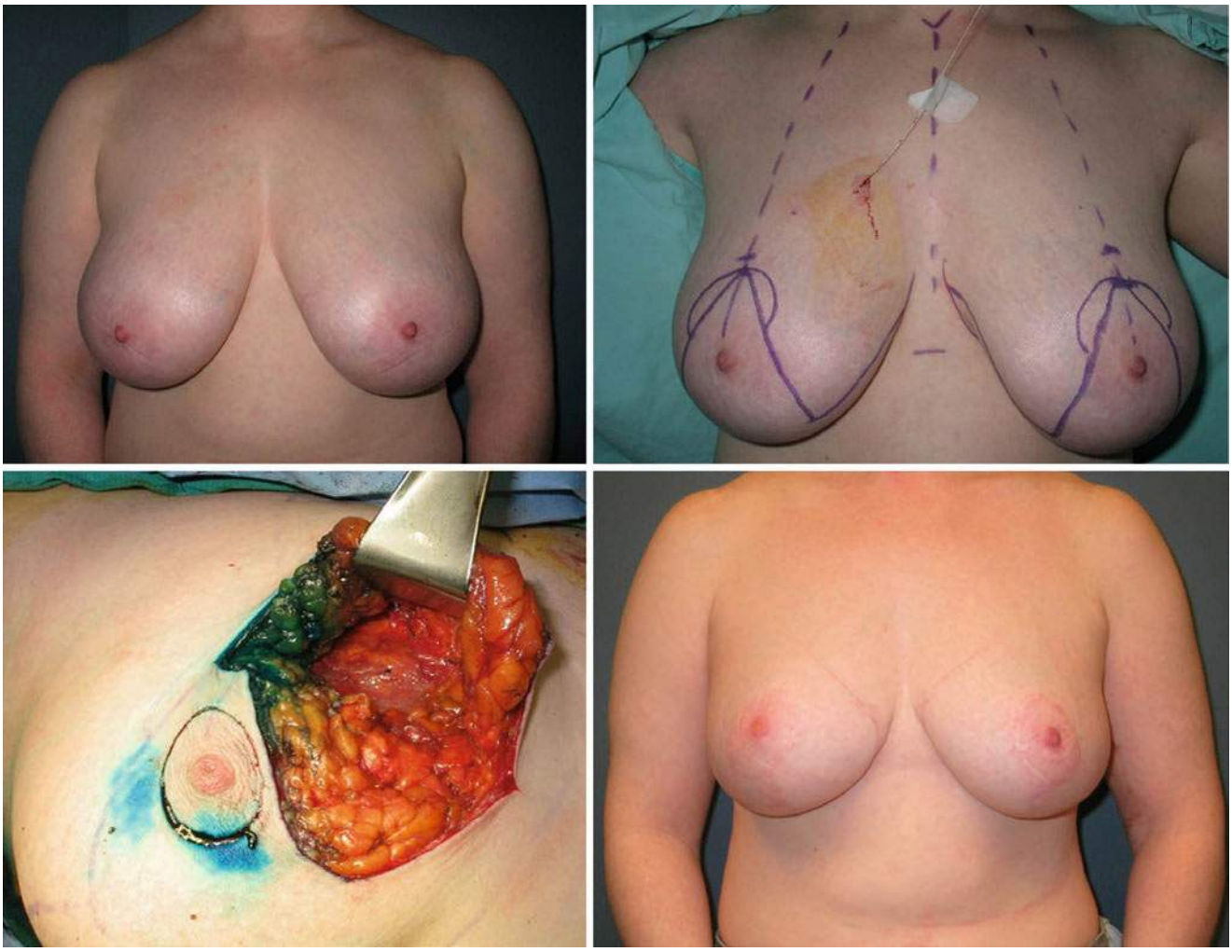

Fig. 30.1 This 33-year-old woman with stage III breast cancer had excellent response to preoperative chemotherapy and desired breast conservation. In order to minimize the potential for a poor cosmetic result with a defect in the upper pole, she underwent a right wire-guided lumpectomy (100 g) with simultaneous bilateral breast reduction (total volumes 250 g left and 150 g right). The nipple was moved based on an inferiorly based dermatoglandular pedicle. The pedicle filled the defect, and her result is shown at 1 year following completion of right breast radiation therapy

can be based more laterally or medially, then it could still be used for lower pole tumors. Adequate base width is required, and the pedicle cannot be detrimental to shaping the breast mound following resection. If it becomes difficult, then a more superiorly based pedicle would be preferable. Central or subareolar tumors that require tumor resection directly beneath the nipple areolar complex could compromise nipple viability with a long inferior pedicle. Choosing a shorter pedicle or even amputation and free nipple graft is safer. Women with a previous infra-areolar biopsy scar or a tumor just inferior to the nipple are not candidates for the inferior pedicle. Appropriate patient selection as always will minimize complications in patients with comorbidities and smokers.

30.5 Timing of Partial Breast Reconstruction

In general partial breast reconstruction, when indicated, is best performed at the time of resection (*immediate reconstruction*). The main concern with immediate reconstruction is the potential for positive margins. When this concern does exist, the reconstruction can be delayed until final confirmation of negative margins (*delayed-immediate reconstruction*). This then allows the benefits of reconstruction prior to radiation therapy with the luxury of clear margins, although at the expense of a second procedure (Fig. 30.2). Such women at increased risk of positive margins included younger age (<40 years old), extensive DCIS, high grade,

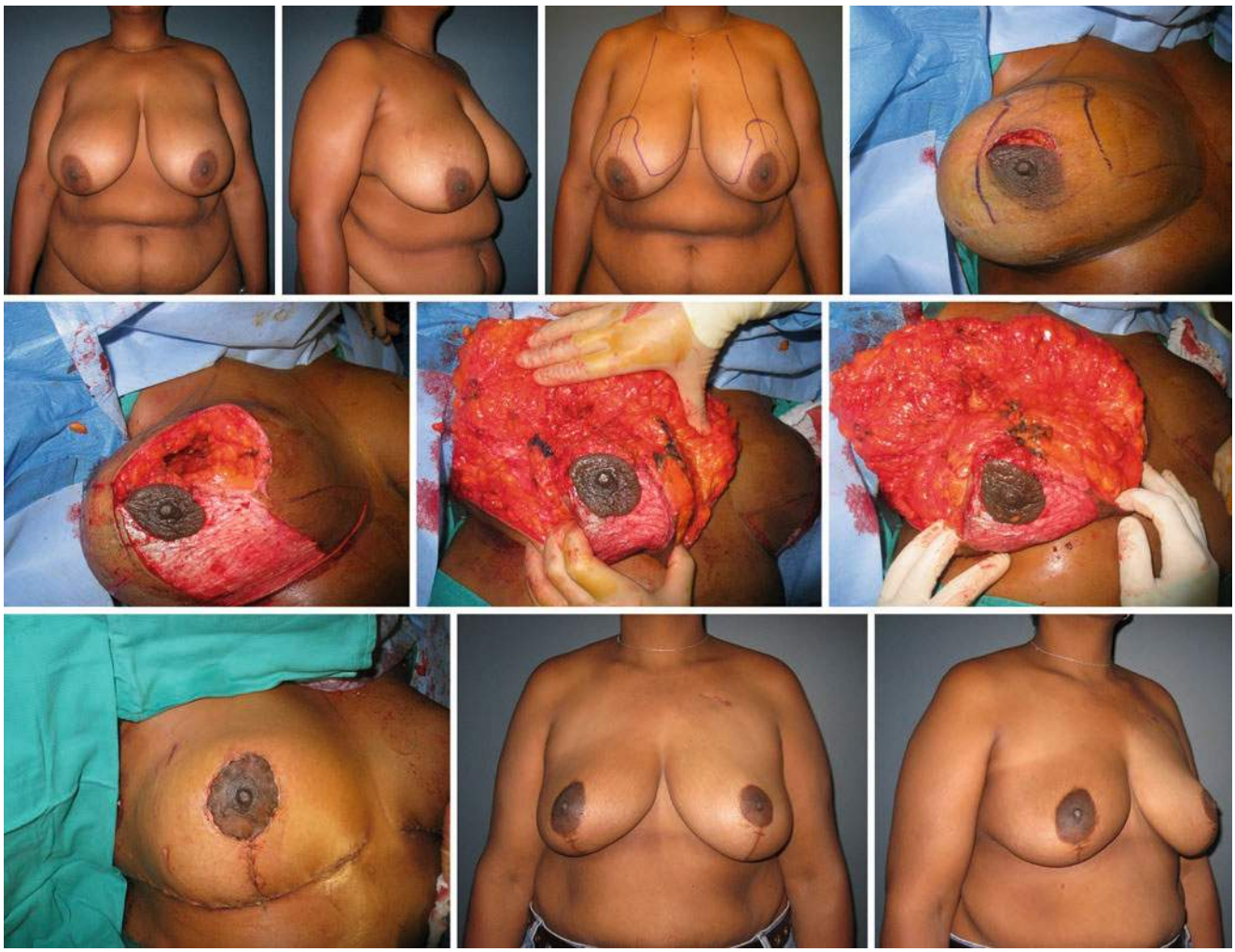

Fig. 30.2 This 49-year-old female with macromastia had a resection above the nipple areolar complex. Her defect was reconstructed using an inferior pedicle breast reduction. Since there is little tissue on the pedicle above the NAC to fill the dead space, the glandular tissue is plicated above the nipple for upper pole volume. She is shown 1 year following completion of radiation therapy (Spear Book, 2009)

history of neoadjuvant chemotherapy, infiltrating lobular carcinoma, and Her2/neu positivity [3, 7, 8]. The main disadvantage is the need for a secondary procedure, which might be unnecessary in the majority of cases. When a flap reconstruction is required, we prefer to confirm final margin status prior to partial breast reconstruction.

There are situations where poor results are encountered years following radiation therapy, which then require correction (*delayed reconstruction*). Reduction techniques should be used with caution in patients who have already been irradiated.

30.6 Surgical Technique

30.6.1 Preoperative Planning

The multidisciplinary team discusses the case and reviews the films. The resective surgeon plans the tumor removal with or without radiographic guidance. The standard Wise pattern markings are then drawn preoperatively making the nipple in the breast meridian about 19–23 cm from the sternal notch. The tumor defect location is anticipated and an inferior pedicle is drawn out. It should be about 8 cm wide in smaller breasts and 10 cm or more in patients with larger breasts. The location of the inferior pedicle can be adjusted either medially or laterally to maximize width and blood flow depending on the tumor location and degree of breast ptosis. A similar pattern is drawn on the contralateral breast for symmetry.

30.6.2 Resection

The breast surgeon then performs the tumor resection, ideally below or through the Wise pattern markings and not through the base of the inferior pedicle. If this approach is

required for tumor resection, then an alternative pedicle design is required. The skin can be resected along with the tumor if desired as long as it is within the proposed area of dermatoglandular resection. It is important for the reconstructive surgeon to be present at the resection until a comfortable working relationship is achieved. Following tumor resection and intraoperative margin assessment, the cavity is clipped for postoperative surveillance and radiation boosting. The tumor specimen is weighed.

30.6.3 Reconstruction

The cavity remaining breast tissue is examined. The goals are to (1) keep the nipple alive, (2) fill the dead space, and (3) reconstruct or reshape the breast mound. The nipple is incised at the appropriate diameter. The standard Wise pattern is cut if not already performed. An inferior pedicle is the de-epithelialized. The dermatoglandular pedicle is then created with a wide enough base to maintain nipple viability. Tissue above the nipple areolar complex is also de-epithelialized and preserved especially in upper pole tumors where the pedicle might be required to fill a defect above the proposed new nipple position. Next step is to fill the dead space (tumor defect). Additional tissue should not be resected until it has been determined that the dead space could be filled with either the inferior pedicle, surrounding breast tissue of breast flaps. Parenchyma could always be plicated above the nipple if need to fill a dead space (Fig. 30.2). Once this is achieved, the additional dermatoglandular tissue can be resected in the usual reduction fashion and weighed. The breast mound is then shaped, skin flaps are closed, and the nipple areolar complex is inset. Drains are placed in the tumor cavity. The contralateral reduction is then performed using the same inferior technique. Ideally the contralateral breast is reduced about 10% more than the tumor side in anticipation for radiation fibrosis. This will maximize symmetry following completion of radiation therapy. Specimens are then all sent separately to pathology. Another option with the contralateral breast is to perform the reduction following completion of radiation; however, this approach would necessitate a second procedure in almost everyone (Fig. 30.3).

The inferior pedicle can be adjusted depending on tumor location (Fig. 30.4) [5]. The medial wedge of parenchyma could be included in the pedicle as an inferomedial design to both enhance blood flow to the nipple and provide additional bulk to fill an upper or inner quadrant defect (Fig. 30.5). An inferolateral pedicle can also be used for lower inner quadrant defects.

Autoaugmentation techniques can be used to fill larger remote defects and broaden the indications for oncoplastic techniques in smaller-breasted women [11]. They could either be used as an extended primary nipple pedicle or a secondary pedicle. Fifteen percent of extended pedicle

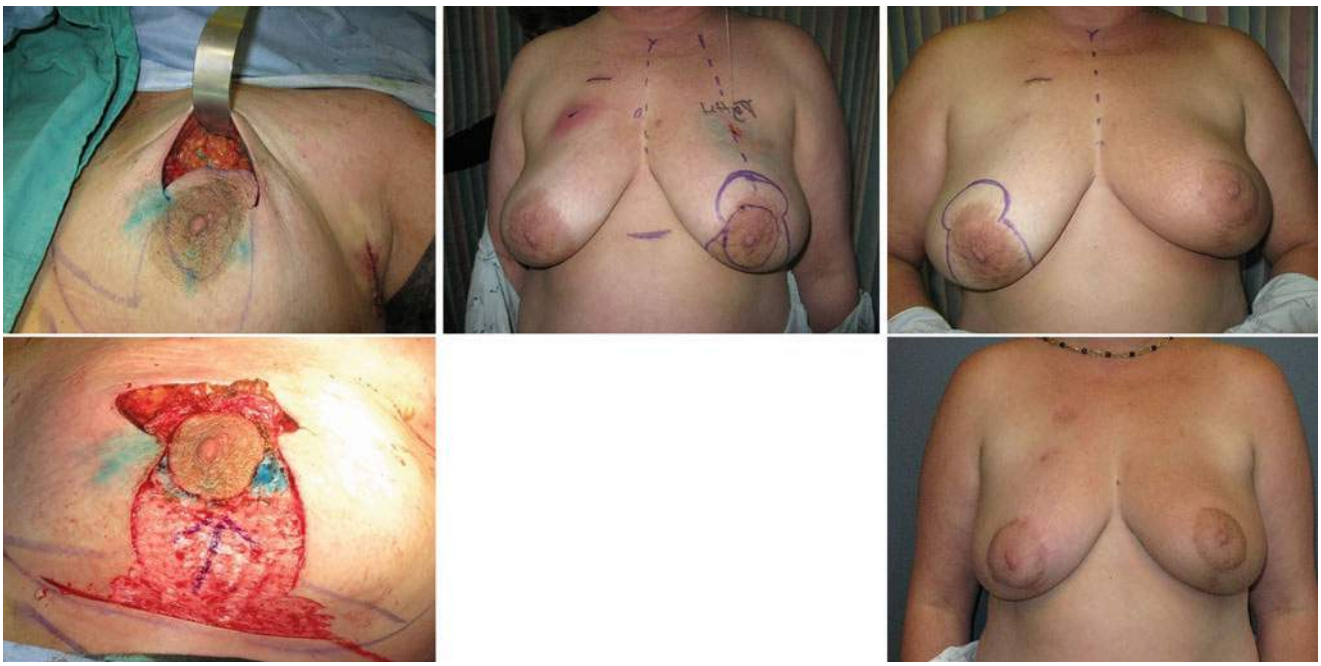

Fig. 30.3 This demonstrates an upper pole breast cancer resected with a wire-guided biopsy leaving a defect above the nipple. A standard inferior pedicle Wise pattern oncoplastic reduction was chosen at the time of lumpectomy. The right reduction was deferred due to an infectious process on that breast. The contralateral breast reduction was delayed until completion of radiation therapy (6 months later). She has reasonable shape and symmetry at 1 year following completion of radiation therapy

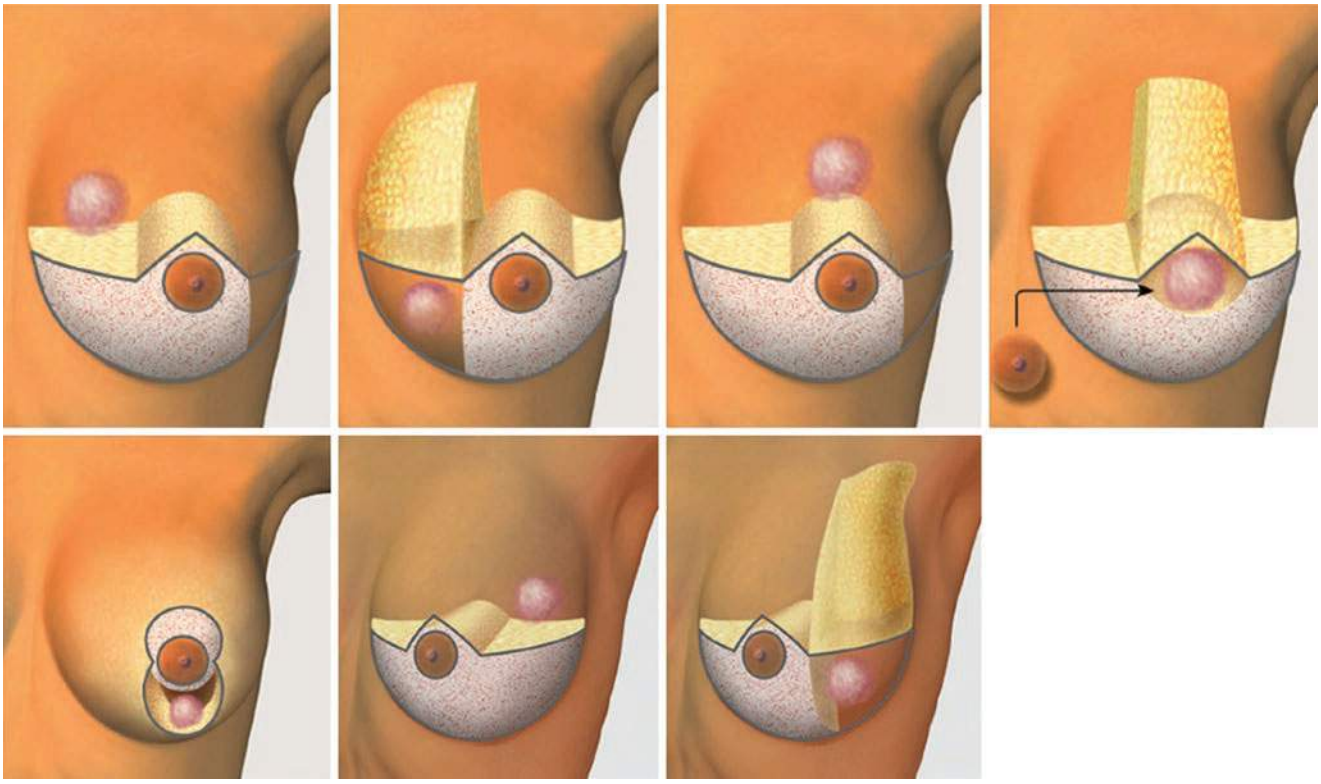

Fig. 30.4 Illustration demonstrating the various modifications to the inferior pedicle based on tumor location

autoaugmentation were extended inferior pedicles. The inferior pedicle was extended by de-epithelializing beyond the NAC to incorporate additional tissue to fill peripheral or upper pole defects. When a secondary pedicle was used, the most common combination was a superomedial NAC pedicle and an inferiorly based secondary pedicle to fill lateral or upper outer quadrant defects. A secondary inferior or inferolateral dermatoglandular pedicle was de-epithelialized and used to independently fill the tumor defect (Fig. 30.6).

30.7 Surveillance

The three main tools when it comes to postoperative surveillance include the physical examination, radiologic imaging, and tissue sampling. It is important that all members of the team are aware of the various surgical components, since differences in presentation might exist. We recently demonstrated that mammography following partial breast reconstruction using reduction techniques was just as sensitive as a screening tool when compared to patients with BCT alone [9]. Although the qualitative mammographic findings were similar in the two groups over the average 6-year follow-up, there was a slight trend toward longer times to mammographic stability in the oncoplastic reduction group (25.6 months versus 21.2 months in the BCT alone group). This means that it might take the oncoplastic reduction patients slightly longer to reach the point where any change in mammographic findings might be suspicious for malignancy. An accurate interpretation requires familiarity with these temporal changes, and mammograms should be compared over time. Microcalcifactions and areas of fat necrosis are easily identified, and no interference in postoperative surveillance has been demonstrated. Other imaging techniques such as ultrasound and MRI will likely become more popular as technology improves. Although routine tissue sampling is not recommended for screening, any clinical concern necessitates fine needle aspiration, core needle biopsy, or surgical biopsy to rule out malignancy. Patients who undergo partial breast reconstruction are expected to have an increase in the amount of tissue sampling requirements, as demonstrated in our series (53% in the oncoplastic group compared to 18% in the BCT alone group over an average of 7 years).

30.8 Complications and Outcomes

The inferior pedicle reduction pattern is relatively sage and affective; however complications can occur. Careful patient selection will minimize the incidence of postoperative complications. Some larger series with volume displacement

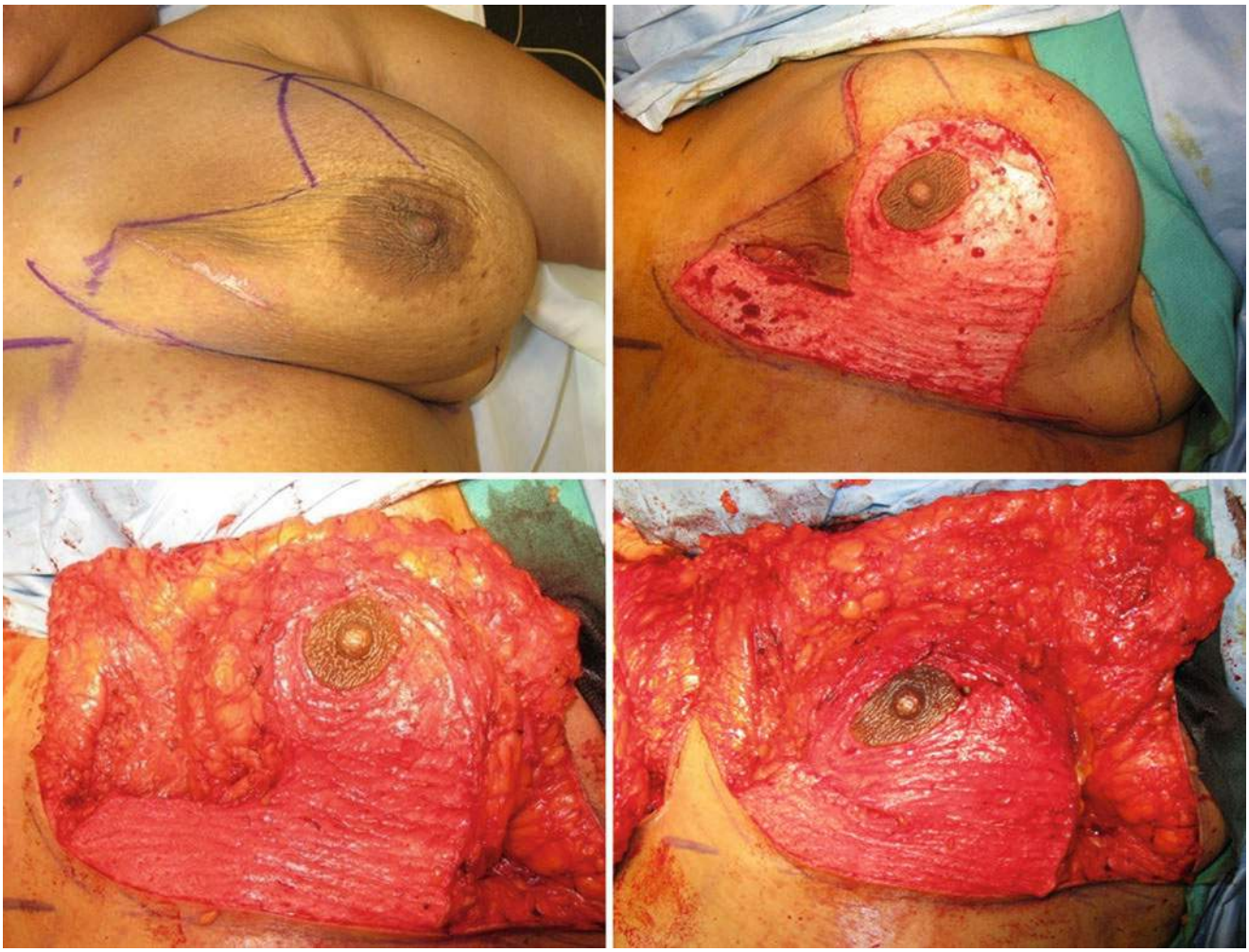

Fig. 30.5 Intraoperative demonstration of retained medial wedge to the inferior pedicle used to fill an inner quadrant defect following wide excision

techniques using a variety of reduction techniques report complications such as delayed wound healing (3–15%), fat necrosis (3–10%), and infection (1–5%) [2, 3, 5]. Loss of nipple is very rare when the pedicle is wide enough and the technique is well designed and executed. Delayed complications with the oncoplastic approach include breast fibrosis and asymmetry. Although the goal of partial breast reconstruction is to prevent the unfavorable cosmetic result, this approach cannot prevent or reverse the effects of radiation therapy. Since these effects will persist, the assessment of shape and symmetry needs to be made in the context of long term. However, with partial reconstruction shape is typically preserved, and it is easier to adjust the contralateral side secondarily if necessary than reconstruct a radiated BCT deformity. Asgeirsson reviewed numerous series with intermediate follow-up and demonstrated cosmetic failure rates of 0–18% (50). *Local recurrence* is another important outcome that needs to be evaluated in the oncoplastic patient. Most reviews in the literature are of intermediate follow-up (up to 4.5 years), with local recurrence rates varying from 0 to 1.8% per year [10]. Actuarial 5-year local recurrence rates range from 8.5 to 9.4%. Longer-term studies are required.

Autoaugmentation techniques potentially carry an increased risk of fat necrosis and complications. We have recently shown in a series of 333 patients (33% with autoaugmentation technique) that the overall complication rate was not significantly different with it being 15% in the standard oncoplastic group and 19.9% in the autoaugmentation group [11]. There was no difference in symptomatic fat necrosis.

30.9 Conclusion

The inferior pedicle oncoplastic reduction is a very reliable and versatile technique for reconstructing the partial mastectomy defects in women with macromastia or ptosis.

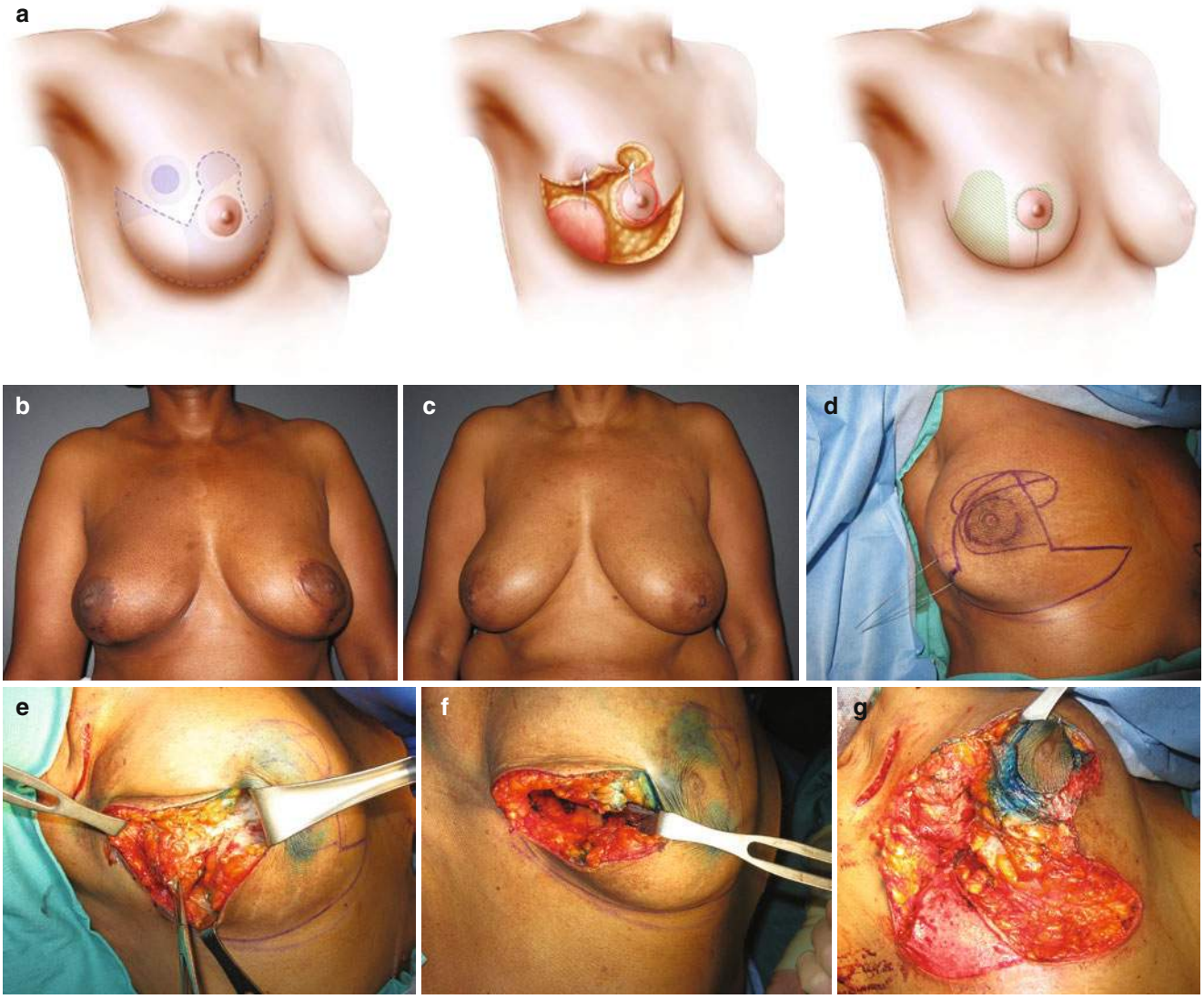

Fig. 30.6 This is a 48-year-old woman with moderate breast size and ptosis who presented with a right-lateral infiltrating ductal carcinoma (**a**). She underwent wire localization (**b**) and a 55 gram partial mastectomy (**c**). The defect was lateral to the nipple and all the way down to the chest wall (**d**). A standard central mound or inferior pedicle reduction might not have given her sufficient tissue to fill the defect high enough. A decision was made to use the lower pole breast tissue to create a secondary inferiorly based pedicle to fill the tumor defect. A superomedial pedicle was created to move the nipple independently to its proposed location. Including the lumpectomy specimen, the total volume removed from that side was 175 g (**e**, **f**). A contralateral reduction was performed removing 190 g using a superomedial pedicle. She is shown 1 year following completion of right radiation therapy (**g**) with decent preservation of volume and lateral breast contour

This technique can be used in almost any breast size or shape, as long as sufficient tissue remains following tumor resection. The inferior pedicle oncoplastic reduction technique is indicated for any tumor location except purely inferior. Complication rates and aesthetic results are favorable, and this approach does not interfere with cancer surveillance. We need to critically evaluate results measuring functional, oncological, and aesthetic outcomes in an attempt to establish safe and effective practice guidelines to maximize outcomes.

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Alternative Oncoplastic Techniques for Challenging Breast Conservative Surgeries

31

Régis Resende Paulinelli

31.1 Introduction

Even in the most favourable cases, a total breast reconstruction does not have the same comfort, ease and sensibility of the original breast, besides having a higher morbidity and a higher risk of complications [1]. In cases in which radiotherapy is mandatory, like locally advanced tumours, the aesthetic results and risks of complications for total breast reconstructions are much worse [2–4]. Therefore, it is important to the patient trying to expand the indications of the conservative treatment through the oncoplastic surgery [5, 6].

Randomized trials have shown that conservative treatment for early breast cancer associated to radiotherapy presents survival rates similar to those obtained by radical mastectomy [7, 8]. Classic indications of mastectomy, such as tumour size greater than 5 cm, skin invasion and multicentricity, have become relative, and recent researches have failed to demonstrate superiority of mastectomy [9–11].

The same is true for other relative contraindications, like young age and unfavourable tumour biology [12, 13]. Neoadjuvant therapy and oncoplastic techniques may increase the rates of conservative treatment and improve its aesthetic outcomes [14–16]. The most important surgical element for local control is "free margins", i.e. pathologic margins higher than 1 mm for invasive and 2 mm for *in situ* tumours [17, 18].

Depending on the relationship between tumour size and breast size, the aesthetic result may be very unfavourable (Fig. 31.1). However, oncoplastic techniques may allow

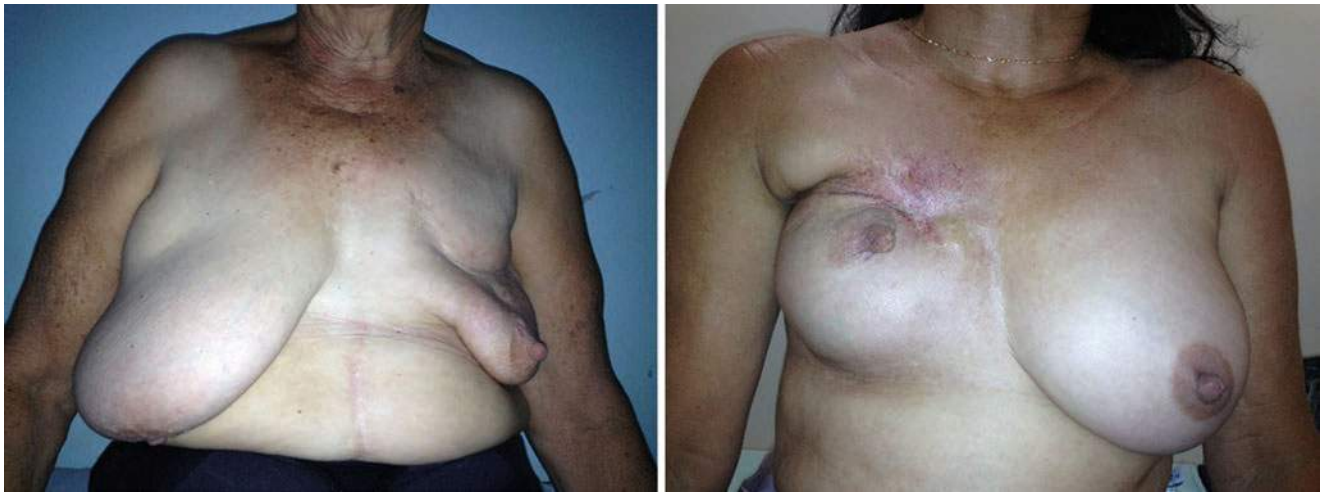

Fig. 31.1 Some deformities of conservative treatment may not be adequately addressed without a mastectomy and complete reconstruction. These deformities could have been avoided if the oncoplastic surgery were available from the first oncological surgical planning

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_31

resection of large areas of the breast, with adequate surgical margins and, at the same time, preventing or correcting deformities, asymmetry and ptosis [6, 14, 19, 20]. Figure 31.2 shows an algorithm for deciding when to indicate a usual lumpectomy, an oncoplastic technique or a mastectomy (Fig. 31.2).

Smoking, obesity, comorbidities and previous radiotherapy are risk factors for complications and demand the use of more limited techniques, or less glandular detachment, to lower the risk of necrosis [1].

Despite controversies, previous breast augmentation does not constitute an absolute contraindication to conservative treatment [21]. Women with implants may have insufficient breast volume for a conservation, depending tumour size. Moreover, there is a greater risk of aesthetic damage and capsular contracture after radiotherapy. Nonetheless, total breast reconstruction is often a more risky procedure, with greater chances of asymmetry, implant loss, necrosis, loss of sensitivity and need for multiple surgeries. Implants may replace volume, but they do not correct partial defects in the breast and may even worsen it. Therefore, it is important to associate some other oncoplastic technique to correct the defect. In the case of retro-glandular implants, it may be preferable changing them to the retro-muscular space to reduce the risk of capsular contracture.

The most popular oncoplastic techniques are: mammaplasty with the areola vascularized by means of the *superior pedicle* for tumours of the lower quadrants; the *inferior pedicle* for tumours of the upper quadrants, and periareolar mammaplasty (*round block*), for small breasts, with little ptosis, when there is no need to resect the skin near the tumour. This approach can solve many cases, with satisfactory results, but having a good domain of other techniques may expand the indications of the conservative treatment and may avoid unnecessary mastectomies (Fig. 31.3).

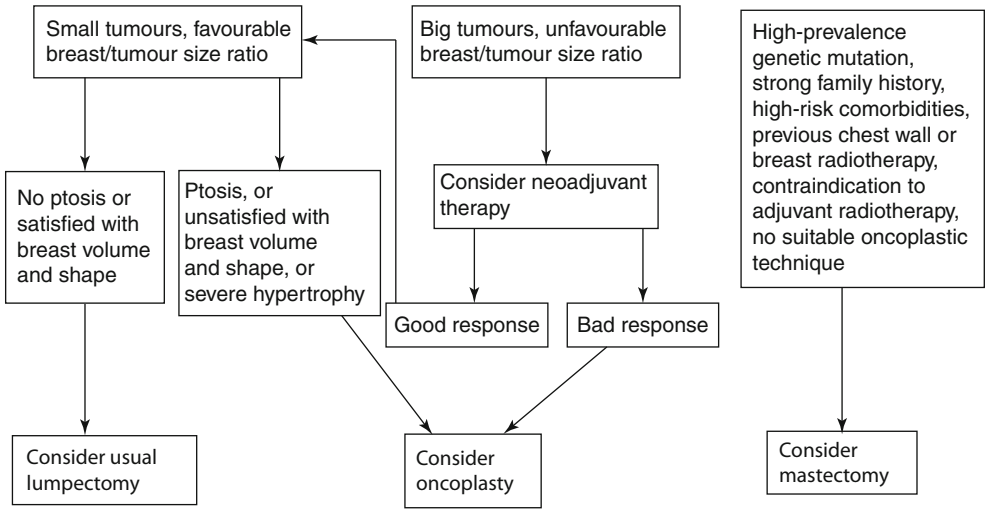


Fig. 31.2 Algorithm for planning breast cancer surgery

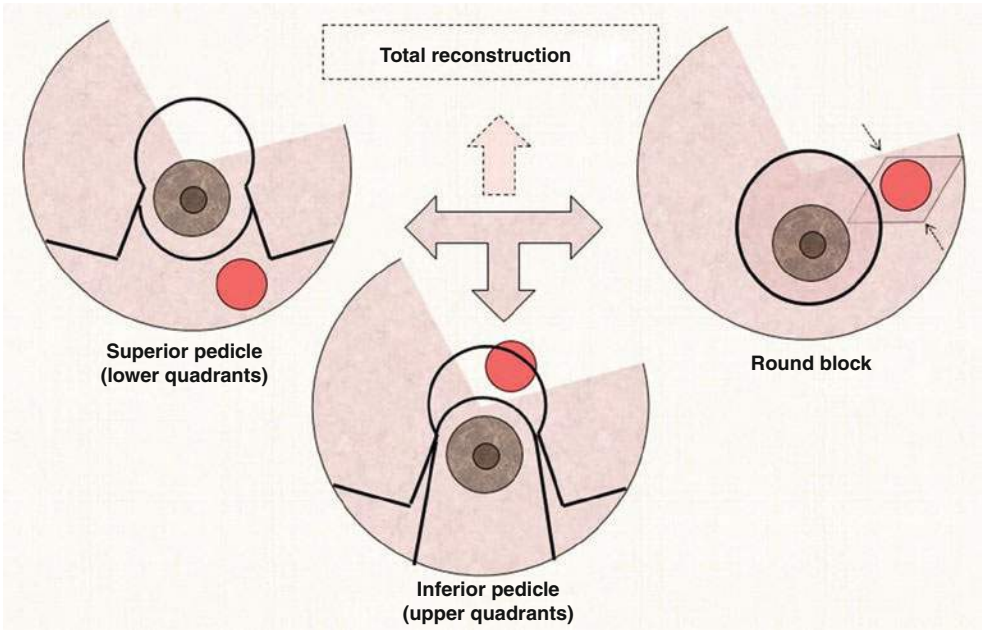


Fig. 31.3 The most common surgical approach in oncoplastic surgery: superior pedicle for tumours in the lower quadrants, inferior pedicle for tumours in the upper quadrants and round block for tumours in breasts with little ptosis. When the tumour or the breast do not fit into one of these techniques, it is usual to choose mastectomy with total reconstruction

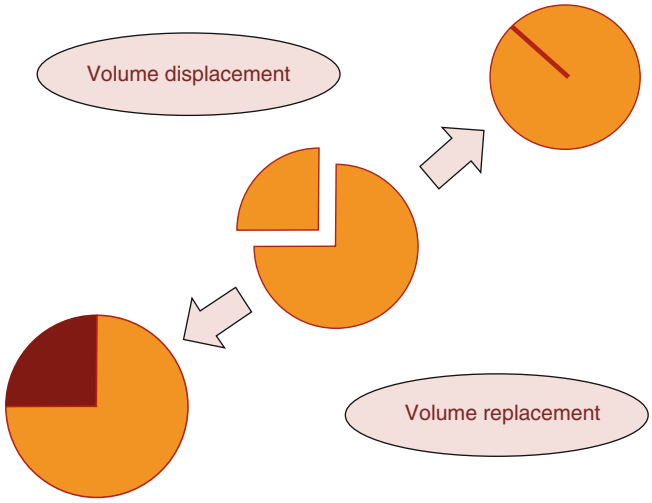


Fig. 31.4 In volume displacement techniques, local breast flaps are moved to conceal the defect, as is the case of glandular flaps, dermoglandular flaps and oncoplastic mammaplasties. In volume replacement techniques, flaps outside the breast are used to restore volume loss because of the quadrantectomy, as is the case of the thoracolateral flap, thoracoepigastric flap, bilobed flap and myocutaneous flaps

There is a more comprehensive classification which divides breast oncoplastic surgeries into two types: volume displacement and volume replacement [22]. In *volume displacement* techniques, local breast flaps are moved to conceal the defect, as is the case of glandular flaps, the dermoglandular flaps and oncoplastic mammaplasties. In *volume replacement* techniques, flaps outside the breast are used to restore the volume loss because of the quadrantectomy, as is the case of the thoracolateral flap, thoracoepigastric flap, bilobed flap and myocutaneous flaps (Fig. 31.4).

This chapter do not intend to comment on all available oncoplastic techniques, because they are numerous and varied, due to the pioneering creativity of many surgeons worldwide. However, I would like to comment on some of the most worthwhile options that I use more often.

31.2 Volume Displacement Techniques

31.2.1 Nipple-Areola Complex Repositioning

The classic lumpectomy with radiated incision usually causes a nipple and areola displacement due to the retraction of the skin scar. Some surgeons still leave the region of quadrantectomy without an approximation of the planes, so that the seroma and hematoma fill the defect. In the short term, the results are acceptable, but after a few months, there is a reabsorption of fluids, intense fibrosis and fixation of the skin to the deep planes, which leaves large defects, depressions and asymmetries (Fig. 31.5).

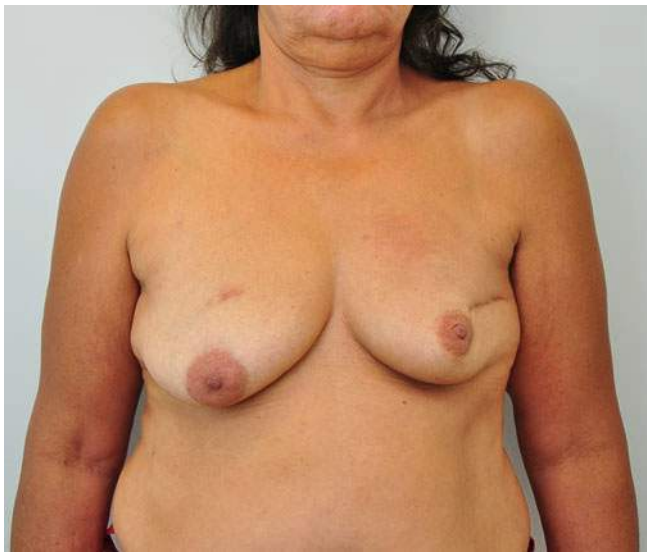


Fig. 31.5 Usual result of a conventional quadrantectomy presenting local depression and breast asymmetry. The radiated incision retracts and deviates the areola to the side of the scar

A very simple alternative may be the primary closure of the skin and parenquima, followed by the repositioning the nipple-areolar complex, 2 or 3 cm in the opposite direction of the radiated scar (Fig. 31.6).

It is particularly useful for old women and/or for almost entirely fat breasts, in which it would be dangerous undermining a large amount of glandular tissue, because of the risk of fat necrosis. It fits better for small tumours in the upper quadrants, in women that do not desire breast reduction or mastopexy, neither contralateral symmetrization.

31.2.2 Glandular Flaps

Among some possible alternatives of glandular flaps, I prefer to use a technique called *glandular rotation* [22, 23]. The incision, instead of radiated, is periareolar or para-areolar, along the Langer's lines. The skin is divided from the glandular tissue in regions close to the tumour. The tumour is, then, removed by means of a radiated resection to the opposite direction of the skin incision, and the defect is closed edge to edge, primarily with nonabsorbable or slow-absorption sutures (Fig. 31.7). It is important to place metallic clips on the margins of the breast resection, to guide the boost radiation therapy, in particular in techniques such as this in that the scar of the skin does not always coincide with the prior tumour area.

For the deep located tumours, or whenever allowed by the adequate surgical margins, it is preferable to keep the skin flap thicker than 1 cm, avoiding skin retraction, and, therefore, reducing the need for an extensive glandular undermining.

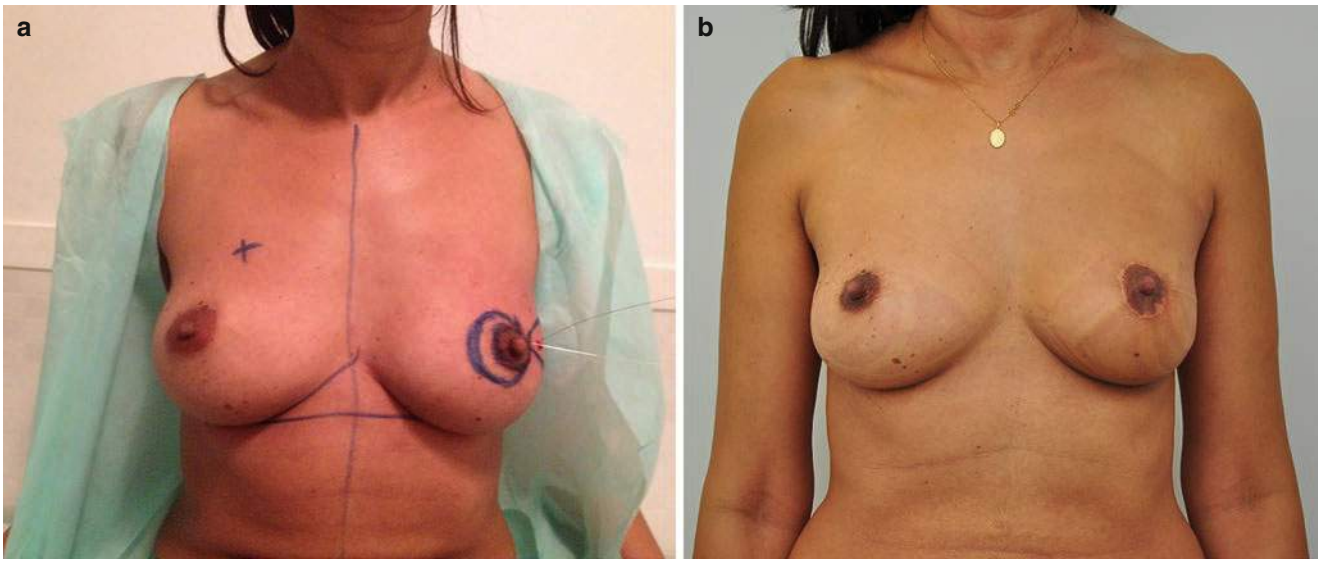


Fig. 31.6 Preoperative drawing (**a**) and result after 1 year of radiotherapy (**b**). The lumpectomy defect was closed in layers and the NAC repositioned

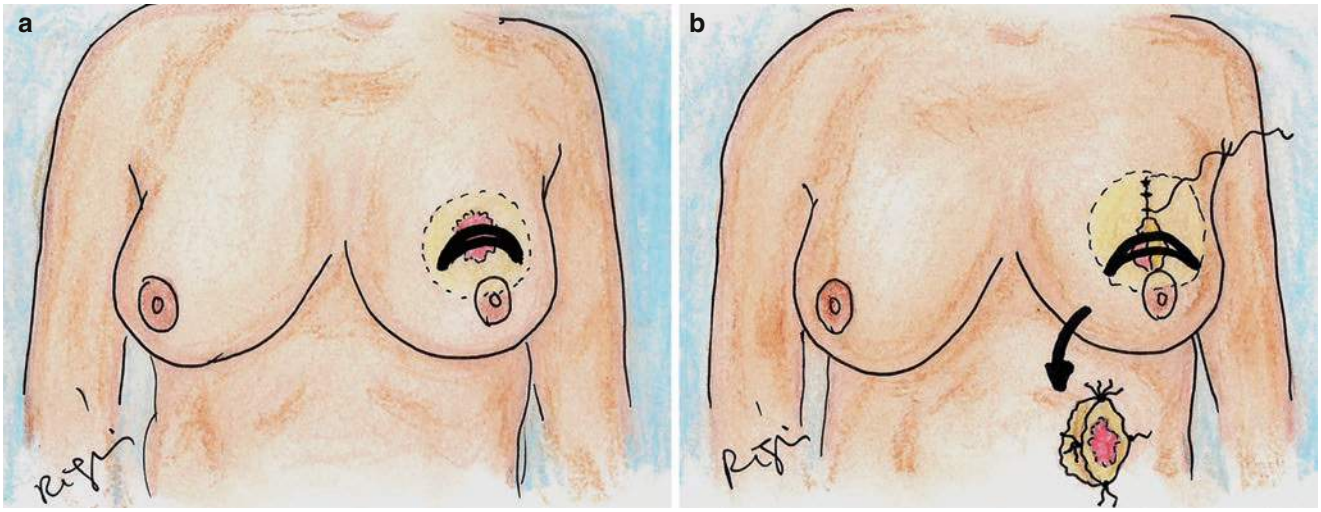


Fig. 31.7 The skin incision is made para-areolar. The area of the glandular undermining corresponds to the dotted area in yellow (**a**). The removal of the tumour is made radiated. Stitches are positioned at the margins of the specimen for the guidance of the pathologist. The defect is primarily closed, edge to edge, in a radiated manner, with simple inverted sutures, with 4-0 nylon or PDS (**b**)

This is a versatile technique, functioning in different breast shapes and varied tumour sites. Nevertheless, the best results are achievable for small tumours (up to 2 or 3 cm, according to breast size), located in the upper quadrants (Fig. 31.8). In larger tumours, it is preferable to use another type of technique that enables replacing of the excised volume or making a reduction in contralateral breast for symmetrization.

Very liposubstituted breasts offer an increased risk of fat necrosis, but it is not an absolute contraindication to this technique. The fat necrosis, mostly, tends to have little clinical significance and often not very different from oil cysts and architectural distortions that occur with some frequency in classic quadrantectomies.

31.2.3 Dermoglandular Flaps

In some cases, it is better to rearrange the glandular tissue keeping it attached to the skin envelope. A dermoglandular flap may be necessary when a large amount of skin must be removed because of tumour invasion or proximity. It could also be utile

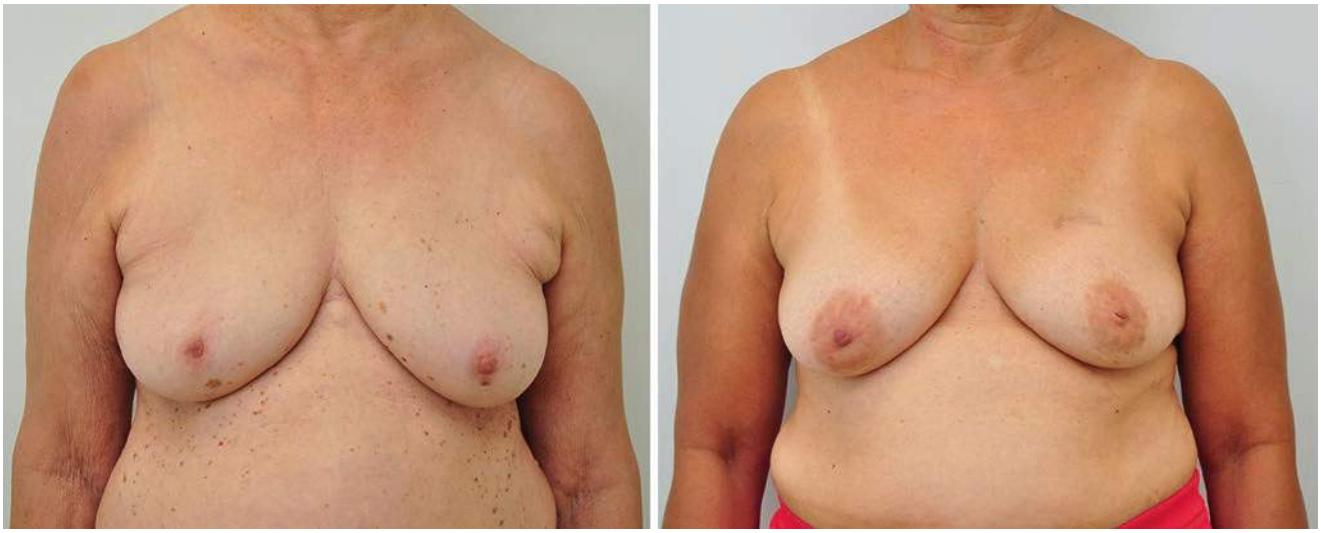


Fig. 31.8 Examples of lumpectomies by means of glandular rotation technique. In the first case, the incision was made periareolar and, in the second case, para-areolar. The glandular resection was done in a radiated form, with glandular tissue detachment and direct closure. Thus, it was possible to prevent the retraction of the nipple towards the scar

in fatty breasts because of the risk of fat necrosis, due to an extensive undermining. Some useful examples are Burow's triangles (also known as matrix), shutter technique and breast rotation [23–26]. The difficulty in reconstructing partial defects in some locations led Grisotti and Calabrese to name part of the upper quadrants as "no man's land" [27]. The oncologic mammaplasties could also be classified as a kind of dermoglandular flap, but they will be better discussed as a distinct topic.

31.2.3.1 Burow's Triangles (Matrix)

The Burow's triangles are indicated for tumours located in the medial upper quadrant or in the union of the upper quadrants (Fig. 31.9). It is possible to resect large areas, including the skin adjacent to the tumour, with little change in body contour (Figs. 31.10 and 31.11). In this technique, the tumour is resected in the form of an inverted triangle. A triangle of similar shape and width is deepithelized in the axillary fold to facilitate flap rotation and distribution of tension on the suture [28, 29]. The nipple-areolar complex should be repositioned 2 or 3 cm lower, to the other end of the radiated scar. Otherwise, the nipple will be displaced superiorly after retraction of the scar.

31.2.3.2 Shutter Technique

The shutter technique may be used for localized lesions in the upper outer quadrant when there is need to remove a considerable amount of glandular tissue and skin [23]. The name of the technique refers to the shutter rotational movement of cameras. Similarly, there is a rotation of the end of the flap, near the areola (Figs. 31.12 and 31.13). It is also a type of dermoglandular flap. The resection of the quadrant is made in a half-moon manner. The defect is closed pulling up the medial side of the breast so as to remain a dermoglandular flap between the area of quadrantectomy and areola. This flap is then deepithelized and in-built using a circular motion to add volume to the breast. The areola is repositioned inferiorly and medially. When the resection is greater than 20% of the breast volume, it is preferable to associate a contralateral breast reduction, to correct the volume difference. In smaller resection areas, this technique allows a unilateral approach (Fig. 31.14).

31.2.3.3 Breast Rotation

Another way of hiding the lumpectomy defect without a mammoplasty is resecting the tumour area and the involved skin in the form of a triangle and rotating the breast towards the defect. The area of detachment must be four times wider than the area of the defect. For the upper quadrants, it is advisable to reposition the areola backwards the radiated scar, to avoid retraction (Fig. 31.15). For the inferior quadrants, usually, there is no need of areola repositioning (Fig. 31.16).

31.2.4 Modified Oncoplastic Mammaplasties

In addition to the techniques of mammaplasty most widely known, like superior pedicle, inferior pedicle and round block, there are other types of mammoplasty, which can be useful, allowing resection of large tumours, in challenging locations. I would like to emphasize here some techniques: superomedial (and superolateral) pedicle, double independent pedicle, plug flap and geometric compensation.

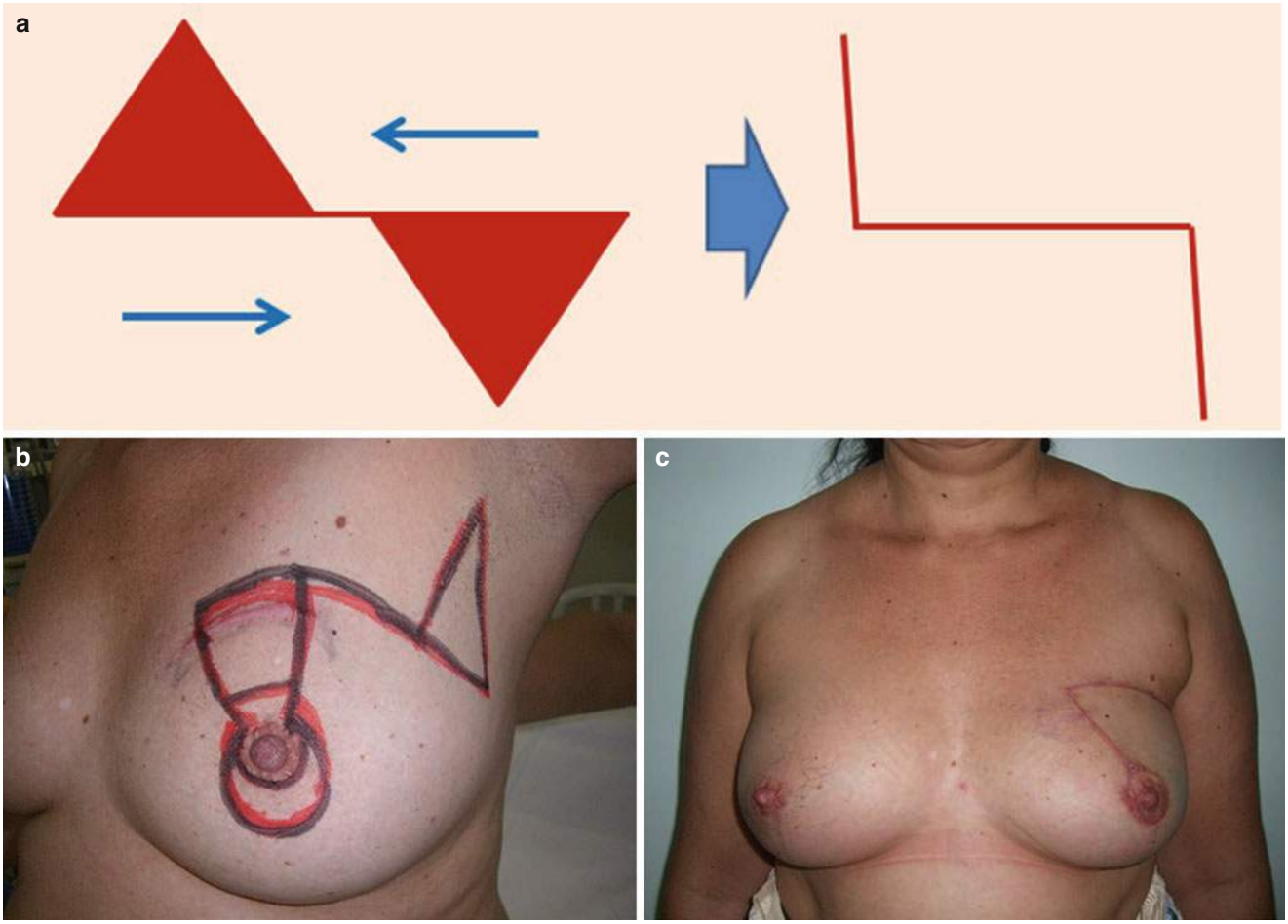


Fig. 31.9 Schematic drawings of a dermoglandular rotation technique (Burow's triangles), which allows resection of large areas of skin and glandular tissue in regions distant from the nipple with a good breast symmetry (**a**). Postoperative result, preserving the breast shape and the position of the nipple, even after resection of a tumour measuring clinically 5 cm, with free margins (**b**)

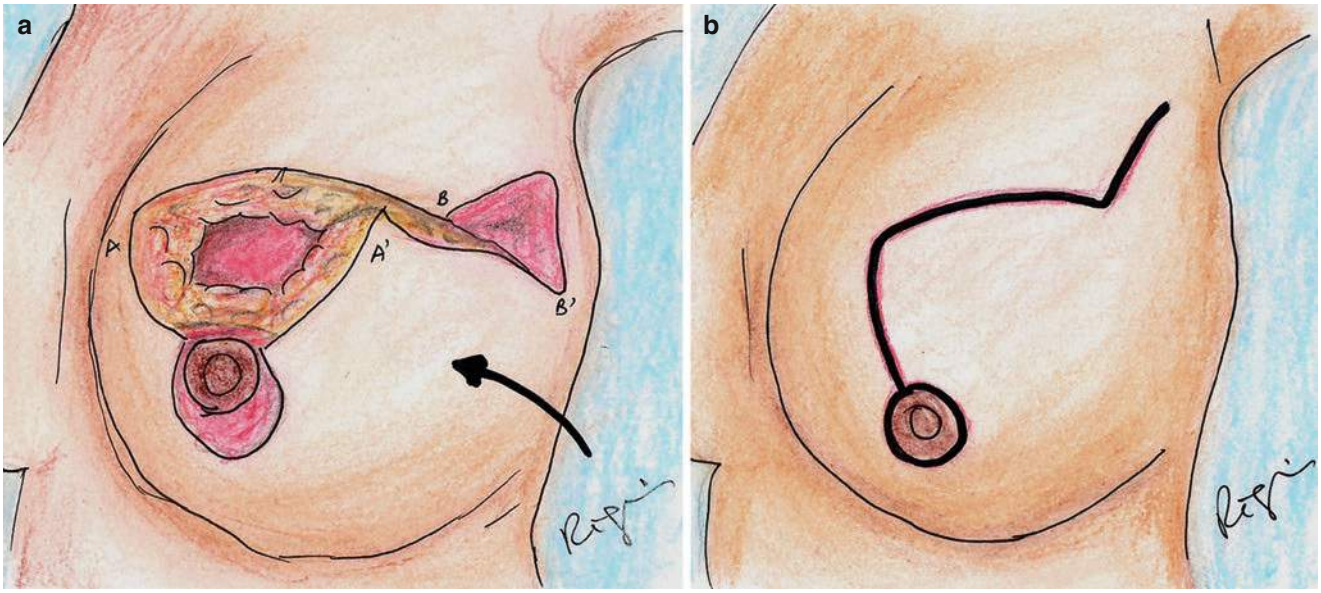


Fig. 31.10 Lumpectomy in form of a triangle or inverted trapezium in the medial upper quadrant of the breast, perpendicularly to the skin. The triangle of the axilla and the periareolar skin were deepithelized and then approximated (**a**). Final appearance of the scar after the closure of the points *A*-*A′* and *B*-*B′* (**b**)

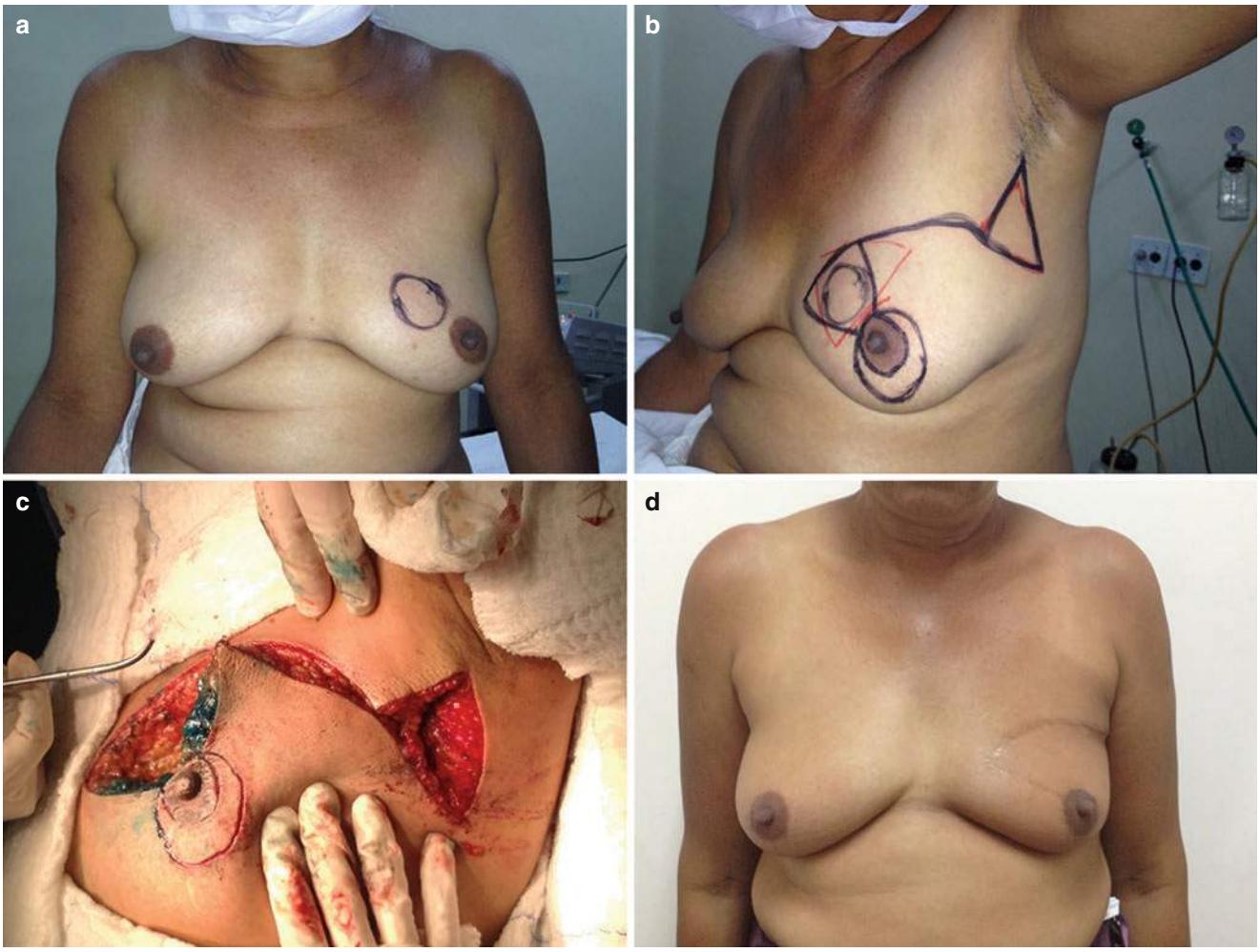


Fig. 31.11 Example of the usage of Burow's triangles for a 3.5-cm tumour in a small breast without ptosis. Preoperative view (**a**). Preoperative drawings (**b**). Intraoperative oblique view, showing the area of lumpectomy and the deepithelized triangle in axilla (**c**). Postoperative view 1 year after radiotherapy (**d**)

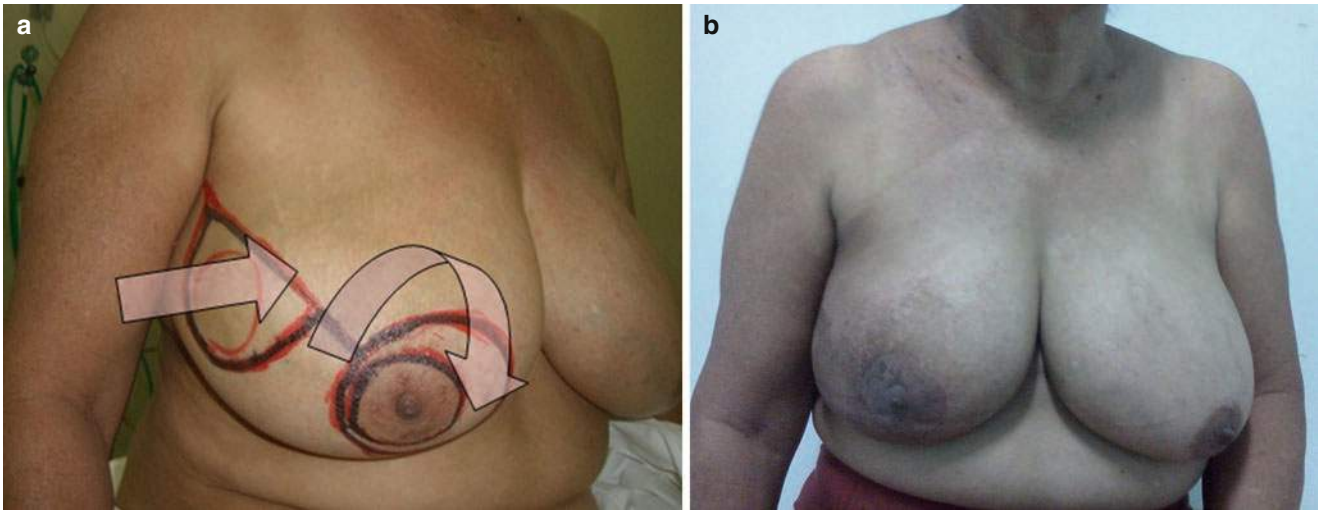


Fig. 31.12 Example of the shutter technique, indicated for tumours in the upper outer quadrants. The arrow indicates the side towards the skin closure. The medial arrow indicates how the area, which will be later deepithelized, should be rotated and in-built to increase breast volume (**a**). In this case, the tumour measured 5 cm, clinically. Even so, the patient refused operating the contralateral breast (**b**)

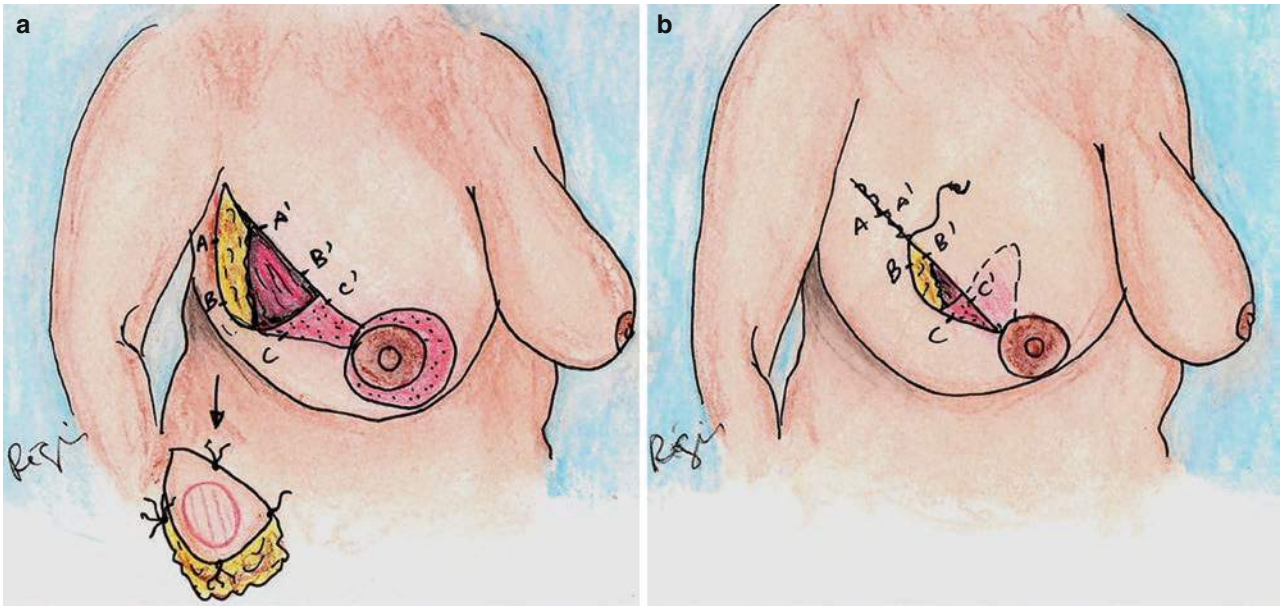


Fig. 31.13 Shutter technique—intraoperative view. The quadrant was excised in a half-moon shape, perpendicularly to the skin and to the pectoralis major. The dotted red area was deepithelized (**a**). The points *A-A′*, *B-B′* and *C-C′* are merged. The deepithelized tip between the quadrantectomy area and areola is in-built, to add volume to the new breast cone. The lateral fat of the chest is pulled by the skin closure and helps to restore part of the excised volume

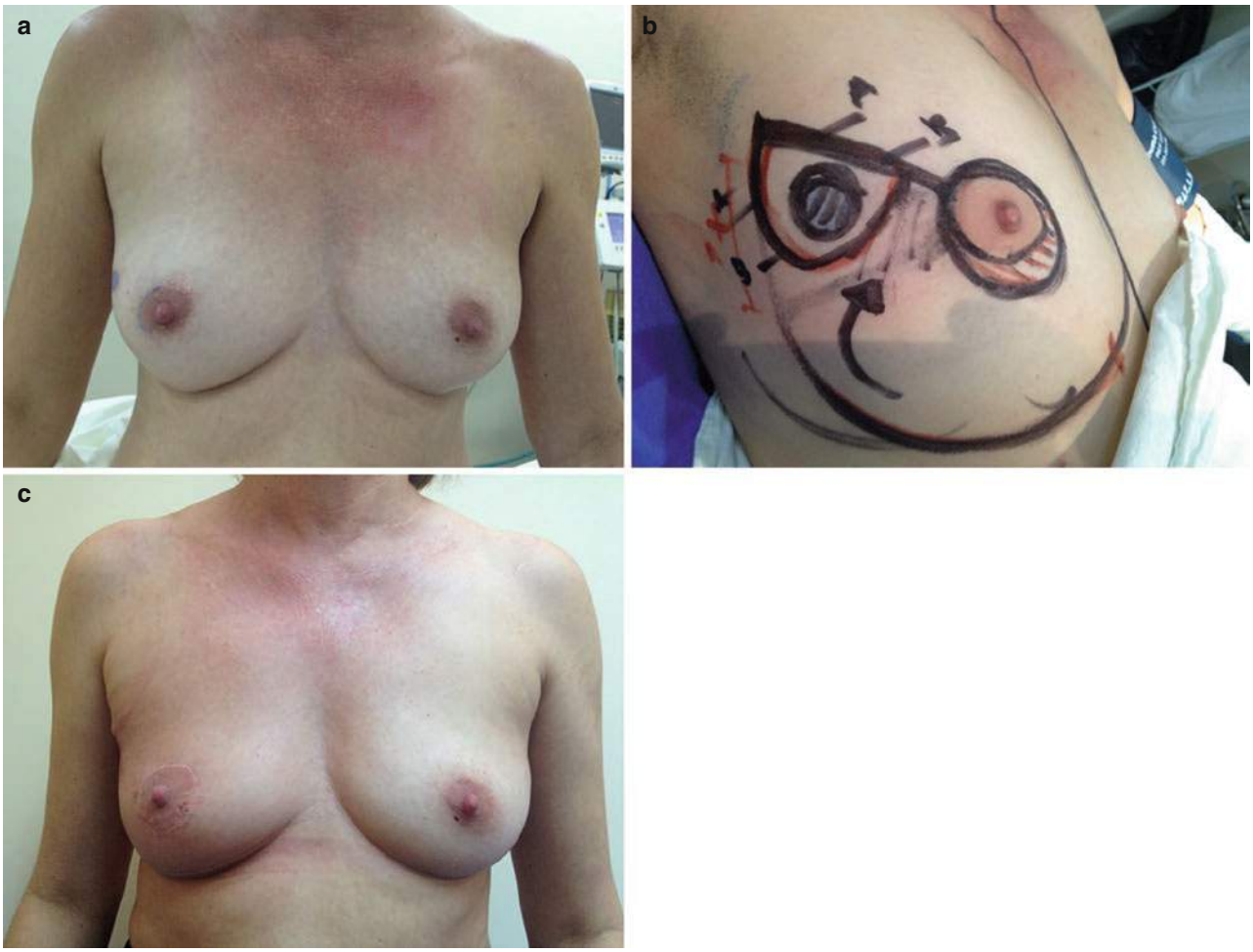


Fig. 31.14 Example of the shutter technique for a 2-cm tumour, close to the skin, in a small breast without ptosis. Preoperative view (**a**). Drawings (**b**). Result 6 months after radiotherapy (**c**)

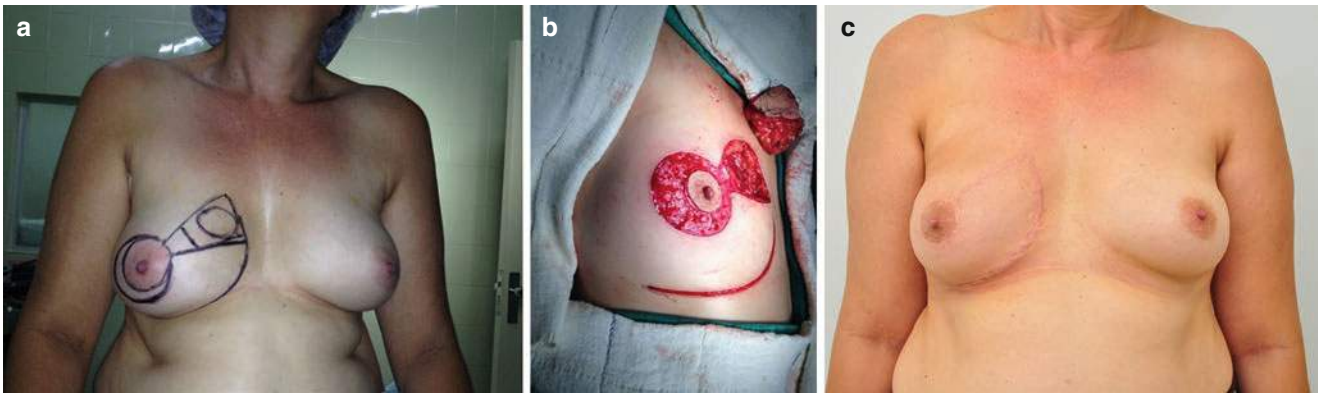


Fig. 31.15 Example of a dermoglandular rotation flap for the correction of the defect of a quadrantectomy in the medial upper quadrant of the right breast. The areola is repositioned in the opposite direction of the radial component of the scar, due to the expected scar retraction. In this case, exceptionally, it was necessary to perform a round block periareolar suture to reduce tension and to prevent the widening of both the areola and the scar. Preoperative view (**a**). Intraoperative view (**b**). Result after 1 year of radiotherapy (**c**)

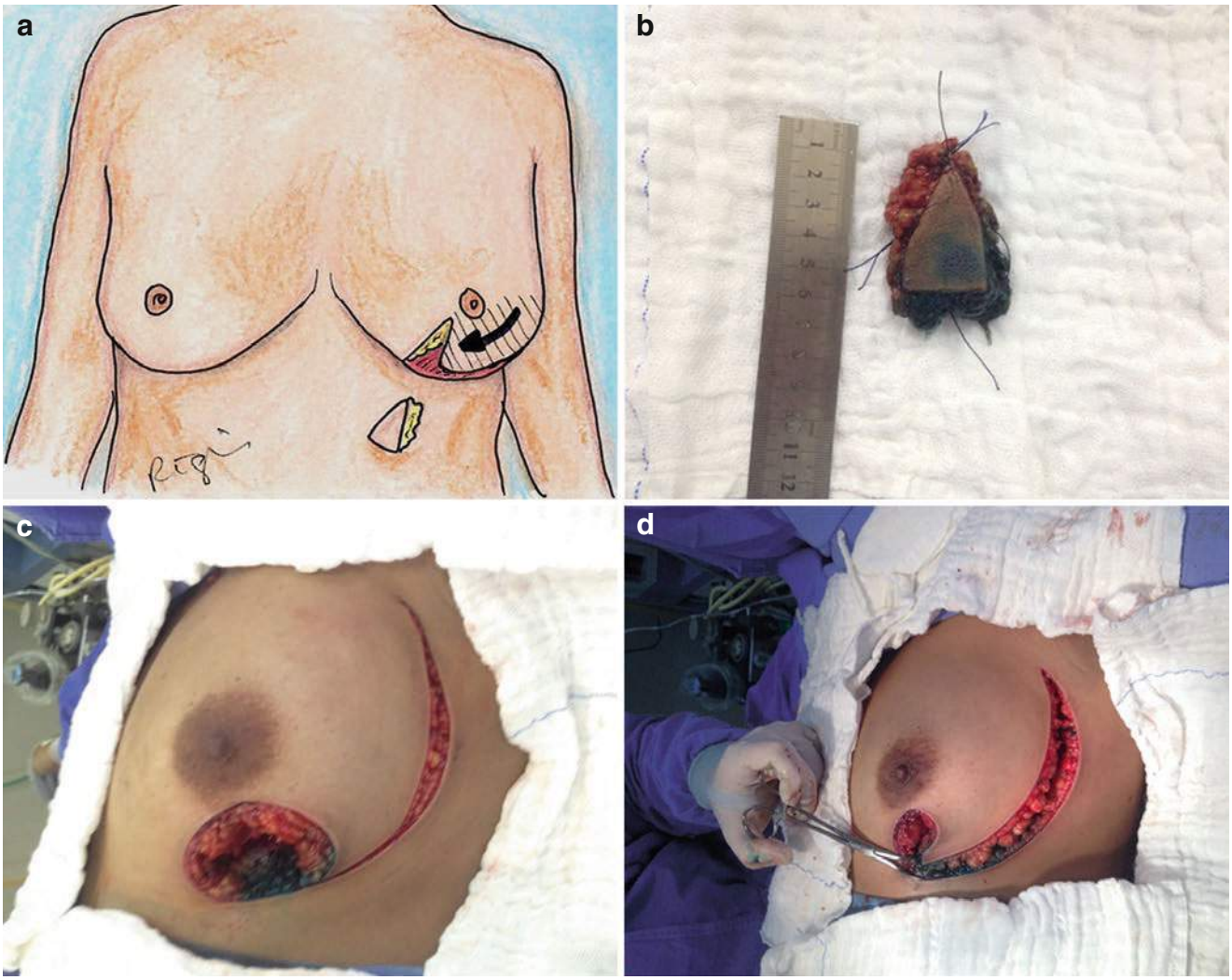


Fig. 31.16 Schematic drawing of a rotation dermoglandular flap (**a**). A triangular resection is performed, in form of a slice of pizza (**b**), and an area four times wider on the inframammary fold is detached and rotated to cover the defect (**c**, **d**). Postoperative outcome of the rotation technique, showing a good symmetry without the need for contralateral surgery (**e**, **f**)

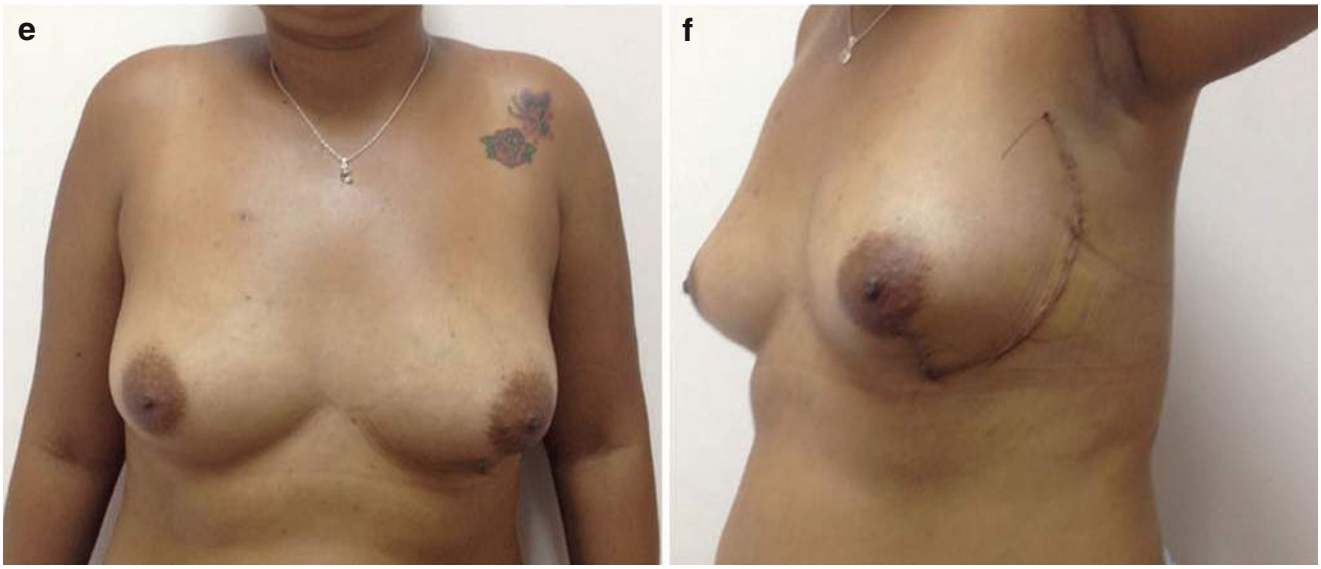


Fig. 31.16 (continued)

31.2.4.1 Superomedial (and Superolateral) Pedicle Mammaplasty

The superior pedicle may allow good access to resections of tumours in the lower quadrants, while the inferior pedicle allows good access to the upper quadrants. However, there are some limitations: the superior pedicle brings some difficulty in climbing the areola to great distances in cases of marked ptosis. The inferior pedicle allows raising up the areola enough but does not allow tumour resections in some parts of the lower quadrants. Furthermore, some surgeons avoid using the inferior pedicle, due to poorer aesthetic results, generating sometimes less-projected and less-rounded breasts and more recurrence of the ptosis in the long run, when compared to the superior pedicle.

In such cases, the superomedial or superolateral pedicles may be preferred (Figs. 31.17 and 31.18) [30, 31]. They may allow resections in the upper and in the lower quadrants, and they may allow raising up the nipple-areola complex at great distances. The superomedial pedicle gives an aesthetic result similar to the superior pedicle. The superolateral pedicle can bring good results but can bring dissatisfaction occasionally due to little filling in the medial quadrants and greater lateral bulging. There is little scientific proof, but it is suggested that superomedial pedicle is more vascularized, while superolateral pedicle better preserves the nipple sensitivity [32]. It is important to notice that there may be impairment of vascularization of the areola in superolateral pedicle, in case of axillary dissection, due to the ligation of the lateral thoracic vessels.

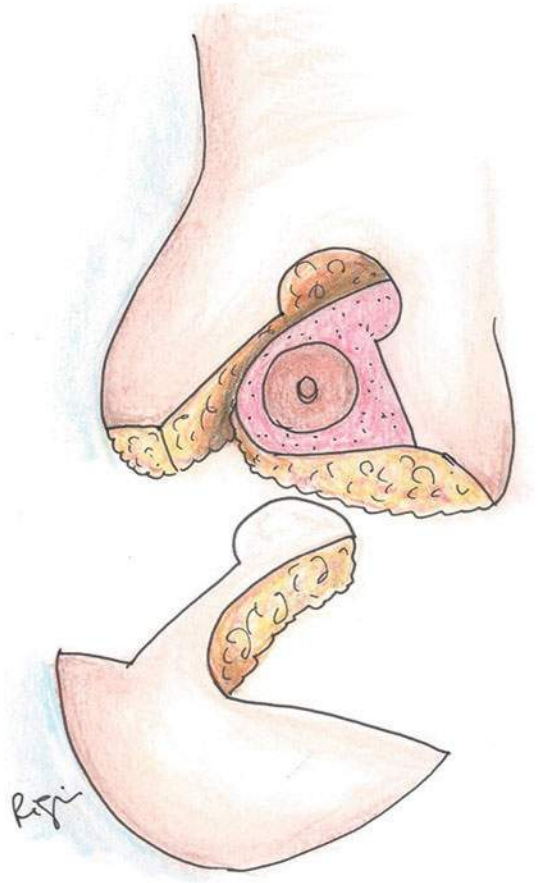


Fig. 31.17 Glandular resection in case of superomedial pedicle. The markings of a superolateral pedicle are similar, like in a mirror

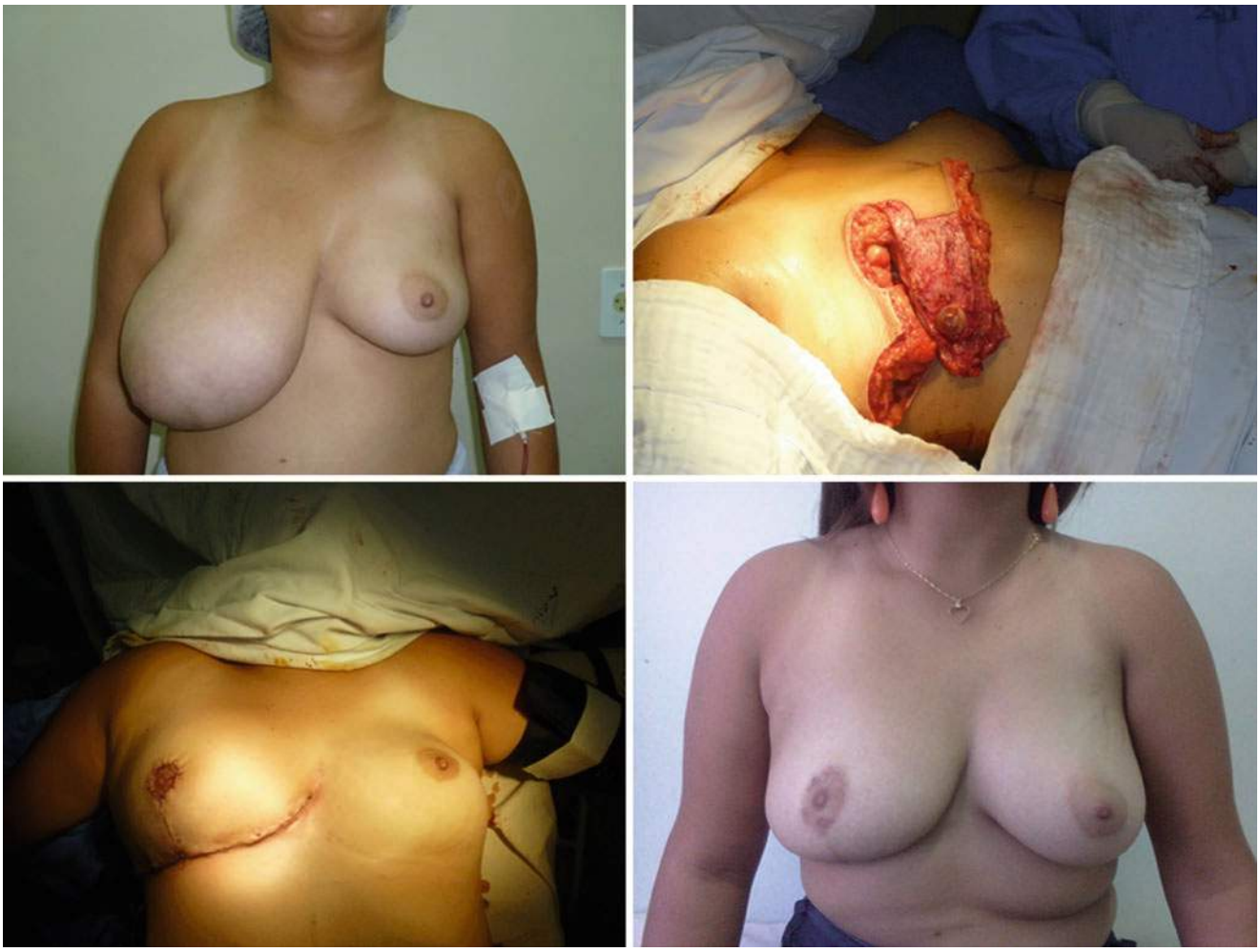


Fig. 31.18 When the nipple-areolar complex (NAC) needs to be raised up more than 9 or 10 cm to the A point, the superomedial and the superolateral pedicles make the repositioning of the NAC easier and safer

Figure 31.19 shows a case of a tumour in the lower quadrants, in a very ptotic breast. It would not be advisable to perform a breast lift with superior pedicle because the nipple would not reach the required position. It would also not possible to perform a lower pedicle because tumour resection would compromise the vascularity of the pedicle. A Torek, or NAC grafting, would be possible but would cause loss of sensitivity of the areola, besides the risk of total or partial loss of the graft and hypopigmentation. In this case, the superomedial pedicle has provided adequate tumour resection, good repositioning of the NAC and good aesthetic result.

31.2.4.2 Double Independent Pedicle Mammaplasty [33]

Although mammoplasty with inferior pedicle is able to correct many defects of quadrantectomies in the upper quadrants, the correction is more difficult if the area of resection is too high or too big. In such cases, there would be a risk of depressions and nipple displacement. If there is no need for skin resection over the lesion, we developed a technique called "double independent pedicle". The marking of the nipple position and skin resection is made by means of the Wise-pattern technique, like an inverted "T". In the double independent pedicle technique, the areola is kept vascularized by a superomedial or superolateral pedicle, thinner than the usual, with less than 1 cm thick. At the same time, we make an extensive central and inferior pedicle, independent of the areola, which is able to fill large glandular defects distant from the areola (Fig. 31.20). This modified independent inferior pedicle is nourished by the inferior and posterior perforating intercostal vascular branches.

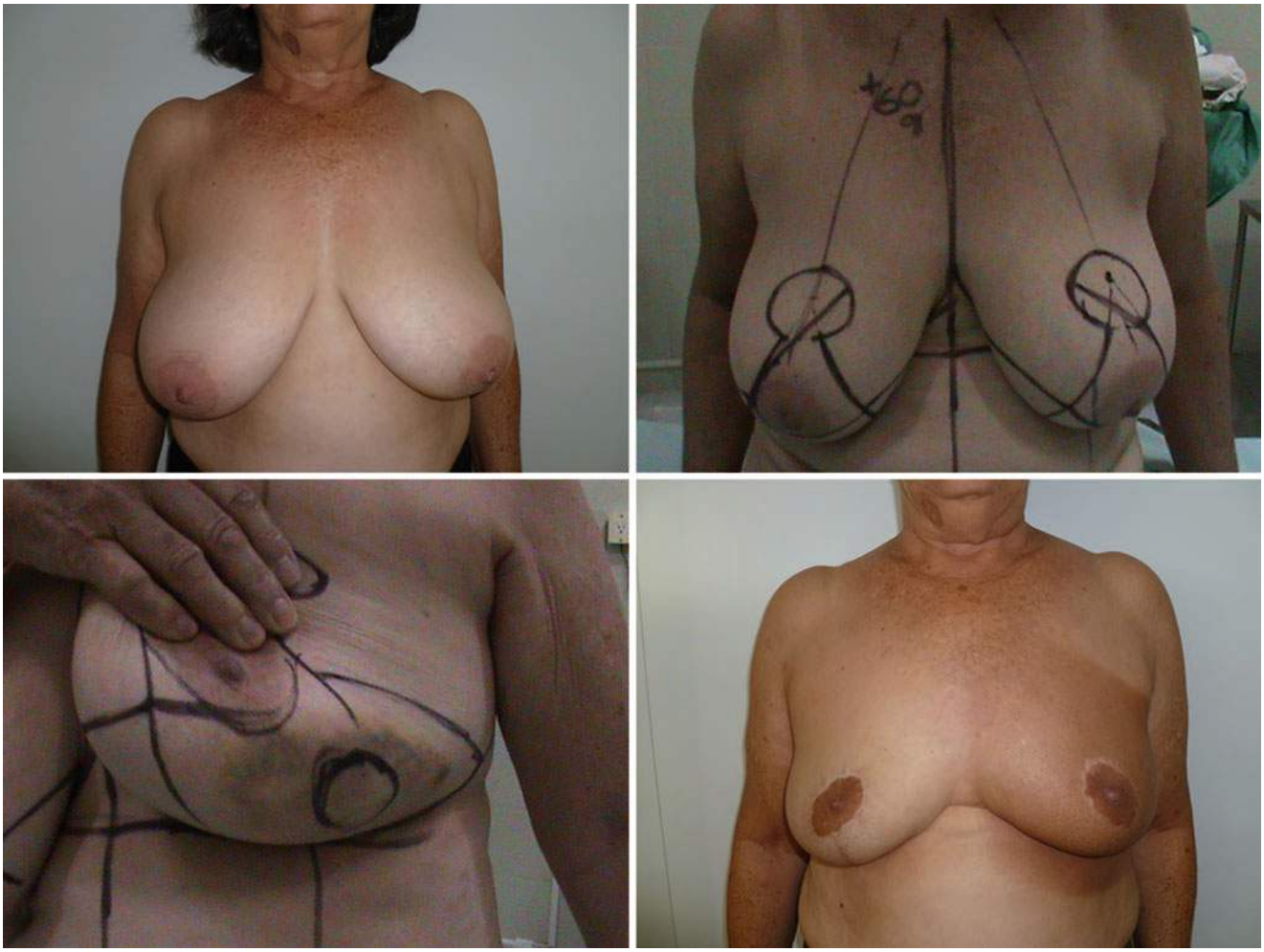


Fig. 31.19 Tumour in the inferior quadrants in a patient with severe ptosis. The superomedial pedicle facilitated both the tumour resection and the NAC repositioning

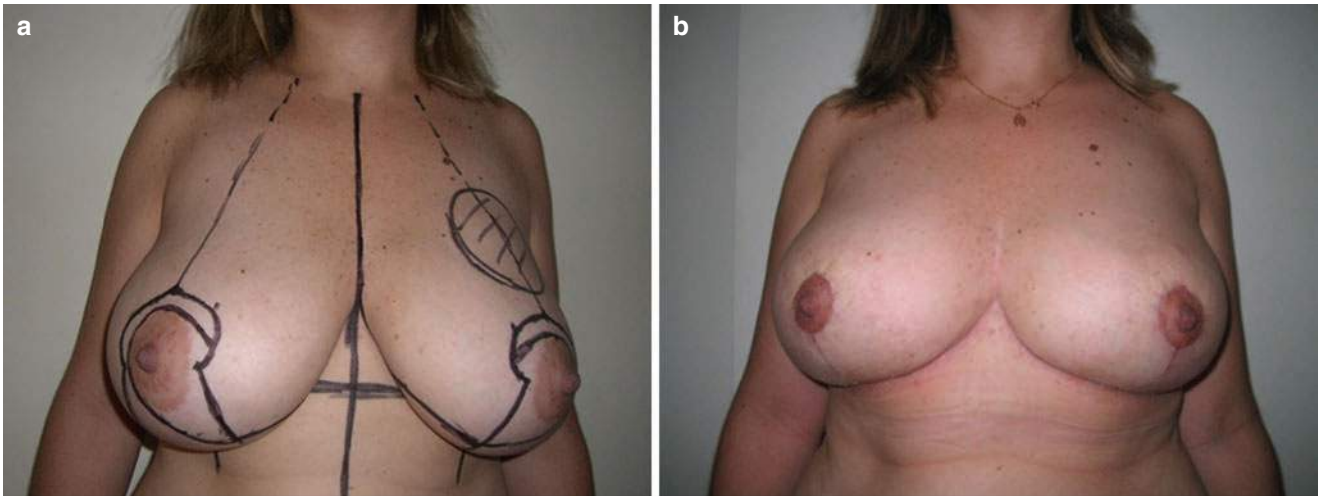


Fig. 31.20 "Double independent pedicle" mammoplasty used for partial reconstruction after the resection of an 8-cm malign phyllodes tumour in the upper quadrants. The defect was too big and too high to a classic inferior pedicle. Preoperative drawings (**a**). Results after 6 months (**b**). Intraoperative view. Good access to the superior quadrants after tumour resection (**c**). The extended inferior-central pedicle was able to fill the defect. The areola had enough mobility and vascularization to be well repositioned (**d**)

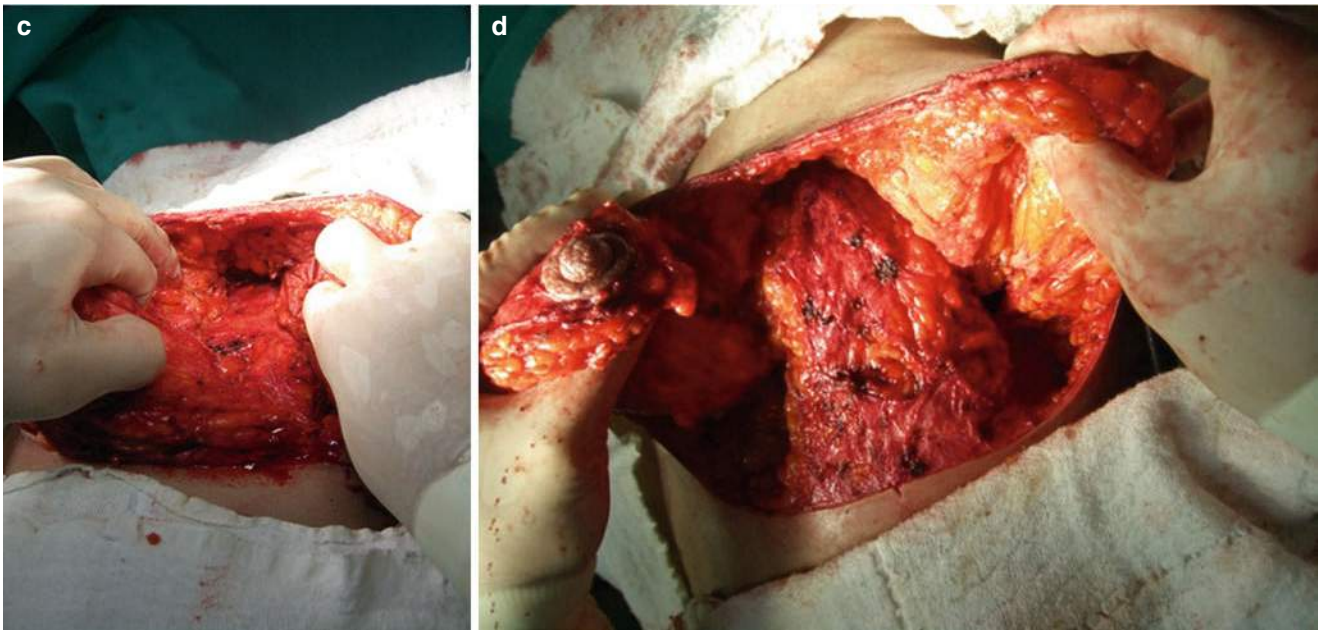


Fig. 31.20 (continued)

31.2.4.3 Plug Flap (Breast Island Flap) [34]

Plug flap is a technique described by a Brazilian plastic surgeon, in which the involved skin near the tumour, in locations out of the markings of mammaplasty, may be replaced by a skin flap of the inferior pedicle. It is particularly useful for central tumours and for the union of the upper quadrants (Figs. 31.21 and 31.22). For central tumours, it resembles the Grisotti technique, but plug flap allows a better correction of ptosis [27]. Depending on the location of the tumour, the plug flap may offer some risk of necrosis, if it leaves parallel scars on the breast, resulting in areas of low vascular perfusion (Fig. 31.23).

31.2.4.4 Geometric Compensation [35]

We have developed and published a technique that allows the resection of large areas of skin in locations unusual to mammoplasties, like in the case of plug flap, named "geometric compensation". We believe that the geometric compensation presents some advantages in certain situations. Besides a good approach to tumours in the upper quadrants, the technique may also be used for tumours located in the pillars of mammoplasty, with good security and less scarring. In this technique, the skin from the lower quadrants, which is usually resected like a triangle in conventional mammoplasties, is otherwise preserved. Their measures are transferred in a geometric way, i.e. in the same height and width, to the area of the tumour that needs to be removed. It is a very eclectic technique, allowing tumour resection in any quadrant (Fig. 31.24). Thus, despite the asymmetric aspect of the scar, the same amount of skin and glandular tissue is resected in both breasts, providing a very acceptable symmetry (Fig. 31.25). The versatility of this technique may allow very bulky tumour resections, allowing free margins and probably a good local control, since associated to radiation therapy (Fig. 31.26). Similarly to the triangle of the lower quadrants that may be transferred to the defect of lumpectomy, the defect area may be transferred to the lower quadrants, resulting in less visible scars, in some cases (Fig. 31.27).

31.3 Volume Replacement Techniques

The volume replacement techniques are commonly used for patients who do not want or who may not reduce the breasts, especially if there is no ptosis, which hinders the realization of a reduction mammaplasty. These techniques are also useful in situations where large amounts of skin must be removed, in atypical locations. It sometimes allows the removal of a large part of the breast due to locally advanced tumours, after a hemi-mastectomy. Some useful examples are thoracoepigastric flaps, thoracolateral flaps, bilobed flaps, immediate lipofilling and myocutaneous flaps. In the last decade it is becoming popular some variations of the thoracoepigastric, thoracolateral, and latissimus dorsi flaps, based on the artery perfurators, using a duplexscan. Some options are the LICAP, MICAP and AICAP (lateral, medial and anterior intercostal artery perforators) flaps, the LTAP (lateral thoracic artery perforator) and the TAP (thoracodorsal artery perforator). Personally, I prefer the former conventional techniques because I find them easier and equally reliable.

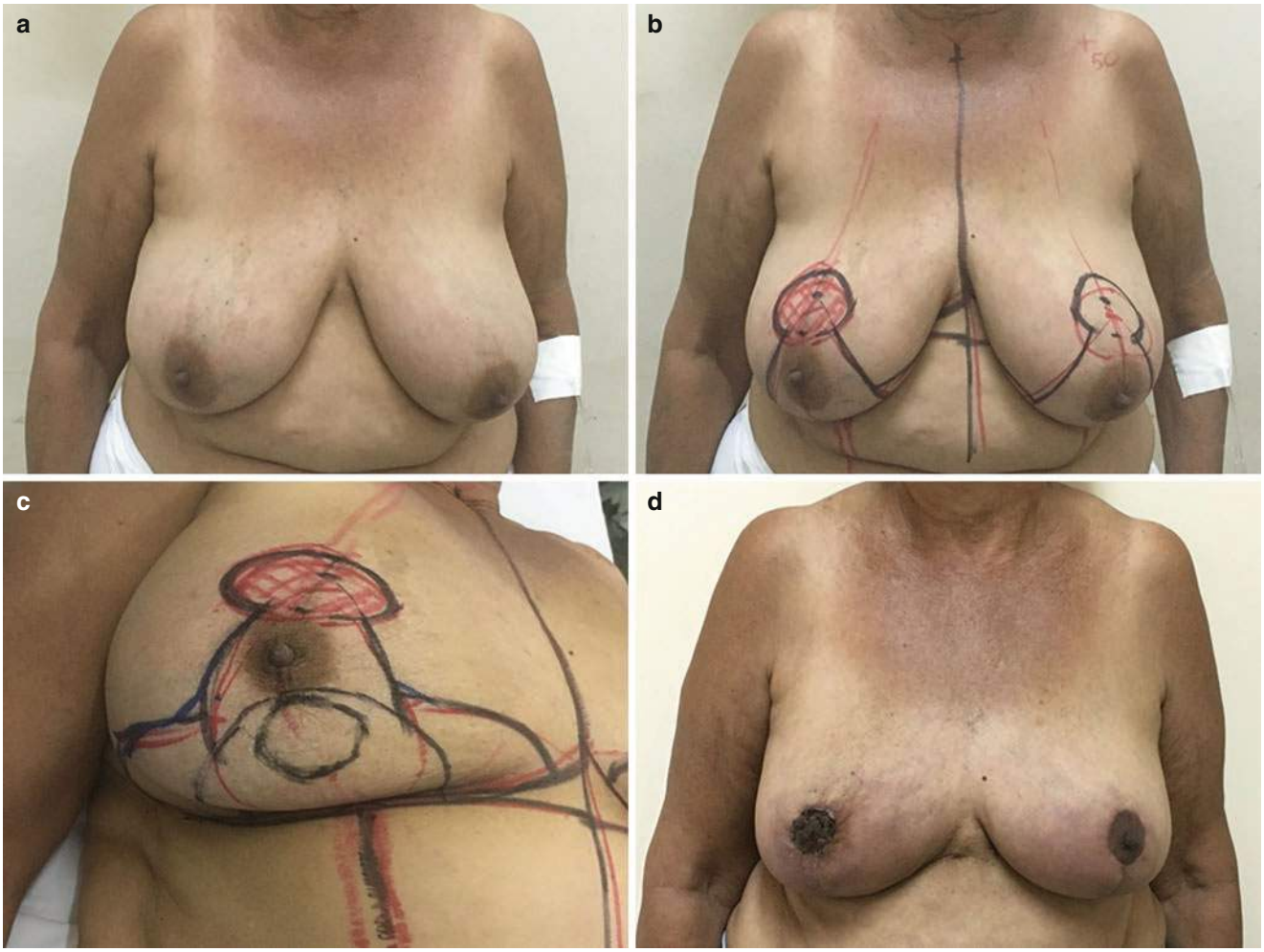


Fig. 31.21 Tumour close to the skin in the union of the upper quadrants, involving the nipple, in a women with a hypertrophic ptotic breast (**a**, **b**). The nipple and the skin over the tumour were substituted with a plug flap coming from the inferior pedicle (**c**). In this case, part of the contralateral nipple and areola was grafted over the plug flap to immediately reconstruct the NAC (**d**)

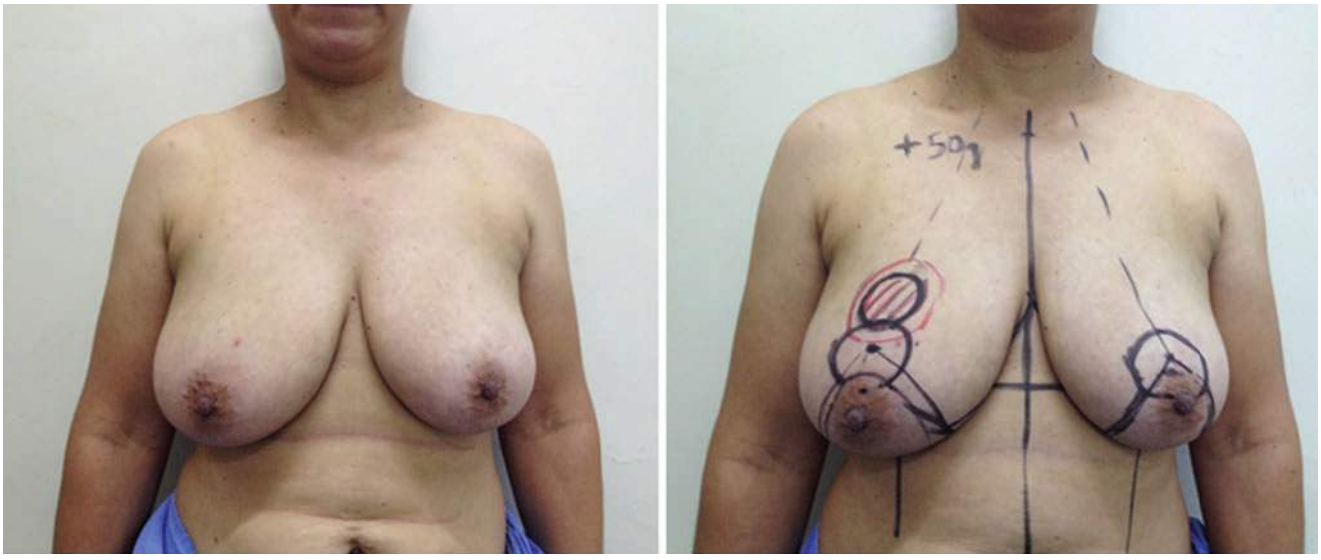


Fig. 31.22 Example of a plug flap coming from the skin above the NAC, attached to an inferior pedicle, for reconstructing the defect of a resection of a tumour in the medial upper quadrant

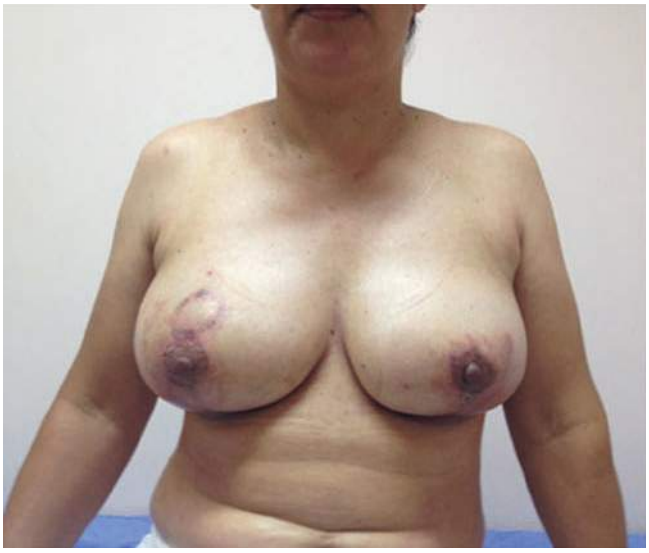


Fig. 31.22 (continued)

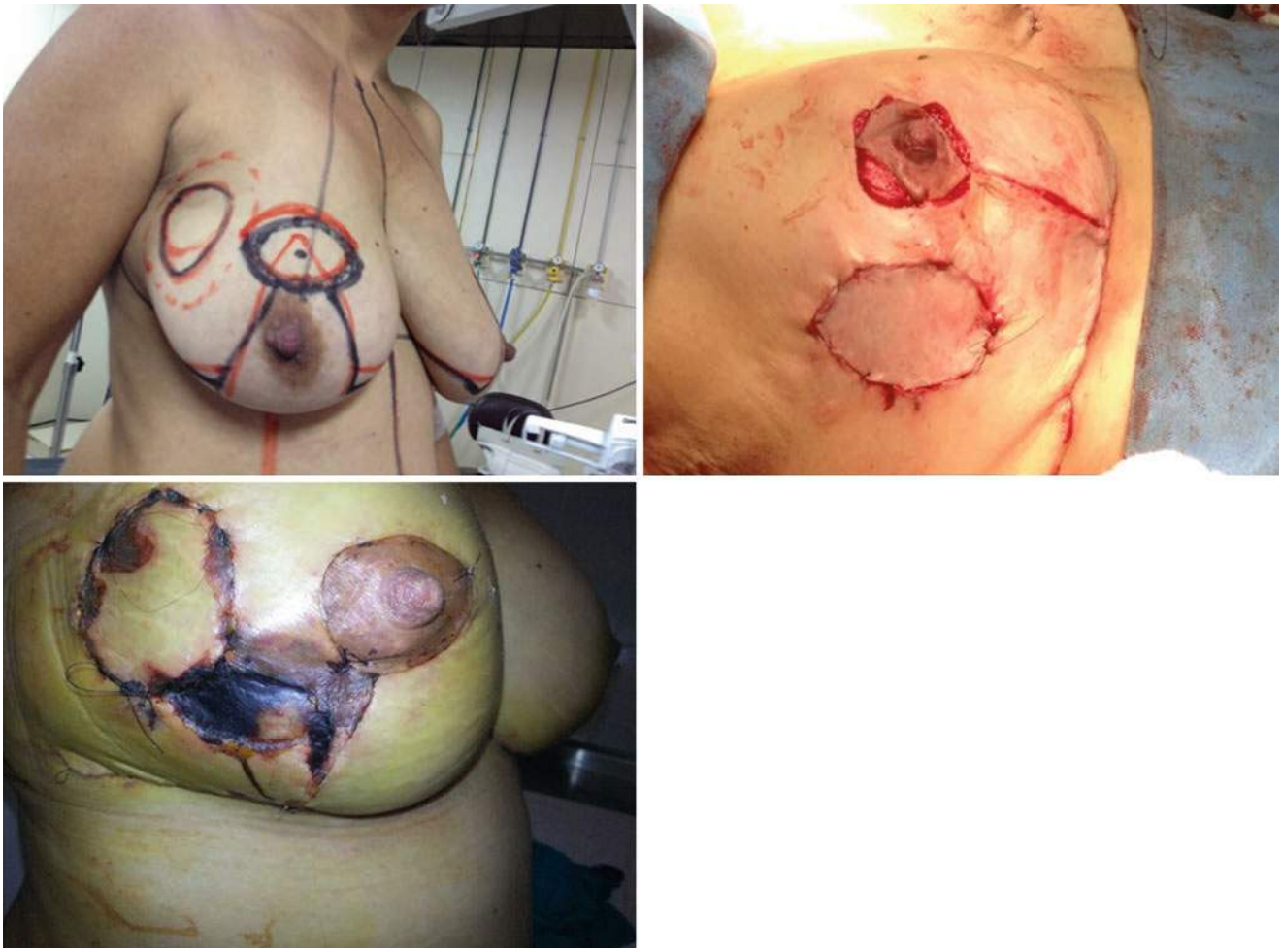


Fig. 31.23 The positioning of the plug flap must be carefully planned, because parallel scars can generate areas of poor vascularization, more prone to necrosis, as in this example

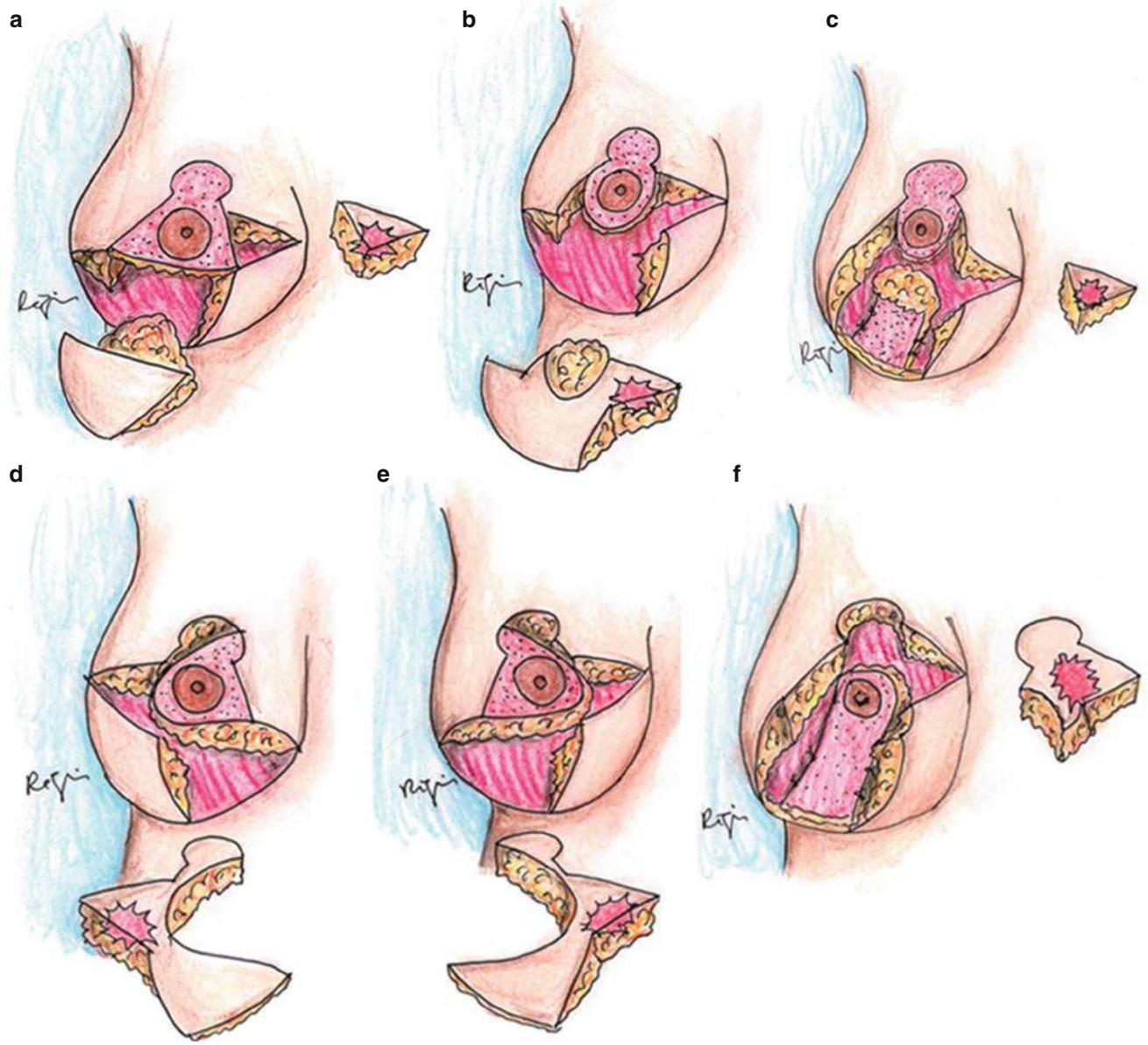


Fig. 31.24 Examples of possible asymmetric skin resections, following the geometric compensation mammaplasty. Figures (**a**) and (**b**) show superior pedicles, which are preferred when the distance between the point A and the nipple is less than 10 cm. Figure (**c**) shows a superior pedicle for the areola and a deepithelized inferior pedicle, to preserve breast volume and give more projection in the case of small breasts. Figures (**d**), (**e**) and (**f**), respectively, show the superomedial, the superolateral and the inferior pedicles, designed according to the best source of vascularization of the areola and depending on the location and size of the tumour

31.3.1 Thoracoepigastric Flap

The thoracoepigastric flap is an interesting option for the correction of the lower quadrants, ideal for patients with little ptosis in small breasts, if the patient wishes to keep the breast volume [6, 36]. It is a kind of transposition flap. Figure 31.28 shows the skin markings for planning a thoracoepigastric flap. The demarcated area must have the same dimensions of the defect to be corrected. The flap base must have at least two thirds of its length, to a greater vascular safety. The tip of the flap is deepithelized to increase the volume. The flap is rotated to cover the defect of quadrantectomy. Part of the upper abdomen should be elevated and sutured to the former inframammary fold.

Figure 31.29 shows the results after a few months, after the rotation of the thoracoepigastric flap, preserving the volume, the breast contour and the position of the nipple. This flap can cover any defects in the region of the lower quadrants, even in some cases of large deficiencies in small breasts (Fig. 31.30). If the defect is in the medial lower quadrant, instead, it is possible to reverse the design, like in a mirror, with similar results. If it is not necessary to remove the tumour next to the skin, the flap can be completely deepithelized and used exclusively to restore volume.

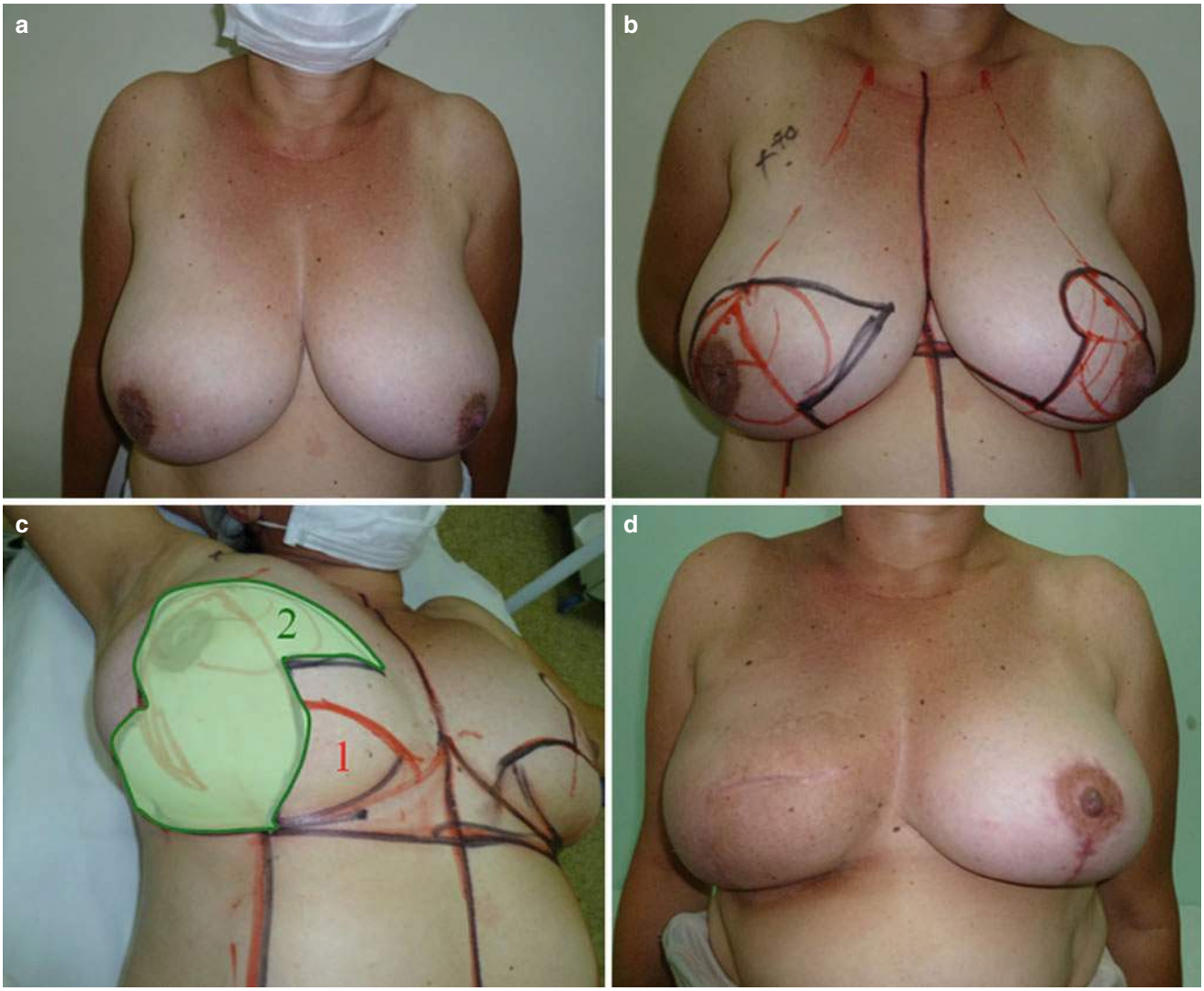


Fig. 31.25 In this case, it was possible to resect a residual 6.5-cm tumour, after neoadjuvant chemotherapy, involving the nipple and the medial upper quadrant of the right breast. Figure (**c**) highlights the area of resection, in green. The area of geometric translocation, named number 1, in red, is transferred to the area number 2, in green. Figure (**d**) shows good symmetry 6 months after radiotherapy

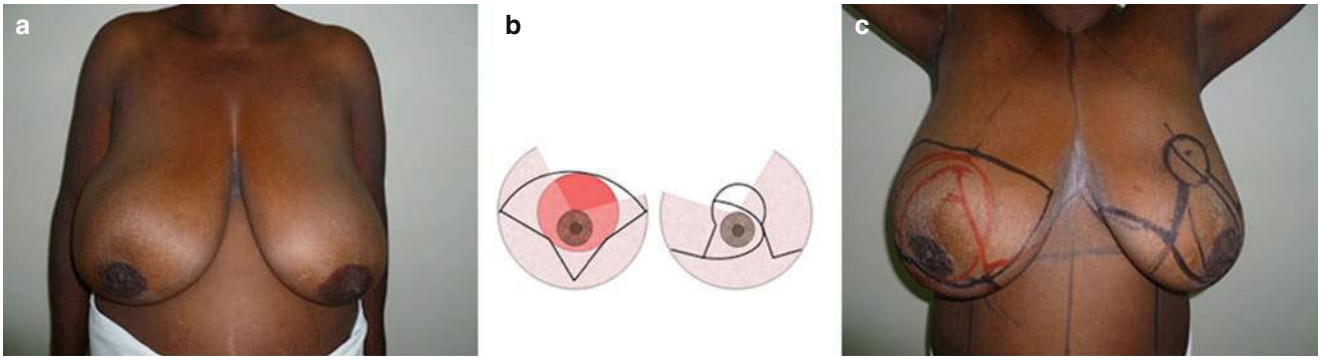


Fig. 31.26 Extreme case of tumour resection, with free margins, of a lesion measuring 14 cm, occupying more than half of the right breast, which progressed during neoadjuvant chemotherapy. It exemplifies the technical capacity of "geometric compensation" to correct large extirpation of skin and glandular tissue, while maintaining a satisfactory symmetry. In this technique, the areas of skin and breast tissue of the lower quadrants, usually resected in mammoplasties, were kept intact, while its geometric measurements were mathematically transferred to the tumour region. The final appearance of the scar in this case was a "T"

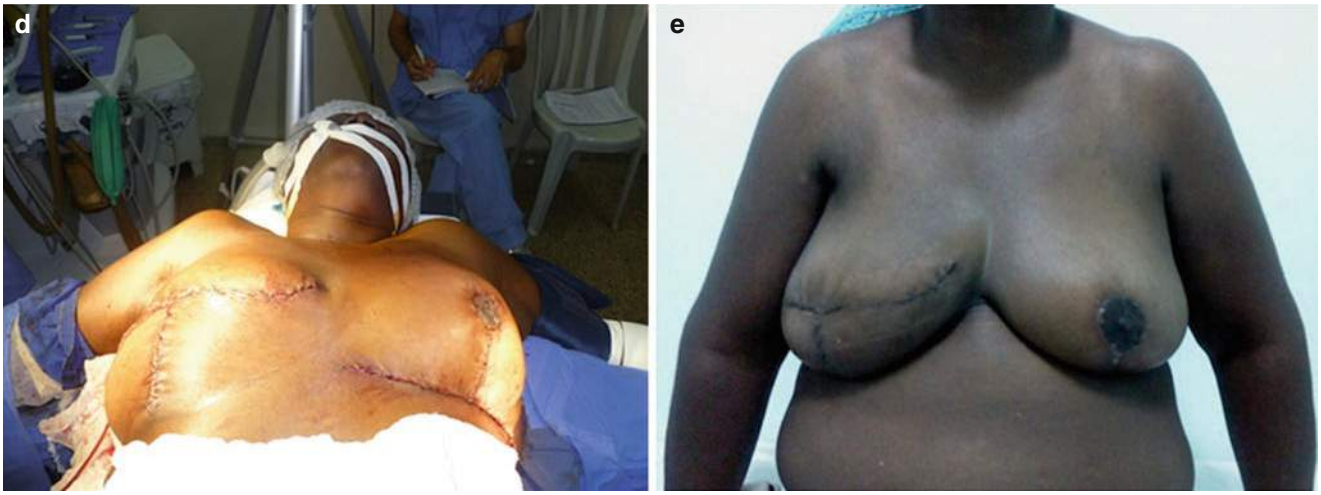


Fig. 31.26 (continued)

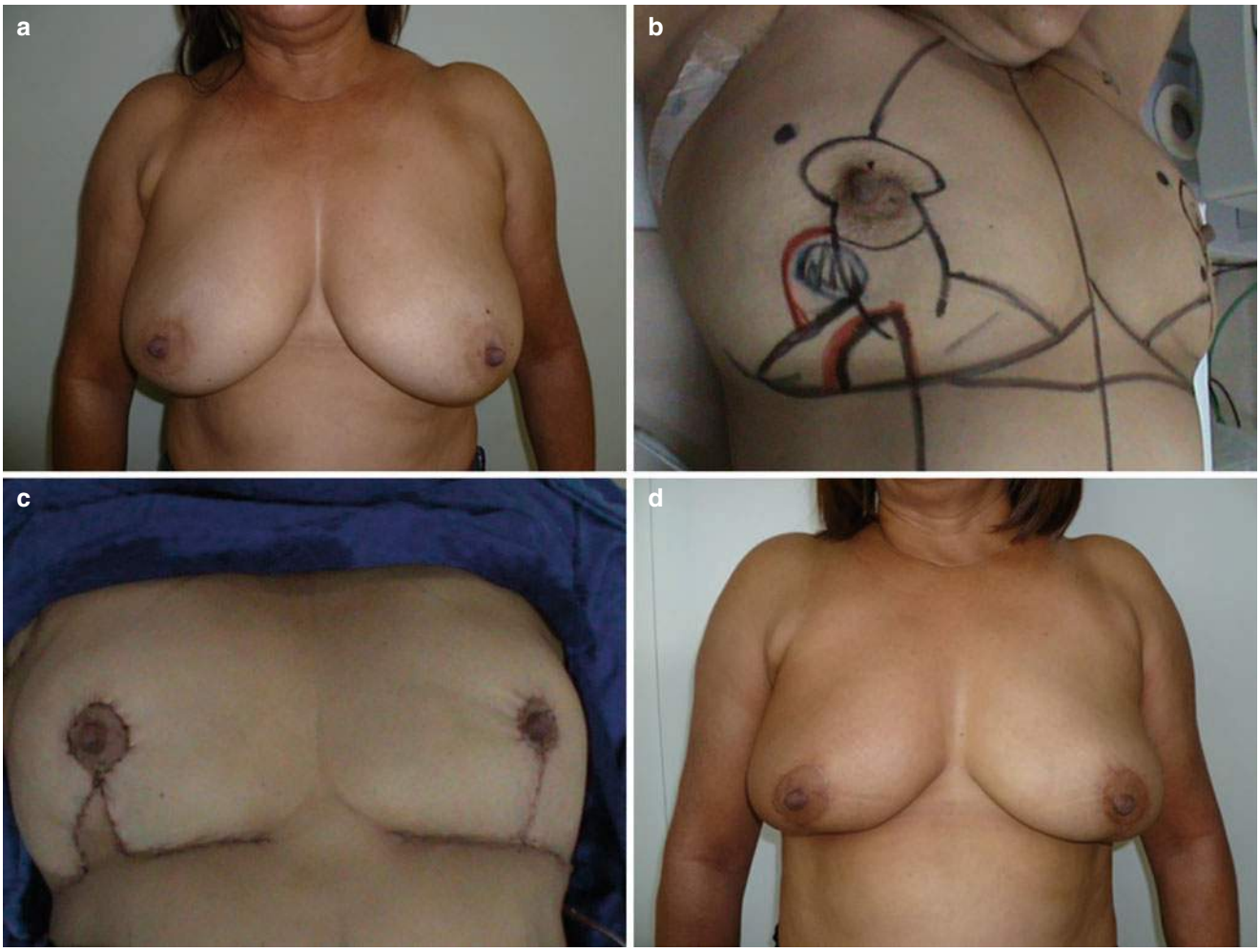


Fig. 31.27 A 53-year-old woman with invasive ductal carcinoma, grade 2, luminal A, close to the skin, affecting the lateral pillar of the mammoplasty (**a**). Instead of transferring the entire lower triangle of the mammoplasty to the defect area, it was decided to transfer the defect area to the lower quadrants, resulting in a less apparent scar (**b**). The principle of geometric compensation persisted: the same amount of skin is preserved in both breasts, even if the scars are asymmetric (**c**). Figure (**d**) shows the results after 6 months of radiotherapy

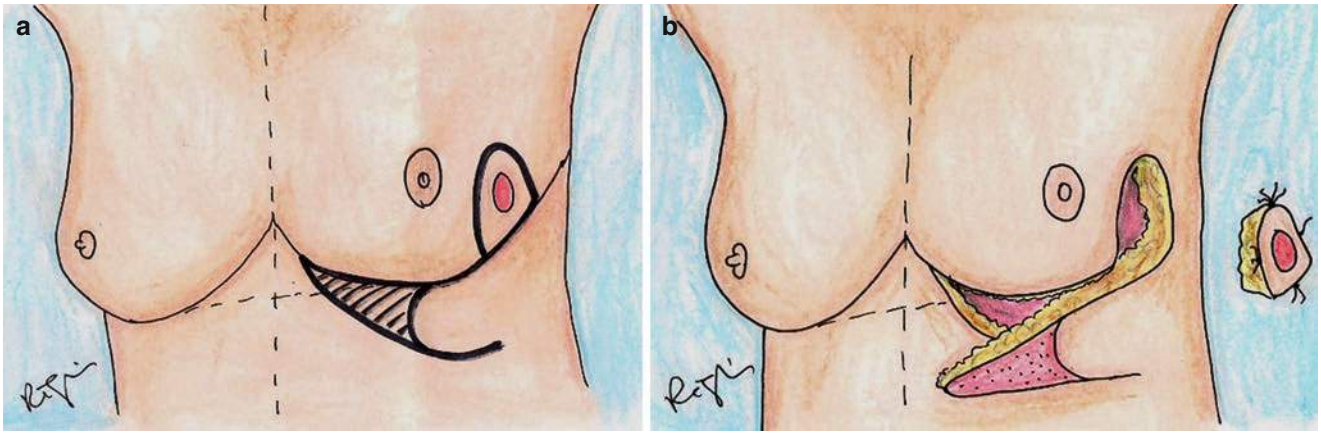


Fig. 31.28 (**a**) Skin demarcation of the thoracoepigastric flap. The hatched tip will be denuded. (**b**) Defect of quadrantectomy and the surgical specimen with identified margins. In this figure, the flap is beginning to be prepared and mobilized

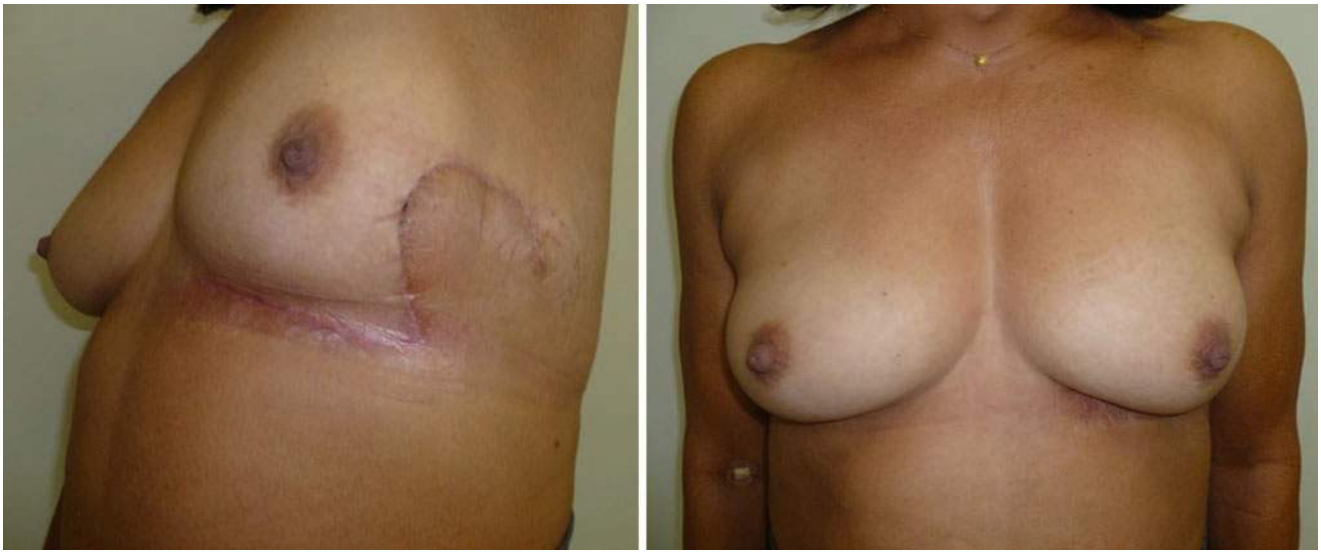


Fig. 31.29 Postoperative result of a quadrantectomy in the lower quadrant of the left breast. The defect was reconstructed with the rotation of a thoracoepigastric flap

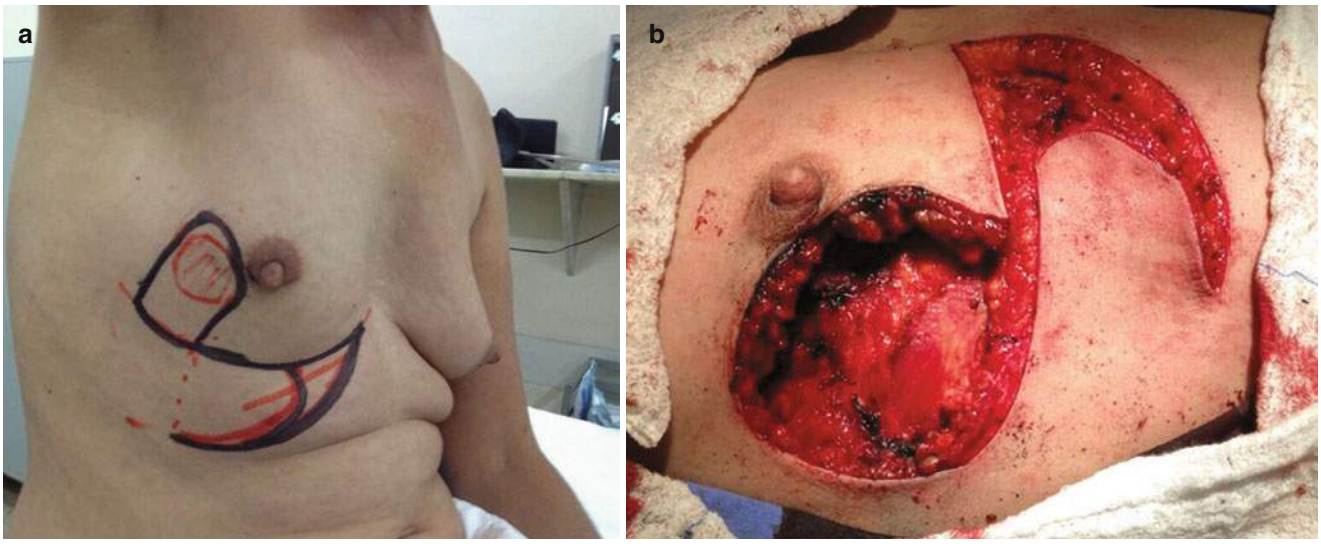


Fig. 31.30 Use the thoracoepigastric flap for large defect correction of the lower lateral quadrant. (**a**) Preoperative planning. (**b**) Quadrantectomy defect and flap confection. (**c**) Flap rotation for defect coverage. (**d**) Intraoperative appearance after flap positioning. (**e**) Results after 3 months of surgery, showing good volume replacement and preservation of breast shape

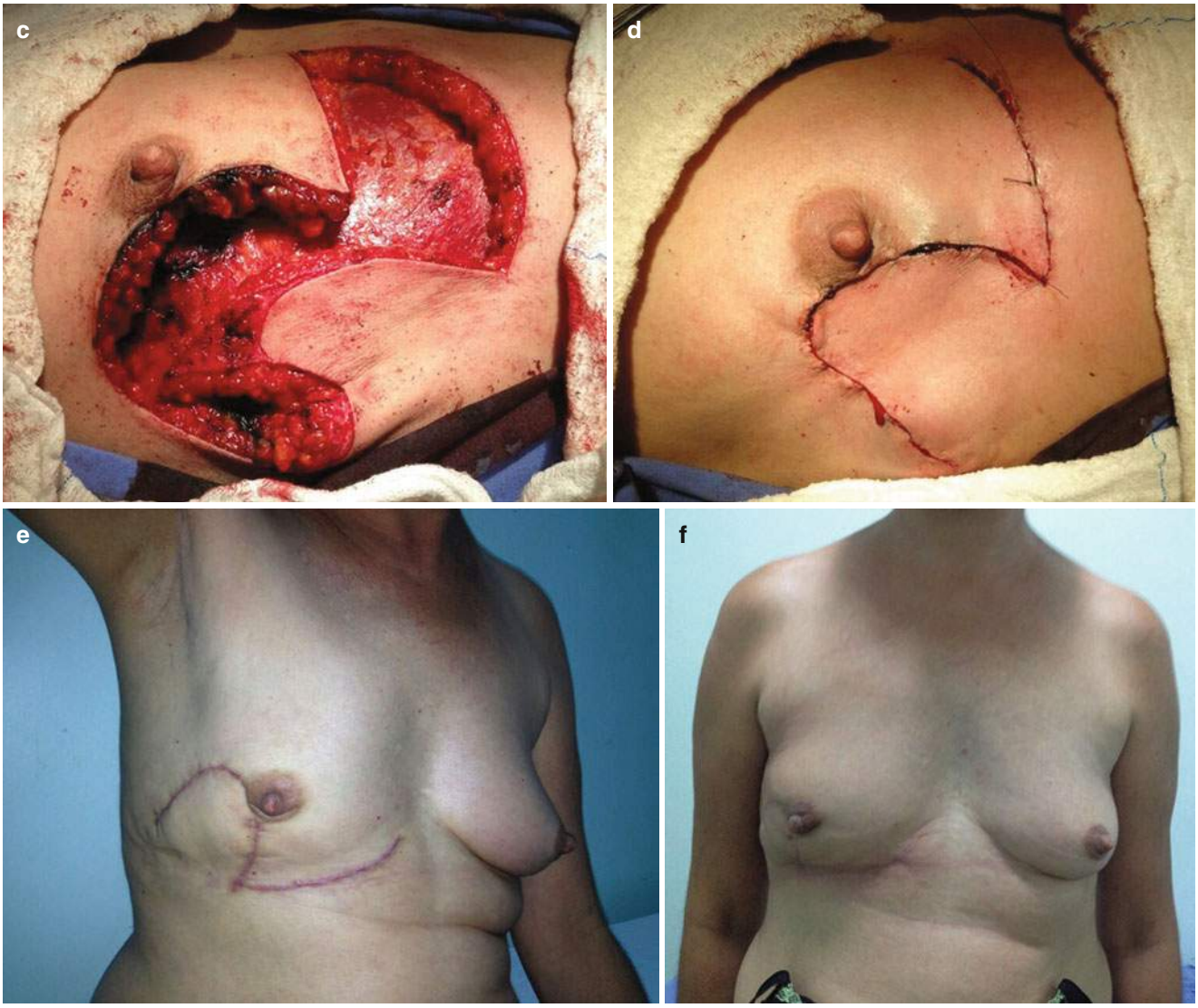


Fig. 31.30 (continued)

31.3.2 Thoracolateral Flap

The lateral thoracic flap takes advantage of the lateral fat of the chest, usually abundant and unwanted, to replace breast tissues [36, 37].

It is ideal for tumours of the lateral quadrants. In this case, it may be transferred to the defect in form of a transposition flap. Figures 31.31 and 31.32 show examples of conventional lateral thoracic flaps of transposition. Figure 31.33 shows an example of a deepithelized flap, in case of unnecessary dermal replacement. For other quadrants, it may also be used in form of an advancement flap. In these cases, the closure of the chest side may be done in V-Y (Figs. 31.34 and 31.35).

The lateral thoracic flap may also reconstruct late sequelae of conservative treatment in the lateral quadrants, in difficult cases of large retractions and large tissue loss, which would require several sessions of fat grafting or the use of a myocutaneous flap, as may be seen in Fig. 31.36.

31.3.3 Bilobed Flap

Depending on the tumour site or defect size, a double transposition flap may facilitate the correction.

Bilobed flap was initially described by a German author to nose reconstruction, in 1918, but since then it has been used for corrections in many sites [38]. Its use for breast reconstruction was first proposed and popularized by a Brazilian plastic surgeon, named Tostes, under the name "bilobed flap".

Among several different proposals for flap design, I prefer the Meadows' markings [39]. Part of the glandular tissue

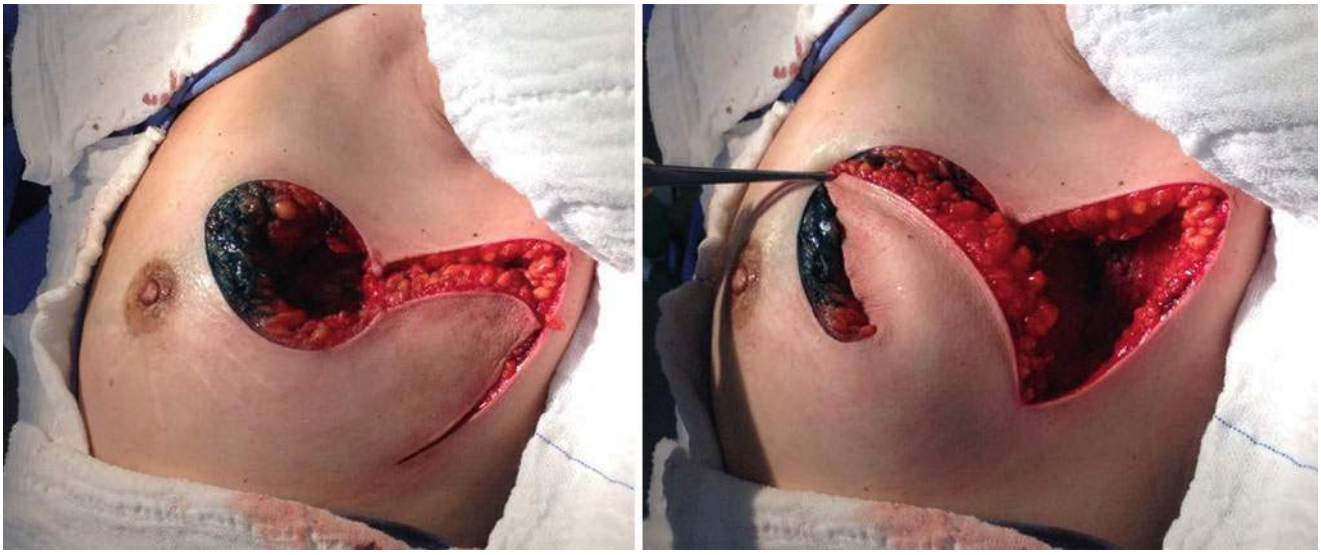


Fig. 31.31 Intraoperative detail of the transposition of the lateral thoracic flap

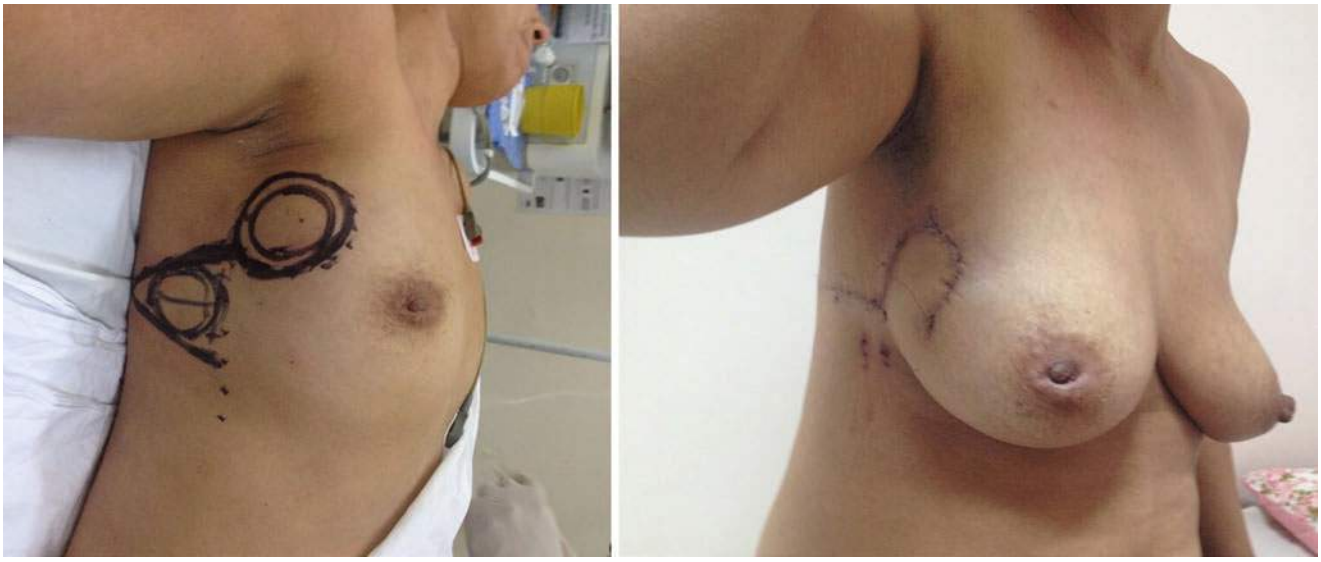


Fig. 31.32 Pre- and postoperative views of a lateral thoracic flap, showing proper defect fill

within the breast is transposed to the lumpectomy defect, and a thoracolateral flap is rotated to the former area near the tumour (Fig. 31.37). This manoeuvre generally allows preservation of breast shape and volume. The good expected aesthetic results justify the less usual scar conformation (Fig. 31.38).

31.3.4 Immediate Lipofilling

The use of lipofilling as part of breast reconstruction is a technique that has become very popular in the last decades and that has been proven to be safe from the oncological point of view [40]. More recently, it was described the possibility of partial breast reconstruction with lipofilling at the same time of the lumpectomy, presenting good aesthetic and oncological results (Fig. 31.39) [41].

Using Coleman's technique it is possible to transfer large amounts of processed fat, to restore partial tissue loss [42]. Fat is not injected into the defect of oncologic resection, because it is required a recipient bed for adipocytes. Instead, the fat is grafted onto the remaining breast. Then, it is made directly the primary closure of the defect or some other oncoplastic technique. It is necessary to overcorrect the volume, because it is expected a reabsorption of fat grafting in 30–50% [41]. Some possible skin retractions or glandular

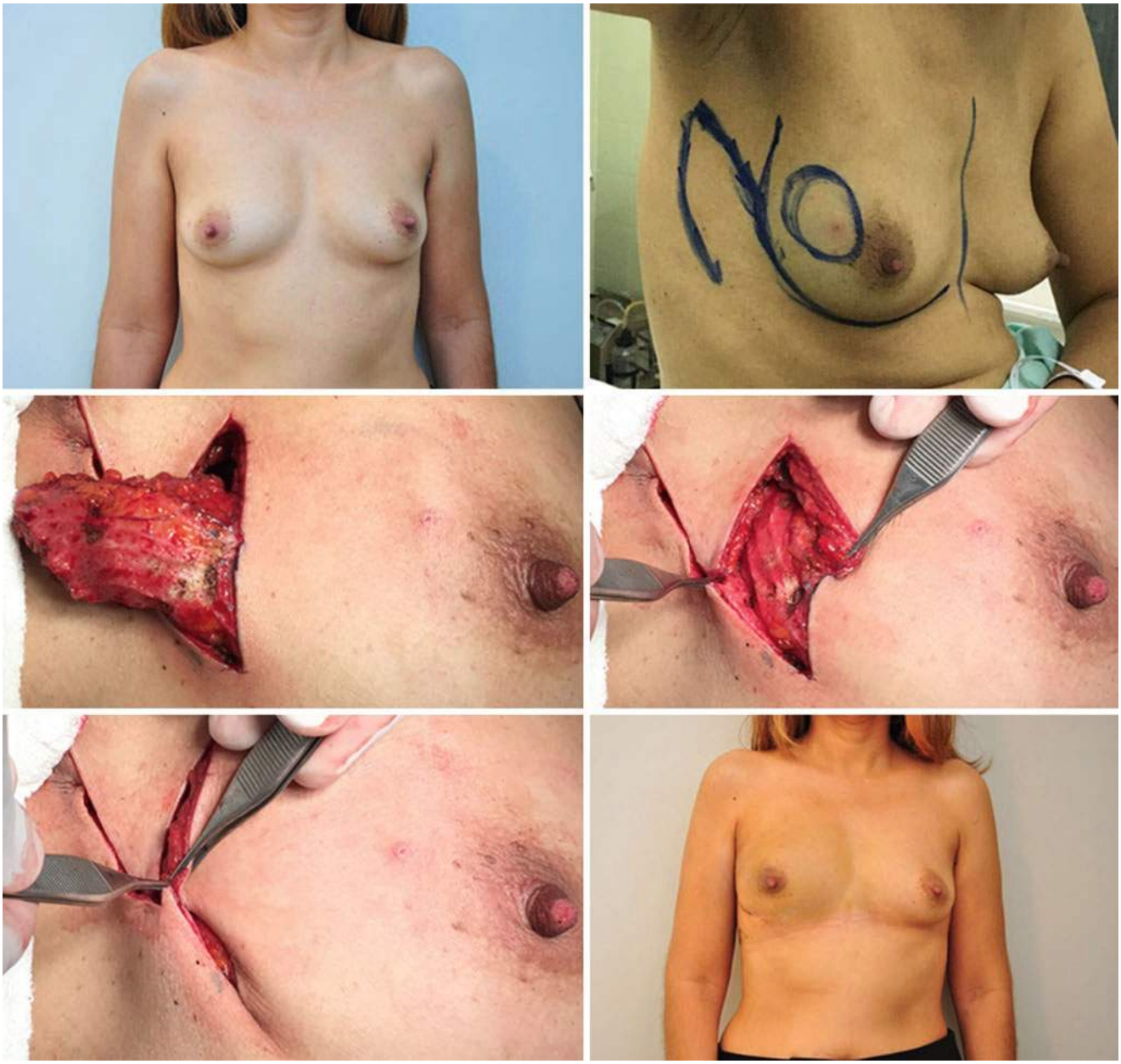


Fig. 31.33 Example of volume replacement in a woman with very small breasts, without ptosis, using a deepithelized lateral thoracic flap

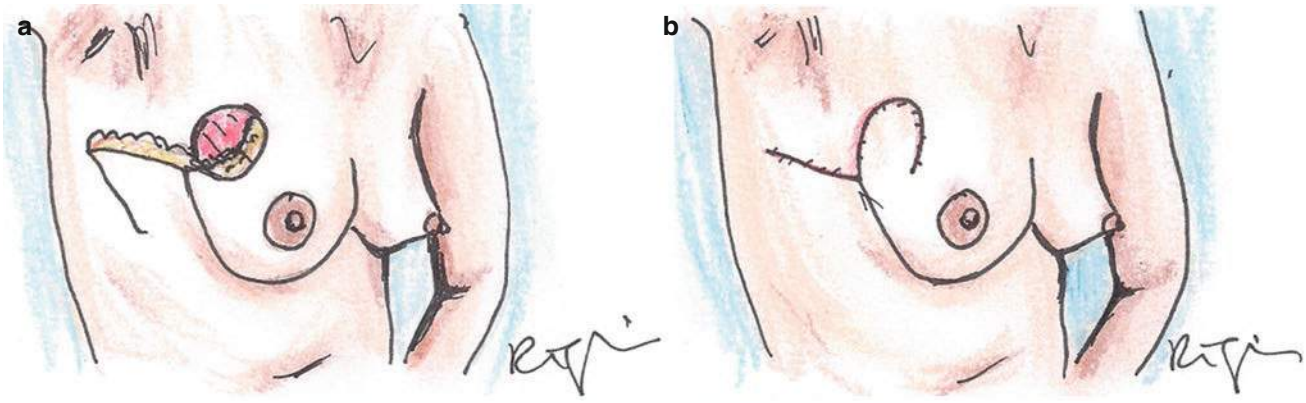
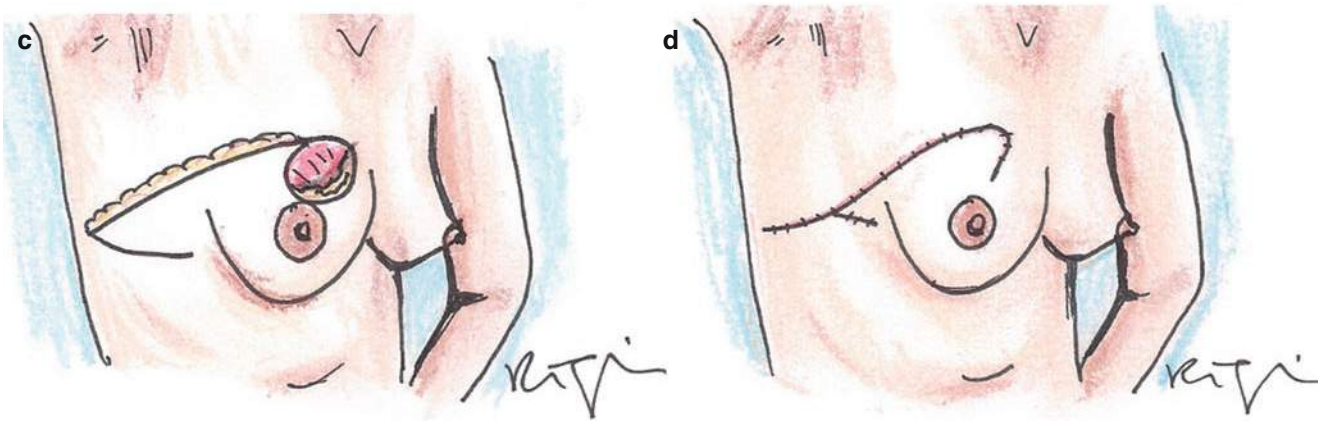


Fig. 31.34 Details of intraoperative lateral thoracic flap, as a transposition flap (**a, b**) and as an advancement flap, with V-Y closure (**c**, **d**)



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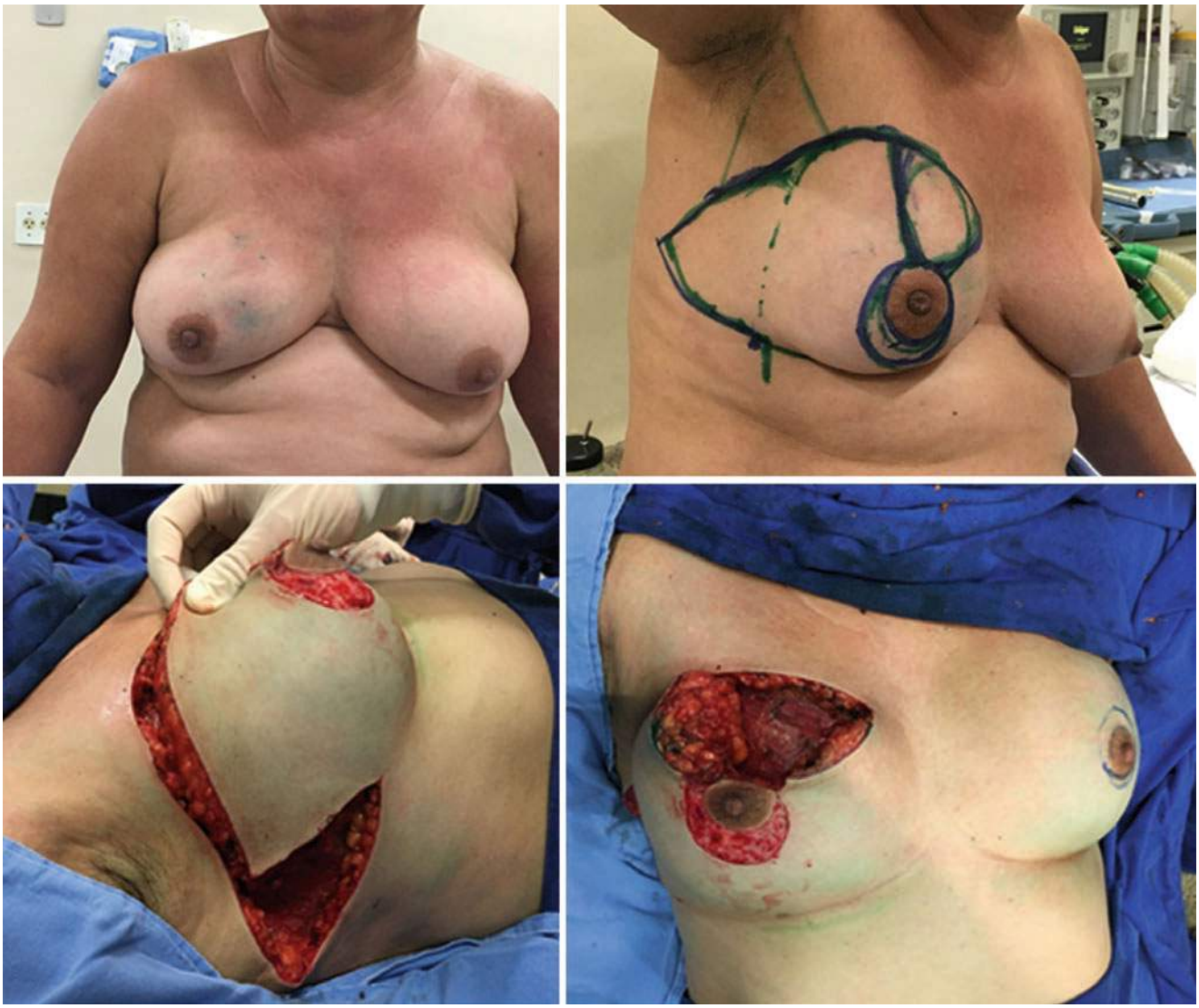
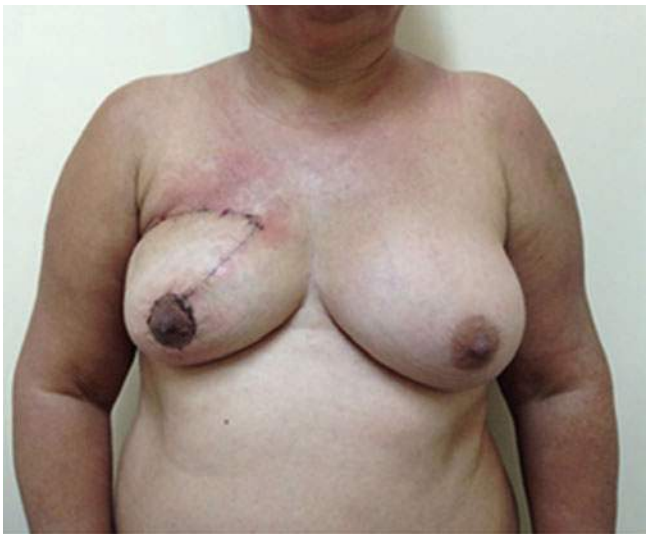


Fig. 31.35 Practical example of a lateral thoracic advancement flap, with closure in V-Y. In this case, repositioning the areola was necessary to prevent its displacement to the side of the scar



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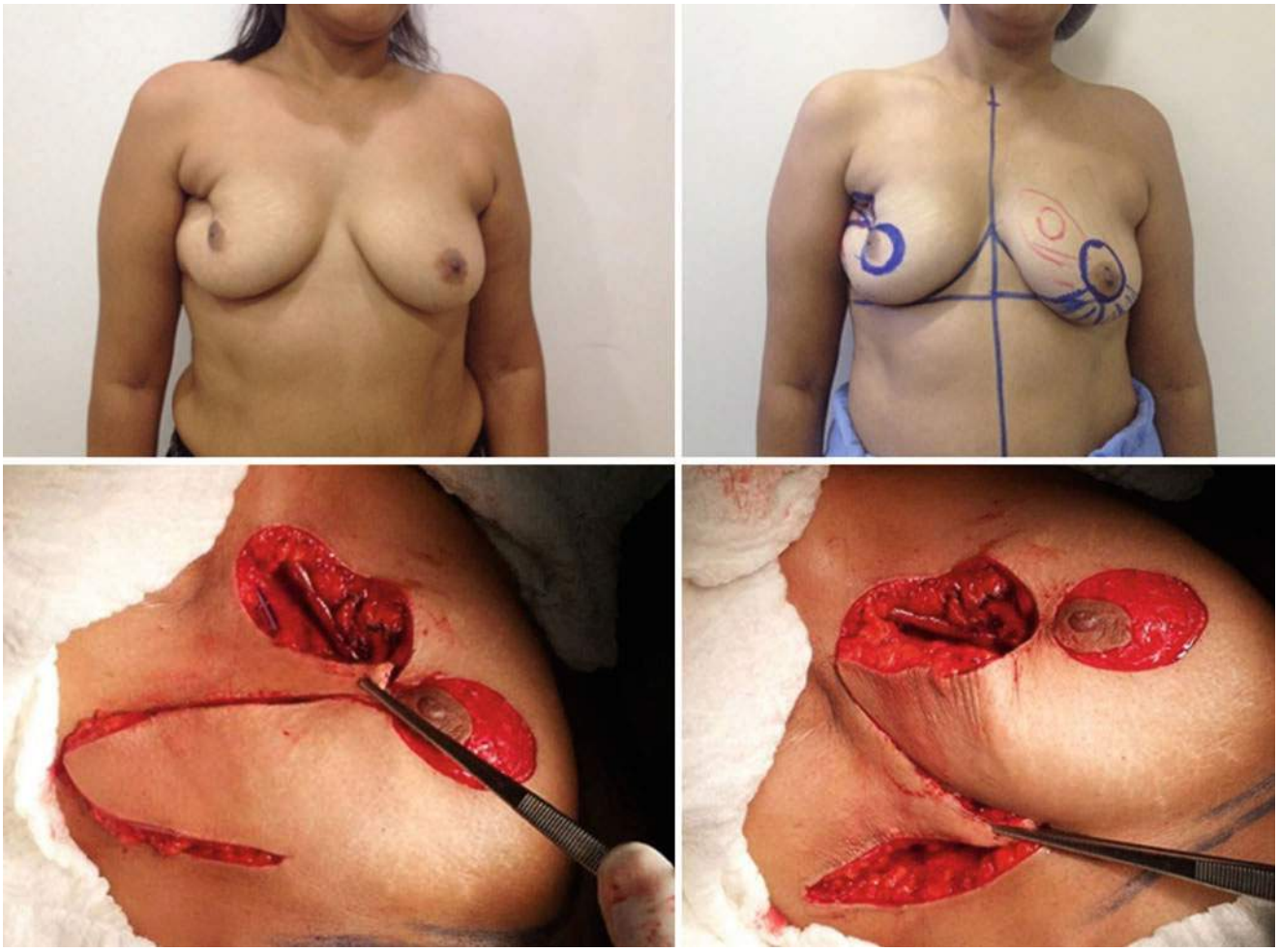

Fig. 31.36 Use of the lateral thoracic flap in case of late sequelae of conservative treatment. In the contralateral breast it was used a periareolar mammaplasty, with round block suture

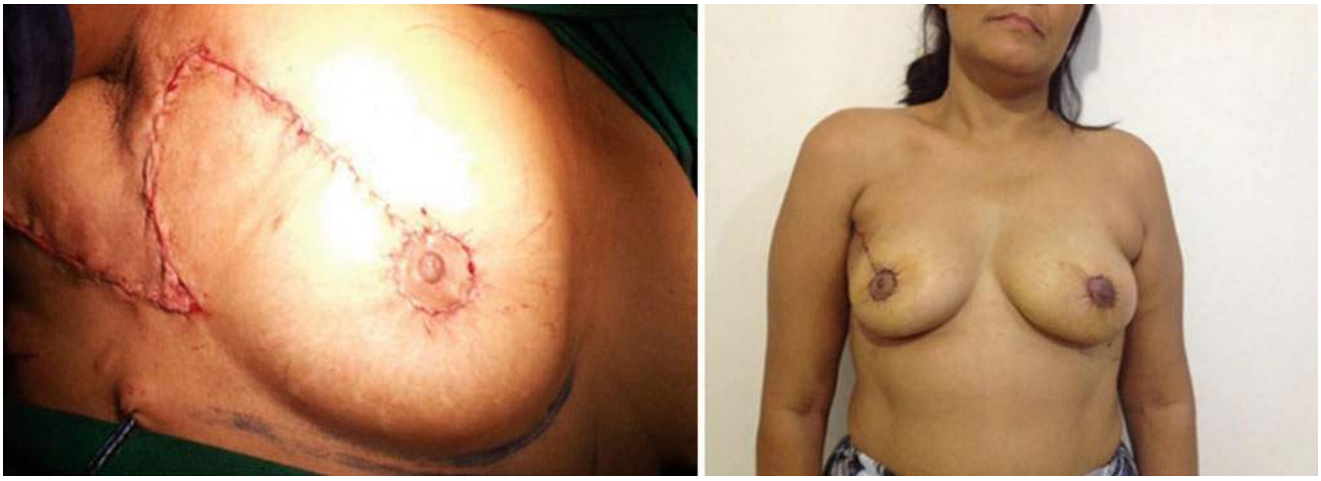

Fig. 31.36 (continued)

Fig. 31.37 Bilobed flap is a double transposition flap, in which part of the glandular tissue, is transposed to the area of the defect, and a thoracolateral flap is transposed to the defect of the flap removal. Instead of the markings proposed by Tostes, we prefer Meadows' markings

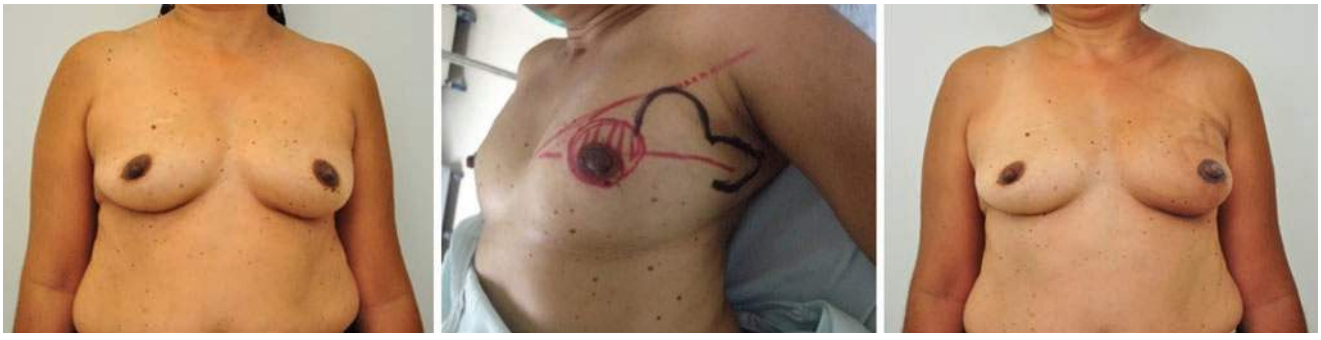

Fig. 31.38 Pre- and postoperative view of a breast reconstruction using the bilobed flap. In spite of the small size of the breast and the lack of ptosis, it was possible to preserve breasts of different sizes and shapes. In this case, it was possible to keep breast volume and shape, avoiding an unnecessary mastectomy

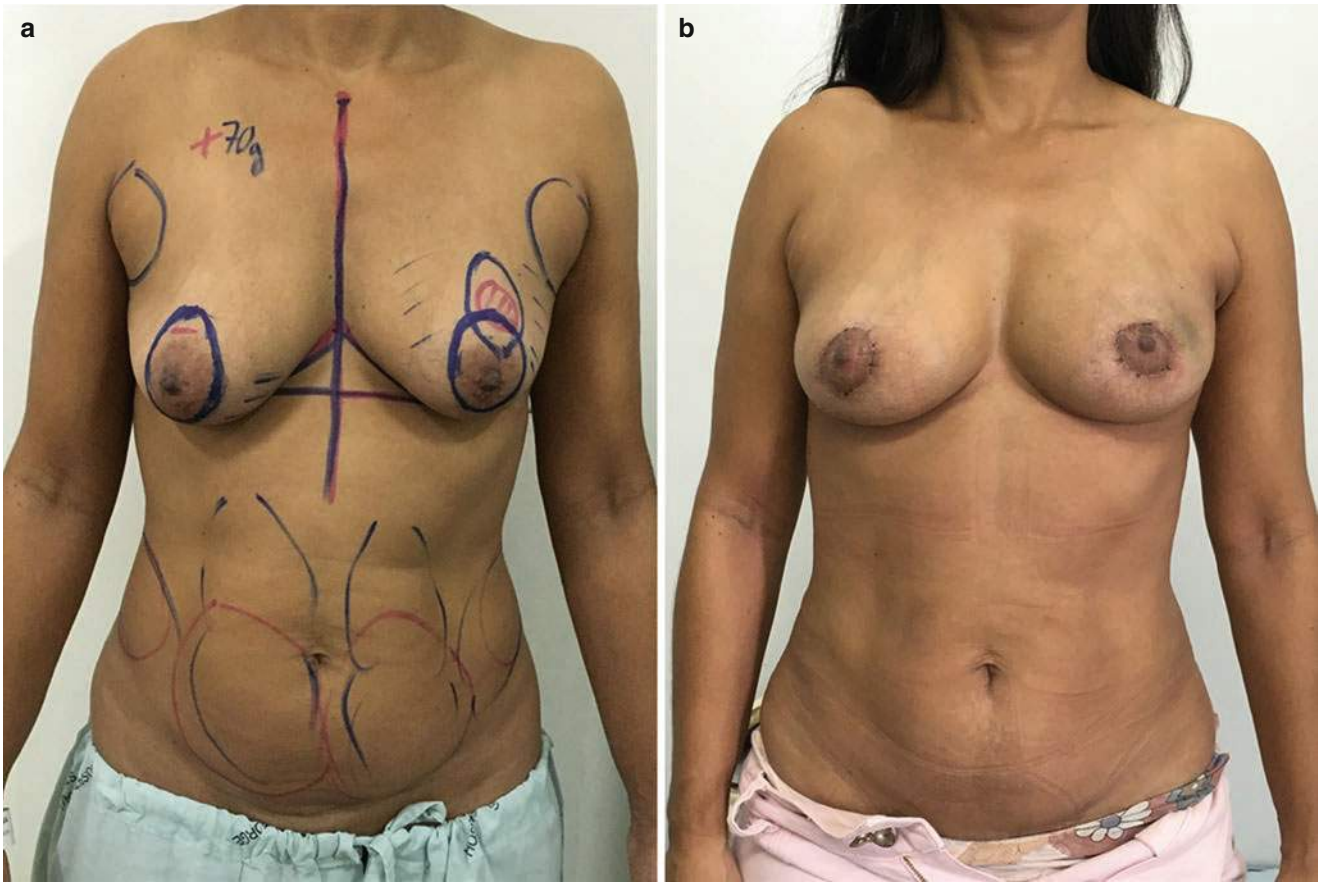

Fig. 31.39 2.5-cm invasive ductal carcinoma at the junction of the upper quadrants of the left breast. The lumpectomy specimen weighed 48 g. The abdomen and outer thighs were lipoaspirated. It was grafted 240 cc of processed fat in the remaining glandular tissue of the left breast, followed by a bilateral periareolar round block mammaplasty. (**a**) Preoperative marking. (**b**) Result after 3 months of surgery

depressions may be corrected with an extra round of fat grafting, after some months, if necessary.

31.3.5 Myocutaneous Flaps

Some authors advocate the use of distant flaps, as the latissimus dorsi or the rectus abdominis muscles, for correction of partial breast defects. Others prefer to preserve these flaps for use in case of necessity of total breast reconstruction (Fig. 31.40) [5, 6, 19, 43].

The main advantage of using the latissimus dorsi in partial mastectomies is the good tolerance to radiotherapy [44]. Compared to the total breast reconstruction, the partial reconstruction usually brings very favourable aesthetic results with low risk of complications [45, 46].

31.4 Late Corrections of Defects Due to Previous Conservative Treatment

The correction of the partial defects should be done, whenever possible, immediately, together with good planning of conservative treatment. Following radiation therapy, the risk of serious complications, when performing a mammaplasty or a breast remodelling, is much larger [47].

Attempts of using silicone implants after conservative treatment may be disastrous sometimes, since the implants often do not adequately address the partial defects and may even accentuate them. Furthermore, the capsular contracture rate is high [48].

Preferably, the irradiated breast should be managed with techniques that require little tissue mobilization, for example,

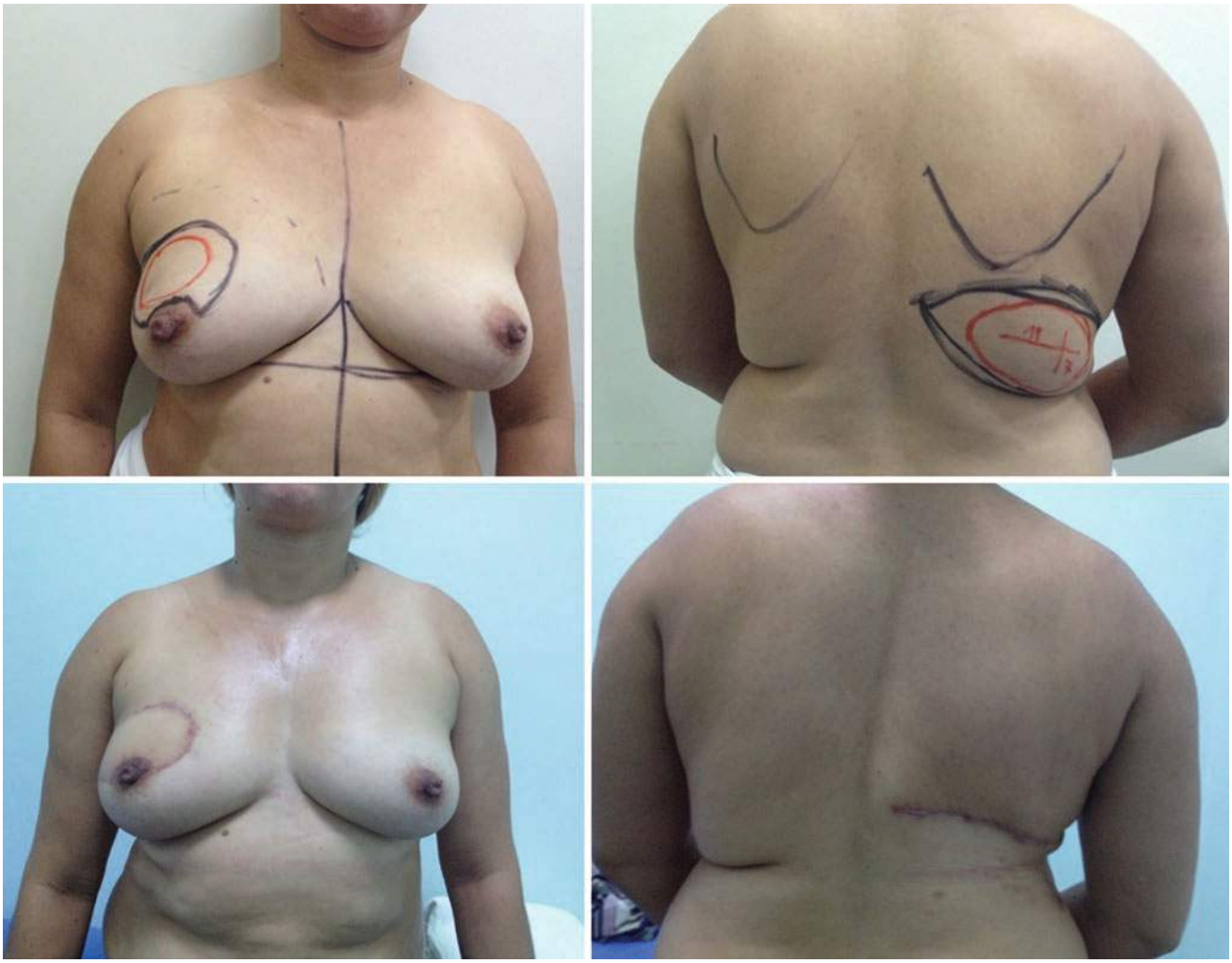

Fig. 31.40 Example of defect correction of a partial mastectomy by rotating the latissimus dorsi myocutaneous flap. As advantage of partial breast reconstruction, it is noticed a lower morbidity and greater tolerance to radiotherapy, using latissimus dorsi, compared to total breast reconstruction with implants with or without flaps. Furthermore, the appearance of the partial reconstruction tends to be more natural than full reconstructions. As a disadvantage, I quote the defect on the back and the difficulty to reuse the latissimus dorsi flap later for the total reconstruction of the breast, in case of recurrence

a cutaneous mastopexy (without glandular rearrangement), or only a repositioning of the nipple-areolar complex [49]. The contralateral breast may be reduced in a modified form, keeping a certain degree of ptosis, or a lower projection, so as to better mimic the irradiated breast (Figs. 31.41 and 31.42).

The free fat graft has been often used for correction of skin depressions and localized volume losses in the last decade. Although there are some questions about its oncological safety, especially in cases of carcinoma *in situ*, more recent researches have failed to show increased risks of recurrence for the procedure [40, 50]. The fat grafting may also be carried in the irradiated breast to increase the global size, avoiding the use of implants (Fig. 31.43). In large partial defects, very challenging to correct, it may be even preferable sometimes a mastectomy and total breast reconstruction with flaps [49].

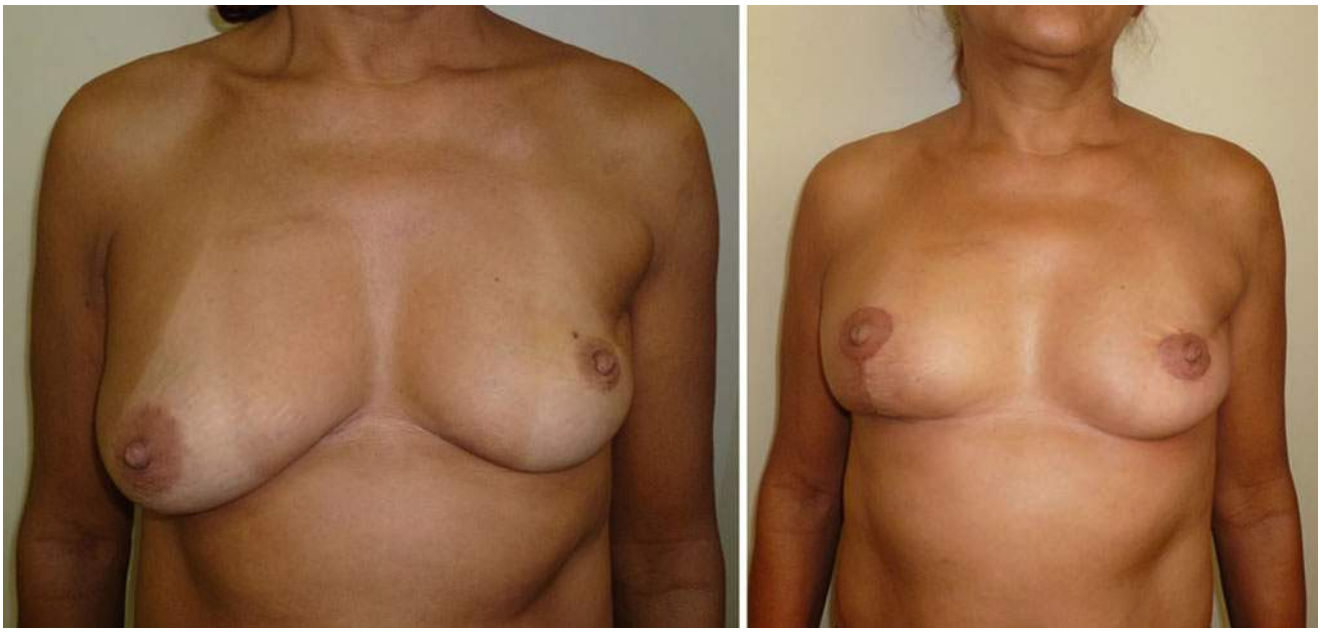

Fig. 31.41 Late correction of asymmetry after conservative treatment and radiotherapy. Because of the risk of complications, we chose to just reposition the nipple of the irradiated left breast. The right breast was remodelled for symmetrization

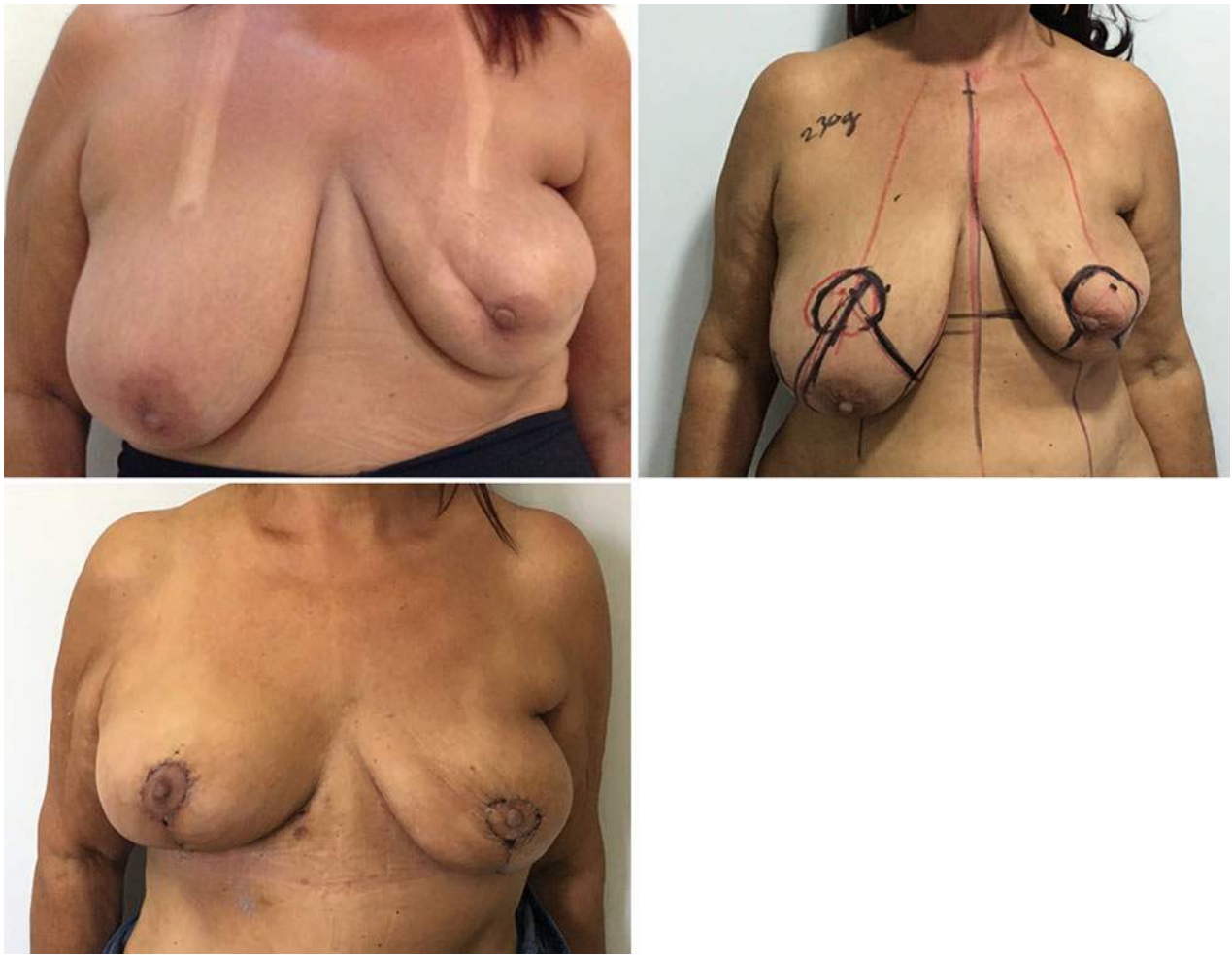

Fig. 31.42 A cutaneous mastopexy was performed in the irradiated breast, omitting conventional glandular rearrangement. The irradiated skin loses its normal elasticity and may be able to avoid much of the ptosis recurrence. Furthermore, the contralateral breast was reduced in a modified form, keeping a certain degree of ptosis, so as to better mimic the irradiated breast

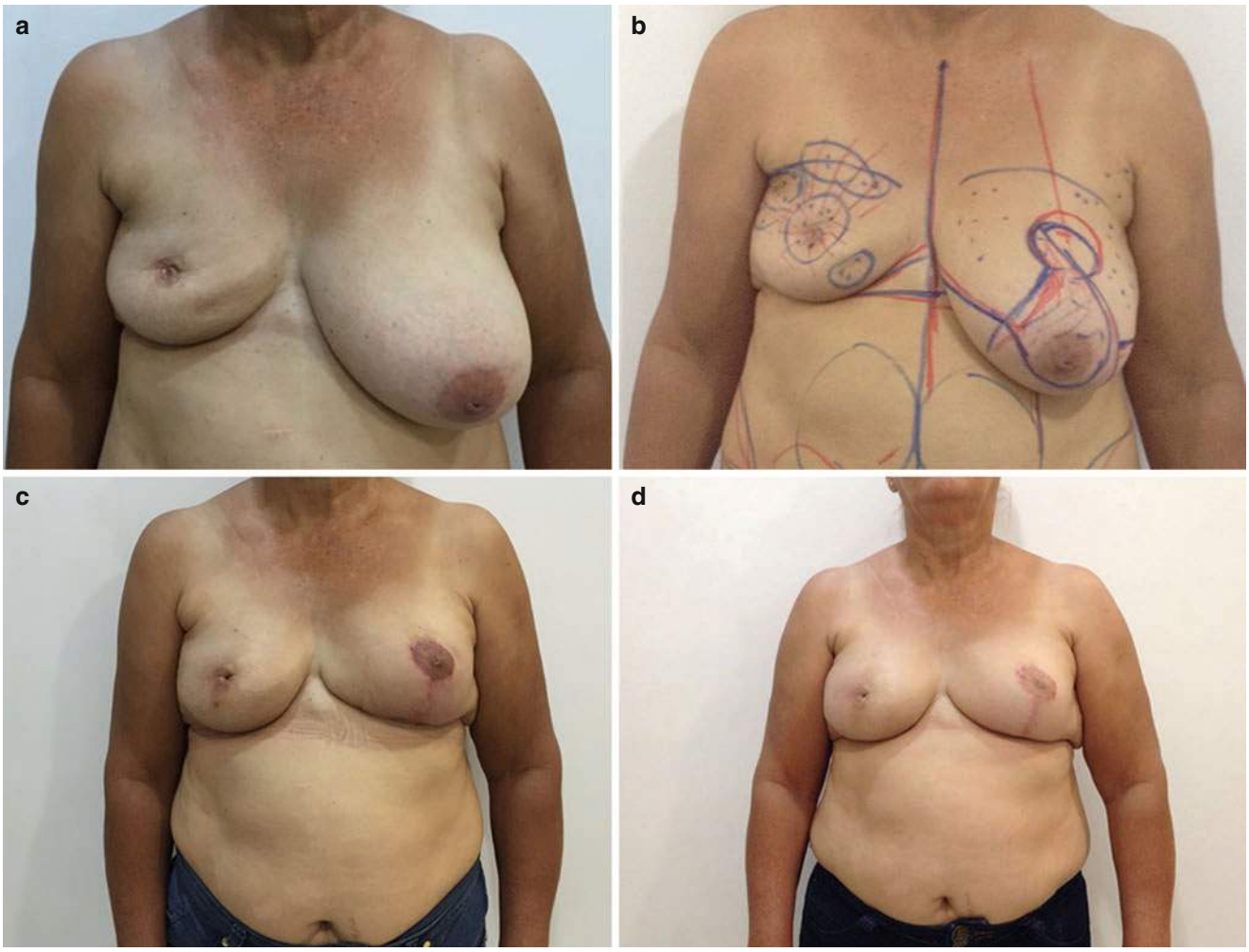

Fig. 31.43 Complex sequel of a conservative treatment, with severe loss of volume and multiple areas of retraction. It was performed exclusive lipofilling to the right breast (280 cc) and contralateral reduction (450 g). (**a**) Preoperative appearance. (**b**) Markings. (**c**) Result after 2 months. (**d**) Result after 1 year

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Pedicled Flaps for Volume Replacement in Breast Conserving Surgery

32

Pankaj G. Roy, Jennifer Rusby, and Richard M. Rainsbury

32.1 Introduction

The proportion of breast excised in breast-conserving surgery impacts on aesthetic outcome and patient satisfaction [1–3]. Women who are likely to have a poor cosmetic outcome from standard breast-conserving surgery as a result of the volume of excision required to attain clear margins were, historically, advised to have a mastectomy. Oncoplastic surgery has extended the role of breast conservation to allow many patients who would otherwise require a mastectomy to preserve their breasts. This has been further extended by volume replacement with lateral chest wall perforator flaps, which could avoid mastectomy in women with small- to moderate-sized breasts.

In 2007, approximately 19,500 women underwent breast-conserving surgery for cancer in the UK [4], so postoperative cosmesis is important to a large number of women. Furthermore, as survival following breast cancer improves [5], the long-term appearance after surgery becomes relevant to larger numbers of patients for longer. Finally, patient expectation is increasing as patients are aware that they need not look deformed after breast cancer treatment, and good aesthetic outcome significantly improves the quality of life [6, 7]. The recent data has shown the survival equivalence of breast-conserving surgery to mastectomy; this information is crucial to guide the women diagnosed with breast cancer to help with decision-making (data presented at San Antonio Breast Cancer Symposium, 2015).

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Oncoplastic breast-conserving techniques can be classified as volume *displacement* or volume *replacement*. Chapters 27–34, describe the various techniques for volume displacement after lumpectomy for breast cancer. Volume replacement after total mastectomy (i.e. breast reconstruction) can be provided by an implant, pedicled flap or a free flap, alone or in combination. Autologous tissue is the preferred approach for partial breast reconstruction. The use of implants for volume replacement in partial breast reconstruction is hampered by problems with postoperative surveillance and by the need for radiotherapy; hence outcomes are generally poor [8]. Further discussion of implants is beyond the scope of this chapter. Defects in the lower aspects of the breast can be addressed using local flaps such as abdominal adipofascial flaps [9, 10] or thoraco-epigastric perforator flaps [11–13]. The defects in the lateral half of the breast can be reconstituted with lateral chest wall perforator flaps that include lateral intercostal artery perforator (LICAP) flap, lateral thoracic artery perforator (LTAP) and thoracodorsal artery perforator (TDAP) flap [14–18]; these are now gaining popularity due to the benefits described below in the chapter. Distant flaps (latissimus dorsi [LD], omental) [19, 20] used for volume replacement after partial reconstruction are most commonly pedicled, though some small case series of free flap volume replacement after partial mastectomy have been published [21, 22]. They are more adaptable and can be used for reconstruction of defects in any breast quadrant.

This chapter focuses on the use of pedicled flaps for volume replacement. Donor options include the latissimus dorsi miniflap (LDm), or skin and subcutaneous tissues of the anterior or lateral chest wall and back in the form of perforator flaps such as intercostal artery perforator (LICAP) and thoracodorsal artery perforator (TDAP) flaps, and flaps from the thoraco-epigastric region (SEAP). Pedicled omental flaps and the LDm can be used to reconstruct inferomedial defects. The superior epigastric artery perforator flap results in very visible donor site scarring. It has previously been described for salvage situations (after recurrent breast

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_32

cancer or DIEP flap necrosis) [23]; however in one of the author's personal experiences, it can be used in carefully selected patients with acceptable scarring, in order to avoid mastectomy (Fig. 32.1).

The anatomy of the latissimus dorsi muscle relevant to reconstruction was first described by Tansini in 1897, who used a primitive LD flap to reconstruct radical mastectomy resection defects. Since the 1980s this reliable flap has been the workhorse of breast reconstruction, with significant advantages over implant-only techniques for many patients. LD was first used for delayed reconstruction of unsightly post-quadrantectomy resection defects in 1985 [24]. The use of the LD muscle for immediate volume replacement after breast-conserving surgery was first described by Noguchi in 1990 [25]. This procedure was redesigned and introduced into the UK by Rainsbury in 1994 using the LDm for immediate reconstruction of often large resection defects [26, 27]. With increasing expertise in perforator free flaps for whole breast reconstruction, and well-recognised morbidity from LD muscle transfer, it was a natural extension to consider pedicled perforator flaps for volume replacement after partial mastectomy.

The history of use of lateral chest wall flaps for breast reconstruction dates back to 1986. Holmstrom and Lossing et al. described lateral thoracodorsal (LTD) flap, a random-pattern local fasciocutaneous flap used to assist implant reconstruction after mastectomy for breast cancer [28]. LTD flap is raised as a random-pattern flap with a broad base still attached on its medial aspect, and the lateral intercostal perforators are not dissected out in the process of raising the flap. The LTD flap has also been described for partial breast reconstruction after breast conservation surgery for tumours in upper-outer quadrant (Munhoz 2006). In the paper by Munhoz et al., this flap was used for patients with small- to medium-sized breasts with no ptosis. The complications encountered includes partial flap necrosis (9%), donor site wound dehiscence (9%) and seroma (15%). A high patient satisfaction and good cosmetic outcome (90%) was reported.

In 1995, Angrigiani et al. reported a feasibility study in 40 cadavers and 5 clinical cases of raising a cutaneous flap as "the latissimus dorsi musculocutaneous flap without muscle" [29]. This flap has been used as a free flap for reconstruction of a wide variety of defects (upper and lower limb, neck, etc.). However, it was not until 2004 that Hamdi et al. published a series of muscle-sparing flaps used for reconstruction of partial mastectomy defects [30, 31] and popularised the pedicled perforator flaps including LICAPs and TDAPs [14, 15]. These flaps extend the indications for breast conservation surgery and are associated with minimal procedure-related morbidity resulting in quick recovery and excellent aesthetic outcomes, therefore gradually gaining favour over the recent years.

Superior epigastric flaps are useful to reconstitute defects in the inner quadrants of the breast and they could be tunnelled into the upper inner quadrant, which often poses significant clinical challenges in terms of aesthetic outcome. The disadvantage of this flap is the extent of scarring although careful planning can hide the scar in the inframammary crease thus making it less of an issue for the patient (Fig. 32.1).

32.2 Anatomy of Perforator Flaps

32.2.1 TDAP Flaps

The TDAP flap is usually irrigated by the proximal perforator of the descending branch of the thoracodorsal artery. The vascular anatomy of the lateral thoracic flap has been described in the literature predominantly by cadaveric dissections [31–36] suggesting reliable presence of the perforator. The perforators larger than 0.5 mm in diameter with discrete pulsations are considered reliable for perfusion of the flap [32]. Most studies report at least three musculocutaneous perforators in the LD muscle, the most constant perforator is present within 2–3 cm of the lateral border of the muscle about 8–10 cm below the posterior axillary fold and the second perforator originates 2–4 cm distal to the origin of the first perforator. A direct cutaneous perforator that courses anteriorly to the lateral muscle border has been described in 55–60% cases in cadaveric studies. Although these make dissection of pedicle easier, they are not preferred due to their unpredictable course, diameter and vein calibre [37].

A muscle-sparing LD flap is an alternative option to TDAP, whereby a small strip of muscle immediately anterior to the perforator(s) is left attached to the flap and the rest of the muscle is left intact with its nerve supply which is dissected free from the thoracodorsal pedicle. This is particularly recommended if the perforator size is less than 0.5 mm due to high risk of avulsion [38] and also renders the procedure safer and easier by circumventing the need to harvest the perforator from the overlying muscle [39].

32.2.2 Lateral Chest Wall Perforator Flaps

These perforator flaps are based on the lateral cutaneous branch of the posterior intercostal vessels (LICAP) as they course through the costal groove of the ribs. They have been described as a perforator flap that may be used as a free or island flap [40] and have since been used for partial breast reconstruction predominantly for lateral defects after cancer resection [31] and for autologous breast augmentation after massive weight loss [41–43]. In a cadaveric dissection study,

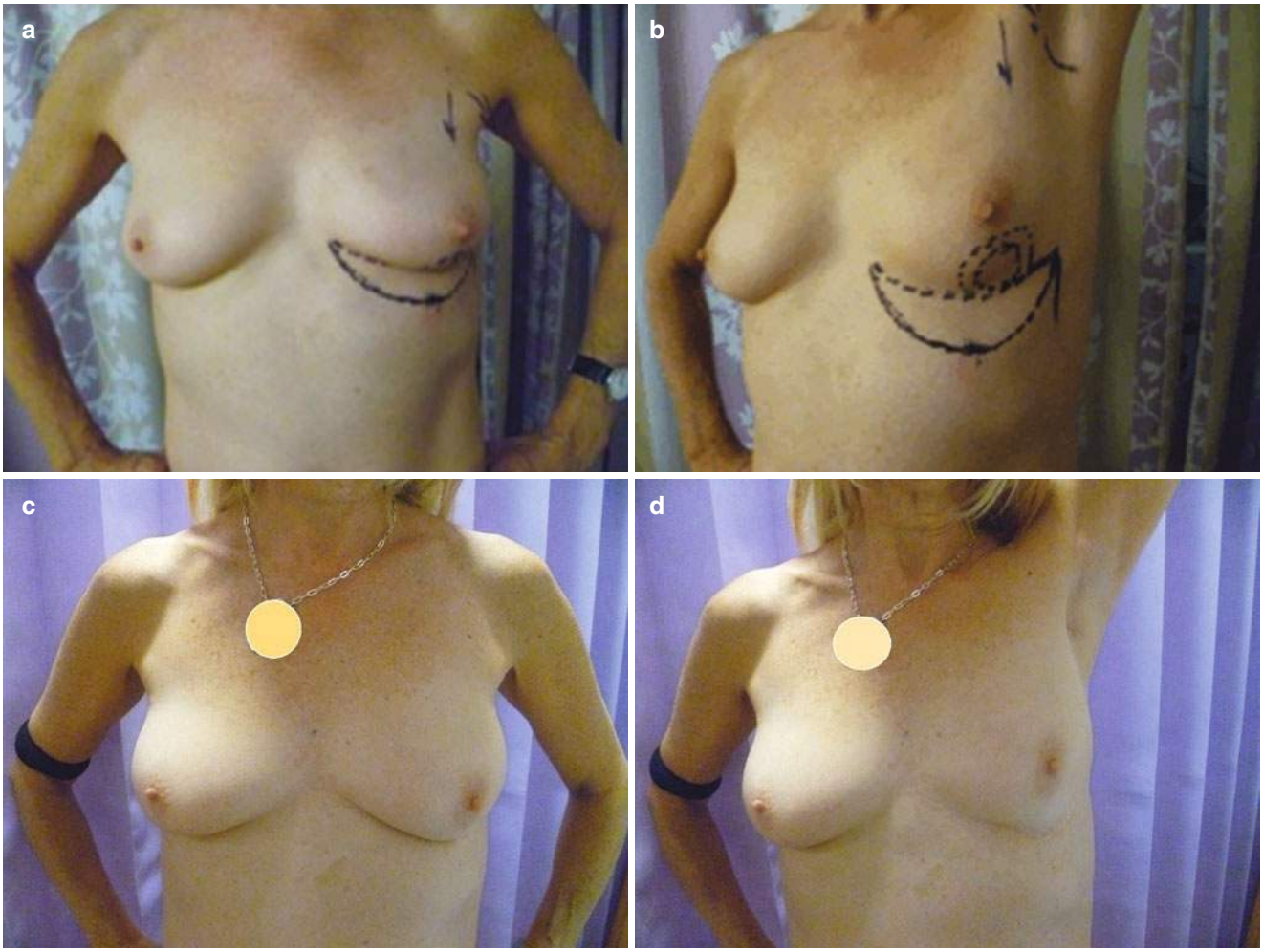

Fig. 32.1 Thoraco-epigastric flap (SEAP). (**a**) 55-year old lady with 20 mm cancer in left lower central quadrant of a small "B"-cup breast. (**b**) Preoperative marking of thoraco-epigastric flap and size of potential defect (shown with arm raised). (**c**) Appearance and maintained symmetry of the breasts 4 years after radiotherapy to the left side. (**d**) Appearance and visibility of the scar (faded) with arm raised (4 years after treatment)

Hamdi et al. [31] showed a variable number of intercostal perforators and a dominant perforator in 92%; these lay, on average, 3.5 cm from the anterior border of the LD.

The posterior intercostal artery gives off several musculocutaneous branches to supply the overlying muscles and skin and the lateral cutaneous branch (which arise in the distal part of the groove) as it courses through the costal groove. The lateral branch is about 1 mm in diameter whilst the main vessel is 1.5 mm and is accompanied by a vein and nerve. The lateral cutaneous nerve is predominantly sensory with only 10% motor fibres. The lateral cutaneous bundle pierces the overlying muscles and emerges from under a slip of origin of serratus anterior muscle in a plane just deep to the skin and subcutaneous tissues [44]. The bundle courses for a short distance superficial to the serratus anterior fascia and divides into a small posterior and large anterior branch. The lateral intercostal artery perforators are relatively constant (about 90% cases as shown on cadaveric dissections) and usually found between the 5th and 8th intercostal spaces. These are located between anterior and posterior axillary lines, at an average of 2.5–3.5 cm from the anterior border of the latissimus dorsi muscle [38].

A vascular connection between the anterior branch of lateral perforator and the serratus branch of thoracodorsal artery was found in 21% of the cadaveric dissections by Hamdi et al. which creates a potential for harvesting a flap with a longer pedicle whilst preserving the thoracodorsal vessels (SAAP-serratus anterior artery perforator flap). The other vessels that can form the blood supply to the flap include a direct cutaneous branch from lateral thoracic artery (branch of the second part of axillary artery); however, the anatomy of lateral thoracic artery (LTA) has been shown to be variable and absent in up to 25% cases [33, 45, 46]. These vessels can form an additional or solo blood supply for the lateral thoracic flap (LTAP flap) and therefore should be kept in mind whilst dissecting for the perfo-

rator. LTA can be dissected along the lateral aspect of the pectoralis muscle, running down vertically at right angles to the orientation of the flap [17].

32.2.3 SEA Flaps (Thoracoepigastric Flap)

The superior epigastric artery (SEA) is a terminal branch of the internal mammary artery (musculophrenic artery being the other branch) and arises opposite the 6th costal cartilage. It then descends along the rectus abdominis muscle and penetrates the muscle and fascia below the xiphoid process to reach the skin [47]. A CT scan-based study has shown that the dominant perforators are mainly localised at about 1.5 and 6.5 cm horizontally from the midline and between 3 and 16 cm vertically below the xiphoid [13, 23]. Similar results were produced by a cadaveric study reported recently [48]. These perforator flaps are oriented horizontally for partial breast reconstruction resulting in a scar along the inframammary crease. The flap can be designed all along the inferior aspect of the breast achieving a length of 15–20 cm depending on patient anatomy. The arc of rotation of the SEA flap allows it to reach the upper inner quadrant, thus making it an option to reconstitute defects in the upper inner quadrant provided there is fat excess that can be harvested along the inferior aspect of the breast.

32.3 Indications, Patient and Flap Selection

Patients with large ptotic breasts may accept or even welcome the option of a reduction in breast volume as a result of tumour excision, and the local defect may be best managed with a volume displacement technique and contralateral symmetrising surgery. But if the patient is keen to avoid contralateral surgery, or the breast is smaller and non-ptotic, volume replacement is a more appropriate option. Smaller-breasted women who wish to avoid local defects and global loss of breast volume are better suited to volume replacement procedures. By choosing this rather than total mastectomy and immediate breast reconstruction, a woman is more likely to preserve the normal shape, movement and sensation of her breast [49] but must accept the need for adjuvant breast radiotherapy.

LDms can readily be used to fill a defect in the lateral aspect of the breast, but also in the central, medial or lower pole of the breast with sufficient flap harvest and mobilisation. Full dissection of the flap inferiorly to the costal margin and posteriorly beyond the scapula, combined with thorough division of all surrounding attachments (see below) is essential in order to capitalise on the full potential of this flap to reconstruct a wide range of resection defects in any location. Perforator flaps tend to have less range, though TDAP flap replacement of volume has been reported in all quadrants [38]. The ICAP is best suited to the lateral aspect of the breast but defects in the superior pole can be addressed if a pedicle of 3–5 cm can be harvested, as this allows rotation of the flap through 180 degrees without torsion of the perforator [14, 30].

The volume of tissue required also affects choice of flap. Hamdi et al. [30] state that a muscle-sparing LD type III (i.e. most of the muscle is included with the flap) is used if the muscle is needed for volume. Most case series of perforator flaps do not provide details of the oncological surgery, but median specimen weight in a series of LDms (equivalent to MS-LD III) was 207 g [19] compared to 164 and 96 g in two different series of LICAP flaps [15, 18].

Although the importance of *prevention* of cosmetic deformity after breast conservation is emphasised, there will always be a cohort of patients with a suboptimal result who require *correction* of deformity in the delayed setting [50]. Partial breast reconstruction with volume replacement is a mainstay of management in this situation. Patients must be informed of the full range of options available to them (including completion mastectomy and immediate whole breast reconstruction), and counselled carefully, to allow them to make an informed choice about their treatment in the knowledge of the likely range of outcomes.

32.4 Technique: General Principles

Whether partial breast volume replacement is carried out by a single "oncoplastic" team or separate surgical oncology and plastic surgical teams, it is important that all aspects of the procedure are carefully planned, particularly the oncological resection and the flap design. If two teams are involved, close preoperative collaboration is essential.

32.4.1 Planning and Patient Positioning

Oncological planning involves careful clinical and radiological assessment of tumour size, position and whether unifocal or multifocal. The tumour should be marked on the breast, together with an "access tunnel" if required (Fig. 32.2), and for more extensive, impalpable and multifocal lesions, stereotactically placed "bracketting" wires can be helpful in guiding more precise tumour resection. The borders of the LD should be marked for any case in which muscle harvest is anticipated. For LICAP and TDAP flaps, a pinch test allows assessment of the amount of skin and subcutaneous tissue available whilst allowing closure

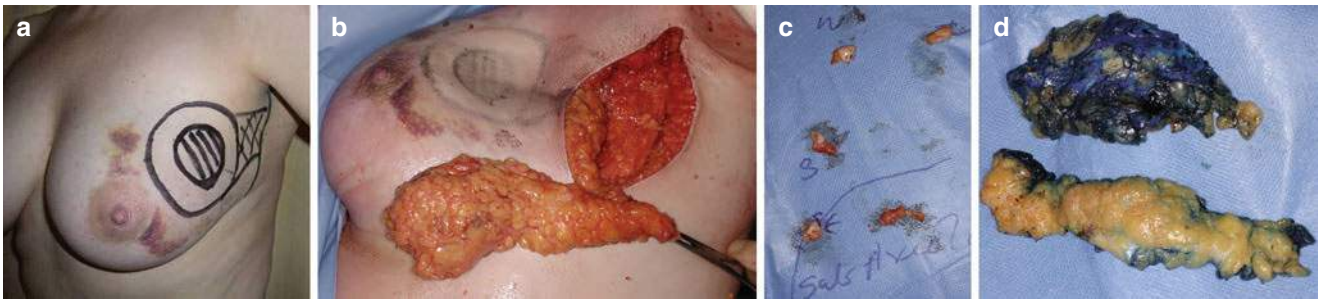

Fig. 32.2 Tumour resection: (**a**) preoperative breast markings. (**b**) A 220 g specimen attached to "access tunnel" tissue, showing the resulting resection defect and lateral incision used to perform the procedure. (**c**) Bed biopsy material sent for intraoperative frozen section. (**d**) "Re-excision specimens" inked in situ with methylene blue to identify the surface adjacent to the cavity

without excessive tension (approximately 12 cm perpendicular to the long axis of the flap [14]). The flap is usually horizontally aligned when used for partial breast reconstruction. This allows it to be placed in the relaxed skin tension lines and the donor site scar to be hidden in the bra. Provided tumour excision can be safely undertaken with the patient in the lateral decubitus position, this approach is optimal for raising both LDm and lateral chest wall perforator flaps. The shoulder should be abducted to 90 degrees and elbow in 90 degrees of flexion. In addition to providing good access, this makes the perforator course more perpendicular to the skin, and the Doppler signal is therefore more discrete. Care must be taken to avoid over-abduction or overextension of the shoulder, as this can lead to a brachial plexopathy.

32.4.2 Incisions and Raising the Flap

The incision depends on whether volume is being replaced in the immediate or delayed setting and which type of flap is planned (LDm or perforator). In the delayed setting, reopening the previous skin incision on the breast often reveals a skin deficit. The wound may gape open, demonstrating that skin replacement is required to allow the remaining breast tissue to return to its pre-surgical position. This may be the case even if no skin was excised at the time of breast-conserving surgery. Despite being an "apparent" skin deficit as a result of scarring and radiotherapy rather than a real deficit, it will need correction to optimise the result.

When the tumour is excised immediately before volume replacement, the breast skin is mobilised in the oncoplastic plane, over and around the tumour. The breast is then mobilised off pectoralis major muscle. The tumour is excised with generous margins and in continuity with lateral tissue to form the access tunnel as required. Bed biopsies may be taken as per local MDT guidelines or if there is a concern regarding margins intraoperatively. These may be sent for frozen section, and a full cavity re-excision is undertaken to maximise the chance of clear margins (Fig. 32.2) [19]; although this is not practiced routinely in the UK, it is common practice in a number of European countries. Frozen section is labour-intensive, requires a dedicated histopathology team of pathologists and technicians and occasionally leads to false-negative results. Alternatively, a "delayed-immediate" (two-stage approach) reconstruction can be undertaken 2–3 weeks after tumour excision and when final histopathology results are available [51]. This is a particularly useful option after neoadjuvant chemotherapy or when resecting lobular carcinoma, when frozen section analysis is more difficult to interpret. It is also a sensible approach if the breast conservation surgery is a borderline option and there are significant concerns preoperatively that the patient may require completion mastectomy in the event of positive margins on histopathology [18]). The two-stage approach is also an option to consider if the patient is a good candidate for autologous LD reconstruction (in the event of needing mastectomy) as a lateral chest wall perforator flap would interfere with that option.

For patients needing axillary node clearance, the axillary procedure may be performed in supine position first followed by a change to the lateral position for flap dissection and inset. This may necessitate separate incision for axillary surgery, because the flap marking is often about an inch below the usual approach for axillary surgery. The other option used routinely during LDm reconstruction is to perform the axillary surgery with the patient in lateral position, a technique which requires orientation and training. The advantage of the latter approach is less scarring as the entire surgery including tumour resection, axillary dissection, flap harvest and reconstruction is performed through the single lateral incision. It is very important that the oncological safety is considered carefully (to ensure complete excision) and the approach is planned preoperatively as deemed suitable for individual cases.

32.5 Specific Flaps

32.5.1 LD Miniflaps

An immediate LDm is best performed via a cosmetically discreet "lazy S" incision in the anterior axillary line, providing access to the breast for tumour excision and the back for raising the LD [52]. The LD flap is raised in the plane just beneath the deep fascia, sparing the subcutaneous fat but taking a layer of fat over the muscle, which contributes to the flap volume (Fig. 32.3). Division of the *entire* fascial attachment of LD to teres major, all serratus anterior branches and the tendon of LD allows full transposition of the flap into the resection defect (Fig. 32.4). This is a particularly important step when reconstructing more remote defects in the medial or lower pole of the breast. Finally, the tendon needs to be secured to pectoralis major to prevent unintentional torsion to the pedicle, before the flap is

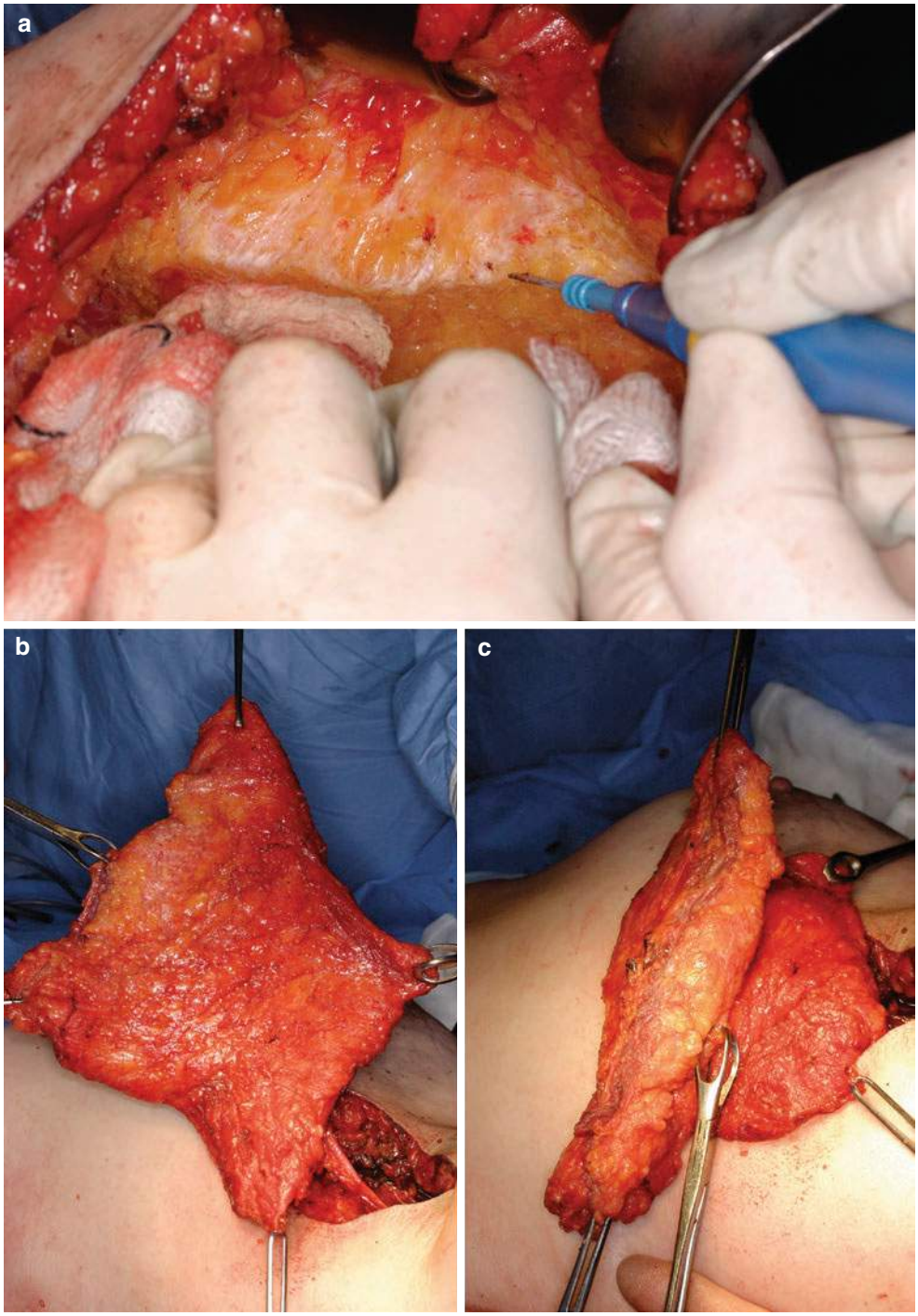

Fig. 32.3 Harvesting the LD miniflap. (**a**) Dissection of the superficial surface of the flap in a plane immediately under Scarpa's fascia (the deep fascia). (**b**) The layer of fat on the superficial surface of the flap harvested as a result of dissecting in this plane. (**c**) View of the divided distal end of flap, showing the layer of superficial fat which is thicker than the flap itself at this level

modelled and sutured into the resection defect (Fig. 32.5). When harvesting the flap, it is best to overestimate the volume required to allow for muscle atrophy over time. As a result, the volume of the reconstructed breast should be larger than the opposite breast at the end of the procedure. A good cosmetic result can be anticipated if these key steps are observed (Fig. 32.6).

The LDm can be harvested either as a myofascial flap with no skin island or as a myocutaneous flap with a small skin island. Myofascial flaps are typically used for upper pole defects, whilst the myocutaneous version is more commonly used for transposing additional volume or skin for nipple-areola or for lower pole reconstruction. The skin island may then be either partially or totally de-epithelialised, depending on whether skin is required to replace a skin deficit, or whether a de-epithelialised island is required for volume. If the flap is totally subcutaneous, Doppler monitoring cannot be undertaken.

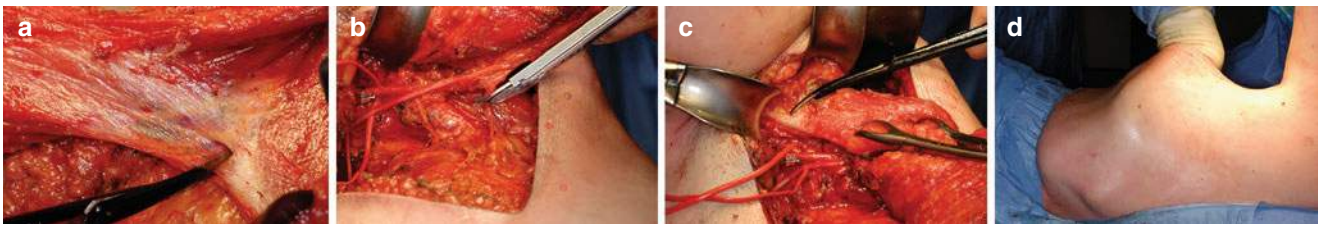

Fig. 32.4 Division of all LD miniflap attachments and the resulting donor defect. (**a**) Division of the well-developed fascia between LD (top left) and teres major (bottom right), dissecting in a cranial direction. The thoracodorsal vessels lie immediately deep to this unnamed fascial layer. (**b**) Clip ligation of a serratus anterior branch in preparation for division of the vessels. (**c**) Protecting the subscapular vessels with a sling during division of the LD tendon. (**d**) The assistant's hand outlines the extent of the LD donor defect following flap harvest

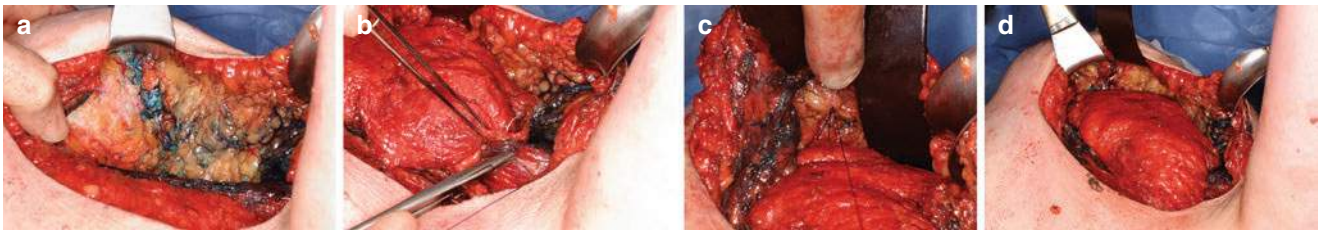

Fig. 32.5 Reconstruction of the resection defect. (**a**) Lateral view of walls of resection defect. (**b**) Suturing tendon of LD miniflap to lateral border of pectoralis major. (**c**) Suturing folder distal edge of flap onto medial cavity wall. (**d**) Appearance of flap at end of procedure after being sutured into the resection defect

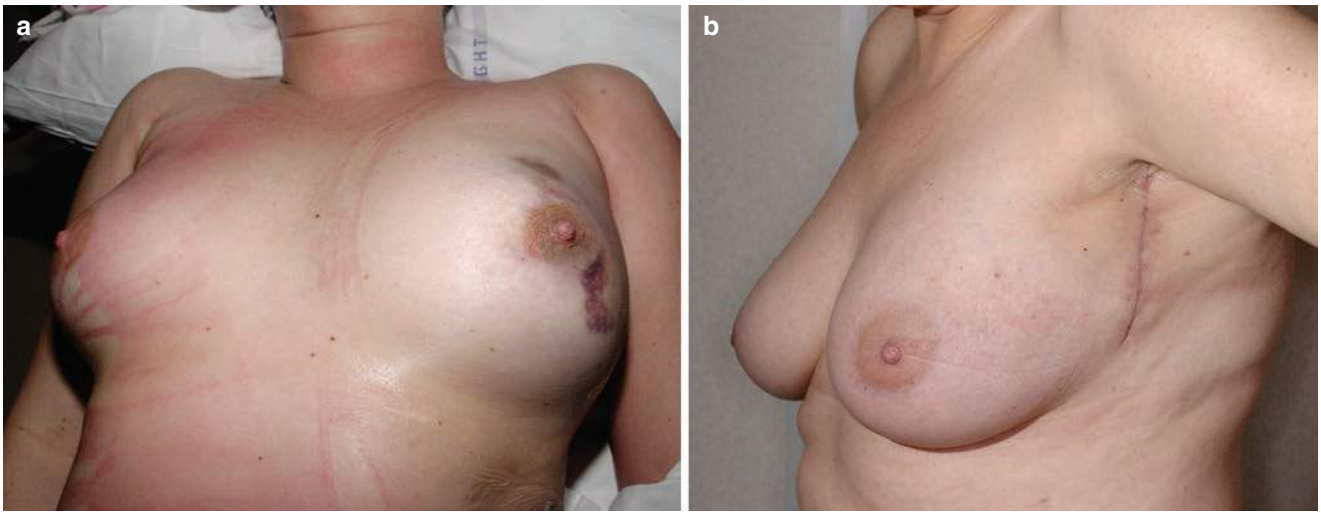

Fig. 32.6 Postoperative appearance. (**a**) Appearance before extubation, showing over-replacement of the resected volume to allow for subsequent volume loss. (**b**) Appearance at 6 weeks, showing short "lazy-S" lateral scar and natural breast shape

32.5.2 Perforator Flaps

When designing the flap, the perforators must be assessed preoperatively. Unidirectional (8 Hz) handheld Doppler assessment usually suffices to identify suitable perforators and should be performed preoperatively to ensure that the flap designed includes the surface marking of the perforator (Figs. 32.7b and 32.8b). Duplex scan could be used in difficult cases and multidetector row CT scanning has also been used [30, 32, 53].

32.5.2.1 Lateral Chest Wall Perforator Flap Planning

LICAP and LTAP Flaps (Figs. 32.7 and 32.8)
These flaps are designed on the lateral chest wall by pinching redundant roll of fat with variable extension around the back depending on the tissue needed to fill the defect. The flap is oriented parallel to the skin tension lines with the tip curving up posteriorly parallel to the underlying ribs and following the angiosome description [54]. Anteriorly the flap design can be altered to suit the incision required to perform the breast cancer resection, usually a curved line following the lateral inframammary fold to the lateral aspect of the breast and to incorporate the best perforators. The perforators are preferably marked preoperatively with a handheld Doppler with the patient lying down simulating the intraoperative position. The LICAPs are found on an average of 3.5 cm from anterior border of LD in the 4th–8th intercostal spaces and most likely to be found in the 6th or 7th intercostal space [31]. The surgery is performed in lateral position with the arm stretched out at 90 degrees in a gutter (Fig. 32.9).

The breast resection is performed through the anterior apart of the incision taking care not to injure the perforators. All the pre-marked perforators are dissected, and none is sacrificed till a dominant pulsatile perforator is found (Figs. 32.7d and 32.8d). The dissection is carried from anterior to posterior aspect as this keeps the option for TDAP or LD flap viable in case there are no reasonable lateral perforators found. Once the perforators are dissected, the rest of the flap is dissected free, islanded and de-epithelialized (Figs. 32.7c and 32.8c). The flap is then inset into the breast by flipping it over on itself or rotating it into the defect (Fig. 32.8e). If the pedicle is long enough, the flap can be rotated through 180 degrees [15, 31]. If the perforator is eccentric within the area of the flap, this rotation may allow significantly greater reach and is often the case with LTAP vessels as the vessels are often long enough and pivot the flaps superiorly, allowing greater flexibility with insetting [17, 18].

The flap usually sits comfortably in the defect and does not require stitches to hold it in place. The donor site is then stitched in two layers and patient is expected to acquire normal range of shoulder movements postoperatively, within a short period with no long-term detriment.

TDAP Flaps
The flap is designed with the patient in the standing position, with the arms at the sides and the hands on the waist. The patient is asked to actively contract her back muscles, at which time the anterior lateral border of the LD muscle appears clearly under the skin and is marked with a line. The proximal perforator branch of the descending thoracodorsal artery branch pierces the muscle in the line of the descending branch (Fig. 32.10), at 8 cm or more from the axillary fold and within 5 cm of anterior border of LD muscle [55]. The piercing point of the perforator must be included in the flap design. The skin marking is similar to the LICAP flap [56].

The exact location of the perforator is difficult to predict preoperatively, so it is useful to mark the potential location of the perforator using handheld Doppler (8 MHz) based on the anatomical landmarks. The perforators are looked for in the area beginning 8 cm below the posterior axillary fold and 2–3 cm medial to the free anterior border of the LD muscle [38], although it may be difficult to differentiate the perforator signal from that from the deep main thoracodorsal pedicle. To overcome this problem, perforator compression test has been suggested whereby applying pressure on the probe tends to dampen the signals if that signal is from the perforator, because the perforator wall is more collapsible as compared to the main vessel [57]. Other forms of imaging such as duplex and CT scan can be used for difficult cases [53].

Thoraco-dorsal artery perforator flaps are raised in a plane above or just below the deep fascia and the perforator identified and dissected through the muscle and up to the thoracodorsal artery itself until the required pedicle length has been achieved (for details see Hamdi et al. [30, 38]). Perforators from the descending branch of the thoracodorsal artery are preferred over the transverse branch, but the inconsistent perforator size, quality, quantity and location mean dissection must be painstaking and are often reported as tedious [38, 55, 58]. If the perforator is less than 0.5 mm in diameter, the flap is at risk of failure, so conversion to a muscle-sparing latissimus dorsi flap is advised. The flap is brought through the muscle and placed in the defect, such that the anterior border lies medially or rotated to lie inferiorly.

32.5.2.2 Superior Epigastric Flap Perforator (SEAP) and Thoraco-Epigastric (TE) Flaps

These flaps are designed along the inferior aspect of the breast. The suitability can be judged by pinching a roll of fat just below the inframammary crease, and the handheld

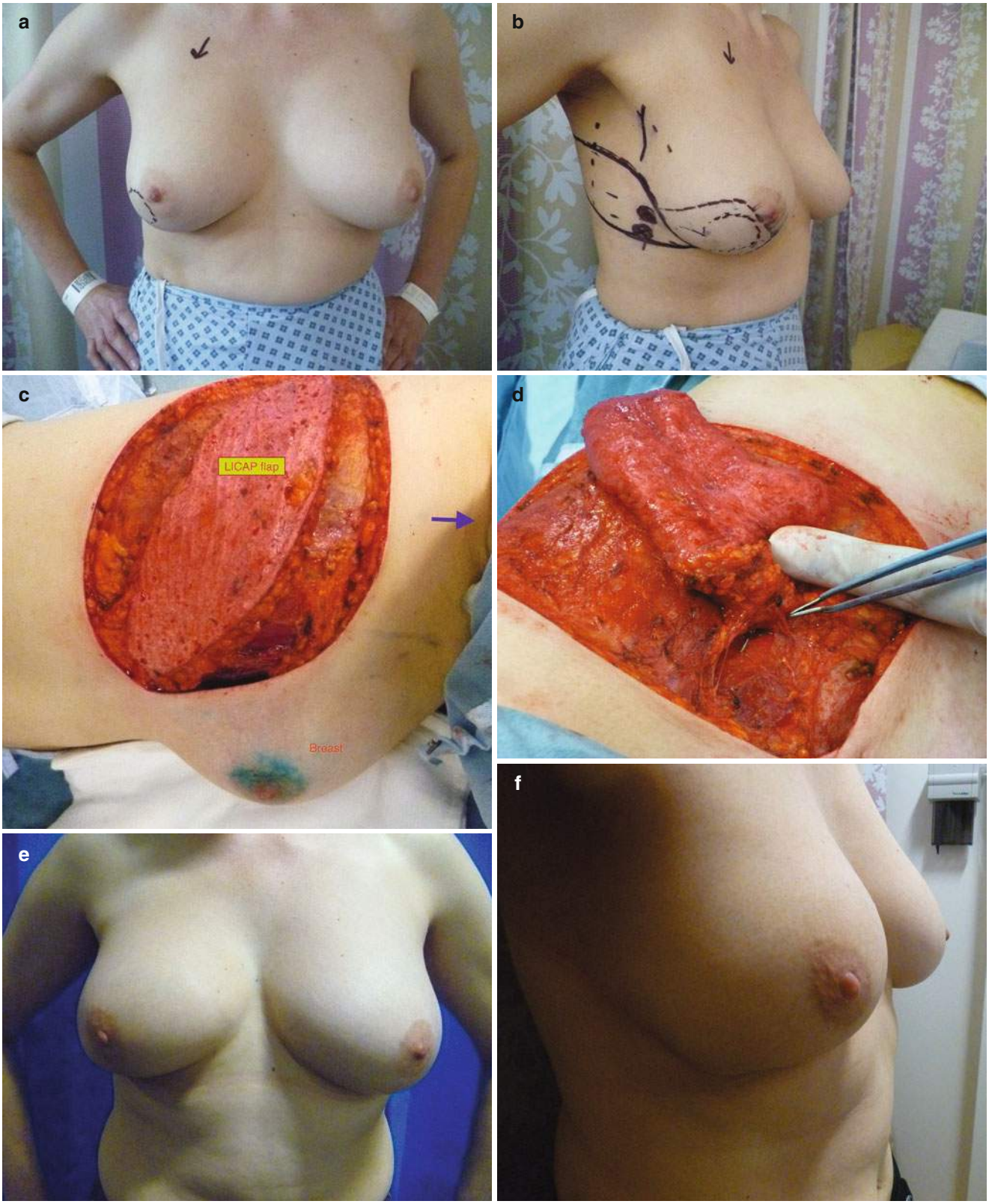

Fig. 32.7 LICAP flap reconstruction. (**a**) 47-year old with 40 mm cancer in the lower outer quadrant of the right breast (preoperative). (**b**) Pre-op marking for LICAP flap. (**c**) Intraoperative picture showing the flap dissected (arrow points towards head with patient in lateral position). (**d**) Intraoperative picture showing the LICAP perforator. (**e**) Appearance at 2 years after radiotherapy on right side. Patient received chemotherapy after surgery. (**f**) Appearance of the lateral chest wall scar 2 years after surgery and radiotherapy

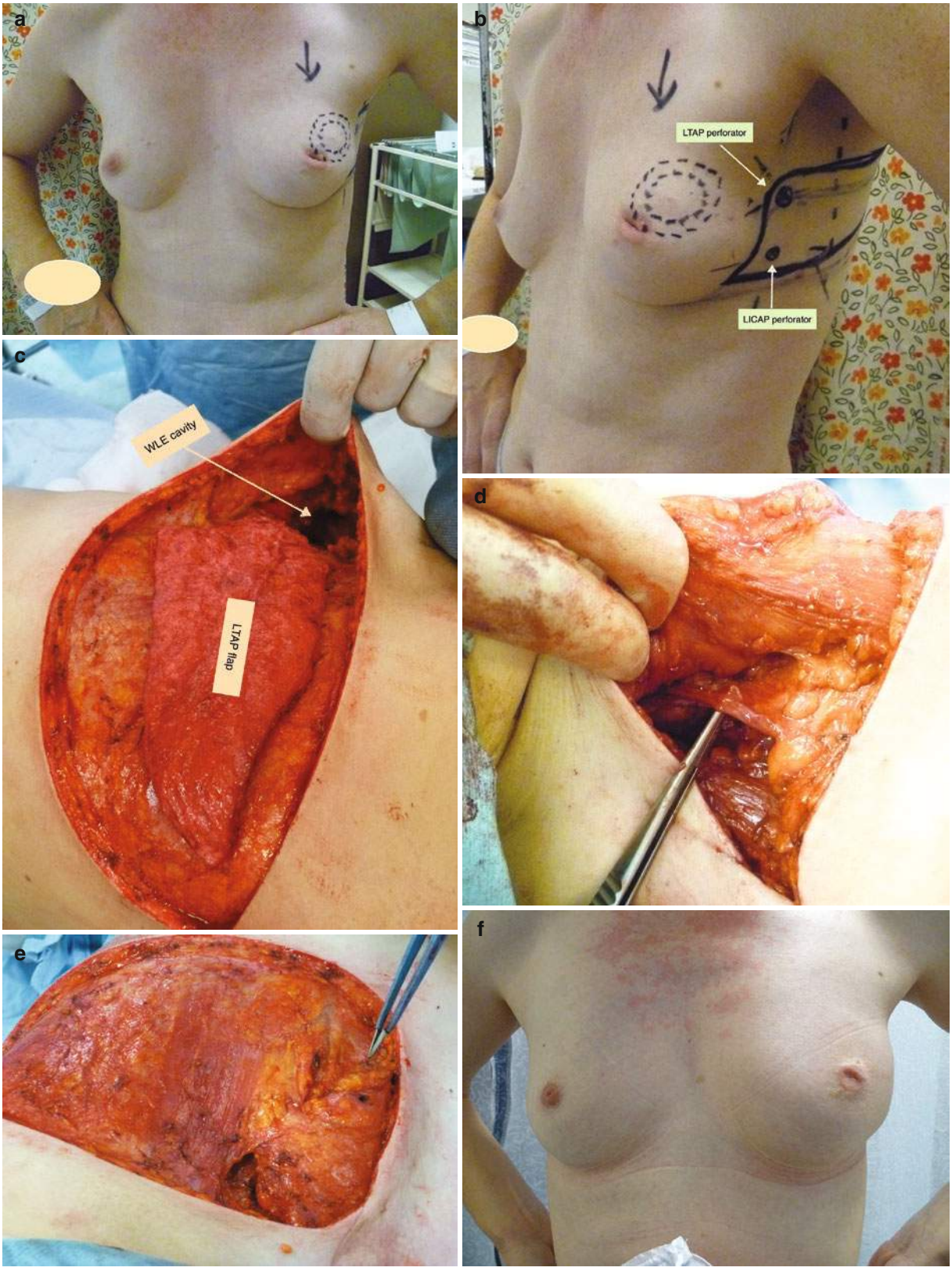

Fig. 32.8 LTAP flap. (**a**) Preoperative picture of 41-year-old lady with a 20 mm cancer in upper outer quadrant of a small "A-cup" breast. (**b**) Preoperative marking of lateral chest wall perforator flap. The X marks refer to the location of the perforators as marked preoperatively using handheld Doppler. The hatched line refers to the surface marking of the lateral border of the *latissimus dorsi* muscle. (**c**) Intraoperative photograph depicting the wide local excision cavity and the dissected LTAP flap (patient in lateral position with head on the right). (**d**) Intraoperative picture focussing on the lateral thoracic artery vessels, descending down from axilla before reaching the flap (patient in lateral position with head on the left). (**e**) Flap folded and flipped in to the defect (patient in lateral position with head on the left). (**f**) Appearance and symmetry 1 year after radiotherapy to the left breast. (**g**) Appearance of the scar 1 year later

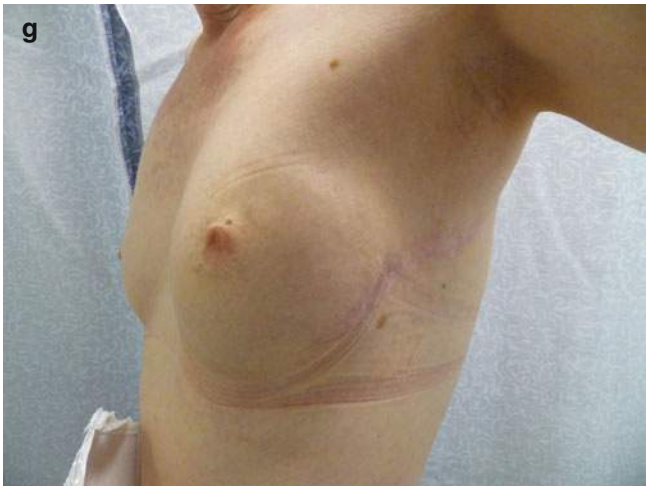

Fig. 32.8 (continued)

Doppler can be used to map out the perforator(s) [48]. These flaps can be used to fill the lumpectomy defects in the lower and inner quadrants of the breast. The ability of the flap to reach the intended distance can be estimated preoperatively whilst mapping out the perforator. Most flaps can be islanded and the arc of rotation allows good reach and flexibility [13]. The defects in upper-inner quadrants need the flap to be tunnelled; therefore, it's important that the flap is not too wide to avoid the bulk, which might interfere with the aesthetic outcome. The downside of this approach is the extent of scar and disruption of inframammary fold (IMF). If the design of the flap is not too wide, most scars can be well hidden in the IMF crease; however, the situation might demand wide design resulting in downward displacement of the scar that is visible below the breast.

The flap is designed as an ellipse along the IMF from the midline and extending laterally following the natural fold of the breast (Fig. 32.1). The incision can be adjusted according to the position of the most prominent perforator, and it is recommended that the flap be islanded to prevent a bulge that would otherwise result due to tethering of flap near the xiphoid process in midline.

Although most flaps designed along the inferior aspect of the breast (in the thoraco-epigastric area) are based on the SEA perforator, this flap design could also be used for the lateral chest wall perforators (depending on the clinical suitability) or for random-pattern advancement flaps to fill the lower midline defects [10].

32.6 Outcomes

The literature on volume replacement comprises mainly single-institution series, i.e. level 3 evidence. There is a lack of objective outcome reporting very few comparative studies, and it is likely that publication bias exists. It is not clear whether volume replacement techniques are being widely used by surgeons other than the recognised experts such as Hamdi, Rainsbury and Munhoz. Those achieving less successful outcomes are less likely to report their results.

32.6.1 Oncological Outcomes

Although the volume of literature on oncoplastic surgery is expanding rapidly, the indications for surgery, the techniques used and the duration of follow-up remain unclear. Overall, oncoplastic breast-conserving surgery has approximately equivalent local recurrence rates to that of standard breast surgery. This may reflect the balance between allowing wider excision for some tumours and being used in patients with more extensive disease [59–62]. A recent meta-analysis compared outcomes in >3000 patients following oncoplastic conservation with >5000 following conventional breast-conserving surgery [63]. Although there are limitations with this approach, women treated by oncoplastic techniques had significantly fewer re-excisions for positive resection margins and experienced significantly fewer local recurrences than those treated by conventional techniques.

Tables 32.1 and 32.2 summarise the limited literature on local recurrence after volume replacement with distant flaps. For LDm series, the local recurrence rates vary from 0 to 5% with a stated follow up of 24–54 months. It is striking that most reports on perforator flap surgery focus on the techniques of surgical reconstruction, rather than the oncological aspects of these procedures. This may reflect the interests of the population of surgeons undertaking the different forms of reconstruction with more breast/general surgeons doing LDms and plastic surgeons carrying out the perforator flaps. Alternatively, it may be simply because perforator flaps have been used in fewer patients and more recently so that follow up data is only now becoming mature enough for scrutiny [15, 17, 18]. Finally, it is reasonable to assume that the oncological decision-making with regard to tumour excision is dissociated from the method used to fill the defect, so local recurrence rate should not vary according to reconstructive technique used. However, Rietjens et al. [62] report that LD volume replacement was used for cases with a large defect and that larger tumours had a higher recurrence rate, so it is possible that over time, a trend will emerge.

32.6.2 Cosmetic and Other Outcomes

Assessment of cosmetic outcome varies from superficial to detailed. Again, the lack of data on cosmetic outcome after perforator flap surgery may simply reflect the proof of principle nature of many of the reports to date. For example, Hamdi et al. give extensive detail on surgical technique but do not comment on aesthetic outcome [38]. Munhoz et al. reported a series of 13 patients who underwent LICAP, all with "satisfactory results," but the assessment method was

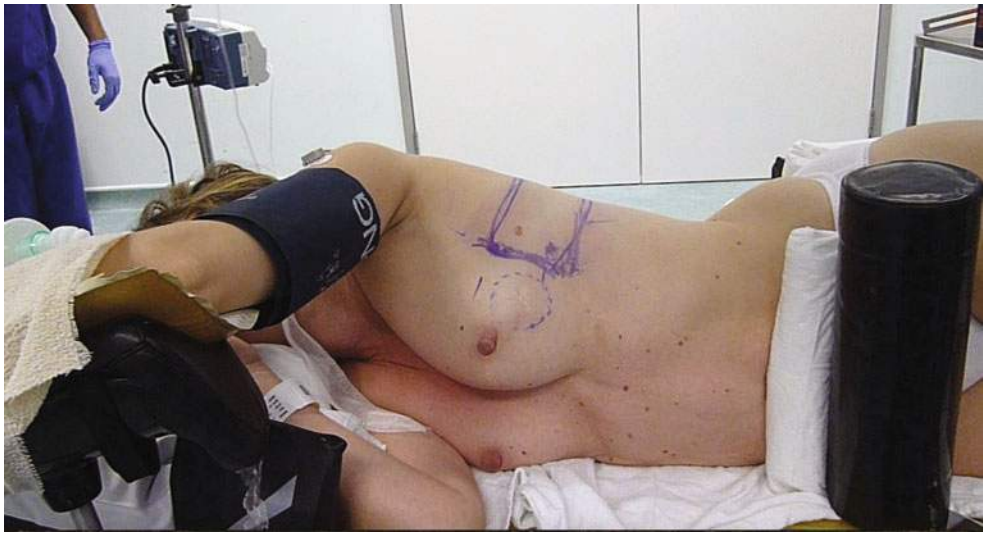

Fig. 32.9 Patient positioning during surgery. All aspects of surgery including wide local excision, sentinel lymph node biopsy and flap dissection including inset can be performed in this position

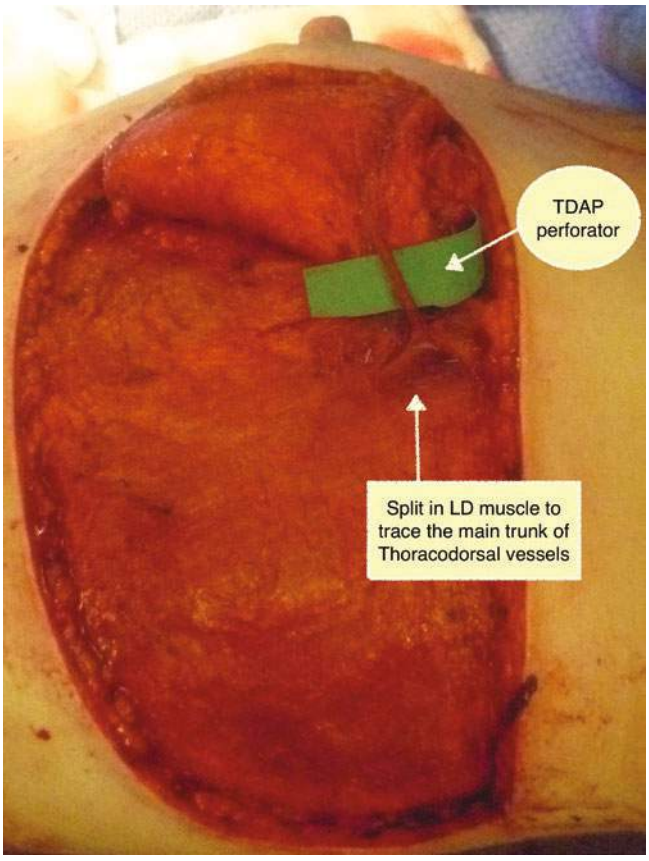

Fig. 32.10 Intraoperative picture of TDAP dissection

not described. However more recent publications including a meta-analysis using pooled results have reported significantly greater satisfaction with cosmetic outcome following both volume replacement and displacement procedures when compared with more straightforward breast-conserving techniques [18, 63].

Not surprisingly, when quadrantectomy was compared with quadrantectomy plus immediate volume replacement, the symmetry (as assessed by Moire topography) was satisfactory after volume replacement, but severe deformity was observed after lateral quadrantectomy and no reconstruction [25]. Hernanz et al. used panel assessment of cosmetic outcome after LD volume replacement initially [64] and then followed-up an overlapping cohort including 19 of the same patients [65] using breast cancer conservative treatment (BCCT) cosmetic results software [66]. This standardised, objective assessment may in the future enable inter-series comparisons and comparisons over time, though since different methods were used in the two Hernanz studies, it is difficult to interpret. He commented that four (21%) had deteriorated from good to fair.

Although comparative studies are always difficult in surgical research because "clinical judgement" often results in a patient being advised to follow one course of action or another, in order to assess the results of volume replacement surgery after breast-conserving surgery, one would need to compare with the alternative, that is, a skin-sparing mastectomy and immediate breast reconstruction. Three studies describe this comparison. Gendy et al. report postoperative complications, further surgical interventions, nipple sensory loss, restricted activities and cosmetic outcome by panel assessment [49]. These were all better in the LDm group than in the group of patients undergoing mastectomy and immediate breast reconstruction. Anxiety about residual cancer and ease of breast self-examination were similar in both groups. Similarly, Dixon et al. compared women undergoing LDm reconstruction with those having standard breast-conserving surgery or mastectomy and immediate whole breast reconstruction. Patients with LDms reported better shape and symmetry and less self-consciousness [51]. Bassiouny et al. compared patients

Table 32.1 Case series of latissimus dorsi miniflap volume replacement

Author	Flap	*N*	Tumour size	WLE weight	LR and follow-up	Cosmesis	Complications
Noguchi 1990 [25]	LDm	5				4/5 good cosmesis by Moire topography	
Raja 1997 [52]	LDm	20	25 mm	57% >150 g		Cosmetic failure uncommon (10% vs. WLE 34%)	
Kat 1999 [82]	LDm	30					Two minor wound infections, six seromas
Dixon 2002 [51]	LDm	25		Median 94 g		Similar to WLE	21 seromas, no other major morbidity
Gendy 2003 [49]	LDm	49	22 mm		2 LR at 53 months but had not had RT	Significantly better than for SSM	6% req. further surgery. One brachial plexopathy
Losken 2004 [83]	LDm	39			5% at 44 months		
Nano 2004 [84]	LDm	18	Median 33 mm	130 g	0 at 24 months	17/18 satisfied (1 required mastectomy)	14 seromas, no major complications
Munhoz 2005 [85]	LDm	48	44% >2 cm				Flap complications in 7, donor site in 12
Naguib 2006 [86]	LDm	29	Median 5.2 cm	219 cm^3		69% cosmetic satisfactory	Persistent seroma 52%. No sepsis or flap viability problems
Navin 2007 [87]	LDm	51	20 mm	217 g	None at mean 33 months	86% of respondents satisfied	1 flap necrosis
Rusby 2008 [19]	LDm	110	34 mm	207 g	1 at median 41.4 months		3 infection/wound problems
Hernanz 2011 [65]	LDm	41	22 mm	Median167cc	1/41 (2.4%) at 54 months	65% satisfactory	

Table 32.2 Case series of other pedicled flaps in reconstruction after breast conservation surgery

Author	Flap	*N*	Median tumour size	Median weight of WLE	LR and follow-up	Cosmesis	Complications
Hamdi 2004 [30]	TDAP ICAP	18 3					2 partial flap necroses
Hamdi 2008 [38]	TDAP to various sites 73 immed. partial reconstruction 5 delayed	99 73 5					90 perf, 10 MS flap One major flap necrosis, partial in 3
Zaha 2010 [88]	Omental flap	24	32 mm	180 cc	None, duration of follow-up not stated	Excellent or good in 93%	
Munhoz 2011 [15]	LICAP AICAP	11 2	9 were <2 cm	165 g	None at mean 32 months	92% satisfied or very satisfied	2 wound dehiscence, 1 fat necrosis
McCulley 2015 [17]	LTAP	31	–	–	–	–	No flap loss
Roy 2016 [18]	LICAP and LTAP	40 (11 with 2-stage approach)	35 mm	96 g	None at median 24 months		1 partial flap loss due to hematoma 2 fat necrosis requiring excision

Several other oncoplastic series excluded, e.g. [14, 62, 67, 89, 90], because it is not possible to separate data for volume replacement after breast-conserving surgery from other cohorts

WLE wide local excision, *LR* local recurrence, *LDm* latissimus dorsi miniflap, *TDAP* thoracodorsal artery perforator, *ICAP* intercostal artery perforator, *SEAP* superior epigastric artery perforator, *LICAP* lateral intercostal artery perforator, *AICAP* anterior intercostal artery perforator, *TUG* transverse upper gracilis

undergoing quadrantectomy and immediate volume replacement with those undergoing nipple-sparing mastectomy and immediate reconstruction with an LD flap with patient self-evaluation questionnaire and two independent observers of photographs using the Harris criteria. They found similar rates of complications and no significant difference in aesthetic results in the two groups [67].

The scar required for chest wall perforator flaps is a long scar on the lateral chest wall, and it is recommended that the women are warned beforehand in order to manage the

expectations (Figs. 32.7f and 32.8g). There is a favourable trade-off between the aesthetic outcome and the scarring (Figs. 32.7e and 32.8f). Moreover more than half the length of the scar is covered by radiotherapy, which fades the scar significantly. Similarly the scar for TE flaps can be cosmetically unappealing but is visible, in majority of the women, only with arms raised, as it sits in the inframammary crease (Fig. 32.1d).

32.6.3 Complications

Complications are common to all volume replacement flaps. Oncologically, these include the possibility of positive margins, which may only be known some days after the procedure. Oncoplastic techniques allow larger volume excisions, so the incidence of positive margins is lower than that in a population undergoing standard breast-conserving surgery [63]; however, there is still a quoted rate of 3–16% [52, 60, 68]. This poses problems when volume replacement is carried out as an immediate procedure. Strategies to prevent this include assessing bed biopsies with frozen section at the time of surgery and carrying out full cavity re-excision until the new margins are confirmed clear [19]. Others advocate a delayed approach, waiting for final pathology results before returning to theatre a week or two after ablative surgery to perform the reconstruction [18, 51]. The downside of this is a second operation, and in the majority of cases, margins are clear if advocated routinely [51]; certainly this has a place for use in carefully selected patients [18].

There have been concerns about mammographic follow-up after volume replacement surgery. The flap may undergo focal necrosis resulting in oil cysts or other mammographic changes. However, several reports state that distinguishing benign postsurgical changes from local recurrence is possible radiologically in most cases [2, 69, 70].

Shoulder girdle dysfunction has been closely studied in patients undergoing full breast reconstruction using the LD muscle with or without an implant. Button et al. [71] used the DASH score (Disabilities of the Arm, Shoulder and Hand) to document changes from preoperative function up to 3 years after surgery and identified a functionally insignificant increase in score in patients undergoing whole breast reconstruction using autologous LD. Gendy et al. [49] investigated physical disability after LDms and whole breast reconstruction with LD and implant reconstruction. They found equivalent degrees of shoulder disability, affecting work in 25% of both groups, although less than 5% of respondents required regular analgesia for symptoms. Hamdi et al. [72] reported on a series of 22 patients who had undergone TDAP flap volume replacement and participated in a functional study of shoulder function. When comparing the LD strength on the operated side with the unoperated side, LD strength seemed to be maintained. Shoulder mobility was similar, but active and possible forward elevation and passive abduction were significantly reduced.

Seroma formation is widely reported after LD reconstruction. Strategies to reduce this include use of drains, quilting, tissue adhesives and steroid injections [73–76]. Interestingly, Hamdi et al. report no seroma formation after TDAP flap [38].

Another symptom unique to LDm reconstructions is that of muscle movement and twitching. The surgeon must decide whether the thoracodorsal nerve should be preserved at the time of primary surgery. This may reduce the volume loss associated with muscle atrophy but does leave the muscle innervated and therefore liable to contract when the patient forcefully adducts the upper arm. Rarely, muscle twitching is spontaneous, repetitive, forceful, visible and distressing for the patient, requiring secondary division of the nerve.

Flap loss rates are hard to gauge as many studies report the use of TDAP and ICAP flaps for a variety of indications and include both free and pedicled flaps [38, 77]. The flap loss rate in descriptions of the TDAP and LICAP flaps for partial breast reconstruction was partial flap loss in 2 of 31 in 1 series [30] and 0 in others [15, 18].

LDm reconstruction of partial mastectomy defects is often criticised as "burning bridges" because if a patient develops in-breast recurrence, the LD muscle is no longer available for a salvage reconstruction postmastectomy. However, recurrence in this context is an uncommon event [19], and when it occurs, mastectomy and free flap reconstruction are the treatments of choice. The weight gain commonly observed following breast cancer treatment (average 1–5 kg [78]) may increase the availability of alternative autologous tissue for reconstruction in this uncommon situation.

32.7 The Future of Volume Replacement

As more surgeons develop oncoplastic skills, the need for secondary correction of partial mastectomy defects should diminish. Alternative methods of filling defects, such as lipomodelling, are already being used (see Chap. 61) [Rietjens and Urban], but the longer-term cosmetic and oncological outcomes of this approach are unknown. Primary reconstruction of resection defects is a safe and established technique, which allows women to choose breast conservation instead of mastectomy without compromising oncological or cosmetic results [63]. This approach is already pushing the boundaries of conservation to include patients with tumours reaching or greater than 50 mm [79]. This "extreme oncoplasty" is likely to gain traction using flaps, which provide sufficient volume to fill these substantial defects. Two-stage approach is a potential option for patients with breast cancer size bordering onto mastectomy, whereby the lumpectomy is performed and cavity filled with saline to

maintain the shape and size of the cavity whilst the histology ensures clear margins [18]. The cavity is then reconstructed with perforator flap as a second operation (done within 3–4 weeks after the first surgery). This approach helps to extend the indications for breast conservation surgery in borderline cases, which otherwise could have ended up with mastectomy and also prevents unnecessary partial breast reconstruction procedure in women needing mastectomy due to tumour extent.

The LDm is a useful option for partial breast reconstruction and can be performed by all surgeons who routinely carry out LD reconstruction after total mastectomy. Several units have published reasonable-sized series suggesting that this is a reliable technique (Table 32.1). Unlike perforator flaps, careful harvest of the LDm can provide enough volume to reconstruct extensive defects. In a recent series, LDms and therapeutic mammoplasty techniques were used to reconstruct large defects following the resection of tumours with a mean span of 67 (50–177) mm, with excellent local control and favourable patient-reported outcomes [80].

The popularity of deep inferior epigastric artery and other perforator flaps for whole breast reconstruction has led to wider availability and reliability of perforator flaps in general. LICAP and TDAP flaps are used in a manner similar to LDm and have the advantage of preserving the function of the muscle. LICAP flaps have the advantage that they do not interfere with the ability to perform LD flaps should that be required in future for total breast reconstruction, although the excellent tumour clearance and local control that can be achieved following LDm reconstruction makes this a rare event [81]. Moreover, the subsequent use of LD to reconstruct a mastectomy defect after perforator flap-assisted breast conservation is likely to require additional implant volume, because of the overall flap volume sacrificed during the perforator flap harvest. As the previous use of radiotherapy is a relative contraindication to the use implant-assisted LD reconstruction, a free flap technique is likely to be the treatment of choice in this uncommon situation.

Perforator flaps do require specific skills and expertise and it seems that the use of these flaps is confined to a few very specialist centres [14, 15, 17, 18, 30]. The experience with the use of these flaps is gradually increasing, even then the individual published series have small numbers. The LICAP (and LTAP) flaps have limited mobility due to short perforator size, thus limiting the indications to the lateral quadrant tumours only; which may explain the small numbers in published series. TDAP flaps have similar mobility to LDms and thus have the potential for wider use, but experience in the published literature is rather very limited, probably due to the expertise required for dissection of the perforator. The perforator flaps are gradually gaining favour and hopefully more data on outcome will be available with gain in wider experience.

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Nonconventional Techniques in Oncoplastic Surgery

33

Mario Rietjens, Cicero Urban, and Visnu Lohsiriwat

33.1 Introduction

The concept of oncoplastic surgery (OP) is not so complicated. If the surgeon can manage three "basic" reduction mammaplasty techniques such as techniques derived from the upper nipple and areola blood supply (superior pedicle) [1–3], techniques derived from the lower/posterior nipple and areola blood supply (inferior pedicle) [4–7], and techniques derived from glandular nipple and areola blood supply (periareolar) [8, 9], it is possible to solve around 90% of the cases. In this chapter, the goal is to show you possible solutions in special cases that seem initially too much complicated due to anatomical variations, tumor locations, or patient's wishes.

33.1.1 Oncoplastic Surgery with Implants

The indication for use of prosthesis is always problematic in cases of partial immediate reconstruction after quadrantectomies as it is difficult to forecast aesthetic results after external radiotherapy. There is a higher risk of periprosthetic capsule formation, which can lead to malpositioning of the prosthesis with unsatisfactory aesthetic results. Nowadays, with the development of the new techniques of external radiotherapy, with an optimal target dose calculation, maybe could be an indication of small breast cases with reduced thickness and by using a wide base and low projection implant just to maintain the volume (Figs. 33.1 and 33.2).

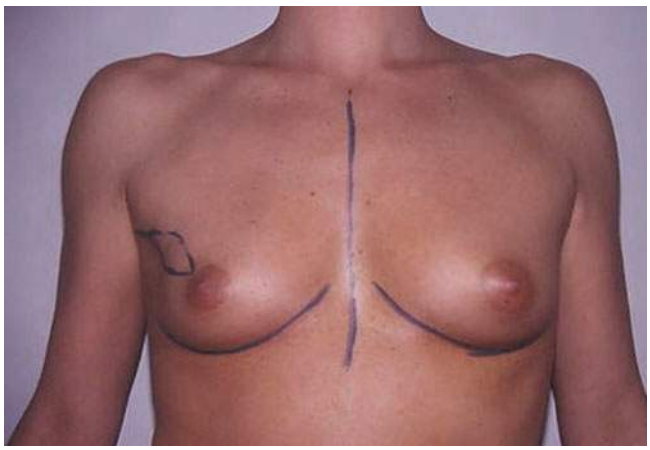

Fig. 33.1 Preoperative image: upper outer quadrantectomy of the *right* breast

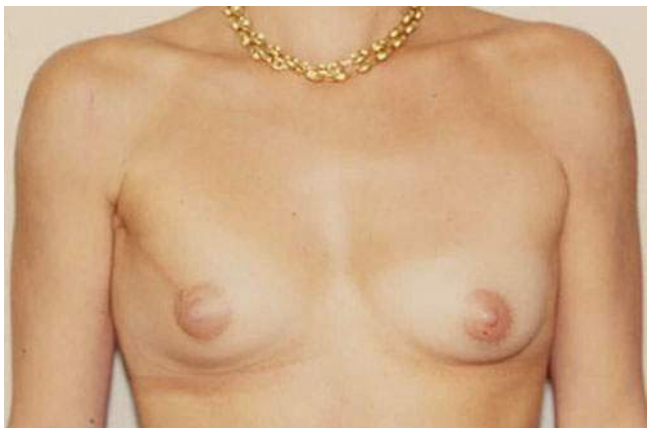

Fig. 33.2 Postoperative results 6 months after subpectoral 90-cm^3 implant insertion and external radiotherapy

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_33

33.1.2 Oncoplastic Surgery Plus Intraoperative Radiotherapy and Bilateral Breast Augmentation with Implants

This is a technique performed routinely in the European Institute of Oncology (IEO) for patients with small tumors and small breasts that wish a conservative surgery and also an increase in the volume of the breast [10–12]. In order to avoid postoperative complications due to the traditional external radiotherapy, an intraoperative radiotherapy can be done. All patients were treated with breast-conserving surgery (quadrantectomy). The ELIOT (electron beam intraoperative therapy) was delivered by two mobile linear accelerators immediately after breast resection with a single dose of 21 Gy that in radiobiology equivalence is similar to the 45 Gy of external radiotherapy. In young patients, only a boost in the tumor bed of 10 Gy is performed, and a complementary external radiotherapy is done after the surgery [13].

The quadrantectomy approach can be done through a periareolar incision. After the tumor resection, the lateral glandular flaps are undermined to allow the insertion of two metallic disks (lead and aluminum) to protect the thoracic wall from the radiotherapy diffusion. After that, the mobile radiotherapy equipment is placed, and the calculated dosage is applied in the gland around the quadrantectomy. Then, the reconstructive step begins with the insertion of the prosthesis below the pectoralis major muscle and with the use of glandular flaps to cover the defect from quadrantectomy. The same implant is also used in the contralateral breast augmentation (Figs. 33.3, 33.4, 33.5, and 33.6).

33.1.3 Combined Mammaplasty Techniques

The oncoplastic surgeon with good experience with the main mammaplasty techniques can in special indications, as breast

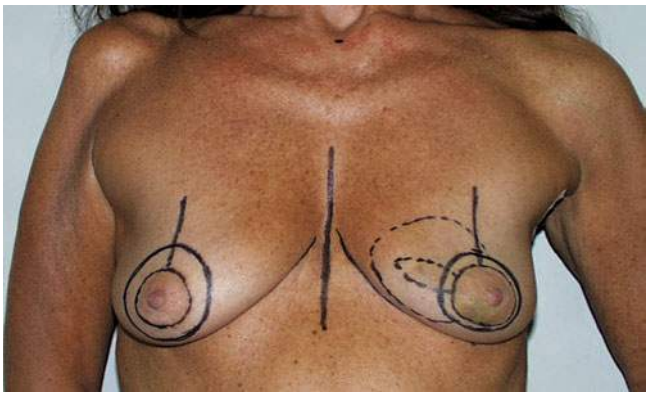

Fig. 33.3 Preoperative drawings: T1 tumor located between the internal quadrants of the *left* breast

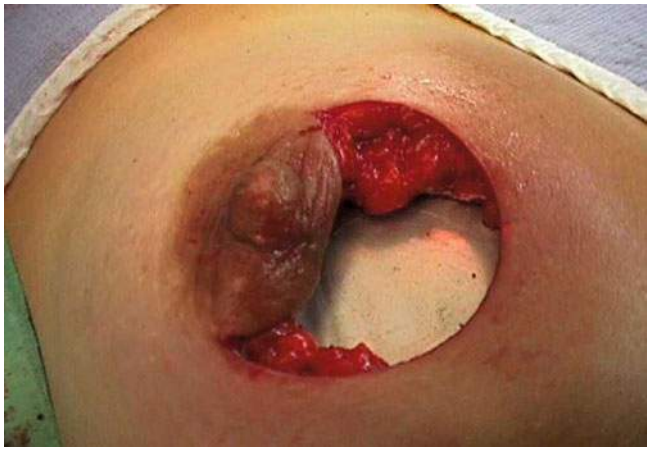

Fig. 33.4 After excision of the tumor, the metallic disks (aluminum and lead) are placed to protect the thoracic wall before starting the electron beam intraoperative therapy

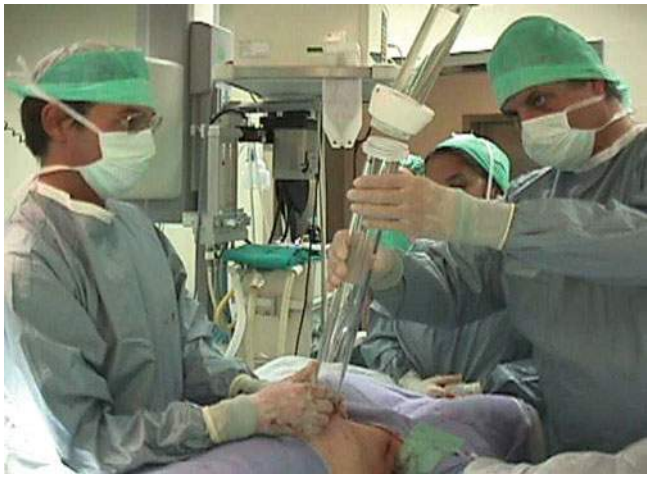

Fig. 33.5 Intraoperative image: sterile collimator adjustment to deliver the intraoperative radiotherapy

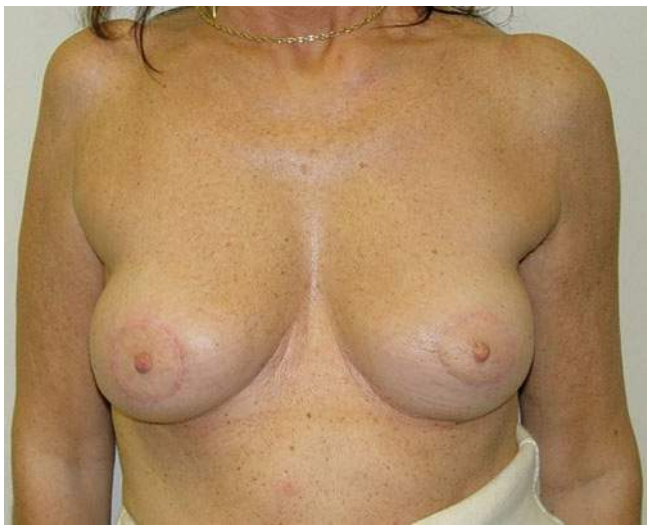

Fig. 33.6 Postoperative image at 6 months: good cosmetic results without capsular contracture or radiodystrophy

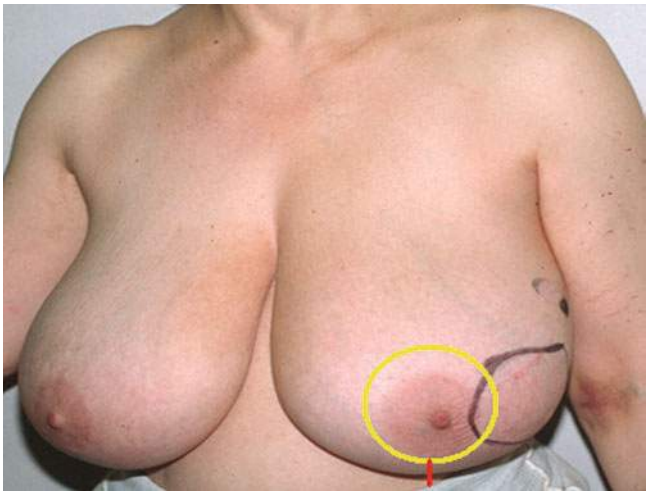

Fig. 33.7 Preoperative image: the *black line* is the tumor circumference

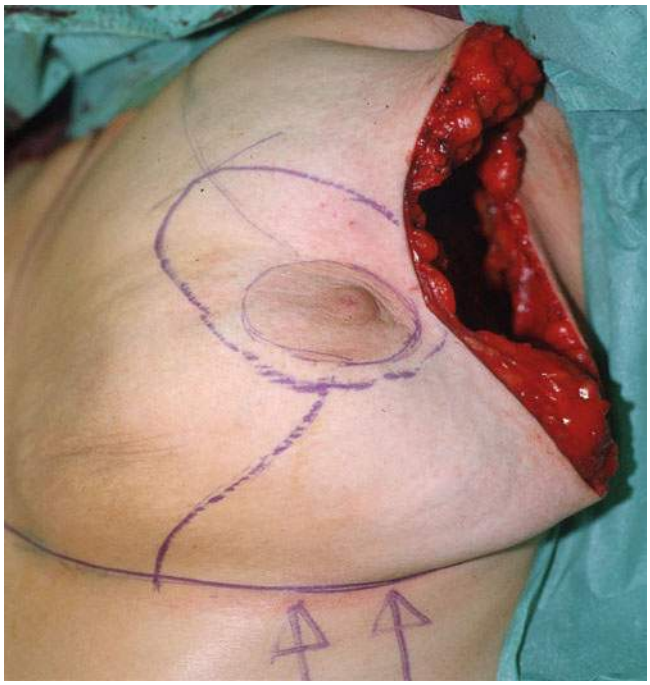

Fig. 33.8 Intraoperative image after the quadrantectomy (weight 420 g) and the drawing for Skoog and lower outer pedicle technique

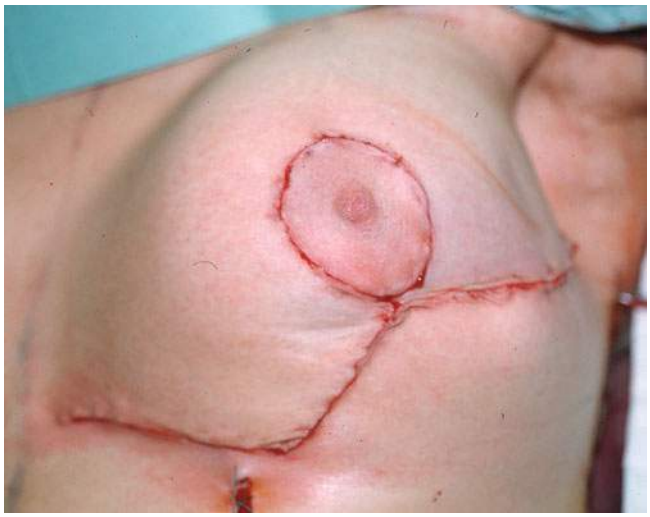

Fig. 33.9 On-table view

size and tumor localization, combine two or more techniques to achieve good cosmetic results. The basic requirement is a good knowledge of breast blood supply, in order to avoid skin and/or glandular necrosis.

A useful technique in cases of big tumors in the upper outer quadrant and huge and ptotic breasts can be a double pedicle. One pedicle is similar to Skoog technique, in order to pull up the nipple and areola complex with good blood supply [14, 15]. A second pedicle is a skin glandular pedicle, based on the vascular pedicles from the lateral border of pectoralis major muscle, and will be used to cover the glandular defect in the upper outer quadrant. This is a good solution in this situation, with tumors very superficial, and the skin over the lump is oncologically necessary to be removed; the only disadvantage is the large scars (Figs. 33.7, 33.8, 33.9, and 33.10).

Another option for tumors located in the upper outer quadrant can be a technique similar to Lejour's technique but using the inferior triangle of glandular tissue rotate to cover the quadrantectomy defect (Figs. 33.11, 33.12, 33.13, and 33.14). This technique can be used in large breasts with medium ptosis degree, and the advantage is the scar shortness.

33.1.4 Fasciocutaneous Abdominal Flaps

Small tumors in small breasts are always a challenge to get good cosmetic results with a conservative surgery. In cases of thin patients with small breast without ptosis and small tumors located in the inferior quadrant, can be indicated a fasciocutaneous flap harvest just above the inframammary fold and rotate to cover the defect. The flap should be taken just above of the inframammary fold and the pedicle oriented in the medial portion to preserve the perforator vessels coming through the upper part of the rectus abdominal muscle. The flap orientations follow the inframammary fold in order to maintain the scar exactly at this level to be less visible (Figs. 33.15 and 33.16) [16].

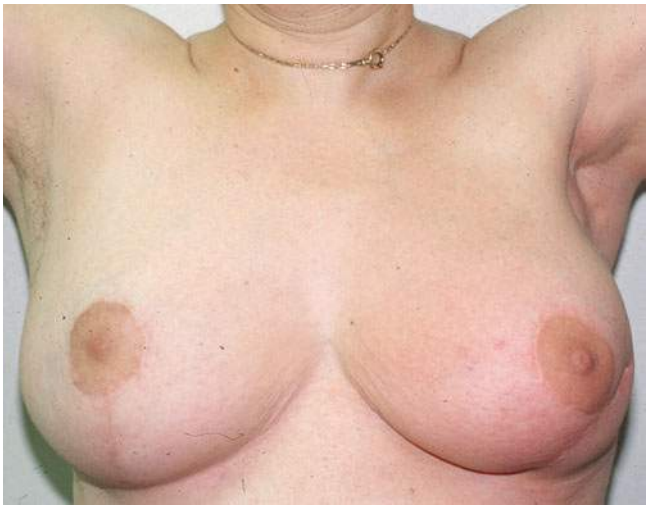

Fig. 33.10 Cosmetic results 3 months after radiotherapy

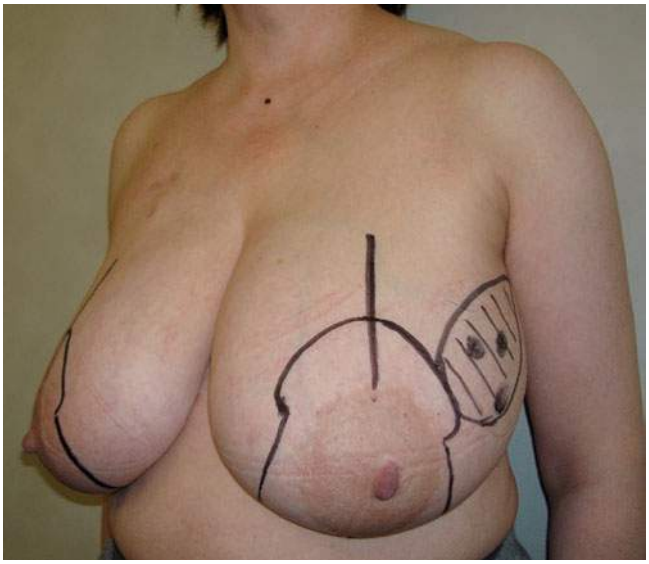

Fig. 33.11 Preoperative image: trifocal tumor in the upper outer quadrant. The drawing pattern is similar to that for the Lejour technique

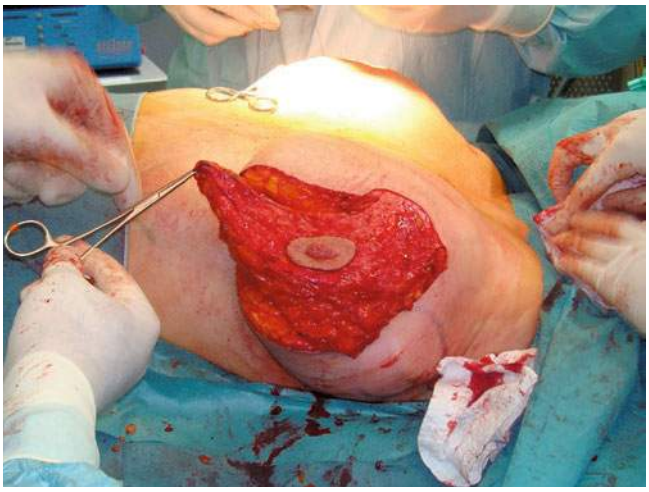

Fig. 33.12 Intraoperative image: after the quadrantectomy, a glandular flap is prepared on the basis of the upper inner quadrant

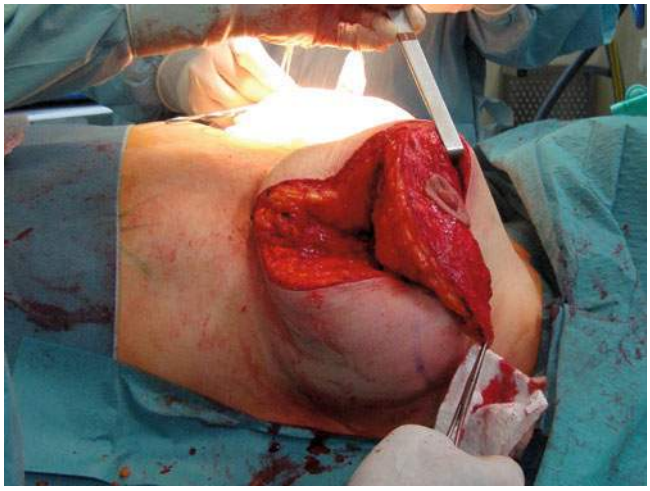

Fig. 33.13 Intraoperative image: the inferior triangle of glandular tissue normally removed with this technique will be rotated to cover the upper outer defect

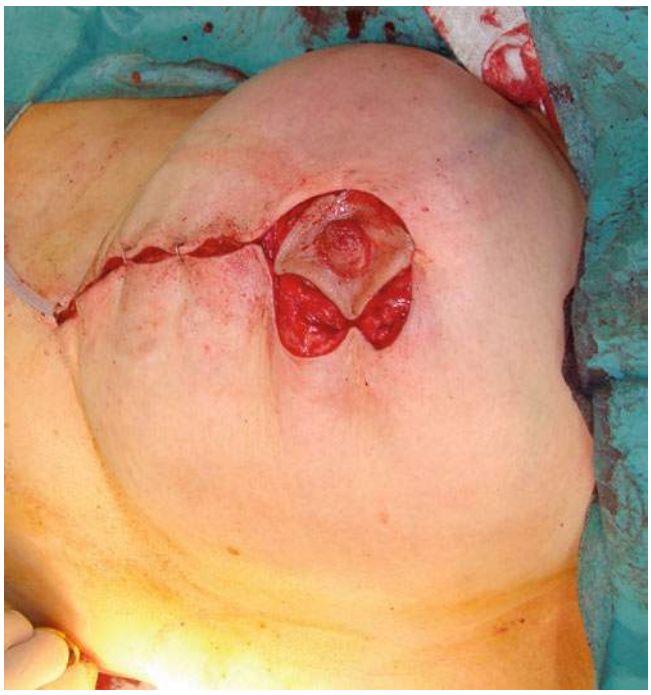

Fig. 33.14 Intraoperative image showing the final reshaping with only periareolar and vertical scars

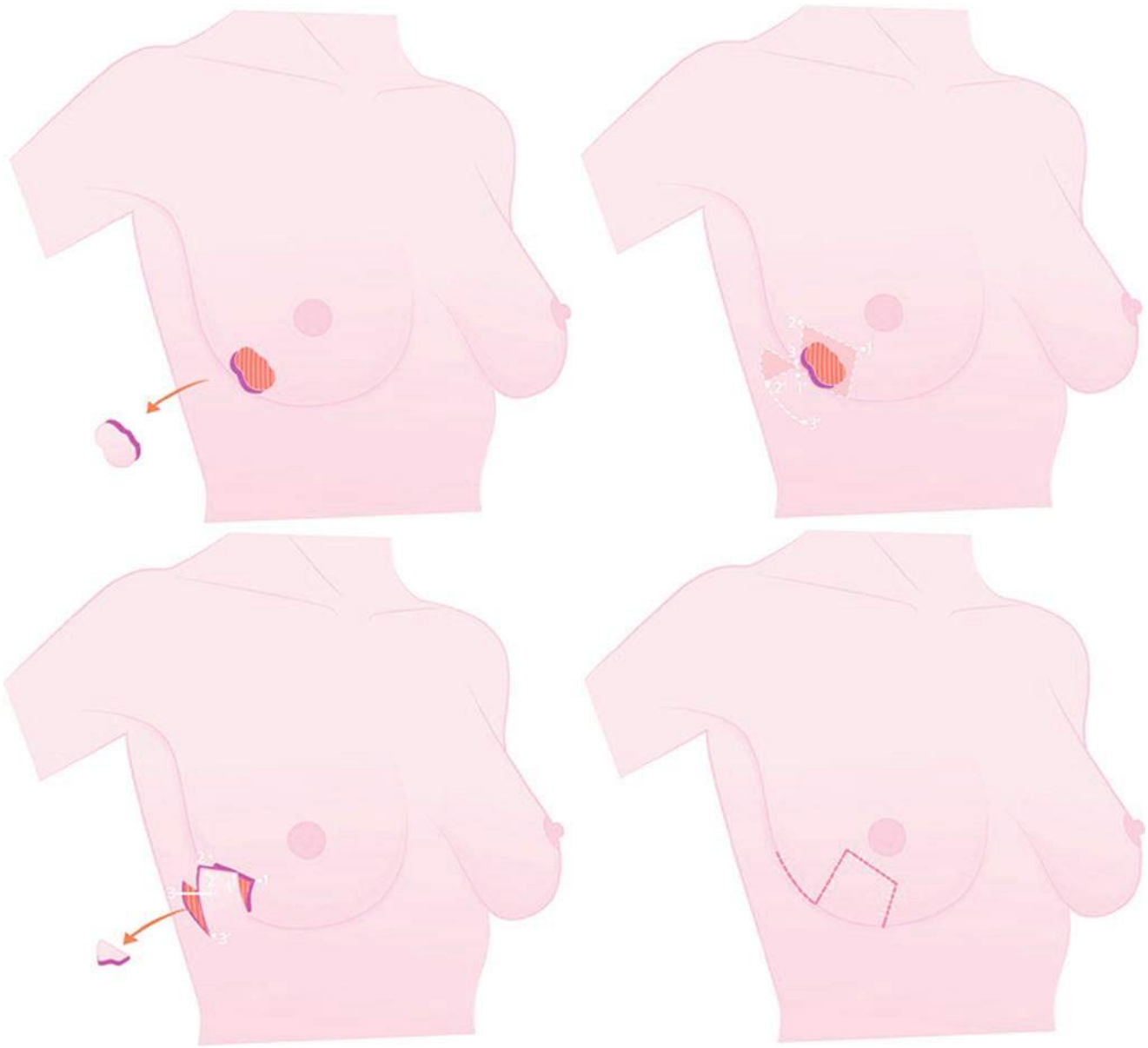

Fig. 33.15 Other options for lateral rotation skin flaps

Fig. 33.16 Options for inferolateral fasciocutaneous flaps

33.1.5 Reshaping with Nipple and Areola Grafting

Some of "special indications" of large conservative surgery can be taken in consideration following the patient's request. In cases of large tumors or multifocal tumors in the superior quadrants, a large quadrantectomy with skin excision can be indicated. In these cases, a complete transposition of the lower pole of the breast in order to have a good breast shape can be available, but the nipple and areola complex should be transposed as a skin graft (Figs. 33.17, 33.18, 33.19, and 33.20) [17].

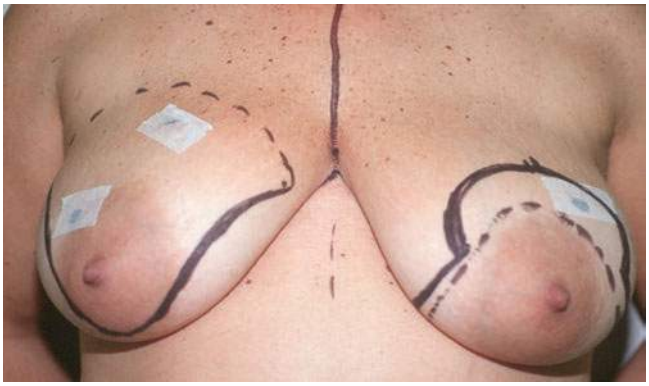

Fig. 33.17 Preoperative planning: bifocal tumor in the upper pole of the breast very close to the skin

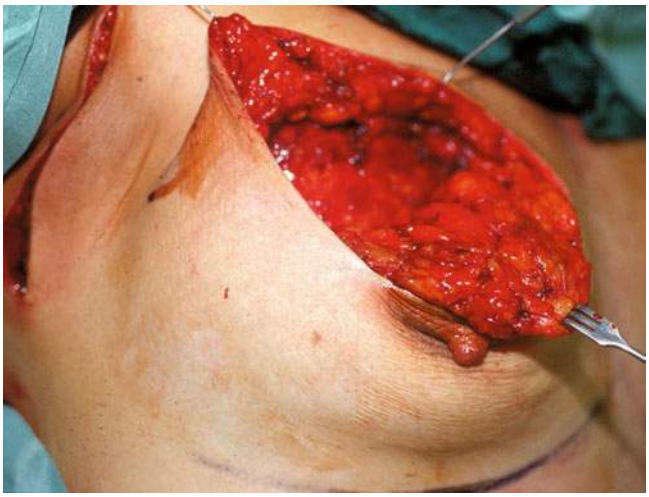

Fig. 33.18 Intraoperative view after the large skin and glandular resection

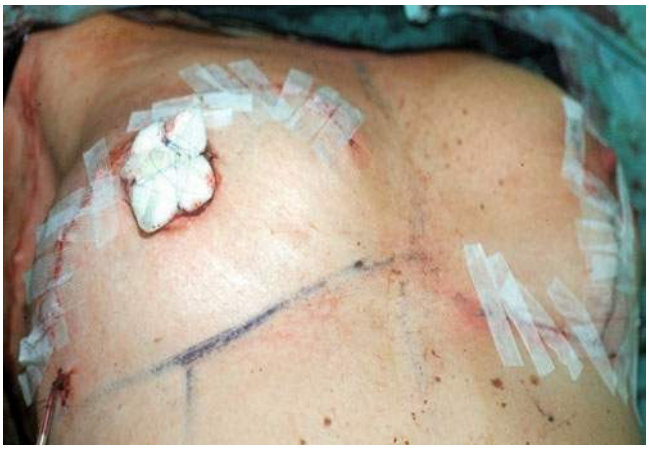

Fig. 33.19 Intraoperative view after glandular reshaping and nipple and areola transposition as a skin graft

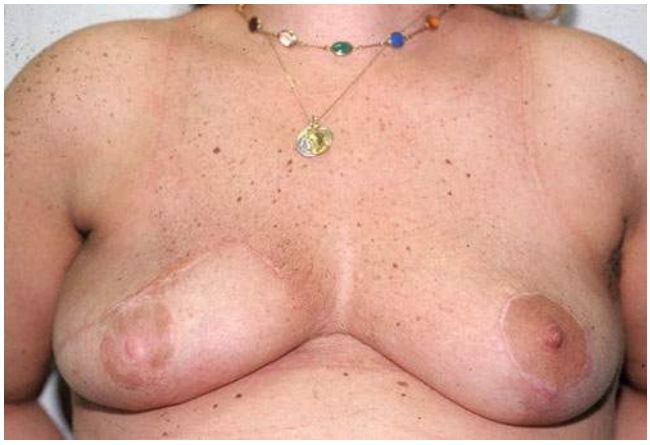

Fig. 33.20 Final results after 6 months

33.2 Fasciocutaneous Superior Abdominal Flap

33.2.1 Indications

This technique is based on Holmstrom's flap [18, 19], which is proposed for breast reconstruction with prosthesis. It could be useful in cases of tumors situated in the inferior quadrants and in small breasts without ptosis, when it is not possible to associate a reductive mastoplasty technique.

33.2.2 Technique

The preoperative drawing is made when the patient is standing up. The superior edge of the flap must be placed exactly in the inframammary sulcus. The inferior edge must be designed in a way that the donating zone can be closed with an advance of the upper abdominal flap up to the inframammary sulcus. The flap must be fasciocutaneous so to preserve vascularization, and a superior rotation must be performed in order to allow for better remodeling of the breast (Figs. 33.21, 33.22, and 33.23).

33.3 Musculocutaneous Flaps

An immediate reconstruction with musculocutaneous flaps may bring some difficulties, mainly due to the need of a postoperative radiotherapy. Either a moderate or a major radiodystrophy could damage the final aesthetic result.

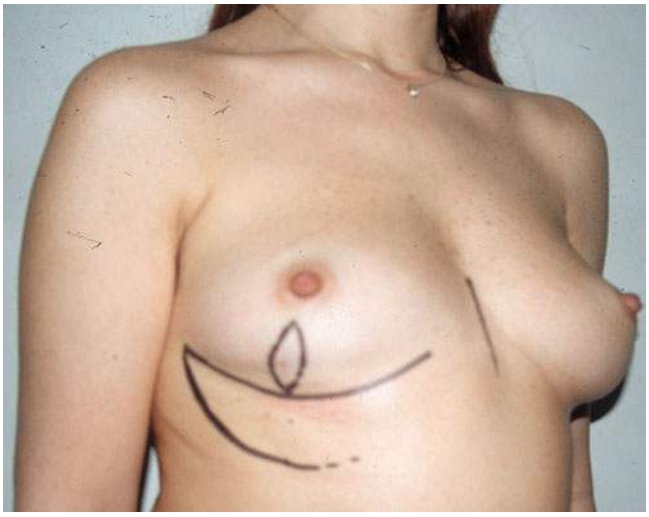

Fig. 33.21 Preoperative drawings: skin excision for lower tumor resection and flap drawing in order to put the final scar in the inframammary fold

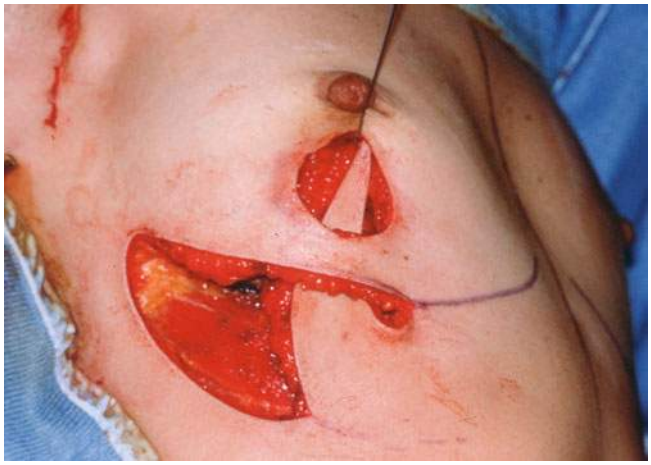

Fig. 33.22 Intraoperative image: flap rotation and the abdominal skin flap should be undermined to fix the final scar at the level of the inframammary fold

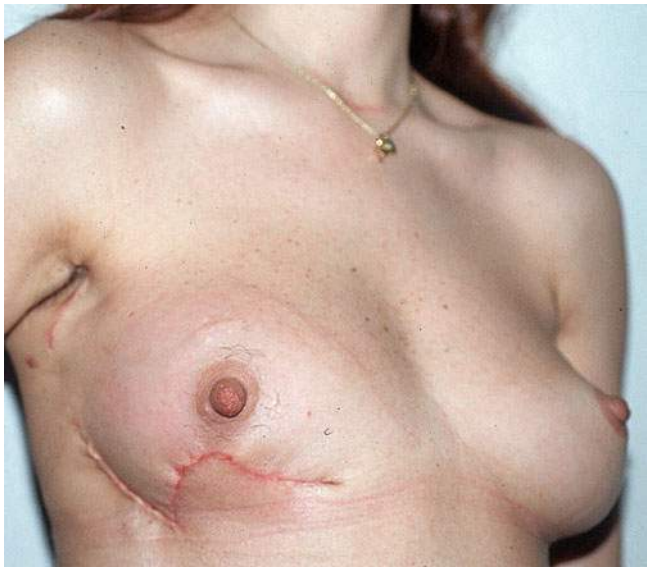

Fig. 33.23 Postoperative image after 1 month

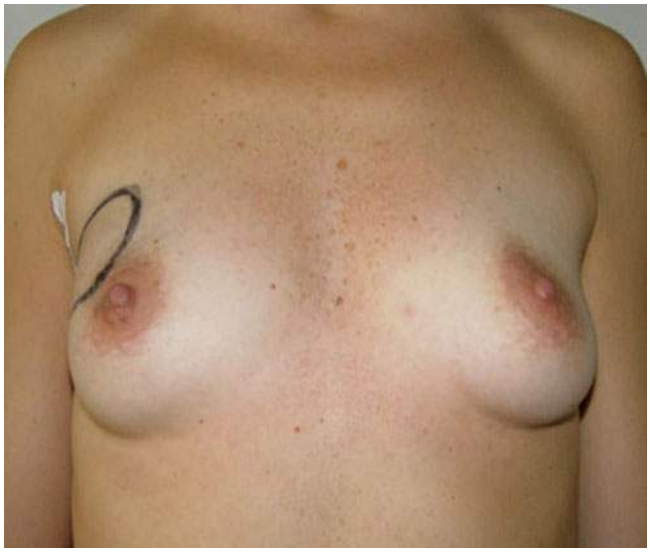

Fig. 33.24 Preoperative image: tumor located in the upper outer quadrant. Patient with small breast and who refused mastectomy

33.3.1 The Latissimus Dorsi

33.3.1.1 Indications

The latissimus dorsi flap technique was first proposed by Olivari [20] for breast reconstruction, and today it is possible to use it in selected cases for immediate partial reconstruction after quadrantectomy. The best indication of this technique is reconstruction of external quadrants or even repair of the central quadrant [21–23].

33.3.1.2 Technique

The traditional technique is described in more details in the specific chapter about it. In this chapter we will focus on the musculo-adipose flap of the latissimus dorsi (with no dorsal scar) for immediate breast repair after quadrantectomy. This technique can be used in cases of supero-external quadrantectomy, with no skin removal, and in small breasts, without ptosis.

After quadrantectomy and biopsy of the sentinel lymph node (or axillary lymphadenectomy), it is possible to prepare a musculo-adipose flap of the latissimus dorsi through the same incision. This flap is placed in the anterior thoracic region to repair the defect from quadrantectomy (Figs. 33.24, 33.25, 33.26, 33.27, and 33.28).

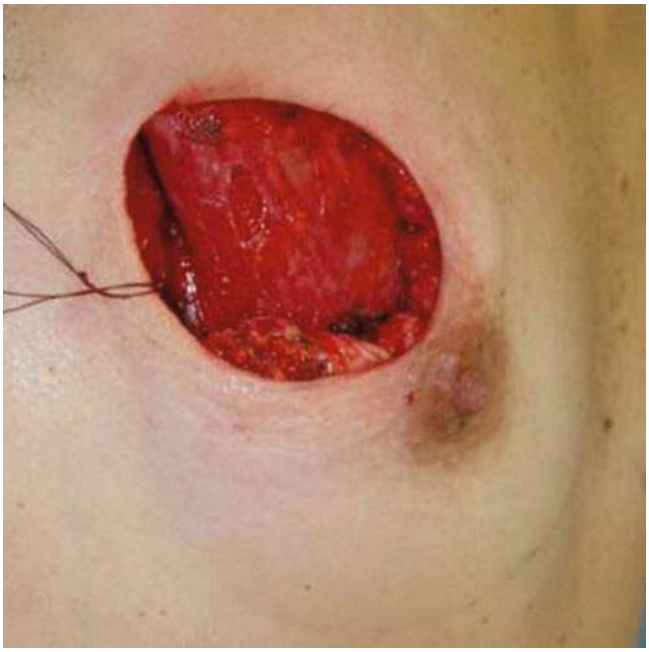

Fig. 33.25 Intraoperative image after the quadrantectomy and axillary dissection

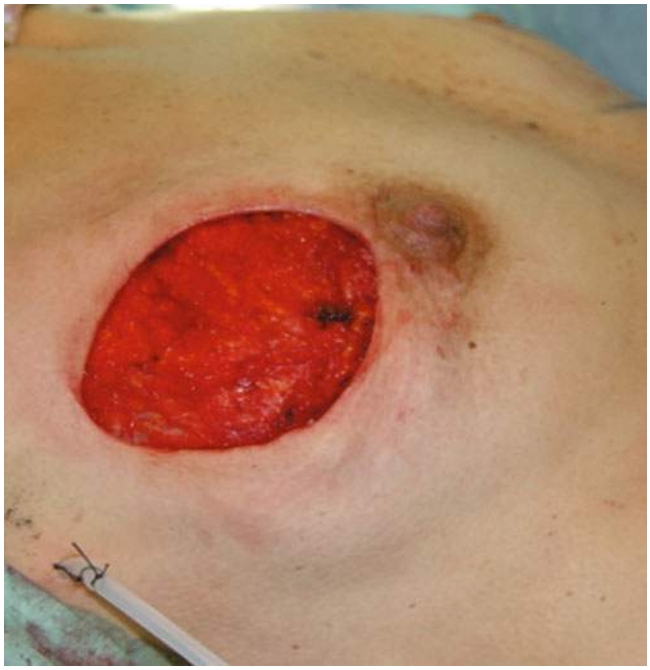

Fig. 33.27 The flap is used to cover the quadrantectomy defect

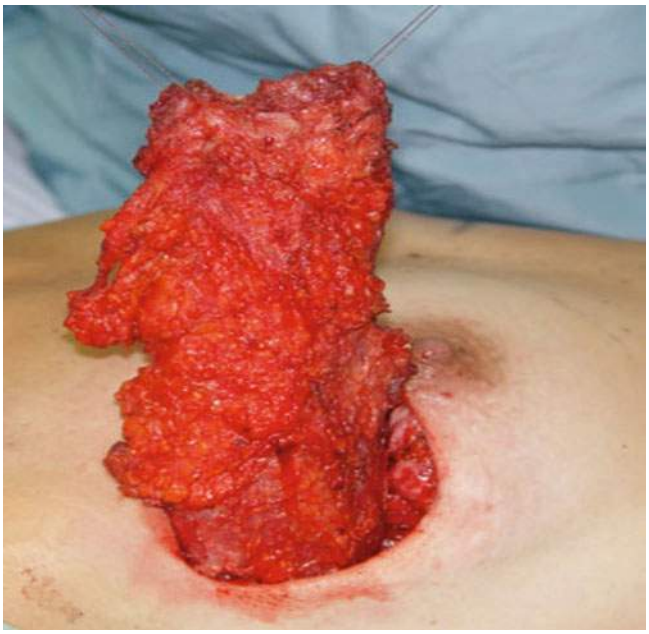

Fig. 33.26 Rotation of the latissimus dorsi musculo-adipose flap

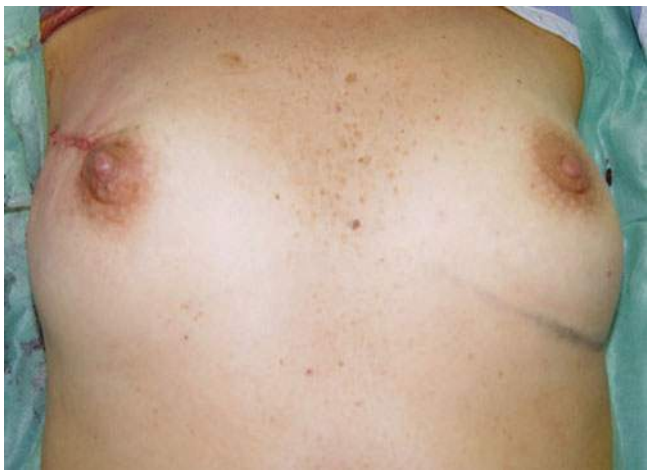

Fig. 33.28 The final results on the table

Fig. 33.29 Options for axillary skin rotation flaps

33.3.2 Rectus Abdominis Flap

From our experience, we do not indicate immediate partial reconstruction after quadrantectomy with musculocutaneous flap from the rectus abdominis muscle. This is a major surgery for a partial repair, and yet there is a risk of an incorrect aesthetic result after radiotherapy on the flap. There is a report of partial breast reconstruction with mini superficial inferior epigastric artery and mini deep inferior epigastric perforator flaps with satisfying results [24].

33.3.3 Other Flaps

There are several other methods related to oncoplasty that have been reported using for partial breast reconstruction, for example, transverse gracilis flap [25], omental flap [26, 27], or combination or axillary skin rotation flaps [28] (Fig. 33.29). However, they are rarely performed and gain less popularity at present.

33.4 Trends and Future of Partial Breast Reconstruction

1. As the absolute indications for total mastectomy are being de-escalated, most of the indications are limited to those with extensive tumor burden, persistent lesion after neoadjuvant treatments, and patients' preference. In contrary, the patient's acceptance for partial mastectomy is escalated so that the total procedure and varietal of partial breast reconstruction is expected to be massive in next years.
2. The donor site morbidity is becoming the major concern for oncoplastic volume replacement procedure for partial breast reconstruction. In order to avoid such morbidities, the perforator flaps are more applicable for both small and large breast reconstructions. These flaps can be raised as propeller flaps or pedicle flaps, for example, thoracodorsal artery perforator (TDAP), lateral intercostal artery perforator (LICAP), and lateral thoracic artery perforator (LTAP).
3. As the major progression and acceptance of tissue engineering in medicine, in particular, development of cellular expansion mechanism both in vivo and in vitro process makes the future of surgery in the next decades. At present, mesenchymal stem cell, especially, from adipose (which is so-called adipose-derived stem cell or ADSC), is the main clinical importance due to the ease of specimen harvesting and promising surgical outcome. The application of progenitor cellular knowledge and tissue engineering may take place for primary oncoplasty or retouch and revisional post oncoplasty procedure. Many translational researches also focus on utilization of biologic and synthetic scaffold along with mesenchymal cell and extracellular matrix applications (Figs. 33.27, 33.28, and 33.29).

33.5 Conclusion

Oncoplastic volume replacement and volume displacement techniques gain more popularity due to technical improvement and expanding indication for partial mastectomy from oncological point of view. In general, the oncoplastic surgery can be performed by mammaplasty techniques. Knowledge and understanding of vascular supply of breast parenchyma and nipple areolar complex are a very important key to success. When simple mammaplasty technique cannot be selected, there are other options for surgeons and patients to discuss. Prosthesis reconstruction can be performed with low capsular contraction rate when introduce the proper intraoperative radiotherapy protocol. Other fasciocutaneous and myocutaneous flaps can be done with promising results, and surgeon should keep in mind the oncoplastic principle to achieve the best oncologic and aesthetic benefit. Adipofascial perforator flaps may reduce donor site morbidity in most oncoplasty volume replacement techniques. In next decades, tissue engineering will be the alternative promising methods for partial breast reconstruction especially from mesenchymal and extracellular matrix component [29, 30].

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Delayed Reconstruction After Breast-Conserving Surgery

34

Eduardo G. González

34.1 Introduction

In recent years, much has been written about the term "oncoplastic surgery of the breast," probably without taking into account its original definition. According to Werner Audretsch [1], who described it for the first time in 1994, "oncoplastic surgery of the breast" originally included all the surgical approaches of plastic and reconstructive surgery that intended to achieve an oncological resection with satisfactory margins, in the context of a conservative treatment, trying to minimize potential deformities and obtaining better cosmetic results.

Later, after going through different definitions related to the surgical technique, such as "cosmetic quadrantectomy" [2], "lower pole tumor reduction mammaplasty" [3], and "central tumor reduction" [4], the concept was extended to the term "tumor-specific immediate reconstruction" [5] proposed by John Bostwick in 1996. This plastic surgeon from the USA not only included techniques for preventing the sequelae of the conservative treatment but also all the spectrum of techniques employed for immediate reconstruction after a partial or complete mastectomy (immediate breast reconstruction) and to correct the sequelae of these (deferred breast reconstruction), as well as the techniques employed for the immediate repair in the surgical treatment of locally advanced and recurrent tumors of the thoracic wall.

Presently, after all these terminological discrepancies, it is usual in the medical community to relate the term "oncoplastic surgery of the breast" to Bostwick's classification.

Conservative treatment of breast cancer (breast conservative treatment) has proved to be an oncologically safe procedure for disease control compared with mastectomy in tumors up to 5 cm according to several publications [6, 7]. This treatment includes a complete tumor resection with an oncological safety margin, the exploration of the axilla (sentinel lymph node biopsy or axillary lymphadenectomy), and breast volume radiotherapy with or without a boost on the tumor bed following the treatment protocols.

By definition, breast conservation not only implies locoregional oncological control of the disease, but it is also essential to preserve the breast with a good aesthetic result.

So, what must the surgeon do to accomplish this 50 premise?

- Know the different approaches and aesthetic incisions required to reduce sequelae (Fig. 34.1). The incisions should be made around the areola in upper quadrant tumors, periareolar in lesions that are next to the nipple–areola complex, and radiated or through the submammary fold in tumors of the lower quadrants. In tumors of the upper and medial quadrant, the periareolar approach may avoid unsightly scars in that region.
- Know the techniques of gland shaping to avoid defects secondary to the loss of part of the gland after resection.
- Know the fundamentals and effects of radiotherapy in conservative treatment: several publications have analyzed the changes in the irradiated mammary gland according to its volume and the homogeneity of the dose delivered. In a prospective and randomized trial, Moody et al. [8] compared the adverse effects of radiotherapy in small, medium-sized, and large mammary glands and found moderate and severe negative aesthetic results in only 6% of small breasts and in up to 39% of large ones. Gray et al. [9] evaluated 267 irradiated patients after conservative surgery. They observed a significant reduction in aesthetic results in patients with macromastia and inadequate treatment, with areas of overirradiation or underirradiation, about 10–15% as a consequence of the lack of homogeneity of the dose owing to the size of the breast. Following these parameters, we can obtain approximately 70% good results, leaving 30% of patients with remaining deformities that would require a secondary surgical cor-

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_34

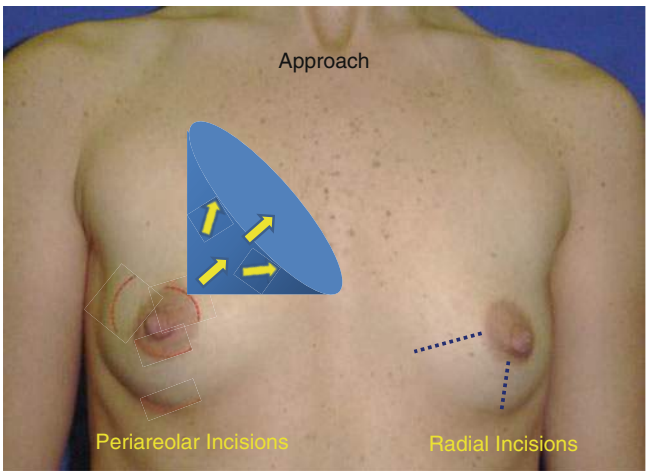


Fig. 34.1 Approaches and aesthetic incisions in conservative surgery. The incisions are indicated according to the place of resection and the Langer lines of the breast. It is interesting to point out the approach of the upper and medial quadrant through the periareolar region to avoid the scars in the region described by A. Grisotti as "no man's land" (in blue)

rection [10]. Oncoplastic surgery of the breast had its origin in the intent to prevent these unsatisfactory results of breast conservation observed in these 30% of patients.

The crucial factor to develop and implement these techniques and the sequence related to other treatments (chemotherapy, radiotherapy) motivated further interdisciplinary analysis to evaluate its safety and results. It is in the limitations of conservative surgery related to the breast and tumor volume or to the site of the lesion (e.g., central tumors), which are classic relative contraindications for conservative treatment, where oncoplastic surgery of the breast achieves breast conservation and immediate reconstruction with oncological safety in adverse anatomical conditions.

On the other hand, oncoplastic surgery of the breast is also indicated in the following cases: superficial tumors that need a skin resection, secondary resections in breasts with multiple scars, widening of resection because of positive margins, and in patients with previous breast augmentation surgery and breast cancer who need oncologically safe margins and breast conservation.

In summary, and to respond to the difficult question of how do we decide who needs immediate reconstruction with breast conservative treatment, we can list three basic situations in which the oncoplastic surgery finds can apply it:

1. Problems related to the site of the tumor (central, in the midline, upper medial quadrants, etc.) or to tumor volume/breast volume relation [4].
2. In the treatment of locally advanced cancer treated with induction chemotherapy and salvage surgery, preserving the breast with wide resection margins and good local control.
3. Special situations such as skin resections in superficial tumors, patients with multiple previous scars, resections with wide margins in patients with ductal carcinoma in situ or secondary to tumorectomy with positive margins, or breast cancer in patients with previous breast augmentation surgery.

Following the previous exposition, we recommend that when the patient has risk factors that increase the possibility of sequelae after breast-conserving surgery, immediate breast reconstruction with oncoplastic techniques is preferable (Figs. 34.2 and 34.3).

34.2 Etiology and Classification of the Sequelae

There are many factors that can be determinant in producing a deformity in the breast that has been operated on. The most important is probably the gland resection itself that produces a reduction in the breast volume. In a planned resection, it is important to calculate the approximate tumor volume and the healthy tissue margin around it, for example, if we resect a tumor of 2-cm diameter with a margin of 1 cm, this is equivalent to 30 g of gland volume, but if we enlarge the margin to 2 cm, the defect enhances up to more than 100 g with a different impact on the final result. The tumor site is the second determinant factor: there are sites of the breast where the defect can be repaired favorably, such as the upper and lateral quadrants, and others such as the medial region or lower quadrants where the structural alteration is maximal and its correction difficult. The size of the breast is also important: many results are conditioned by this factor, the damage being less when the relationship between the breast and the tumor volume is larger. A body mass index greater than 30 is also related to a higher number of sequelae [12].

Breast retraction and fibrosis are the usual changes after radiotherapy, but there are some factors that can increase the sequelae secondary to this treatment. A total dose of 66 versus 50 Gy worsens the cosmetic results [13], and, as mentioned before, the gland and fat tissue volume also have a negative influence on this last issue [8, 9]. Chemotherapy can worsen the results, administered either simultaneously or sequentially with radiotherapy [14].

When patients seek consultations because of sequelae of a conservative treatment, there are some parameters related to the patient's anatomy that have to be evaluated, as well as the characteristics of the breast that has been operated on and the symmetry of both breasts and the nipple–areola complex.

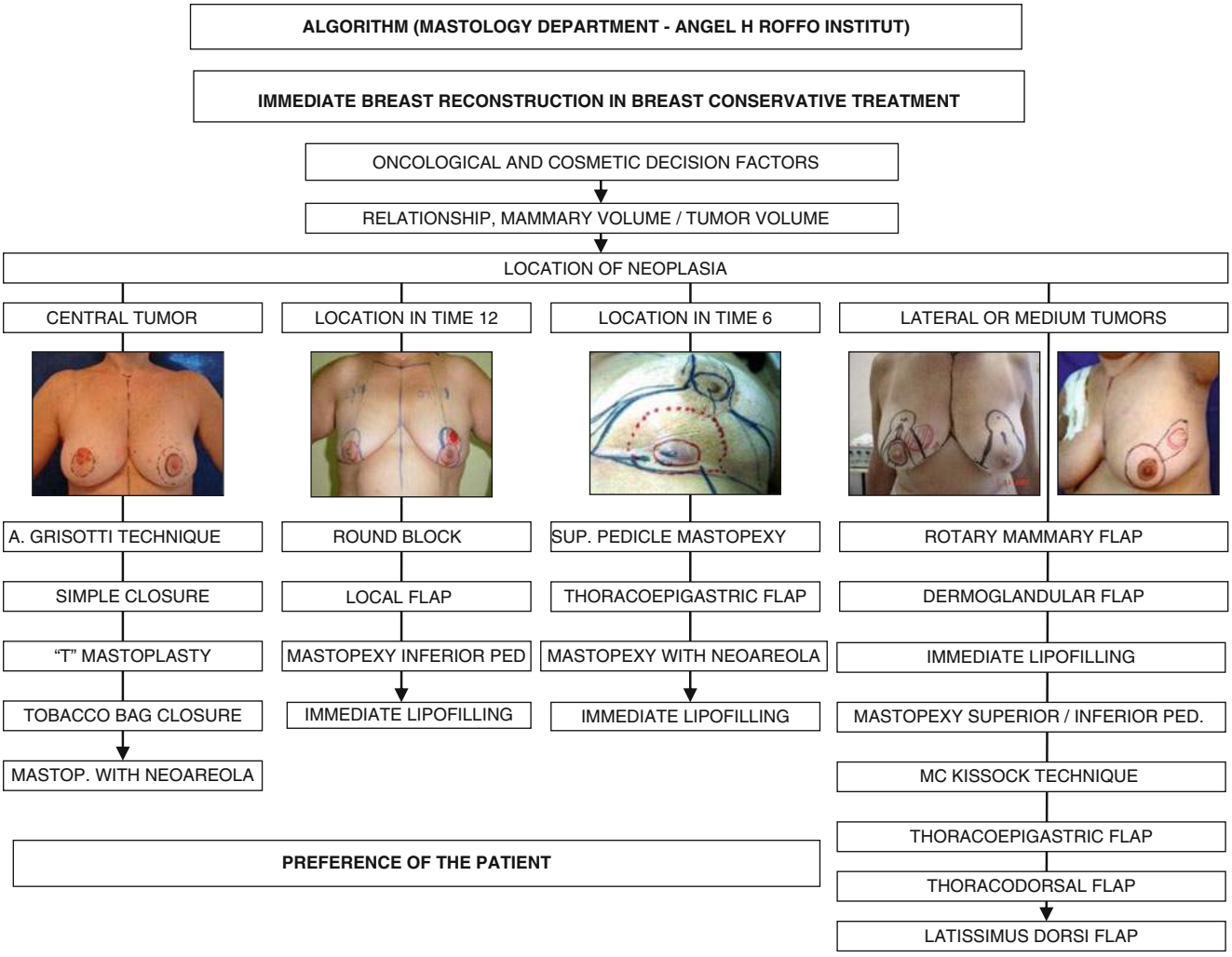


Fig. 34.2 Algorithm that we currently use in the Department of Mastology, Institute of Oncology Ángel H. Roffo, to avoid the sequelae of conservative treatment of breast cancer

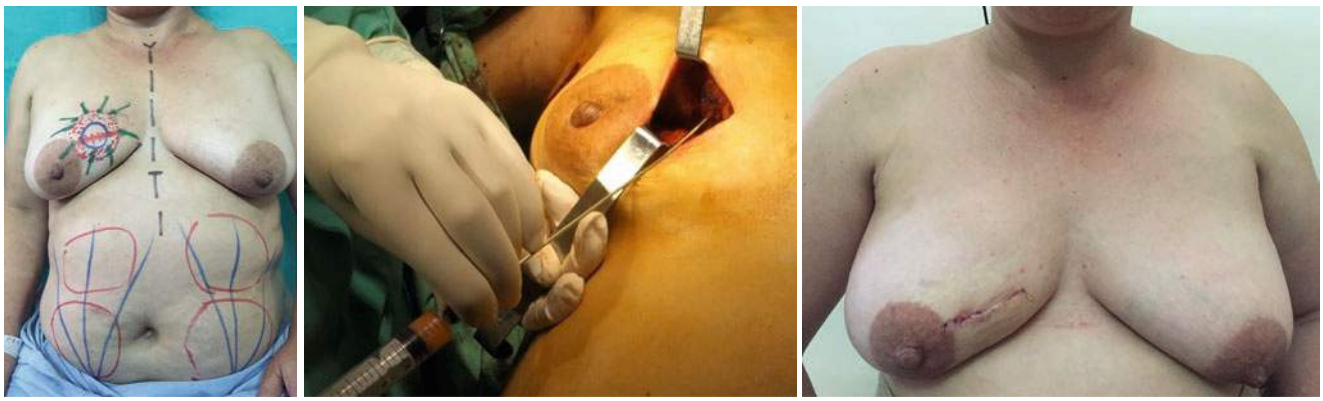


Fig. 34.3 Cuadrantectomy and immediate breast reconstruction with lipofilling in the right breast. Fat injection with a curved Khouri needle in the tissue surrounding the resection and posterior glandular modeling. Final results (Biazus technique) [11]

Deferred breast reconstruction of these deformities is limited by five determinant factors: the lack of skin or gland tissue, scar retraction, radiodermatitis, and fibrosis.

Evaluation of sequelae is highly subjective, and the concordance between surgeons and patients or between different surgeons is generally low [15]. In recent years some

Table 34.1 Cosmetic sequelae after conservative treatment for breast cancer: classification

	Berrino P-1987 [17]	Clough K-1998 [18]	Fitoussi A-2010 [10]
Type I	Malposition and distortion of the NAC and is mainly due to postoperative fibrosis and scar contracture	Asymmetrical breasts with no deformity of the treated breast	Low ipsilateral deformity does not affect shape or volume of the breast
Type II	IIa. Localized tissue insufficiency is observed, which may be due to skin deficiency IIb. Subcutaneous tissue deficiency IIab. Both	Deformity of the treated breast, compatible with partial reconstruction and breast conservation	Good shape and sufficient volume but with obvious asymmetry in relation to the contralateral healthy breast
Type III	Deformity is characterized by breast retraction and shrinkage and is mainly due to the effects of radiotherapy on residual breast parenchyma	Major deformity of the breast, requires mastectomy	Asymmetry does not maintain the shape and volume, frequent dislocation of the NAC
Type IV	Severe radiation-induced damage to the skin, nipple–areola complex, and subcutaneous and glandular tissues are present	–	Greater deformity, lack native tissue, scarring, and radiation effects
Type V	–	–	Severe deformity of both surgery and radiation therapy prior, where the breast is too small and/or completely sclerosed

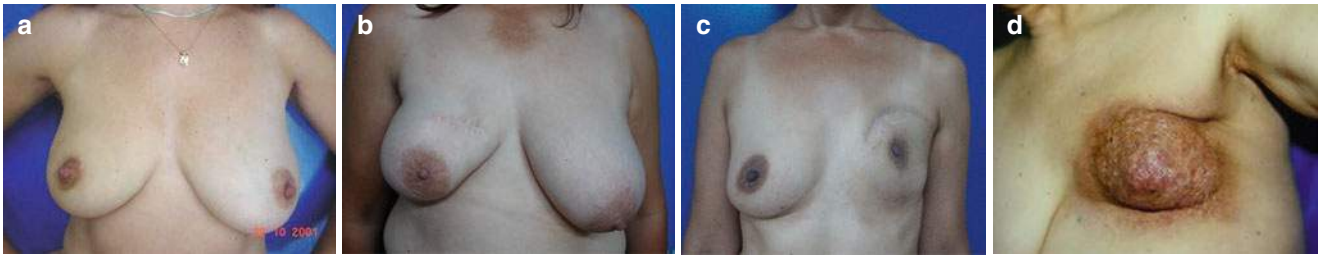


Fig. 34.4 Cosmetic sequelae after conservative treatment for breast cancer: classification. *Left*: asymmetry without deformity (Type I Clough–I–II Fitoussi). *Center left*: asymmetry with moderate deformity and mild dislocation of the nipple–areola complex (Types I–II Berrino, II Clough, III Fitoussi). *Center right*: breast deformity and asymmetry as well as of the nipple–areola complex (Type III Berrino, Clough–IV Fitoussi). *Right*: fibrosis and severe actinic sclerosis with severe disappearance of the nipple–areola complex (Type IV Berrino, III, Clough–V Fitoussi)

informatic models have been designed (3dMD, BAT Software) to systemize this evaluation and improve the planning of reconstruction [16, 17]. A number of classifications have been proposed with the intention to evaluate the defects and plan corrections as shown in Table 34.1. In all of them, there is generally coincidence in the evaluation of minor sequelae (type I or II), involving only asymmetries without or with minimal changes in the shape of the treated breast, except for Berrino's classification [18], which added the displacement of the nipple–areola complex (Fig. 34.4). Most of the "problematic" patients present with major sequelae that range from moderate deformities to severe sequelae with sclerosis of the whole breast that even sometimes needs mastectomy. For these sequelae the classifications are confusing, and the indications for corrections range between simple treatments such as lipofilling and mastectomies with immediate reconstruction with microsurgical or pedicled flaps associated or not associated with prosthetic material [10, 18, 19].

34.3 Timing of Reconstruction of the Partial Mastectomy Defect: Our Experience

In our institutional experience after using the classifications mentioned previously for some years, we tried to simplify the evaluation of the sequelae and systemize the reconstruction techniques by employing a more functional concept related to each particular patient.

We analyzed the following parameters: age, biotype, time between the first medical consultation and the surgery and primary radiotherapy, grade of complexity of the sequelae, previous reconstruction intents, and presence of a prosthesis in the previously irradiated breast. Generally, in relation to all these parameters, we waited for a least 1 year after radiotherapy had finished before recommending reconstruction, with the condition that the breast was stable and did not show signs of edema or radiodermatitis, and that physical examination and imaging (mammography, ultrasonography, MRI) confirmed the absence of local recurrences.

We divided the patients in two large groups based on the type of sequelae and also the complexity of the reconstruction technique needed for each particular patient: group A had minor defects and group B had major defects.

In group A we included the sequelae that did not compromise or only produced a mild change in the shape of the breast, with or without asymmetry of the nipple–areola complex or the breast. We divided this group into three subgroups:

1. Breast asymmetry without alteration of the shape of the breast that had been operated on.
2. Minor sequelae in the breast that had been operated on without asymmetry of the nipple–areola complex, with or without associated breast asymmetry.
3. Minor sequelae in the breast that had been operated on with asymmetry of the nipple–areola complex, associated or not associated with breast asymmetry.

In group B we included the sequelae that compromised moderately or severely the breast's shape with asymmetry of the nipple–areola complex. In this group we also added the damage produced by severe actinic sclerosis and fibrosis and a special subgroup that corresponds to patients with prior reconstruction attempts with unsatisfactory results, who generally have implants and ask for a second procedure. We can divide this group into three subgroups:

1. Moderate or severe sequelae in the shape and volume of the treated breast without or with moderate actinic damage
2. Moderate or severe sequelae in the shape and volume of the breast that has been operated on without or with moderate actinic damage and a previous reconstruction attempt with or without implants
3. Severe actinic damage with loss of the shape and alteration of the volume of the treated breast. Marked sclerosis and fibrosis

It is important to explain that in both groups the cause of breast asymmetry can be due to several factors related not only to the primary treatment but also to the biotype of the patient, changes in body weight, adjuvant oncological treatments, age, etc. (Table 34.2).

Analyzing the patients according to this classification, we used a treatment algorithm to choose the most suitable surgical technique (Tables 34.3 and 34.4).

The indication for the surgical technique depends not only on the algorithm but is also influenced by the surgeon's experience and the opinion of the patient if there is more than one possibility, always preferring the least aggressive one and evaluating quality of life [20].

Another interesting point is how this algorithm has changed in recent years according to the publication and application of new surgical techniques. Below, when we describe the different procedures we used, we will see, for example, the influence of lipofilling in minimizing the procedure's aggressiveness, optimizing results, and diminishing the rate of complications.

34.4 Reconstruction Techniques for the Partial Mastectomy Defect

Breast reconstruction has evolved in some aspects in recent years, and the description of new techniques with the optimization of results was accompanied by the priority given to diminish morbidity and to offer procedures that not only have good result but also have fewer sequelae and allow patients to return early to normal activity.

Following the proposed algorithm and highlighting this evolution, we have an interesting number of techniques to use depending on the complexity of the patient's defects, background, and wishes, previous morbidity, potential of the reconstructive procedure, and implications for the quality of life.

Numerous publications [1, 3, 4] described local, myocutaneous or microsurgical flaps, prosthesis implantation, etc., to correct these defects, and established guidelines that were applicable for years, but they always emphasized the complexity, unpredictable results, and higher complication rate of these procedures compared with immediate reconstruction after conservative treatment.

In our experience, we went through different phases, and it is our intention to describe subsequently the techniques we can use presently, in which cases to apply them according to the algorithm we employed and the results and to mention complications and how they changed in relation to the different indications.

Table 34.2 Cosmetic sequelae after conservative treatment for breast cancer: IAR functional classification (IARfc)

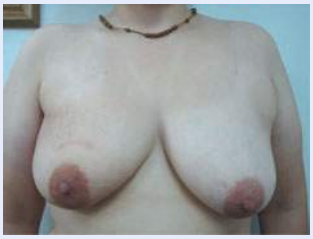
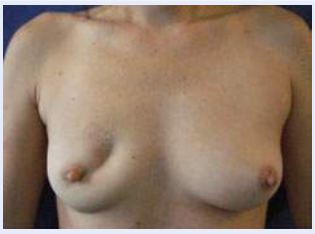
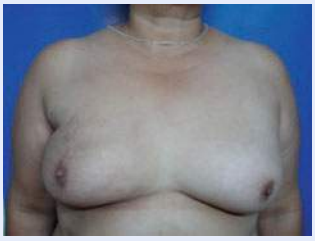
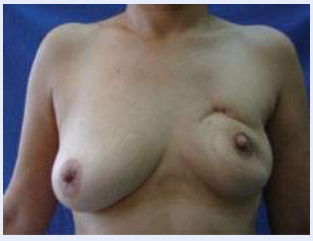
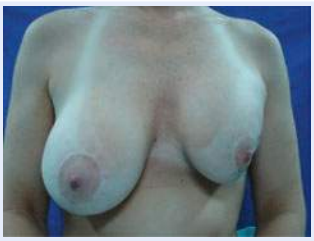
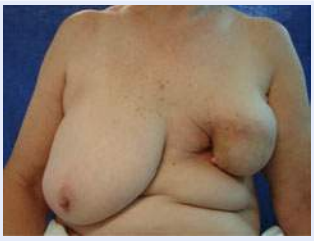
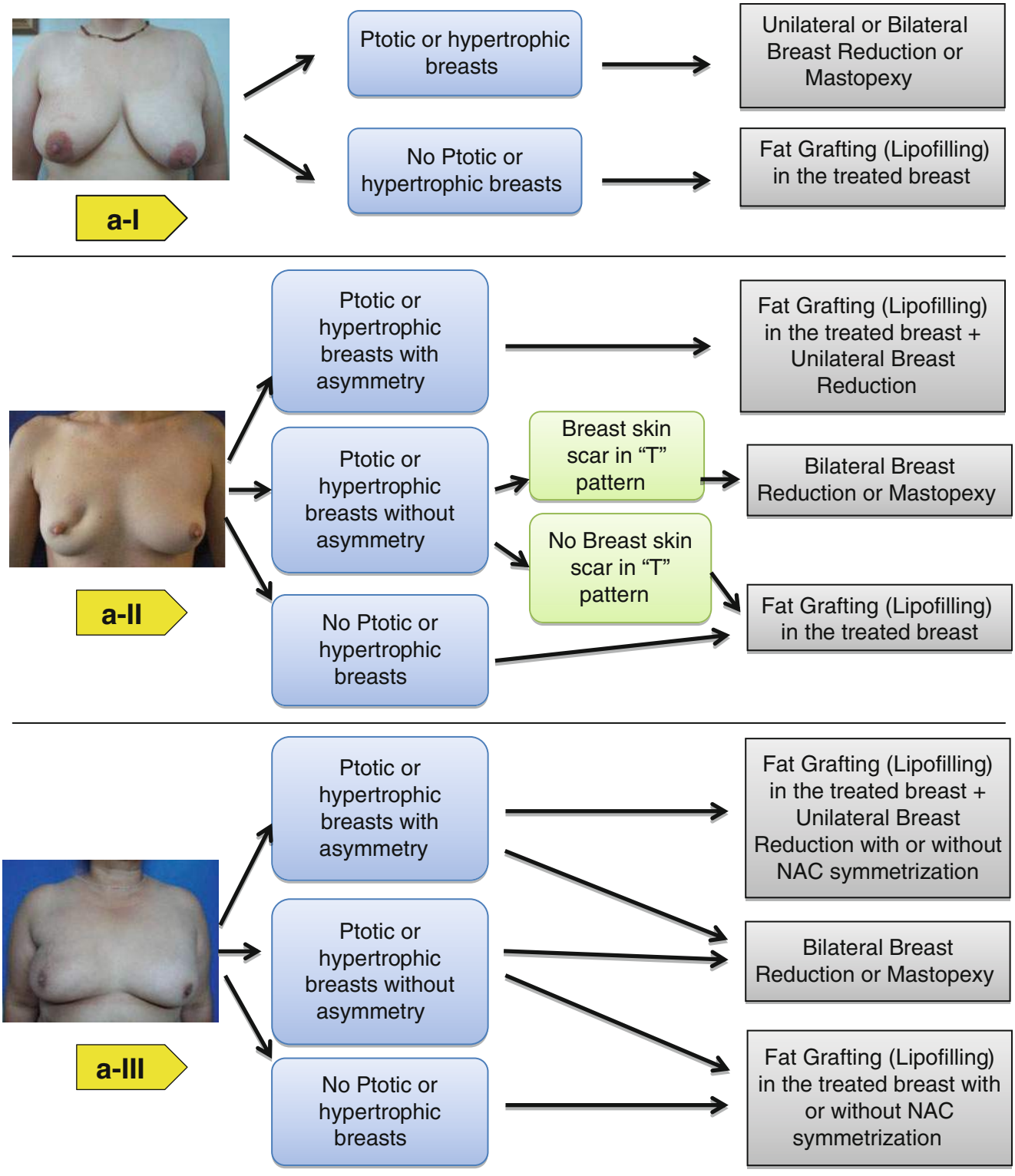
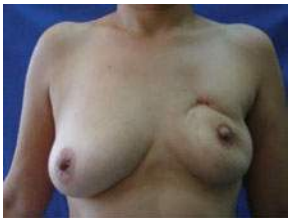
	a-Defectos menores	b-Defectos mayores	Ejemplo
a-I	Breast asymmetry without alteration of the shape of the operated breast	–	
a-II	Mild sequelae in the shape of the breast operated without asymmetry of the NAC. They can be associated or not associated with breast asymmetry	–	
a-III	Mild sequelae in the shape of the breast operated with asymmetry of the NAC. They can be associated or not associated with breast asymmetry	–	
b-I	–	Moderate or severe sequelae in the shape and volume of the treated breast without or with moderate actinic sequelae	
b-II	–	Moderate or severe sequelae in the shape and volume of the treated breast without or with moderate actinic damage with a previous attempt at reconstruction with or without implant insertion	
b-III	–	Severe actinic sequelae with loss of the shape and marked alteration in the volume of the treated breast. Marked sclerosis and fibrosis	

Table 34.3 Cosmetic sequelae after conservative treatment for breast cancer



Management algorithm for repair of partial mastectomy defects. Minor defects. NAC nipple–areola complex

Table 34.4 Cosmetic sequelae after conservative treatment for breast cancer



b-I

Ptotic or hypertrophic breasts

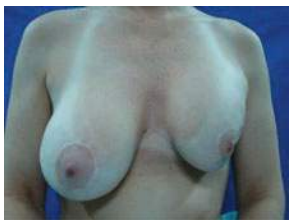
No Ptotic or hypertrophic breasts

Fat Grafting (Lipofilling) with or without external expansion (Brava System)+ Breast reduction in the opposite breast

Latissimus Dorsi Flap or Local flaps + Breast reduction in the opposite breast

Latissimus Dorsi Flap or Local flaps

Fat Grafting (Lipofilling) in the treated breast with or without external expansion (Brava System)



b-II

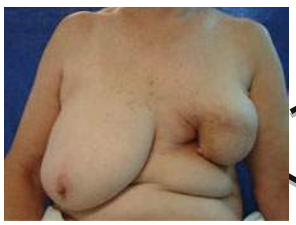
Primary BR with implants

Primary BR without implants

Latissimus Dorsi Flap+ Expander or prosthesis + Breast reduction or pexia in the opposite breast

Tram/DIEP/Extended Latissimus Dorsi Flap +/- Breast reduction or pexia in the opposite breast

See b-I



b-III

Ptotic or hypertrophic breasts with asymmetry

No Ptoticor hypertrophic breasts

Mastectomy + Tram/DIEP/Extended Latissimus Dorsi Flap +/- Breast reduction in the opposite breast

Management algorithm for repair of partial mastectomy defects. Major defects
BR breast reconstruction, *DIEP* deep inferior epigastric perforator, *Tram* transverse rectus abdominis myocutaneous

34.5 Reduction or Pexia of the Opposite Breast

In selected cases when only breast asymmetry occurs, and the breast with conservative treatment and radiotherapy has a good cosmetic structure without breast shape alterations or malposition of the nipple–areola complex, we generally indicate correction of the opposite breast with mastopexy or reduction mastoplasty and good results (Fig. 34.5).

34.6 Mastopexy or Reduction Mastoplasty with Repositioning of the Nipple–Areola Complex

We use reduction or pexia techniques in cases of breast asymmetry in ptotic or hypertrophic breasts without shape alterations in the breast operated on or with minimal alterations with or without asymmetry in the nipple–areola complex (IAR functional classification, IARfc, a-I–II–III).

This technique should be avoided in patients with moderate or severe radiodystrophy or when the scar from the previous surgery can change the design, diminishing the safety of the vitality of the pexia or reduction flaps. Previous radiotherapy produces capillary fragility and fibrosis in the tissues, increasing complication rates, interfering with wound healing, and worsening the final aesthetic result. In cases of moderate or severe actinic damage, we can use lipofilling and omit reduction.

The technique chosen depends on the breast volume and shape and previous scars. The site of the incisions is chosen not only taking into account the cosmetic result but also in the attempt to reduce further complications. They can be designed in a "T" pattern, vertically or periareolar, always taking care of the vascularization of the skin and subcutaneous tissue flaps. We generally manage the gland pedicles that irrigate the nipple–areola complex according to the concept of "zone designations" proposed by Kronowitz et al. [21] (Fig. 34.6).

34.7 Fat Grafting (Lipofilling)

Lipofilling is a centennial practice indicated for defect correction. Certain qualities of the fat, such as its easy acquisition, constant availability, and interminability, made its use very important in plastic and reconstructive surgery as a primary procedure or in combination with other methods.

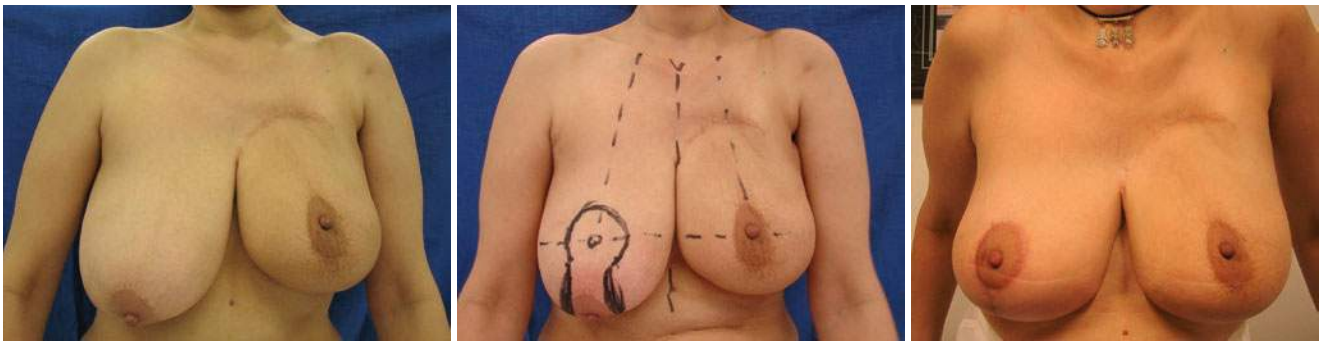


Fig. 34.5 Cosmetic sequelae after conservative treatment for breast cancer in the upper quadrants of the left breast. Breast asymmetry. Only correction with breast reduction of the opposite breast. Final result

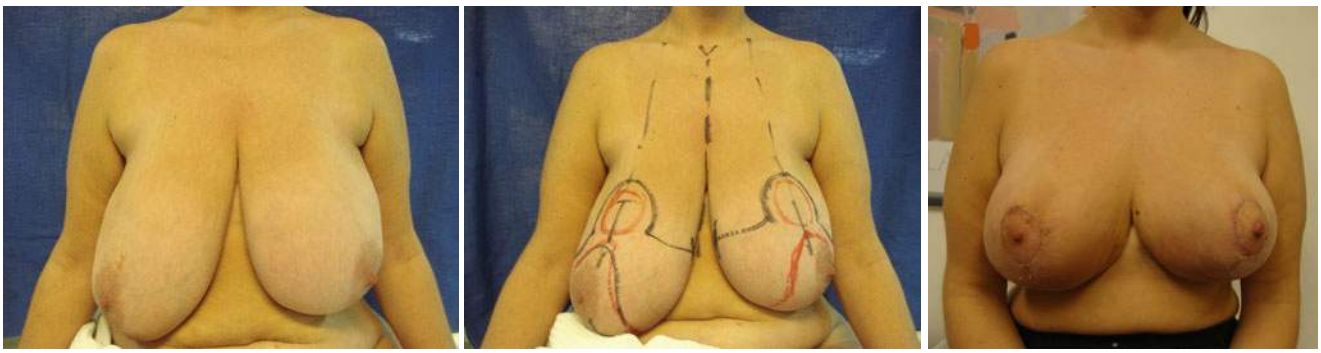


Fig. 34.6 Cosmetic sequelae after BCT in a patient with a tumor in the lower lateral quadrant of the left breast. Mild radiodermatitis without clinical manifestation. Breast hypertrophy and asymmetry and mild asymmetry of the nipple–areola complex. (IARfc: a-III). Breast reduction with an inverted "T" nurtured by an inferior pedicle

After lipofilling had been forbidden in 1987 by the American Society of Plastic and Reconstructive Surgery (ASPS) because of the radiological consequences and the possibility of interfering in the mammographic diagnosis of breast cancer [22], in 2007 Rigotti et al. [23] published their experience with and described the regenerative power of "adipose-derived stem cells" in the reconstruction of the damage produced by conservative treatment and irradiation of the breast because of their "proangiogenic ability" in a territory with a "chronic ischemic status" secondary to radiotherapy.

Owing to the lack of publications and because the procedure was not standardized after the new publications, the ASPS created a work group in 2007 (ASPS Fat Graft Task Force) [24] to evaluate the safety and efficacy of autologous fat grafts in the breast and to establish recommendations for future investigations. In relation to conservative treatment and follow-up, they stated that there would not be any difficulty because the microcalcifications that are seen afterward are generally of benign character in 5% of cases.

On the basis of a limited number of studies with a small number of patients, there seemed to be no interference in breast cancer detection. The oncological safety was also evaluated by the ASPS Fat Graft Task Force, and in 2009 it concluded that until that time there had been no reports indicating an increase in the risk of disease recurrence associated with autotransplantation of fat tissue. Nevertheless, it concluded that more studies are necessary to confirm these preliminary considerations [24].

To repair severe damage from conservative treatment, in some situations we have to provoke an external stretching and suctioning of the skin, producing in this way a neovascularization and favoring fat injection, maintaining its vitality and allowing its regeneration. This is achieved by means of an external tissue expander (Brava system) described by Khouri [25], which is placed for approximately 10 h a day for long periods of time between lipofilling sessions.

Lipofilling is indicated nowadays for most of the minor sequelae of conservative treatment (IARfc a-I–II–III) and in most of the cases probably should be the first option, especially in patients with small- or medium-sized breasts without or with little ptosis. This indication is because it is an outpatient treatment, minimally invasive, easy to perform, and has good results and a low rate of complications.

In cases of major damage, its indication is limited to some cases of IARfc b-I group patients with a small breast volume or patients who accept various procedures including the use of the Brava system to avoid reconstruction with myocutaneous flaps (CLD, transverse rectus abdominis myocutaneous flap, etc.). Lipofilling has no local contraindications and only has the disadvantage that more than one procedure might be necessary to achieve in some situations an optimal result, with intervals of approximately 3 months between each fat application. It is not recommended to indicate lipofilling when there is high risk of thromboembolism (contraindication of liposuction) or loss of fat tissue at the donor sites.

It is clear that it is important to choose the right areas to obtain the fat, with an adequate amount of fat tissue according to the preference of the surgeon and the patient.

The commonest sites are the abdomen, flanks, and hips. The liposuction, after injection of Klein's solution, is performed with 2–4-mm cannulas to allow a major recollection of adipocytes without damaging neurovascular structures. There must be delicate manipulation to avoid negative pressure and minimal exposure to air. The ideal processing of the fat is the one that can separate the blood cells, the infiltrated fluids, the oil, and the adipocytes with the least trauma possible. The major consensus is to centrifuge the sample at 3000 rpm for 1–3 min [23] or manual centrifugation with a low number of revolutions per minute [25]. It is essential to optimize the results and avoid oil cysts and to prepare the graft receptor site with transcutaneous punctures made with 14G needles (rigottomies) leaving the surgical bed like a honeycomb [23]. The injection of fat tissue is probably the most critical point to obtain good and enduring results with this technique, without increasing the rates of fat necrosis and complications. The fat grafts are nurtured by plasmatic soaking up to 1.5 mm from the edge of the graft. We use a curved duck-billed cannula with only one anterior opening (Khouri) and syringes of 5 and 10 mL, according to the defect we are going to correct, and we make a retrograde infiltration in various lineal directions without leaving empty cavities. It is important not to overcorrect defects and not forget that the best results are obtained with more than one procedure [23]. Some cases of breast reconstruction with lipofilling are shown in Figs. 34.7, 34.8, 34.9, 34.10, 34.11, and 34.12.

34.8 Fasciocutaneous Flaps

These are skin–fat flaps that vascularize through a superficial pedicle (regional perforating vessels). They only have limited indications. Presently the most used fasciocutaneous flaps are the thoracoepigastric and thoracodorsal flaps. We use them in particular situations when there is no possibility to use other techniques in the lower and lateral quadrants (Fig. 34.13).

34.9 Latissimus Dorsi Myocutaneous Flap

The latissimus dorsi myocutaneous flap is a noble, safe, and easy-to-harvest flap which allows, in general, repair of defects in the thoracic wall and breast. It consists of the

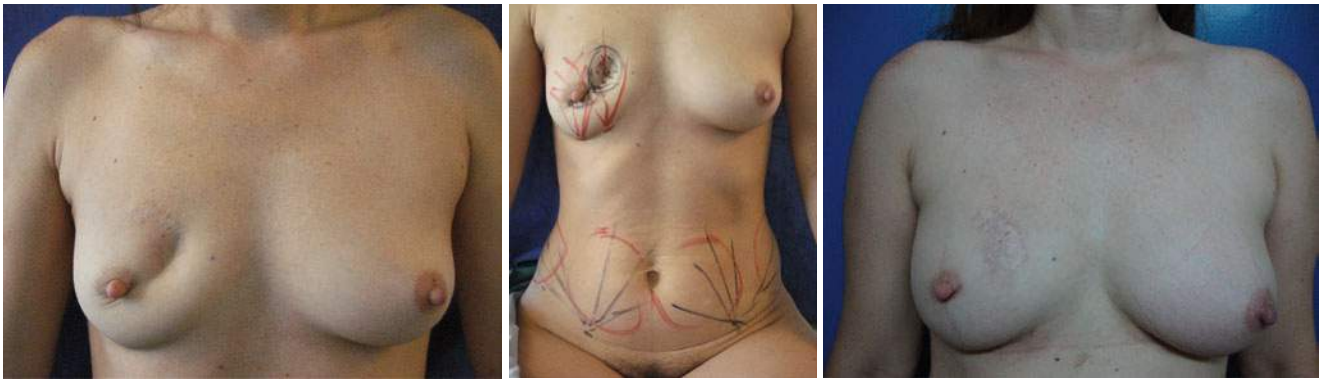


Fig. 34.7 Cosmetic sequelae after BCT in a patient with a tumor in the upper and medial quadrant of the right breast. Loss of volume with skin retraction and marked asymmetry (IARfc: a-II). Results after two procedures of lipofilling with correction of the defect and additional breast augmentation (60 and 120 g)

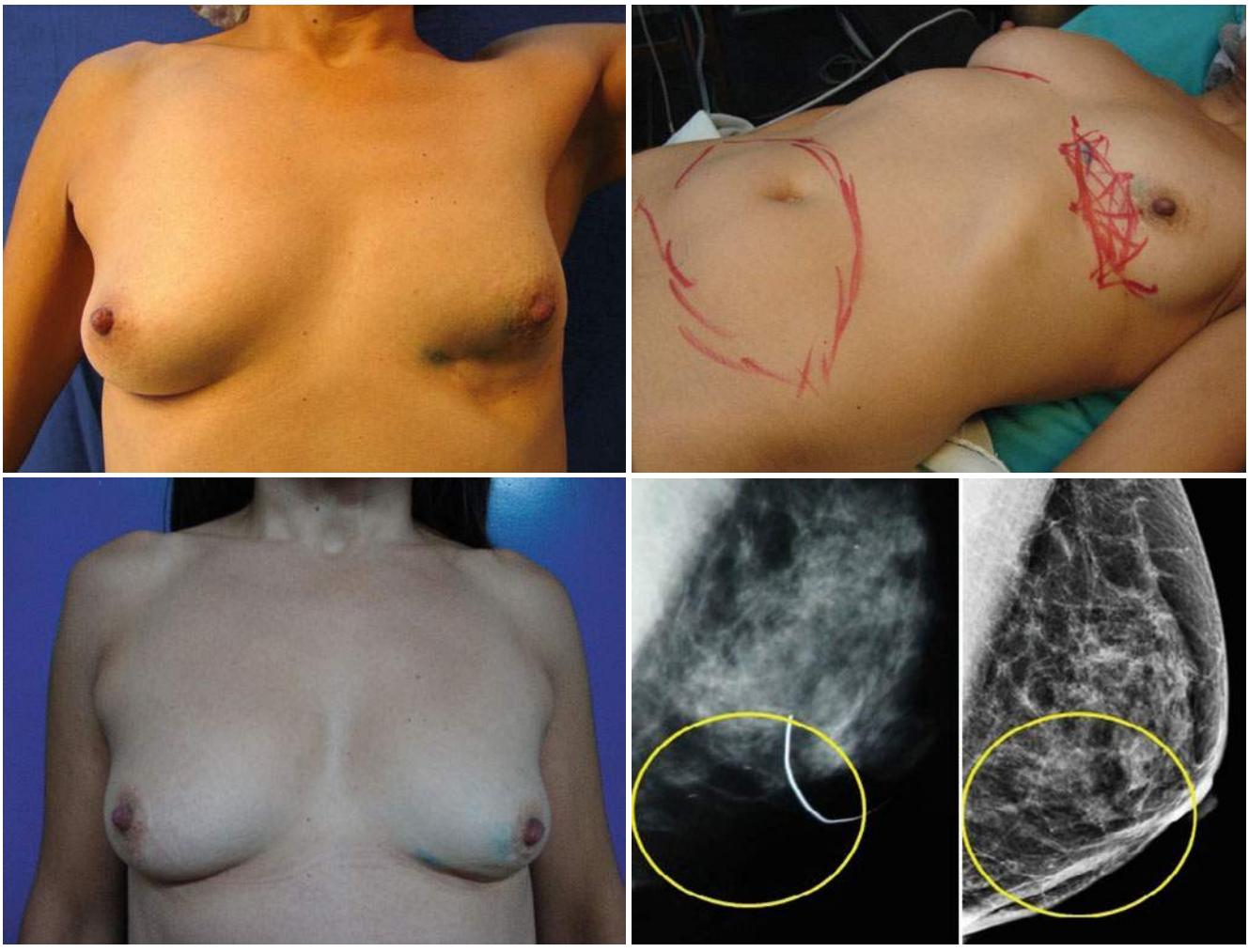


Fig. 34.8 Cosmetic sequelae after BCT in a patient with a tumor in the inferior quadrants of the left breast. Marked loss of volume with skin retraction and without asymmetry (IARfc: b-I). Abdominal donor site. Results 2 years after one lipofilling with correction of the defect (110 g). Preoperative and postoperative mammography, showing 2 years after the breast volume augmentation procedure without radiological consequences

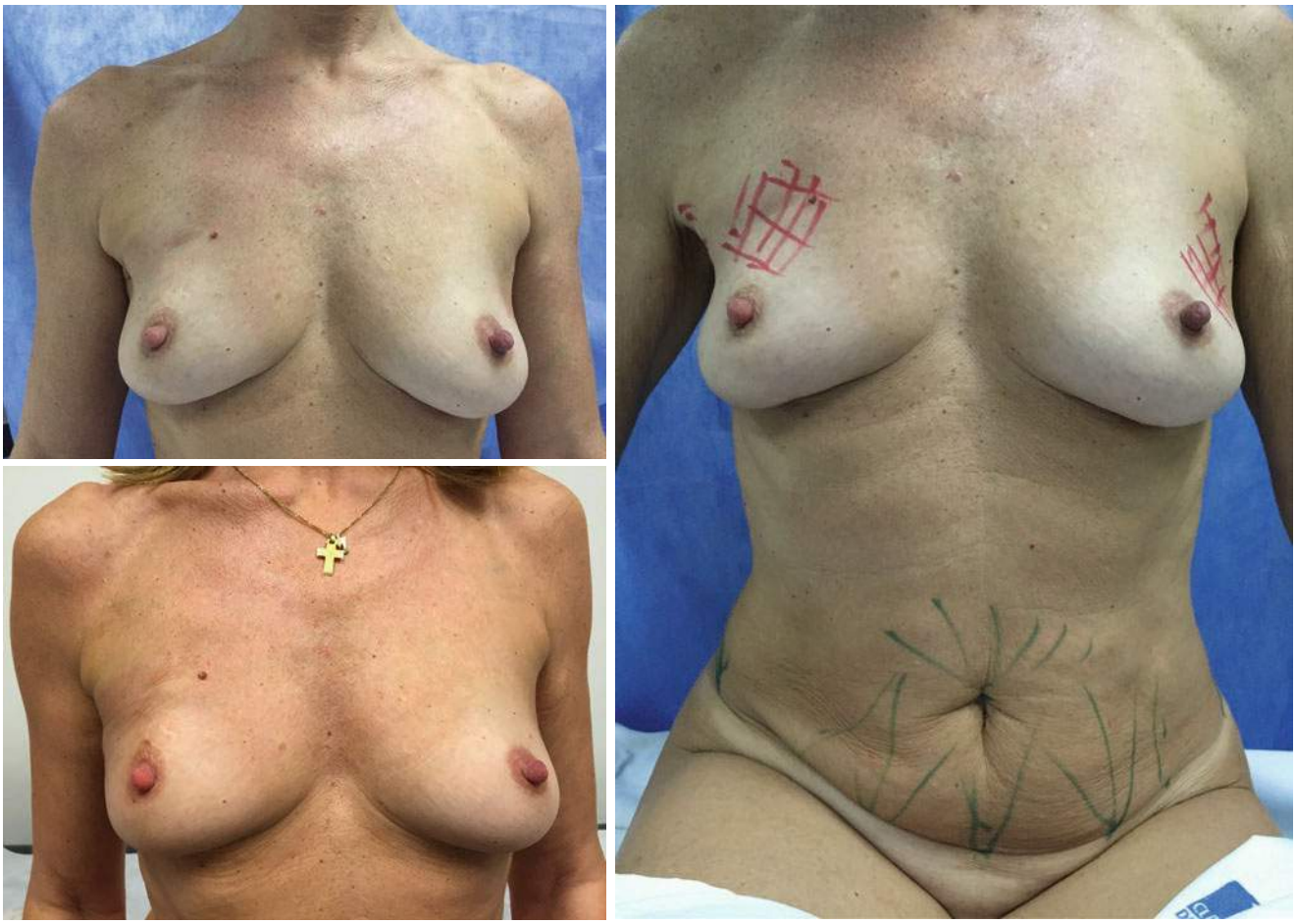


Fig. 34.9 Cosmetic sequelae after BCT in a patient with a tumor in the upper quadrants of the right breast. Small asymmetry. Marked loss of volume with skin retraction (IARfc: a-II). Abdominal donor site. Results 2 years after one lipofilling with correction of the defect (150 g) in the right breast and lipofilling in the opposite breast

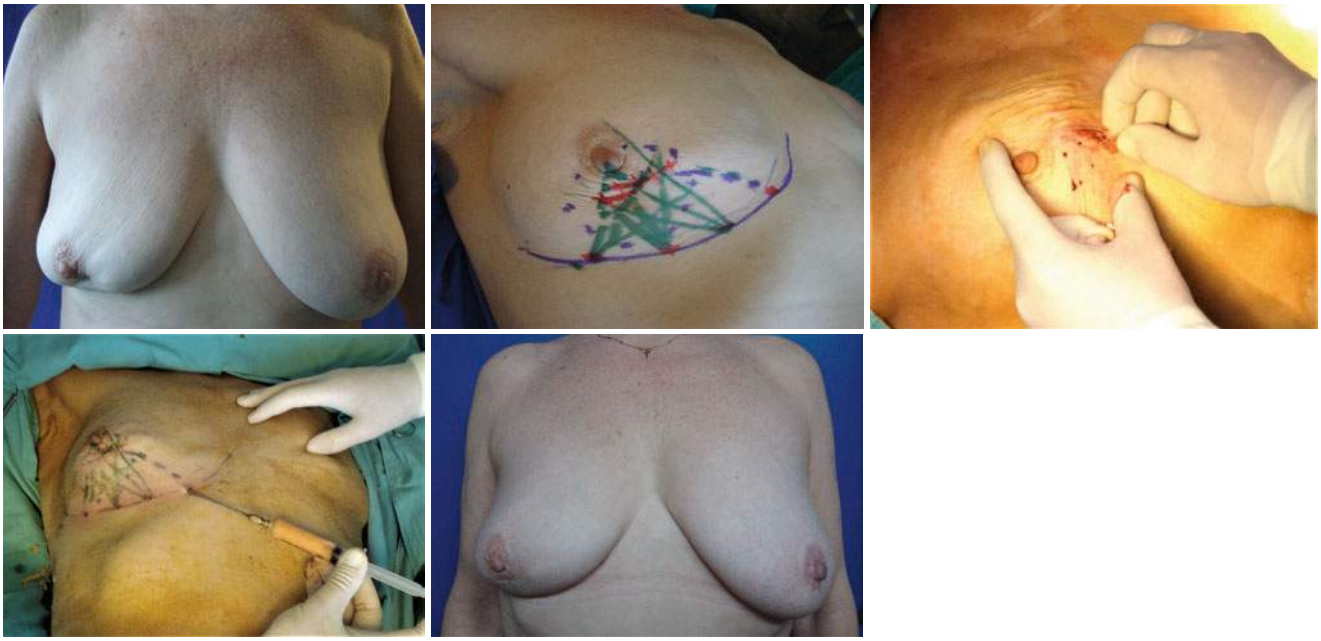


Fig. 34.10 Cosmetic sequelae after BCT in a patient with a tumor in the lower quadrants of the right breast. Sequel of form with marked asymmetry. Marked loss of volume with skin retraction and asymmetry of the NAC (IARfc: b-I). Design of the entry spots and directions of the fat injection. Rigottomies. Result after two procedures of lipofilling with correction of the defect (130 and 150 g, respectively) and good cosmetic result before to the correction of symmetry

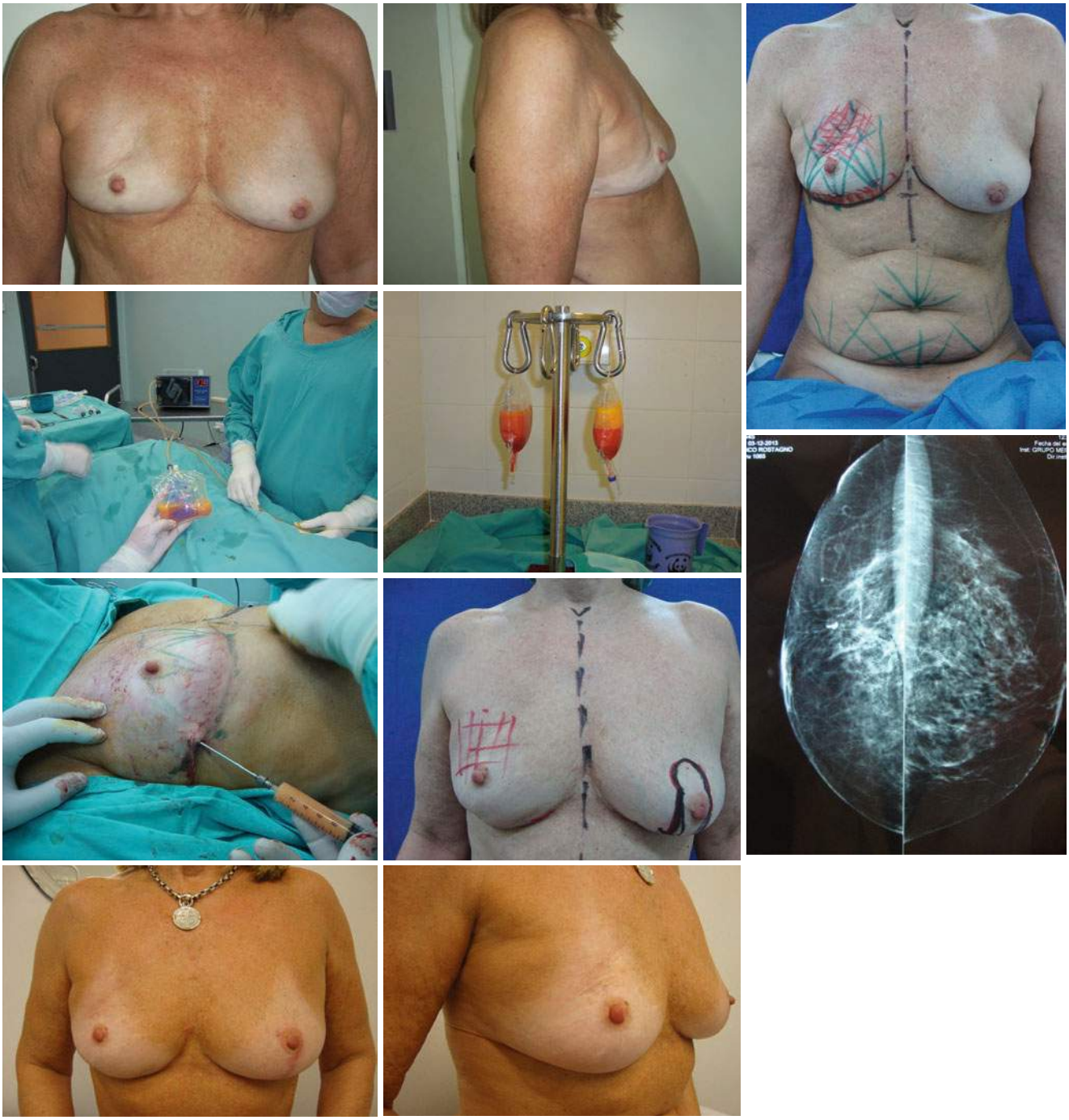


Fig. 34.11 Lipofilling surgical technique. Cosmetic sequelae after BCT in a patient who presented with a tumor in h12 of the right breast. Marked loss of volume with severe skin retraction and asymmetry, elevation of the inframammary fold, an old indication for a latissimus dorsi flap (IARfc b-I). Design of the entry sites and directions of fat injection. Abdominal donor site. Lipofilling surgical technique. Obtaining the fat with liposuction with a low-pressure pump. Manual centrifugation showing the aspirated liquid, fat, and oil. "Rigottomies." Retrograde fat injection with a curved Khouri needle. Lipofilling surgical technique. Final result after two procedures (150 and 200 g, respectively) and reduction of the opposite breast. Postoperative mammography showing the volume augmentation without radiological consequences. Final results

transposition of the whole or part of the latissimus dorsi muscle to the anterior thoracic wall, with a skin and subcutaneous tissue paddle of adequate dimensions to repair the defect. It has some disadvantages: it does not generally give sufficient volume to the reconstructed breast in cases of total breast reconstruction or in cases of huge defects requiring in some cases the association with a prosthesis or expanders, it leaves a scar in the back, and it generally needs intraoperative exploration to ensure the integrity of the thoracodorsal pedicle.

This flap is useful to correct the damage produced by breast conservative treatment in any part of the breast.

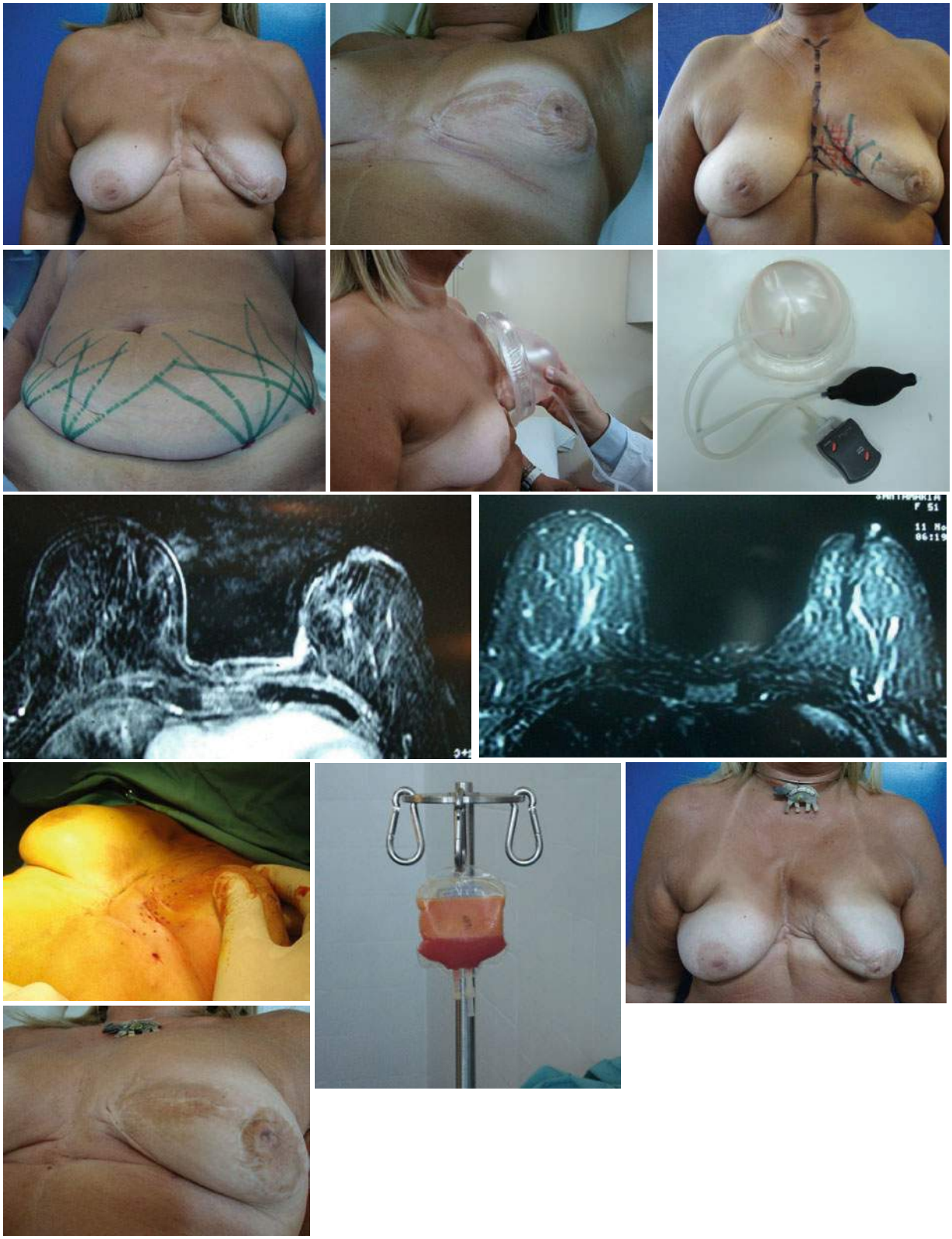


Fig. 34.12 Lipofilling surgical technique + Brava system. Severe cosmetic sequelae after BCT in a patient that presented a tumor in the lower and medial quadrant of the left breast and various intents of reconstruction without prosthesis. Marked volume loss with severe skin retraction and moderate asymmetry, old indication for latissimus dorsi flap (IARfc: b-II). Design of the entry spots and direction for fat injection. Abdominal donor site. Lipofilling surgical technique + Brava system. External expander and his placement, producing vacuum and expansion. Control with MRI previously and after expansion, evaluating the increase in volume and breast vascularization. Lipofilling surgical technique + Brava system. "Rigottomies" preparing the surgical bed for the fat graft. Fat centrifugation. Final result after three procedures (130 g, 120 g, and 110 g, respectively) with good shape and symmetry

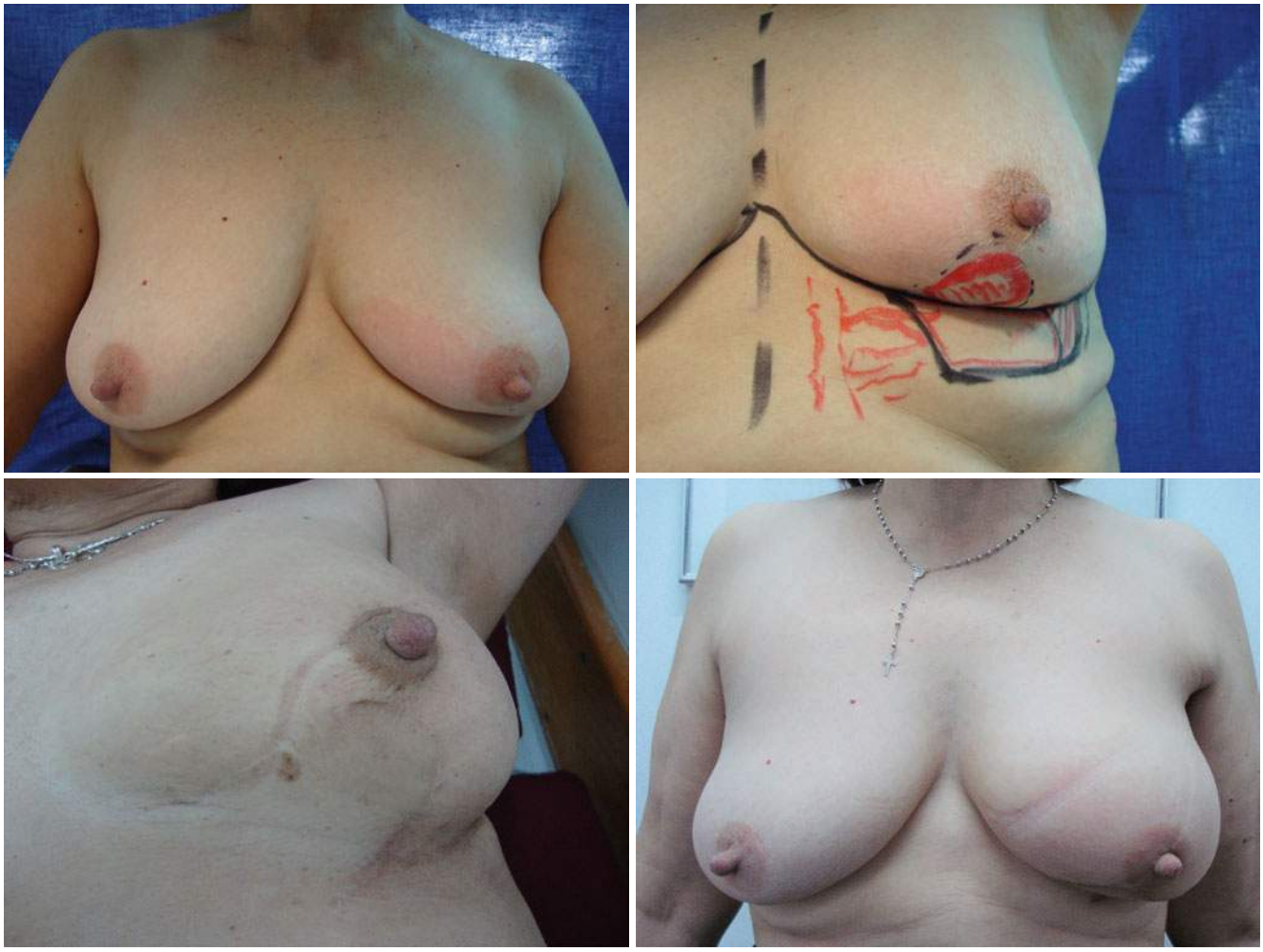


Fig. 34.13 Thoracoepigastric flap. Cosmetic sequelae after BCT in a patient that presented a tumor in the lower and medial quadrant of the left breast. Loss of volume, skin retraction, and moderate asymmetry (IARfc: a-II). Final result

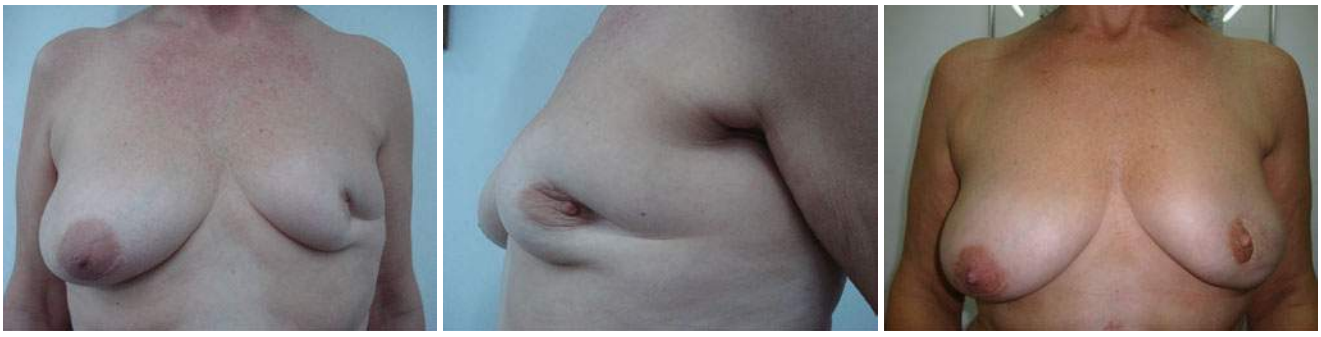


Fig. 34.14 Latissimus dorsi extended flap (fat tissue and muscle). Cosmetic sequelae after BCT in a patient that presented a tumor in the lateral quadrants of the left breast. Marked loss of volume with severe skin retraction and asymmetry of the breast and nipple–areola complex (IARfc: b-I). Design of the paddle that was deepithelized conserving only a small periareolar skin paddle to monitor the vitality of the flap. Final result

Presently, we use it only in patients with severe damage or when this damage cannot be repaired with minor procedures (lipofilling) (IARfc b-I–II–III). It can be associated with expanders or prosthesis if the flap alone is not sufficient to repair the volume of the defect. Its indication in minor sequelae is actually being revised since the implementation of lipofilling techniques (Figs. 34.14, 34.15, and 34.16).

The surgical technique for this flap is well known, and in this chapter we will only detail some important steps for the correction of partial defects. We can synthesize them into:

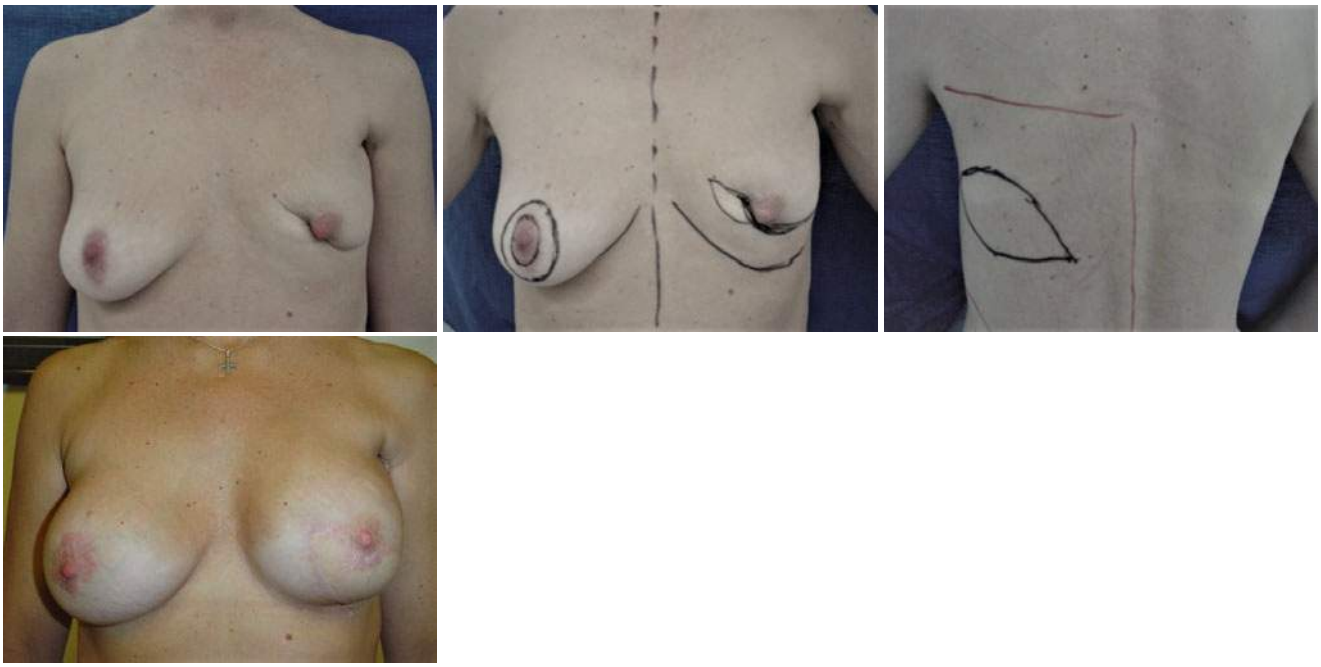


Fig. 34.15 Latissimus dorsi flap + definitive expander. Cosmetic sequelae after BCT in a patient that presented a tumor in the lateral quadrants of the left breast. Marked loss of volume with severe skin retraction and asymmetry of the breast and nipple–areola complex (IARfc: b-II). Design of the paddle that is going to replace the skin defect and addition of a definitive expander to gain volume and give a shape to the breast. Breast reduction of the opposite breast. Final result

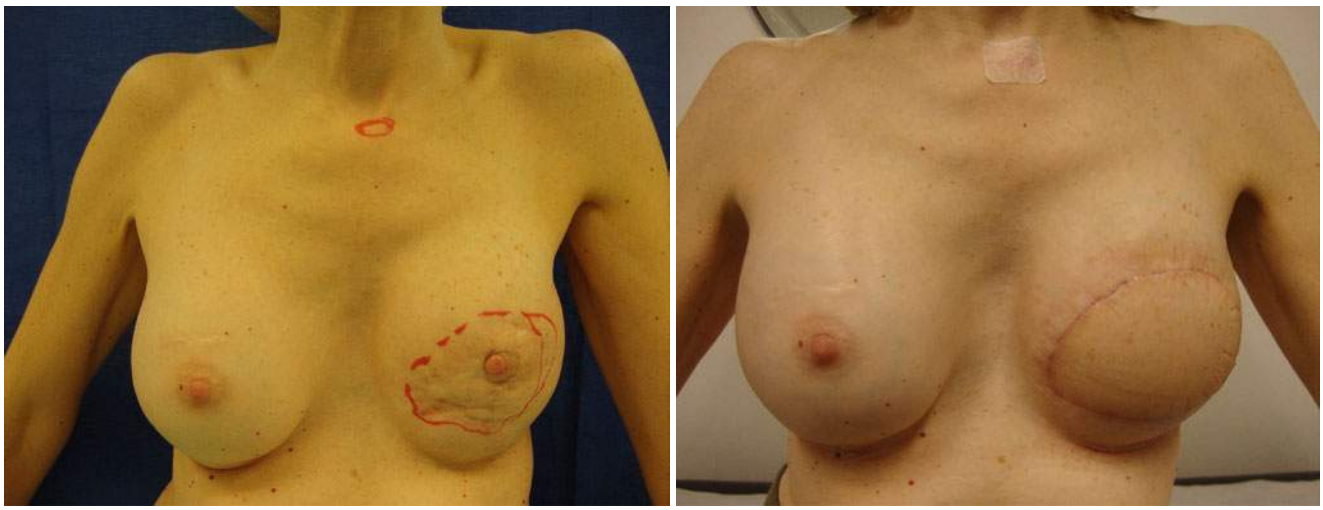


Fig. 34.16 Latissimus dorsi flap + prosthesis. Cosmetic sequelae after BCT in a patient that presented a tumor in the central region of the left breast and underwent an intent of reconstruction with prosthesis and augmentation of the other breast. Loss of volume with severe actinic sclerosis, skin retraction, and asymmetry of the breast and nipple–areola complex (IARfc: b-II). Resection of the patch of necrosis and replacement with a latissimus dorsi flap and definitive prosthesis. Final result

- Detailed design of the paddle in the back to cover the defect, analyzing if the flap is going to be enough (skin, fat tissue, and muscle) [26] or if a prosthesis or an expander is necessary. In some particular situations, it is only necessary to harvest a muscular flap to repair volume defects without need for a skin paddle (miniflap).
- Evaluation of the integrity of the thoracodorsal pedicle before harvesting the flap to avoid complications secondary to damage to it caused by primary surgery or actinic sclerosis.
- Careful modeling of the paddle to optimize the final result.

34.10 Transverse Rectus Abdominis Myocutaneous Flap and Its Variants

Exceptionally, the transverse rectus abdominis myocutaneous flap and its variants are indicated to repair partial defects. In particular situations, in patients with severe defects with actinic sclerosis with or without suspicion of local recurrence and indication of mastectomy, this technique is indicated because of its advantage of giving a good shape and volume to the reconstructed breast and a better chance of symmetry [27] (Fig. 34.17).

34.11 Prosthesis

When we add a silicone prosthesis, in addition to the damage produced by conservative treatment, the high rate of severe capsule contractures and other complications produced is well known. This, despite changes in radiation treatments in relation to the new techniques that improve the homogeneity of the dose and reduce skin and gland damage, still leaves an interrogation in the indication of this technique to correct this damage. Probably, in individual cases with good skin quality and minor sequelae without asymmetries, its use could be indicated exceptionally (Fig. 34.18).

34.12 Complications

The complications are coincident with the description in numerous publications that report a higher complication rate in deferred breast reconstruction compared with immediate procedures after conservative treatment. These high complication rates (between 40 and 60%) are probably a consequence of the secondary changes produced by radiotherapy (scar retraction, radiodermatitis, and fibrosis), which make the procedures difficult and interfere with the cosmetic results [21–29] (Fig. 34.19). In our experience [28], we observed coincidently a high complication rate, around 60%. This rate represents a significant reduction in the last 5 years as a consequence of a change in the surgical technique chosen, with an increased number of patients reconstructed with lipofilling, a procedure that has lower morbidity than the conventional techniques [30].

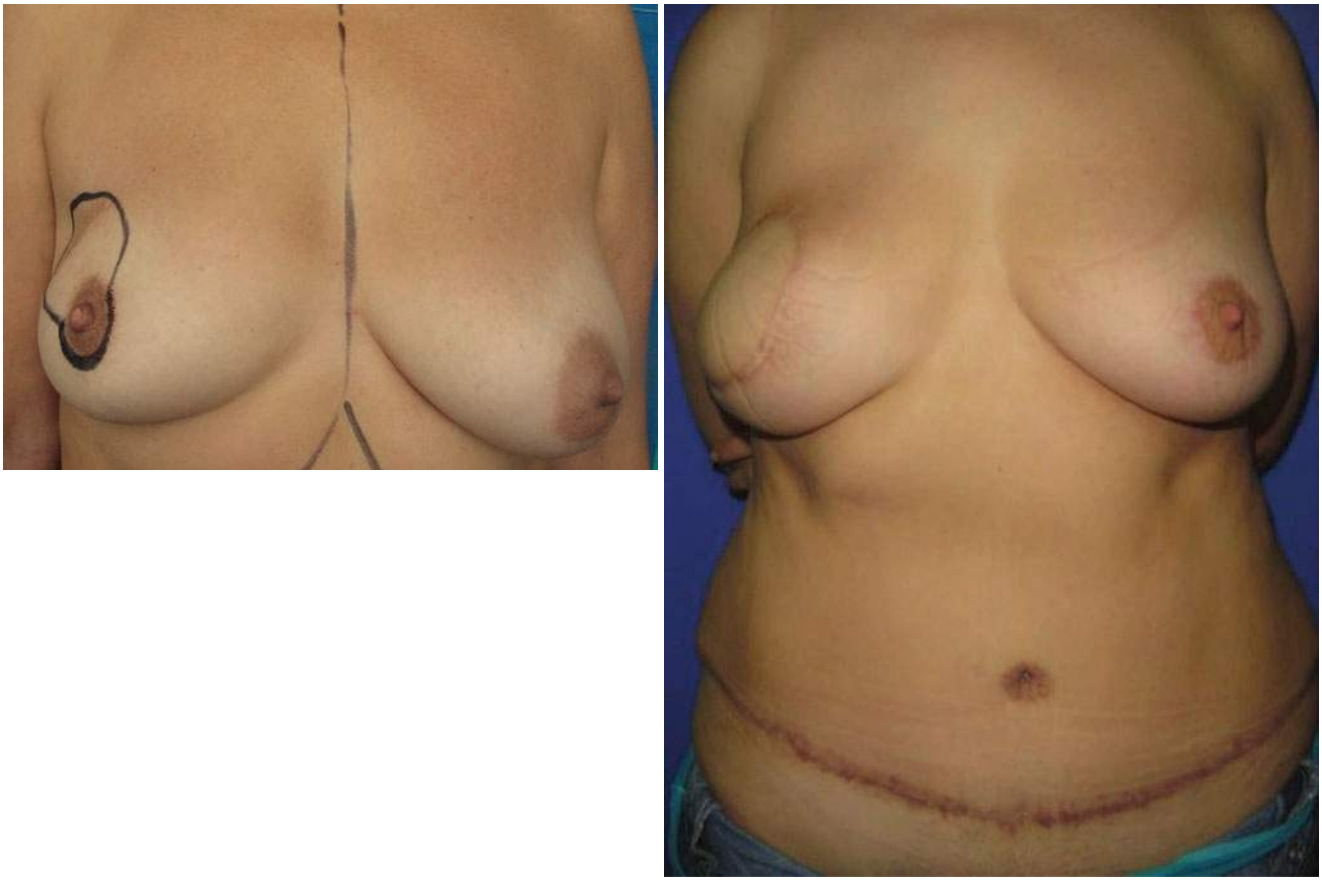


Fig. 34.17 Pediculated TRAM flap. Cosmetic sequelae after BCT in a patient that had a tumor in the upper and lateral quadrant of the left breast. Loss of volume with moderate actinic sclerosis, skin retraction, and asymmetry of the breast and nipple–areola complex (IARfc: b-I). Resection of the area with sclerosis and fibrosis and the nipple–areola complex and replacement with a TRAM flap. Final result

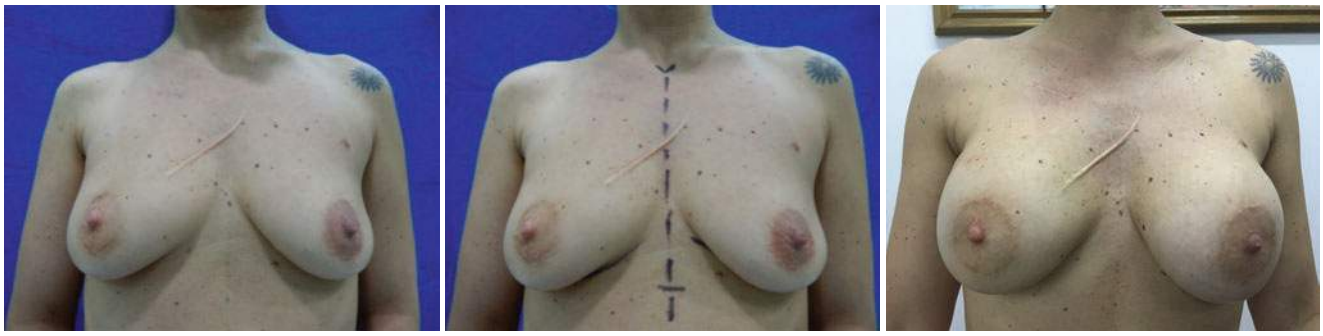


Fig. 34.18 Breast reconstruction with prosthesis. Cosmetic sequelae after BCT in a patient that presented a tumor in the upper and lateral quadrant of the right breast. Small loss of volume with mild actinic sclerosis (IARfc: a-II). Bilateral augmentation mastoplasty with prosthesis. Final result with good correction of the defect in shape and asymmetry

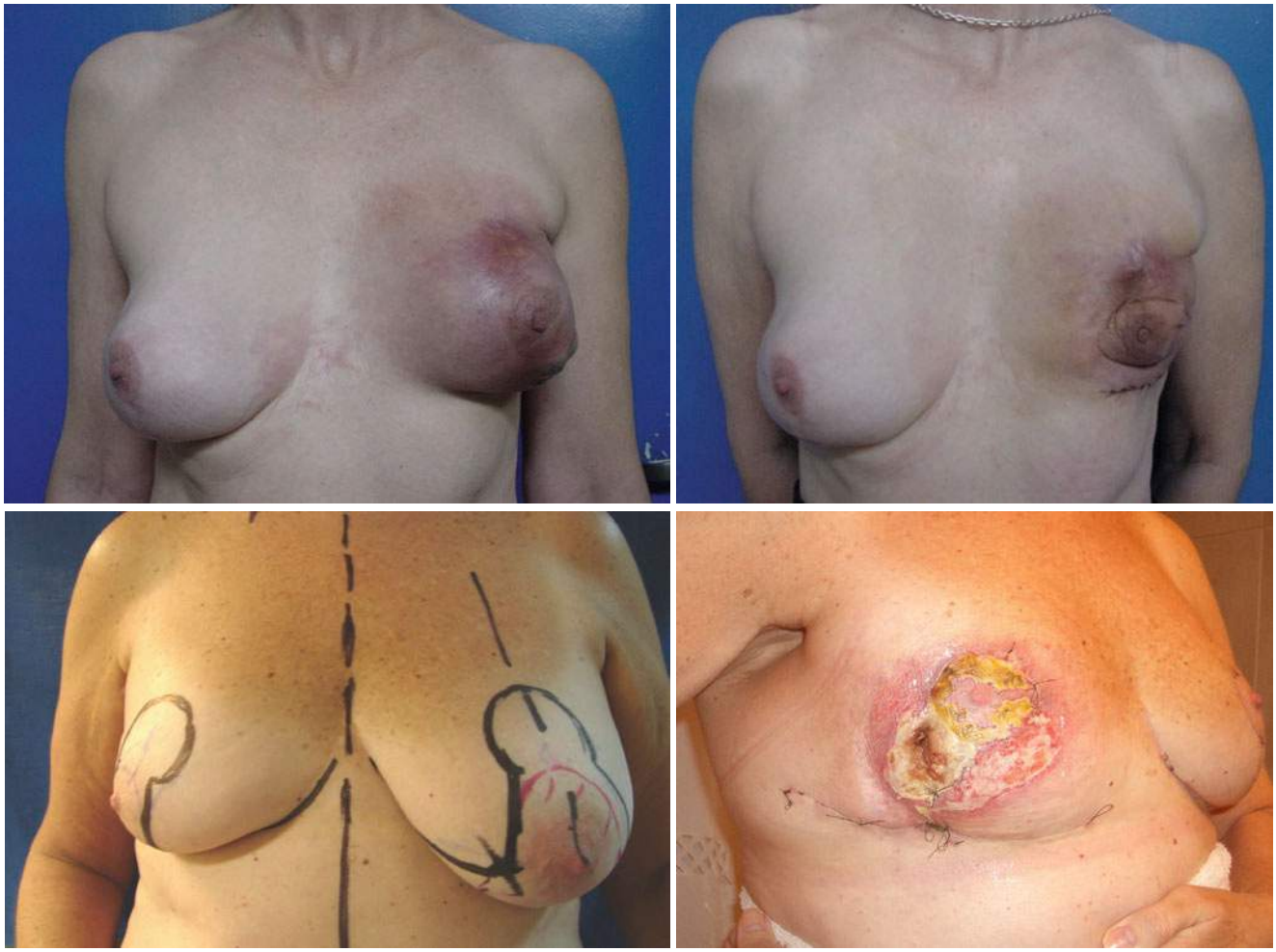


Fig. 34.19 Complications. *Above*: cosmetic sequelae after BCT in the left breast, reconstructed with augmentation mastoplasty. Spontaneous and late prosthesis extrusion. *Below*: cosmetic sequelae after BCT in the right breast, reconstructed with reduction mastoplasty. Infection and skin necrosis

34.13 Conclusions

Oncoplastic surgery was incorporated into primary treatment of breast cancer to prevent the damaging consequences of this treatment and produce important aesthetic and psychological benefits without altering oncological safety. In conservative treatment, despite the existing multiple reconstructive techniques to prevent sequelae, there are still a number of patients who for different reasons have unsatisfactory results magnified by the effects of radiotherapy. Traditionally, aggressive techniques with high complication rates (autologous tissue, prosthesis) and unstable results were employed for the reconstruction of these defects. However, in recent years the introduction of lipofilling has opened up a new and promising stage, achieving in many cases highly satisfactory and stable results, with lower morbidity.

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Part IV

Breast Reconstruction After Mastectomy

History and Development of Breast Implants

35

Mario Rietjens, Marco Aurélio da Costa Vieira, Cícero Urban, and Visnu Lohsiriwat

35.1 Introduction

The first breast implants were created by Cronin [1] in 1962, and after that there was a big evolution in them. The initial concern was to find a biocompatible sort of material: properly tolerated by the body and also inert. In 1958, Scales [2] proposed a review of the criteria needed for implant considering biocompatibility:

- No chemical activity
- No physical transformations when in contact with the body
- No stimulus to inflammatory reactions or foreign material
- Not being carcinogenic
- Able to stand mechanical forces
- Easy to produce at considerable low cost
- Able to be sterilized

At first, liquid silicone showed these characteristics and started to be used for aesthetical purposes through injections. Such a practice was subsequently abandoned when it was verified that liquid silicon particles could migrate towards regional lymph nodes and then to other organs such as the lungs and the liver [3, 4].

The first concern of silicone manufacturers was to make an implant with an envelope that could prevent the migration of silicon particles and simultaneously that this envelope was not excessively thick in order to keep a more natural consistency of the reconstructed breast. The problem found with this first generation of implants was the durability of the envelope as there was a waste of the envelope after some time of use resulting in rupture and spread of the silicone gel. This event contributed to a decision of the FDA to prohibit the use of silicone gel breast implants in 1992 [5], as in the United States and also all over the world, there was a huge increase in the use of implants with silicone gel, and patients did not control the integrity of the implants and were not informed as to the need to replace the implants in case of a possible rupture. From then on, there was a new evolution of materials, with the reintroduction of implants containing a physiological solution, eliminating the use of silicone gel. The ulterior problem of these implants with saline contents is the high level of deflation, due to technical problems inherent to the valve.

The next challenge was to fight against the periprosthetic capsule, which was one of the most frequent complicators of breast implants. A change in the position of the implants from the subcutaneous space to the retropectoral space contributed to an important reduction of the periprosthetic capsule phenomenon. The introduction of implants covered with a coat of polyurethane contributed to the reduction of the capsular contracture, but the use of these implants was prohibited by the FDA, as it was proved in experimental studies that the degradation of polyurethane produced a substance that is potentially carcinogen for bladder tumours [6]. This originated the development of implants with external texture, which could have the same effect of the polyurethane in the reduction of periprosthetic capsules, even though some randomized studies comparing implants with smooth envelope and those with textured envelope did not present a significant reduction in the level of capsular contracture [7]. A new generation of a more cohesive silicone gel, allowing for the production of form-stable implants with anatomic shapes, are improving the aesthetic results of breast cancer reconstruction (Table 35.1).

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_35

Table 35.1 Evolution of breast implants

1962: Implants in silicone gel Sialastic® type—first generation
1965: Implants in saline solution Simaplast type
1975: Implants in silicone gel "low bleed"—second generation
1976: Implants with double chamber
1976: Anatomic implants
1986: Implants coated in polyurethane
1988: Implants with textured surface
1990: Implants with hydrogel
1992: Prohibition by the FDA of use of silicone gel implants
1993: Implants with Trilucent lipid
1995: Anatomic implants in cohesive silicone gel—third generation
1997: Breast Implant Associated Anaplastic Large Cell Lymphoma
2002: Anatomic implants in silicone gel with differentiated shapes (right and left)
2003: Implants coated in a titanium microstructure
2011: PIP and Rofill implant crises

35.2 Types of Implants

There are various types of breast implants that vary according to the characteristics of the material or indication of use:

- Smooth, textured, polyurethane and micro-textured in titanium envelopes
- Filled with saline solution, regular or cohesive silicone gel, mixed gel and other nonhomologous substances (soybean oil, peanut oil, hydrogel, etc.)
- Round and anatomic shapes or differentiated shapes
- Fixed or variable volume

35.2.1 Saline Implants

These implants are made with a silicone envelope and a valve that allows for the insertion of the physiological solution during the operatory procedure. The envelope may be either smooth or textured. The envelope shows good elasticity, therefore promoting a small variation in the volume of saline solution to be inserted in order to obtain better volumetric symmetry with the opposite breast. It is recommendable that 10–20% of the volume recommended by the implant manufacturer be exceeded, so a better distension of the envelope is obtained aiming to avoid implant folds. These folds could, after some time, cause a rupture or even an ulcer opening with prosthesis extrusion, especially in cases of thin and irradiated coetaneous coating. The shape might be round and anatomic, considering that there is a bigger difficulty in keeping the anatomic shape when inserting the saline solution, as the implant does not have the same consistency of cohesive gel. The valve may be anterior or posterior, according to the technique with small incisions allowing for the insertion of the completely empty implant and subsequently the insertion of the physiological solution.

Fig. 35.1 Round prostheses: physiological solution (with a valve for filling) and prosthesis in silicone gel

Technically, it would be simpler to use implants with anterior valves if the incision is periareolar and posterior valves for axillary incision cases. The valve is one of the critical points of saline implants, as a small production defect may originate a partial or total leakage of the physiological solution. Usually this leakage does not cause any pathological damage to the patient, as it is a physiological solution, so it is reabsorbed by the organism. The biggest problem is aesthetic, with a reduction of volume and the need for a new surgery to replace the implant (Fig. 35.1). Some studies have reported different levels of leakage or disruption of saline implants. A French group has demonstrated a level of 15% of leakage in 650 patients with average follow up of 5 years [8].

35.2.2 Silicone Gel Implants

These implants have a fixed volume, made up of an envelope of silicone gel. Currently the thickness of the envelope is more carefully considered so it can get more resistant and also avoid the "perspiration" of silicone gel particles. Silicone gel is elastomeric, and its viscosity depends on molecular mass, so nowadays it is possible to manufacture a more cohesive gel. This kind of gel is used in the making of anatomical implants, which need to be slightly more rigid in order to keep the anatomical shape. The anatomical implants with cohesive gel were a great advance to improve the aesthetic results in breast reconstruction, as it is possible to achieve a better shape with less projection of the upper pole of the breast.

By using these implants, it is possible to refine a technical point in immediate breast reconstruction: when it is possible to place the mastectomy scar completely on the pectoralis major and the mastectomy flaps are thick and well vascularised, it is possible to make a partial cover of the implant, using only the pectoralis major muscle. This technical element contributes to a better aesthetic result, with more projection of the lower pole of the breast, differently from what happened when a round prosthesis completely covered by the pectoralis major and the serratus anterior muscle [9] were used, frequently obtaining a

round, less natural shape. Another advantage of this type of gel could be patient's security. By reducing the perspiration phenomenon of the particles and by being more cohesive, this gel may also reduce the migration for the lymph nodes, even in cases of disruption of implants. The main advantage of anatomical implants is the possibility to choose different shapes and volumes, as some manufacturers make up different models of implants that vary according to three parameters: height, width of base, and anterior projection. This makes it easier for the ideal choice of implants according to the different morphological characteristics of the patient (Fig. 35.2). Other manufacturers propose innovative features such as designed and moulded prostheses for the right breast or for the left breast and with a concave posterior wall for a better adaptation of the thoracic wall convexity. Although this was an interesting idea, this manufacturer went to a crisis in 2011 due to suspicion of the use of industrial (nonmedical and non-approved to use in humans) silicon in their implants [10].

The disadvantages of anatomical implants with cohesive gel are:

– Harder consistency of the reconstructed breast, which can be taken for a periprosthetic capsule.
– The size of skin incision is another inconvenience of anatomical implants when used in cases of mammaplasty for aesthetic improvement. Round implants can be inserted even through a small periareolar incision, compatible with the resistance and elasticity characteristics of the material, while the anatomical implants need bigger incisions in the inframammary fold allowing for an insertion of the implants free from compression, as even a slight compression could deform it.

35.2.3 Double Chambered Implants

These implants are made with an internal coat of silicone gel and an external chamber that can be filled with 20–50 cc of physiological solution. The initial target of this sort of prosthesis was to obtain a more fragile external chamber able to reach degradation some 3 or 4 months after implantation, therefore reducing implant volume by 20–50 cc when the periprosthetic capsule stabilizes. A reduction in the incidence of periprosthetic capsules was not observed, when compared with single-chamber implants, so the use of such prostheses was discontinued.

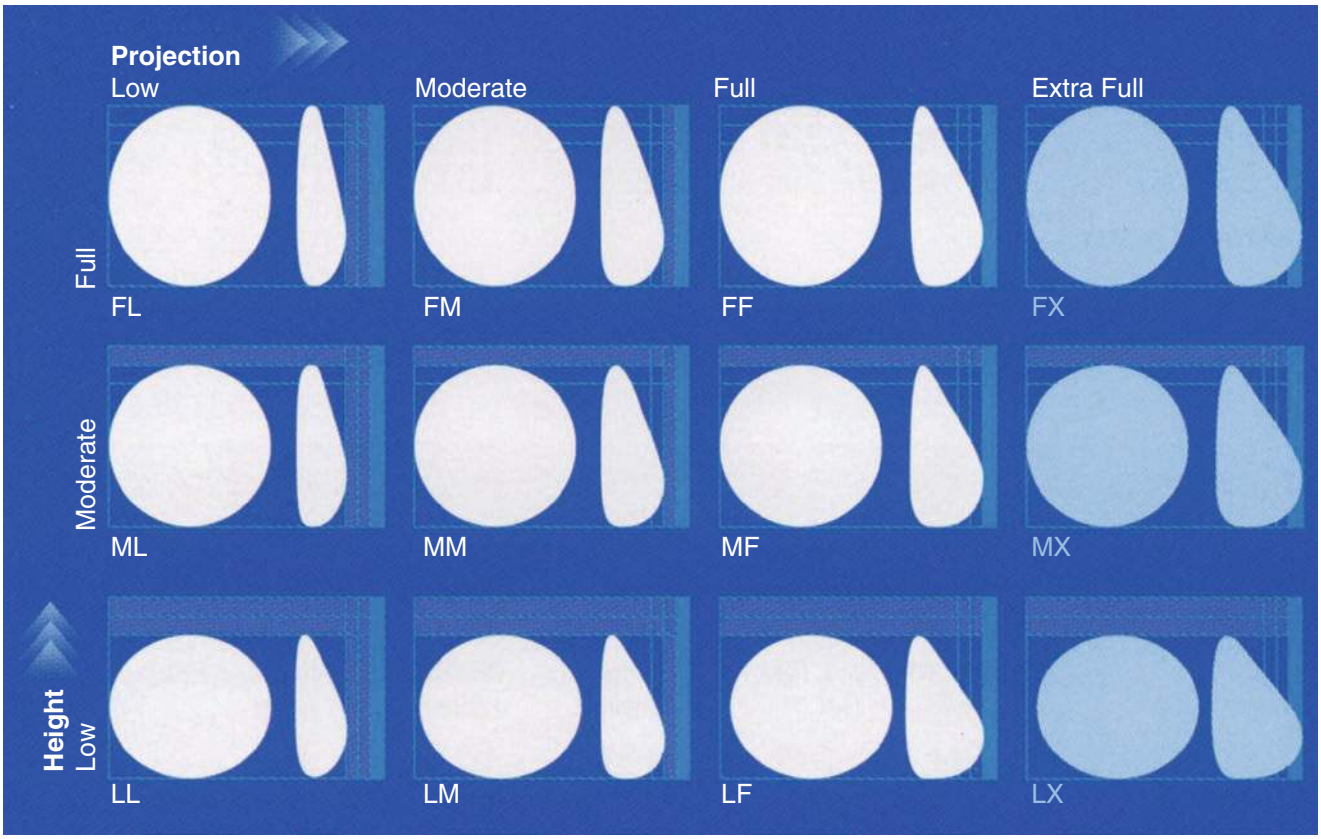

Fig. 35.2 Examples of different models of anatomic prostheses following the parameters of base, width, height and projection in Allergan/Natrelle portfolio

35.2.4 Polyurethane-Coated Implants

These implants are made with an external coat of polyurethane, and they are considered more efficient to avoid the capsular contracture, when compared with those of smooth envelope. The explanation from physics is that the polyurethane coat allows for a disorientation in the direction of collagen fibres; the contrary would happen with implants coated in smooth envelope [11]. Some publications have demonstrated that the metabolization of polyurethane originated a substance called 2,4- and 2,6-toluene diamine (TDA), which could be carcinogenical [6, 12]. Some surgeons keep using prostheses coated in polyurethane for aesthetic augmentation mammaplasties, though there are no recent publications about the incidence of periprosthetic contracture and other complications. It is important to know that in case of infection with a polyurethane prosthesis, the removal of the prosthesis with all residue of polyurethane is mandatory, so post-operative coetaneous fistulae are avoided.

35.2.5 Titanium Microstructure Implants

These are relatively new implants, launched in the market in 2003, and they present the following characteristics: internal part in silicone gel and external envelope in silicone with a titanium microstructure. The aim of this type of implants is to result in fewer reactions against foreign bodies and consequently to reduce the incidence of periprosthetic capsules. There are no randomized trials comparing the efficiency of this sort of implants yet.

35.2.5.1 Definitive Expanders

These implants have a variable volume: they consist of an external chamber filled with silicone gel and an internal chamber that can be filled with physiological solution up to a controllable volume so it can better adapt to the volume of the opposite breast. The chamber is placed at the lower portion of the implant, and its filling favours the anatomic shape of the prosthesis. There is an external valve connecting with the internal chamber through a tube approximately 2 mm large; this device can be removed in some sorts of implants (Becker's prosthesis), or it is not removable in some other sorts of prosthesis (Allergan Style 150). The valve can be placed in the axillary region and in a more superficial position in relation to the skin so that placement is not difficult. A parasternal placement causing discomfort to the patient is avoided [13]. One of the advantages of this sort of implants is the possibility of volume variation, which might be useful for an immediate breast reconstruction with fragile coetaneous grafts and risk of skin necrosis if a high tension is found. In such cases, the implant can be inserted without filling of the internal chamber, and correction of the volume can be done after 3 or 4 weeks, when vascularization of grafts are already stabilized. There is also the possibility of small corrections of volume when body weight variations occur in the post-operative period due to chemotherapy or hormone therapy (Fig. 35.3).

Fig. 35.3 Definitive expanders: these are prostheses with a silicone gel chamber and a second chamber with physiological solution, where the volume can be modified through a small subcutaneous valve. Prosthesis filled to a maximum level (left) and prosthesis partially filled by phisiological solution filling (right)

Two disadvantages in the use of this type of implants are:

1. Patients experience some discomfort by using an axillary valve. If the implant being worn has a removable valve, it can be removed at the moment of the first operation of reconstruction of the areola and the nipple; if the valve cannot be removed and the final volume is obtained, placing the valve behind the implant is possible at the second surgery.
2. The point of insertion of the tube in the implant is rather vulnerable. Considering implants in which the tube can be removed, there is a risk of significant draining of the physiological solution through the protection valve. Considering implants in which the tube cannot be removed, there is a major mechanical traction in the region of the tube insertion that may result in an earlier disruption of the implant.

35.2.5.2 Temporary Expanders

These are implants with an envelope of elastic silicone and a filling valve that allows for inserting a physiological solution and, consequently, a postoperative skin distension that can help to achieve a breast volume similar to that of the contralateral one. A second surgery for substituting the expander with the definitive implant is needed. There are different models and shapes of expanders: round, anatomic, with integrated valves, and with valves at distance. The older models have a round shape and a valve at distance, connected with the device through a 2 mm-diameter silicone tube. The disadvantage of these models is that they produce a generalized global distension, with a significant distension of the upper pole of the breast and consequently a distension of the pectoralis major muscle. Such distension causes some

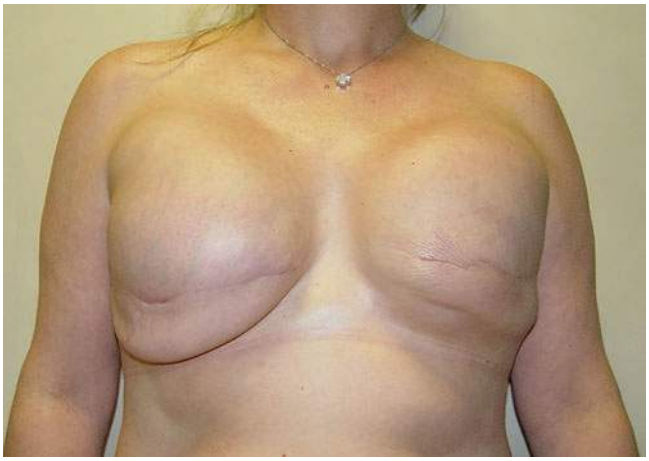

Fig. 35.4 Round expanders (not anatomic) produce a distension of the upper part of the breast with pain and an unacceptable aesthetic result

discomfort to the patient and pain when moving the upper limbs, besides resulting in a gain of skin distension of the upper pole, while it would be better to achieve skin distension of the lower pole (Fig. 35.4). Another disadvantage is the positioning of the valve usually in the axillary region. It may cause pain or discomfort if the valve is too big, or it may even cause difficulty for the filling if the valve is rather small or the patient is obese. The most frequently used models are those with various heights, external textured envelope, and valve incorporated in the device. The anatomic shape is appropriate for a distension only of the lower pole of breast, producing a skin distension that can result in a symmetric shape in relation to the opposite breast. It does not cause discomfort due to distension of the pectoralis major muscle (Fig. 35.5). The various heights of prosthesis may help decide for a global expansion only of the lower pole, which is usually applied to low-volume breasts. The textured envelope may avoid mobility of the prosthesis, and according to some authors, it may reduce the incidence of periprosthetic capsule formation. The most spread mechanical hypothesis is that textured envelopes produce a heterogeneous disposition of the fibroblasts, which reduces the tension of the periprosthetic capsule. The valve incorporated in the prosthesis represented an evolution that brought comfort to patients and also avoided the problems found in valves placed at distance or at the axillary area.

Special attention must be given to positioning of the anatomic textured expander with an incorporated valve:

- Make sure that the expander is placed with the valve on the anterior wall of the prosthesis.
- Make sure that the lower base is placed exactly at the infra-mammary fold, as the exact position of the implant may favour a minor surgery for change of implant, without the need of capsulotomies or ulterior fixation of the infra-mammary fold.

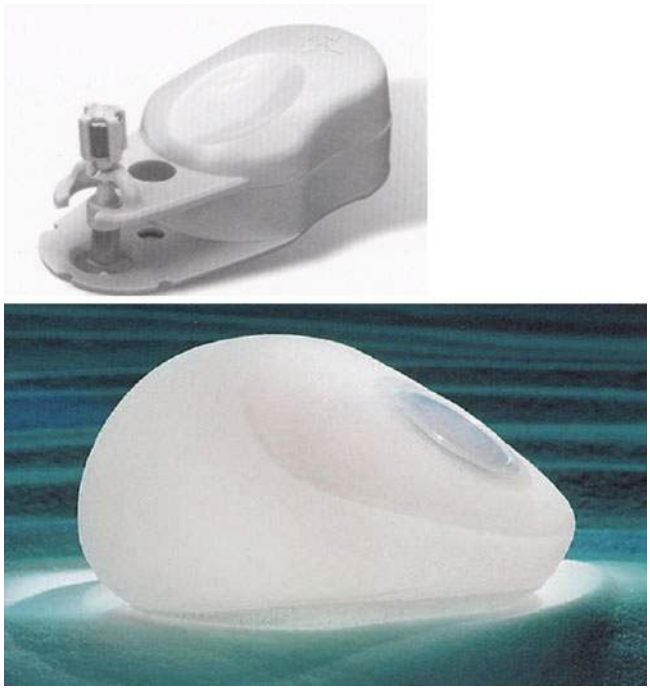

Fig. 35.5 Temporary expander with incorporated valve: the magnet for external use specifies the exact point for placing the needle in order to fill the prosthesis with the physiological solution

- Make sure that there is not a fold in the lower portion of the expander over the region with low filling, as there is risk of perforation of the prosthesis at the moment the needle for tilling skin distension is inserted.
- Try to place the expander horizontally in the thoracic region, in order to avoid a bigger distension either medially or laterally.

Time and frequency of filling the expander depend on the healing of coetaneous grafts and the elasticity of tissues. The notion that a quick distension is more efficient and less uncomfortable to the patients is always valid. The expander must be filled intra-operatively without tension of the mastectomy graft suture. A bit of methyl blue is added to the physiological solution which is injected intra-operatively in order to it make easier for proper placement of the postoperative needle.

If the mastectomy flap has good vascularization, we can fill the expander with 60 cc physiological solution every week until the aimed volume is achieved.

35.3 Controversy About Silicone

It is estimated that millions of women have undergone implants of silicone gel implants in the United States over the past decades. Controversy about silicone began with the suspicion of a relation between silicone and autoimmune diseases (rheumatoid arthritis, scleroderma, lupus erythematosus, etc.), neurological diseases [14] or even those that

could be carcinogenic. After significant public pressure, the FDA (Food and Drug Administration) prohibited the use of silicone gel implants [5], except for cases of mammary reconstruction or aesthetic mammaplasty for breast augmentation as part of clinical studies. After several countries adhered to that, a great number of studies started to be performed aiming to establish this relation.

A review of the literature proposed by the American Academy of Neurology [15] excludes the relation between implants in silicone gel and neurological diseases. Other major epidemiological studies [16–21] concluded that there is not a connection between silicone gel and autoimmune diseases. And other clinical [22, 23] and epidemiological [24–26] studies point to an absence in the relation between implants in silicone gel and an increase in the incidence of breast cancer.

Currently, one problem that concerns the FDA the most considering the use of silicone gel implants is the diagnosis of subclinical rupture of the prosthesis. Such are cases in which the implants have an external envelope with no rupture but extremely thin, allowing the silicone gel to perspire, or those cases in which the envelope disrupts significantly but such a disruption is not clinically noticed. Studies by Marotta [27], through a meta-analysis of about 10,000 prostheses, have shown that the rate of rupture increases with the passing of time from the occasion of the implant, and the percentage is 26% of ruptures at 3.9 years, 47% of ruptures at 10.3 years and 69% of ruptures at 17.8 years ($p < 0.001$). Through the literature, it is known that the breast tests available mammography, ultrasonography and magnetic resonance (MRI) show some limitations for the diagnosis of rupture. Mammography can diagnose a late rupture, when the periprosthetic capsule is basically calcified. Ultrasonography has variable sensitivity ranging from 47 to 74% and variable specificity between 55 and 96%. Ultrasonography depends very much on who is operating it and demands some time to be learned so one can achieve a good evaluation of mammary implants. MRI would be the best type of test to diagnose rupture [28], as its variable sensitivity ranges from 46 to 100% and the variable specificity ranges from 92 to 100%, but it is also a difficult test to be considered as follow-up due to its high cost and complex performance (it cannot be performed in obese patients, claustrophobic ones and those holding an artificial pacemaker). Today, we can use MRI to perform a hepatic spectroscopy and therefore diagnose the migration of silicone particles to the liver, in cases of rupture of the breast implant in silicone gel [29, 30]. FDA recommended to implant manufacturers to do postmarketing studies in 2006. Thousands of women enrolled in Mentor and Allergan studies to evaluate complications had lost follow-up, 79% in Mentor's Study and nearly 40% in Allergan's Study.

Poly Implant Prosthèse (PIP) crises in 2011 showed the fragility of current data on safety of breast implants and the need of reliable postmarketing surveillance independent studies [30].

35.4 European Institute of Oncology Biomechanical Study

Concerned with the problem of subclinical ruptures of silicone gel prostheses, we propose a diagnostic-clinical-biomechanical study of prostheses in patients that must undergo a replacement of the breast prosthesis in silicone gel due to a suspicion of rupture or by aesthetic reasons (asymmetry, periprosthetic capsule, increase in weight).

Diagnostic stage: all patients should undergo a pre-operative MRI to set the level of sensitivity and specificity of the method for subclinical rupture, through a blind experiment.

Clinical stage: a pre-operative evaluation to spot the level of the periprosthetic capsule according to Baker [31] and clinical signs of rupture (inflammation of the site or deformity of the prosthesis) must be performed, as well as an intra-operative evaluation with a bacteriological test of the periprosthetic liquid and a histological test of the periprosthetic capsule and the pectoral muscle, which could measure the diffusion of silicone gel particles in adjacent tissues according to the time of implantation and the conditions of the prosthesis.

Biomechanical stage: once the prosthesis is removed, it will go through mechanical analyses both static and dynamic (integrity of the envelope, resistance to pressure, elasticity, etc.) and chemical analyses (viscosity, molecular weight, spectroscopy, etc.). Results are compared with the initial characteristics of each prosthesis; and in order to obtain a commercial authorization, these prostheses must have all the initial tests. This stage will allow for an evaluation of the material degradation according to the implantation timing of each type of prosthesis and of different manufacturers.

35.5 Breast Implant Anaplastic Large Cell Lymphoma

The first publication in this unique and rare entity was in 1997. Since then there has been an increase in the number of cases, now over 600 reported in the literature, and possibly this number is underestimated. There is a probable link between the texturization pattern of the breast implant and the appearance of this lymphoma. Cochle-Wilkinson et al. in Australia and New Zealand reported an implant-specific risk of 1 in 3817 with macrotextured implant (Biocell, Allergan), 1 in 7788 with polyurethane microtextured device (Sientra/Silimed) and 1 in 60,631 with microtextured implant (Mentor Siltex, Mentor Worldwide LLC). The reason for this, probably is related to larger surface area of the macrotextured implant which allows for greater bacterial contamination and stronger inflammatory reaction [32]. A recent Dutch popula-

tion study suggests a risk of 1 ALCL in 35,000 at the age of 50 years, 1 to 12,000 at the age of 70 years and 1 in 7000 at the age of 75 years in women with breast implants. In this same study the risk happens to be 1 every 6920 before the age of 75 years [33]. Clemens et al. states that this risk is 1 in 30,000 patients [34]. The behavior pattern of this entity is the same of solid tumors, even being a lymphoma. Thus, local treatment is of fundamental importance: Removal of the prosthesis and the entire capsule, with free margins, no indication for sentinel lymph node biopsy. Staging with PET-CT is indicated. Systemic treatment only in more aggressive cases, those with solid tumors clinical presentation or with systemic metastases. All patients who are candidates for breast implant surgeries should be alerted of ALCL risks.

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Breast Reconstruction with Temporary and Definitive Tissue Expanders

36

Cicero Urban

36.1 Introduction

Although one-step direct form-stable implant breast reconstruction has continued to grow in terms of popularity, immediate one- or two-stage tissue expander (definitive or temporary ones) remains as the preferred approach due to its relative simplicity. In our Breast Unit, one-step surgery with definitive implant is the preferred one, and expanders (definitive or temporary ones) are limited to less than 10% of cases. More conservative mastectomies, with the preservation of the inframammary fold, skin envelope, and nipple and areola complex, allowed more anatomical reconstructions and better outcomes. In addition, patient's expectations are greater than when the implants were first used in 1960s [1].

Radovan [2] has introduced gradual expansion with tissue expanders, with positive psychological benefits to breast cancer patients, avoiding the mutilation and donor site morbidity of autologous flaps. Progress in breast cancer treatment with more individualized and less aggressive approaches permitted improvements in breast reconstruction with implants. The importance of new generations of silicone implant on two-stage tissue expander reconstruction cannot be overstated, as earlier limitations of them were in part responsible to bad aesthetical appearance and softness in the beginning. Adjustable implants one-stage immediate breast reconstruction is an option to selected patients too. There is, however, a constantly evolving debate about the comparative benefit of one- or two-stage approach. The final result of the reconstruction is largely dependent on the status of the tissues after mastectomy—a good mastectomy is the better way for a good reconstruction outcome—and the anatomy of the patient. And two-stage approach allows more predictable outcomes in the hands of most surgeons.

Optimal aesthetic and functional results using one- or two-step approach using temporary or definitive expanders demand attention to details in planning and technique, which are showing in this chapter.

36.2 Patient Selection

Patient's selection is the most important consideration to the success of breast reconstruction. The breast and tumor's characteristics are crucial, but understanding their expectations and showing that the reconstructed breast will not look exactly like the natural breast are critical, too [3–5]. Then, there are 5 factors in surgeon's preference in relation to reconstructive techniques: surgeon's training in different techniques, costs, tumor's characteristics, and patient's anatomy and expectations (Table 36.1).

Careful assessment of relevant medical and oncological issues is critical. Since most patients will need adjuvant chemotherapy, which will typically begin somewhere between 4 and 6 weeks following mastectomy, everithink should be able to heal by this time. Then, patients with some medical problems or history of severe tobacco abuse may not be appropriate to this kind of reconstruction. It is not the case in patients after neoadjuvant chemotherapy, but if radiation therapy is previously planned (which is a specific topic in this book), a multidisciplinary decision must be made, and sometimes the delayed reconstruction is a good option. Previously irradiated patients (which is discussed in other chapters, too) are not good candidates to expanders. Inflammatory cancers or patients without response to neoadjuvant chemotherapy are relative contraindications too (Table 36.2). Between January and September 2014, 121 immediate breast reconstructions were done at our breast unit, 104 (86%) of them with definitive form-stable implants and 17 (14%) with temporary expanders.

Electronic Supplementary Material The online version of this chapter (doi:10.1007/978-3-319-62927-8_36) contains supplementary material, which is available to authorized users.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_36

Table 36.1 Patient's selection for two-step temporary expander, one-step definitive adjustable expander, or one-step definitive form stable implant

Characteristics	Temporary expander	Definitive expander	Definitive implant
Breast's characteristics	Small- or medium-sized breasts with no ptosis	Small-, medium-, or big-sized breasts, with or without ptosis	Medium- or big-sized breasts, with or without ptosis
Surgeon's expertise	Less demanding than the other two techniques, because there is a second surgery to correct	Intermediate demanding because there is a possibility to adjust the projection	More demanding because it is necessary to have a symmetry in one-step procedure
Costs	Higher (two surgeries and usually temporary expanders cost more than definitive implants)	Intermediate (one surgery but the definitive expander usually has higher costs than definitive one)	Lower (one surgery with a definitive form-stable implant which has lower costs than the other two alternatives)
Patient's expectations	Lower in the first procedure, as in two surgeries there is time to correct the asymmetry in the second surgery	High since the beginning, because there is a compromise to achieve symmetry in one-step surgery	High since the beginning, because there is a compromise to achieve symmetry in one-step surgery
Immediate contralateral mammoplasty	Not necessary in the first surgery (but necessary in most of second surgeries)	Indicated in most of the cases	Indicated in most of the cases
Tumor's characteristics	Big tumors and in proximity to the skin and bad quality of flaps	All size tumors, with or without proximity to the skin (but without necessity to resect a lot of skin), and moderate quality of flaps	All size tumors, with or without proximity to the skin (but without necessity to resect a lot of skin), and good quality of flaps
Mastectomy	Non-skin-sparing and skin-sparing mastectomies	Skin- and nipple-sparing mastectomies	Skin- and nipple-sparing mastectomies

Table 36.2 Relative contraindications to breast reconstruction with temporary and definitive expanders

Severe tobacco abuse
Uncontrolled diabetes
Bad quality of flaps
Previous radiotherapy
Inflammatory cancers
Locally advanced tumors with no response to neoadjuvant chemotherapy
Unrealistic patient's expectations with breast reconstruction

36.3 Expander Selection

Which is better: temporary or definitive expander? They are different devices and concepts and, most of times, they are indicated for different patients. The principle behind both is the same: to expand tissues in order to have a desired volume, shape, and contour of the breast. But definitive expanders can be used when there is less need to expand the skin following the mastectomy. In these cases, usually it is necessary to do a contralateral mammoplasty, and it can be done, most of times, in a first surgery, or in a second one, when the implant's port is then removed. Temporary expanders usually have the shape, basis, and volume parallel to definitive implants and are indicated when it is necessary to expand more tissue and particularly when the patient wants an augmentation mammoplasty. They can be used in autologous flaps, like latissimus dorsi, or in very selected cases of TRAM flaps. Incorporated valves in temporary expanders are the most used lines, and the rationale to use low or high height and projection devices depends on the breast's characteristics and patient's individuality. One advantage of two-stage approach is the possibility to convey, in selected cases, patient's wishes and views in the process of tissue expansion.

36.4 Planning and Technique

In Figure 36.1 it is illustrated the evolution of mastectomies and breast reconstruction and in Figure 36.2 is shown two generations of patients, mother (Halsted mastectomy) and daughter (nipple-sparing mastectomy with immediate reconstruction with definitive expander), both with breast cancer but three decades between them, are shown. The skin pattern for mastectomy today is decided according to oncologic necessities and previously discussed with the patient. The most important measurement is the base width; followed by the breast shape and volume, which are compared to the contralateral breast; and the ideal width, shape, and volume of the planned reconstructed breast (Fig. 36.3). The type of mastectomy is relevant, too, as in the nipple-sparing mastectomy; it is possible to do one-step surgery with definitive expanders or definitive implants and contralateral mammoplasty whatever necessary.

Preoperative markings include sternal midline, the inframammary and lateral folds, breast limits, and proposed incision (Fig. 36.4). Expander's choice is based on the base width and desired shape and choice for definitive implant (Fig. 36.5). Following the mastectomy, there are two classic

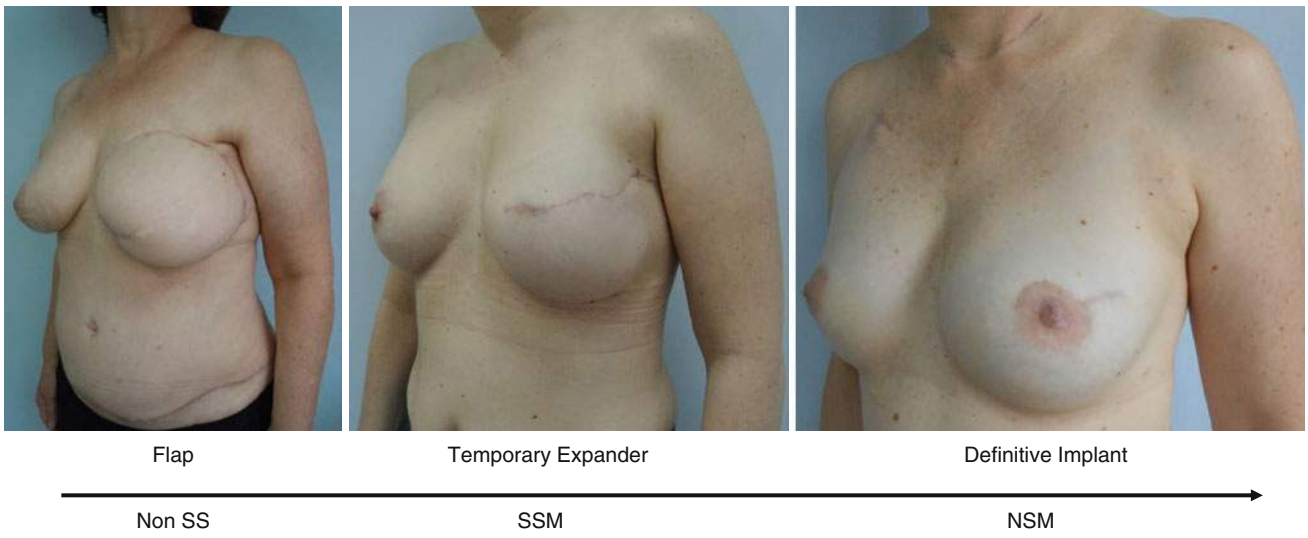


Fig. 36.1 Evolution of mastectomy and breast reconstruction's techniques

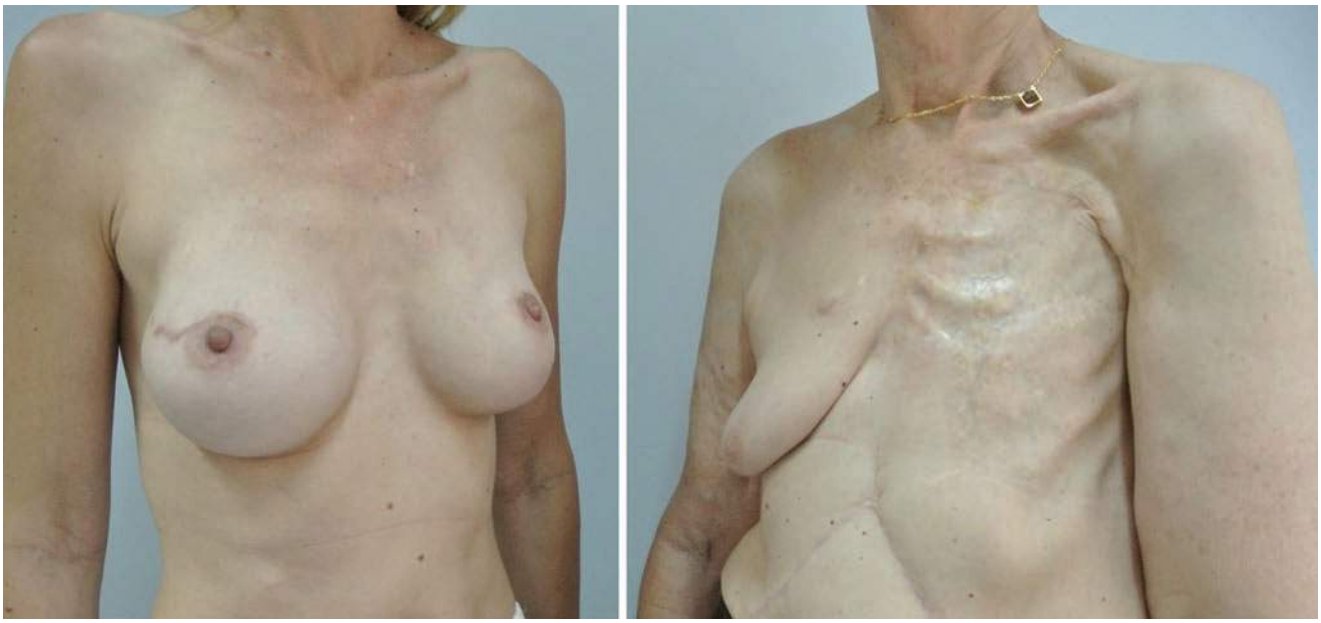


Fig. 36.2 Two generations of patients and three decades of evolution of concepts—mother (Halsted mastectomy) and daughter (nipple-sparing mastectomy and immediate breast reconstruction with definitive expander)

options for implant placement: total or partial muscular coverage. Some surgeons are placing in subdermal place using bioprosthetic materials, as described in a specific chapter in this book. Although the most frequent is the total muscular cover, the dual plane is gaining popularity due to the potential to eliminating the high-riding implant, less pain, and short surgery. This is the preferred approach for all implant reconstructions at our breast unit.

One-shot cephalosporin is given before surgery, and usually patients recovered for 1 day. Serial inflation of the expanders is performed in the office and begins 4–6 weeks after surgery. Generally, 50–100 cc of saline are instilled every 3 weeks. Expansions are done even during chemotherapy. When the patient goes to radiotherapy, expansion is interrupted (and most of the time, it is partially deflated during this process) until the end and then it begins 1 week after

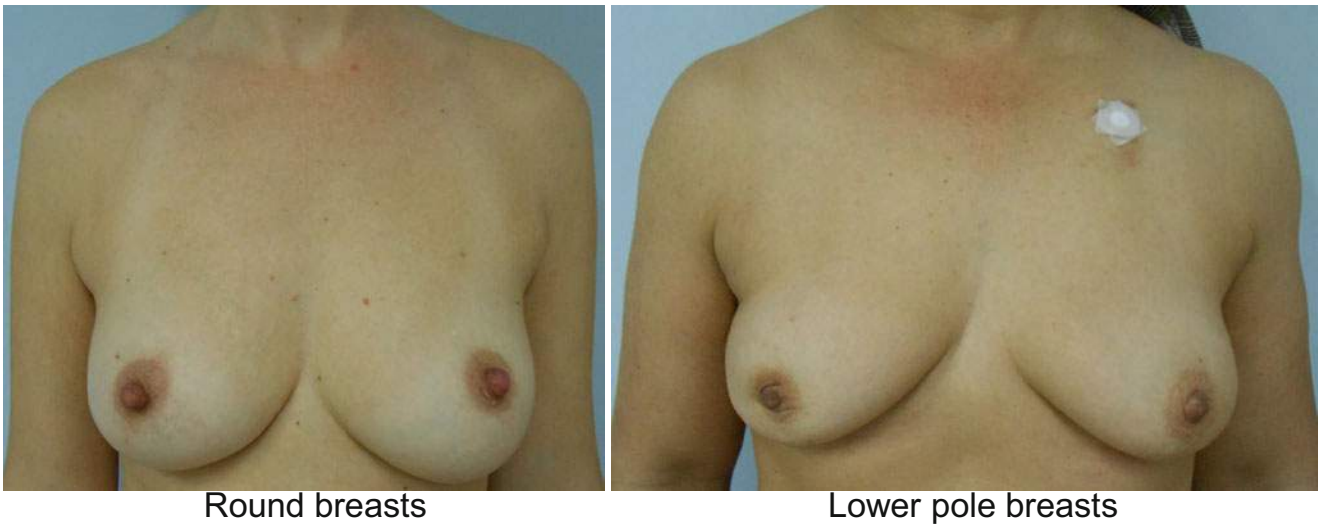


Fig. 36.3 Different breast shapes

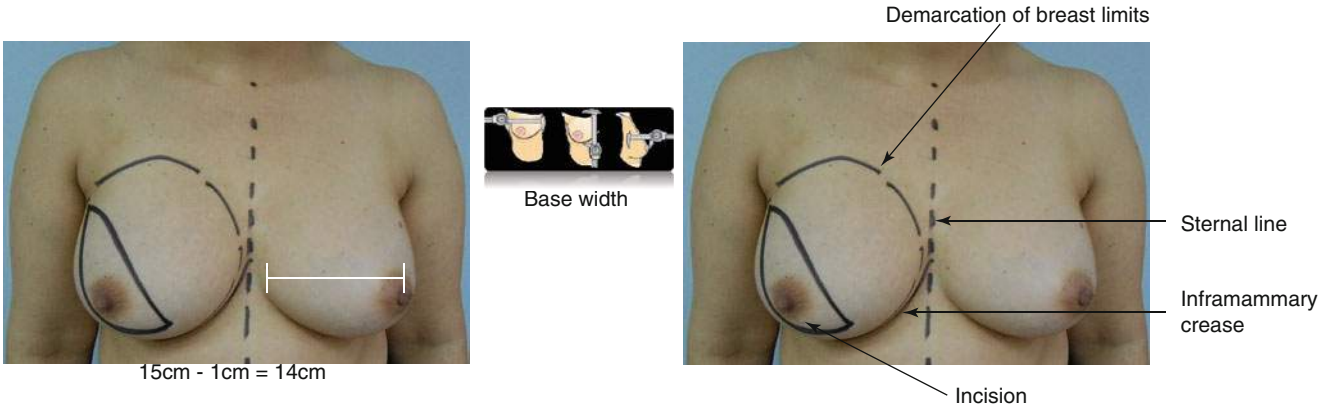


Fig. 36.4 Calculation of the breast width to choose the right expander and preoperative skin markings

the end of treatment. Some examples of classical clinical cases are presented in Figs. 36.6, 36.7, 36.8, and 36.9. In these cases, it is illustrated as in the second surgeries; in cases of temporary expanders, it is possible to plan to correct the symmetry. Even in more difficult cases as after lactation or after reconstruction with flaps, temporary expanders are allowed for secondary corrections and achieving good symmetry (Figs. 36.10, 36.11, 36.12, 36.13, 36.14, and 36.15).

36.5 Complications

Complications can occur in an early or delayed stage and must be explained and reviewed with the patient preoperatively. They include bleeding, infection, extrusion, scars, rippling, wrinkling, capsular contracture, fill-port failure, rupture, pain, seroma, distortion, and asymmetry. All of them are well-described in the literature, and the risks are, most of the time, related to medical and oncological issues. Prevention and treatment of them are described in a specific section in this book.

36.6 Conclusions

Breast reconstruction with temporary or definitive expanders is the preferred approach in many breast units, but proper patient and device selection is important to more predictable and safer results.

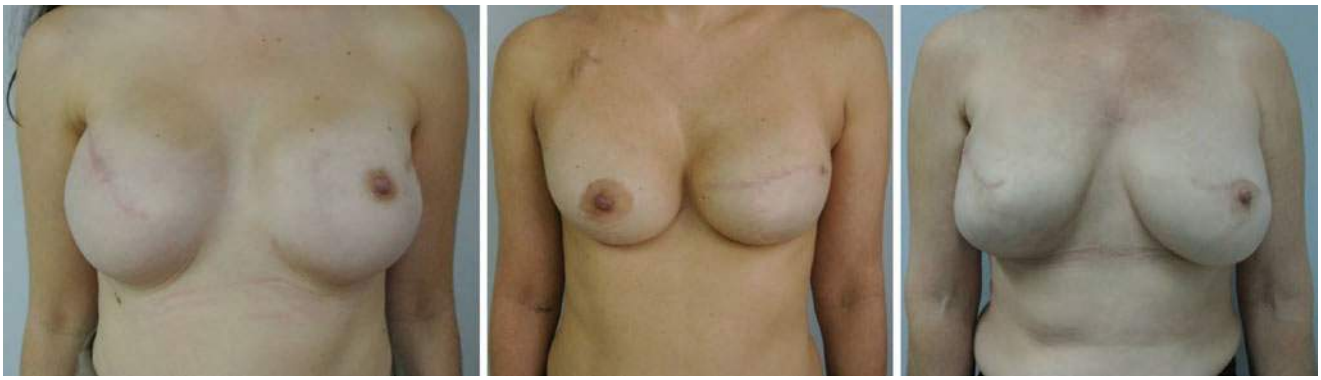


Fig. 36.5 Examples how implant's shape choice affects the final outcomes

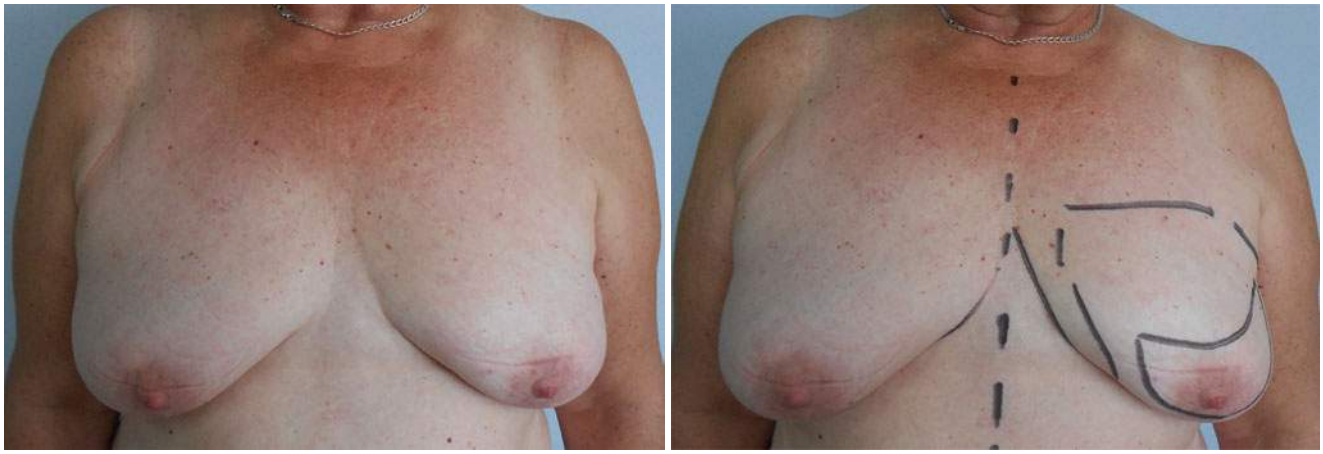


Fig. 36.6 Preoperative view and skin markings of a 68-year-old patient with a left breast T1C invasive ductal carcinoma close to the nipple and areola complex. Marked breast asymmetry

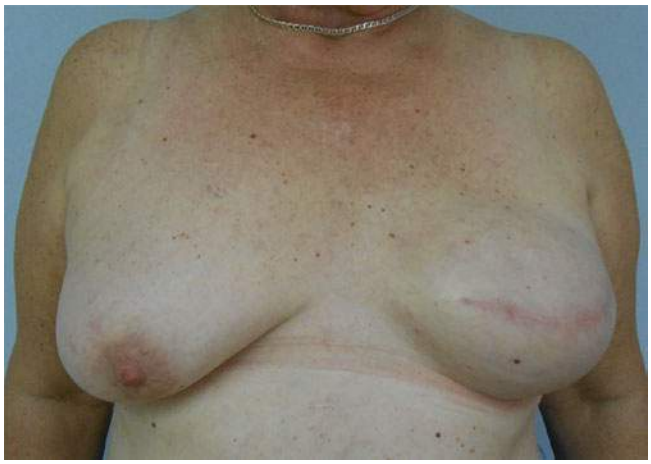


Fig. 36.7 Postoperative result after immediate breast reconstruction with temporary expander

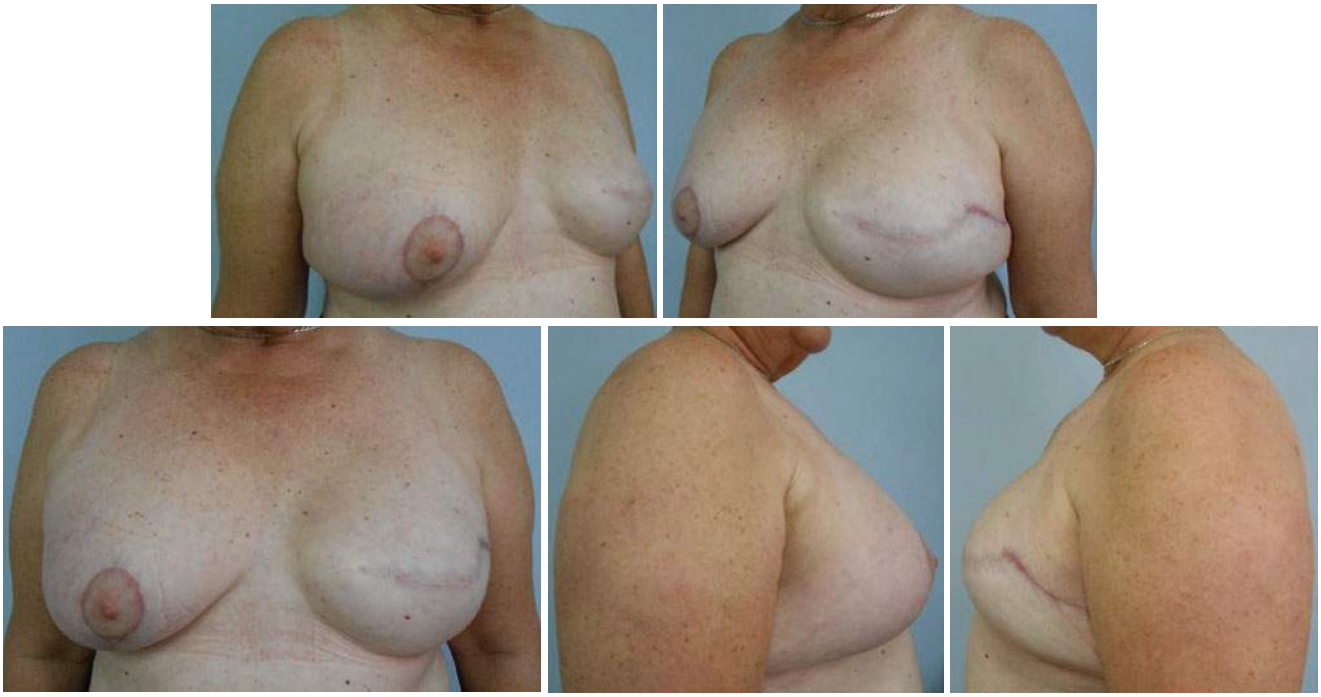


Fig. 36.8 Postoperative result after changing the temporary expander by a definitive implant and contralateral mastopexy

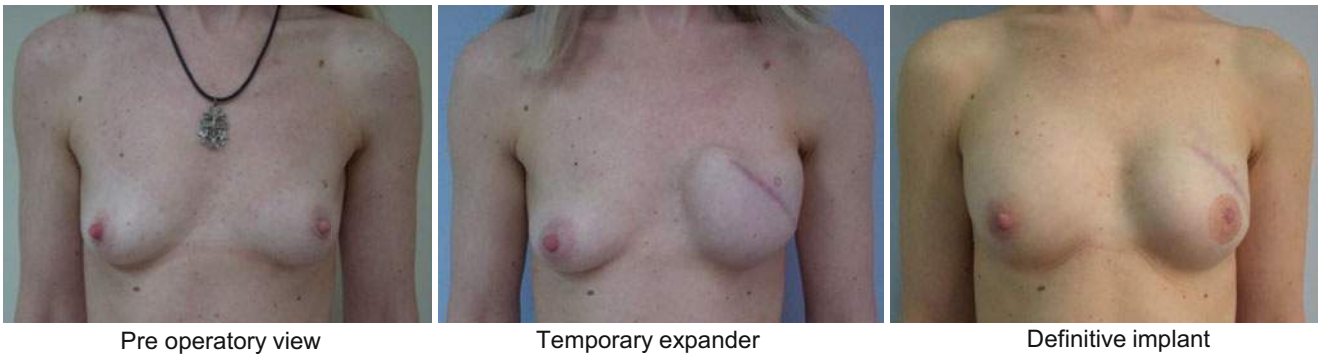
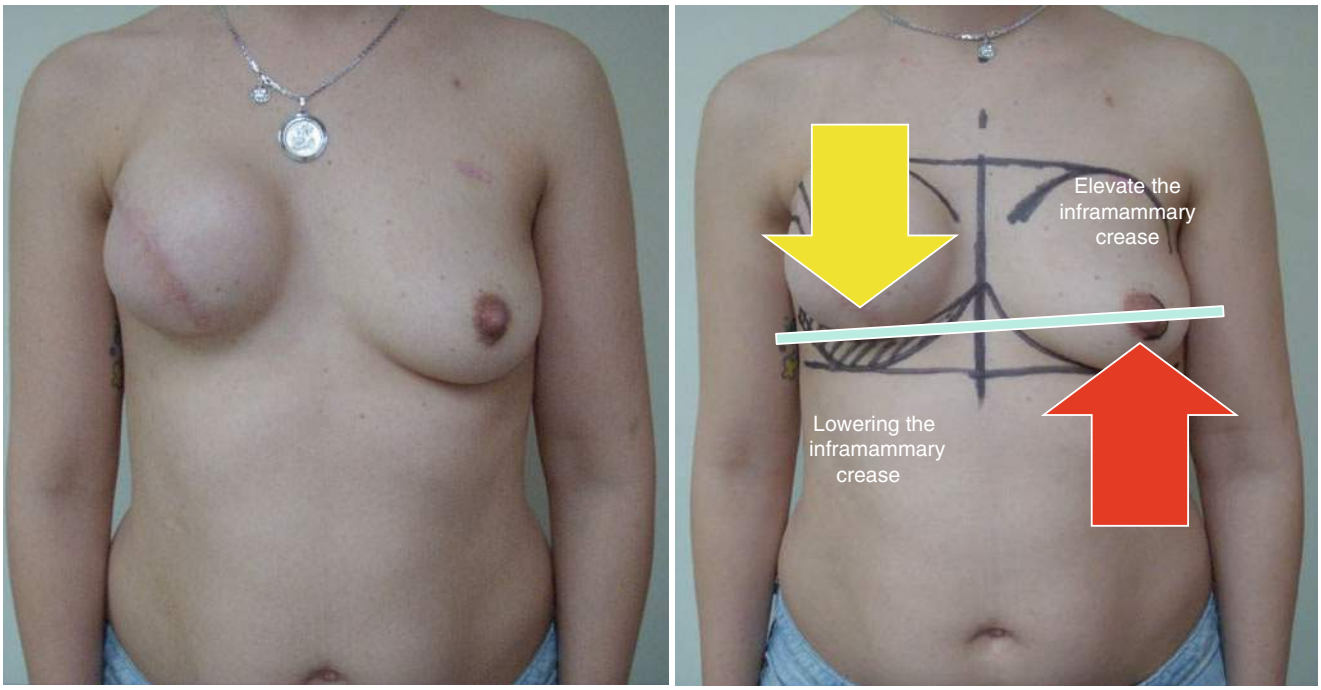


Fig. 36.9 Pre- and postoperative view after skin-sparing mastectomy and immediate breast reconstruction with temporary expander and definitive implant with contralateral augmentation mammoplasty



32 anos, CDI, pT2N1(14/29), ER/PgR+, HER2-, 6 meses pós parto (lactação)

Fig. 36.10 Preoperative view of a 39-year-old patient with T2 N2 invasive ductal carcinoma, 6 months after delivery, with surgical planning for changing the temporary expander by definitive implant and contralateral augmentation mammoplasty (radiotherapy was planned after the surgery)

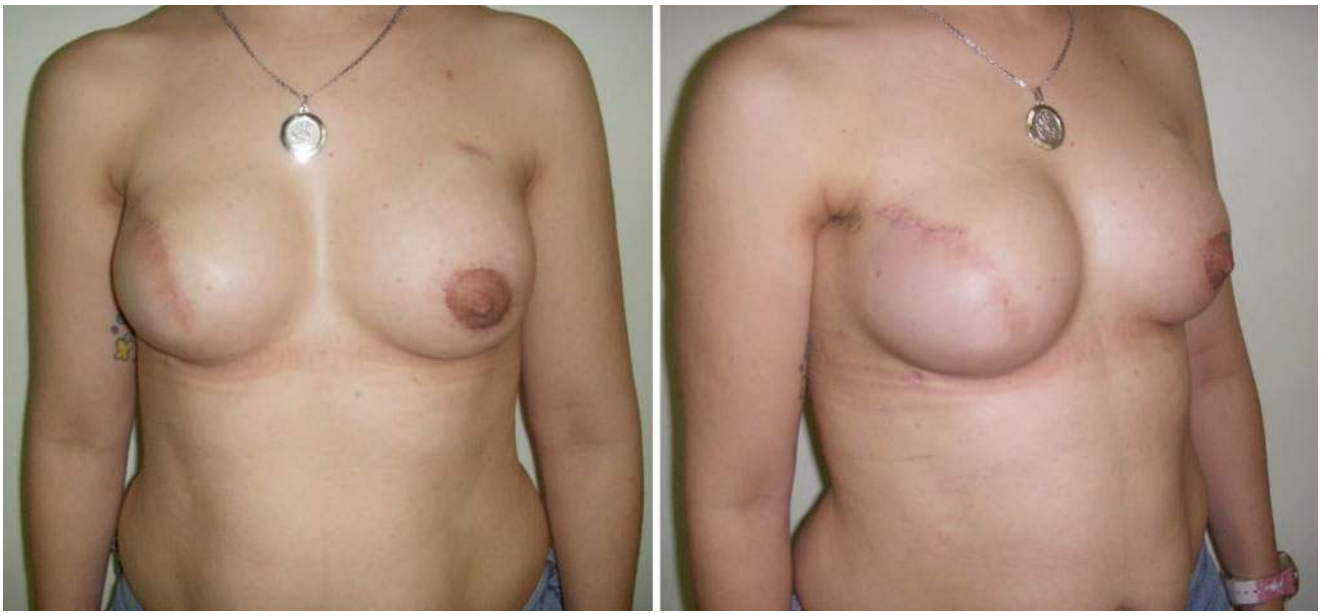


Fig. 36.11 Postoperative view after 2 months

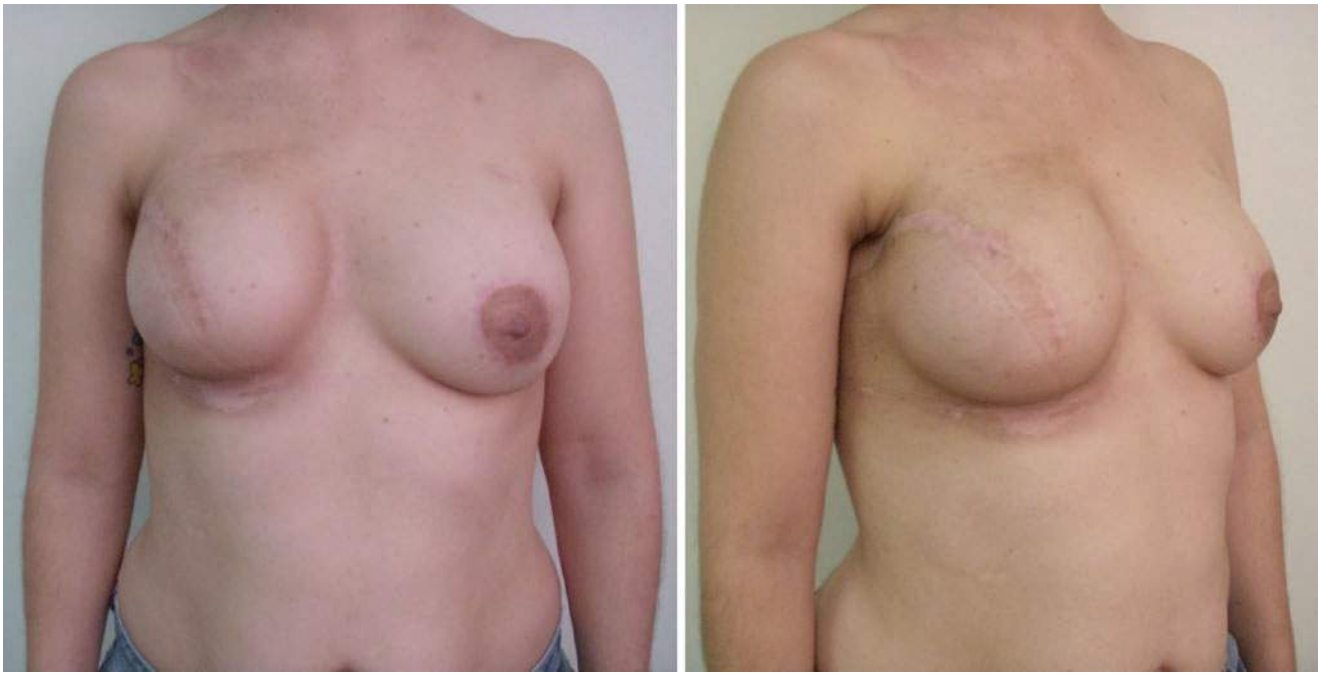


Fig. 36.12 Postoperative view 4 months after radiotherapy

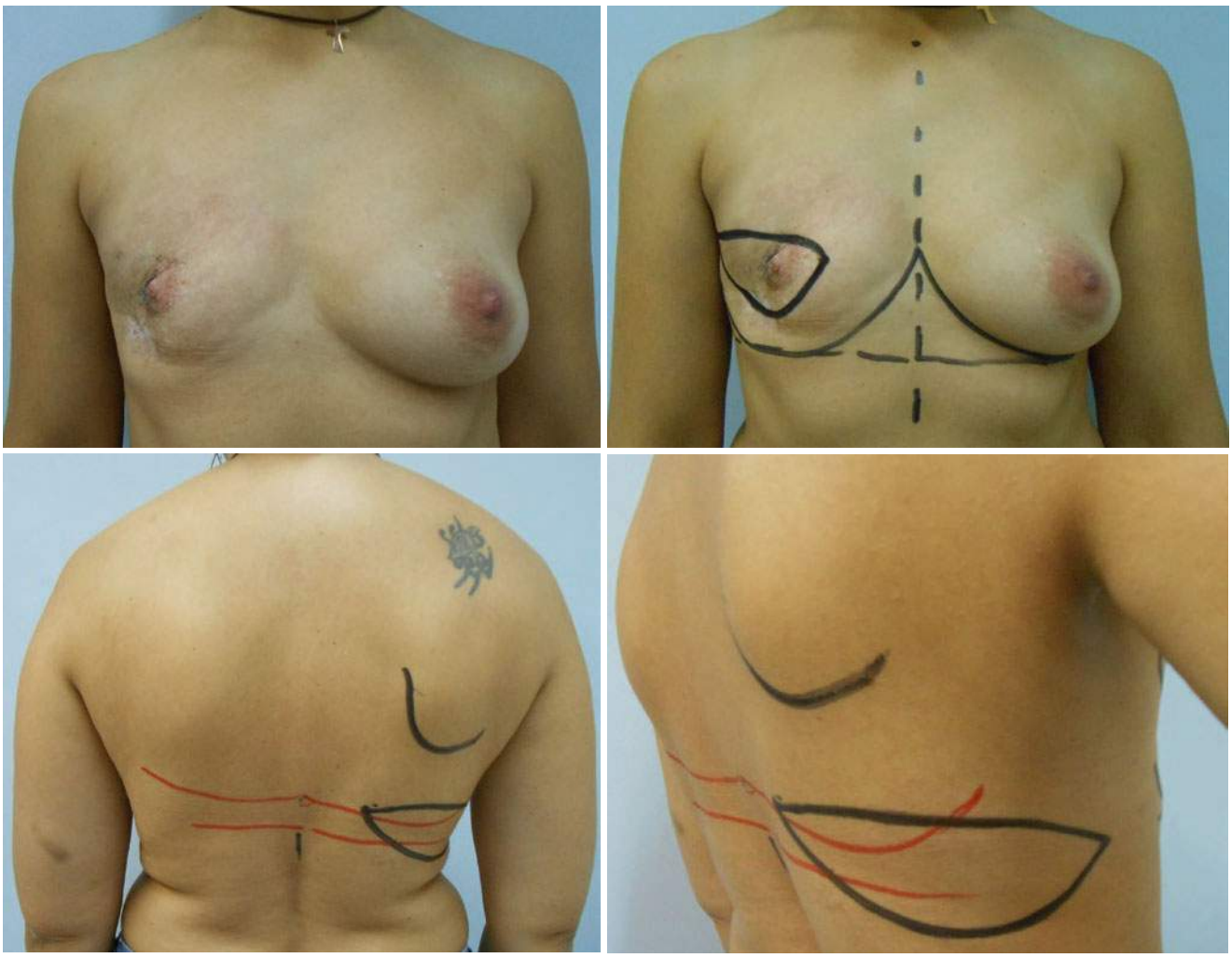


Fig. 36.13 Preoperative view and surgical plan of a 39-year-old patient with a previous ulcerated and bone metastatic disease (T4 N1M1). She had a complete response to systemic treatment and radiotherapy and was 1 year free of disease

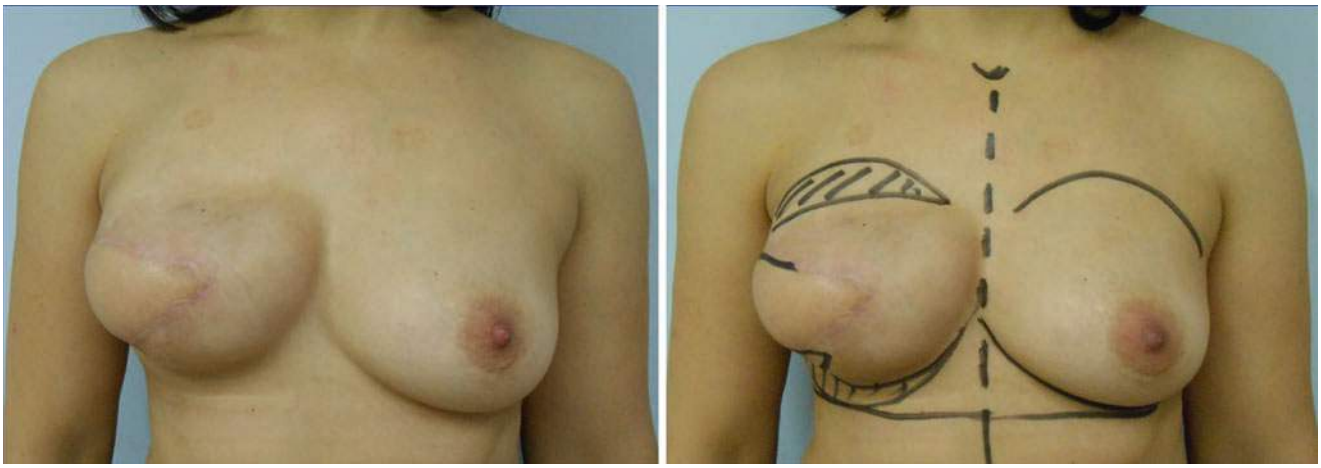


Fig. 36.14 Postoperative view after immediate breast reconstruction with LD flap and temporary expander. Preoperative markings for changing temporary implant by a definitive one and contralateral augmentation mammoplasty

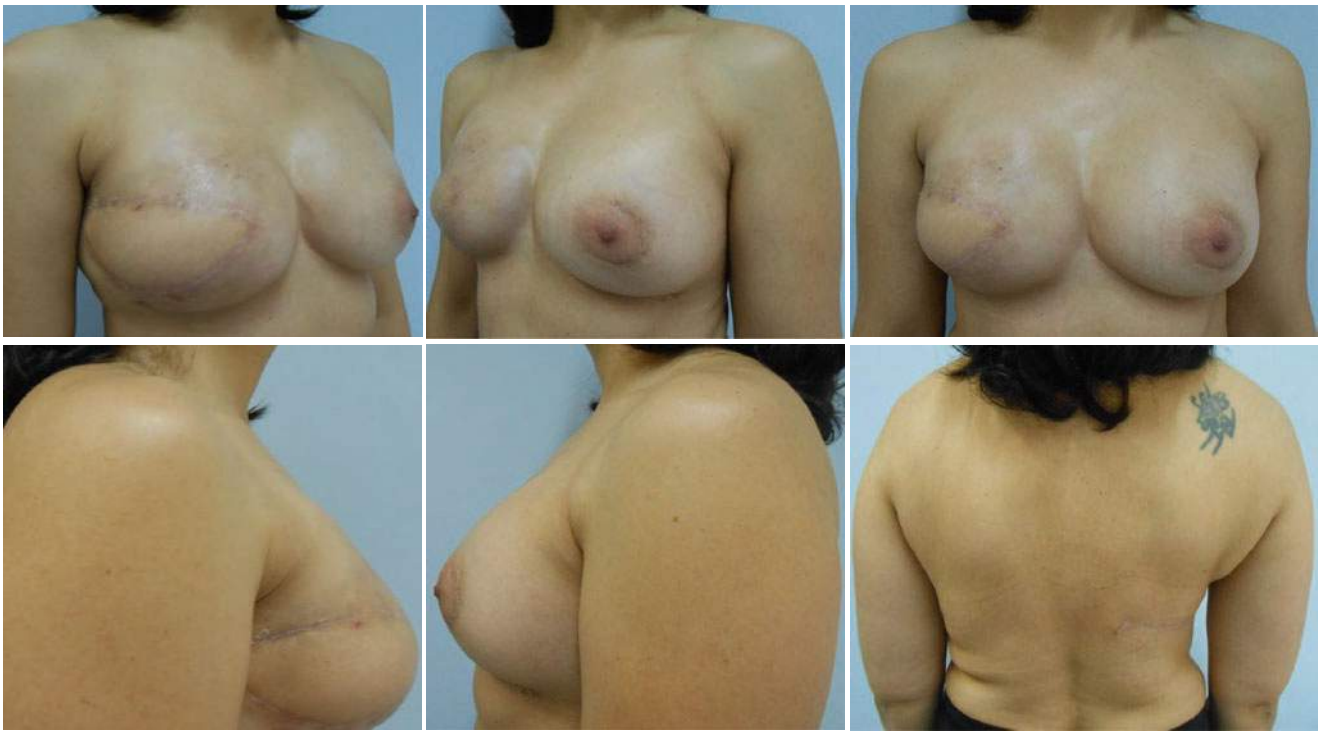


Fig. 36.15 One-year after the second surgery with a good symmetry and without evidence of disease

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One-Stage Breast Reconstruction with Definitive Form-Stable Implants

37

Cicero Urban, Mario Rietjens, Flavia Kuroda, and Marylin Sanford

37.1 Introduction

Breast cancer treatment at the beginning of the last century was frankly mutilating to patients. Standard surgery removed large amounts of skin and adjacent muscles. Aggressive external radiotherapy further degraded the tissues with significant deleterious aesthetic, functional and psychological sequelae. In that era, few options existed for breast reconstruction and even less for a single-stage immediate breast reconstruction using definitive implants. The evolving understanding of the biological characteristics of breast cancer has allowed for refinement in treatment making those less mutilating. Concurrently, it has been developed a greater appreciation for the psychological effects of treatment. Modern breast cancer treatments need to take into account and try to maintain the quality of life for the patient while providing excellent oncologic control. A single-staged breast reconstruction evolved with that goal in mind.

Immediate breast reconstruction with implants started in the 1980s. At that time, large clinical trials (Milan and NSABP) established the efficacy of less aggressive surgery for local control of the disease [1–3]. This technical evolution with breast-conserving surgery established the role of partial mastectomy. It also affected the future techniques used for mastectomy by demonstrating that much of the breast envelope, skin, pectoralis muscle, and inframammary fold could be preserved. These more refined and tissue-conserving mastectomies (skin-sparing and nipple-sparing) associated a better design and technology of new generations of anatomical implants made immediate breast reconstruction with implants a viable option [4]. Definitive implant reconstruction reduced the number of additional surgical interventions and reduced the indications for more complex breast reconstruction techniques like pedicle or free flaps. A single-stage procedure can have economic benefits both to the patient and to the medical system, avoiding temporary expanders. Definitive implant reconstruction also improves patient's quality of life, lowers the feeling of mutilation caused by the oncologic treatment, and encourages faster social reintegration [5, 6].

So the aim of this chapter was to show how to select the patients and the implants for the procedure. It reviews the evolution of the technique and examines the technical advantages, limits, and complications of immediate breast reconstruction as a single-step surgery with definitive form-stable implants and contralateral mammoplasty for symmetry.

37.2 Patient Selection

The best candidates for immediate breast reconstruction with implants are those in which the breast volume is small or medium, the planned mastectomy does not involve resection of large amounts of skin, and there is no evidence of tumor infiltration of the skin or chest wall musculature (Figs. 37.1 and 37.2). Larger-volume breasts or those with important mammary ptosis can be candidates for the procedure but in combination with either a reduction of the contralateral breast or a mastopexy for correction of mammary ptosis [6, 7]. Particularly in these cases, it is possible to achieve some degree of ptosis (Fig. 37.3).

Multidisciplinary preoperative evaluation is necessary when deciding on the reconstructive technique and assessing

Electronic Supplementary Material The online version of this chapter (doi:10.1007/978-3-319-62927-8_37) contains supplementary material, which is available to authorized users.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_37

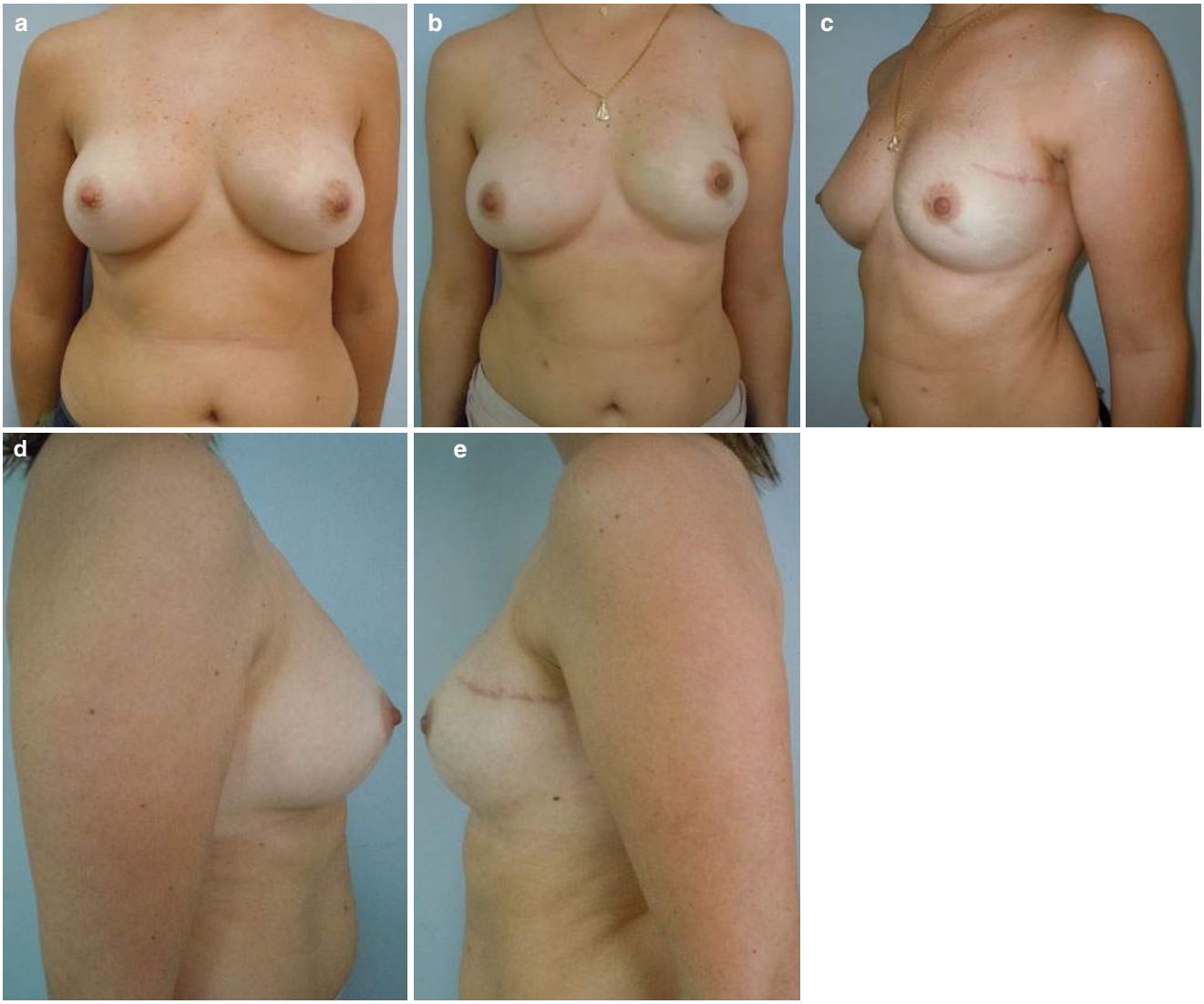

Fig. 37.1 (**a**) Preoperatory view of a 38-year-old patient with invasive ductal carcinoma in the left breast (T2N0). (**b**–**e**) Postoperatory view 1 after a nipple-sparing mastectomy and immediate breast reconstruction with anatomic form-stable implant

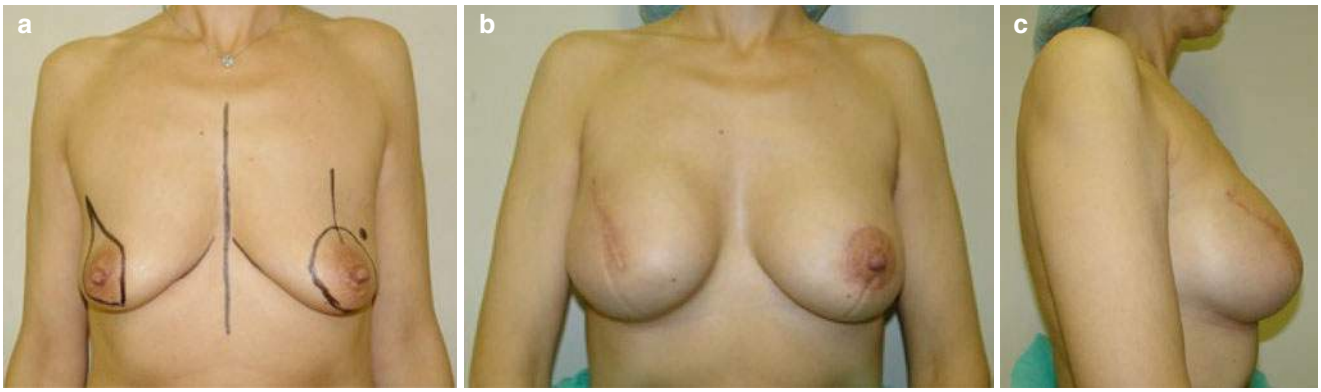

Fig. 37.2 (**a**) Preoperative example of right-side skin-sparing mastectomy with immediate breast reconstruction with definitive anatomic implant and partial muscular pocket. A left-side mastoplasty of augmentation and correction of ptosis were programmed. (**b** and **c**) Frontal and lateral view 3 months later

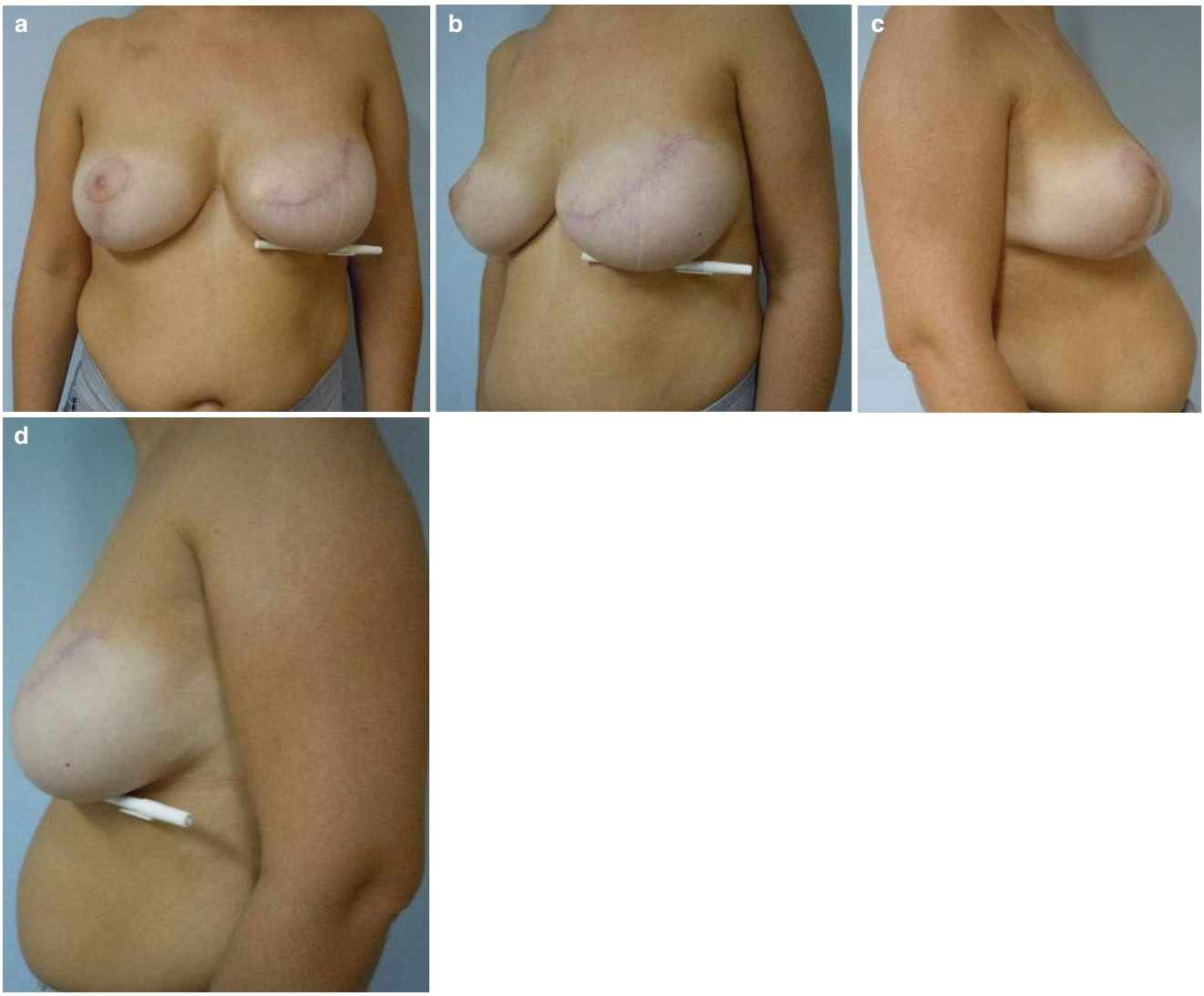

Fig. 37.3 (**a**–**d**) Postoperatory view 1 year after skin-sparing mastectomy and immediate breast reconstruction with anatomic form-stable implant and contralateral breast reduction in a big breast preserving some degree of natural ptosis

Table 37.1 Potential advantages of one-stage immediate breast reconstruction with definitive form-stable implants

Advantages
• A single procedure that can avoid a second surgery to change the temporary expander
• No donor site morbidity
• Short operative time and recovery
• Skin with similar color, texture, and sensation

for possible oncologic *contraindications* of immediate breast reconstruction, including (Tables 37.1 and 37.2):

- Technical problems: tumor infiltration of the skin or muscles, which complicates the technical performance of breast reconstruction with implants and is a formal indication for postoperative radiotherapy of the chest wall.
- Risk of delay in adjuvant treatments: patients with aggressive tumors (e.g., young patients with clinic and histopathologic evidence of growth of the tumor after neoadjuvant chemotherapy and significant involvement of axillary lymph nodes).
- Psychological problems: it is appropriate to be observant of signs that suggest an underlying psychological issue that could impede the success of a reconstruction. Prior hospitalizations for psychiatric issues, inappropriate effect, and disorganized thought processes are just some of the red flags that could indicate a psychological disorder. Psychological assessment can be helpful to assist in appropriate patient selection and assure that unresolved psychological issues do not derail the reconstruction, like excessive expectations with breast reconstruction or difficulties to collaborate in the postoperative

Table 37.2 Relative contraindications for one-stage immediate breast reconstruction with definitive form-stable implants

Characteristic	Difficulty
Chest wall or skin infiltration	Adjuvant radiotherapy
Aggressive tumors	Early beginning of chemotherapy and/or adjuvant radiotherapy
Psychological problems	Incapacity to understand the limits and potential complications
Several breast hypertrophy morbid obesity	Increase factors II, VII, VIII, IX, X, fibrinogen
Previous irradiation	Higher risks of infection, bad aesthetic outcome, and loss of implant
Tobacco	Higher risks of infection, wound healing problems, and loss of implant
Failed previous reconstruction with implants	Retraction

period, or even to accept complications and limitations.

- Severe breast hypertrophy: presents as a relative contraindication for even with major reduction of mammary volume, it can be very hard to obtain a satisfactory aesthetic result. Morbid obesity poses additional difficulties too.
- Previous breast irradiation: mastectomy due to a recurrence after conservative surgery with adjuvant radiotherapy is a relative contraindication. In these cases, the use of a musculocutaneous flap is a good option. It is possible to try an immediate reconstruction when the breast is small or when there is minimal sequela from the radiotherapy (i.e., the skin is soft and pliable). Caution is advised, and any attempt must be exhaustively discussed with the patient, with a focus on the high level of complications (cutaneous necrosis, infection, exposure or dislocation of the prosthesis, and periprosthetic capsular contraction [8]). There is a specific chapter in the book in this topic.
- Smoking: a significant association between smoking status and postoperative complications exists. Overall complications, reconstructive failure, mastectomy flap necrosis, and infection are more common in smokers. Smokers who undergo postmastectomy expander/implant reconstruction should be informed of the increased risk of surgical complications and should be counseled on smoking cessation [9].
- Failure in previous reconstruction with temporary/definitive expander and/or implant: this can cause a severe tissue retraction.

37.3 Preoperative Evaluation

A multidisciplinary team must evaluate patients who are candidates to undergo a breast reconstruction procedure before being admitted in hospital. The preoperative evaluation considers reconstructive options and aims to choose the best technique for each situation. The patient is provided with detailed information on perioperative care and expectations. The assessment includes selecting the model, shape, and size of implants to be inserted. It is necessary to do the measurement of the basis of the breast and see the shape of the breast, in order to do the correct choice. Planning process includes photos of the patient standing and preoperative drawings. Technical details such as the type of incision and oncologic details such as the need for any additional workup of the contralateral breast are determined at this time. Preoperative breast evaluation must include bilateral mammography and breast ultrasound in combination with the physical exam to assess the extent of disease. MRI is useful for young patients, dense breasts, hereditary cancers, and invasive lobular carcinomas (see specific chapter about breast imaging). Antibiotic prophylaxis is done with cephalosporin, prior to skin incision, and re-dose the antibiotic intraoperatively in the limited number of cases that last over 4 h [10].

37.4 Technique

The patient is placed on the operating table with both arms extended out on arm boards. This position allows for two teams to work concomitantly whenever a contralateral procedure planned, therefore reducing surgical time. After completion of the oncology portion of the procedure, the site is cleaned again with povidone-iodine or chlorhexidine solution, and the surgical instruments used in the oncology step are removed. An initial evaluation is made in order to check the integrity of the pectoralis major muscle, as well as the vascularization of the mastectomy skin flaps, and inframammary fold. The degree of abduction of the arm is adjusted relative to the thorax to allow for relaxation of the pectoralis major muscle. The table is flexed at the waist so that the patient's thorax is raised 45°.

There are three techniques for immediate breast reconstruction which are most used in practice. The techniques have evolved in an effort to improve the cosmetic outcome:

Immediate breast reconstruction with complete muscular pocket. This original technique was described by Little [11] with the title "muscular bra." The technique gave more protection to the implant in cases of limited skin necrosis, and it allowed for isolation of the axillary cavity and thus helps to limit migration of the implant toward the axilla. This was the only immediate reconstruction option available before the advent of form-stable implants. Prior to that, the only implants available were round, and that limited the options for improving aesthetic results. With anatomic form-stable implants, the technique for immediate reconstruction evolved for it is possible to achieve a better shape to the reconstructed breast if it is not laterally

recovered by the serratus muscle as this allows for better inferior and anterior projection. This creates a more natural shape to the reconstructed breast. However, there were two significant problems associated with eliminating the serratus portion of the muscular pocket. First, some mastectomy incisions, especially those that remove that nipple-areolar complex as a horizontal ellipse, would end up with the lateral part of the sutured incision directly on the implant with no intervening tissue. There is no protection of the implant in cases of skin necrosis and/or dehiscence of the scar. If this complication occurs, there is an increase in the risk of exposure of implant leading to removal. A second problem occurs in situations of thin flaps with a fragile vasculature. In these cases, the complete muscular pocket places well-vascularized muscle directly underneath the entire skin flap. This underlying muscle may help maintain the viability of the compromised skin flap. The layer of muscle may also reduce the tactile effect of "feeling" the implant, which is very frequent when the lateral skin flap is rather thin.

Immediate breast reconstruction with partial muscular pocket. This technique had started to be developed in the Plastic Surgery Department of the European Institute of Oncology in Milan (Italy) in 2003 and at the Our Lady of Grace Hospital Breast Unit in Curitiba (Brazil) in 2004. It came about with the introduction of new anatomic form-stable implants and with the acceptance of a refinement of the mastectomy technique, which allowed preservation of nearly all the breast skin. The technical aim was to improve the cosmetic outcome of the implant reconstruction by eliminating the serratus portion of the muscular pocket but to also avoid placing the sutured incision directly over the implants. Incision placement is critical, as one wants to be sure that the final scar from the mastectomy can be placed completely on the pectoralis major muscle. One also wants to select patients where the final skin flaps will not be very thin and at risk of necrosis. With this technique, it is possible to achieve a much more natural lateral contour of the breast (Fig. 37.4). The biggest drawback is the tactile feeling that patients have when they touch the inferior-lateral region of their breasts, as they can feel underlying implant. With this technique, the lower and medial detachment of the pectoralis major muscle is performed as in the traditional technique (Fig. 37.5). After inserting the definitive implants, the lateral border of the implant pocket is formed by suturing

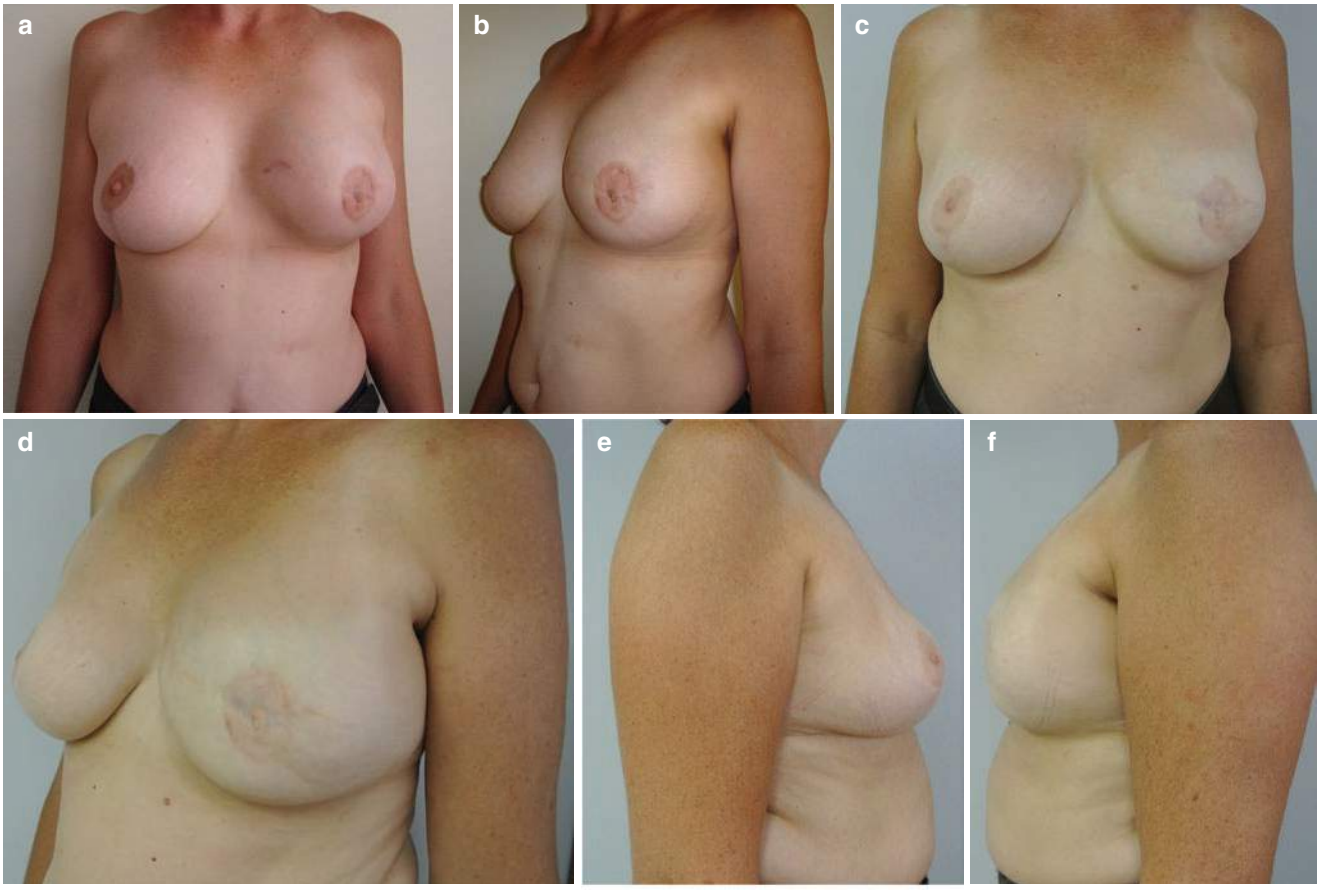

Fig. 37.4 (**a** and **b**) Postoperatory view 2 years after skin-sparing mastectomy and immediate breast reconstruction with anatomic form-stable implant and contralateral breast reduction with partial cover muscular pocket. (**c**–**f**) Postoperatory view 8 years after, demonstrating a stability of the aesthetic outcomes

the skin flap down to the musculature of the chest wall with absorbable suture. It is critical to prevent both the lateral and the axillary migration of the implant. Lateral muscular cutaneous fixation is also needed in cases in which the breast base is too wide and when we have to insert a smaller base implant. This fixation also helps to avoid the lateral movement of the breast implant. In this case, closed suction drains to drain the whole cavity should be considered. When axillary dissection is performed, the risk for losing the implant is about three times higher than when only sentinel node biopsy is performed (unpublished data from the Our Lady of Grace Hospital Breast Unit). This could be related to surgical time, drains, and the alteration in postoperative lymphatic drainage. In these cases, a pectoralis minor flap can be useful to cover the lateral part of the implant and prevent implant malposition from dislocation to the axilla (Fig. 37.6).

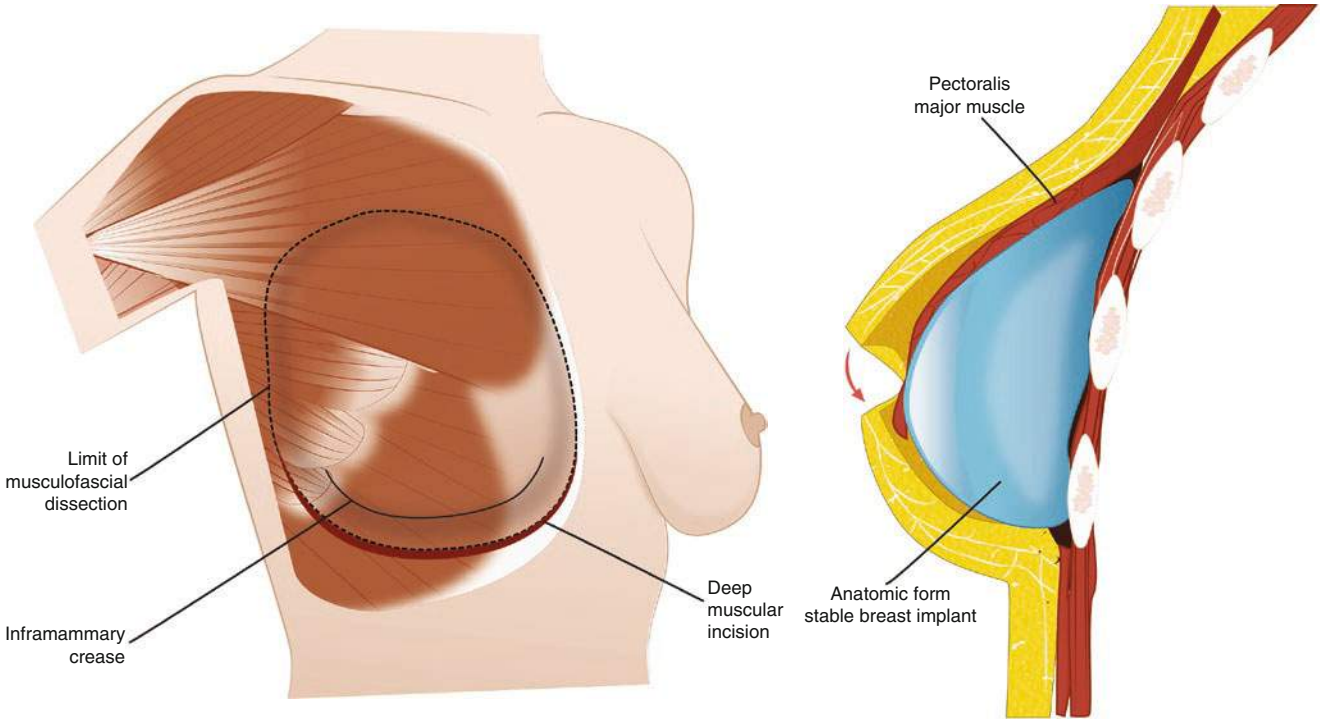

Fig. 37.5 Limits and localization of the implant in partial cover muscular pocket

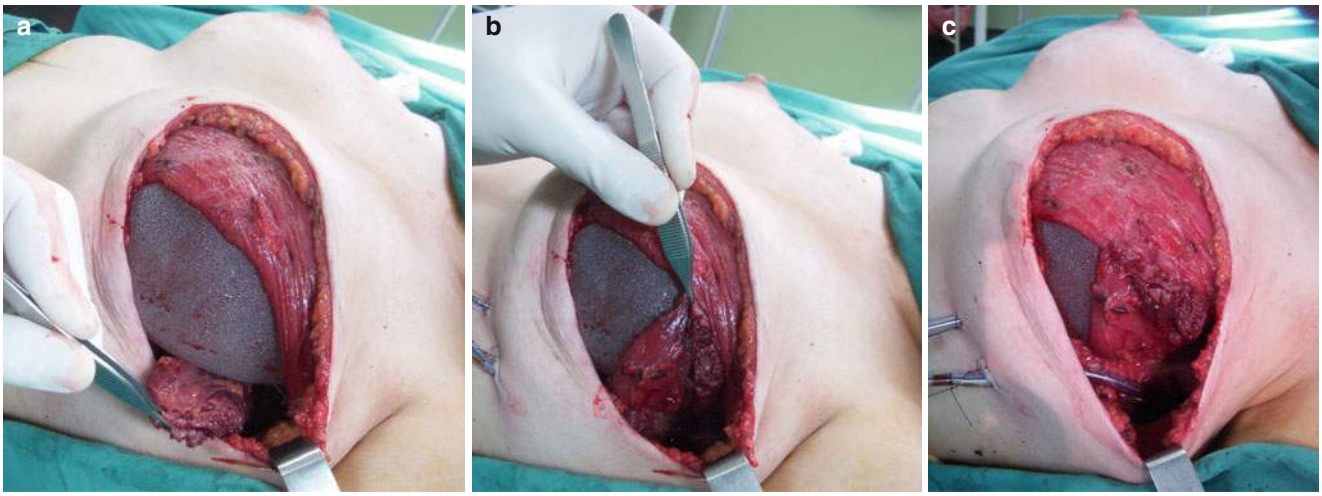

Fig. 37.6 (**a**–**c**) Pectoralis minor flap technique to cover the lateral part of the implant and prevent implant malposition from dislocation to the axilla

Immediate breast reconstruction with the cutaneous suspension technique. This technique was described and developed by Rietjens [12]. It uses a complete muscular pocket to allow for implant coverage, but it also utilizes an abdominal advancement cutaneous flap with Mersilene mesh fixation to create a more natural inframammary fold with better inferior and external projection. The best candidate for this technique would be a small-breasted woman with limited ptosis who does not need to get the contralateral breast corrected. The preoperative marking includes an assessment of the elasticity and mobility of the cutaneous tissues of the upper abdomen while the patient is standing. This assessment allows the surgeon to calculate the size of the cutaneous flap to be used. Afterward, both the current and the future inframammary fold are marked; the latter is marked between 4 and 6 cm below the current inframammary fold. After the mastectomy is completed, the reconstruction is started with the preparation of the complete muscular pocket: medial undermining of the pectoralis major muscle and lateral undermining of the serratus. An extensive subcutaneous undermining is performed below the current inframammary fold extending down past the line demarcating the future inframammary fold. This dissection allows for adequate mobility of the cutaneous flap. After that, a mesh of nonabsorbable material (usually Mersilene, as it is durable and malleable) is used to fix the flap in place. The mesh is cut so that one of the edges is rounded off to a curve that will match the newly planned inframammary fold. This edge will be sutured to the dermis and superficial fascia of the pre-marked new inframammary fold level with nonabsorbable stitches. They need to be well anchored to resist inferior traction. Taking these "healthy" bites can cause small skin retractions where the sutures are placed. In our experience, these retractions soften with time until they eventually disappear as the skin heals and the periprosthetic capsule is formed. Once the mesh is fixed to the future inframammary fold, the mesh is pulled superiorly until the created fold comes to the same level as the contralateral side. The free edge of the mesh is then fixed with one or two nonabsorbable stitches on the fifth or sixth coastal cartilage, and the surplus of the skin is removed. The implant will be placed between the mesh and the pectoralis major muscle, and then the muscular pocket will be completely closed with the suture between the lateral edge of the pectoralis major muscle and the anterior edge of the serratus muscle. Two drains are placed: one in touch with the implant, inside the muscular pocket, and the other draining the subcutaneous space and the axilla. It's advisable to keep the patient in a semi-sitting position (at 45°) as this lessens the traction on the sutures anchoring the advancement flap and thus less postoperative pain. This technique can be applied to avoid the use of expanders when there is not a need to remove large amounts of skin [13]. It avoids a second surgical step with general anesthesia. This technique has been used in 67 cases of immediate breast reconstruction and in 6 cases of delayed reconstruction. In 14 cases (19.2%), it was necessary to perform a second surgery with general anesthesia for capsulotomy, replacement of implant, and reconstruction of the nipple and areola complex. In three cases (4.1%), the implant was removed due to exposure or infection. In the remaining 33 cases, only local anesthesia was needed for reconstruction of the nipple and areola complex and for finishing the reconstructive phase. In this series, the evaluation of the capsular contracture was Baker I in 24 cases, Baker II in 16 cases, Baker III in 9 cases, and Baker IV in 1 case only. The breast symmetry, the patient's satisfaction, and the surgeon's aesthetic evaluation were graded 7.56, 7.75, and 7.60 (with a degree of 1 = extremely low to 10 = excellent) (Figs. 37.7, 37.8, 37.9, 37.10 and 37.11).

An additional option for immediate, single-stage breast-implant reconstruction is the use of allogeneic tissue (Alloderm, LifeCell Corporation, Woodlands, TX). This is an immunologically inert acellular dermal matrix, which is used with the intent to reduce the risks of rejection or implant extrusion. Allogenic dermal grafting provides an additional layer of tissue between the skin and the implant with minimal complications, eliminates the need for tissue expansion/implant reconstructive process, prevents capsular contracture and implant migration, and improves cosmetic outcomes [14]. Its aim is to create a pectoralis-AlloDerm pocket to

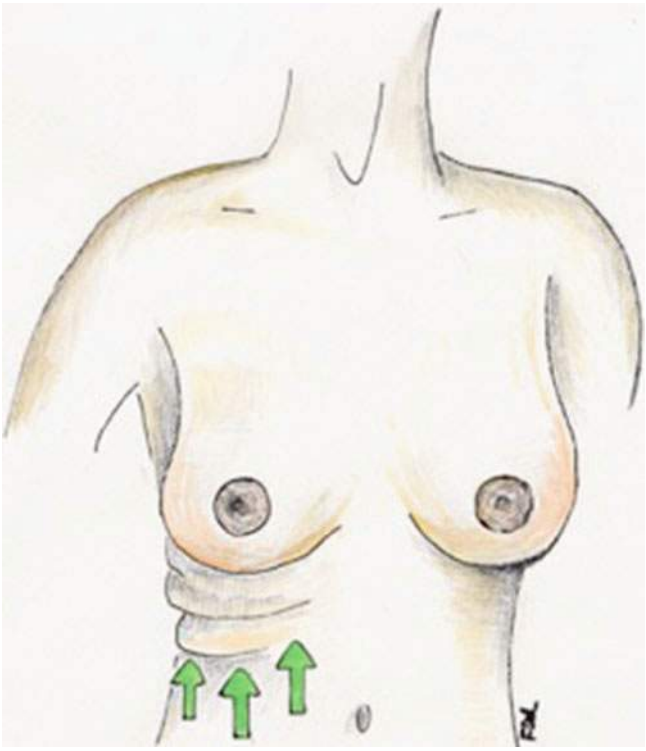

Fig. 37.7 Evaluation of the amount of skin that can be used in the upper abdominal cutaneous flap

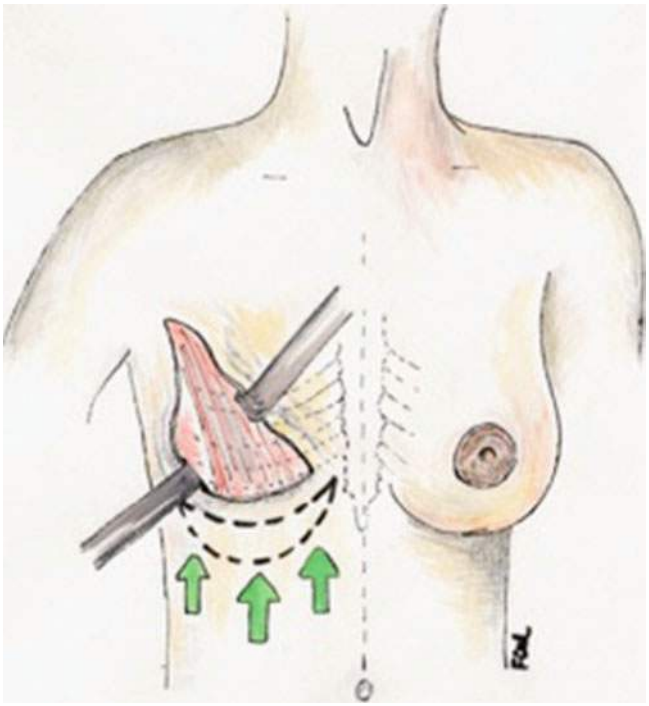

Fig. 37.8 Preparing the complete muscle pocket: pectoralis major muscle and serratus

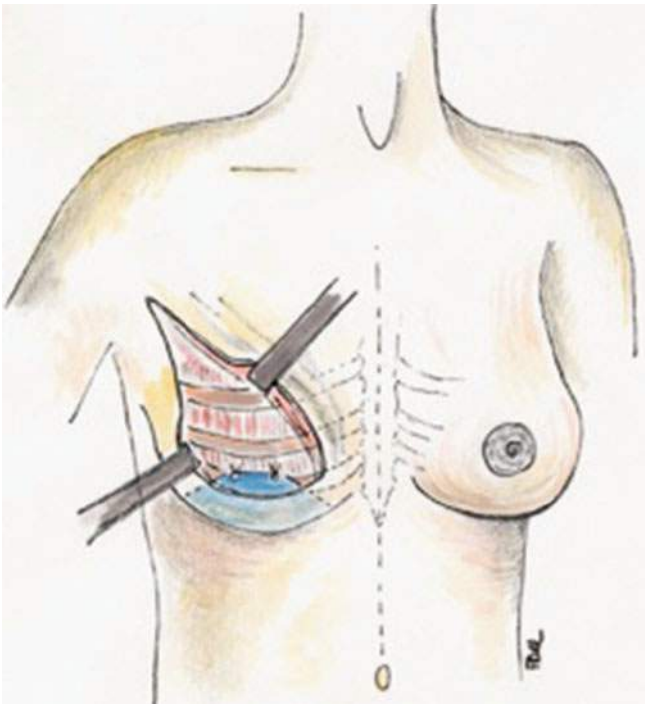

Fig. 37.9 The mesh of nonabsorbable material is fixed in the future sulcus, superiorly pulled and fixed on the fifth or sixth coastal cartilage

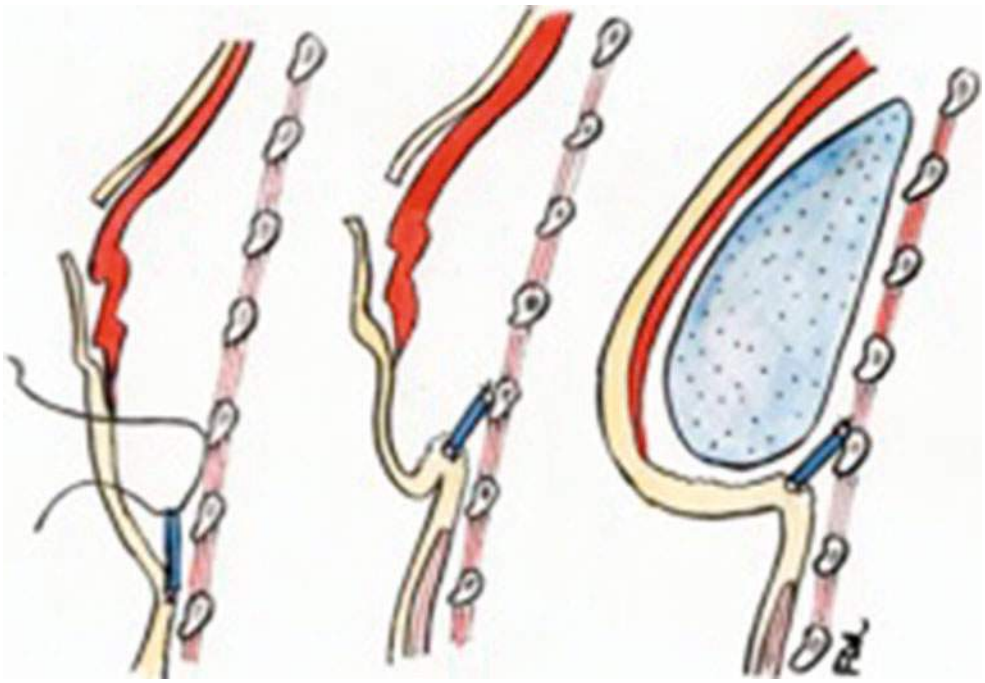

Fig. 37.10 Lateral view of the mesh position. The prosthesis is anteriorly placed

cover and position the implant. It has been used an inferolateral AlloDerm hammock as an inferior extension of the pectoralis major muscle to provide a mechanical barrier between the implant and skin and to control implant position [15–17]. It is not approved yet to current use in Brazil. A decellularized bovine pericardium which is used in vascular and heart surgeries was recently described as an option to cover the implant [18] (Fig. 37.12).

Most of the time, it is necessary to use anatomical implants in immediate breast reconstruction. Round implants are rarely indicated. Sometimes definitive expanders can be indicated, in order to avoid tension in the suture, and muscular

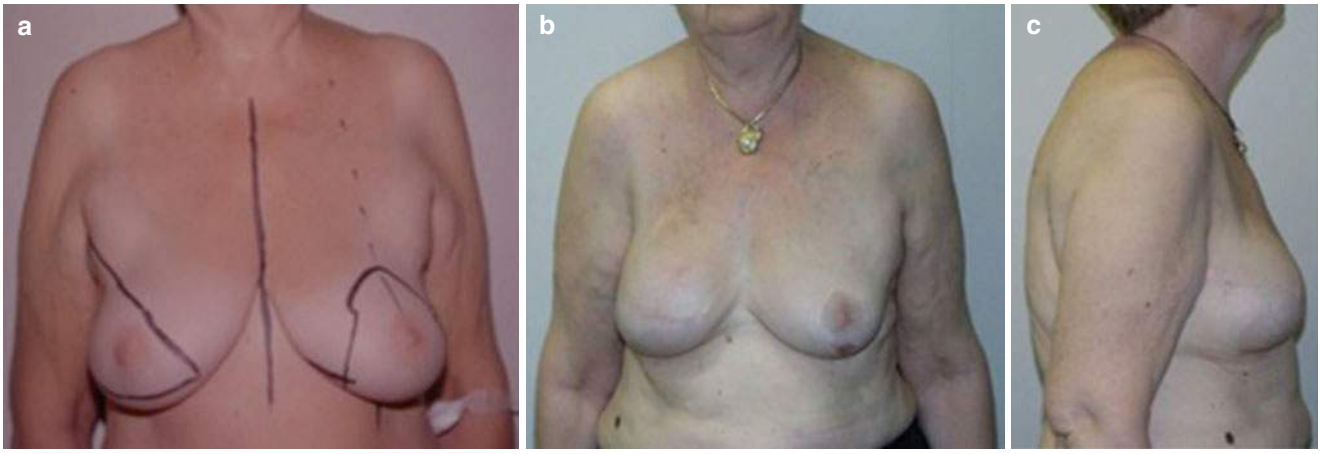

Fig. 37.11 (**a**) Preoperative drawings programming a right-side mastectomy with broad removal of the skin, immediate breast reconstruction with the mesh and with definitive prosthesis, as well as a left-side mastopexy to be performed in the same surgery. (**b** and **c**) Postoperative photo with frontal and lateral views after 6 months

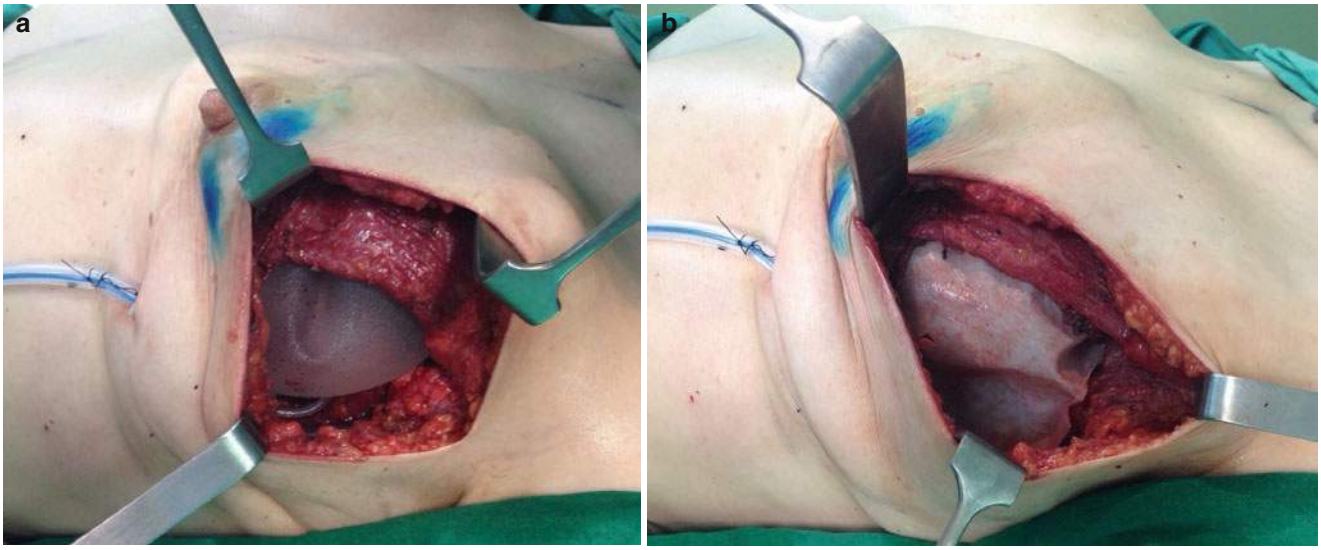

Fig. 37.12 (**a** and **b**) Implant covered by bovine pericardium.

pocket is not enough to maintain it safe and allow for optimal postoperative size and shape adjustment to better enable the achievement of symmetry [19]. The disadvantages of these definitive expanders are higher costs, pain and discomfort with the valves (which are necessary to remove), filling port dislocation, filling port failure, pain on expansion, tube detachment, and valve obstruction [20], and they usually are more rigid than silicone ones.

37.5 Contralateral Mammaplasty

Correction of the opposite breast is often necessary in order to obtain the best symmetry in breast reconstruction. Contralateral surgery is performed in more than 80% of cases, and it is generally proposed as part of the first reconstructive surgery with the aim of avoiding a second operation with general anesthesia, reducing admission time in hospital, and consequently reducing the costs of reconstructive breast procedure. Some authors tend to perform contralateral symmetry mammoplasty most of times in reconstruction with implants, if compared to reconstruction with musculocutaneous flaps [21].

The techniques applied are proposed according to the patient's desires and to the possibilities to obtain better symmetry to the reconstructed breast. It is important to bear in mind that each technique has its limitations. For example, the surgeon must be able to anticipate the amount of ptosis that can be created in the reconstructed breast. In some situations, it is difficult, if not impossible, to create a breast with ptosis when using implants. But for well-selected cases, where there

is large amount of remained skin, it is possible to achieve a natural ptosis (Fig. 37.2). Reconstructions with musculocutaneous flaps from the rectus abdominis muscle, on the other hand, can often have a natural-appearing amount of ptosis. In the right circumstances with some breasts and appropriable skin-sparing and nipple-sparing mastectomies, it is possible to achieve some degree of ptosis in immediate breast reconstruction with implants. These details must be considered when we plan the final result of a symmetry mammaplasty.

The techniques most frequently applied are:

- Reductive mammaplasty with medial-lateral posterior pedicle, initially based on traditionally periareolar techniques [22, 23]: this is usually applied to cases of reduction up to 200 g, with low level of ptosis and for young patients with elastic skin.
- Reductive mammaplasty based on a superior pedicle as described by Lejour [24] or Pitanguy [25]: this technique is usually applied to reduction procedures between 200 and 700 g, without associated major initial ptosis.
- Reductive mammaplasty with infero-posterior pedicle as described by Ribeiro [26] or Robbins [27]: this technique is generally utilized for reductions above 700 g, with a moderate degree of initial ptosis.
- Reductive mammaplasty with graft of areola and nipple as described by Thorek [28]: this technique is rarely indicated in practice. It is for cases of important gigantomasties combined with a major initial ptosis.
- Mastopexy: periareolar technique is preferred when there is a small ptosis and Lejour technique for those cases with a higher degree of ptosis in which a great amount of skin has to be removed.
- Augmentation mammaplasties: most of the time with the use of round implants with a wider base and smaller projection, in order to obtain a better symmetry of the reconstructed breast. The position can be subglandular if the breast is more than 1 cm thick in the upper quadrants. For small breasts and those less than 1 cm thick in the upper quadrants, implant is placed in the subpectoral position and leave the implant subglandular once it is outside the borders of the pectoralis. In some cases, the patient needs both volume augmentation and a mastopexy. In this situation, the *dual plane* technique is useful, which involves inferior detachment of the pectoralis major muscle and correction of the glandular ptosis with the crossing of flaps. The incision can be inferior periareolar, complete periareolar, or vertical periareolar (Lejour type). The choice of incision depends on the degree of ptosis to be corrected and the amount of skin to be removed [29, 30].

It is important to bear in mind that both clinical and radiological evaluation of the contralateral breast must be performed prior to mammaplasty. A palpable nodule, skin retraction, pathologic nipple discharge, or an abnormality on imaging needs an appropriate evaluation. Your community standard can guide the workup, but strong consideration should be given to preoperative core biopsy of all abnormalities. Breast MRI may also be appropriate. Additionally, imaged localized biopsies such as wire localization or a ROLL procedure can be done. All tissues removed during the reduction mammaplasty are submitted to histological exam, and it is important to provide specimen orientation for the pathologist so that appropriate margin evaluation can be done if an unsuspected malignancy is found. The literature shows that the average incidence of a contralateral lesion is about 5% [31–33].

37.6 Secondary Revisions

Secondary revisions are frequent in cases of breast reconstructions with implants to improve symmetry and aesthetic results. The most frequent indications are:

- Formation of periprosthetic capsule, Baker grade III or IV.
- Malposition of the implant after healing.
- Asymmetry: this may be due to changes in body weight (either intentional or as a result of chemotherapy and hormonotherapy) or due to a suboptimal choice in the volume and/or shape of implant during the first surgical step.
- Rotation of an anatomic implant.

Revision techniques that can be used are:

- *Capsulectomies*: indicated when there is a rather thick periprosthetic capsule, causing pain and an unsatisfactory aesthetic result. In rare cases, the patient may actually have a reaction to the prosthetic material. Chest wall radiotherapy greatly increases the risk of capsular contraction. Capsulectomies should be done, if possible, through the existing scar. Ideally, the incision is located over the pectoralis major muscle as this provides a protective layer between the implant and the suture line. After making the skin incision, the dissection is in the subcutaneous space over to the lateral edge of the pectoralis major. In cases where the edge of the pectoralis is too far away to be reasonably reached from this approach, the technique is to split the pectoralis major muscle in the same direction of the fibers. When the inferior-lateral cutaneous flap is thick, it is recommended the excision of the entire periprosthetic capsule. However, when this cutaneous flap is fragile and thin, or if it has been subjected to a postoperative radiotherapy, a partial excision of the capsule is performed. The portion of capsule associated with the inferior-external flap is left intact to avoid damaging the flap. Removal of

the posterior capsule is also avoided to minimize the risk of hematoma and seroma in the postoperative period. Capsulectomies are done under general anesthesia and with placement of a drain.

- *Capsulotomies*: indicated in cases of adherence or retraction of the periprosthetic capsule, leading to malpositioning of the implant or an unacceptable aesthetic result. As noted above, we try to place the incision within the previous scar if possible. Find the capsule either by dissecting through the subcutaneous tissues over to the edge of the pectoralis or split the fibers of the pectoralis to get down to the capsule. The capsule is opened and the implant is explanted. The location and type of capsulotomy to be performed is determined preoperatively with the patient standing up. Our most common approach is to make a circular incision in the base of the capsule. Following that, radical incisions are added to allow for better distension of the reconstructed breast and consequently a better shape after the implant is reinserted. We commonly use general anesthesia for these cases, but in less complex cases, local anesthesia with sedation is enough.
- *Repositioning of the inframammary fold*. The inframammary fold is an important landmark that needs to be properly positioned to achieve good symmetry in breast reconstruction. Malpositioning of it may occur after the first surgery as a result of the formation of the periprosthetic capsule. When the inframammary fold ends up too high, corrective surgery is easier. An inferior capsulotomy should allow you to place it in the correct position. When it is placed below the ideal position, correction becomes technically more difficult (Fig. 37.13). The drawing to determine the repositioning of the inframammary fold must be made before the surgery with the patient standing up. The operation is preferable to be done with the patient at 90°, if possible. An inferior circular capsulotomy is made and the implant removed. A inframammary crease is created by suturing the anterior wall of the capsule to the inferior superficial aponeurosis (superficial fascia of the underlying chest wall musculature) in the posterior capsule at the level of the new inframammary fold. Capsule wall to capsule wall fixation allows for the portion of the capsule that was inferior to the desired inframammary fold to be excluded. In some cases, the repair will not be durable, and the inframammary fold will again drop down. This is due to excessive tension in the stitches or fragility of the capsule. In such cases, correction using nonabsorbable meshes could be an option (Fig. 37.14). A drain is used and the patient is kept in a semi-sitting position for 48 h. For this surgery, the patient undergoes general anesthesia.
- *Implant replacement*. Indicated when there is asymmetry of shape or volume or in cases of a possible rupture of implant. The technique used will depend on the surgical plan. When implant volume needs to be increased, it is usually necessary to perform a capsulotomy to increase the volumetric capacity of the pocket. Capsulotomy is generally not required in cases that involve implant replacement of lower volume. Special attention must be given to replacing a round implant with a smaller anatomic one because if the pocket is too large, the anatomic

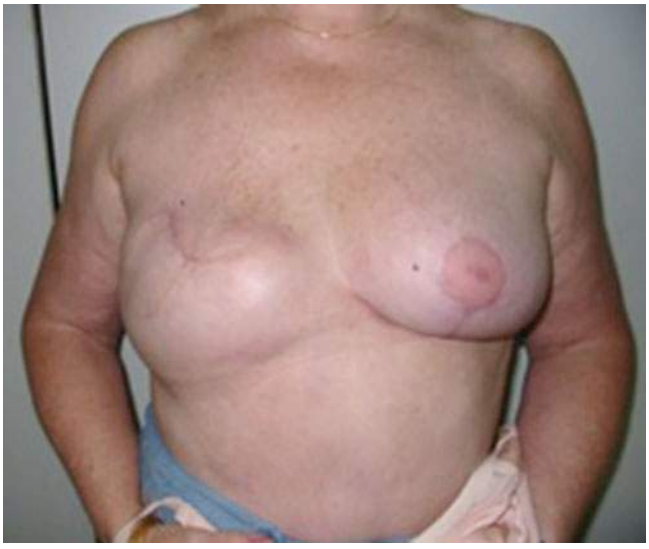

Fig. 37.13 Malpositioning of the sulcus 3 months after immediate reconstruction with anatomic form-stable implant

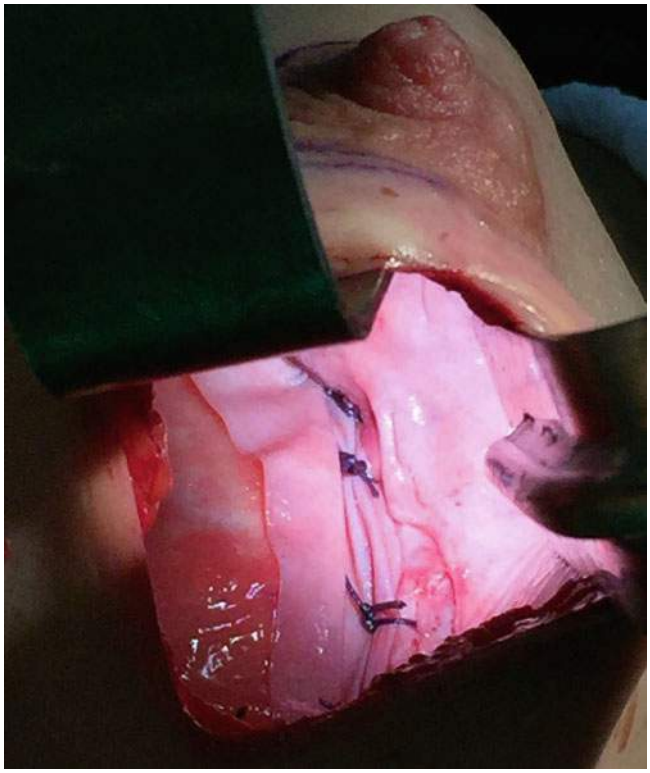

Fig. 37.14 Correction of the inframammary crease with mesh

implant may rotate with subsequent deformation of the reconstruction. Usually, this type of surgery can be performed with local anesthesia and sedation.

37.7 Complications

Complications related to breast reconstruction with implants can be classified as immediate (during the first 2 months after the surgery) or secondary (after this period). The most frequent complications include:

- Hematomas: the expected incidence of hematoma after breast reconstruction procedures is 1–2%. The risk of hematomas is inversely proportional to the length of the skin incision. With the current trend for using some aesthetic incisions, it becomes harder to achieve excellent hemostasis. Other factors that may contribute to hematoma formation are the frequent use of prophylactic antithrombotic therapy, general anesthesia, and the sitting position of the patient during the surgical procedure. The latter two contribute by keeping a relative hypotension intraoperatively, which can cause bleeding in the postoperative period when the arterial blood pressure returns to normal. When large hematomas occur, surgical exploration and evacuation are appropriate for two reasons. First, it allows for controlling the source of the bleeding. Second, a significant postoperative hematoma, with a prolonged reabsorption, is a risk factor for periprosthetic capsule that is Baker levels III or IV.
- Seromas: the physiopathology of seromas is linked with liberating inflammatory mediators from traumatized tissues and to an interruption of blood and lymphatic flow. Even though the use of closed suction drains is a routine for the prevention of seromas, they frequently occur. Axillary lymphadenectomy significantly increases the risk of a postoperative seroma. Closed suction drains are used routinely in almost all breast prosthesis surgeries, except for small capsulotomies and/or prosthetic replacements performed with local anesthesia. Drains are removed when the output is serous and the volume is below 70 cc in the past 24 h. In case of abundant drainage, the patient is discharged to home with the drain in place and will return to the clinic for removal. When seromas occur after the drains have been removed, the volume of the seroma should be monitored. The evaluation can be clinically done by an experienced surgeon, or, in case of doubt, an ultrasound can clarify the situation. In cases of a small seroma around the implant, patients are reassessed after 4–7 days in order to check if there has been increase or decrease of the seroma. If the seroma is in the axilla, the implant is not at risk of damage from the needle, and aspiration can be utilized more liberally. Care must be done with large seromas around the implant. They can be aspirated under ultrasound guidance or displacing the implant away from the point of puncture in which case the aspiration can be done without ultrasound control. Purulent fluids must be sent for gram stain, cultures, and antibiotic sensitivity studies. Empiric antibiotic therapy may be started prior to definitive cultures. Patients with large seromas can frequently experience fever peaks at 37.5 or 38 °C, though no infection is found.
- Infection and dehiscence of scar: these two topics may be dealt with as a set for they frequently occur together. Review of the literature shows an incidence of infection after breast reconstruction with expanders or definitive prosthesis that may vary from 1% to 24% [34–36]. This same study analyzed the possible factors that could influence the incidence of infection, and it was clear that the axillary lymphadenectomy, obesity, and radiotherapy are statistically significant risk factors for an increased risk of infection [37–40].

  One must consider how to manage this set of complications. A very interesting study grouped patients according to these clinical factors: quality of cutaneous cover, dehiscence of scar, and infection level (absent, average, or severe), and according to the group the patient belongs to, a therapeutic approach was proposed [39]. From our experience, this classification into clinical groups can be done, but we use a simpler classification. The simplification is based on a study that shows that previous radiotherapy does not affect the success of the treatment for infection or cutaneous dehiscence [41]. The groups and strategies could be classified as:
  - Dehiscence of scar without infection: for recent dehiscence (less than 48 h) with good skin cover, a conservative approach can be proposed, which includes culturing of the prosthesis capsule, thorough washing out of the wound with saline plus a disinfectant, placement of an closed suction drain, reinsertion of the same implant, and re-suture of the dehiscence and empiric oral antibiotic therapy (until culture and sensitivity is known) with appropriate adjustment of antibiotic therapy once the specific organism is identified. For dehiscence over 48 h and/or poor quality of the skin cover, the procedure will be the same, but it is advisable to replace the implant due to contamination or even to substitute with a lower-volume implant or exchange for an expander.
  - Dehiscence of scar with evident infection: for cases of light infection with good skin cover, it is possible to try a conservative approach; the patient must be informed about the risk of failure. For severely infected cases or when the conservative approach has failed, it is necessary to remove the implant altogether, thoroughly rinse out the prosthetic capsule, place drains, and place the patient on antibiotics until the infectious process has resolved. The patient is reevaluated in 6 months,

and at that time a plan for the new reconstructive technique is made. Occasionally, a musculocutaneous flap must be used.

  - Infection of the prosthetic capsule without dehiscence of scar: a study performed in our department at European Institute of Oncology [31] has shown an increase in the risk of delayed infection of the prosthetic capsule in cases involving postoperative chemotherapy (mainly in cases of high-dose chemotherapy), and strangely the bacteriological test of removed purulent secretion is negative. The initial approach is aspiration of the fluid found in the periprosthetic capsule, bacteriological test (gram stain, culture, and sensitivity), and oral or intravenous antibiotic therapy, according to the intensity of infection and the patient's general condition. In cases of failure of conservative approach or spontaneous drainage from the capsule of pus, the following will be necessary: removal of the prosthesis, thorough rinsing of the cavity, draining of the periprosthetic capsule, and antibiotic therapy until there is resolution of the infectious process.

- Implant extrusion: this is the most feared complication after reconstruction with implants. It occurs after an infection, flap necrosis, or a dehiscence of suture. Extrusions without infection can be sutured or submitted to a rotation of a small flap, maintaining the implant (Fig. 37.15).

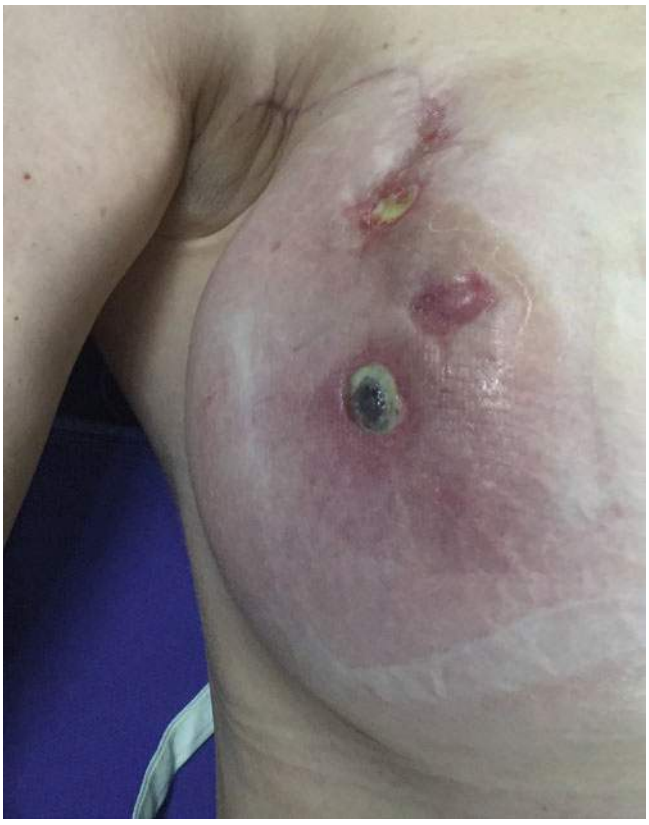

Fig. 37.15 Implant extrusion with infection

- Periprosthetic capsular contraction and rupture of implant: Baker types III and IV capsular contraction are a complication that presents with a rather variable incidence in the literature. The most recent generation of anatomic textured prosthesis is expected to reduce the incidence of capsules that need surgical correction through capsulotomy and capsulectomy as previously described. The factors that result in the formation of an excessive capsule are not yet completely known. Subclinical infection and intraoperative contamination are two possible causes that have been studied so far. The mechanism of implant rupture is related to the natural degradation of the implant envelope and to the quality of the periprosthetic capsule. Implants with cohesive gel tend to remain in place, with no extravasation of silicone into the neighboring tissues. The extravasated silicone does not cause collagen vascular or neurological diseases and does not have oncogenic potential or teratogenicity. The life span of these latest generation of implants is not yet completely known. Prophylactic exchange of these implants is not necessary (see the chapter about history of breast implants).
- Rotation of implants: this is a new complication that appeared with the use of anatomic implants. It is not frequent, and it is probably related to pockets with excessive volume and/or insufficient capsule formation to keep the implants in their correct orientation.
- Rippling: it is not well known the real incidence and causes of this aesthetic long-term complication, which nowadays can be corrected by the use of lipofilling (there is a specific chapter about this) (Fig. 37.16).
- Local recurrences: these are not exactly a complication of the reconstruction. They are more related to margin status, age of the patient, treatment protocols, and tumor biology rather than the surgery itself. Local recurrences in skin-sparing mastectomies are statistically similar to those of the traditional modified radical mastectomies. Preserving the inframammary fold and uninvolved skin does not bring major oncologic risks or effect patient survival. Local recurrences after mastectomies must be considered as systemic until staging studies show otherwise.

37.8 Aesthetic Result

Aesthetics is a branch of philosophy dealing with the nature of art, beauty, and taste. It is clearly difficult and maybe impossible to define what is a beautiful or a perfect breast [42]. A recent study at Our Lady of Grace Hospital Breast Unit in Curitiba (Brazil) that evaluated aesthetic and quality of life results after immediate breast reconstruction with definitive form-stable anatomical implants and contralateral symmetrization, comparing objective and subjective instruments, showed a positive impact on the quality of life

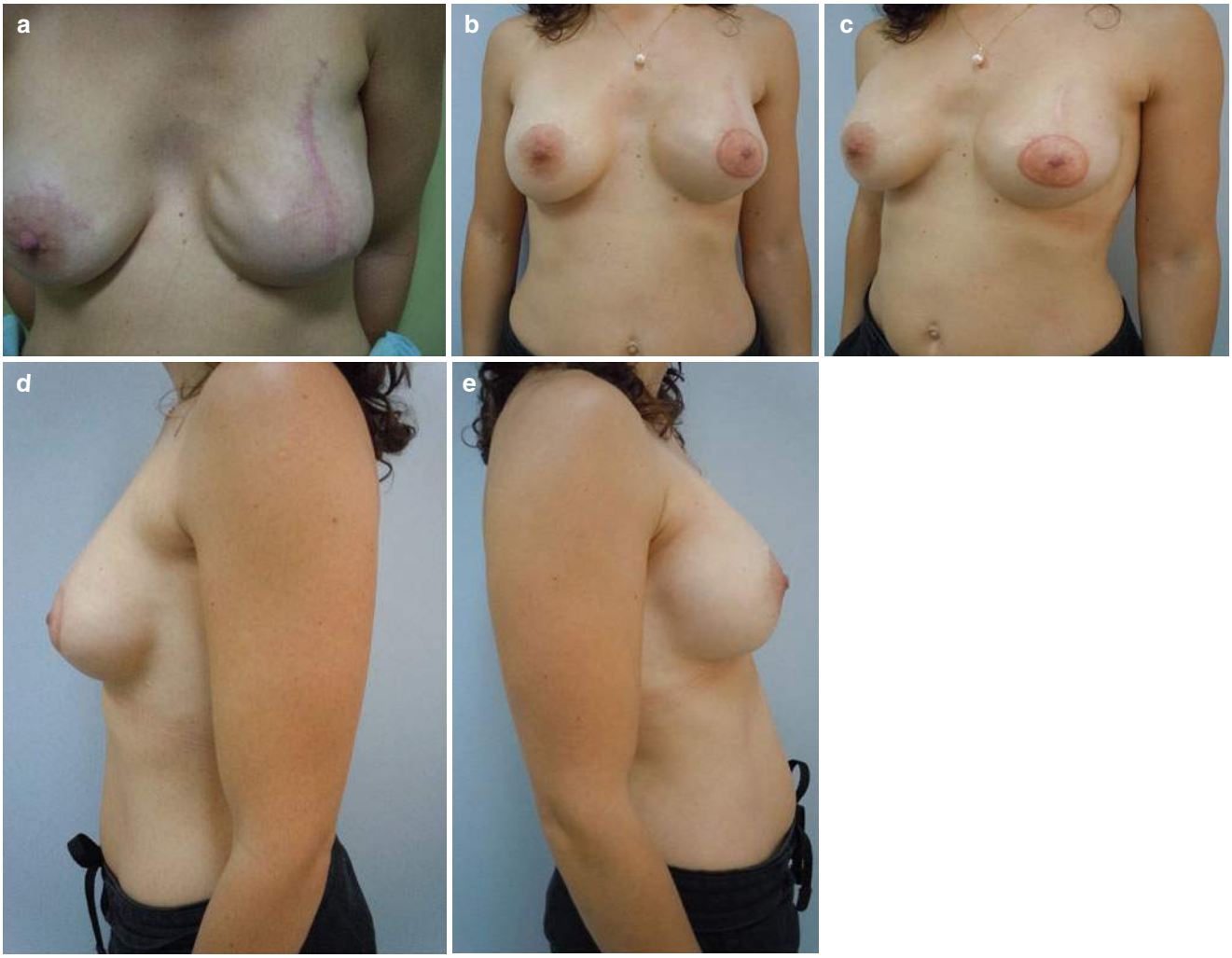

Fig. 37.16 (**a**) Rippling after breast reconstruction with anatomic form-stable implant. (**b**–**e**) Postoperatory view 4 months after rippling correction with lipofilling

and excellent and good aesthetic results more frequent in the patient's evaluation than by software and specialists [43]. There is a specific chapter about it.

37.9 Conclusions

Immediate breast reconstruction with anatomic implants associated with skin and nipple-sparing mastectomies represented one of the greatest advances in reconstructive breast cancer surgery in the past few years. It has a low level of complications. It decreases both the time spent in reconstructive surgeries and the number of surgeries for most patients. Surgical revisions of the reconstruction are still needed in some cases and are one of the biggest limitations. However, these are surgical procedures that represent minor risks, and many of the procedures can be performed under local anesthesia. Currently, this is our most commonly used technique in our departments due to its practicality, lack of long-term complications as we see with musculocutaneous flap, and satisfactory aesthetic results with the various anatomic implants available in the market.

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The Use of Acellular Dermal Matrices in Implant-Based Breast Reconstruction

38

Glyn Jones

Implant-based techniques are the most widely used approaches to breast reconstruction of the world today. In the United States alone, they account for six times the number of reconstructions compared with all autologous reconstructive techniques combined. Two-stage expander-implant reconstruction is one of the most widely used forms of breast reconstruction, although single-stage direct-to-implant reconstruction is becoming increasingly popular. Despite the popularity of implant-based techniques, they have been fraught with the problems of capsular contracture, rippling of implants beneath the overlying thin skin envelope, and pseudoptosis of the device as the lower pole skin attenuates with time. Numerous solutions to these issues have been tried often with little success. During the past 14 years, acellular dermal matrices have been increasingly incorporated into implant-based reconstructions and appear to offer a degree of resolution to many of these troublesome issues.

Additionally in recent years, there has been renewed interest in the pre-pectoral approach to breast reconstruction. This has included both two-stage and single-stage reconstructions, and both techniques have relied heavily on the use of ADM for their success. The results achieved with the pre-pectoral approach have been exceptionally good in terms of both form and function.

While autologous techniques remain the gold standard of breast reconstruction, for many surgeons, time constraints, resource allocation, availability of operating time, and decreasing reimbursement have all contributed to the ongoing popularity of prosthetic device-based techniques despite their problems. Many patients are also concerned about the magnitude of some of the autologous approaches, including free tissue transfer, and see implant reconstruction as a quick and relatively easy answer to their reconstructive needs. In the United States in 2015, implant-based reconstruction was performed six times more commonly than all autologous techniques combined.

Surgeons familiar with all of these approaches are only too painfully aware of some of the major negatives associated with implant reconstructions.

Problems with implant-based reconstruction:

- Window shading of the pectoralis muscle release
- Difficulty controlling the expander or implant pocket size and location
- Visible implant ripples
- Visible animation deformity
- Tightness and functional upper extremity limitation
- Postoperative infection
- Inadequate lower pole expansion
- Capsular contracture rates in the long term
- The negative impact of radiation on implant-based reconstruction

At the time of surgery, coverage of the device with pectoralis major provides upper pole cover which can reduce long-term visible rippling of an underlying implant. Unfortunately inferomedial pectoralis major muscle release is complicated by window shade retraction of the muscle in a cephalad direction. Traditionally this has been countered by placing percutaneous sutures to anchor the muscle to the mastectomy skin envelope, an approach complicated by necrosis of marginally vascularized skin. The technique only provides cover to the upper pole, leaving the lower pole devoid of anything but thin skin coverage. Attempts at raising rectus muscle or fascia and the serratus fascia laterally can aid in resolving this dilemma but come at the expense of creating tight banding across the bottom of the reconstruction right where fullness and suppleness are most

Electronic Supplementary Material The online version of this chapter (doi:10.1007/978-3-319-62927-8_38) contains supplementary material, which is available to authorized users.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_38

necessary. Having a biologic material to bridge the gap between the caudal edge of pectoralis major and the inframammary crease provides reliable, supple cover which can stretch with time or expansion.

In addition to the dilemma of providing cover, surgeons are faced intraoperatively with the difficulty of maintaining an expander or implant in its exact location within a larger mastectomy pocket than the device requires. Without the ability to control pocket size, particularly laterally, a device can shift or even rotate, creating major problems later. Having a biologic mesh to help shape and control pocket size is a desirable advantage in achieving excellent outcomes, particularly when one-stage direct-to-implant reconstructions are attempted. Tabbed expanders have made a significant difference in this regard, but the use of some form of mesh further enhances the surgeon's ability to control pocket size and shape.

With the acute intraoperative issues dealt with, we face the task of achieving successful expansion with subsequent expander-implant exchange. Isolating a prosthetic device from the mastectomy space could potentially reduce infection and device loss.

Once exchanged for a permanent implant, we encounter the problem of visible rippling and wrinkling of the implant beneath the skin. While cohesive gel implants have reduced this issue substantially, it remains a cause for concern. Any biologic material that places more thickness between the skin and the implant can only serve to improve this troublesome problem and enhance esthetic outcomes.

Another significant issue encountered following implant reconstruction in the subpectoral plane is that of animation deformity. It can be found in almost all patients having a subpectoral implant-based reconstruction. Patients find this condition troubling, and its association with decreased pectoral muscle thickness and reduction in pectoral muscle power combines to make this a very distressing problem impacting patients' lives on a daily basis. The use of a prepectoral approach to breast reconstruction has almost eliminated these two issues.

Probably the most troubling complication of all remains that of capsular contracture.

With all of these complications in mind, acellular dermal matrices have become a useful and simple adjunct to our surgical armamentarium, providing significant improvement in clinical outcomes. The last 15 years have seen a dramatic increase in the number of patients receiving postoperative radiation as radiation criteria have expanded to include earlier forms of breast cancer. Radiation exerts a negative influence on implant reconstruction by tightening the overlying skin envelope and increasing the incidence of capsular contracture, resulting in deteriorating symmetry and increasing deformity with time. Acellular dermal matrices appear to be a valuable adjunct to improving the outcomes of implant-based reconstruction.

In addition, the author has moved from two-stage expander-based subpectoral reconstruction to single-stage direct implant pre-pectoral reconstruction, which is greatly facilitated by the use of ADMs.

In the past 14 years, numerous biologic materials have been introduced for use in reconstructive breast surgical procedures. Theoretically biologically derived materials should allow a surgeon to achieve a better, more natural clinical outcome than by using synthetic materials. However, along with the many choices in biologic materials available to plastic surgeons comes very little published data on most of these materials and considerable confusion as to the differences between them. Surgeons must be equipped with a fundamental understanding of these materials and how they work so they can make educated choices when developing a reconstructive strategy.

38.1 Currently Available Biologic Materials

Numerous allogeneic and xenogeneic tissue scaffolds have been introduced commercially, and a table indicating the nature and source of some of the most widely marketed is shown in Table 38.1.

The goal of using regenerative tissue matrices in reconstructive surgery is to establish an environment that enables the patient to "regenerate" tissue other than scar or foreign-body capsule that mimics the autologous tissue and allows the surgeon to achieve an excellent outcome with durable esthetics and function.

38.2 Biologic Matrix Applications in Breast Reconstruction

Reconstructive options for using biologic matrices in breast reconstruction include the following:

- Implant reconstruction
- Expander reconstruction

Table 38.1 Biologic materials available for breast reconstruction

Name	Company	Source tissue	Alpha-gal removed
DermaMatrix	MTF (Synthes)	Human dermis	N/A
Flex HD	MTF (Ethicon)	Human dermis	N/A
Neoform/ AlloMax	Tutogen (Mentor)	Human dermis	N/A
AlloDerm	LifeCell	Human dermis	N/A
Strattice/Artia	LifeCell	Porcine dermis	Yes
SurgiMend	TEI Biosciences	Fetal bovine dermis	No
Veritas	Synovis	Bovine pericardium	No

- Augmentation of the reconstructed nipple
- Abdominal wall reinforcement
- Reducing capsular contracture after radiation therapy

The aim of this chapter is to discuss the use of ADM in expander-implant reconstructions.

38.2.1 Subpectoral Implant Reconstruction

Patients undergoing skin-sparing mastectomy for breast cancer may be candidates for either immediate implant or expander insertion. Direct-to-implant insertion is becoming an increasingly attractive proposition as methods to assess skin viability become more available. Prerequisites for successful direct-to-implant insertion include a well-vascularized skin envelope and adequate skin surface area. The use of indocyanine green-based fluorescence imaging has revolutionized our ability to assess skin vascularity at the time of mastectomy. If the skin envelope is viable, an implant of similar size to the original breast volume may be inserted without fear of postoperative necrosis. Unfortunately, such implant placement requires accuracy of implant positioning and maintenance of that position if the esthetic outcome is to be acceptable to both patient and surgeon. The mastectomy pocket is, by definition, larger than the space occupied by the implant. The tendency for the implant is to fall laterally and inferiorly as well as to slide out from beneath the pectoralis major into a subcutaneous plane. To correct both of these issues, a sheet of acellular dermal matrix can be used to reduce both pectoralis major window shading and controlling the implant pocket dimensions and location. The larger the implant and the greater the degree of ptosis required, the larger this sheet of matrix should be. My personal preference for a sheet 8 × 16 cm in size for most subpectoral is expander reconstructions, while an additional 6 × 16 cm sheet may be necessary for large (700–800 cc) implant reconstructions. In addition, the surgeon can use AlloDerm as a lower pole reinforcement to reduce both lower pole implant rippling and long-term capsular contracture.

38.2.1.1 Operative Technique

The perfusion and viability of the mastectomy skin envelope should be carefully assessed prior to committing to a direct-to-implant approach. It is the author's preference to use indocyanine green laser fluorescence for this assessment as it is quick, easy, and exceptionally accurate. The inferolateral border of pectoralis major is grasped with Alice tissue forceps (Fig. 38.1), and the subpectoral plane is entered (Fig. 38.2). Pectoralis major is released from 6 to 3 o'clock on the right and 6 to 9 o'clock on the left (Fig. 38.2a) producing a release that gives rise to the window shade effect of the muscle. A sheet of AlloDerm or

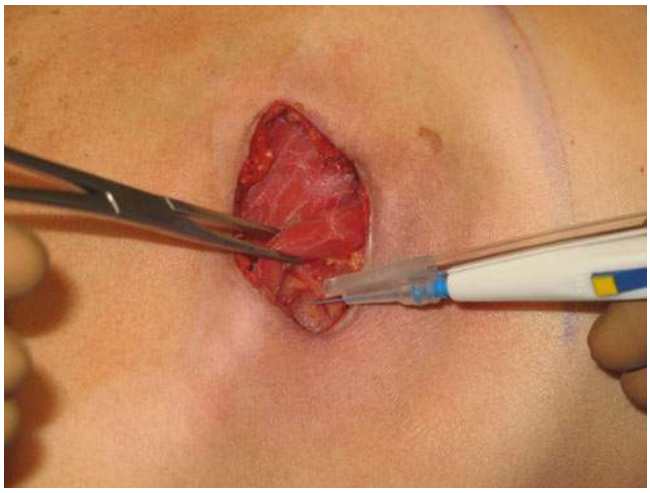

Fig. 38.1 The inferolateral border of pectoralis major is elevated with cautery

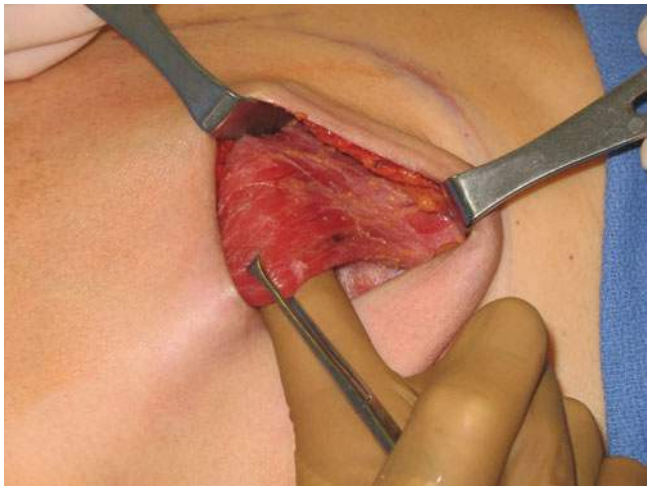

Fig. 38.2 The subpectoral plane is elevated

Strattice (LifeCell Corp., Branchburg, New Jersey) is washed for 2 min in saline to rinse off preservatives (Fig. 38.3). The superomedial corner of the matrix is sutured to the inferomedial cut edge of the pectoralis major muscle with running 2-0 polydioxanone suture (Fig. 38.4). The suture is run along the medial breast border (Fig. 38.5) and then across the curve of the inframammary crease and can be sutured to a raised cuff of serratus anterior fascia laterally which provides additional domain for an implant if required. This creates an inferior sling of AlloDerm into which an implant or expander can be placed (Fig. 38.6). The device is placed beneath the AlloDerm inferiorly and the Strattice superiorly, following which the caudal edge of pectoralis major is sewn to the cephalad edge of the AlloDerm with running 2-0 PDS suture (Fig. 38.7). This creates complete coverage of the implant with the mesh. It is essential that a drain be placed

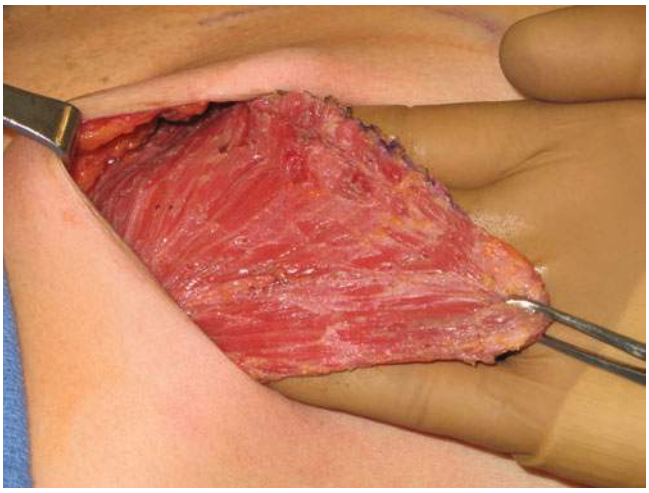

Fig. 38.3 The pectoralis major muscle is elevated after incising the origin inferomedially

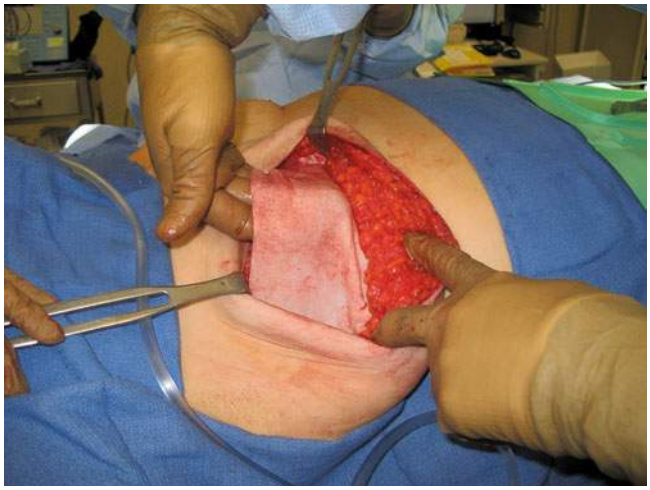

Fig. 38.6 The completed sling is shown

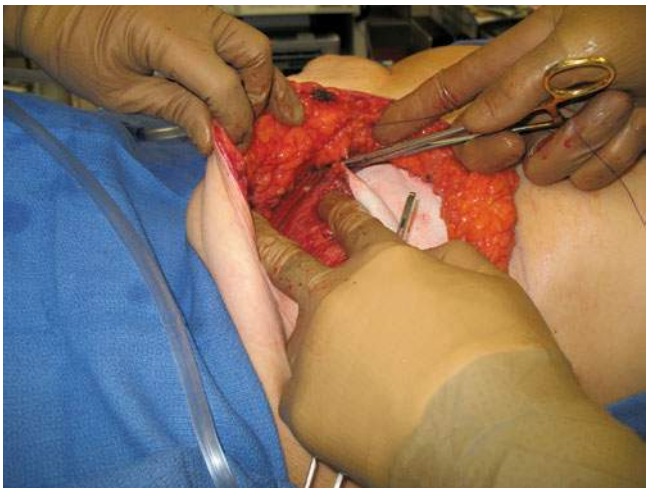

Fig. 38.4 The sheet of acellular dermal matrix is sutured to the cut origin of pectoralis major medially

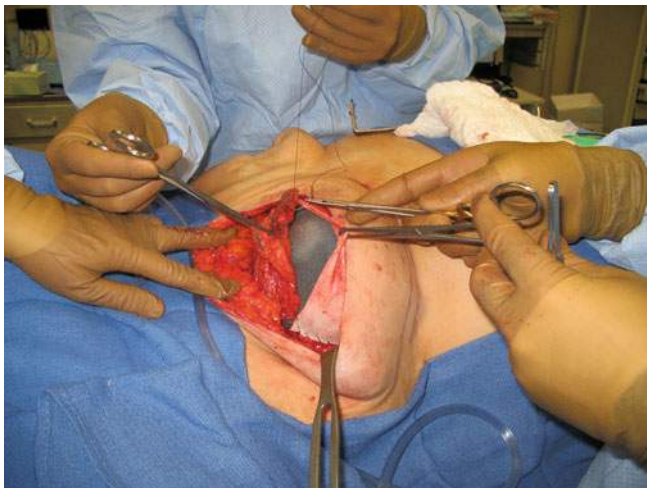

Fig. 38.7 The prosthetic device (expander or implant) is placed beneath the acellular dermal matrix inferiorly, and the matrix is sutured to the caudal border of pectoralis major muscle superiorly

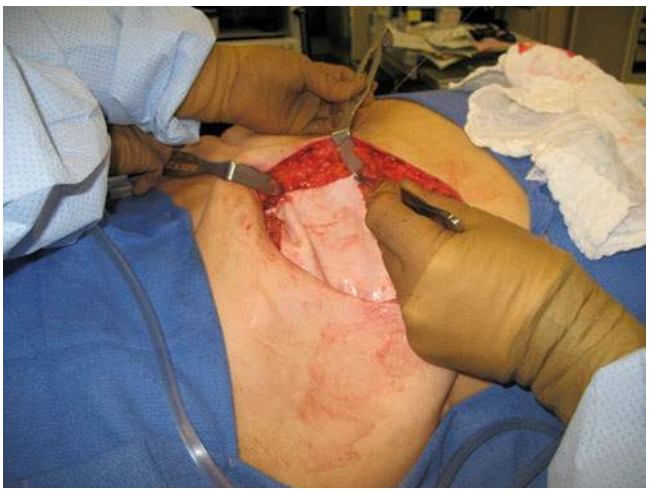

Fig. 38.5 Suturing is continued inferiorly along the inframammary crease and laterally to serratus anterior fascia to complete the creation of an inferior sling of acellular dermal matrix

between the AlloDerm and the overlying skin in order to minimize seroma formation which could inhibit contact between the mesh and the skin, thereby reducing vascular ingrowth and incorporation. The skin is then closed with absorbable subcutaneous and subcuticular sutures in a two-layer closure sealed with cyanoacrylate cement, Steri-Strips, and an occlusive waterproof dressing such as Tegaderm (Fig. 38.8).

38.2.1.2 Direct-to-Implant Reconstruction

This 55-year-old woman with cancer of the left breast and cancer phobia requested bilateral mastectomies with immediate implant reconstruction. She was a nonsmoker and had well-perfused skin flaps. AlloDerm was placed in the lower poles of both breasts, and high-profile 650 cc gel implants were placed subpectorally. She is shown 9 months after nipple reconstruction; the result is soft and stable, with good symmetry (Fig. 38.9).

38.2.2 Expander Reconstruction

Tissue expander insertion after mastectomy is subject to the potential problems of poor lower pole coverage, expander migration, and capsular contracture. The use of ADM provides thicker lower pole coverage and support and may reduce capsular contracture. In addition, the complete coverage of an expander by the muscle and ADM compartmentalizes the device from a potentially more contaminated mastectomy pocket. This may reduce acute infection rates associated with expanders and could increase expander salvage in the presence of cellulitis of the mastectomy skin postoperatively. The technique of insertion is identical to that used with implant insertion. The expander should be inflated to the maximum intraoperative volume permissible that would allow adequate skin perfusion as it is preferable to have the matrix compressed up against the overlying mastectomy skin to encourage vascular ingrowth into the matrix as rapidly as possible. Drain insertion is mandatory to prevent seroma formation between the matrix and the skin (Fig. 38.10).

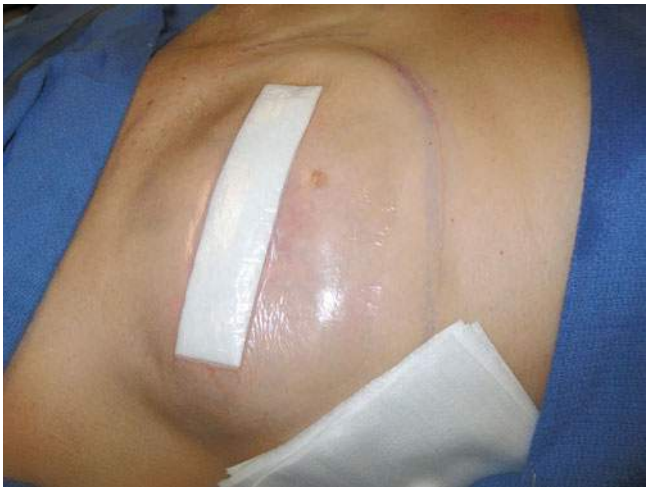

Fig. 38.8 The completed closure with dressings applied

38.2.3 Pre-pectoral Direct-to-Implant Reconstruction

This technique has become my procedure choice for almost all implant-based breast reconstruction at this time. I no longer perform expander-implant two-stage reconstruction unless the patient has a dramatic lack of skin availability at the initial operation or if delayed reconstruction is planned. In the immediate sitting, the only time I will perform a subpectoral implant-based direct implant reconstruction arises in the situation of a patient with an extremely close posterior tumor margin which threatens invasion of the pectoralis major muscle. Under such circumstances, traditional subpectoral reconstruction can be performed so as to allow the anterior border of the pectoralis major muscle to lie immediately beneath the skin flap for long-term tumor recurrence monitoring.

For all other clinical scenarios, I use pre-pectoral implant placement in a direct-to-implant fashion. This technique has revolutionized my breast reconstruction results, creating much more natural breast contours as well as reducing the need for fat grafting and almost completely eliminating the problem of animation deformity. Postoperative recovery is much more comfortable given that the pectoralis major muscle does not have to be divided at any point and our motion at the shoulder is regained much more rapidly. There is absolutely no negative impact on upper extremity power.

38.2.3.1 Operative Technique

Once the mastectomy has been completed, skin viability is assessed with ICG perfusion techniques. This is invaluable

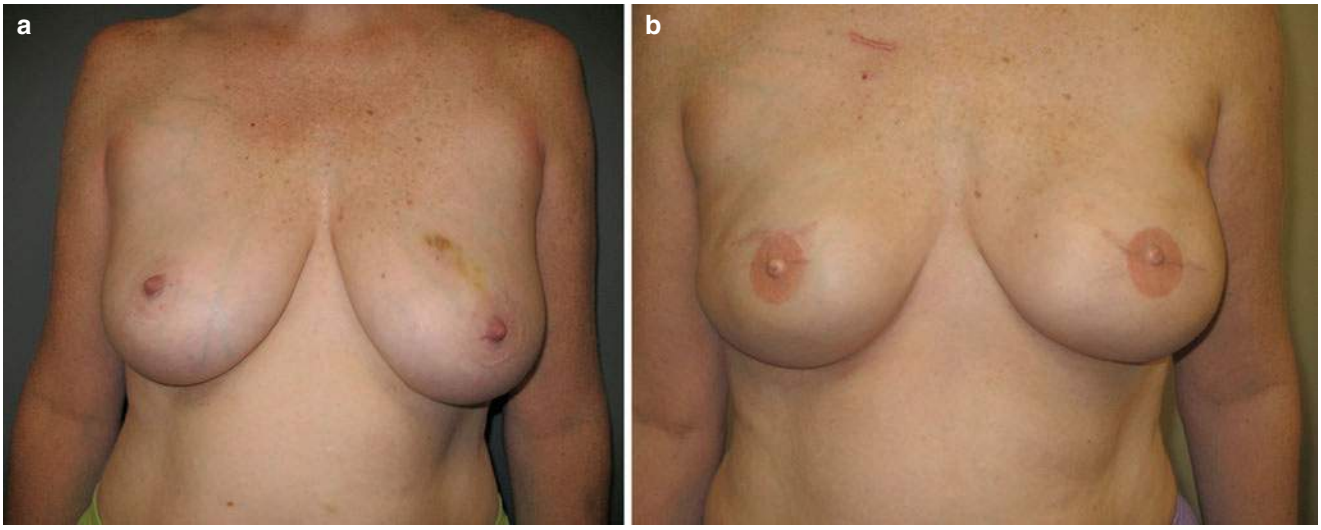

Fig. 38.9 Pre and post operatory view 55y bilateral mastectomy with immediate implant reconstruction associate with AlloDerm placed in the lower poles of both breasts

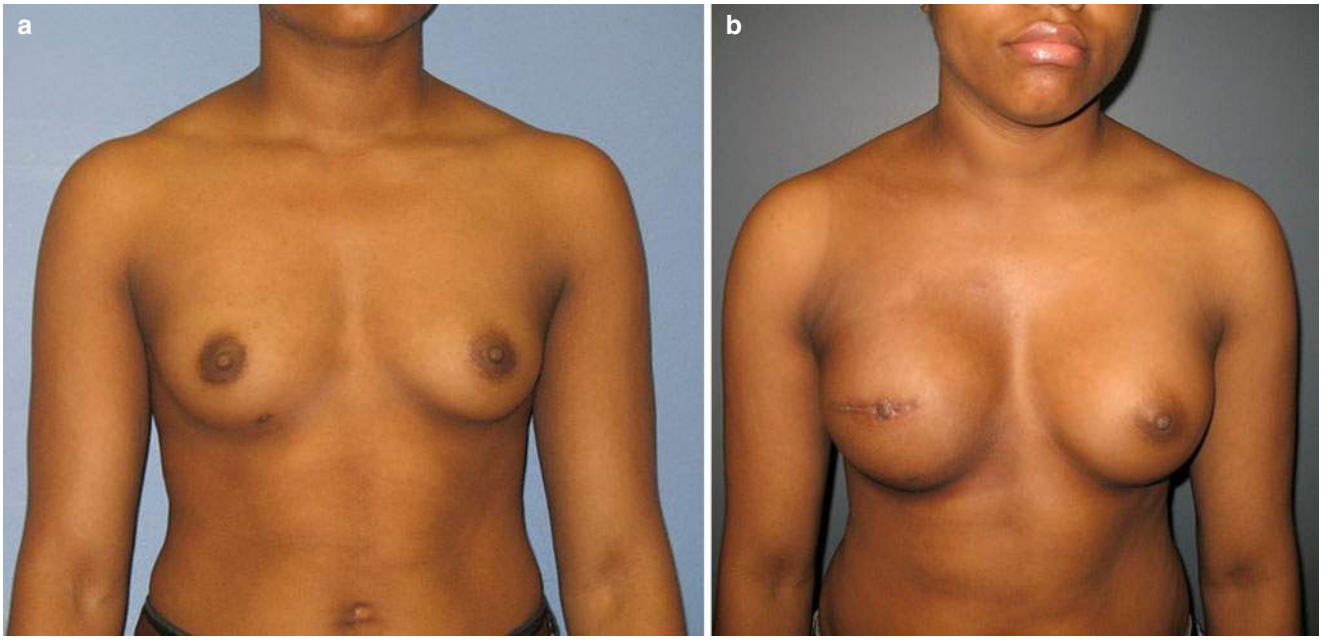

Fig. 38.10 This patient underwent expander insertion after right mastectomy for breast cancer. She had an implant exchange followed by radiation therapy and nipple reconstruction. No tattoo was performed. She is shown 1 year after treatment (**a**) Her breast remains soft and symmetry (**b**), with excellent shape and maintenance of symmetry despite radiation therapy

for determining whether or not the overlying mastectomy skin envelope will be able to tolerate the volume of the reconstruction without impacting skin viability negatively. I will typically insert a temporary breast size based on the mastectomy volume and staple the skin closed over the device. ICG perfusion is then performed, and if the skin appears healthy and well perfused, I proceed with direct implant reconstruction.

A sheet of 16 × 20 cm ADM (AlloDerm, Strattice, or Artia—LifeCell Corp., Branchburg, NJ) is rinsed for 2 min to remove any preservative solution. The material can be perforated with a 3 mm dermatology punch unless the pre-perforated version is available. Once washed, I cut off the upper edges of the ADM to create a teardrop-shaped sheet of matrix which will aid in reducing the risk of implant rotation in the long term. Using this approach I have seen only 1 implant rotation in over 150 patients operated on using pre-pectoral techniques.

The ADM is then placed into the pre-pectoral pocket and suited to the anterior aspect of the pectoralis major muscle using 2-0 PDS. Suturing is performed from 12 to 7 o'clock and 12–5 o'clock, leaving an inferior access window open for implant insertion. Next, the implant pocket is copiously localized with a liter of irrigation. I always start with a 50–50 dilution of Betadine solution, followed by a triple antibiotic solution containing 1 g of cefazolin, 80 mg of gentamicin, and 50,000 units of bacitracin. I have added Betadine wash in recent months based on discussions with Clemens at MD Anderson Cancer Center, regarding the potential for development of breast implant-associated anaplastic large-cell lymphoma. While there is no certainty regarding the etiology of this extremely rare condition, there is some data suggesting that an association with bacterial contamination from *Ralstonia pickettii* may be an inducing agent. This organism is sensitive to Betadine but not chlorhexidine and can be further reduced by treating the patient with doxycycline postoperatively. It is now my preference to use doxycycline as my preferred postoperative antibiotic.

Having selected the appropriate implant size, I change my gloves, and I am the only person on the operative team to handle the implant. I always insert the device using a Keller Funnel, which allows for no contact with the skin insertion technique. The implant is carefully oriented within the pre-pectoral space. The ADM is then pulled taut over the surface of the implant and is sutured to the inframammary crease with the remaining tails of running 2-0 PDS.

A 15 French fully fluted round hubless channel drain is inserted between the skin and the ADM. If the mastectomy is particularly large, or an axillary dissection has been performed, I insert a second drain to this area (Figs. 38.11 and 38.12).

38.2.4 Augmentation of the Reconstructed Nipple

Nipple reconstructions undergo a degree of atrophy over time. Nipples reconstructed from expanded mastectomy skin are most prone to this phenomenon because of the thin dermis

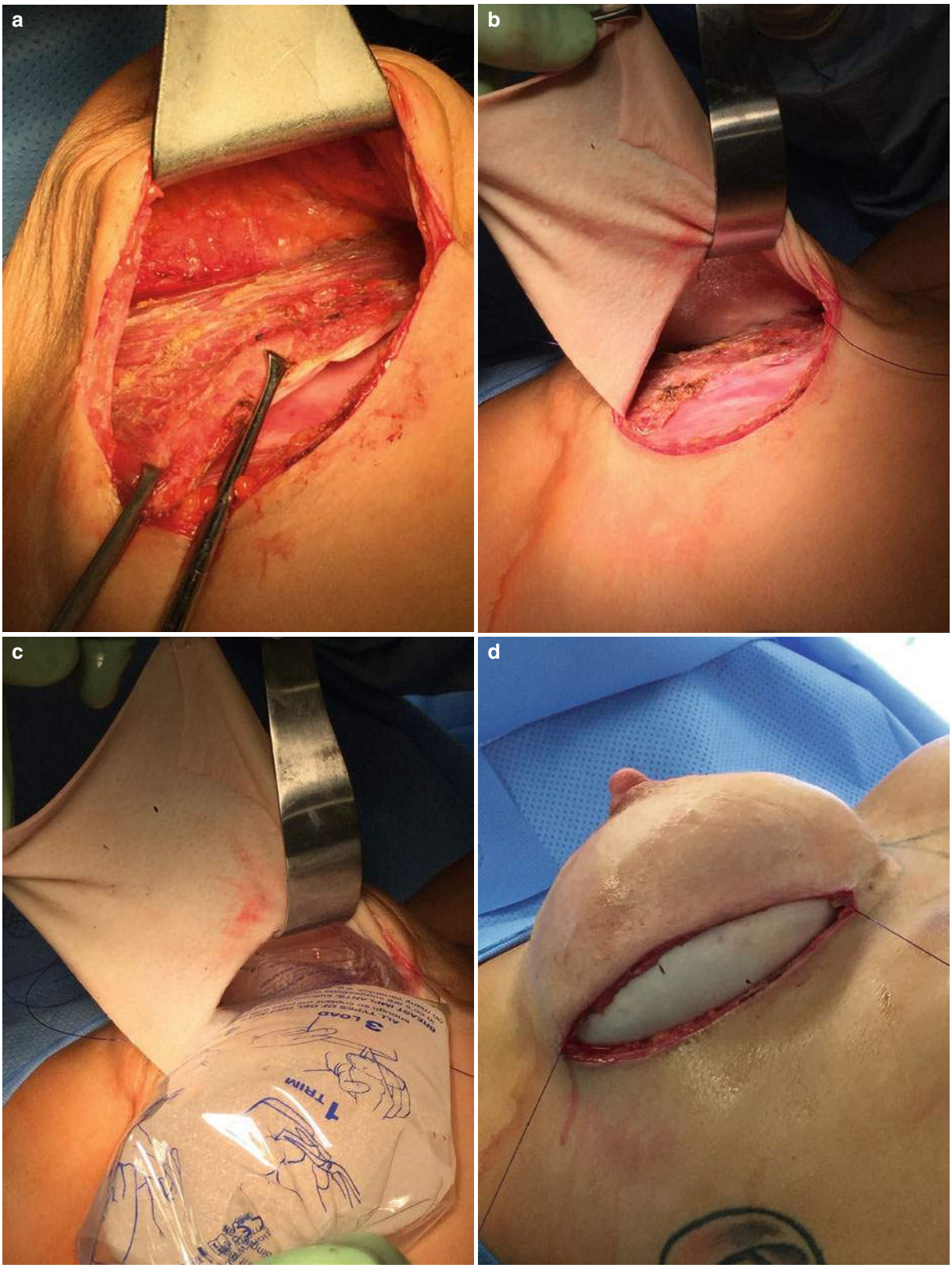

Fig. 38.11 (**a**) The pre-pectoral pocket showing the skin elevated on the retractor and the pectoralis major muscle held in Allis tissue clamps. (**b**) The ADM sutured from 12 to 7 o'clock and 12–5 o'clock with running 2-0 PDS sutures, showing the ADM elevated with the skin flap and the pectoralis major muscle below. (**c**) The anatomic textured cohesive gel implant being inserted using a Keller Funnel, ensuring no contact between the implant and the skin. (**d**) The ADM draped over the lower pole of the implant and sutured to the inframammary crease with the remaining tails of 2-0 PDS

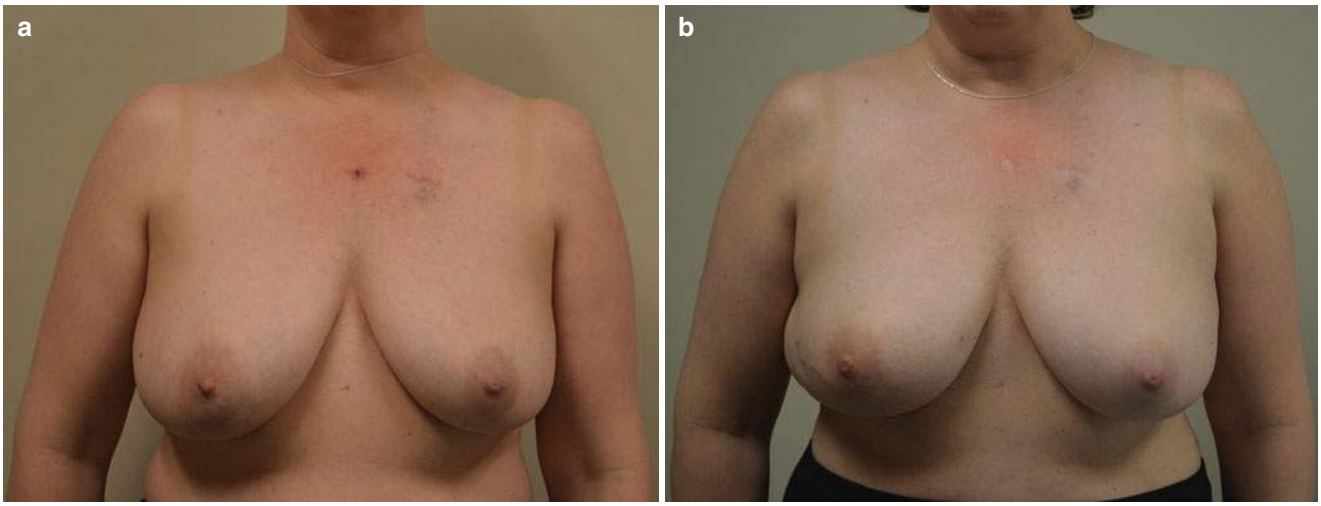

Fig. 38.12 (**a**) Preoperative view of patient with right breast carcinoma. (**b**) Same patient shown 1 year after right immediate single-stage pre-pectoral direct-to-implant reconstruction with ADM coverage over a cohesive gel anatomic implant. No symmetry surgery has been required for the contralateral normal breast

present in breast skin and the lack of subcutaneous tissue following skin-sparing mastectomy. Several techniques have been used as possible solutions to this problem. These include staged autologous fat injection before elevation of the nipple-skin flaps, implantation of additional autologous dermal grafts, or the use of commercially available ADMs. The latter technique obviates the need for a donor site.

Nahabedian and others have described the use of AlloDerm in secondary nipple reconstruction using C-V flaps, with satisfactory maintenance of projection over time. Although histologic evaluation of mature AlloDerm in the nipple has not been reported, Silverman conducted an animal study analyzing the cell repopulation and vascularization of AlloDerm sutured into a roll and implanted within a subcutaneous flap in rabbits. Results demonstrated revascularization of all layers of the matrix, with maintenance of projection.

38.2.4.1 Data Regarding Capsular Contracture in Non-radiated Patients

While numerous ADMs exist on the market today, many of them are products formerly used with varying degrees of success or failure in the hernia market, and few have undergone rigorous pre-market testing and clinical trials in breast surgery. Currently the most widely tested and used products are AlloDerm and Strattice, both developed and marketed by the LifeCell Corporation. This chapter is not intended to be an endorsement of any product or company but reflects the author's experience with this particular product series as well as the fact that the literature is replete with hundreds of articles on the successful use of AlloDerm and Strattice in breast reconstruction, while there are few if any papers attesting to the long-term success of most of the other products. This data may, however, be forthcoming in the future, and comparisons will be interesting to observe.

Experience with AlloDerm in breast reconstruction goes back approximately 14 years. Capsular contracture data is steadily emerging, and more and more papers are attesting to the fact that ADM incorporation in immediate or delayed breast reconstruction appears to be associated with significant decreases in capsular contracture. Breuing reported a zero contracture rate at 3 years in non-radiated breast in a series of 97 immediate and 4 delayed reconstructions with either implants or expanders, while Salzburg has reported 0.5% contracture rates at 14 years for subpectoral direct-to-implant reconstruction. Most recently Sigalove and Maxwell reported 0% contracture in a multicenter series of over 300 patients treated with two-stage expander-implant pre-pectoral reconstruction.

Although data to support this contention are still emerging, we are beginning to see an encouraging trend in this direction. Research in my own subpectoral patient population has demonstrated grades II–III capsular contracture occurring in 22 of 79 breasts treated without ADM but only grade II contracture in 14 of 109 patients treated with ADM, the remainder being grade I. Infection rates between the two groups were similar, but expander salvage was significantly higher in the ADM-treated patients than in those without ADM insertion. In our immediate pre-pectoral series of 70 direct-to-implant reconstructions, capsular contracture at 2.5 years has been 0% in non-irradiated breasts with a 3% periprosthetic infection rate requiring explantation.

Jansen reviewed the recent literature and found a spread of capsular contracture rates of 0–8% with AlloDerm usage,

all of which were well below reported averages for non-AlloDerm-based capsular contracture rates historically. Basu et al. demonstrated a highly statistically significant difference in capsular structure histologically between conventional fibrous capsules and the more elastic AlloDerm-based capsules seen with ADM usage resulting in more supple, soft clinical outcomes. In our own experience, we have seen a reduction in capsular contracture based on AlloDerm usage when compared with our historic controls of non-AlloDerm patients.

Capsular contracture grade	No AlloDerm used (%)	AlloDerm used (%)
I	72	87.1
II	21.5	1.6
III	6.3	0
IV	0	0

38.2.4.2 Data Regarding Reduction of Capsular Contracture After Radiation Therapy

Expander-implant reconstruction in the face of prior or subsequent radiation therapy has been associated with worse clinical outcomes than in the non-radiated patient population. Spear demonstrated dramatically increased complication rates, including capsular contracture, distortion, increased infection rates, and loss of the reconstruction. He reported an 84% complication rate, with 39% of patients requiring conversion to an autologous technique. The incorporation of ADMs into expander-implant reconstruction appears to be helpful in reducing these complications based on 5-year observations in our practice.

The stimulus for their use was triggered by some of the earlier animal studies suggesting that subcutaneous AlloDerm insertion followed by radiation therapy did not appear to adversely affect vascularization, cell density, or graft thickness. In our own early data in patients undergoing adjuvant radiation therapy, only two of eight breasts (25%) treated with ADM developed grade II capsular contracture, whereas six of seven breasts (85%) without ADM developed grade II to III capsular contracture ($p < 0.05$). Of these non-AlloDerm-radiated patients, 14% were grade II, while 71% were grade III capsules, a highly significant difference between the two groups. This trend has been borne out over a 5-year period. We have been so impressed by these sustained outcomes that conversion to autologous reconstruction after radiated implant reconstruction has decreased by at least 50% in our practice. Furthermore, the patients who have maintained an implant-based reconstruction in the face of radiation have maintained at most a grade II capsule without progression to grade III or IV capsules as was so common in the past. The trend has saved both patient morbidity and health-care costs in this important patient subset.

38.2.4.3 Data on Cost Analysis

An additional cause of concern about the use of ADMs in breast reconstruction has been the issue of cost. Jansen et al. reviewed cost outcome analyses of AlloDerm usage based on the Canadian health-care system and found that AlloDerm usage reduced operative times and postoperative complications resulting in less take backs, greater usage of direct-to-implant reconstruction, and less re-operative events for capsular contracture. Based on their estimates, direct-to-implant reconstruction with AlloDerm was particularly cost-effective.

38.2.4.4 Data on Infection Rates

Infection following expander-implant reconstruction is a major cause of postoperative morbidity. This is exacerbated by radiation therapy as evidenced by Spear's data. While user experience and familiarity with the product may affect infection rates, the use of ADMs certainly does not seem to increase infection rates and may even decrease them due to separation of the mastectomy pocket from the implant pocket by both the pectoralis major muscle and the ADM. Nahabedian found that in their series, the use of ADM neither increased nor decreased infection rates in expander-implant reconstruction, a conclusion which is similar to our own experience. In our current series of 70 patients treated with pre-pectoral direct-to-implant reconstruction and 49 patients treated with pre-pectoral conversions for animation deformity, infection rates have been 3% and 0%, respectively.

38.3 Conclusion

Acellular dermal matrices have assumed a pivotal role in the prevention of complications of expander-implant-based breast reconstruction. An increasing body of data from multiple centers confirms this trend. While costly at the outset, the short-, medium-, and long-term benefits of these materials far outweigh the negatives associated with their use, and it is likely that they will become a standard of care in the management of expander-implant-based breast reconstruction in the future.

Pre-pectoral reconstruction as a single-stage immediate direct-to-implant approach has become the author's preferred technique for immediate reconstruction in 95% of implant-based reconstructions. Traditional two-stage expander-implant reconstruction is now reserved only for patients who have too little skin available at the time of mastectomy or who require delayed reconstruction in my practice.

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Immediate Implant-/ADM-Based Breast Reconstruction

39

Michel Sheflan, Iain Brown, and Tanir M. Allweis

39.1 Introduction

Implant-based breast reconstruction continues to be the mainstay of the reconstructive repertoire and yet remains a challenge. While the use of an implant may appear to be the simplest and most straightforward option, this apparent simplicity belies subtle complexity, which must be overcome if a predictable, natural-appearing and reliable reconstruction is to be created. Awareness of potential complications and risk factors for postoperative and long-term complications is paramount if these are to be minimised.

Successful outcomes require:

39.1.1 Individualised Selection, Analysis and Planning

As with any other technique, implant-based breast reconstruction requires the careful analysis of the patient's general health and body habitus, oncological status, specific tissue characteristics and bio-dimensional measurements and careful consideration of individual desires and expectations as well as planned postoperative therapy such as irradiation.

The surgeon must:

- Have an understanding and appreciation of the individual aesthetic components that contribute to the 'natural' breast form (a gradual upper pole, proportionate lower pole curvature, medial-to-lateral take-off and defined infra-mammary and lateral folds).
- In patients with breast cancer, be cognizant of tumour location and extent, the need to achieve negative margins, and whether or not postoperative radiation is being planned.
- Be able to select the correct implant to recreate the natural breast form and fit to the patient's specific soft tissue limitations, capacity and desires if possible.

39.1.2 Creation of a Perfect Skin Envelope

The perfect reconstruction begins with the perfect mastectomy; an oncologically sound dissection must not compromise the viability of the skin envelope. With careful planning and technical care, it is commonly possible to preserve an optimal thickness of well-perfused skin to drape over the implant, muscle and ADM.

When sentinel lymph node biopsy or axillary lymph node dissection is indicated, it is often better to perform it through a separate axillary incision rather than risk crushing the subdermal plexus in the upper outer quadrant with retractors in order to gain exposure of the axilla.

Another point to consider regarding axillary surgery in conjunction with breast reconstruction is that of lymphatic mapping for identification of the sentinel lymph node. The agents used for mapping are either colloid-bound Tc^{99} or blue dye (isosulfan or patent blue) or both. The blue dye, even when injected into the breast parenchyma, often seeps into the skin and creates a blue discoloration which persists for months and may interfere with evaluation of flap viability in the immediate postoperative period. We prefer using the isotope alone for sentinel lymph node identification, and adding blue dye only in cases where isotope uptake is not apparent on lymphoscintigraphy, or when dual tracer is

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_39

required, such as after neoadjuvant chemotherapy, especially if lymph node was documented at the time of diagnosis.

39.1.3 Creation of a Stable Pocket (Internal Domain)

The standard complete sub-muscular pocket has largely been abandoned since the introduction of ADMs, as it often fails to produce natural ptosis and projection or create a well-defined infra-mammary fold. *Implant malposition*, capsule contracture and increasing asymmetry are common after reconstruction with a complete sub-muscular pocket. Hence there may be an increased need for additional, revisional procedures to the reconstructed side, the contralateral breast or both. Further surgeries may be avoided if a natural ptosis is achieved with the primary reconstruction, and capsule contracture is dramatically reduced using ADM in the primary surgery.

The use of enhanced lower pole support to the upper subpectoral pocket with an acellular dermal matrix (ADM) or a de-epithelialised lower pole dermal sling (LPS) in selected patients may overcome many of these challenges. The creation of a precise, stable pocket improves the likelihood of a long-term fit between tissues and implant and hence a more reliable and predictable long-term outcome. While there is good evidence that ADMs reduce the incidence of capsular contracture, no such data exists to support the use of LPS.

39.1.4 The Case for Lower Pole Support

39.1.4.1 Better Support of the Implant

By creating a partial subpectoral pocket with a lower pole dermal sling (LPS) or an acellular dermal matrix (ADM), the implant device is positioned in such a way as to cradle the lower pole of the implant between the cut end of the muscle and the IMF and offload pressure of the overlying soft tissues at the most dependent portion of the reconstructed breast. Recent advances in pre Pectoral implant/ADM positioning has gained popularityu in the last two years and has been our "go to" choice whenever possible.

39.1.4.2 Better Defined IMF

Whether the infra-mammary fold (IMF) is sutured, as with use of an ADM, or reinforced with a dermal lower pole sling (LPS), the implant is cradled above and anterior to the fixed IMF. This produces a more natural ptosis, with the IMF hidden behind the lower breast curvature.

39.1.4.3 Better Defined and Anchored LMF

The lateral contour and overall breast shape are further defined by a smooth but nevertheless fixed lateral mammary fold (LMF). Whether the LMF is created with accurate lateral suturing of the ADM, or precise sub-serratus anterior lateral pocket dissection (as in the LPS technique), a smooth, natural and more predictable lateral curvature can be achieved. This prevents lateral shift of the implant and medial cleavage depression. Suturing the ADM to the lateral confines of the implants prevents lateral implant drift and a stepped cleavage when patient lies supine. The serratus anterior muscle has not been elevated for lateral coverage and definition in any of our patients. As the implant is always narrower based than the breast footprint, it is always necessary to obliterate the lateral gutter of the breast with sutures to prevent dead space, seroma and infection.

39.1.4.4 More Natural Medial-to-Lateral 'Take-Off'

For optimal cleavage and gradual medial 'take-off', the implant must rest as medially as possible in the pocket created. Careful fixation of the ADM to the most medial divided fibres of the pectoral muscle allows the surgeon to control this area of the pocket. It is also essential to choose the correct width of the device and adequate lateral control to optimise the implant's medial position.

39.1.4.5 More Possibility of Using a Fixed Volume vs a Double Lumen Device

Even with an adequate, tension-free, healthy skin envelope, a traditional complete subpectoral pocket does not allow for direct to definitive implant in the first setting. While, permanent shaped-adjustable (combined expander/implant) devices have improved outcomes [1–3], the use of an ADM made one-stage reconstruction with a definitive fixed volume implant possible. If volume is not adequate, or there are concerns about skin envelope viability, then a tissue expander with an ADM will produce a more natural breast than a standard complete sub-muscular pocket. Gradual expansion is carried out after an initial healing and relaxation phase to allow a more predictable descent to the final natural outcome. A definitive somooth round or shaped textured device is placed in the second surgery often combined with fat grafting.

39.1.4.6 Reduced Need for Contralateral Surgery

The use of a LPS or ADM creates a more natural final breast aesthetic than a traditional complete sub-muscular reconstruction. There is therefore a greater likelihood of achieving an initial match with the contralateral breast. Producing a stable long-term outcome will also improve the chances of maintaining symmetry thus reducing the need for contralateral surgery later [4].

With lower pole support techniques, it becomes possible to offer an implant-based reconstruction to women who, in

the past, may have declined because they were reluctant to have surgery to their contralateral (healthy) breast.

39.1.4.7 Better Harmony of Tissues and Device

In the authors' experience, the use of an ADM creates a better harmony between the device and patient's tissues, thus creating a stable pocket, like a 'hand in glove'. The ADM and LPS both cover the lower two thirds of the implant, resulting in decreased compression of the soft tissues (pectoralis and lower pole skin envelope). A more stable environment is therefore created, with a better distribution of pressure by the implant. Using ADM to enhance lower pole support has led to a reduction in capsular contracture and re-operation rates.

Better perfusion of soft tissue microcirculation may help to minimise both acute radiotherapy-induced vasculitis and long-term objectionable fibrotic sequelae of radiation therapy and hence offer some protection against radiotherapy-induced complications.

39.1.5 The 'Lower Pole Sling' (LPS) or Acellular Dermal Matrix (ADM)?

39.1.5.1 Selection of the Lower Pole Sling Technique

The LPS technique is well suited to patients with larger, ptotic breasts, who desire a smaller volume and a more uplifted final breast. It is also reserved for surgeons familiar and experienced in this type of surgery. The technique involves a skin-reducing mastectomy (SRM) using a 'Wise-pattern' breast reduction design, resulting in a section of excess lower pole skin, hinged on the IMF. When this area between the legs of the wise pattern is de-epithelialised, it provides a vascularised autologous lower pole dermal support [5, 6].

A well-perfused non-traumatised skin envelope after mastectomy is essential for a good outcome in immediate reconstruction [7–9], but never is this better demonstrated than when using the LPS technique. Problems with skin envelope perfusion, ischemia and necrosis with risk of infection and need for implant removal have discouraged many surgeons from using this technique (see Sect. 1.8.1).

The likelihood of envelope necrosis or wound healing complications is increased in certain scenarios. Although not contraindicated, obese patients, patients with a history, smoking, prior breast irradiation and small vessel disease should be advised of an elevated risk of immediate postoperative complications which may lead to failure of the reconstruction. Many surgeons that have ADMs available and reimbursable in their countries have abandoned the use of LPS due to necrotic complications in the overlying skin envelope along both sides of the vertical scar in the lowert pole.

In selected patients by experienced surgeons, this technique may still be useful.

39.1.5.2 Selection of the Acellular Dermal Matrix Technique

Most patients and most surgeons managing immediate implant-based breast reconstruction in either one or two stages have been using ADM to provide lower pole support for the last ten years.

There are several different types of ADM currently available and other innovative materials already in the advanced stages of product development (Table 39.1). The choice of ADM must consider several factors: size, cost, thickness, solid or meshed, perforated, and fenestrated products.

- Other considerations are: Immune reactivity, i.e. host adoption without inflammation.
- Handling properties.
- Structural support and tensile strength.
- Collagen matrix properties (no chemical cross linking).
- Tissue incorporation and integration ability.
- Tissue regeneration ability.
- Matrix revascularisation ability.

ADMs are produced from allogenic human cadaveric/bariatric dermis or from xenogenic tissues (porcine or bovine; dermis, pericardium or intestinal submucosa). They differ in thickness from less than 1 to 3 mm, with the latter best suited for cosmetic purposes where bulking is desired or for large ventral abdominal hernias, where more strength is desired.

While human-derived ADMs typically come in various rectangular sizes, some xenogenic ADMs are provided in shapes more suited to the subsequent three-dimensional conformation a flat sheet will take when placed over an implant. Such shaping, as well as pre-made fenestrations, helps the ADM to conform to the implant profile without pleating or wrinkling. In the last three years we have chosen a 2:1 meshed Bovine derived Adm.

The senior author (MS), having used human cadaveric, porcine-derived and bovine-derived ADMs for 10 years, has a preferance of the latter in most patients.

SurgiMend, a foetal bovine-derived ADM, has the following advantages: predictable thickness, terminally sterile, 30% type 3 collagen, non-cross-linked, fine fenestrations or 2:1 mesh, and variable shapes.

Table 39.1 ADM types

ADM	Year introduced	Supplier	Location	Material	Cross-linked	Sterilized (method)	Lyophilized	Hydration/ soak time	Refrigeration required	Shelf life
Allografts										
AlloDerm	1994[a]	LifeCell	Branchburg, NJ	Human Dermis	No	No (aseptically processed)	Yes	10–40 min (2 steps)	Yes	2 years[a]
AlloMax		Davol (CR Bard) (processed by RTI Biologics)	Warwick, RI	Human Dermis	No	Yes (gamma irradiation)	No (supplied dehydrated)[b]	"Rapidly"	No	5 years
DermaMatrix	2005[a]	Synthes CMF (processed by MTF)	West Chester, PA	Human Dermis	No	No (aseptically processed, passes USP <71> for sterility)	Yes	3 min	No	3 year
DermaSpan	2011[b]	Biomet	Warsaw, IN	Human Dermis	No[b]	Yes (Gamma irradiation)	Yes	15–45	No	
FlexHD	2007[a]	Ethicon (J&J) (processed by MTF)		Human Dermis	No[b]	No (aseptically processed)[a]	No	None	No[a]	
Repriza	2010[b]	Specialty Surgical Products	Victor, MT	Human Dermis	No	Yes (irradiation)	No	None	No	2 years
Xenografts										
Permacol	2000[b]	Covidien	Norwalk, CT	Porcine Dermis	Yes (HMDI)	Yes (gamma irradiation)	No (supplied moist)	None	No	
Strattice	2008[a]	Lifecell	Branchburg, NJ	Porcine Dermis	No	Yes	No (supplied moist)	≥2 min	No	2 years[a]
SurgiMend	2006	TEI Biosciences	Boston, MA	Bovine Dermis	No	Yes (ethylene oxide)	Yes	60 s	No	3 years
Veritas	2001	Synovis	St. Paul, MN	Bovine Pericardium	No, Propylene oxide capped amine technology	Yes (irradiation)	No	None	No	2 years[a]
XenMatrix	2006	Davol (CR Bard)	Warwick, RI	Porcine Dermis	No	Yes	No	None	No	

Information from Product Sheets except as noted

[a]Maxwell, G.P. and A. Gabriel, Bioprosthetic materials for plastic surgery of the breast, in Surgery of the Breast: Principles and Art, S.L. Spear, et al., Editors. 2010, Lippincott Williams & Wilkins. p. 1488–94

[b]Moyer, H. R. and A. Losken, The science behind tissue biologics. Plastic Surgery News

39.1.6 Technique and Surgical Considerations

39.1.6.1 The Perfect Skin-Sparing Mastectomy

The perfect breast reconstruction depends much upon the perfect mastectomy. Although the planning, decision-making and technical execution of the reconstructive component are important, many of the short- and long-term complications from immediate reconstruction are mostly related to a suboptimal mastectomy, with irregular, traumatised and/or ischaemic skin flaps.

Who Should Perform the Mastectomy?

It is not important whether a general or plastic surgeon performs the mastectomy, provided they have the appropriate training and skills to find and then stay within the mastectomy plane and handle the skin flaps delicately while assuring that all breast tissue (in cases of risk-reducing mastectomy) and all the tumour (in cases of breast cancer) are removed.

Where Is the Mastectomy Plane?

The mastectomy plane lies between the subcutaneous fat and the superficial fascia of the breast, crossed by the ligaments of Cooper that travel through the subcutaneous fat to anchor in the dermis. There is a conventional view that the superficial fascial plane is not reliably present and thus the plane may not always be identifiable. This appears to be based on an often-quoted small observational study [10] of breast reduction specimens. There is however a compelling embryological explanation for the constant presence of this fascia, even if patient factors (extremes of BMI) or surgical factors (poor or closed techniques) mean that it is not always visualised. The superficial fascia is formed as a condensation from the sixth embryological week, when the primary ectodermal breast bud invaginates into the underlying mesochyme [11].

Regardless of technique and instruments used, achieving the correct dissection plane is essential for optimal oncological safety and viability of the skin envelope. A 'thin' or traumatised skin flap is more likely to have compromised perfusion. A 'thick' skin flap is more likely to carry residual breast tissue with an unnecessary increased risk of future disease or local recurrence. There are several well-designed studies that demonstrate residual breast tissue left on mastectomy skin flaps in up to 50% of biopsies looked at [12–14]. Without evidence of intact superficial fascia on the mastectomy specimens removed, such studies should be interpreted with caution.

It should be remembered that the subcutaneous fat thickness is proportionate to a patients BMI and body habitus and is therefore 'patient-dependent'. Mastectomy skin flap is however surgeon-dependent. It should be possible to aim for complete removal of the breast tissue, and breast surgeons should continue to strive for the cleanest possible dissection in the plane, i.e. over the fascia, with division of ligaments of Cooper as close to the subcutaneous fat as possible.

Mammography in general and high-definition breast tomosynthesis in particular may help preoperatively identify the thickness of the subcutaneous fat. Clearly subcutaneous fat thickness varies from one patient to another and with it the depth of the subdermal plexus (Malliniac 1943). Leaving paper-thin mastectomy flaps in all patients therefore makes no sense.

What Is the Best Technique for Performing Skin-Sparing Mastectomy?

Planning the mastectomy must take into account the three-dimensional shape of the envelope, the likely tension on the skin and the access that the incision will give, for both the least traumatic removal of the gland and the safest, most accurate insertion of the implant.

Once the optimal amount of skin (± nipple) for the best envelope and reconstruction has been decided upon, the joint surgical objectives are:

- To optimise oncological safety—removing all breast tissue while respecting the mastectomy plane and envelope landmarks.
- To optimise envelope viability—not compromising the perfusion of the skin envelope.

There is no agreement, or need there be, of a single best technique for carrying out skin-sparing mastectomy. Some surgeons find infiltration helpful to develop the plane (with or without adrenaline). Alternatively, a dry technique with direct visualisation of the fascia and ligaments may be preferred. Scalpel, scissors, diathermy electro-dissection, ultrasound, laser and argon all have their advocates. In selecting the technique for mastectomy, every surgeon must decide how best to reconcile the compromise between ease of dissection, speed, haemostasis and the development of complications such as seroma, haematoma or skin necrosis. In general, sharp instruments (knives and sharp-tipped scissors) should be kept at a distance from the subdermal plexus as they may irreparably injure it.

Finally, the appropriate selection of technique and instrument to use for a specific mastectomy should be based not on a surgeon's routine preference but after consideration of that patient's individual soft tissue characteristics and risk factors for skin necrosis (obesity, smoking status, previous radiation, breast size, etc.).

39.1.6.2 Classification of Skin-Sparing Mastectomy with Use of ADM Technique (Algorithm 1)

Skin-Sparing Mastectomy (SSM) in the Non-ptotic Breast

When the nipple is to be sacrificed, our preference is for a short ellipse including the nipple with an oblique orientation. Dimensions and exact orientation of the ellipse should take into account the desired final three-dimensional shape and volume of the breast. The incision must be large enough to allow safe access for mastectomy and accurate insetting of the ADM. Excess skin should be excised with caution and after consideration of the characteristics of the skin envelope (elasticity, compliance, possible perfusion problems) as well as how to achieve a comfortable fit between implant domain and skin envelope. It is always possible to modify and excise further, if there is large skin excess when the envelope is re-draped over the newly created mound. The oblique scar created is usually not conspicuous after nipple-areolar reconstruction (Fig. 39.1a–e).

Skin-Reducing Mastectomy (SRM) in the Large or Ptotic Breast

If an ADM is to be used rather than a lower pole dermal sling, then our preference is for the trans-vertical approach which combines two vectored skin excisions—the larger horizontal one is placed lateral or oblique to the nipple areola complex (NAC), and the shorter vertical elliptical excision overlaps the former in the NAC area. The resultant skin envelope has a more pleasing final shape and a better positioned scar than if a longer wider oblique or transverse ellipse is used. The trans-vertical approach avoids the potential ischaemia-related wound healing problems encountered by some surgeons when using the Wise-pattern skin envelope (Figs. 39.2a–c and 39.3a–d).

Nipple-Sparing Mastectomy (NSM) in the Small- to Moderate-Sized Breast

Traditional periareolar and circumareolar incisions have been shown in the best centres to have an increased risk of nipple-areolar necrosis [15, 16]. Although it is possible to use an oblique upper outer quadrant incision, our preference is for the use of an infra-mammary incision whenever possible. While this is more technically challenging, there is even less of a risk to nipple viability. The resultant access to the lower pole is ideal for the accurate insertion of the ADM and affords precise control and fixation of the infra-mammary fold.

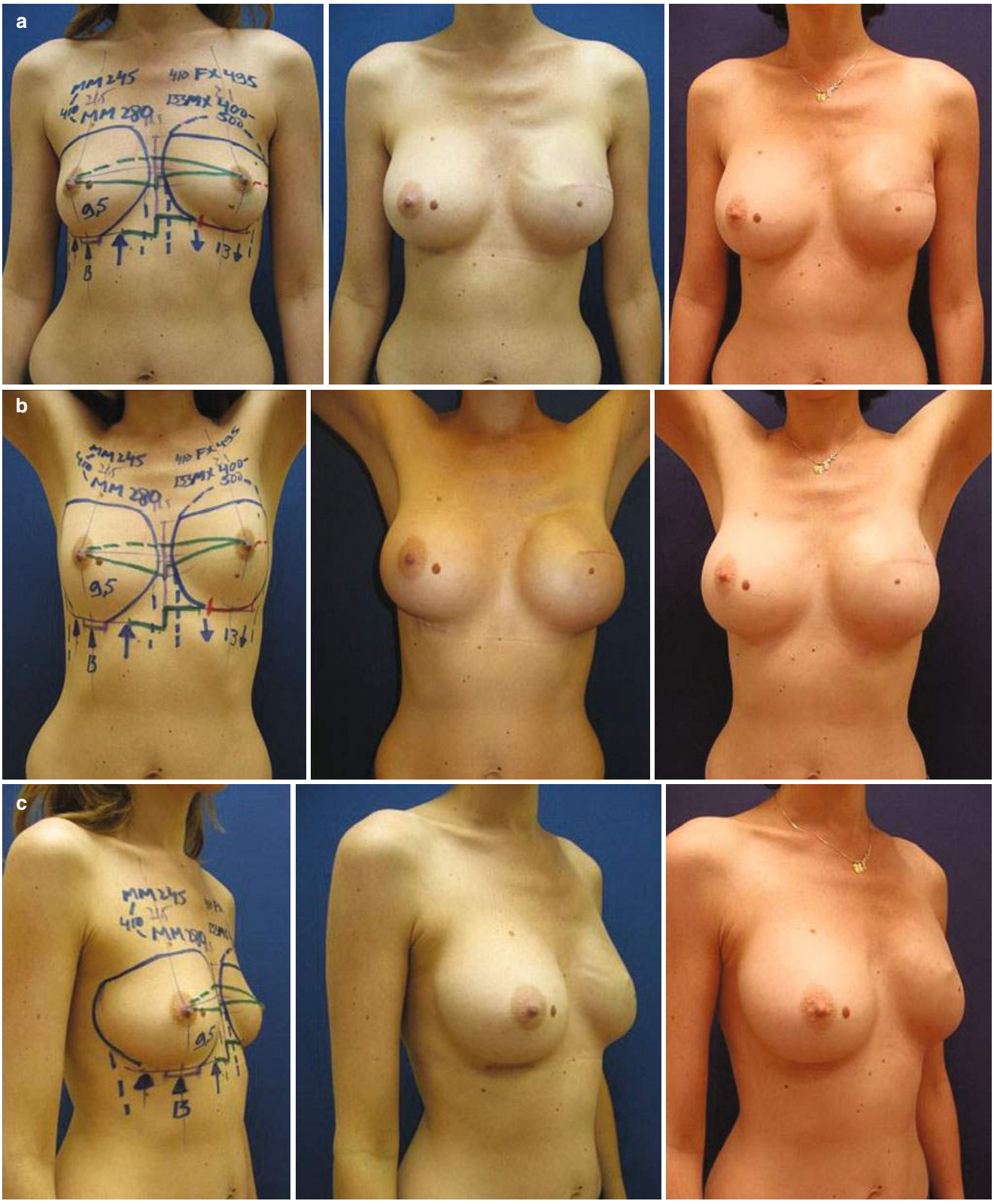

Fig. 39.1 (**a**–**e**) Left skin-sparing mastectomy (270 g) with short elliptical oblique incision and two-stage reconstruction with expander and ADM (Natrelle Style 133 MX500, SurgiMend 10 cm × 15 cm) and then definitive implant (Natrelle Style 410 MX550). Contralateral right dual-plane augmentation at first stage (Natrelle Style 410 MM280). Pre- and postoperative views demonstrating intermediate and final outcome following refinement with fat grafting (in section "**Who** Should Perform the Mastectomy?")

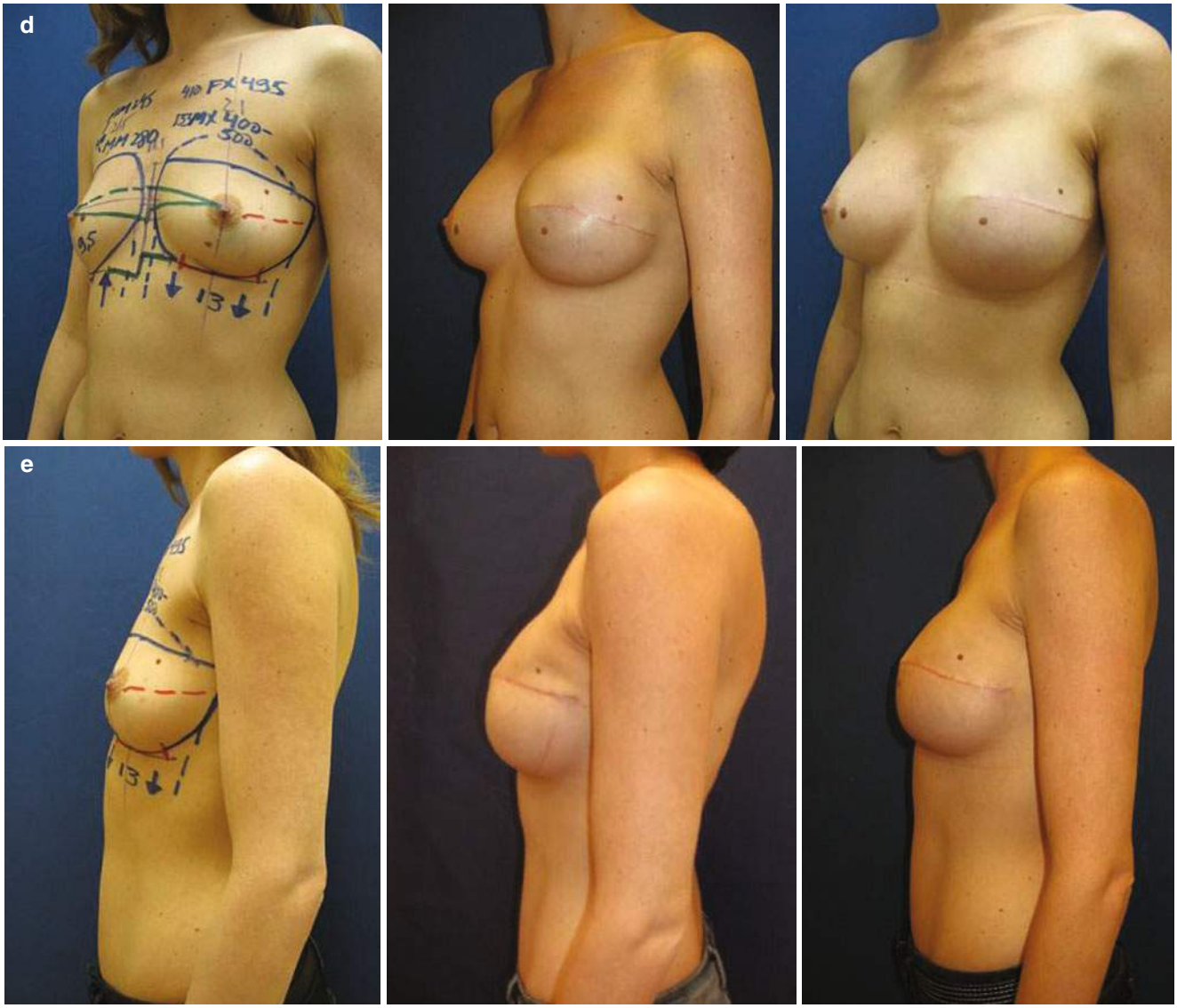

Fig. 39.1 (continued)

It also produces a very favourable and 'hidden' scar (Figs. 39.4a–f and 39.5a–c).

As mentioned earlier, the technique and instrumentation chosen for mastectomy through the IMF incision are less important than the surgeon's ability to produce a healthy, non-traumatised skin envelope and a well-perfused nipple. Where access is difficult, the use of a headlight and delicate use of retractors are essential. Great care must be taken by the surgeon and assistant to avoid mechanical crush to the lower pole skin. An endoscope may be useful in the larger breast (video-assisted mastectomy) for direct visualisation of the medial, superior and lateral extent of the envelope, thus minimising retraction injury or damage to the important skin perforator vessels.

Although the risk of occult nipple involvement or future nipple disease is acceptably low, provided predictive criteria for further nipple disease are followed [17, 18], we would still recommend a sub-areolar ductal biopsy in all cases of nipple preservation with intraoperative frozen section. This requires close collaboration with an experienced histopathologist, with a low false-negative rate for detecting occult disease on frozen section. Others may prefer to perform preoperative MRI, staged sub-areolar duct excision or sub-areolar vacuum-assisted biopsy, prior to making a decision about the safety of nipple preservation. If the frozen section (or subsequent pathology report) demonstrates occult sub-areolar disease, then the nipple must be excised intra-operatively (or at a second procedure).

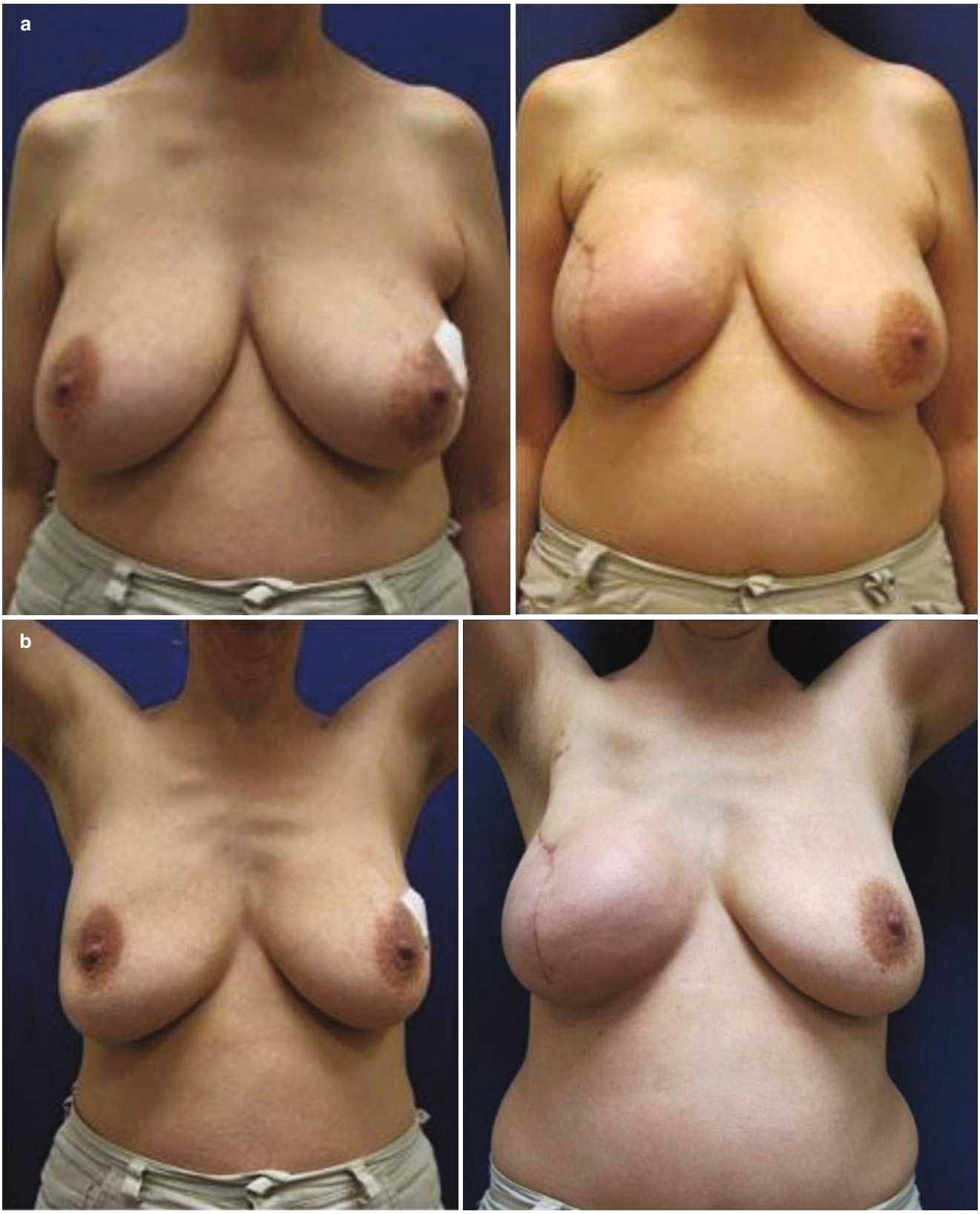

Fig. 39.2 (**a**–**c**) Skin-reducing mastectomy with trans-vertical incision and immediate implant and ADM reconstruction (Natrelle Style 410 FX615, SurgiMend 10 cm × 20 cm). Pre- and postoperative views: a 42-year-old with multifocal carcinoma right breast (872 g) (in section "Skin-Reducing Mastectomy (SRM) in the Large or Ptotic Breast")

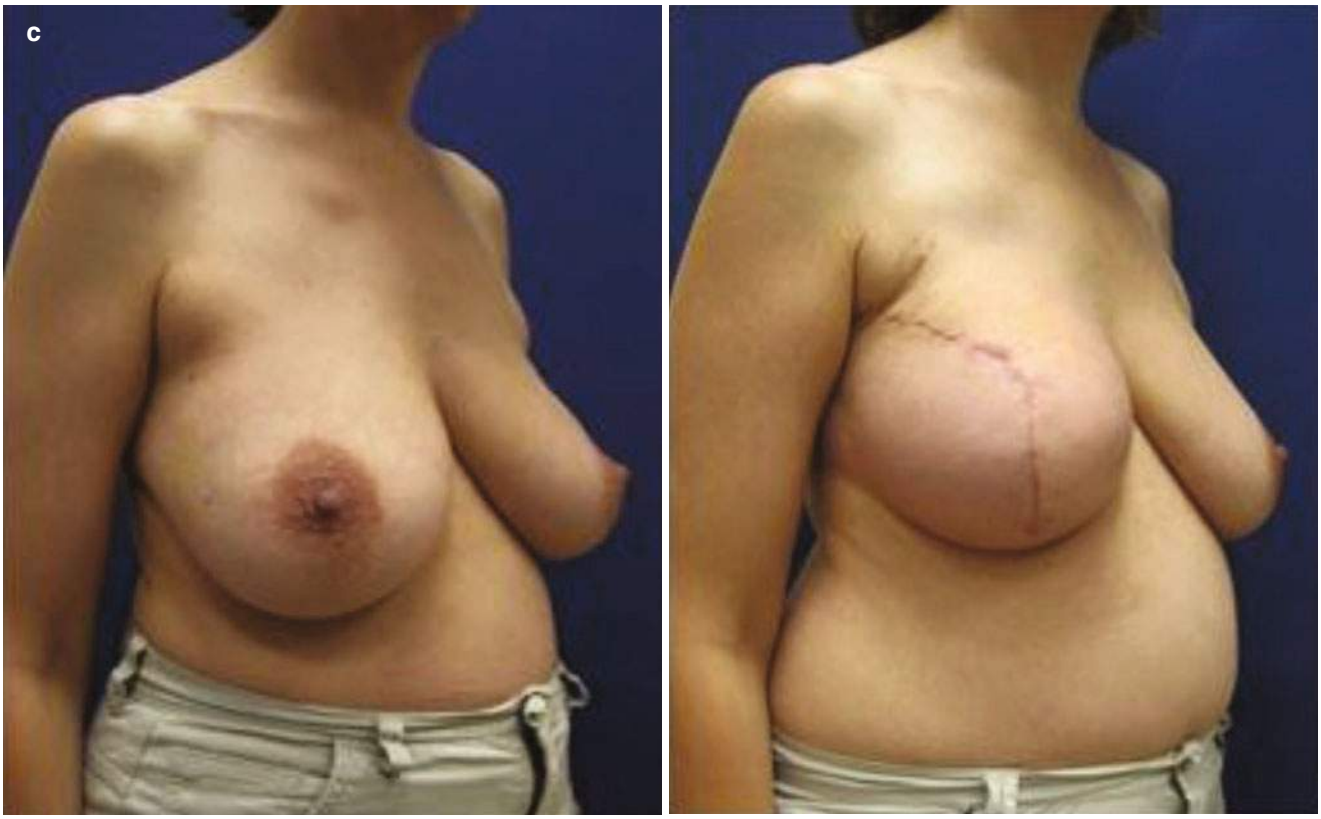

Fig. 39.2 (continued)

Previous concerns regarding the oncological safety of nipple preservation in breast cancer patients appear to have been overcautious, as the nipple is only rarely the site of tumour recurrence.

39.1.6.3 Classification of Skin-Reducing Mastectomy with the LPS Technique (Algorithm 1)

Skin-Reducing Mastectomy (SRM) in the Large and Ptotic Breast

A 'Wise-pattern' skin excision provides both excellent access for mastectomy and creates the surplus lower pole skin necessary to create the de-epithelialised LPS and a natural ptosis. Great care must be taken to avoid tension on closure caused by excising the skin too widely, particularly at the 'T-junction'. This can be prevented by intentionally leaving the vertical limbs 1–2 cm longer than for a standard Wise-pattern marking or wedging a skin dart into the T-junction. The vertical scar is subsequently concertinaed to below the height of the maximum projection of the breast mound (after the definitive implant volume is in place or the maximum temporary implant volume has been inserted into the expander).

The LPS is fixed internally to reinforce the infra-mammary fold with interrupted absorbable sutures. This stops the IMF from drifting down under the weight of the implant, which then will rest in the dermal sling in front of the fixed IMF. A stable IMF facilitates an evolving but predictable natural ptosis (Figs. 39.6a–g and 39.7a–c).

When using the LPS, it should be remembered that unlike the relatively non-distensible ADM, the autologous LPS is stretchable. Even with a fixed IMF, one should avoid the use of excessively large implants, which may lead to 'over-stretching' of the lower pole and a 'bottomed-out' appearance over time.

Nipple-Sparing Mastectomy (NSM) in the Ptotic Breast

A 'Wise-pattern' skin reduction may be carried out with preservation of the nipple-areolar complex on a superior or superior-medial dermal pedicle. The LPS may then be created and inset in the standard method. Nipple viability is increasingly at risk, the larger the skin envelope and the greater the elevation required to achieve its new position on the reconstructed breast mound. If more than 3–4 cm of elevation is required and the patient wishes to keep her nipple, then our preference would be for a free transplantation of the

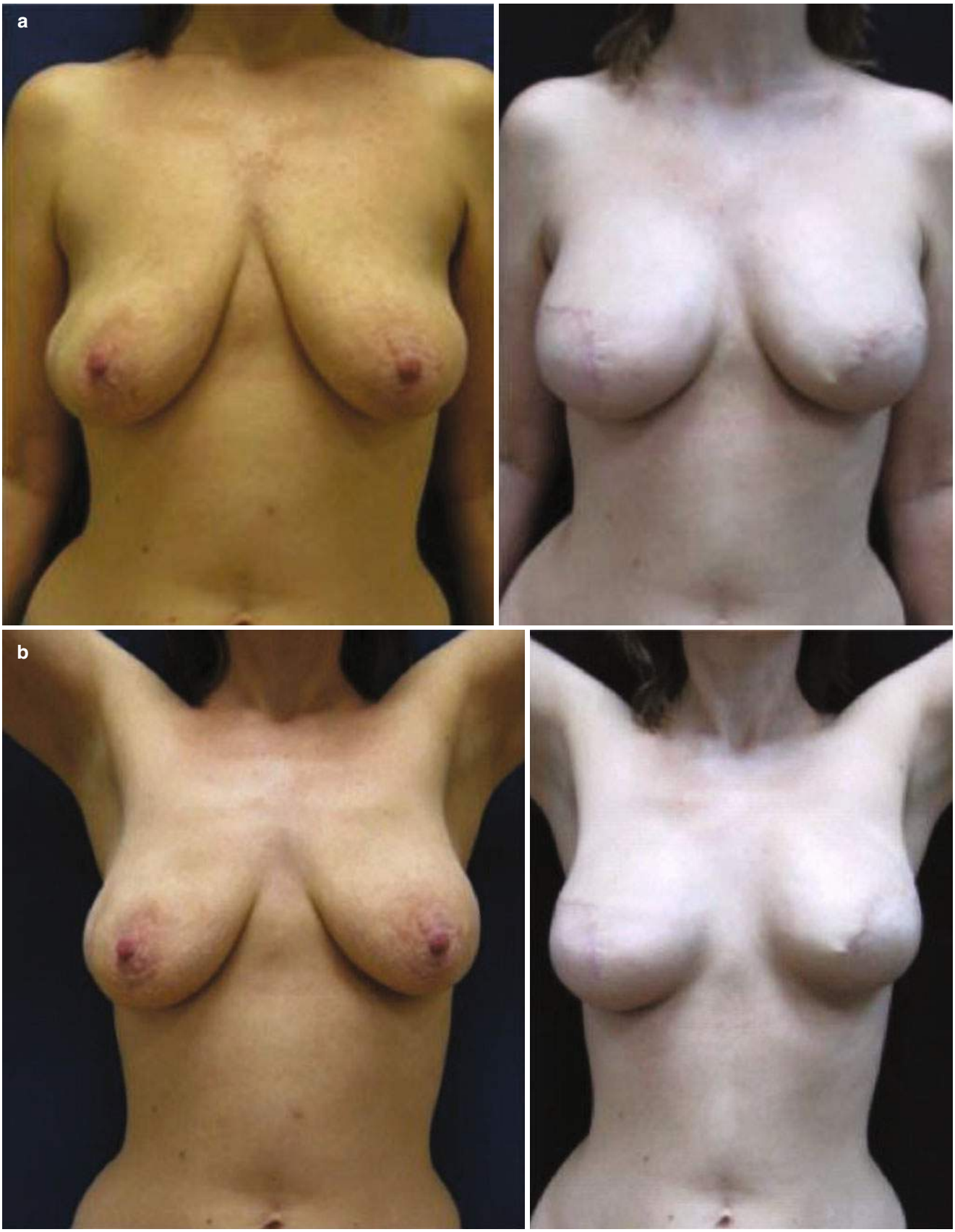

Fig. 39.3 (**a**–**d**) Bilateral skin-reducing mastectomies with transvertical incisions and immediate implant and ADM reconstructions (Natrelle Style 410 FF335, SurgiMend 10 cm × 15 cm). Pre- and postoperative views: a 47-year-old, BRCA1 carrier (right breast 295 g, left breast 315 g) (in section "Skin-Reducing Mastectomy (SRM) in the Large or Ptotic Breast")

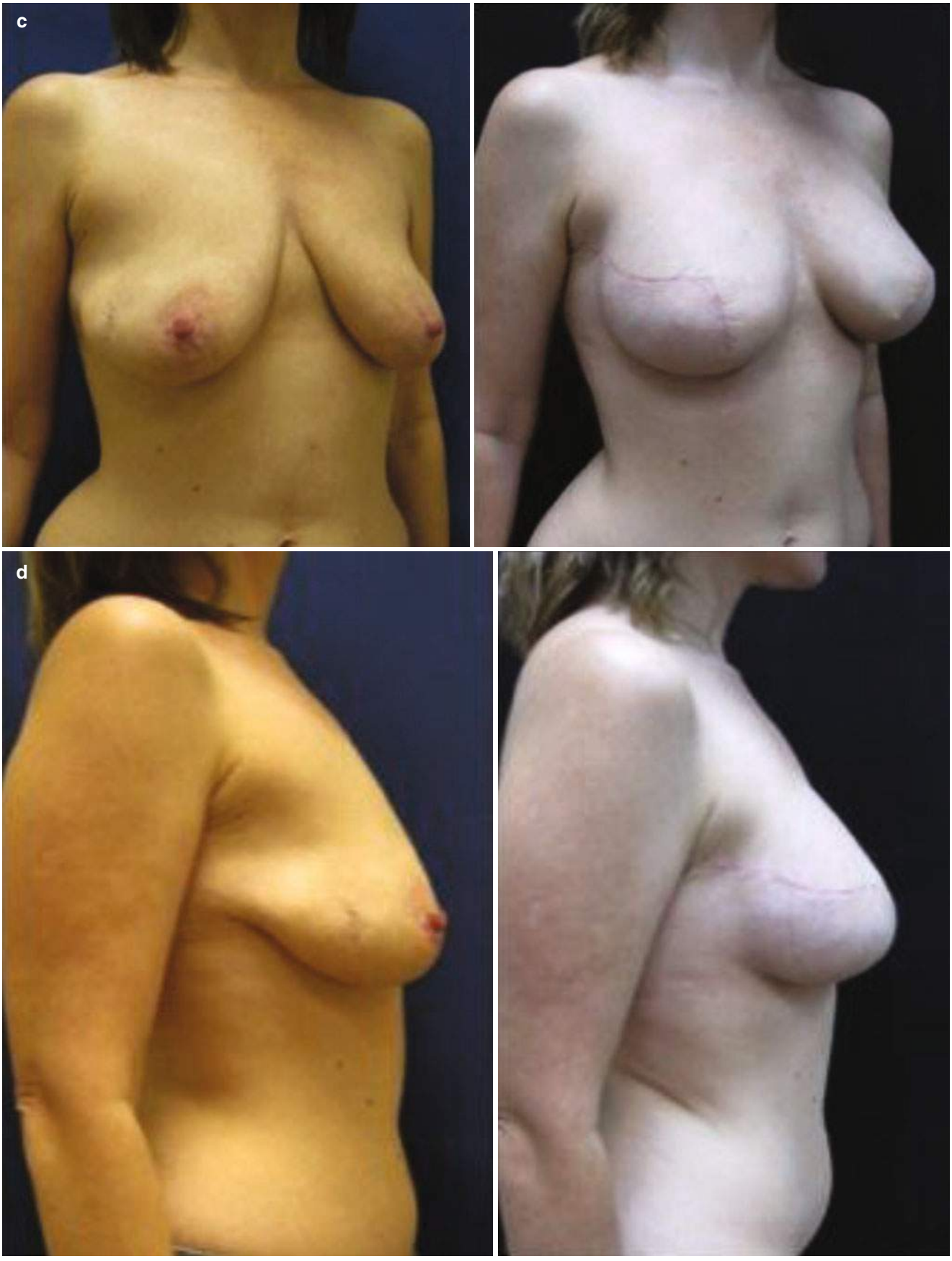

Fig. 39.3 (continued)

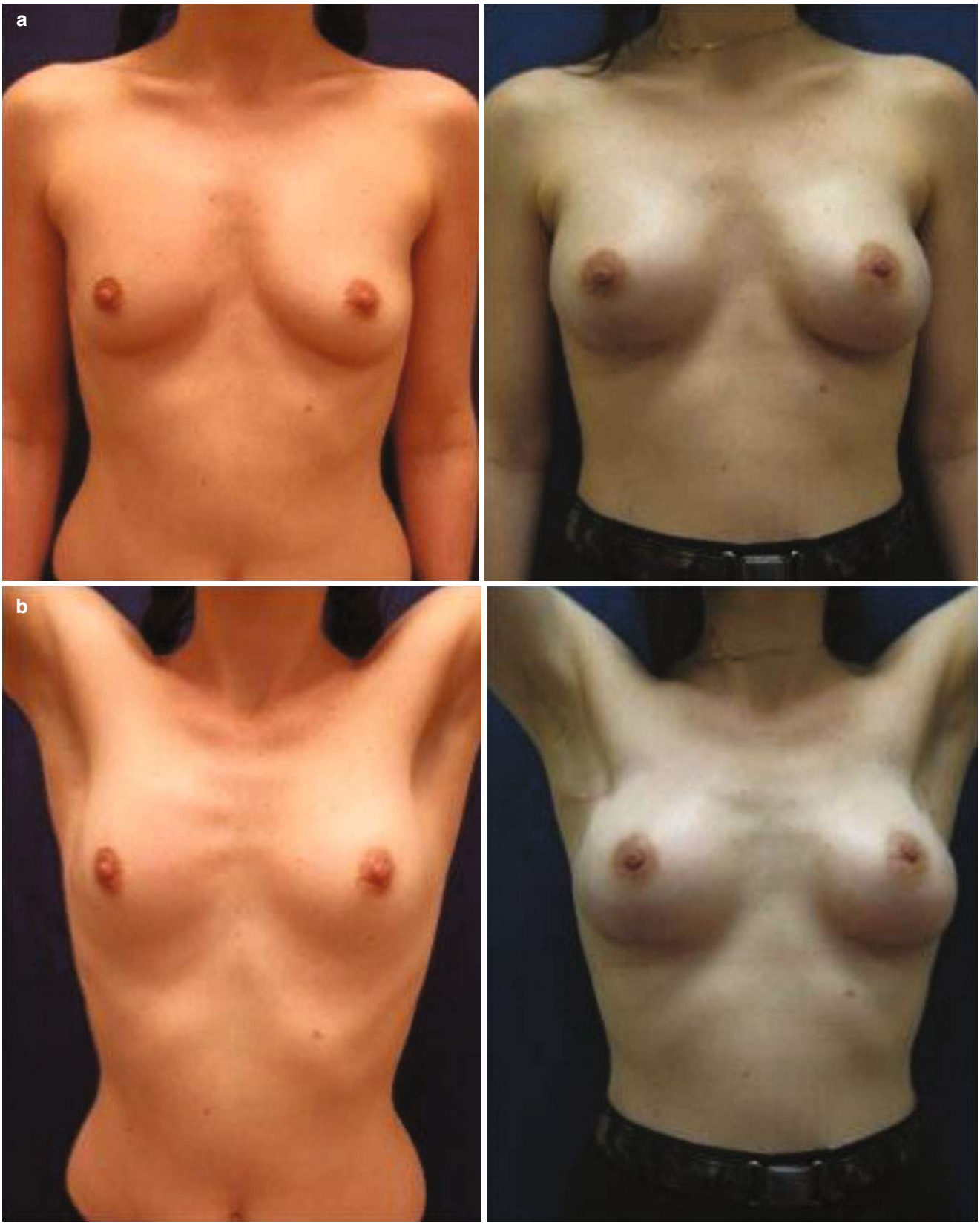

Fig. 39.4 (**a**–**f**) Bilateral nipple-sparing mastectomy with inframammary incision and immediate implant and ADM reconstructions (Natrelle Style 410 MX325, SurgiMend 10 cm × 15 cm). Pre- and postoperative views: a 38-year-old, BRCA1 gene carrier with carcinoma right breast (120 g) and risk-reducing mastectomy left breast (133 g) (in section "Nipple-Sparing Mastectomy (NSM) in the Small- to Moderate-Sized Breast")

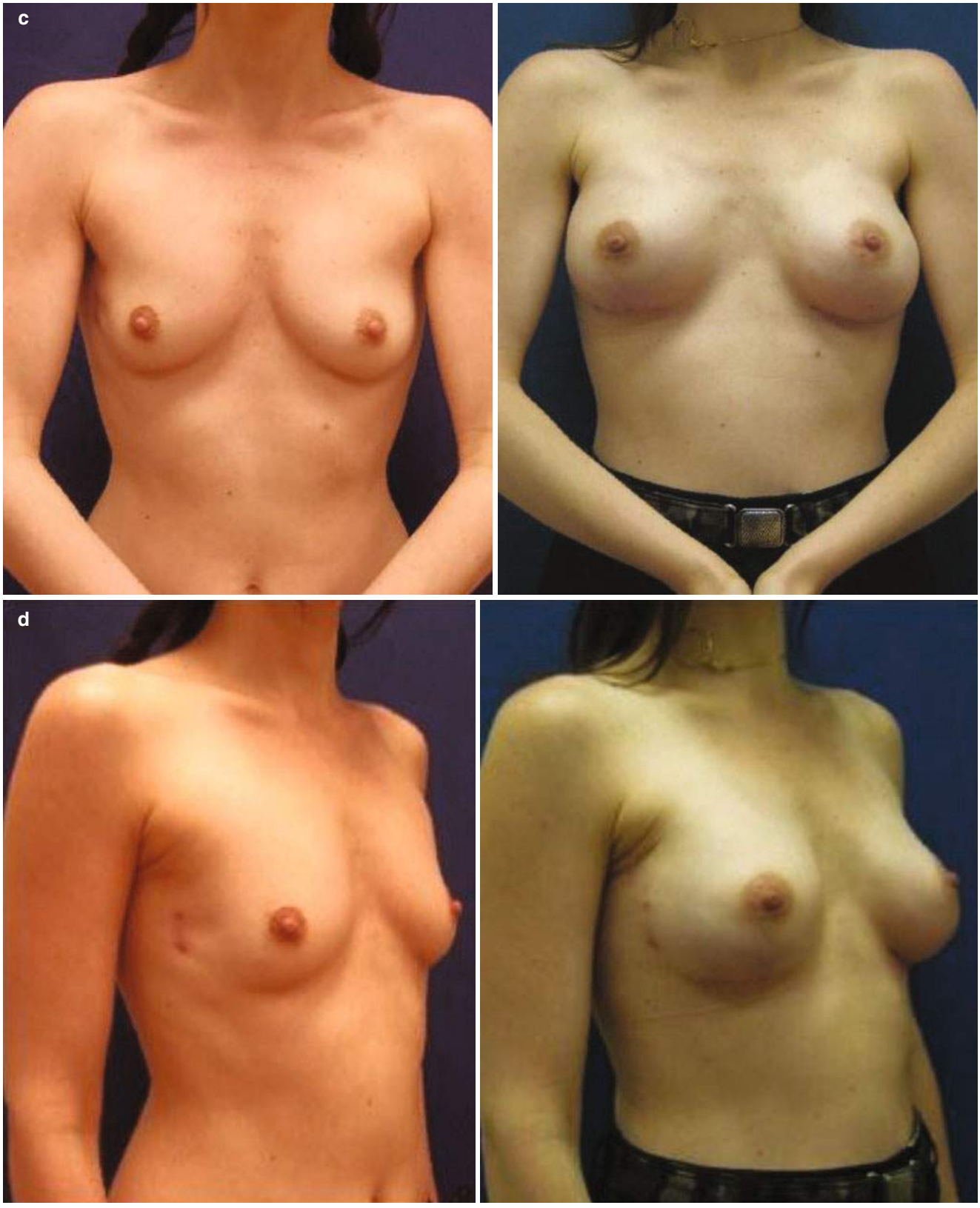

Fig. 39.4 (continued)

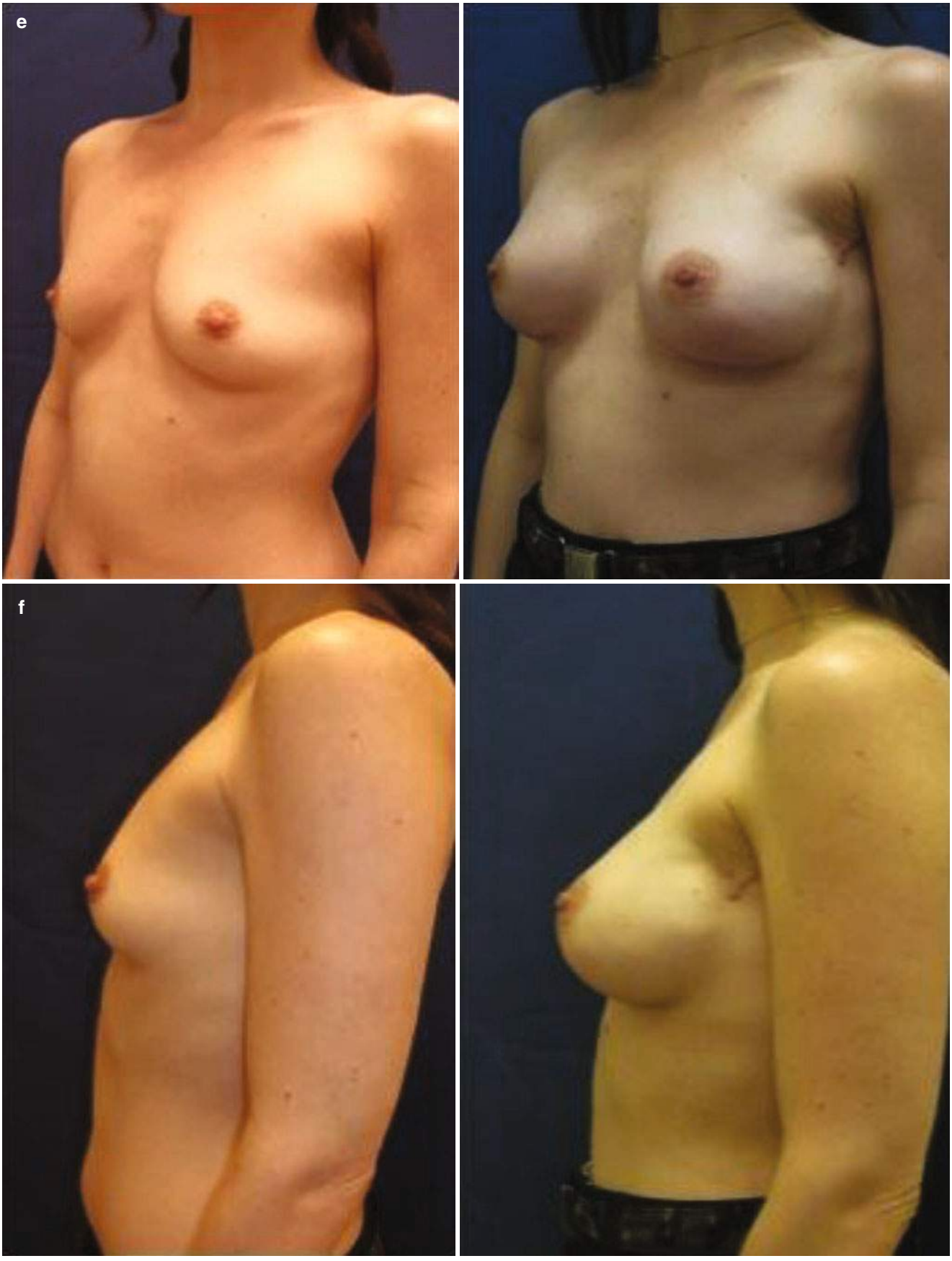

Fig. 39.4 (continued)

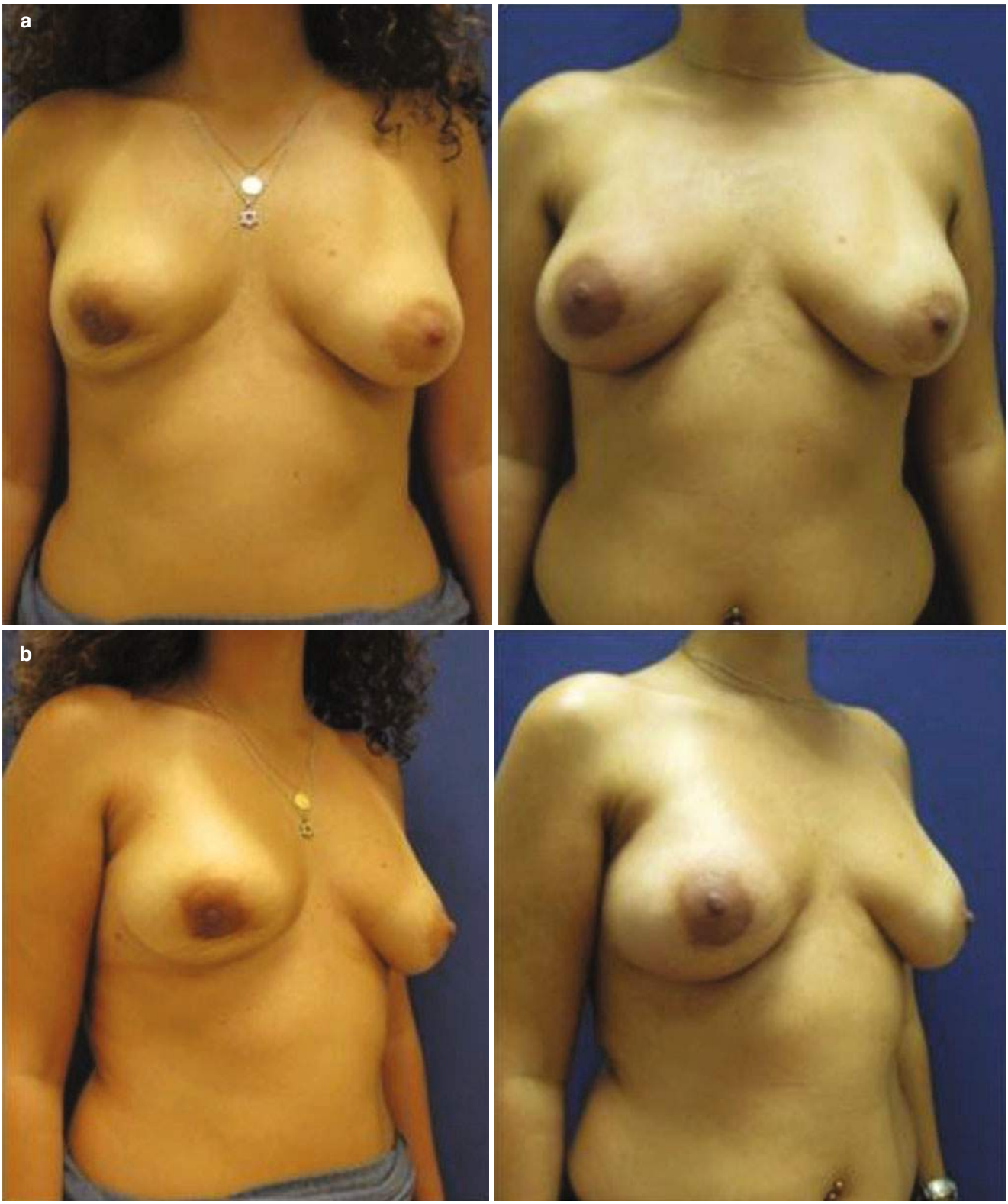

Fig. 39.5 (**a**–**c**) Nipple-sparing mastectomy with infra-mammary incisions and immediate implant and ADM reconstructions (Natrelle Style 410 FX410, SurgiMend 10 cm × 15 cm). Pre- and postoperative views: a 35-year-old requiring completion right mastectomy (350 g) after incomplete excision of carcinoma (wide excision 75 g) (in section "Nipple-Sparing Mastectomy (NSM) in the Small- to Moderate-Sized Breast")

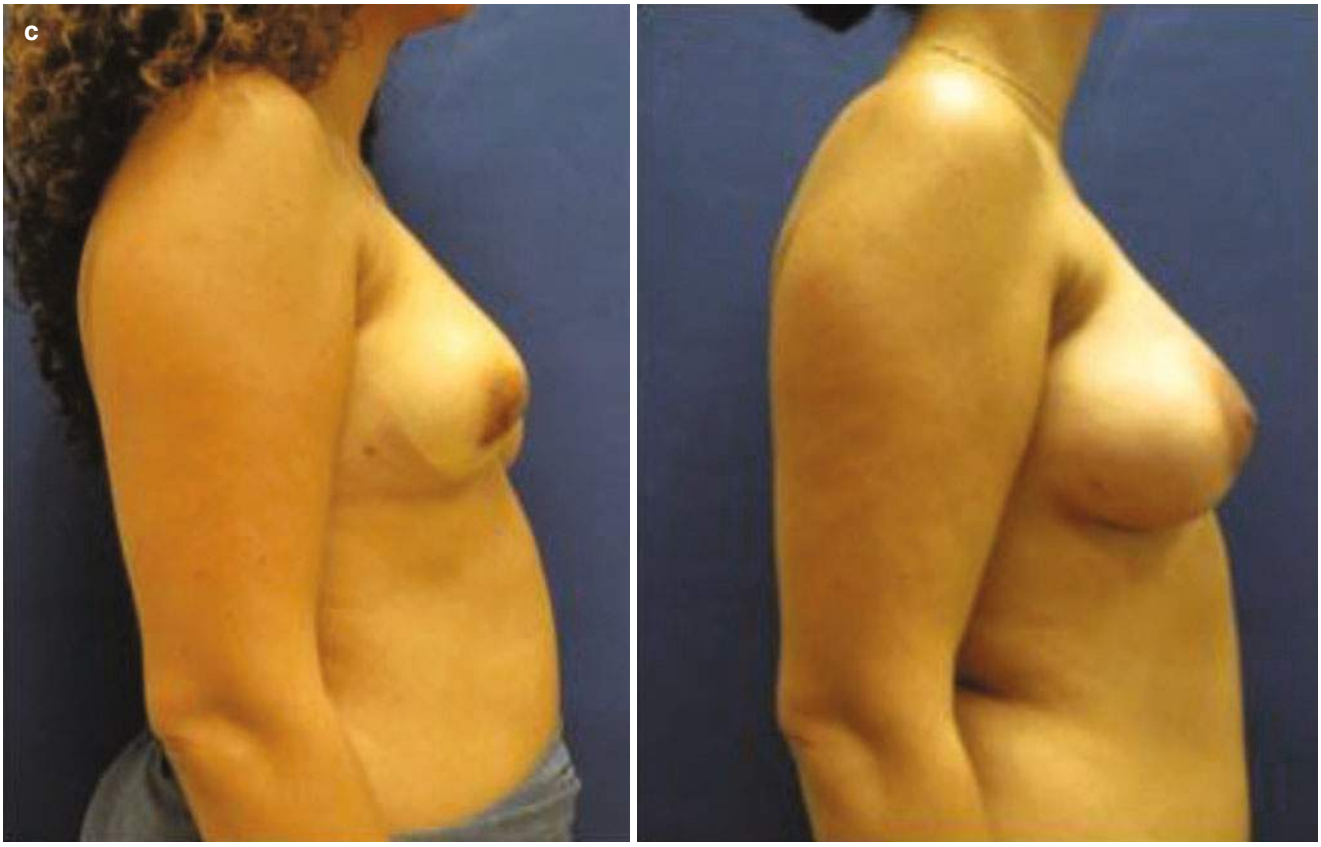

Fig. 39.5 (continued)

nipple-areolar complex as a full thickness graft onto a de-epithelialised recipient areolar bed.

39.1.7 Implant Selection

39.1.7.1 Definitive Implant vs Tissue Expander

In deciding whether to use a fixed volume or variable volume adjustable implant, the surgeon must consider both the quality and the quantity of the skin envelope. These may restrict the initial volume of the device to be implanted.

Skin Envelope Tension/Viability Restricting Implant Volume

There are several reasons why the skin envelope may still prevent the use of a definitive final fixed volume implant:

- Previously irradiated skin (e.g. following lumpectomy and irradiation) may not initially accommodate the intended implant volume.
- If for oncological safety more skin needs to be excised at mastectomy than planned like in SRM.
- The perfusion and hence viability of the skin envelope are uncertain after the mastectomy. This can be assessed more accurately using intraoperative full-field laser Doppler imaging technology (Sect. 1.8.1) or SPY technology.

Pocket Characteristics Restricting Implant Volume

Intra-operatively the composite pocket of pectoralis and dermal support may also be found to prevent use of the final planned volume. Reasons for this may or may not be predictable preoperatively:

- Previously irradiated chest wall—progressive atrophic change and fibrosis may lead to a reduced compliance of the pectoralis major muscle.
- Poor quality and adequacy of muscle.
- Traumatised or resected pectoralis following the skin-sparing mastectomy.

The use of a variable volume device can partially overcome some of these problems. With the expander implant devices currently available (e.g. Natrelle Style 150

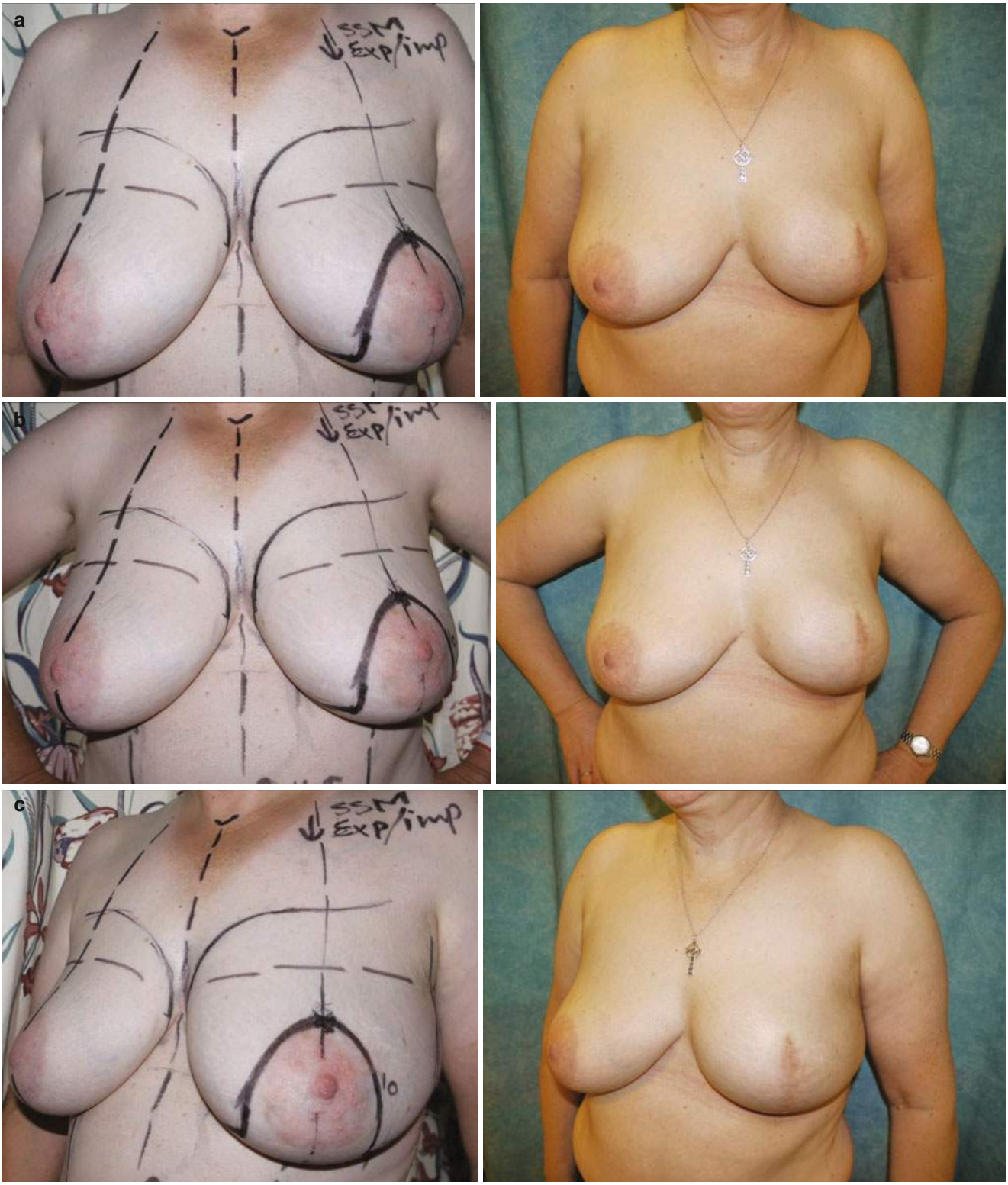

Fig. 39.6 (**a**–**g**) Sequential bilateral skin-reducing mastectomies with Wise-pattern incision and lower pole sling technique with adjustable volume expander/implants (Natrelle Style 150s–SH520). Pre- and postoperative views: a 51-year-old after left mastectomy (630 g) for multifocal high-grade DCIS followed by right mastectomy (675 g) for risk reduction 1 year later. Demonstrating reliability and reproducibility of outcomes (in section "Skin Reducing Mastectomy (SRM) in the Large and Ptotic Breast")

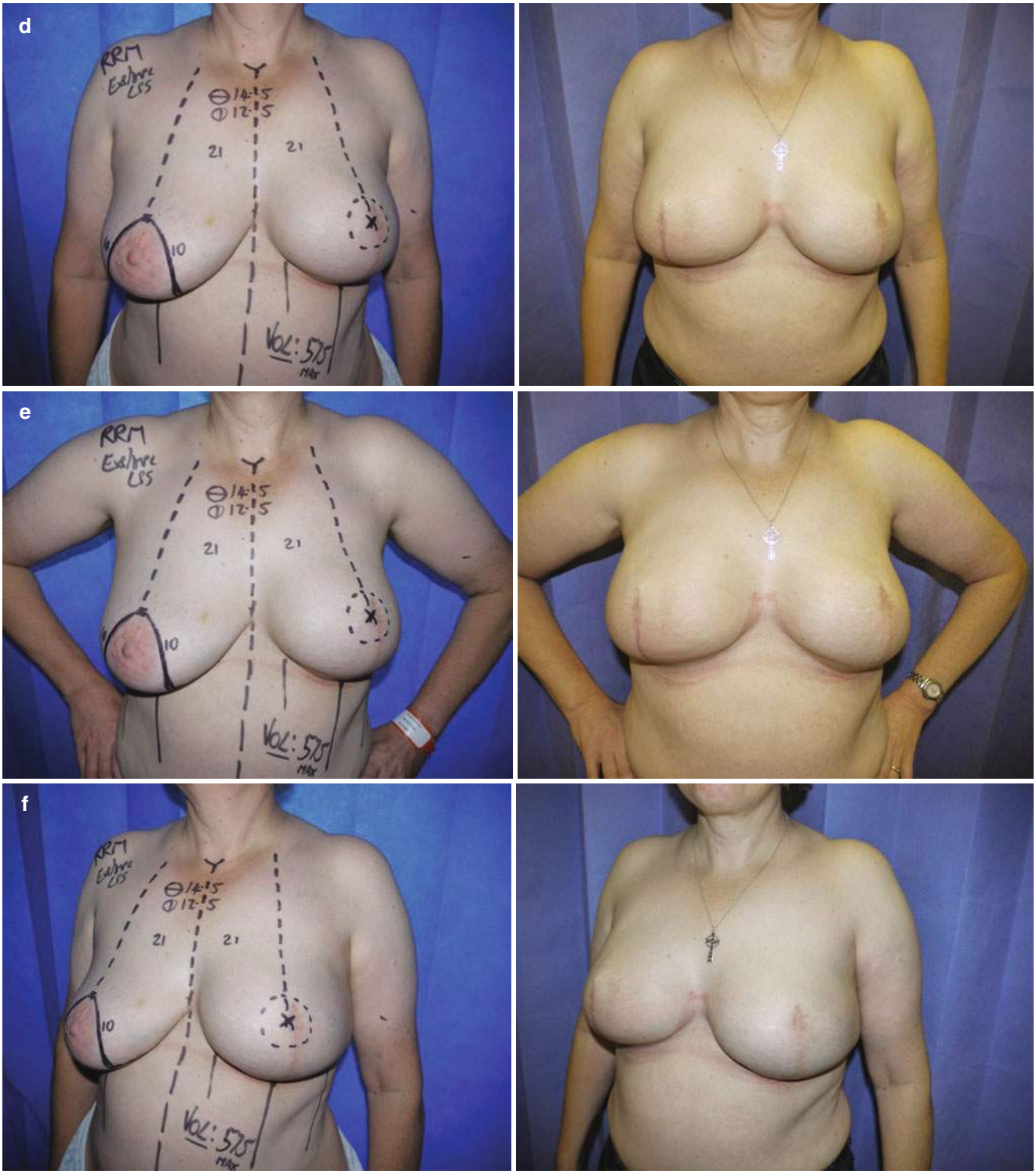

Fig. 39.6 (continued)

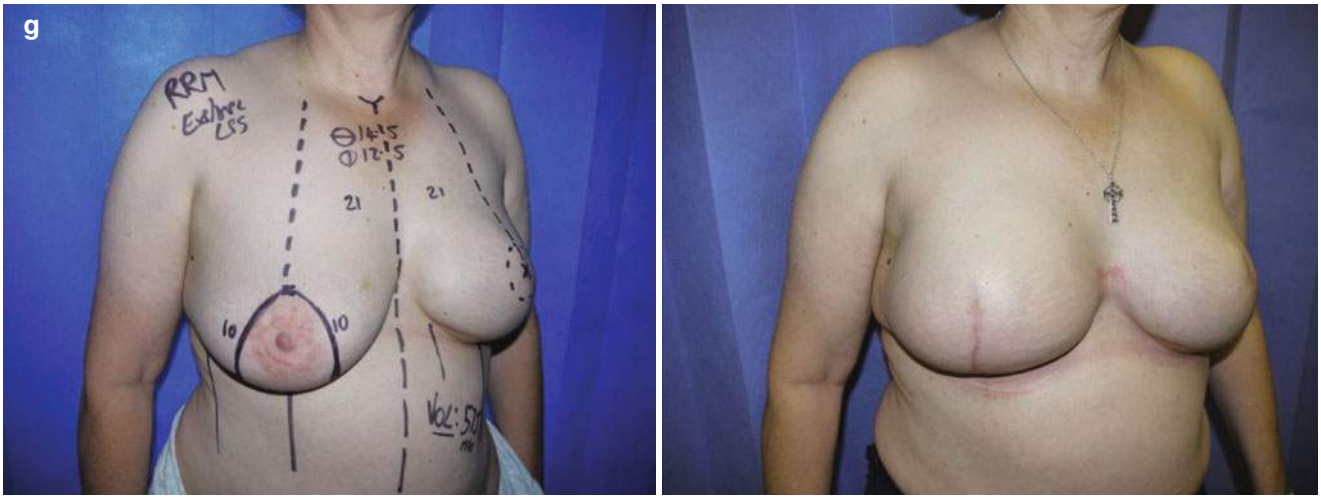

Fig. 39.6 (continued)

(Allergan), Becker 35 (Mentor)), it may still be possible to offer a one-stage solution. Gradual expansion may then take place after the initial relaxation and healing phase, as an outpatient procedure over the subsequent weeks. The long-term disadvantage of double-lumen, adjustable volume implants is that they feel less natural long term, have more visible wrinkles than fixed volume form stable implants and tend to fail more. In cases where it is deemed safer to have a minimal initial volume in the pocket (or to have the ability to completely remove any tension from the soft tissues if skin envelope viability is threatened), then a shaped tissue expander, such as the Natrelle Style 133 (Allergan), may be used. Second-stage exchange to a permanent fixed volume device would take place only once final expansion and desired volume are settled upon.

39.1.7.2 Implant Selection/Dimension Assessment

Base Width

The defining dimension for a natural breast shape is the base width. The desired breast width may be assessed preoperatively in discussions with the patient and with demonstration of likely positions of cleavage medially and breast contour laterally. Allowing for overlying soft tissue, the estimated base width of the implantable device is approximately 1.0–1.5 cm (the average soft tissue pinch thickness) less than the desired breast width.

Intra-operatively, the final base width of the device can be measured more accurately by direct measurement of the pocket created. The authors prefer to have a range of base widths available above and below the predicted preoperative implant width.

Implant Height

With the available matrices of shaped anatomical or round devices, there is a choice of available implant heights for any given base width. The implant height selected must take into account the preoperative patient-specific chest wall characteristics. A greater height implant than the natural breast base height may prevent a 'step-off' deformity in situations where excess chest wall subcutaneous tissue has been excised beyond the visible upper pole of the breast due to an overenthusiastic mastectomy. The final height of the pocket can be re-assessed intra-operatively before the final implant selection is made. In the last three years and whenever possible a round smooth implant has been chosed for bilateral reconstruction.

39.1.8 ADM-Based Lower Pole Support: Technical Points (Fig. 39.8)

39.1.8.1 ADM Insertion

After mastectomy, the pectoralis major is divided from its origin inferiorly and medially (3 or 9 o'clock position, respectively). Posterior-laterally the pectoralis major is freed from underlying pectoralis minor.

Depending on the choice of ADM, it may need to be cut to an appropriate curved shape. Our preference is for a semi-oval sheet of SurgiMend, a terminally sterilised bovine-derived ADM, which is fenestrated and measures 15 × 10 cm. It is large enough to provide lower pole support to most commonly used implant base widths. Larger or smaller sizes are used for different size implants and expanders.

A common practice is soaking the ADM in a triple antibiotic solution as an added measure against microbial contami-

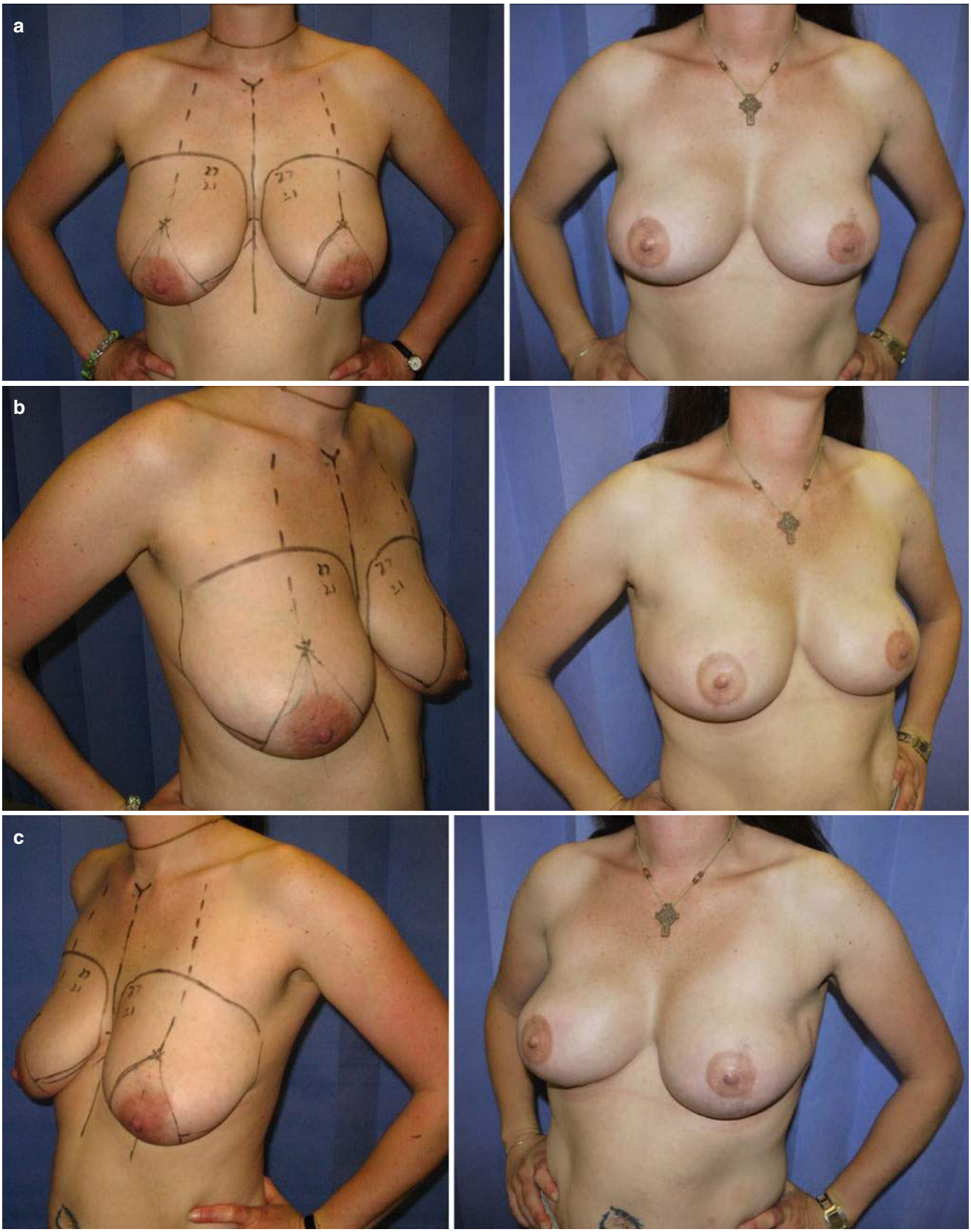

Fig. 39.7 (**a**–**c**) Bilateral skin-reducing mastectomies with Wise-pattern incisions and lower pole sling technique with adjustable volume expander/implants (Natrelle Style 150s–SH520). Pre- and postoperative views: a 34-year-old BRCA 2 gene carrier undergoing bilateral risk-reducing mastectomies (right breast 610 g and left breast 595 g) (in section "Skin Reducing Mastectomy (SRM) in the Large and Ptotic Breast")

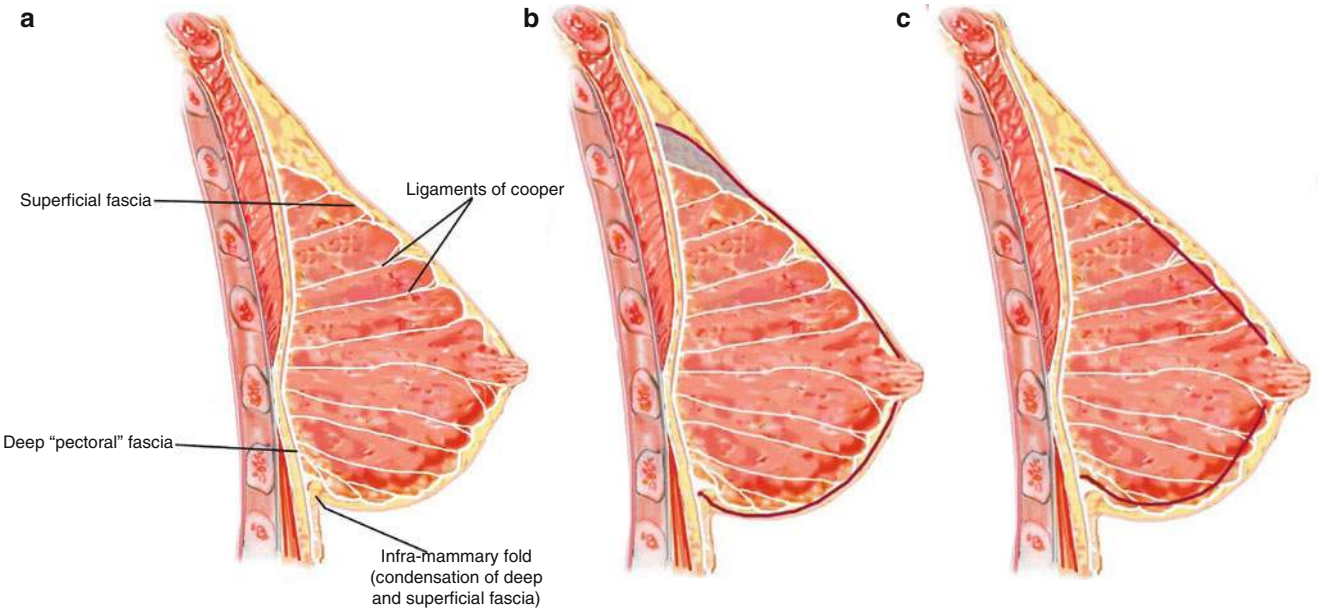

Fig. 39.8 (**a**–**d**) Sagittal views of the breast demonstrating: (**a**) Fascial planes and ligamentous anatomy. (**b**) 'Thin' skin flaps (increased risk of skin necrosis and unnecessary subcutaneous fat excision above the breast). (**c**) 'Thick' skin flaps (increased risk of residual breast tissue and local recurrence). (**d**) 'Ideal' mastectomy plane over superficial fascia (in section "**Where** Is the Mastectomy Plane?")

nants originating from the patient's skin or nipple. ADMs should be soaked in room temperature fluids; hot saline from a warming oven can denature native dermal collagen and lead to a foreign body response and rejection. Many ADMs are supplied sterile, while some are aseptically processed and packaged with antibiotics that must be rinsed from the ADM by multiple saline soaks prior to use. This is to avoid the potential for 'red breast syndrome' or hypersensitivity reactions to antibiotics. We have found this phenomenon to be more common in ADMs derived from humans and porcine origins when compared to SurgiMend from bovine foetuses.

The superior edge of the ADM is sutured from medial to lateral, superiorly to the cut end of the muscle, using an absorbable, interrupted, braided suture. Care should be taken to firmly anchor the material medially and to define the important medial IMF/cleavage area. The ADM must not be pulled too tight but held gently to allow it to find its own tension-free position that best accommodates the lower ventral curvature of the implant. Once the ADM is fixed medially, the use of an appropriate anatomical sizer in the developing pocket will allow more precise positioning and fixation of the ADM, so it may fit like a 'hand in glove' over the selected implant without wrinkling or pleating. Once the definitive sizer or implant is in position, the lateral most cut end of the pectoralis major muscle should be wedged downwards into a slit made in the ADM. This will put the muscle under moderate tension in a way that will prevent upwards 'window-shading' of the muscle.

39.1.8.2 Lateral Fold (LMF) Definition

The ADM is then fixed laterally to the interface of fascia over serratus anterior. Even if the mastectomy has progressed beyond the intended new lateral fold and the base width of the implant, the ADM should be fixed in a way that defines the lateral border of the intended internal domain and allows the lateral skin envelope to be draped comfortably over it. With footprint of the original breast being often wider than the width of the implant, the lateral border of the new breast should be where the implant ends. We have also had excellent uncomplicated results using separate strips of material to act as a lateral buttress. Any dead space in the lateral breast gutter resulting from base width differences between old and new footprints of the breast should be sutured closed to minimise seroma formation.

39.1.8.3 Infra-mammary Fold (IMF) Definition

Lateral and medial fixation sutures are accurately inserted from the lower border of the ADM to the fascial condensation of IMF. If the IMF has been breached or stretched during mastectomy, then the IMF can be reconstituted with these sutures.

39.1.8.4 Insertion of Definitive Implant Device

Depending on the mastectomy incision, the implant is inserted into the pocket via the most convenient route, either

over the superior border of the ADM or under the inferior or lateral border. After removal of the sizer implant and insertion of drain(s), standard 'minimal handling' precautions are employed following no-touch principles.

39.1.9 Autologous Lower Pole Sling (LPS): Technical Points (Fig. 39.9)

39.1.9.1 Pocket Dissection

For accurate lateral definition, we use a sub-serratus inferolateral extension of the muscular pocket. The inferior division of the pectoralis origin is continued laterally in a horizontal line to the required pocket width through the fascia and costal digitations of the serratus anterior. The subserratus pocket is developed gradually upwards from the cut edge until the lateral pocket opens up to join the subpectoral dissection.

Great care must be taken to elevate serratus digitations from the lateral ribs without breaching the intercostal musculature underneath or the often-flimsy serratus muscle at the lateral pectoral margin. If the serratus layer is attenuated, then a small lateral portion of adjacent pectoralis minor maybe freed and transposed to reinforce the serratus layer ('lateral pectoral slide manoeuvre'). The reward for meticulous dissection laterally is a precise muscular pocket that will hold the entire upper portion of the implant and controls the lateral border of the prosthesis without the need for lateral sutures. The lower cut border of the muscular pocket is then easily sutured to the dermal sling over the definitive implant or sizer.

39.1.9.2 The Infra-mammary Fold (IMF)

Even if the IMF is left intact after mastectomy, it is often stretched and somewhat displaced on the chest wall. It should be routinely reinforced at the desired position using interrupted absorbable sutures. This will prevent it from drifting inferiorly under the weight of the implant. When the implant is in position on the lower dermal sling, it is sitting in front of the newly fixed IMF. This facilitates an evolving natural ptosis, on a stable IMF.

It is worthwhile noting here that in some patients, the LPS, which basically is a de-epithelialised vascularised dermis, may stretch and produce exaggerated bottoming out especially with larger implants (Figs. 39.10, 39.11 and 39.12).

39.1.9.3 The 'Medial Corner'

When using the LPS, there may be occasions when the dermal sling is deficient medially. The pectoralis major origin should still be divided in the same way as when using an ADM, but in this scenario it may not be possible to oppose muscle to dermal sling over the implant in the medial corner of the pocket. In our experience leaving the pocket open medially has not lead to any complications, but our preference would still be to use an ADM patch if there is any risk whatsoever of the implant lying immediately under the wound.

39.1.10 Minimising Complications

As ADM use increases and newer materials become available, there is a growing body of literature to support safety and acceptable complication rates with the use of ADMs in implant-based immediate and delayed breast reconstruction [19–26].

Some of the published meta-analyses however have shown increased rates of infection, seroma, haematoma and explantation, compared to total sub-muscular implant reconstructions [27, 28]. Recent clinical trials to be published soon demonstated significantly lower complication rates specifically Seroma and infection when 2:1 meshed ADM is used [29]. Our experience with ADM has shown that this technique offers significant benefits in terms of cosmesis, reduced expander times, decreased capsular contracture and number of maintenance surgeries and a reduced overall time to completion of reconstruction [30, 31].

In our experience, while aesthetic results remain unquestionably better, complication rates when using lower pole support are comparable with standard subpectoral pocket-based implant reconstructions for haematoma, necrosis, infection or implant loss. Our infective complications and implant loss occurred exclusively in the presence of seromas and skin necrosis and only in of patients who had adjuvant chemotherapy, radiotherapy or both (Tables 39.2 and 39.3). This has been dramatically reduced since the use of 2:1 meshed Surgimend in our practice.

The only complication that has been shown in meta-analysis to increase when ADMs are used, when compared to total muscle coverage without ADMs, is seroma. We have been able to keep seroma rates down by pocket irrigation with saline solution that removes free-floating fat particles, reduction of dead spaces, perfect fit between muscle/ADM/implant and perfect fit between the latter and the overlying skin envelope. Two 10 mm drains placed in the lateral gutter and the IMF ease effective drainage for the first 2–3 days at which time one drain is removed. The second drain is removed when there is less than 30 cc/24 h 2 days in a row usually at 7–11 days.

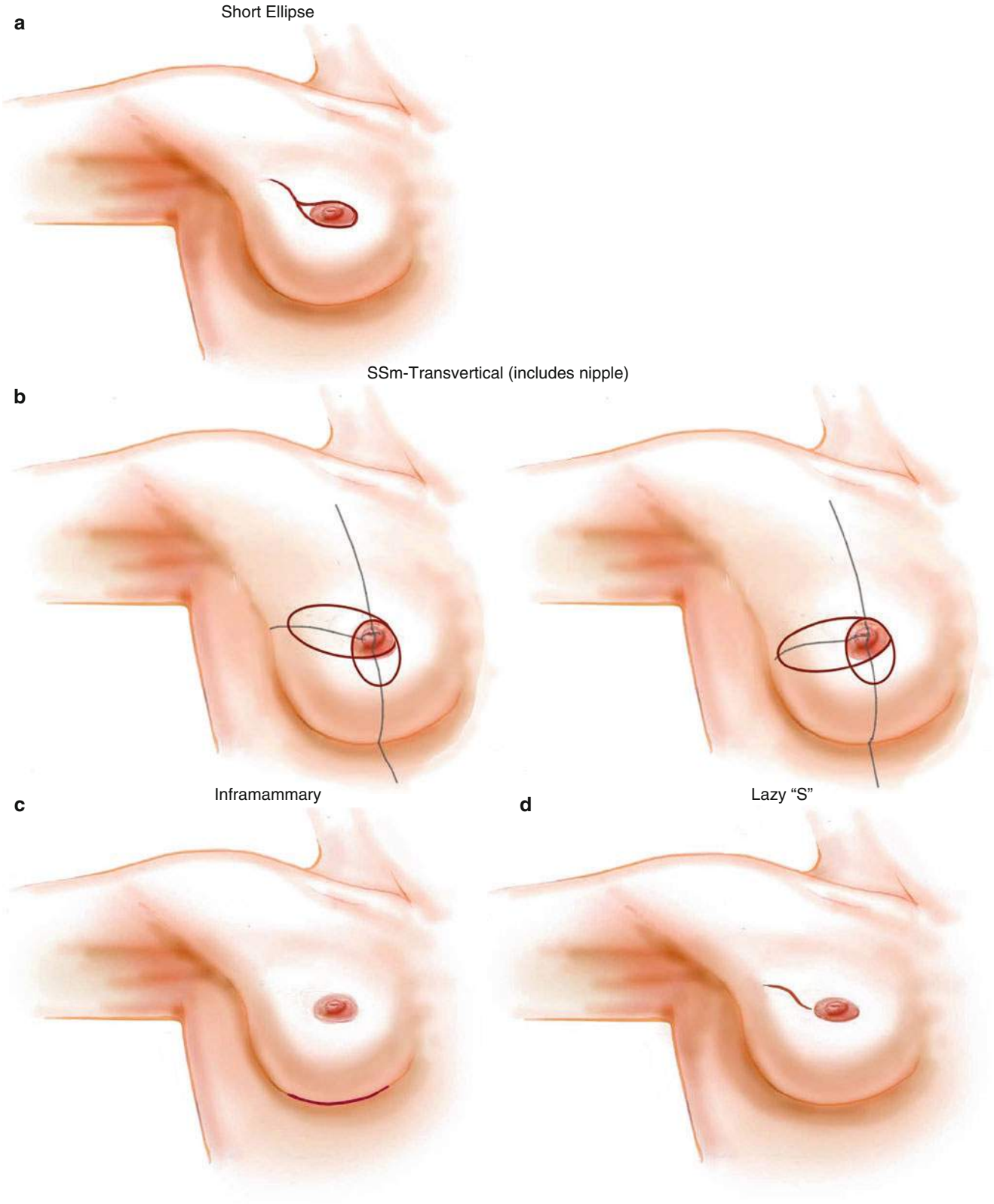

Fig. 39.9 (**a**–**c**) Mastectomy incisions for use with the ADM technique. (**a**) Short ellipse incision ± 'lazy-S' lateral extension (skin-sparing mastectomy (SSM)). (**b**) Trans-vertical incision (skin-reducing mastectomy (SRM)). (**c**) Infra-mammary incision (nipple-sparing mastectomy (NSM)). (**d**) 'Lazy-S' oblique lateral incision (nipple-sparing mastectomy (NSM)) (Sect. 1.6.2)

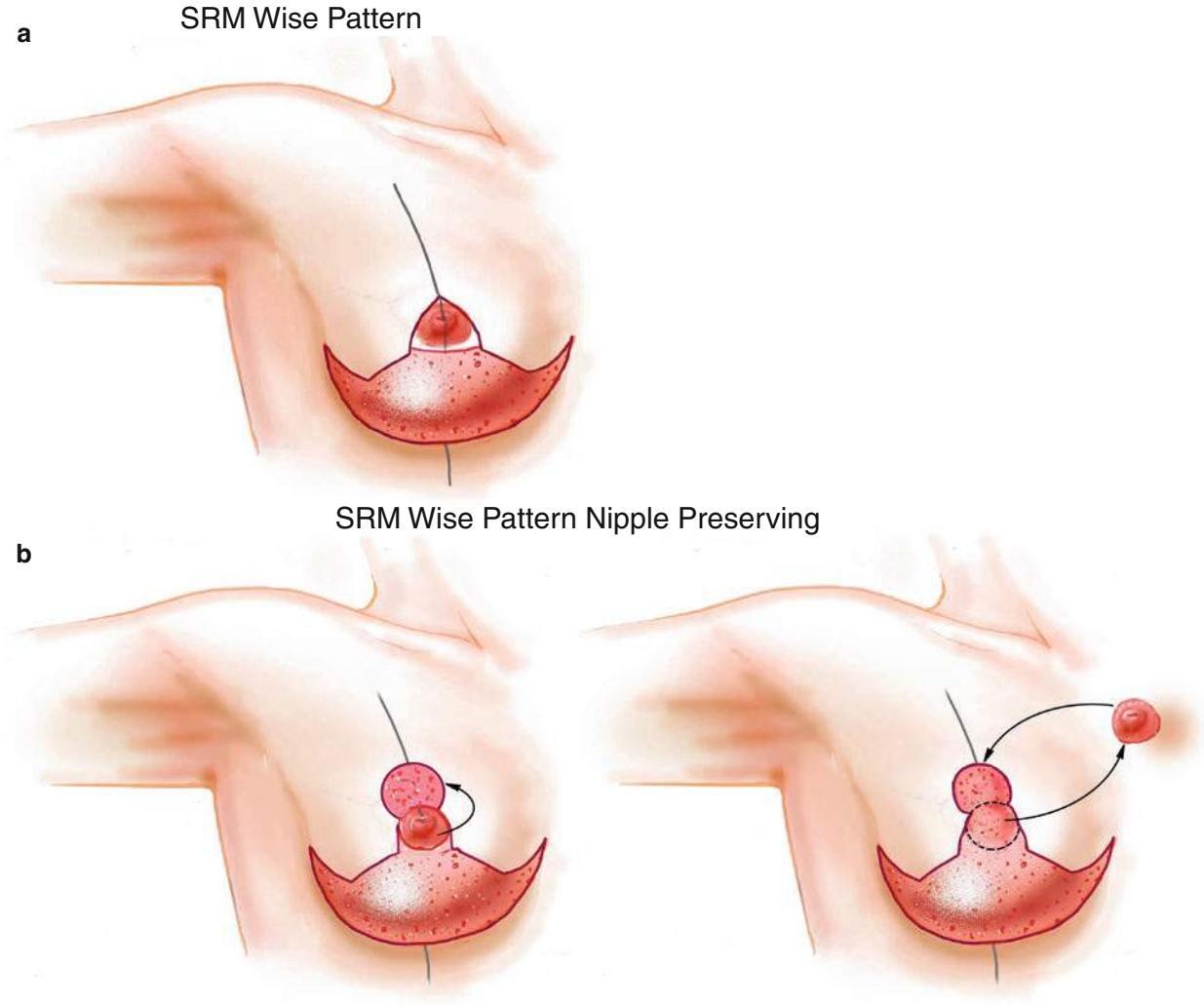

Fig. 39.10 (**a** and **b**) Mastectomy incisions for use with the LPS technique. (**a**) Wise-pattern incision (skin-reducing mastectomy (SRM)). (**b**) Wise-pattern incision, nipple sparing on dermal pedicle or free graft (nipple-sparing (NSM), skin-reducing mastectomy (SRM)) (Sect. 1.6.3)

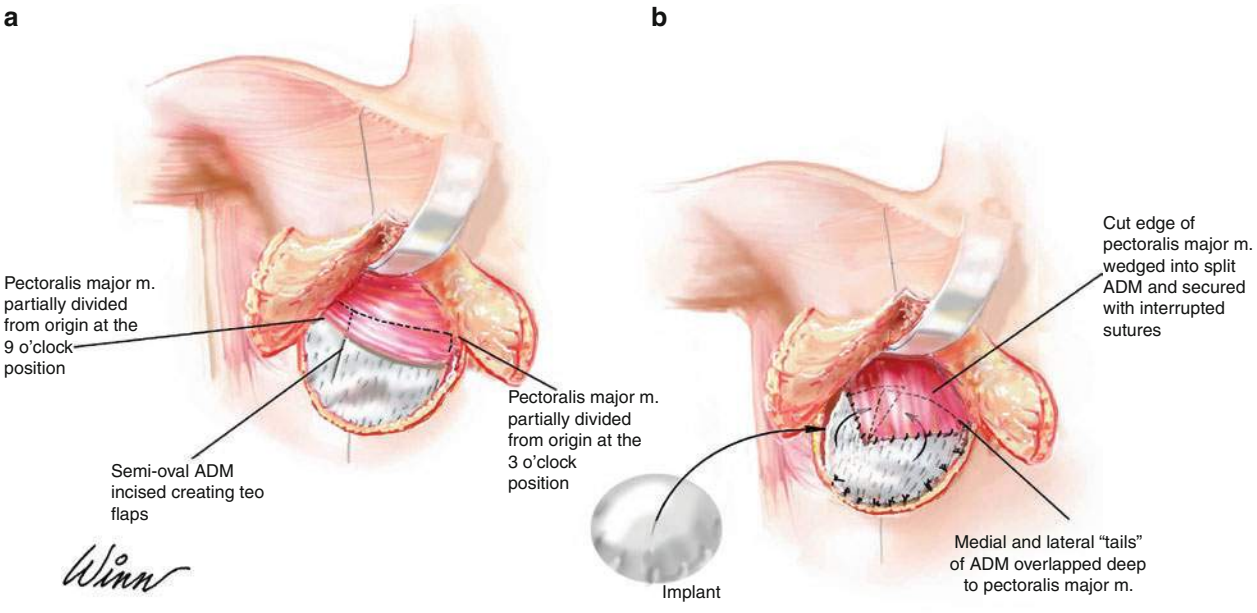

Fig. 39.11 (**a** and **b**) ADM technique—technical points (Sect. 1.8)

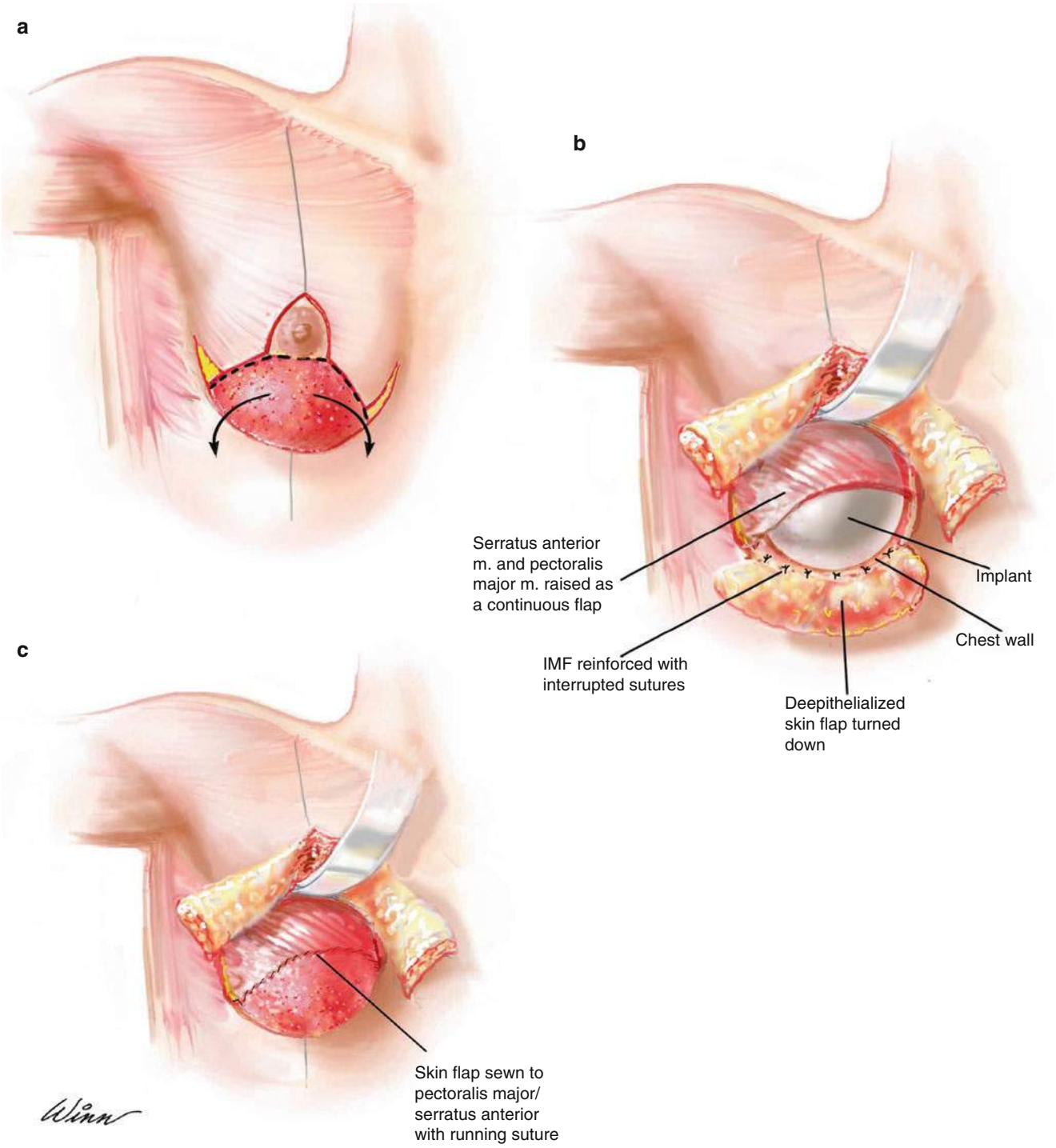

Fig. 39.12 (**a**–**c**) LPS technique—technical points (Sect. 1.9)

39.1.10.1 Skin Envelope Necrosis

To optimise perfusion and minimise the risk of skin envelope, necrosis requires adherence to all of the technical points discussed so far. Excellent mastectomy technique requires careful patient assessment, accurate incision planning, meticulous tissue handling and tension-free draping and closure.

Avoiding the use of retractors and sharp hooks to lift the skin and expose the breast has been helpful in reducing crushing of the subdermal plexus by enthusiastic assistants or the surgeon's non-dominant hand. Using gentle finger traction instead has worked for us.

If the reconstructive team involves a general surgeon and a separate reconstructive surgeon, then close cooperation,

Table 39.2 Combined authors' experience 2007–2011

	ADM experience (SurgiMend) 341 immediate implant econstructionsr March 2001 to July 2011 (Tel Aviv, Israel)	LPS experience 102 immediate implant reconstructions Jan 2007 to Jan 2012 (Cornwall, UK)
Total skin-sparing mastectomy	341	102
Bilateral	262 (131 patients)	50 (25 patients)
Unilateral	79	52
Direct to implant (one-stage)	270	90
Tissue expander (two-stage)	71	12
Radiotherapy		
Preoperative	32	4
Postoperative	25	8
Chemotherapy		
Preoperative	43	0
Postoperative	19	10

Table 39.3 Complications

	ADM experience (SurgiMend) 341 immediate implant reconstructions March 2001 to July 2011 (Tel Aviv, Israel)	LPS experience 102 immediate implant reconstructions Jan 2007 to Jan 2012 (Cornwall, UK)
Necrosis	18 (5.2%)	10 (9.8%)
Necrosis and infection	7 (2.0%)	1 (1.0%)
Infection (no necrosis)	1 (0.3%)	4 (3.9%) all after chemotherapy
Haematoma	7 (2.0%)	5 (4.9%)
Seroma	9 (2.6%)	4 (3.9%)
Failure	6 (1.75%)	4 (3.9%) all after chemotherapy
Capsule (grades 3–4)	7 (2.0%) all after radiotherapy (7/57 = 12.3% radiotherapy cases)	4 (3.9%) all after radiotherapy (4/12 = 33.3% radiotherapy cases)
De-rotation	1 (0.3%)	1 (1.0%)

joint planning and an agreed strategy are essential. Good communication with the anaesthetic team throughout the procedure is also important. To optimise skin perfusion, it is essential to ensure adequately monitored and stable normotensive haemodynamics as well as core temperature.

If, despite best efforts, the skin envelope viability remains uncertain, then further intraoperative monitoring of skin perfusion can help inform decision-making regarding the need for further skin resection or whether to use a tissue expander. Different strategies may be employed to assess skin envelope perfusion; intraoperative temperature or oximetry probes may not be reliable or practical during surgery. Our preference is to use intraoperative full-field laser Doppler imaging (FFLDI) technology to assess skin perfusion and viability. The laser signal illuminates an area of 7 × 7 cm of the skin envelope and is transmitted to a depth of up to 2 mm. The frequency shift caused by laser interaction with circulating red blood cells (laser Doppler effect) is used to calculate concentration, speed and perfusion of the skin flaps, which is then displayed as a real-time perfusion colour map on the monitor. Poorly perfused skin should be excised. An indocyanine green scanner (SPY) is another useful alternative to evaluate intraoperative skin flap perfusion [26]. All these are applicable and reliable only when no adrenaline is used in the infiltration solution aimed to hydro-dissect the soft tissue envelope off the breast and reduce bleeding. It is also only useful when core and skin temperature are kept to near optimal. The sensitivity and specificity of both devices are not very high in these conditions. The use of scanners and laser Doppler devices is therefore useful only when no infiltration is used, when temperatures are kept near normal and when the plastic surgeon is not present when the general surgeon performs the mastectomy.

If the planned closure with a fixed volume prosthesis is no longer possible or the tension likely to be too great, then we would recommend the use of a tissue expander.

39.1.10.2 Capsular Contracture

To some extent capsule formation is an inevitable consequence of device implantation. Symptomatic and troublesome capsular contracture (grades 3 and 4) requiring intervention however can be minimised by adherence to recognised precautions—such as careful tissue handling and haemostasis, strict asepsis and the use of an ADM.

The use of an ADM creates a less inflammatory domain which contributes to reduced capsular contracture rates. Recent meta-analyses and reviews of the early published experience with ADMs appear to bear this out [32, 33]. Our personal experience supports the same conclusion.

39.1.10.3 Capsular Contracture Secondary to Radiotherapy

Whether postoperative radiotherapy treatment is unexpected or pre-planned and a patient chooses to have an implant-based reconstruction, she must be informed that with radiotherapy there is an inevitable increased risk of aesthetic compromise [34–36].

It is this that has led some to advocate avoidance of implant-based reconstruction in the face of radiotherapy, in favour of either delayed autologous reconstruction or a delayed-immediate reconstructive approach with temporary expanders during radiotherapy [37, 38]. Expansion during or after radiotherapy, even as part of a two-stage strategy, is not effective on its own to minimise radiation-induced aesthetic compromise [39].

Modern, individualised radiotherapy planning can go some way to ameliorating the unwanted effects of radiotherapy on the reconstructed breast; the use of the 3D treatment planning system for exact dose calculation, hyperfractionation of dose schedules and avoidance of specific skin boluses are all important advances in radiotherapy administration. A patient-specific approach to the intended treatment target, with attention to dose depth from the skin, minimising radiation at the implant/tissue, has led to improvements in our implant-based reconstruction outcomes even in irradiated patients.

The use of lower dermal support seems to also improve outcomes in irradiated reconstructions. We believe this to be related, once again, to having established a better cushioning, padding, perfusion and harmony between soft tissues and stable internal domain, as well as careful optimisation of the health of the overlying skin envelope. Lower dermal support minimises the tension within and exerted by the internal domain on the skin envelope. This ensures the best possible perfusion of skin and soft tissues in preparation for the radiotherapy. There is good evidence for enhanced fibroproliferation with radiotherapy in the presence of implants, and some important signalling pathways have been identified [40]. We hypothesise that in addition to this, both ADMs and LPS maintain the overlying soft tissue vasculature less collapsed (due to extra tension in skin, muscle and developing capsule) which in return may be less susceptible to radiotherapy-induced vasculitis and hence subsequent fibrosis.

39.1.10.4 Acute and Chronic Pain

The reduced tension and stability of a subpectoral and ADM/LPS pocket, as compared to a full sub-muscular pocket, or when the serratus muscle has been elevated should lead to less immediate postoperative pain on early pectoral movement. There is the potential for increased discomfort from the subpectoral and lateral pocket sub-serratus dissection from injuring the costal periosteum. The use of intercostal blocks and other regional local anaesthetic techniques (intra-pectoral blocks) can improve acute pain in the initial postoperative period.

As discussed earlier, the use of lower pole support techniques, specifically an ADM, seems to reduce the incidence of capsular contracture. We believe that this may then in turn lead to a reduction in development of chronic pain.

39.1.11 Refining Long-Term Results

39.1.11.1 Fat Grafting

Lipofilling with autologous fat may be very effective as a secondary adjunct to improve outcomes in breast reconstruction generally [41] and in implant-based reconstructions specifically [42] by:

- Creating a more natural cleavage and upper pole take-off.
- Smoothing out and filling uneven areas of the skin envelope where mastectomy flaps may have been taken too thin.
- Improving contour/shape and transitional area irregularities.
- Covering thin areas where there may be implant rippling or edge palpability.
- Reducing radiotherapy-induced skin change and fibrous capsule formation.

The attendant risk to the underlying implant is small, but if soft tissues are thin, a preliminary step using hydrodissection with either saline or micro-/nano-fat particles further reduced the risk of inadvertent intra-capsular fat injection and injury to the implant.

Three-dimensional imaging (e.g. Vectra system) will demonstrate (and quantify) contour and volume discrepancies. Better objective and quantitative assessment can improve the quality of consultations and allow accurate planning for fat grafting refinement procedures.

It is worth remembering and cautioning patients that fat grafting can sometimes cause localised fat necrosis, often exhibiting as a firm irregular mass, clinically indiscernible from breast cancer. The sonographic appearance of fat necrosis may also be very similar to that of breast cancer; however, a fine needle or core biopsy is usually diagnostic, and the patient may be put at ease.

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Skin-Reducing Mastectomy

40

Gustavo Zucca-Matthes, Raphael Luis Haikel, and Angelo Matthes

40.1 Introduction

Breast cancer surgery has evolved from radical mastectomy, with excision of as much tissue as possible, to subcutaneous mastectomy, with sparing of as much tissue as possible (Table 40.1). Notably, the choice of the procedure depends on both the location and the stage of the cancer. The development of diagnostic imaging techniques has increased the medical profession's awareness of breast cancer and led to earlier diagnoses.

Nowadays the principle of oncoplastic surgery is amplified and was incorporated to the idea of an immediate breast reconstruction. Veronesi et al. [1] published the term conservative mastectomy regarding a surgical technique demanding an oncological treatment by removing the breast parenchyma and trying to spare as much skin envelope as possible, including nipple–areola complex, in other words to remove breast glandular tissue without disruption of the breast appearance. It allows an IBR and the contralateral symmetric approach. It also boosts the patient's self-esteem and quality of life. The association between plastic surgical techniques and mastectomy with immediate breast reconstruction is one of the best alternatives to treat breast cancer and also improved overall aesthetic outcomes and favors the achievement of contralateral breast symmetry [2].

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Because a greater percentage of cancers are detected at earlier stages, the need for skin-sparing techniques has increased [3].

Skin-sparing mastectomy was classified further by the type of incision used and the amount of skin removed (Table 40.2) (Fig. 40.1). Type I SSM was used commonly for prophylactic purposes and for patients whose cancer was diagnosed by needle biopsy. Lateral extension of the incision may be necessary to improve exposure to the axillary tail. Type II SSM was used when the superficial tumor or previous biopsy was in proximity to the areola. Type III SSM was used when the superficial tumor or previous incision was remote from the areola. Type IV SSM was used in large, ptotic breasts when a reduction was planned on the opposite breast [4].

Type IV Wise pattern skin-sparing mastectomy (SSM) has had excellent results as immediate implant reconstruction in heavy- and pendulous-breasted patients who require a conspicuous reduction of the skin envelope and a contralateral reduction or mastopexy. However, on the side undergoing the SSM, the skin flaps are thin, and wound-healing problems are well described, particularly skin necrosis at the "T" as frequent as 27%, predisposing to prosthesis exposure and therefore limiting its utility [5]. Therefore technique modifications that recruit local tissue to protect these areas of breakdown and support the implant have been proposed and has been called skin-reducing mastectomy (Type V) [5–8].

Reconstruction surgery in this subset of mastectomies can be performed by means of totally submuscular expanders or permanent prostheses rather than autologous flaps. Final scarring is similar to that from cosmetic surgery (inverted T) [5].

40.2 A Brief History

In different series of inverted "T" mastectomies, relatively high morbidity (up to 27%), which usually involved skin viability at the inverted "T" junction, was reported [5]. In this way, many authors have tried to overcome necrosis and poor results using a modified Wise pattern rather than a subcutaneous pouch.

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_40

Table 40.1 Evolution breast cancer surgical treatment

Author	Year	Surgery	Description
W Halsted	1894	Radical mastectomy	Removal of the breast, two muscles, and axillary lymph nodes
Stewart	1915	Radical modified mastectomy	Transverse incision, better aesthetic result
Urban	1956	Ultra-radical mastectomy	Removal of the breast, two muscles, axillary lymph nodes, and internal mammary lymphatic chain en bloc
Patey-Dyson	1948	Radical modified mastectomy	Resection of the breast, pectoralis minor, and axillary contents en bloc
Madden-Auchincloss	1965	Radical modified mastectomy	Resection of the breast and axillary contents en bloc, preserving both pectoral muscles
Fisher	1985	Breast conservative treatment	Tumor resection (lumpectomy and quadrantectomy), axillary dissection and radiotherapy
Veronesi	1986	Breast conservative treatment	Tumor resection (quadrantectomy), axillary dissection, and radiotherapy
Toth and Lappert	1991	*Skin-sparing mastectomy*	Mastectomy appeared in order to conserve skin as much as possible and facilitate breast reconstruction
Audretsch	1994	Oncoplastic	Association of plastic surgery techniques for conservative treatment
Giuliano	1994	Sentinel node biopsy	Axillary lymph node resection of the first, being able to avoid complete axillary dissection
Petit	2006	*Nipple-sparing* mastectomy	Mastectomy appeared in order to conserve skin and nipple–areola complex (NAC), facilitating breast reconstruction. Associated with intraoperative radiation of the NAC
Nava	2006	*Skin-reducing mastectomy*	Combined flap technique to reconstruct large- and medium-sized ptotic breasts in a single-stage operation by the use of anatomical permanent implants

Table 40.2 Modified classification of skin-sparing mastectomy

Type	Classification
I	Only nipple–areola removed
II	Nipple–areola, skin overlying superficial tumors, and previous biopsy incision removed in continuity with nipple–areola
III	Nipple–areola removed, skin overlying superficial tumors, and previous biopsy incision removed without intervening the skin
IV	Nipple–areola removed with an inverted or reduction pattern skin incision

In 1990 Bostwick [9] tried to preserve a lower deepithelialized dermal flap during the Wise reduction pattern mastectomy to create a musculodermal pouch for the location of a definitive permanent silicone prosthesis that provided appropriate coverage of the implant. At that time there was no information about the possibility of saving the skin during oncological procedures, so it was used for prophylactic mastectomies.

Hammond et al. [8] introduced Bostwick's method in the treatment of breast cancer, in most cases using a two-step surgical approach with temporary expanders, followed by a second operation for permanent insertion of implants.

In 2006, Nava et al. [5] described a modification of this last type of skin-sparing mastectomy, renamed skin-reducing mastectomy, by which mammary reconstruction in selected patients is done in a single stage in which an anatomical silicone gel implant is placed in a dermal-muscle flap pocket. They aimed to avoid complications of the type IV operation, such as lack of space in the inferior and medial aspects of the submuscular pouch that sometimes requires release of the inferior insertions of pectoralis major with an incision, leaving the implant subcutaneously with a high risk of exposure, particularly when it is put under the long (and possibly ischemic) superior mastectomy flap.

40.3 Definition

Skin-reducing mastectomy (SRM) is a single-stage technique that helps us to overcome the cosmetic inadequacy of a Type IV Wise pattern skin-sparing mastectomy (final T-inverted scar) in heavy and pendulous breasts by filling the lower-medial quadrant with adequate volume.

Its virtue lies in the manner it provides for adequate implant coverage using muscle and a deepithelialized dermal flap, thus reducing the risk of implant extrusion and providing good inframammary contour [6].

SRM with a complete release of the pectoralis muscle inferiorly and the sparing of a lower dermal flap sculpted down to the inframammary fold allow the creation of a dermomuscular pouch, achieving total implant coverage and overcoming all of the inadequacies of type IV SSM (upper pole fullness and lack of projection). By augmenting the pocket and providing a new tissue layer at the lower pole of the breast, complications are reduced and aesthetic outcomes are improved compared with the traditional inverted "T" mastectomies.

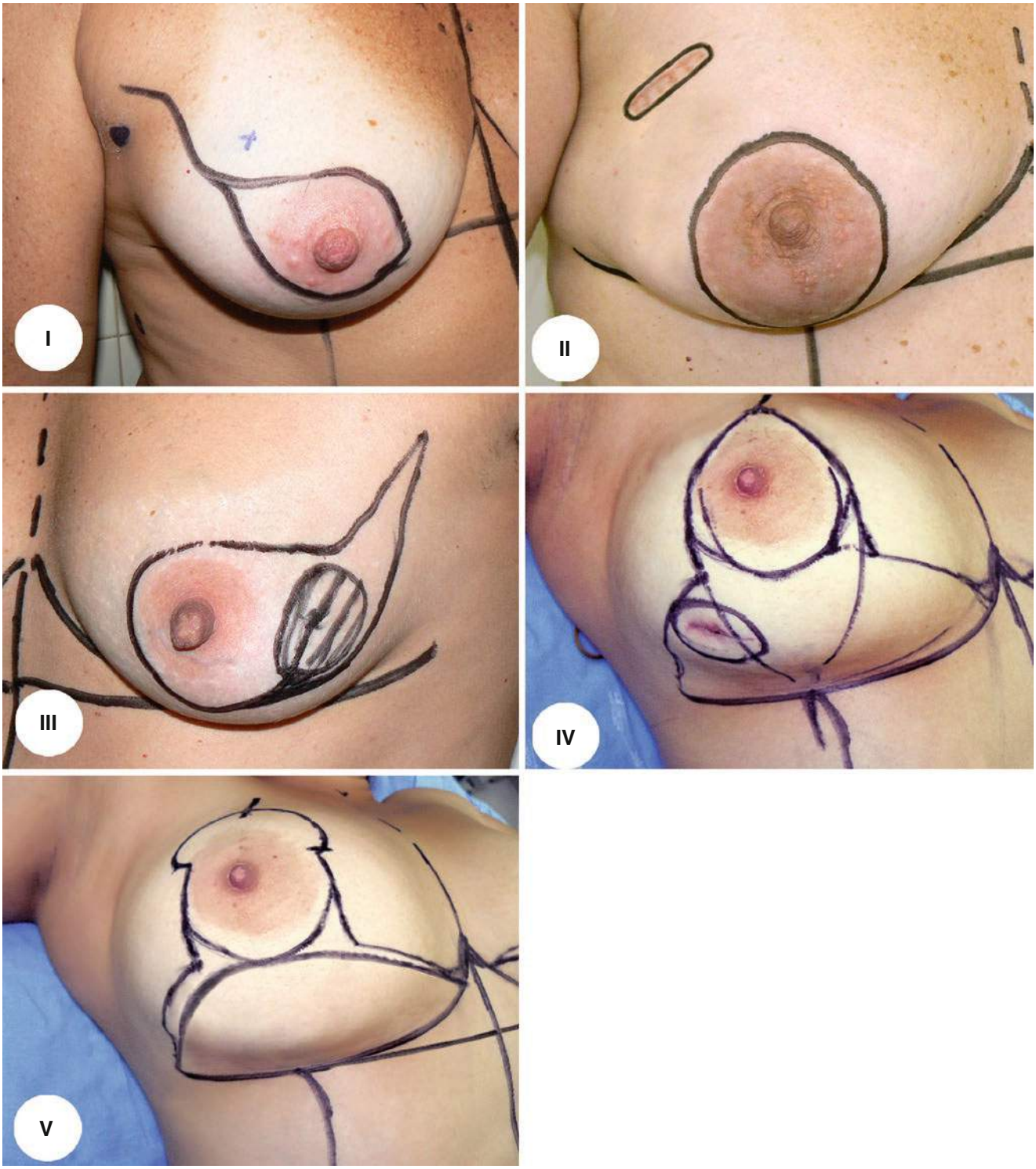

Fig. 40.1 Classification of skin-sparing mastectomy including skin-reducing mastectomy

40.4 Indications

The indication of SRM originally deemed most suitable for early-stage breast cancer and risk-reduction patients with medium- to large-sized breasts; however it could be expanded.

Ongoing controversies continue to debate the issues of skin-sparing mastectomy and sparing of the nipple–areola complex. These controversies are focused on problems of nipple–areola survival and the reliability of methods from an oncologic point of view. Many published reports describe the reliability of subcutaneous mastectomy under certain indications. In early-stage breast cancer, immediate breast reconstruction after subcutaneous mastectomy is used with increasing frequency.

Recently, prophylactic mastectomy has been performed for patients displaying the following oncologic risk factors: a positive family history, BRCA-1 and BRCA-2 gene mutation, atypical ductal hyperplasia, a history of skin cancer, intensive lobular carcinoma in situ, and ductal carcinoma in situ and still when an extreme fear of breast cancer is manifested. Prophylactic mastectomy has been performed increasingly due to either patient demand or oncologic surgeon proposal. Sparing of the nipple–areola complex is extremely important for aesthetic results and patient satisfaction in both early-stage breast cancer and high-risk groups [10–12].

Nair et al. [6, 13] reported their experience with performing SRM. They expanded the indication of SRM to more locally advanced tumors (T3 and T4), eventually downstaged by neoadjuvant chemotherapy, and to small-volume non-ptotic breasts by using expandable implants. Furthermore, they included patients who also need adjuvant radiation.

To sum up, the SRM is able to be performed for patients who had moderate- to large-sized ptotic breasts and no history of previous reduction mammoplasty and absence of tumor affecting the skin, excluding smokers (five cigarettes/day) and patients with microvascular problems (previous radiotherapy, diabetes) [11].

40.5 Preoperative Planning

Breast ultrasound and mammography are advised to encourage a perfect preoperative surgical planning.

All the patients should be informed about the surgical procedure, the details of their breast disease, the risk factors of redundant breast tissue, and the possible advantages and disadvantages of the surgical technique.

Operation planning was performed with patients in the standing position. First, the region of the mass nearest the skin was marked, followed by marking of the inframammary fold. A distance of at least 4 cm (4–6 cm) between the inframammary sulcus (IMS) and the nipple is the projectional distance on the sternum. On the breast, it becomes 5–7 cm. The marking then follows the steps used for a normal breast reduction or mastopexy using a conventional Wise pattern. However, on the mastectomy side, some surgeons [5] erase the semicircular drawing representing the position of the new nipple–areola complex and prolong the two vertical limbs up to the new nipple position. The length of the two limbs on this side depends on the degree of reduction we want to achieve and is usually between 5 and 7 cm, plus the 2 cm radius of the nipple–areola complex. The distal ends of the two limbs are then extended medially and laterally with patient lying in the supine position, so as to intercept the previously marked IMS.

At the beginning of planning, drawing the projection of the IMS on the sternum shows whether there is any vertical asymmetry with the thorax. Generally, 1–2 cm of asymmetry between the IMS and thorax is common. Showing this situation is helpful in planning to achieve postoperative symmetry. The new nipple projection is drawn 4 cm above the IMS projection on the sternum. A horizontal line is drawn from this mark to the breast to determine the new nipple position. Using this technique, much more breast skin reduction was achieved, and the final scar was located at the inferior mammary fold.

Illustrated case can be seen below at Fig. 40.2a–d.

40.6 Operative Procedure

The area between the marked incisions was deepithelialized including the nipple–areola complex (diameter, 4–4.5 cm). The NAC will be prepared for a free graft at the end. Total subcutaneous mastectomy was performed from the lateral vertical incision via a full incision.

Before the mastectomy is started, the lower flap is sculpted down to the inframammary fold, whose anatomy must be always identified to allow careful preservation. The gland has to be removed with accurate sparing of the superior flap's subdermal vascularization. Cooper's ligament, oncologically reliable and harmless for the subdermal plexus, was followed as a surgical plan during mastectomy. It allows to minimize ischemia without compromising oncologic safety and complete the removal of breast tissue.

This access usually allows for easy axillary dissection or sentinel node identification and biopsy. The pathologic specimen beneath the nipple–areola complex was marked. There is still concern regarding the oncologic safety of nipple preservation in cancer patients. In this case, we normally perform frozen section analysis of retroareolar breast ducts.

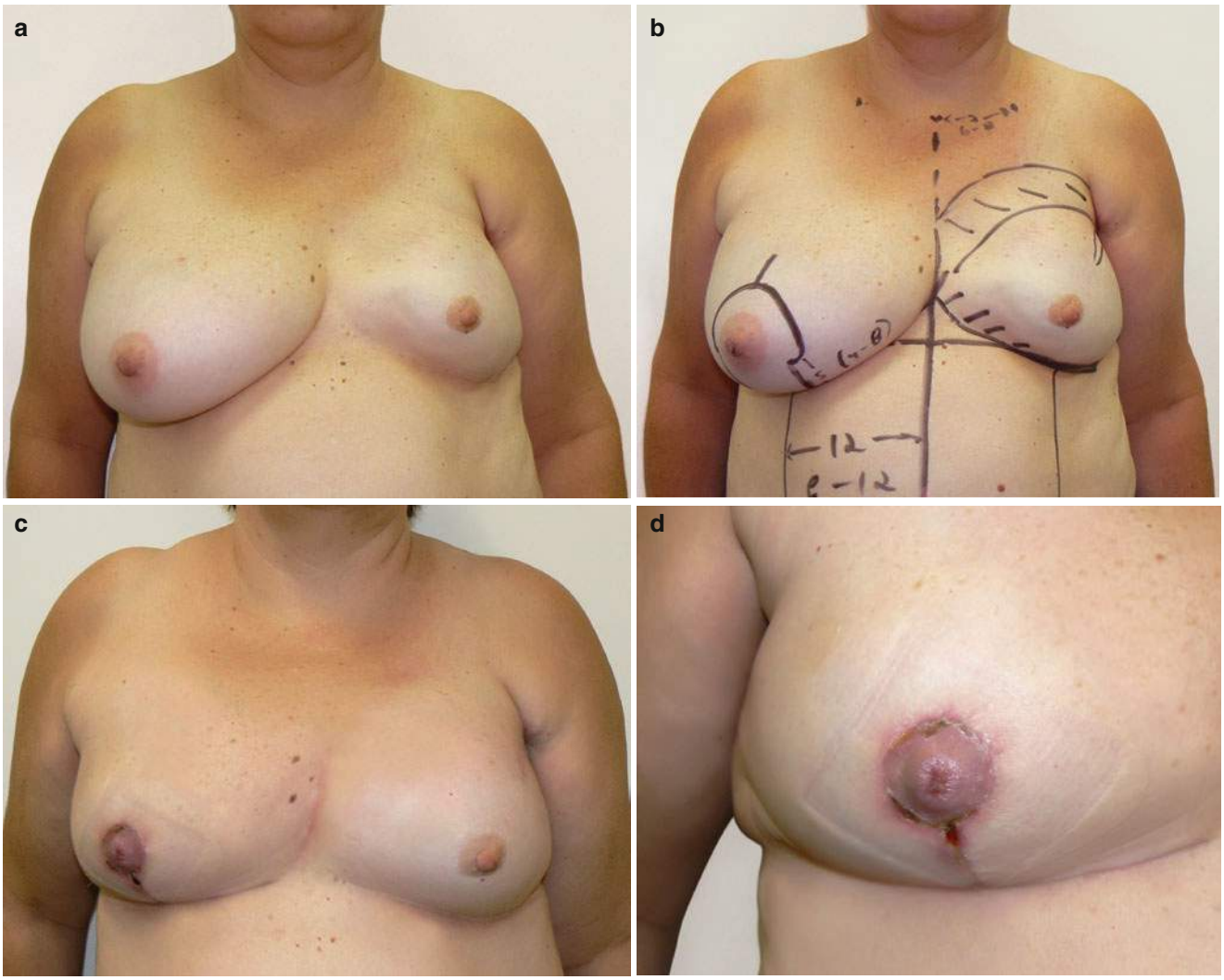

Fig. 40.2 (**a**) Preoperative view, bilateral breast cancer. Left, bad results from previous breast reconstruction. Right, medium-sized breast, 4 × 4 cm tumor at upper outer quadrant, positive axillary nodes. (**b**) Preoperative drawing. Left, prosthetic replacement and remodeling of the parenchyma. Right, skin-reducing mastectomy. (**c**) Final result after 1 month. (**d**) Final result after 1 month. Right breast closer view

We advise anatomical breast implants with medium and high-profile cohesive silicone gel filled when reconstructions were performed. After the oncologic procedures are completed, we start the reconstruction by incising along the lateral border of pectoralis major. The inferior and lower-medial insertions of this muscle are divided and sutured to the superior border of the dermal flap. The dermal barrier flap, this deepithelialized area in the mid-inferior region, was moved laterally without folding, and the lateral and medial incisions were sutured to each other. A large pouch is then created to accommodate an anatomically shaped permanent implant.

In our point of view, the choice for a total or partial muscular pocket to cover the implant depends on the scar position. If a scar remains over the pectoral muscle, a total muscular pocket will not be necessary. On the other hand, if the incision is long and remains on the implant, covering with the serratus anterior muscle is essential.

A schematic point of view can be followed below at Fig. 40.3.

40.7 Complications

Although subcutaneous mastectomy offers excellent cosmetic results with small breasts, obtaining optimum results for moderate-sized and large breasts is more challenging and requires repositioning of the areola as well as decreasing the breast skin surface area.

Wound-healing problems usually are not encountered during subcutaneous mastectomies with no skin reduction.

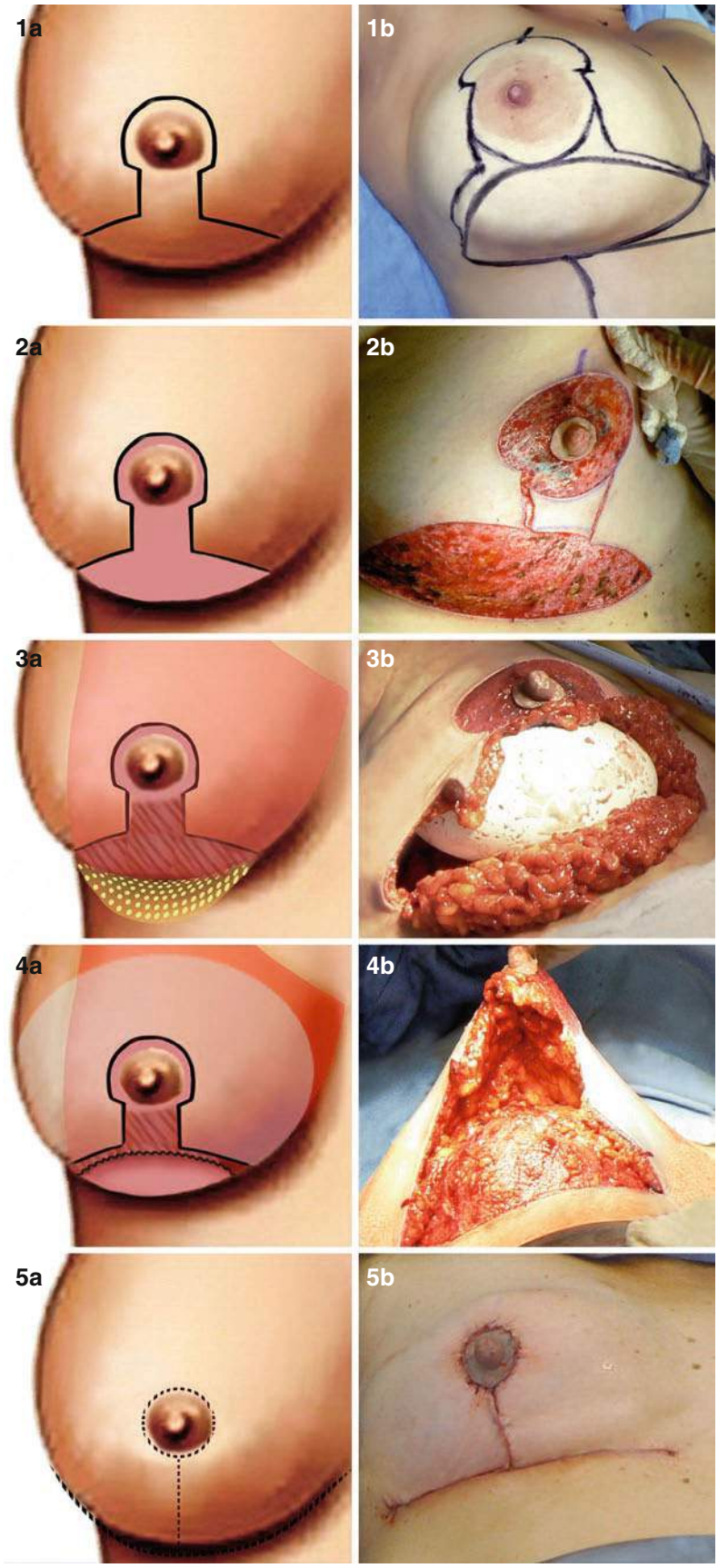

Fig. 40.3 Skin-reducing mastectomy: step-by-step. (1A and B) Wise pattern. (2A and B) Dermal barrier flap (deepithelialized area). (3A) Total subcutaneous mastectomy was performed from the lateral vertical incision via a full incision. (3B) Prosthetic sizer among the flaps of skin-reducing mastectomy. (4A and B) Dermal barrier flap sutured to muscular pocket to cover the implant. (5A and B) Final T-inverted scar

Skin blood perfusion is jeopardized during breast reduction mastectomy. Two mechanisms can be proposed that explain these wound-healing/perfusion issues: long flaps created as a result of skin excision and aggressive surgery that causes very thin skin and jeopardizes the subdermal plexus.

With the SRM, full-cut incisions from only the lateral side and deepithelialization instead of skin excision reduce wound-healing problems at suture lines. The use of the inferior dermal barrier flap provides double-layered protection at the suture site and avoids implant exposure even when wound dehiscence occurs. Although the submuscular area is more protective of the prosthesis, it is not optimal for larger prostheses. Pressure on the prosthesis can cause low-level breast projection. In addition, preparation of the submuscular area increases the mean time for the surgical procedure.

Radiotherapy, if necessary, can be offered to women after mastectomy for breast cancer to decrease risk of local recurrence. Breast reconstruction with breast implants after radiation can prove troublesome because of subsequent capsular contracture, infection, and unsatisfactory cosmetic results [13].

Patients should also nonetheless be advised of the risk of implant complications due to adjuvant therapy. There is thus a small but definite risk of needing revision surgery to achieve the final intended cosmetic outcome. Careful patient selection and improvement in the learning curve may reduce the complication rate. A special attention should be paid for smokers (more than five cigarettes/day) and patients with microvascular problems (previous radiotherapy, diabetes) [11].

Finally, exposure of the implant and failure of reconstruction often become inevitable [3].

40.8 Suggestions to Avoid Complications

The SRM is associated with high rates of complications. In 2015, 187 conservative mastectomies were performed in Barretos Cancer Hospital. Six (11.22%) cases underwent SRM. Loss of implant was observed in one (16.6%) case related to seroma relapse. To reduce the complications in Barretos Cancer Hospital, the surgical technique was changed. Nowadays we follow the SRM technique but with some changes:

1. **Nipple–areola complex (NAC) free graft** (Fig. 40.4)
2. **Definitive expander (Becker or Style 150)** (Fig. 40.5)
3. **Acellular dermal matrix or mesh—ADM** (Fig. 40.6)

There are good reasons for those changes. The SRM technique is potentially harmful for the blood supply to the NAC so the free graft must solve that problem. At the end nipple–areola complex was grafted to the planned position.

Furthermore the SRM presents high levels of necrosis. The Becker implant [14] is a definitive expander, a mixture of saline expander and silicone implant. In other words we have the benefits of both kinds of implants. If necessary in case of skin flap sufferance, the surgeon will be able to bargain with the saline volume to adjust the skin and to figure out the breast reconstruction.

Fig. 40.4 Nipple free graft

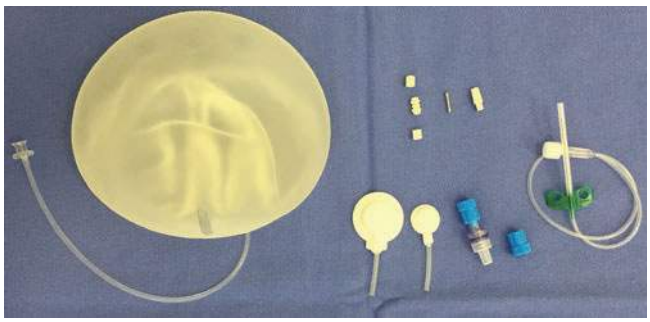

Fig. 40.5 Definitive expander

In case of tumor in the inferior part of the breast and the resection of the inferior dermis become unavoidable, the use of ADM may be a solution. The use of acellular dermal matrix (ADM) may allow the total coverture of the implant or to substitute the dermis in case of oncological compromising. Our first choice is the mesh called BIO A (67% polyglycolic acid (PGA), 33% trimethylene carbonate (TMC)) by GORE [15]. It is a synthetic mesh able to support and protect the implant

from skin dehiscence during the first months, highlighting the inframammary fold of the breast, and after 6 months it will be totally absorbed and incorporated by the local tissues providing a natural shape and soft touch (Fig. 40.7a, b, preoperative and immediate postoperative outcome after SRM with free NAC graft, ADM, and definitive expander).

Drains should be inserted and left in place for about 5–10 days. Tight bandages or special bras should be used for 4–6 weeks.

40.9 Psychological Aspects

Immediate breast reconstruction after mastectomy has the potential to minimize the psychological insult associated mastectomy alone. The applicability of immediate reconstruction has expanded in recent years with the understanding that such procedures do not affect the incidence or detection of breast cancer recurrence. Additionally, there is no appreciable delay in the institution of adjuvant therapy with this approach. Existing techniques of immediate implant-based breast reconstruction as well as SRM revolve around prosthesis placement in either subcutaneous or sub-pectoral planes.

In this context, patients with macromastia who require a combination of skin-sparing mastectomy and a degree of skin envelope reduction benefit from the "skin-reducing mastectomy because the Wise keyhole or inverted T pattern can then be applied equally to both breasts to create symmetry, protecting with dermomuscular pocket the mastectomy site from scar breakdown and implant exposure [15].

Therefore this technique allows greater security and self-confidence for patients with valuable repercussions during the recovery and adjuvant treatment.

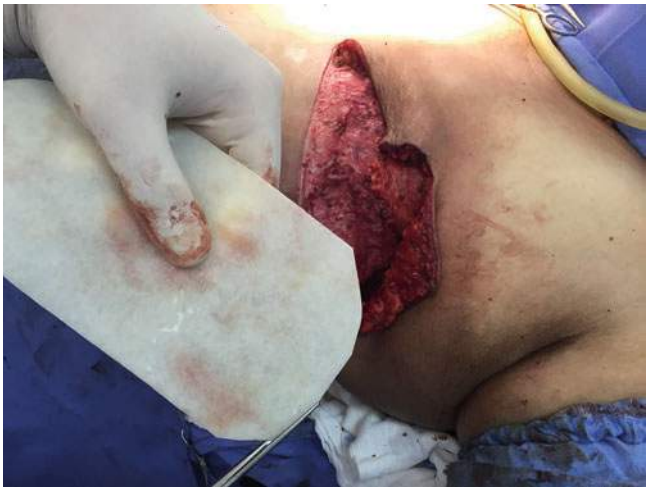

Fig. 40.6 Synthetic mesh

40.10 Conclusion

Skin-reducing mastectomy (SRM) is a method of breast oncoplastic surgery responsible for immediate breast reconstruction derived from a Wise breast reduction incision pattern that enables immediate sub-pectoral implant placement after mastectomy and a contralateral symmetry if necessary. It also conceals scars as an aesthetic operation and at the same time provides satisfactory and safe coverage of the implant. SRM provides good results for selected patients even in cases of advanced tumor stages. Patients should also nonetheless be advised of the risk of small but definite rate of complications. The aid of a NAC free graft associated to a definitive expander and ADMs could help to avoid or to solve eventual complications.

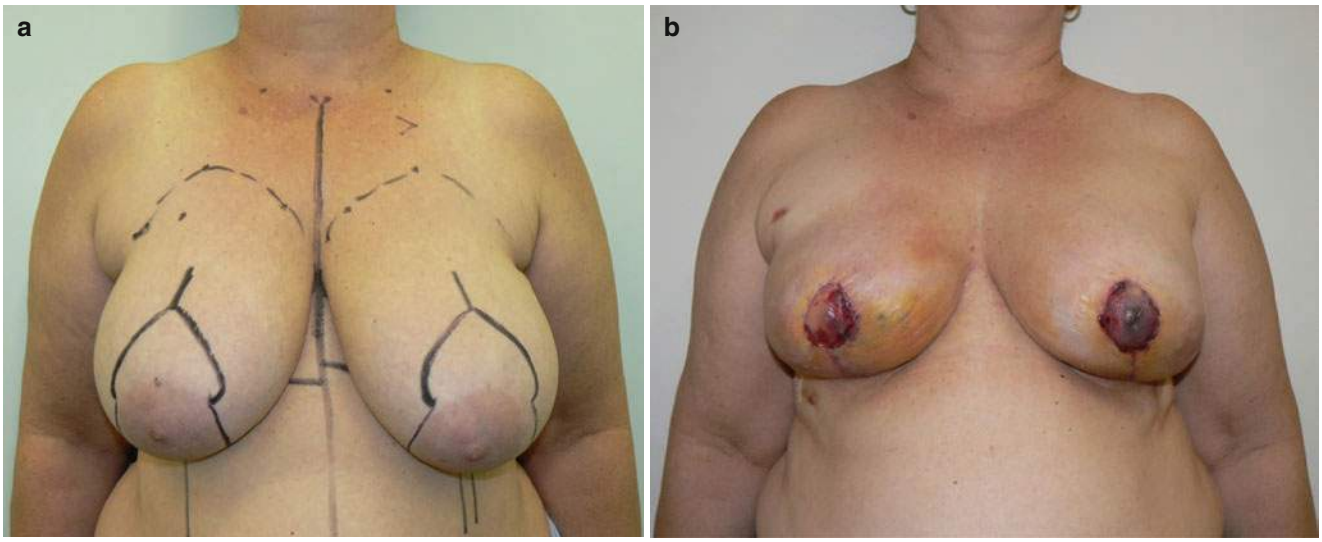

Fig. 40.7 Skin-reducing mastectoy case example

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Autologous Latissimus Dorsi Breast Reconstruction

41

Emmanuel Delay, Oanna Meyer Ganz, and Christophe Ho Quoc

41.1 Introduction

Breast reconstruction is an integral part of breast cancer treatment. An increasing number of patients benefit from immediate or delayed reconstruction. Autologous reconstruction is nowadays the gold standard [1, 2] as it provides excellent and long-standing results in terms of shape, consistency, sensitivity, and integration in the body image.

The musculocutaneous latissimus dorsi flap was first described by Tansini in 1906 for reconstruction of the chest wall after breast amputation [3]. Under the influence of Halsted, which was hostile to plastic surgery, coverage or reconstruction using this flap fell into disuse. Rediscovered in 1976 by Olivari, the latissimus dorsi flap had become a major option in breast reconstruction [4]. From the 1980s onward, several authors have described the latissimus dorsi as an autologous flap [5, 6], but the results were often unsatisfactory, and the dorsal sequelae were considered to be too important. We have been using the technique of autologous latissimus dorsi breast reconstruction since 1993, as described in our article published in Plastic and Reconstructive Surgery Journal in 1998 [7]. As our experience increased within an intensive practice of breast reconstruction (first author's personal experience of more than 100 reconstructions a year), the autologous latissimus dorsi became our technique of choice.

The volume of the reconstructed breast may be insufficient if the patient is very slim or if there is marked atrophy of the flap. The traditional solution for such cases was secondary insertion of an implant under the flap. Therefore the reconstruction was no longer autologous only and held the disadvantages of an implant such as capsular contracture and a less natural cosmetic result. The development of fat grafting to the breast (lipomodelling) and its use in our department since 1998 have been the ideal solution for the lack of volume of the reconstructed breast and have contributed to the predominant use of this flap.

In the following chapter, we will present our technique of autologous latissimus dorsi flap and its recent developments, the means of obtaining an autologous reconstruction, the indications and contraindications, the complications, the results to be expected, and finally its advantages and drawbacks.

41.2 Surgical Anatomy of the Autologous Latissimus Dorsi Flap

41.2.1 The Latissimus Dorsi Muscle

The latissimus dorsi is a thin and wide muscle. It inserts anteriorly on the lower four ribs, where four attachments converge with the digitations of the abdominal external oblique muscle. The medial and lower part of the muscle inserts on the thoracolumbar fascia which extends over the spinous processes of the lower six thoracic vertebrae, the five lumbar vertebrae, the sacral vertebrae, and the posterior third of the iliac crest. Its upper border covers the inferior angle of the scapula, where an accessory bundle of teres major is often observed. Together with the later, it defines the posterior wall of the axilla before ending its insertion at the bicipital groove of the humerus, between the pectoralis major and the teres major tendons. Its deep aspect carries attachments that are common to the latissimus dorsi and the serratus anterior muscles.

The latissimus dorsi vascular supply is a type V according to Mathes and Nahai classification, with a main thoracodorsal pedicle and accessory segmental pedicles arising from the intercostal and lumbar arteries. When the thoracodorsal pedicle penetrates in the deep aspect of latissimus dorsi, it divides into two branches of equal importance: the descending branch

Electronic Supplementary Material The online version of this chapter (doi:10.1007/978-3-319-62927-8_41) contains supplementary material, which is available to authorized users.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_41

and the transverse branch. The thoracodorsal nerve provides the motor function originating from the posterior secondary trunk C6-C8. Its origin is about 3 cm medial to the vascular pedicle. It then joins the vascular pedicle before penetrating the muscle. Exceptions are cases where the artery originates more proximally and then the nerve is found between the artery and the vein.

Latissimus dorsi allows adduction, backward and internal rotation of the upper limb.

It is therefore involved in weight-bearing movements such as walking with crutches and in vertical traction with the arms raised above the head. Its removal has little effect on daily activities or amateur sports practice, but its lack can be more significantly felt in cross-country skiing and in rock climbing.

41.2.2 The Fatty Extensions of the Latissimus Dorsi Muscle

The autologous latissimus dorsi flap aims to increase the volume provided by the latissimus dorsi muscle by incorporating fatty areas which are true extensions of the flap (Fig. 41.1a–c); they are especially important since muscle atrophies after transfer when it is no longer used. We have described six fatty areas [1] that are harvested as a complement to the muscle:

- Zone 1 corresponds to the fatty area of the crescent of the dorsal skin paddle.
- Zone 2 represents the deep layer of fat lying between the muscle and the Scarpa's fascia (superficialis fascia); it is harvested all over the surface of the flap.
- Zone 3 consists of the scapular hinge flap which continues on the upper margin of the muscle.
- Zone 4 lies just forward to its external margin, forming an anterior hinge flap.
- Zone 5 corresponds to the supra-iliac fat deposits or "love handles."
- Zone 6 is the adipose tissue of the deep aspect of the muscle.

The amount of fatty tissue gained depends on the extent of the patients' fat deposits.

These zones are reliably vascularized by muscular perforating pedicles. Zone 3 has the advantage of a vascular plexus between several cutaneous branches (vertical branch of the circumflex scapular artery, intercostal branch, lateral thoracic branch) and two perforating pedicles of the thoracodorsal artery which anastomose between themselves.

41.3 Objectives of Breast Reconstruction

Both objectives of breast reconstruction are clear:

- To restore the skin, shape, volume, and consistency of the reconstructed breast
- To reestablish the symmetry and harmony of both breasts

From a technical viewpoint, the breast requires restoration of the container, or skin envelope, and of the content, or volume. Two months after the first stage of breast reconstruction with the autologous latissimus dorsi flap, the muscle has undergone some atrophy, and the second stage can be considered to restore breast symmetry and reconstruct the nipple-areola complex.

41.4 Indications/Contraindications

The latissimus dorsi is a flap of choice because of its safety and reliability. It can be used in the vast majority of clinical situations. Whether the patient is slim or overweight, her morphology is not in itself a contraindication to this technique. It can be used in delayed or immediate breast reconstruction. It can also be used in case of an adjuvant radiotherapy needed.

Contraindications are very rare: a lesion of both the latissimus dorsi pedicle and the serratus anterior pedicle or a congenital absence of latissimus dorsi (Fig. 41.2). It is important to check the muscular contraction by the resisted adduction test to ensure the presence of a functional latissimus dorsi with a preserved motor nerve. The preservation of the nerve is almost invariably associated with a patent thoracodorsal pedicle. Relative contraindications of the flap are dorsal pathologies (scoliosis, chronic rachis wounds) and when the patient refuses a scar on her back.

41.5 Surgical Procedure

41.5.1 Preoperative Planning

Preoperative assessment will take into account all data obtained during the preoperative consultation. Particular attention should be paid to the function of latissimus dorsi [1], which generally indicates that the thoracodorsal pedicle is intact. Other important points are the skin and fat that can be harvested in the laterodorsal region, assessing dorsal adiposity by a pinch test. The estimated harvested volume should be compared with the desired volume of the breast. If the estimated volume, after atrophy of the muscle, is inadequate

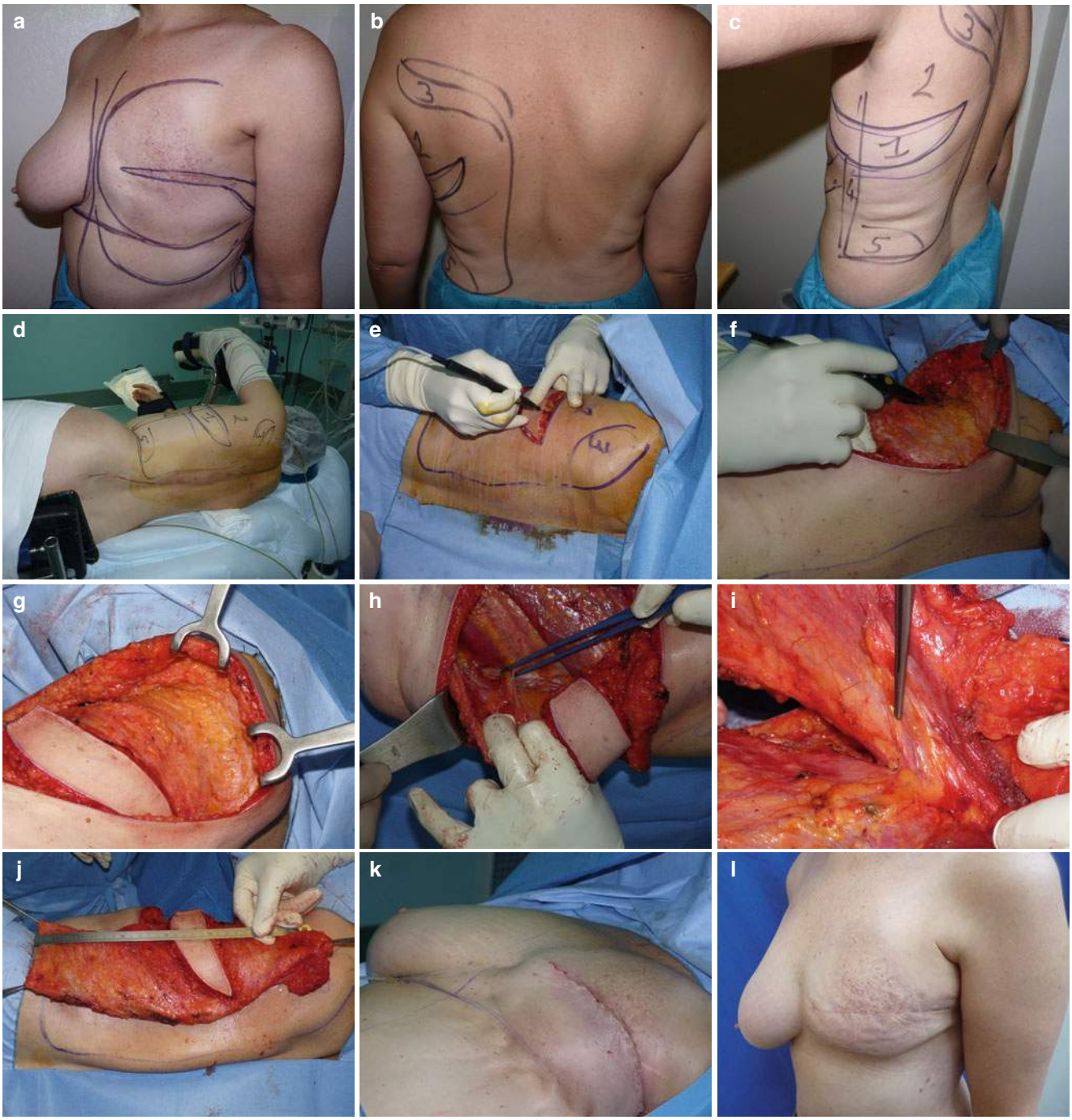

Fig. 41.1 Surgical procedure. (**a**) Preoperative thoracic wall markings. (**b**) Skin paddle and fatty extensions harvested with the autologous latissimus dorsi flap (preoperative back view). (**c**) Skin paddle and fatty extensions harvested with the autologous latissimus dorsi flap (preoperative oblique view). (**d**) Patient in the lateral decubitus position for harvesting the latissimus dorsi flap. (**e**) Skin paddle incision. (**f**) Undermining in an upward direction in the plane of the superficialis (Scarpa) fascia. Surgical procedure (bis). (**g**) Elevation of the scapular fat flap (zone 3). (**h**) Cauterization of the accessory segmental pedicles using bipolar forceps. (**i**) Dissection of the pedicle. (**j**) Autologous latissimus dorsi flap harvested. (**k**) Result at the end of the procedure after total burial of the flap. (**l**) Postoperative oblique view

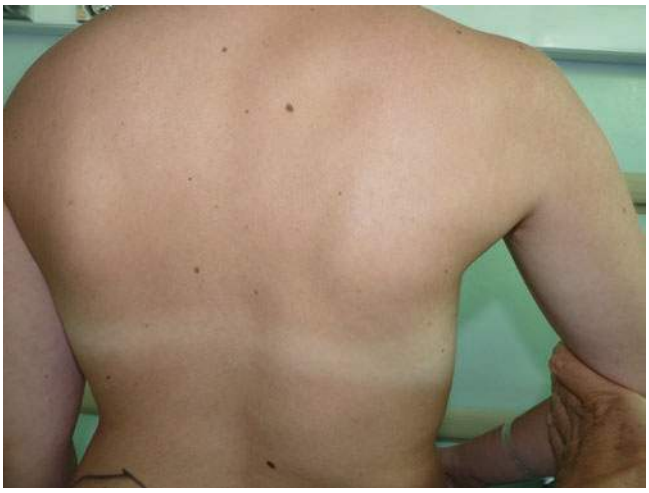

Fig. 41.2 The forced adduction maneuver. Here a congenital absence of latissimus dorsi is characterized by the "coup de hache"

when compared with the opposite breast, secondary fat grafting should already be included in the operative planning. Patients are informed about a horizontal, curved dorsal scar. In delayed reconstruction, the mastectomy scar often continues with the dorsal scar in order to decrease scar length (short scar latissimus dorsi flap).

41.5.2 Design

The reconstruction is designed (Fig. 41.1a) with the patient in upright position [1]. She is asked to lean sideways (Fig. 41.1b, c) in order to reveal the natural folds of the skin and fat. The dorsal skin paddle follows these lines, forming a crescent with a concave upper curve (Fig. 41.1c). The amount of the skin available should be carefully assessed using the pinch test so that closure can be carried out tension-free. The medial extremity of the paddle lies between the inferior angle of the scapula and the spine, while the lateral extremity may extend a few centimeters beyond the anterior margin of the muscle, depending on the patient's morphology. In delayed reconstructions, in the presence of an important sub-axillary dog ear resulting from the mastectomy, it is interesting to integrate the dog ear into the flap, in order to avoid a bigger dog ear following the abdominal advancement flap.

41.5.3 Surgical Technique

The patient is placed in a lateral decubitus position (Fig. 41.1d), with the arm in abduction to open the axilla. The dorsal area is infiltrated with a diluted adrenaline and saline solution. This helps to distinguish Scarpa's fascia (superficialis fascia) during harvest. The skin paddle is incised by a single cut down to the superficialis fascia (Fig. 41.1e, f). Dissection then follows the deep aspect of the superficialis fascia, taking care to leave the deep fat on the muscle (zone 2). The upper limit of the undermined area reaches the inferior angle of the scapula. The medial limit is the trapezius muscle. The whole area of fatty tissue (Fig. 41.1g) between the superior border of latissimus dorsi, trapezius, and the upper limit of the undermining defines the surface of the scapular hinge flap (zone 3). The flap is then harvested respecting the trapezius, teres major, and rhomboid muscles. The cutaneous prolongation of the circumflex scapular pedicle should be carefully cauterized. In the lower part, undermining should be a little wider than the strict area over latissimus dorsi in order to facilitate the following release of the muscle. The lower limit lies above the iliac crests in order to harvest fat from the love handles (zone 5). An alternative option is to harvest the love handles fat by the lipomodelling technique and inject it in the pectoralis major in order to enhance the low neckline. In that case, the lower limit of the latissimus dorsi harvest stops just above the waist. The cutaneous perforators of the intercostal posterior arteries that lie above the transverse processes mark the medial limit. In the lateral part, dissection begins a few centimeters anterior to the anterior margin of the latissimus dorsi in order to harvest fat in zone 4. The muscle is then separated in the deep plane from the serratus anterior by starting at about 12 cm from the axilla, because muscle harvest is easier there [1]. Submuscular undermining is continued by harvesting the deep fat (zone 6) and by carefully cauterizing the accessory pedicles (Fig. 41.1h). When latissimus dorsi is completely undermined, its distal part is sectioned, from the deep part toward the surface, as horizontally as possible in order to include as much fat bulk as possible. Fat located in zone 5 is now often harvested by fat grafting canulas. In the axillary region, the pedicle is then freed so that it can be transposed without tension or kinking, and the latissimus dorsi tendon is sectioned. The pedicle is approached posteriorly by separating the teres major muscle from the latissimus dorsi, in a distal to proximal direction. The origin of the latissimus dorsi pedicle (Fig. 41.1i) is identified by following the serratus anterior pedicle up to the Y-shaped bifurcation. The branch to the serratus anterior should be carefully preserved to ensure blood supply to the flap in case of a lesion of the thoracodorsal pedicle above the bifurcation. The scapular angular artery is cauterized in order to make flap transposition easier. When the pedicle has been identified, a finger is passed under the tendon (between the pedicle and the tendon) to protect it during partial proximal section of the tendon. Ninety-five percent of the tendon is sectioned. The flap is then ready (Fig. 41.1j) to be transposed to the breast area via a subcutaneous tunnel or directly if the dorsal scar is in continuum with the thoracic scar. The donor site [8] is irrigated and hemostasis

checked. The whole area of harvest is closed with quilting sutures done every 3 cm with barbed sutures, and one suction drain is placed.

41.5.4 Positioning and Modeling of the Flap

Patient positioning and modeling of the flap differ in delayed breast reconstruction, in immediate reconstruction or in conversion of implant-based reconstruction to autologous reconstruction.

- *Delayed reconstruction*

We generally try to avoid the use of a dorsal paddle on the breast. The skin of the breast is recruited from a thoracoabdominal advancement flap [9]. The flap is then placed in position in the newly created breast pocket. After making sure that closure can be done without tension, the decision is made to totally bury the flap and the skin of the flap is removed. The flap is then modeled very simply by placing zone 1, with the dermis removed, in a vertical position oriented along the mammary axis, without folding or need for any particular modeling (the cutaneous compartment gives the shape of the breast). Two suction drains are inserted, and then closure is carried out in two planes (Fig. 41.1k, l).

- *Immediate reconstruction*

We usually reserve immediate reconstruction for patients who will not receive adjuvant radiotherapy, although irradiation is well tolerated by the autologous latissimus dorsi flap.

Modelling is begun by recreating the limits of the normal breast compartment with absorbable sutures. The inframammary fold and its axillary extension are the most important structures to recreate. The flap is secured at the upper limit of the mastectomy area by two absorbable sutures. The distal part of the muscle and its underlying fat are folded under the breast mound to increase volume and projection. After placing the latissimus dorsi flap in position, the skin paddle is brought out through the mastectomy incision. We used to shape it as an asymmetrical U, but nowadays we rarely use this design. Instead we place the flap in its breast cutaneous envelope with the skin paddle oriented vertically. As the position of the areola is predefined and since secondary nipple reconstruction using local flaps or composite nipple grafts is known to give disappointing results such as flat nipples lacking projection, we tend to reconstruct the nipple at the same time as the breast. We reconstruct the nipple using the skin paddle of the latissimus dorsi flap (Fig. 41.3d, e). A bifoliate design is used with two rectangular dermal-fat flaps with a central pedicle of about 2 cm by 1 cm; the skin flaps are then rolled around each other recreating the nipple [10].

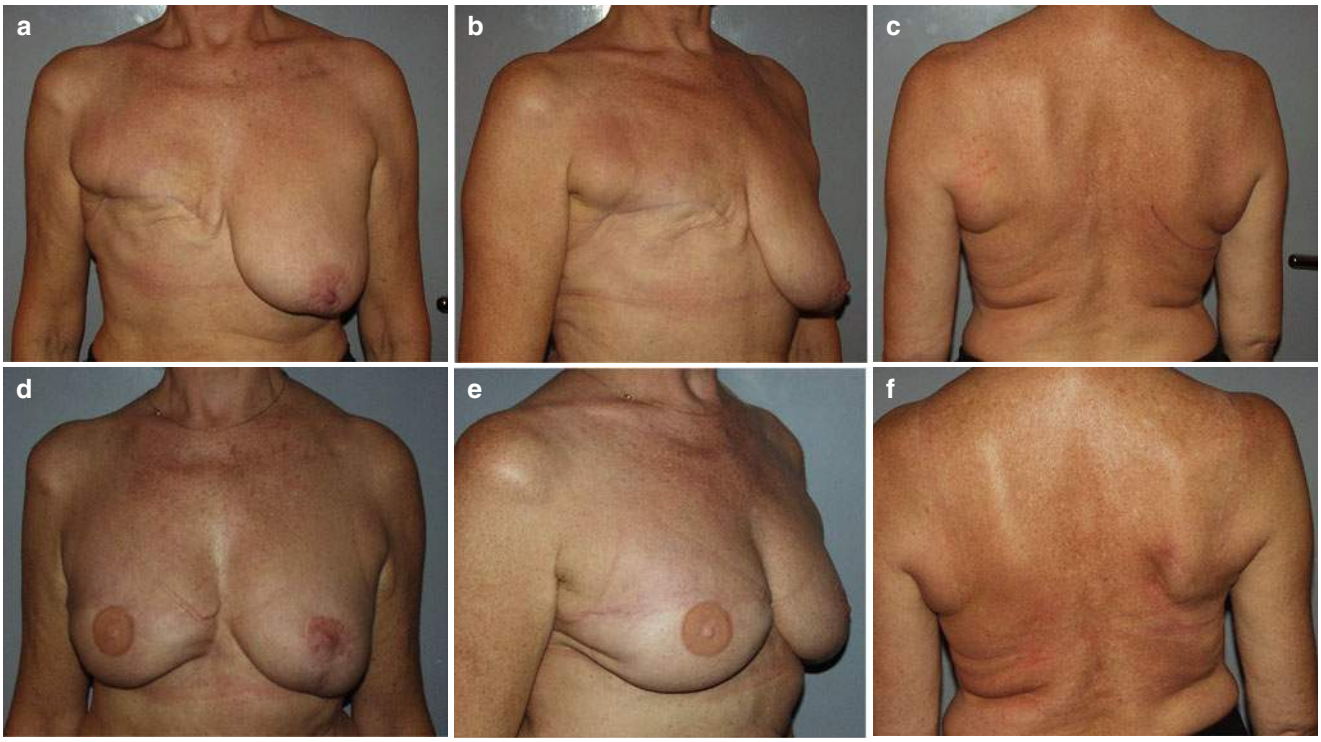

Fig. 41.3 A 61-year-old patient after reconstruction failure with breast implant. Delayed right breast reconstruction combining an autologous latissimus dorsi flap with an abdominal advancement flap. Left breast mastopexy. Result at 12 months. (**a**–**c**) Preoperative views. (**d**–**f**) Postoperative views

The reconstructed breast must be larger than the expected final result and the nipple-areola complex 1 cm higher at the end of the procedure [11]. Since 2007, in order to shorten operative time and avoid position change, we try to make the modeling in the lateral decubitus position. We only make the dorsal dressing in lateral decubitus position. The patient is then put on her back in a sitting position to control the shape of the reconstructed breast: in case of an unsatisfying result, the wound is reopened in order to improve modeling. This approach saves half an hour of operative time and is interesting for very experienced surgeon.

- *Conversion of implant-based breast reconstruction to autologous reconstruction*

Following implant-based breast reconstruction, patients sometimes develop a capsular contracture or express some unsatisfaction about their reconstruction: not being comfortable with a foreign body, feeling their breast cold, or unsatisfied about the aesthetic outcome. In these conditions, conversion of the prosthetic reconstruction to an autologous reconstruction with the autologous latissimus dorsi flap is a good option.

A key point is to underline the mammary base with a nicely marked inframammary fold and lateral fold. If the inframammary fold is already well designed, the intervention can be entirely performed in the lateral decubitus position. Fat harvest of the supra-iliac region allows lipomodelling of the décolleté; the implant is replaced by the autologous latissimus dorsi, and the flap is then totally buried.

41.5.5 Lipomodelling

Lipomodelling is an integral part of the breast reconstruction with the autologous latissimus dorsi flap. Fat grafting of the pectoralis major is already performed during the first operation, but a second sequence is needed approximately 2 months later in order to recreate breast volume. If the patient is expecting a bigger volume and is willing to, a third sequence is planned as well. We try to plan the lipomodelling early enough, before muscle atrophy takes place so the recipient for fat grafts is large as possible. This technique is safe and efficient and became a standard procedure for reconstruction not only after mastectomy but also after breast conservative treatment and for breast or thorax malformation [12–16].

41.5.5.1 Markings

Areas of the breast requiring correction are marked on the upright standing patient. The various fatty deposits areas of the body are identified. In the reconstruction setting, the abdominal fat is often harvested first as it is greatly appreciated by patients, and it does not require position change during the procedure. Other areas often harvested in dorsal decubitus are the anterior and internal thighs and the internal knees.

41.5.5.2 Anesthesia

Lipomodelling is performed under general anesthesia because of the important amounts of harvested fat in the majority of patients. IV prophylactic antibiotics are given at anesthesia induction.

41.5.5.3 Fat Harvest

Fat infiltration is made with infiltration cannulas with a solution of 0.5 l saline and 0.5 mg adrenaline. Fat is suctioned manually with a blunt tip, 5-hole cannula of 3.5 mm diameter connected to a 10 ml syringe. Suction depression is moderate to minimize adipocytes damage. Enough fat has to be harvested to compensate for the loss during centrifugation and the expected resorption after transfer. Finally, harvested areas are infiltrated with a ropivacaine-saline solution before closure in order to reduce postoperative pain.

41.5.5.4 Fat Preparation

The assistant prepares the fat during the harvesting process. Fat is centrifuged for 20 s at 3200 rpm. The top layer of oily fluid and the bottom layer of serum remnants are then discard in order to keep the middle layer of purified fat. Using a three-way tap, the 10 ml syringes are filled with purified fat.

41.5.5.5 Fat Transfer (Fig. 41.4)

Punctiform incisions are made in the breast with a 18G needle. Fat is injected to the breast with a 2 mm diameter cannula of 13 or 20 cm length connected to a 10 ml syringe. Several incisions are made in order to create multiple microtunnels for fat transfer in different directions, but tunnels must be always parallel to the thorax in order to avoid pneumothorax. About 2 ml fat is transferred at each cannula withdrawal, creating fine fat lines resembling to spaghettis. Spatial visualization is needed to form a three-dimensional matrix and to avoid areas of fatty collections that would lead to fat necrosis. Adherences are freed by fasciotomies done with a hook over the adherence and a 18G needle for release.

41.6 Results

The results of breast reconstruction with the autologous latissimus dorsi flap were first evaluated in 1998, followed by a study of 400 cases in 2001. Both patients and surgeons

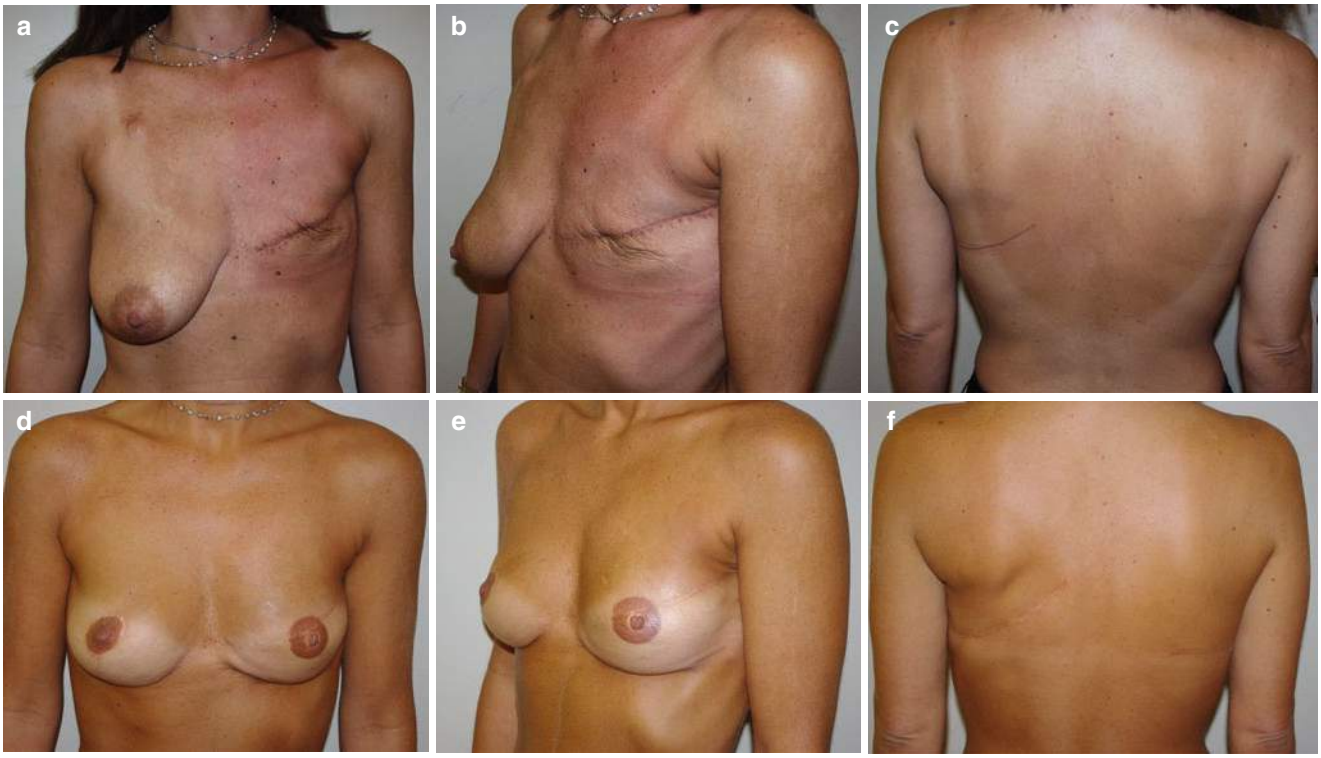

Fig. 41.4 A 45-year-old patient after radiotherapy. Delayed left breast reconstruction in a slim patient with an autologous latissimus dorsi and abdominal advancement flap. Right mastopexy and left lipomodelling (251 cc) at 5 months. Results at 12 months postoperatively. (**a**–**c**) Preoperative views. (**d**–**f**) Postoperative view

showed a very high satisfaction rate in 97% of cases (87% of the cases were rated "very good" by the surgeons versus 85% of cases by the patients, 10% of the cases were rated "good" by the surgeons versus 12% of cases by the patients). There was no case considered a failure. Residual scarring of the back was assessed as minimal by 96% of patients and moderate by 4%. In addition to the satisfying cosmetic result, autologous latissimus dorsi breast reconstruction enabled patients to better integrate their new body image and to recover their feminity, due to the sensitive supple, warm, and natural feeling of the flap [17]. Lipomodelling improves perception of the flap as well, by making it supple enough to imitate the consistency of a natural breast.

We present some clinical cases with long-standing results (Figs. 41.3, 41.4, 41.5, 41.6 and 41.7).

41.7 Complications

We describe the complications possibly associated with the procedure (1290 surgical procedures done by the senior author), the strategies used to prevent their occurrence, as well as the techniques available for managing such complications when they occur.

41.7.1 Immediate Complications

- *Latissimus dorsi myocutaneous flap necrosis:* There was one case of complete flap necrosis (non-patent vascular pedicle) and two cases of partial necrosis. In the first case, early surgical debridement was required on postoperative day 6 to remove the latissimus dorsi flap before the onset of an infection. Creation of a small abdominal advancement flap allowed subsequent breast reconstruction with subpectoral prosthesis implantation [1]. In the two cases of partial necrosis, we could maintain a pure autologous reconstruction thanks to fat grafting at a second stage.
- *Postoperative dorsal hematoma:* The risk for hematoma formation is related to the extent of flap harvesting and is similar to the risk of patients undergoing traditional musculocutaneous latissimus dorsi flap, which is less than 1%. Careful ligation or cauterization of secondary segmental pedicles and compressive dressing of the back are required to achieve good hemostasis. However since we use barbed sutures as quilting suture to close the dead space of the back, we have no more hematoma.

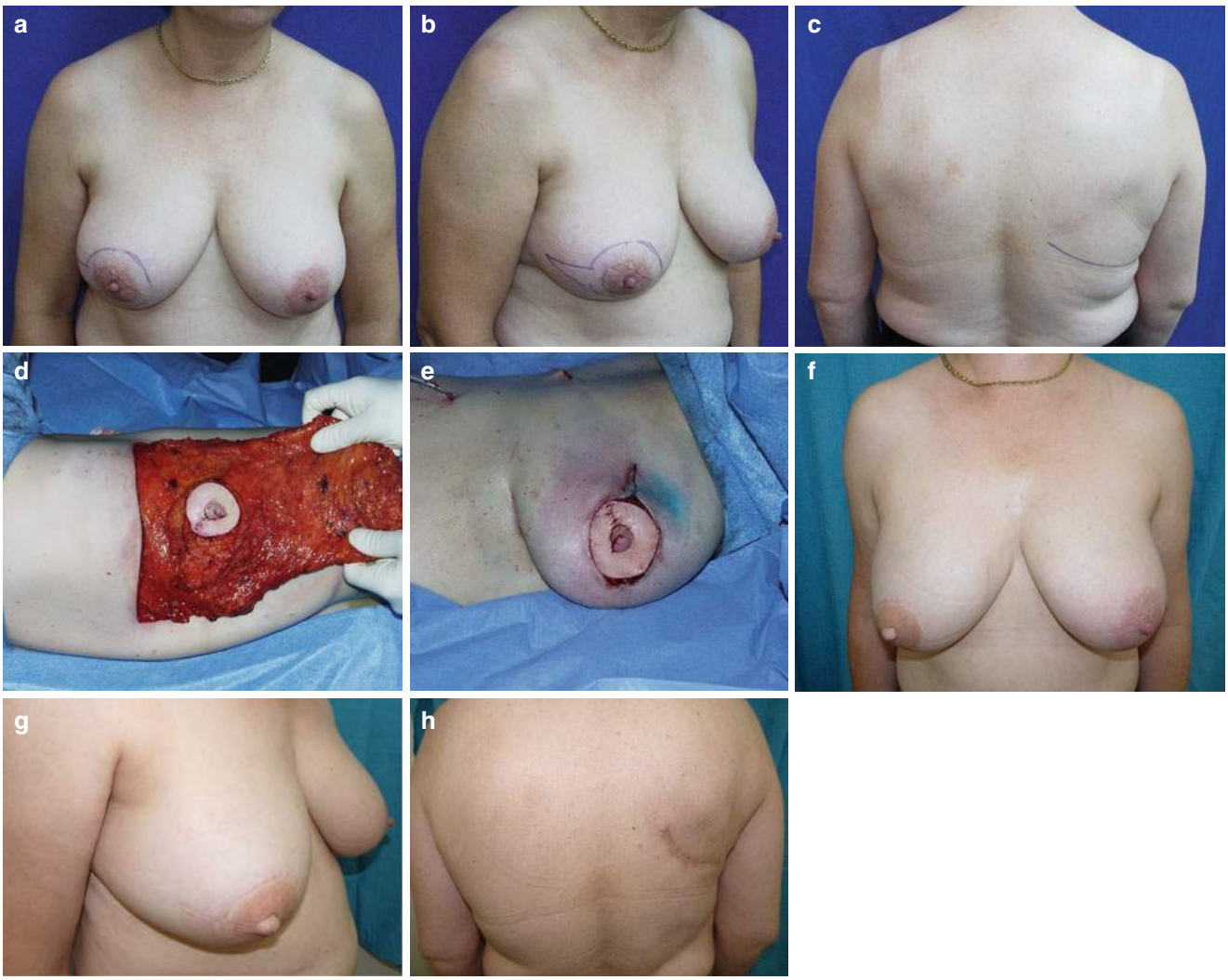

Fig. 41.5 A 43-year-old patient. Right immediate autologous latissimus dorsi reconstruction and immediate nipple reconstruction after skin-sparing mastectomy. Lipomodelling of right breast (231 cc). Results at 12 months postoperatively. (**a** and **b**) Preoperative views. (**c**) Preoperative latissimus dorsi flap. (**d**) Preoperative nipple areolar complex reconstruction. (**e**–**g**) Postoperative views

- *Infection:* The risk of infection is extremely low, less than 1% owing to the autologous nature of the procedure and the high vascularization of the muscle. Infection of the dorsal seroma is reported in approximately 1% of cases. It is generally attributed to secondary infection in patients undergoing draining puncture.

41.7.2 Early Complications

- *Skin morbidity at the donor site:* The extensive dorsal undermining required for elevating the myocutaneous latissimus dorsi flap with its fatty extensions could compromise the skin. The risk stays relatively low (1% of our patients). Skin necrosis happens when the flap harvest is too thick, with a dissection carried out above the superficialis fascia [1]. Skin necrosis also occurs when an extensive dorsal paddle is harvested. We report no skin necrosis of the donor site in our series.
- *Skin morbidity at the recipient site:* In patients undergoing immediate breast reconstruction, the skin of the breast is preserved. Skin morbidity in these patients is thus not directly related to the technique used for reconstruction [10]. In case of delayed breast reconstruction with thoracoabdominal advancement flap, marginal skin necrosis is seen in approximately 5% of the patients. Marginal necrosis (0.5–1 cm) can be excised and closed under local anesthesia or by secondary closure with insertion of a local flap.
- *Seroma formation at the donor site:* Before using quilting sutures, this was the most common and the mildest complication of latissimus dorsi flap. In our experience, seroma occurrence is more of a nuisance than a complication, and

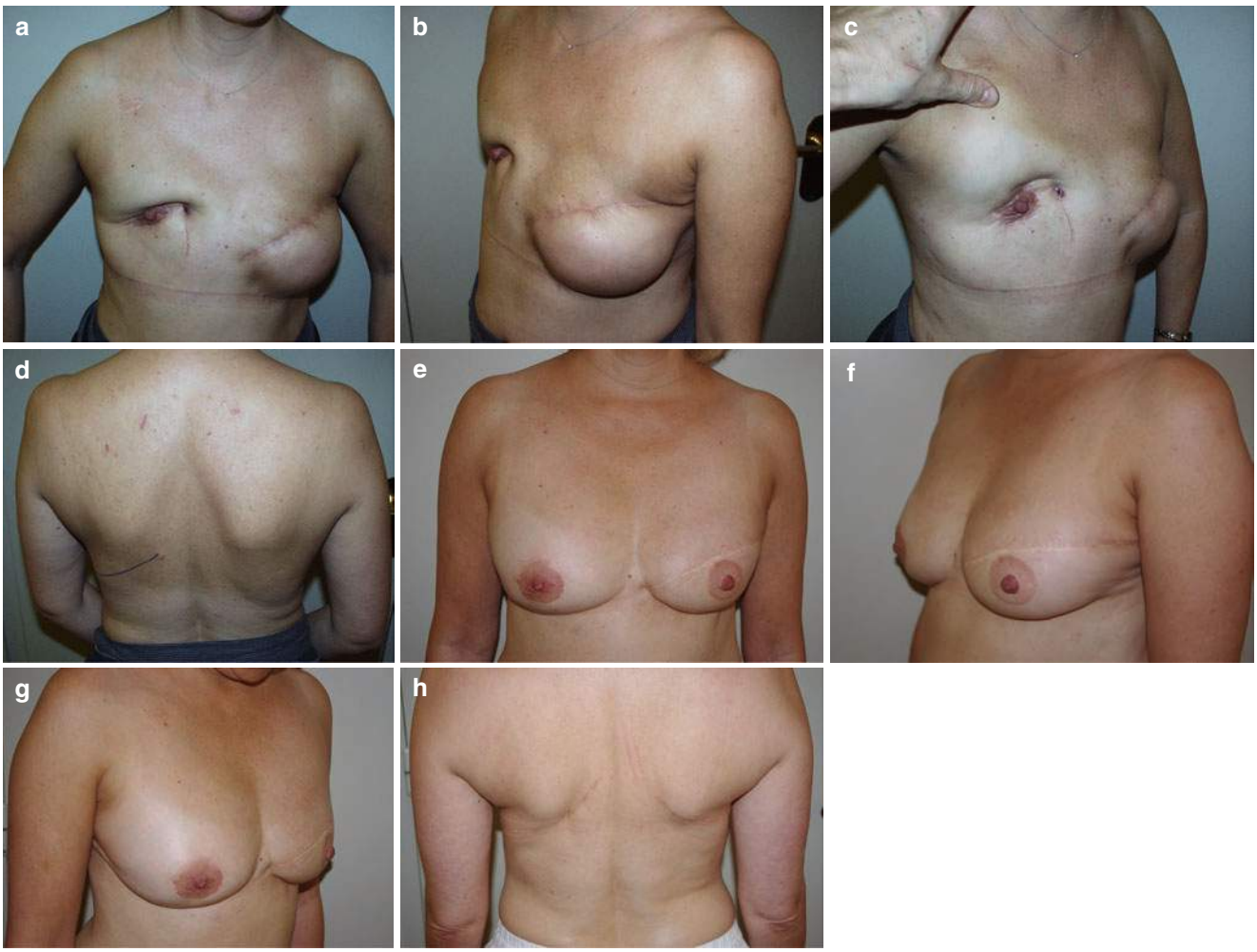

Fig. 41.6 A 43-year-old patient. Secondary case of capsular contracture stage 3 after left breast reconstruction with implant and right implant extrusion after prophylactic mastectomy and breast immediate reconstruction. Conversion of the left reconstruction with autologous latissimus dorsi flap and right breast reconstruction with a second-stage autologous latissimus dorsi flap. Both flaps are totally buried under thoracic and abdominal skin. Results at 3 years after a complementary lipomodelling session

it has not prevented the extensive development of the technique in our institution. In 2006, we started to use quilting sutures in all our patients. The technique [8] consists in placing numerous stitches between the superficialis fascia and the thoracic wall (10 stitches on the upper cut dorsal flap and nearly 16 stitches on the lower dorsal flap). Seroma incidence rates decreased from 21% to 9% in our patient population. Since we use barbed sutures for quilting (making zigzags to close the dead space), our seroma incidence seems even lower, and we had no more chronic seroma.

- *Scapular sequelae:* Latissimus dorsi muscle harvest may result in long-term deficit of shoulder function. However, the loss of the latissimus dorsi is well compensated by other muscles of the shoulder. In some rare cases (1%), the patient may experience transient shoulder stiffness or even develop scapulohumeral periarthritis. This damage is more frequent after immediate breast reconstruction, when the constraints of reconstruction cumulate with those of mastectomy and axillary dissection, but it may also occur in patients undergoing mastectomy alone. Coping and psychological follow-up are very important to limit scapular and dorsal pains.

41.7.3 Late Complications

- *Loss or insufficient breast volume:* A breast volume decrease is observed at 3 postoperative months due to muscle atrophy [12]. Plastic surgeons involved in these procedures must have thorough knowledge of the outcome of fat grafting after autologous latissimus dorsi flap reconstruction. Lipomodelling [2, 12] should always be offered to the patient as a second stage. If the volume of the reconstructed breast decreases after a few months, it

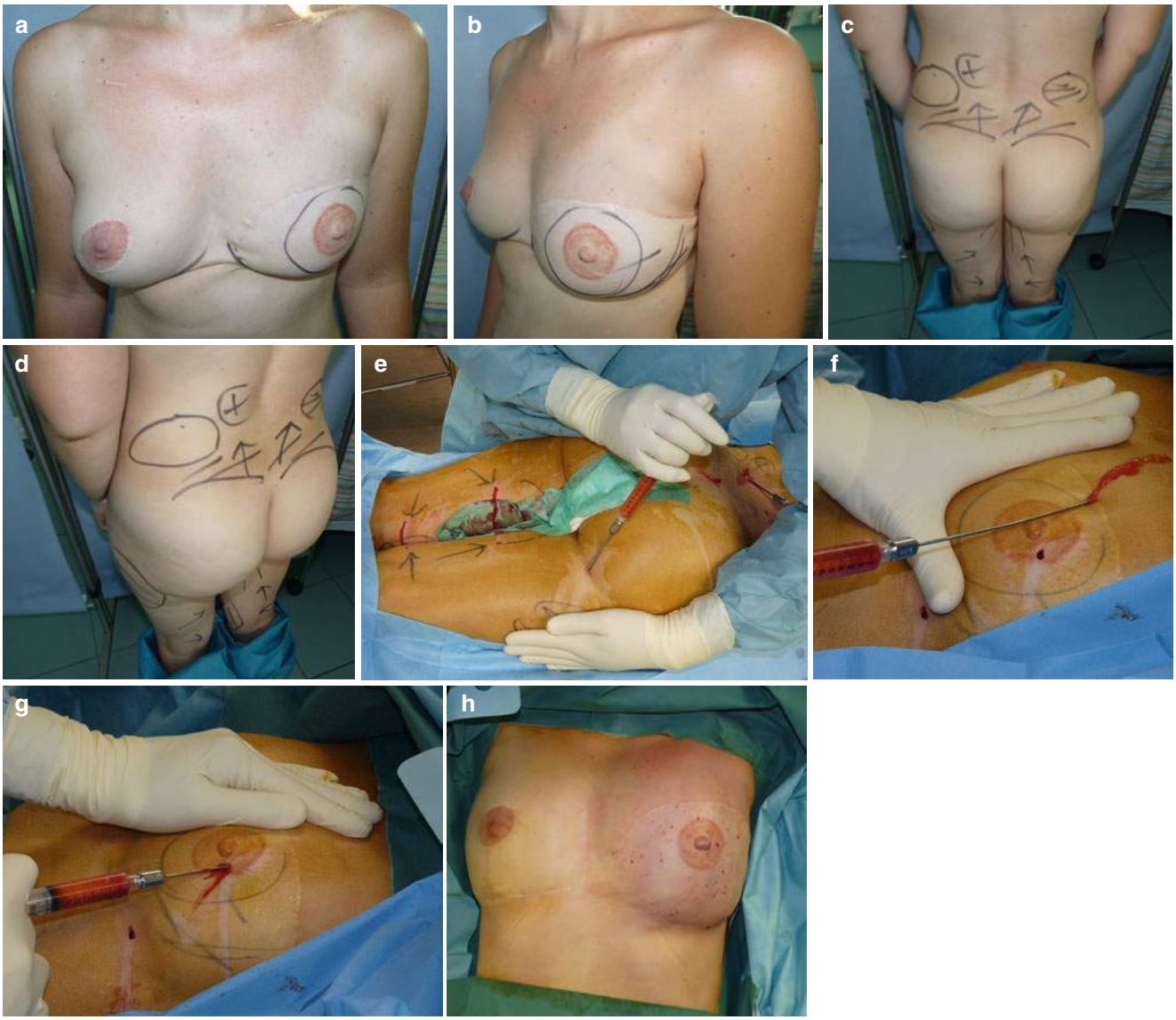

Fig. 41.7 Delayed left breast reconstruction wit autologous latissimus dorsi and a complementary stage of lipomodelling. (**a**, **b**) Preoperative views. (**c**, **d**) Preoperative markings. (**e**) Fat harvesting with 3.5 mm cannula. (**f**) The spaghetti principle. (**g**) Fat transfer into the breast. (**h**) Preoperative result, the breast is mildly hypercorrected

could be possible to improve the match with the natural breast by lipomodelling [13] with very good long-standing results. A transient overcorrection of the volume of the breast is necessary to obtain satisfactory results on the long term [13, 14]. When large breast augmentation is required, repeated lipomodelling sessions are performed [15, 16].

- *Dorsal pain:* The intensity of pain may vary according to the patient's physical and psychological state, ranging from "no discomfort at all" to "dorsal pain." Pool physiotherapy is also a fundamental tool to achieve early and complete back and shoulder rehabilitation.
- *Dorsal hematoma:* The late occurrence of a seroma-hematoma is reported in 2% of our first 400 patients. Hematoma is caused by the collection of blood at the donor site, possibly due to the rupture of a vein while making violent movements. Like dorsal seroma, this complication has dramatically decreased with the systematic use of quilting suture for the closure of dorsal wounds and has completely disappeared with the use of barbed sutures for quilting.

41.8 Conclusion

The autologous latissimus dorsi flap has become a perfectly adapted procedure for pure autologous breast reconstructions. After various technical improvements, its ease of use; its versatility, reliability, and acceptable constraints; and its low complication rate make this technique our major surgi-

cal procedure for autologous breast reconstruction. Because of its excellent blood supply, it can be used in difficult cases as in radiation sequelae. A second stage of fat grafting is required to optimize results in order to obtain a reconstructed breast with a volume, shape, and consistency close to a normal breast. We consider the autologous latissimus as an ideal matrix for fat transfer.

This procedure needs a learning curve and a specific training to get good results. In our experience, this technique provides excellent long-standing results for autologous breast reconstruction. With the new approach of the short scar latissimus dorsi flap, this technique appears as the new "gold standard" in breast reconstruction.

Disclosure None.

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Monopedicled TRAM Flap

42

Andrea Manconi

The transverse rectus abdominis myocutaneous (TRAM) flap revolutionized breast reconstruction, allowing surgeons to create a breast that is soft, warm, and with good and long-lasting result [1]. Despite advances in free flap breast reconstruction, pedicled TRAM flap breast reconstruction remains an excellent option for unilateral breast reconstructions. Unlike microsurgical breast reconstruction, the pedicled TRAM flap does not require sophisticated postoperative monitoring and can be performed efficiently in any hospital setting.

42.1 History

Robbins [2] described the use of a vertical rectus abdominis flap for breast reconstruction in 1979. Drever [3], Dinner [4], and Sakai [5] refined variations on the use of vertical rectus abdominis myocutaneous flaps for breast reconstruction, but initially Hartrampf observed during abdominoplasty procedures that the lower abdomen could survive as an island of tissue as long as the attachments to the rectus muscle were kept intact. Hartrampf and colleagues [6–8] took the bold step of changing the skin island orientation to a transverse one across the midabdomen, making a larger volume of tissue available for breast reconstruction with a cosmetically desirable donor site describing in 1982 the TRAM flap as the use of the excess skin and subcutaneous fat that is routinely discarded in an aesthetic abdominoplasty for breast reconstruction. From these beginnings, the TRAM flap was destined to become the gold standard procedure for breast reconstruction, and nowadays, it remains a very good surgical option. Subsequently, several free flap options have developed as refinements of the original pedicled technique, including the free TRAM, the muscle-sparing free TRAM, and the perforator flaps.

42.2 Anatomy

The skin and fat of the lower abdomen are supplied by five major sources:

- Superior epigastric vessels arising from the termination of the internal mammary vessels
- Deep inferior epigastric vessels
- Superficial inferior epigastric vessels
- Intercostal segmental vessels
- The superficial and deep circumflex iliac vessels

The predominant blood supply of these areas is from the deep inferior epigastric system [9–11]. The vessels from both epigastric systems perforate the rectus muscles on their deep surfaces and travel as single or duplicated vessels up and down the flap arising to the skin in two rows, a medial one and a lateral one (Fig. 42.1). This system is cranially connected with the superior epigastric vessels, which represents the unique vascular pedicle used when raising a pedicled TRAM flap, even if the eighth intercostal vessels can be incorporated into the pedicle to augment blood supply if necessary.

Rectus muscles can be vascularized by three different patterns:

Type I: single superior and inferior arterial supply (29%)

Type II: double-branched system from each source artery (57%)

Type III: has a triple-branched system from each vessel (14%)

Symmetrical vascular pattern symmetry was described in only 2% of patients.

Electronic Supplementary Material The online version of this chapter (doi:10.1007/978-3-319-62927-8_42) contains supplementary material, which is available to authorized users.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_42

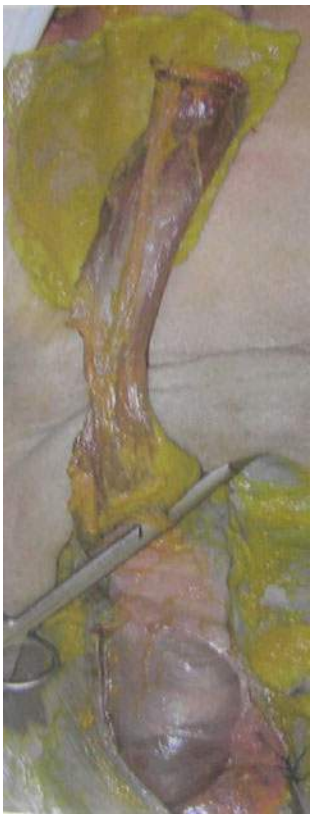


Fig. 42.1 Corpse dissection of a TRAM flap: scissors are collocated behind superior pedicle, and flap is rotated toward the chest. It is clearly visible the inferior pedicle running posteriorly to the rectus muscle

Millory found that only 40–50% of patients have macroscopic communication between the two systems, while 60% of patients have choke vessels of microscopic caliber [12]. The superior vessels pass into the muscle from the deep aspect of the costal margin and run inferiorly. The distal supply enters the posterolateral aspect of the muscle below the arcuate line and passes up to anastomose with the superior vessels in the periumbilical area. Major vascular supply is provided by the deep inferior vessel with venous drainage system supported by two large venae comitantes into the iliac vein. The inferior and the superior venous systems create an anastomotic web at the umbilical level. When a pedicled TRAM flap is raised, distal venous flow has to reverse and follow the drainage pattern of the superior veins, overcoming the venous valves within the choke system described by Taylor and colleagues [11]. Arterial perforators arise in two rows aside the linea alba. The lateral row lies 2–3 cm within the lateral border of the rectus sheath, while the medial row lies 1–2 cm from the linea alba. These vessels vary significantly in both size and number; their caliber may vary up to several millimeters in diameter.

The anterior rectus sheath is tightly adherent to the muscle at the tendinous inscriptions. It is formed by two layers provided by external and internal oblique muscles in the lower rectus muscle and by a single layer in upper rectus muscles. During flap elevation, it is possible to harvest a gentle strip of fascia within the muscle in order to keep it more resistant to tractions or to spare as much fascia as possible in order to provide a more stable closure of the door site [13]. A muscle-sparing technique can be used to leave strips of the muscle laterally and medially to assist in maintaining abdominal wall strength, but it has been demonstrated that any left muscular segment loses neurovascular inputs [14, 15]. For these reasons nowadays, muscle-sparing pedicle TRAM flap can be considered obsolete. Two major vascular classifications exist for TRAM flap blood supply. The most classical description was introduced by Hartrampf (Fig. 42.2a), who divided the supply into four zones:

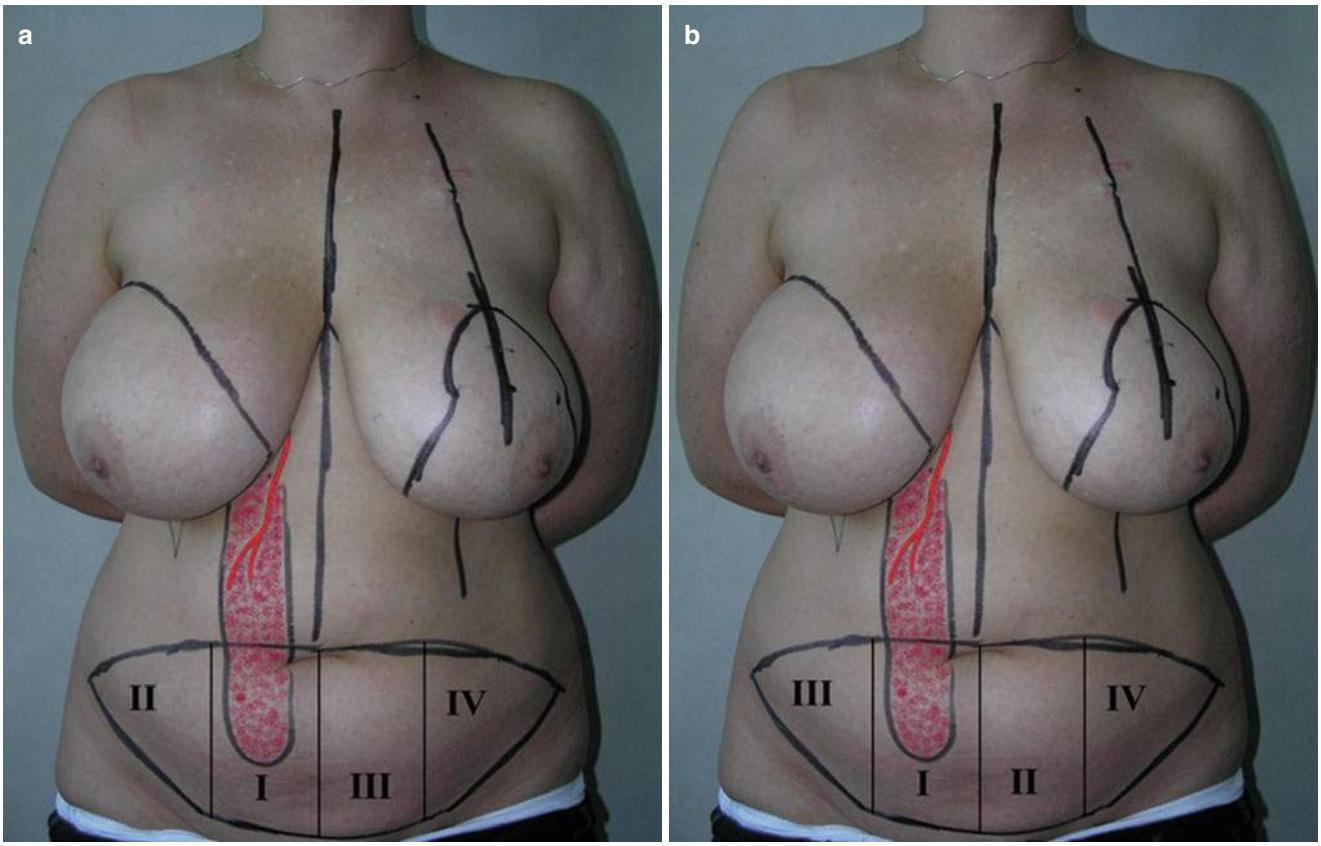
- Zone I: overlying the muscle pedicle
- Zone II: lying across the midline, immediately adjacent to zone I
- Zone III: lying lateral to zone I on the ipsilateral side
- Zone IV: lying lateral to zone II on the contralateral side from the pedicle

Zone I has been found to be the most reliable portion of the flap. The medial portion of zone III is the next most reliable portion of the flap, but it decreases in blood supply close to the ipsilateral tip. The medial portion of zone II is also usually reliable, but the lateral part is less predictable. Finally zone IV should be always considered not vascularized and discarded routinely. Holm and colleagues [16] demonstrated that while zone I remains the most reliably perfused portion of the flap, any flow across the midline is more precarious than ipsilateral flow. So the classification proposes that Hartrampf's zone III should be renamed zone II, while Hartrampf's zone II should be renamed zone III (Fig. 42.2b) .

Moon and Taylor [11] recommend surgical delay of the TRAM flap 1 week before definitive elevation. The procedure focuses on ligation of the superficial and deep inferior epigastric systems in an outpatient setting. It increases arterial supply, but TRAM flap partial necrosis is often related to venous congestion rather than arterial inadequacy. Bigger flap can be raised with a bipedicled approach or as a free flap.

42.3 Surgical Technique

Appropriate patient selection is the key to achieving predictable results. Candidates for TRAM flap breast reconstruction must have sufficient lower abdominal tissue to achieve a successful reconstruction. Clinically, this can be evaluated by estimating the amount of superficial fat in the lower abdomen



Figs. 42.2 (**a**, **b**) TRAM flap vascular zone classification by Hartrampf on the right and by Holm on the left

by squeezing the tissue between one's index finger and thumb (i.e., the "pinch test"). Patients with prior abdominal surgery should be carefully selected before undergoing to TRAM flap reconstruction. Pfannestiel and McBurney incision can be considered safe. Surgical technique for flap harvesting can be considerate similar in immediate or delayed reconstruction. Preoperative markings consist in midline drawing (very effective in donor site closure to achieve a good symmetry and result) and cutaneous palette drawing. This is obtained marking a sovrapubic transverse straight or arcuate line from one inguinal fold to the other. Laterally it continues upward in the inguinal fold or parallel to it up to the superior transverse mark. This line is drawn 1 or 2 cm above the navel, and laterally it creates an angle aside the anterior superior iliac spine. Markings are variable in function of the amount of the skin and fat available in the lower abdomen. Also inframammary folds are marked. Preoperative Doppler is useful in order to find perforators, but it isn't mandatory. Recipient site markings are different in case of immediate or delayed reconstruction. In immediate breast reconstruction, the breast ongoing to mastectomy is marked on oncological patterns such as Patey mastectomy, skin-sparing mastectomy, or nipple-sparing mastectomy.

In case of delayed breast reconstruction, it is suggested to mark inframammary fold in the contralateral breast and to recreate the opposite one with the same footprint but 2 cm above: it will be lowered during the donor site closure by donor site suture tension. The skin between this marking and mastectomy scar should be removed in order to recreate a natural new inframammary fold, but the surrounding skin should be excised if radiodystrophic. Tight mastectomy scar can also be cut in a Z-style incision if releasing skin tension is needed.

Perioperative assessment consists in heparin prophylaxis associated with pneumatic leg pumps. Blood transfusions can be required but should be prevented. Patient is positioned on a folding surgical bed.

Surgery starts undermining the epigastric flap in a suprafascial plane. The skin is incised to the sheath with an upward 45° inclination in order to include as many perforators as possible and also in order to face donor site skin flap with similar thickness (Fig. 42.3).

Rectus abdominis muscles are both individuated up to the rib arc and xiphoid. Rectus muscles and external oblique muscles are dissected on a suprafascial plane keeping a very thin layer of fat on the fascia in order to respect suprafascial vascularization as much as possible (Fig. 42.4).

After that, a tunnel is undermined to the breast. Tunnel should be large enough to let surgeon fist pass. Before continuing dissection, it is helpful to tilt the patient in order to check donor site closure (Fig. 42.5).

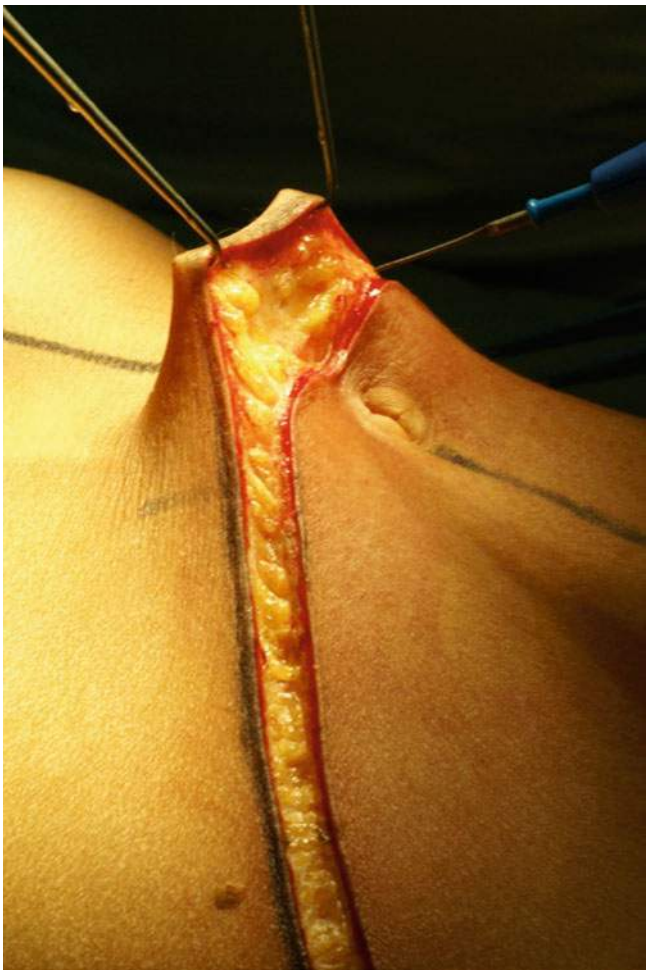


Fig. 42.3 Elevating the epigastric skin flap. A 45° initial incision can obtain several improvements such as better skin vascularization and better donor site close with nice aesthetic result

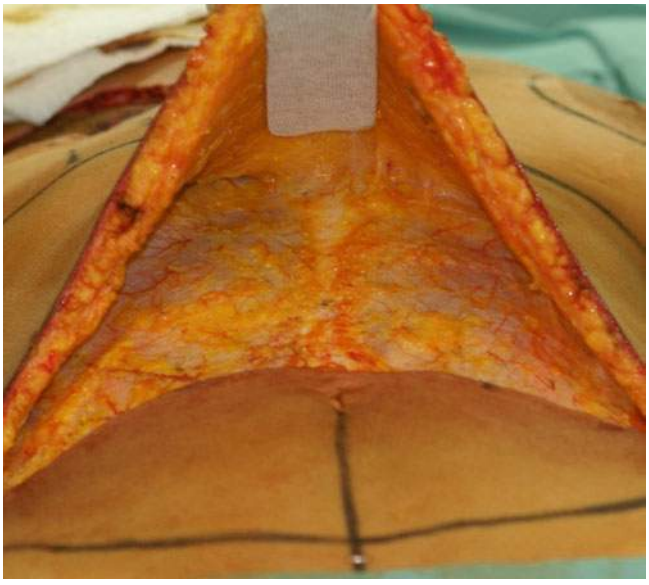


Fig. 42.4 Epigastric skin flap is elevated: rectus muscles are both individuated up to the rib arc

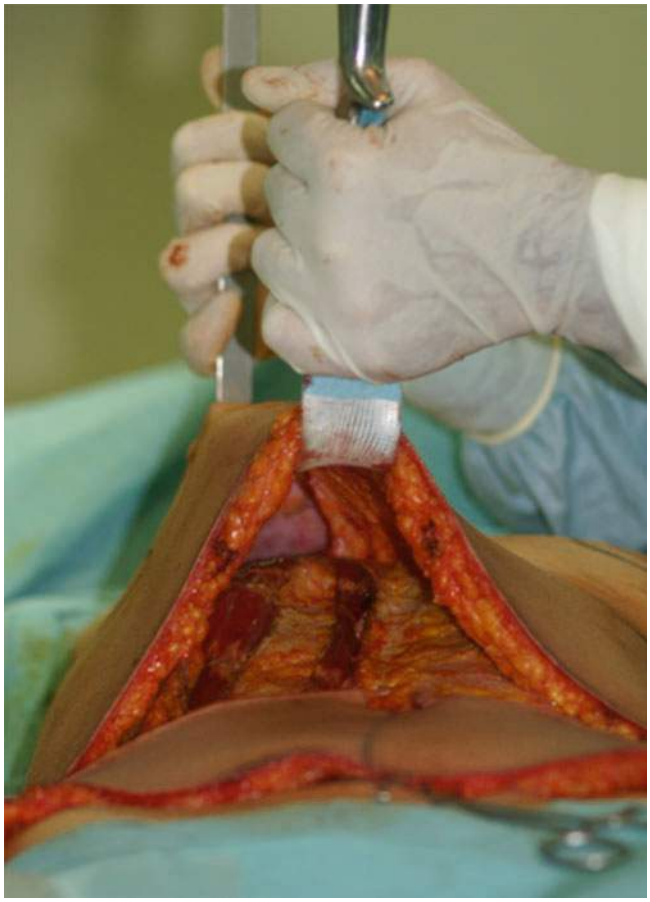


Fig. 42.5 A tunnel is undermined to let transpose the flap to the chest. It should be large enough, but it is suggested that dissection should not exceed midline in order to respect the inframammary fold

Before continuing the flap dissection, it is suggested that donor site closure should be checked (Fig. 42.6). In case of excessive skin tension, it is possible to modify preoperative lower markings.

Flap dissection continues with sovrafascial dissection of the TRAM flap skin island from lateral to medial identifying perforators (Fig. 42.7). The choice of an ipsilateral or a contralateral pedicle can be based on the availability of good perforators. If possible it is suggested to harvest an ipsilateral pedicle because it has been described to have a better perfusion [17] and also a better arch of rotation. Also ipsilateral pedicle avoids to have a muscle bulge in xiphoid after flap rotation.

Once the side to be dissected is decided, rectus sheet is incised all along its length medially the lateral border and few millimeters laterally the perforators. Fascia is also incised 1 cm lateral to the medial border of the muscle down to skin palette (Fig. 42.8).

The muscle is dissected from the fascia and intercostal segmental vessels, and nerves are ligated (Fig. 42.9). Main vessels run just beneath the muscle, so it is suggested that posterior fascia should be dissected by fat surrounding main vessels.

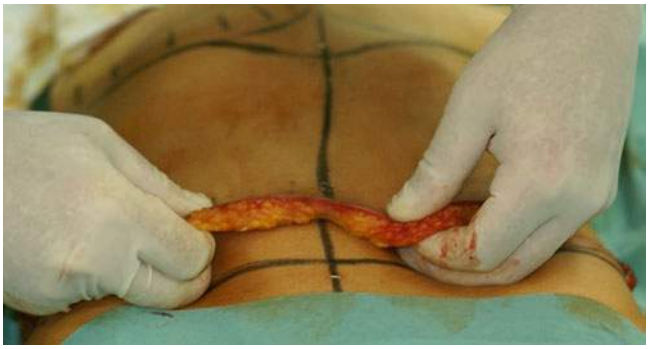


Fig. 42.6 Checking donor site closure. Patient can be moved to a slightly sitting position, but skin tension should be avoided

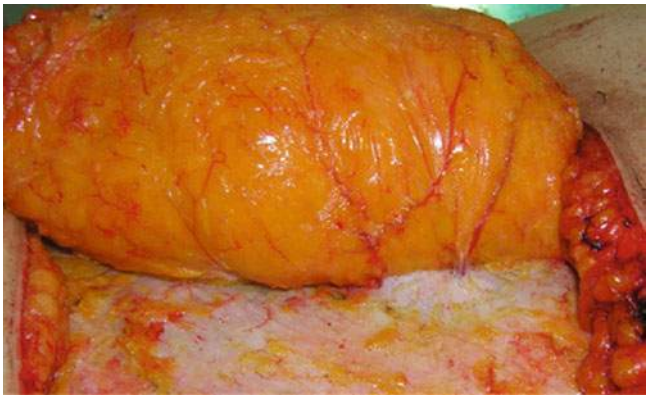


Fig. 42.7 Lateral view of the skin island after dissection. Perforators are usually identified on a row

Fig. 42.8 Fascial dissection exposes the rectus muscle

Then inferior pedicle is ligated and the muscle divided downward the pedicle insertion in the muscle, if possible upward the Douglas arcade (Fig. 42.10).

Rectus sheath can be now incised from the inner, few millimeters aside the linea alba, in order to spare as much sheet as possible, so to repair the fascial defect more easily. After that it is suggested that muscle perfusion should be checked: in case of bad perfusion, it will be still possible to harvest a bipedicled TRAM flap. In case of good muscular perfusion, the navel is isolated and cutaneous palette is dissected. Once the flap is harvested, it can look congested but soon after it achieve a well-perfused looking (Fig. 42.11).

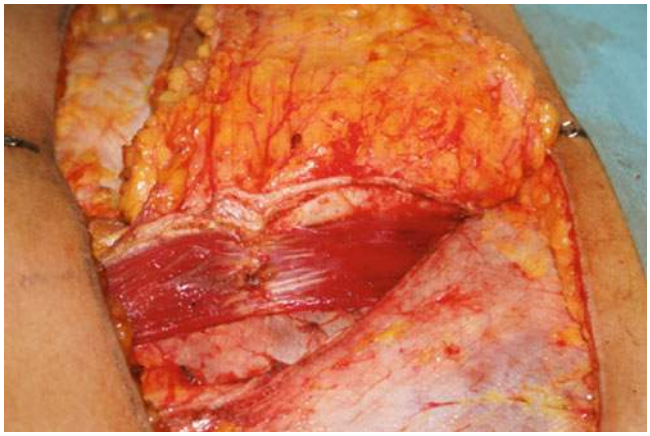


Fig. 42.9 Rectus muscle is exposed by surrounding aponeurosis

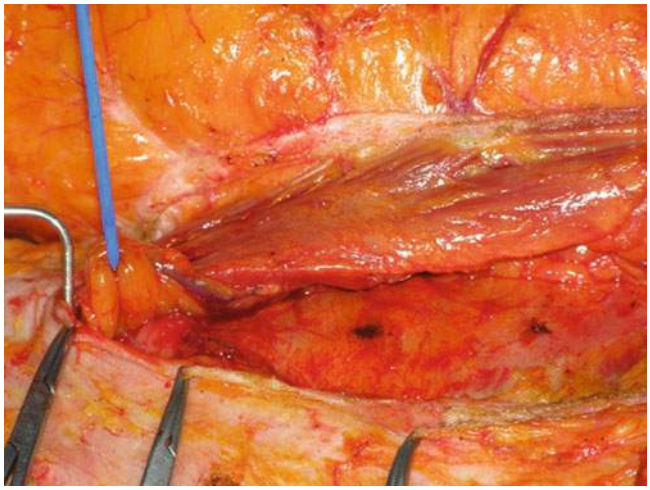


Fig. 42.10 Inferior pedicle is identified (by blue loop) and ligated before cutting the rectus muscle inferiorly

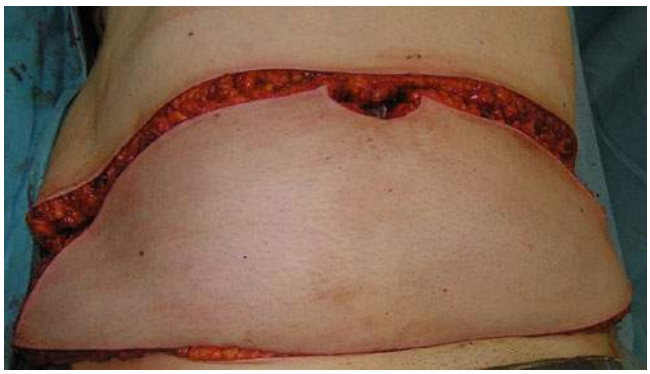


Fig. 42.11 TRAM flap skin island is congested after dissection. Skin color can be reddish or bluish, and it is possible to identify superficial vein net

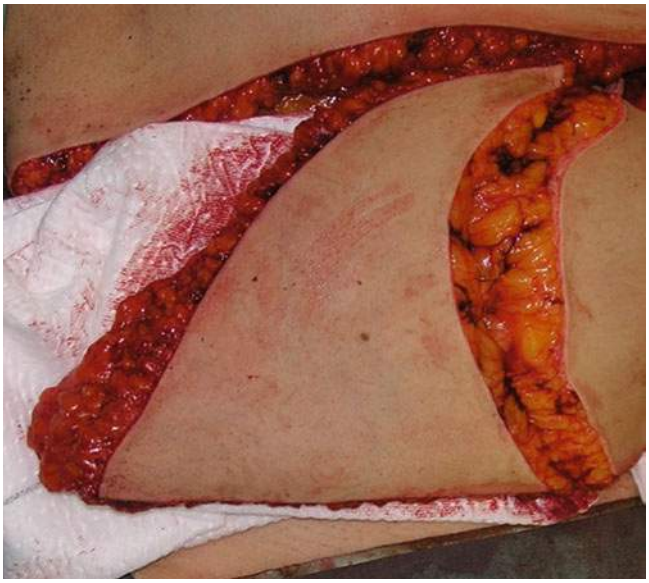


Fig. 42.12 TRAM flap extremities are less perfused, so it'd better to be excised. It is clearly visible a venous bleeding

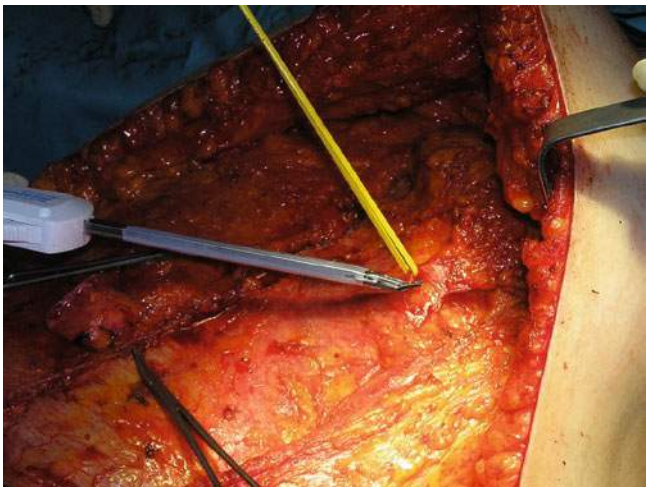


Fig. 42.13 Eighth intercostal nerve is isolated on the rib edge

It is a normal phenomenon, due to the gradual opening of choke vessels that improves venous drain. Zone IV and partially zones II and III are resected, and the flap is now ready to be transferred (Fig. 42.12).

It is essential to denervate the eighth intercostal nerve at the costal margin in order to avoid unpleasant muscle contraction after reconstruction (Fig. 42.13).

42.4 Donor Site Repair and Closing

Competent rectus sheath closure is an essential procedure in any TRAM flap surgery as far as it should prevent the risks of hernia formation. It is essential to incorporate both the internal and external oblique aponeuroses into the sheath closure [18]. We suggest to incorporate a Mersilene mesh or an acellular matrix [19] in the closure, but some surgeons prefer not to use it, if not necessary, because of the risk of infection [20]. First mesh is sutured to the medial edge of the remaining rectus fascia, and then it is sutured laterally with single stitches transfixing external oblique muscle (Fig. 42.14). After that the lateral edge of the remaining rectus fascia is sutured above the mesh in order to reinforce the closure (Fig. 42.15) .

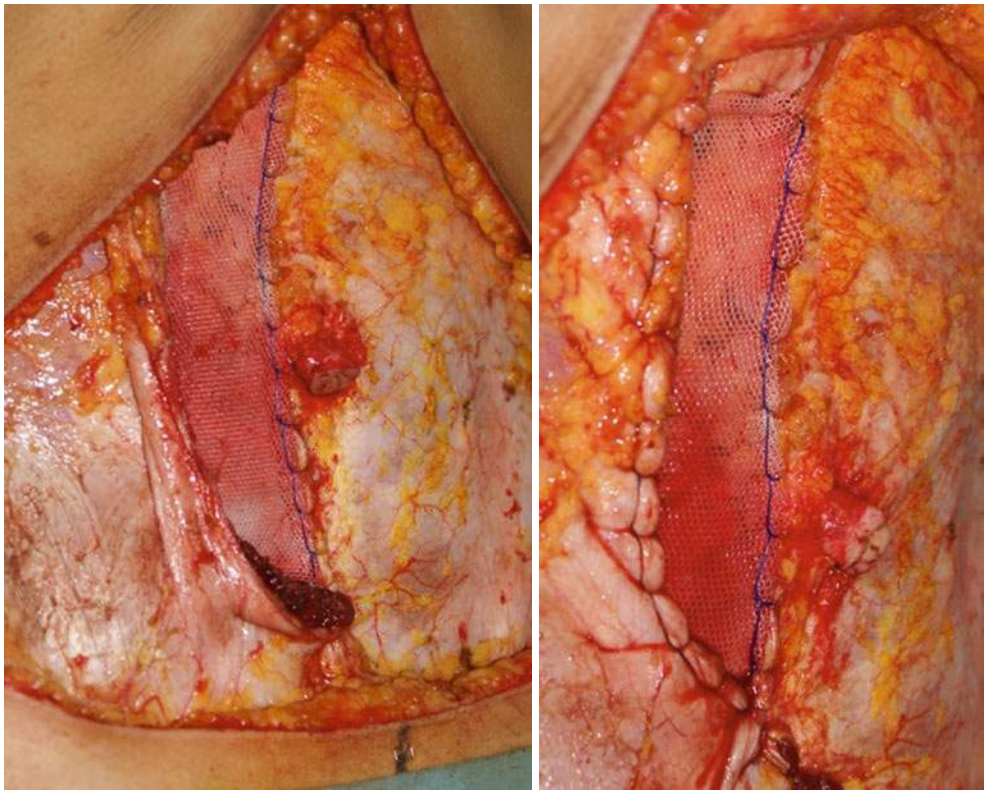
Before closing, the navel is repositioned in the midline, at the level of ankle crease, defatting the epigastric flap. Quilting suture can avoid postoperative seroma formation and also prevents tension in the abdominal triple-layer suture. Prineo is an automatic system of closure that can be effective and time-sparing (Fig. 42.16). Please notice that donor site closure should be considered a very important phase of the procedure as abdominal results are very important in demanding patients.

42.5 Flap Remodeling

Once the flap is harvested and transposed to the chest, the job isn't yet completed: the following steps are probably the most important for patient satisfaction. We can distinguish different approaches in delayed or immediate reconstruction. In delayed reconstruction, scar should be excised and the skin undermined in the whole breast footprint. It is important first of all to determine the new inframammary fold. It is possible to compare the contralateral side after donor site closure or to draw it in a line that will lay 1 or 2 cm upper the contralateral inframammary fold (that is because of the skin tension after donor site closure). Mastectomy scar can represent a challenge because it can push the flap down to the chest wall with a retracted appearance. Most of the times, the solution is to excise completely the retracted scar and also most of the inferior mastectomy skin flap. Skin paddle can be orientated in different ways, but the principal two suggestions are 180° or 90°. First the skin paddle is fixed to the new inframammary fold, and then flap is put under mastectomy skin flaps after checking a good bleeding all along the skin and fat margins. In case of poor or venous bleeding, it is suggested to excise less perfused area in order to avoid partial skin necrosis as much as possible. Contralateral symmetrization is often required. Volume should be compared to the contralateral breast. Also Wagner and colleagues [21] devised a formula to calculate flap volume:

$L \times W \times T \times 0.81 = V$ where L is weight, W is width, and T is thickness of the TRAM flap, and V is flap volume.

Once the symmetry is achieved, undermined flap skin is deepithelized and flap can be sutured.



Figs. 42.14 and 42.15 Donor site repair with mesh. It is essential to fix the mesh to the surrounding muscle compartment and then to suture the rectus sheath edges to the mesh in a dual-layer approach

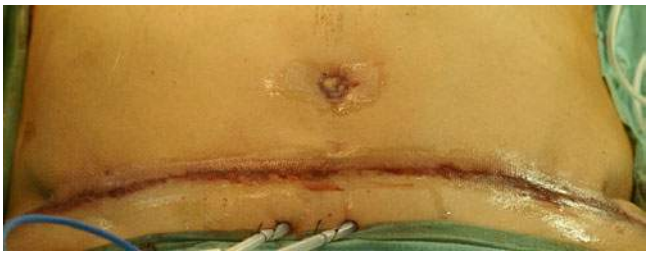


Fig. 42.16 Donor site closure with Prineo

In case of immediate breast reconstruction, breast reshaping is somewhat similar, but it is easier in case of nipple-sparing or skin-sparing mastectomies, whereas TRAM flap skin paddle is completely or almost totally deepithelized and then sutured to the chest wall, allowing an easy remodeling like putting the jelly in the mold. It is suggested to spare the original inframammary fold in order to keep the original ptotic appearance of the breast, obtaining a symmetrical result.

42.6 TRAM Flap and Implant?

Somebody can identify a breast implant beneath a TRAM flap as an adulteration of one of a pure autologous reconstruction, but it represents a very good indication in selected cases. First of all it is indicated in case like the following:

- Breast augmentation demanding patient without possibility to harvest a latissimus dorsi flap
- Patient refusing contralateral breast reduction
- Very large mastectomy or delayed breast reconstruction in patients presenting wide radiodystrophic area to be excised
- Bad perfused flap

The last one represents a revolutionary way to manage bad perfused flap. In fact, if a bad blood supply is identified during dissection, it is suggested to harvest a bipedicled TRAM flap, but, if the flap looks poorly perfused after transposition, the idea is to excise as much skin as needed. It doesn't matter how much volume you can lose because it can be replaced by an implant or an expander. In our series of patients with TRAM flap associated with implants, at European Institute of Oncology, they have very good outcomes in most of cases. Delayed volume augmentation is still possible with implant or fat grafting (Figs. 42.17, 42.18, and 42.19).

42.7 Complications

The major complications of delayed TRAM flap reconstruction include scarring, skin and fat necrosis, flap loss, hernia formation, deep venous thrombosis, asymmetry, abdominal tightness, and the psychosexual issues associated with breast reconstruction. Some degree of fat necrosis is common in

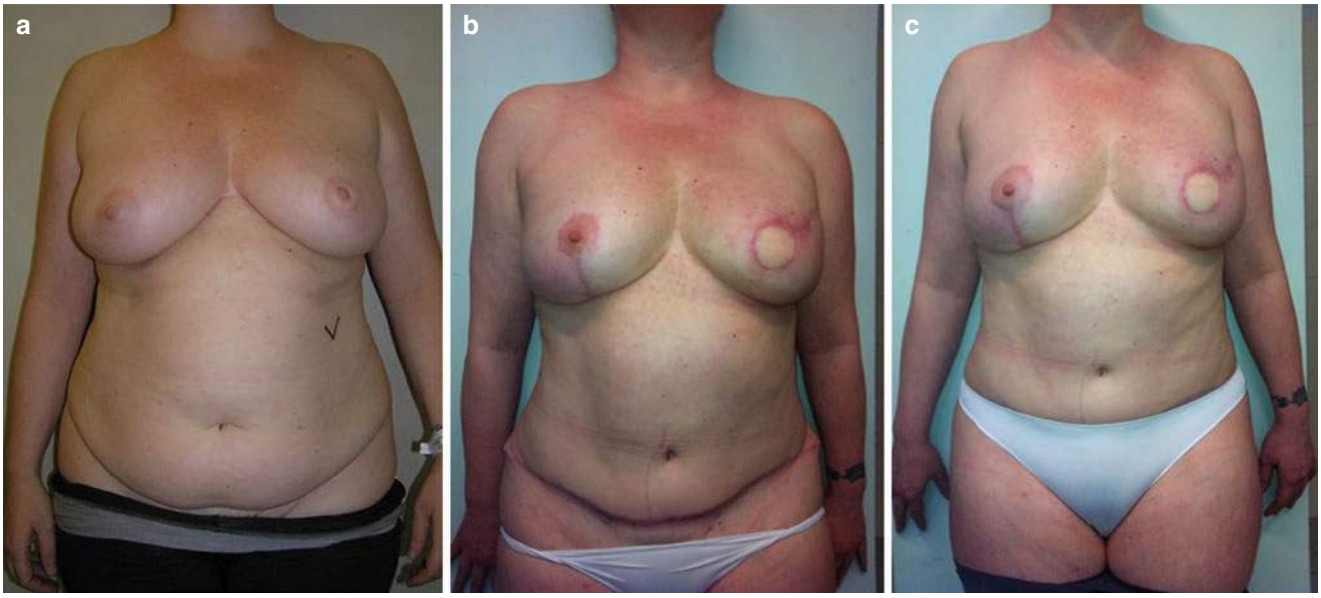


Fig. 42.17 (**a**–**c**) Immediate left breast reconstruction with ipsilateral pedicle TRAM flap after skin-sparing mastectomy, preoperative and postoperative views. Please notice that abdominal scar can be easily hidden by pants

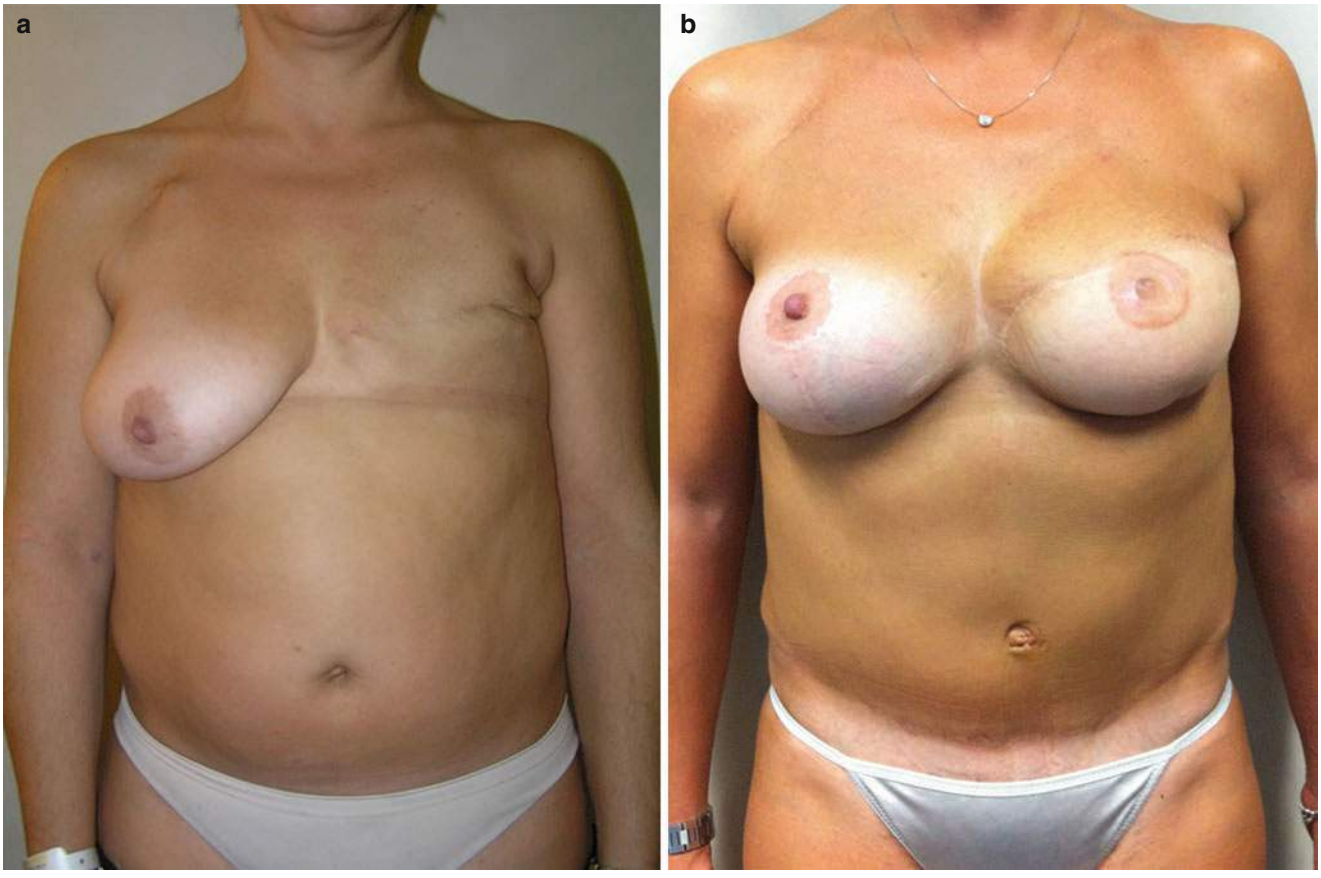


Fig. 42.18 (**a**, **b**) Delayed left breast reconstruction with ipsilateral TRAM flap, preoperative and postoperative views. Please notice a good symmetry but a lateral deviation of the navel and a little bulge aside of it

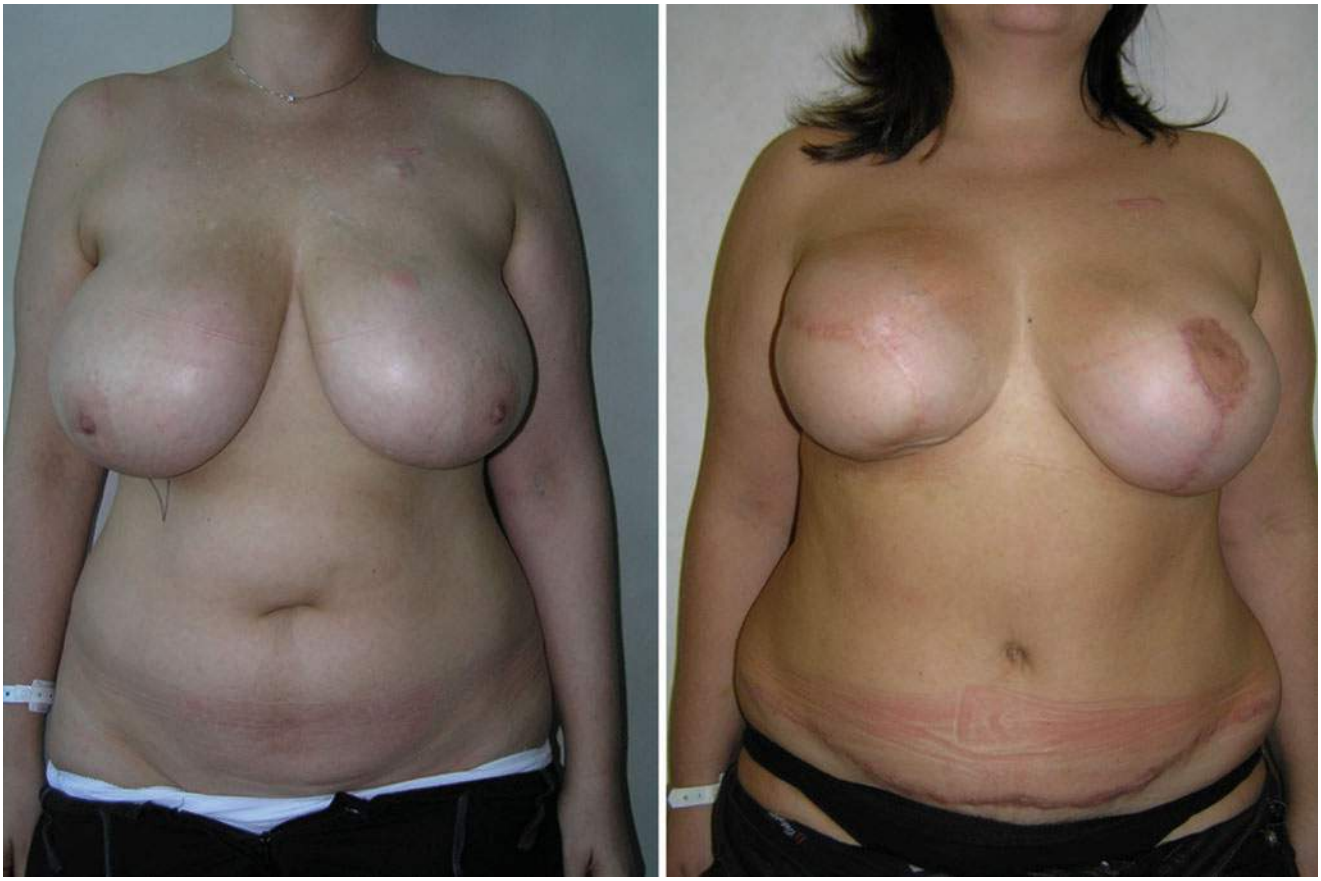


Fig. 42.19 Immediate breast reconstruction with TRAM flap and implant: preoperative and postoperative view

Table 42.1 TRAM flap necrotic complication, EIO series 1994–2007

	Ipsilateral TRAM flap	Contralateral TRAM flap	Bipedicled TRAM flap	TRAM flap and implant
Partial necrosis	12.22%	14%	3.26%	7.89%

any TRAM flap reconstruction whether free or pedicled. In our series, we observed different rates of partial necrosis (requiring surgical debridement). Also very rare total flap necrosis has been observed (Table 42.1).

42.8 TRAM Flap and Pregnancy

Despite the loss of muscle function after pedicled TRAM flap harvest, it is still possible for patients to conceive and carry a pregnancy to term as well as to achieve normal vaginal delivery [21]. Johnson and colleagues [22] described the successful vaginal delivery of monozygotic twins after bilateral pedicled TRAM flap reconstruction. Parodi and colleagues [23] caution against patients becoming pregnant within 12 months after TRAM flap surgery, reporting a single case of a woman becoming pregnant at 4 months postoperatively and developing a hernia. She delivered vaginally at term. We also observed some pregnancies after TRAM flap without major diseases (Fig. 42.20).

42.9 Secondary TRAM Flap Reshaping

The possibility of a natural and symmetrical result with TRAM flap is high, but still be possible to improve it with a secondary reshaping. It isn't a standardized procedure. Surgical tips consist of mastectomy flap separation from TRAM flap that can be reduced, mobilized, liposucted, or lifted based on inferior pedicle. Then the skin is adeguated to the breast mount. In case of breast augmentation, implant pocket can be easily obtained under the flap. Also fat grafting is a valid alternative. A unique case of immediate breast reconstruction splitting a previous bipedicled contralateral TRAM flap in two was described by Rietjens et al. [24] (Fig. 42.21).

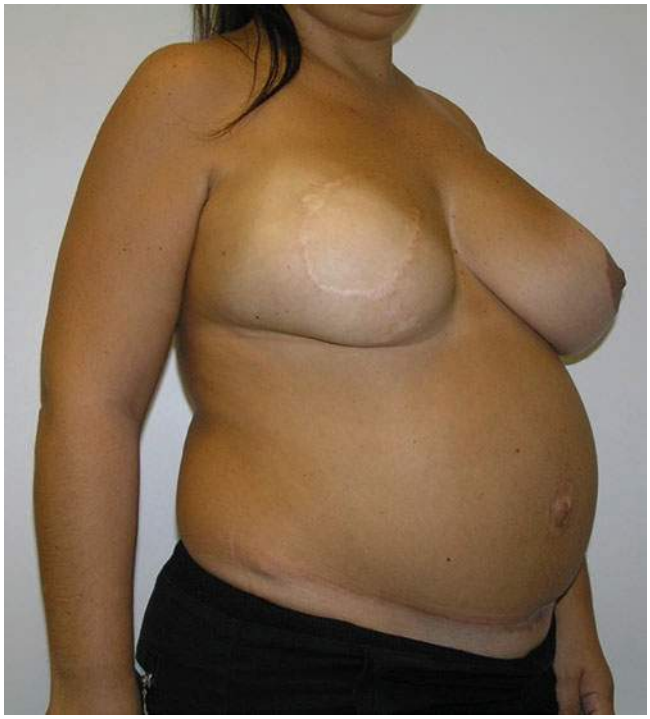


Fig. 42.20 Pregnancy after immediate reconstruction with TRAM flap. This patient underwent to cesarian delivery without complication for her and for the newborn. Abdominal bulge was observed 1 year post-delivery

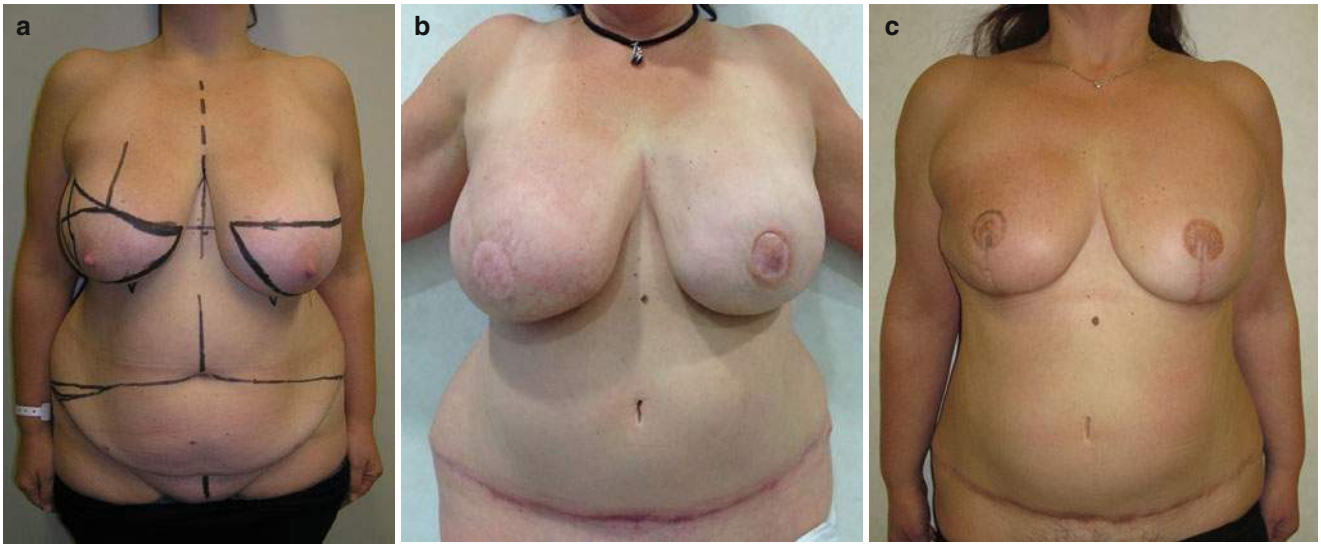


Fig. 42.21 (**a**–**c**) A case of bilateral tram flap reshaping with breast reduction. Preoperative view with marking (**a**), postoperative view after bilateral TRAM flap (**b**), and postoperative view after bilateral breast reshaping with inverted T mastopexy and liposuction (**c**)

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Bipedicled TRAM Flap

43

Paulo Roberto Leal

43.1 Introduction

Described by Hartrampf et al. [1] in 1982 and popularized by many authors during the last 30 years, the use of the transverse skin and fat harvested from the lower abdominal region, the so-called transverse rectus abdominis myocutaneous (TRAM) flap, is still considered by many to be the gold standard for breast reconstruction. It gives the surgeon the possibility to recreate a breast of a desirable size with controlled shape.

The pioneer publication suggested that use of the flap could be delayed to improve vascular perfusion (and the authors did this in their first three cases). In four cases the authors used preoperatively selective angiography in order to confirm the anatomic continuity between the internal thoracic and the deep epigastric system. Therefore, they recognized the potential incapacity for efficient blood perfusion of the total abdominal flap through a single pedicle.

This deficiency was demonstrated later by Moon and Taylor [2] in their radiographic studies of the deep superior epigastric artery. Their publication is considered to be a landmark in the breast reconstruction literature and created the basis for the understanding of the complex circulation of the TRAM flap.

It was shown that blood perfusion can be unpredictable beyond the midline. This potential difficulty was experienced by many surgeons. Fat and skin necroses are frequently seen in different degrees when the flap is harvested in its total length.

Many suggestions were made to support a reliable blood supply to the entire flap. Delaying, supercharging, free flap transfer, and the bipedicled version of the TRAM flap are techniques that could effectively bring about better perfusion and therefore the possibility to enhance considerably the length of the abdominal flap [3–7].

The use of two pedicles for unilateral reconstructions has been demonstrated to be a simple way of improving the blood supply to the classic monopedicled TRAM flap. With this approach, theoretically, one could harvest the flap totally, beyond the safe zone [8] (Fig. 43.1).

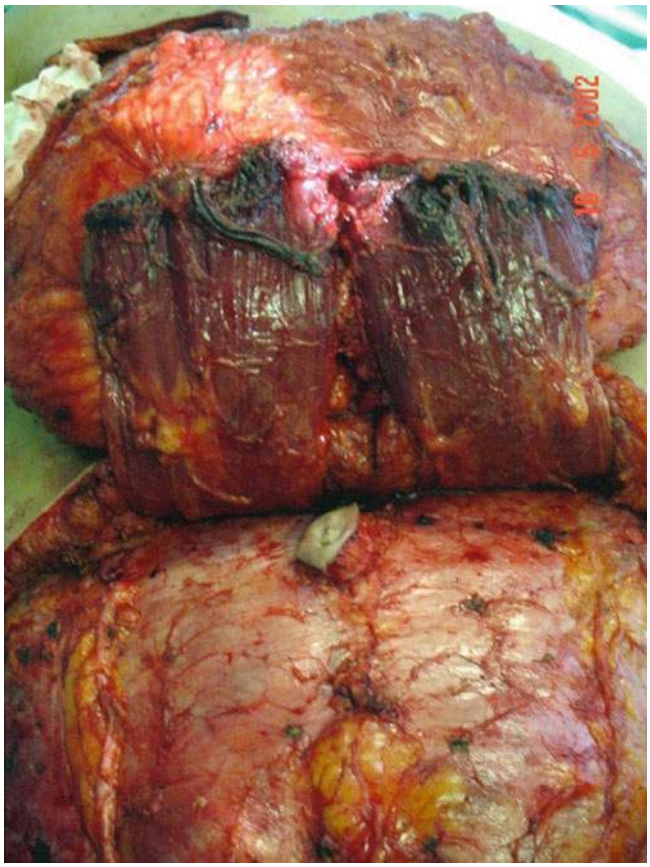

Fig.43.1 The transverse rectus abdominis myocutaneous (TRAM) flap with its two pedicles

Electronic Supplementary Material The online version of this chapter (doi:10.1007/978-3-319-62927-8_43) contains supplementary material, which is available to authorized users.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_43

Although currently I use the procedure only in very select cases, it is able to provide the surgeon with an excellent amount of well-perfused abdominal tissue comparable only to techniques using free flap transfer.

43.2 Indications

Its principal indication is to increase the circulation to the abdominal flap; therefore, the blood supply can be doubled, and complications such as fat or cutaneous necrosis can be essentially minimized.

Maneuvers to improve the flap perfusion are used for patients with risk factors that can impair the perfect blood supply to the abdomen.

The most relevant risk factors are smoking, obesity, previous abdominal surgery, radiotherapy, and existence of systemic disease (diabetes, hypertension) [9] (Fig. 43.2).

43.3 Free Flap or Bipedicled TRAM Flap?

The apologists for the use of microsurgical technique to transfer the abdominal tissue for breast reconstruction (free TRAM flap, muscle-sparing flap, deep inferior epigastric perforator (DIEP) flap) are extremely emphatic when describing its many advantages.

The main one is the unquestionable better blood supply, once the flap nutrition is provided by the inferior epigastric system (it is the primary blood supply to the lower abdominal skin and subcutaneous fat). The second one relates to the significant abdominal wall injury caused by the bilateral flap harvesting [10].

However, the free flap transfer demands especial skills of trained surgeons and nurses. The full control of the technique also depends on specialized staff to closely evaluate the patient during the postoperative period. Operating in a center where the patient can be safely taken to the operating room anytime for an urgent revision is also mandatory.

43.4 The Abdominal Wall Issue

It has been widely recognized that a unilateral or bilateral pedicled TRAM flap can lead to a considerable reduction of the abdominal strength (Fig. 43.3). Many publications on this subject witness the discomfort of authors with this topic.

An early study published by Hartrampf and Bennet [11] showed that the postoperative assessment of 300 women after bilateral harvesting resulted in a remarkable decrease of the abdominal strength, represented by an incapacity to perform sit-ups.

Also Petit et al. [12] in evaluating unilateral and bilateral pedicled TRAM flaps in 38 patients showed that 50% of the

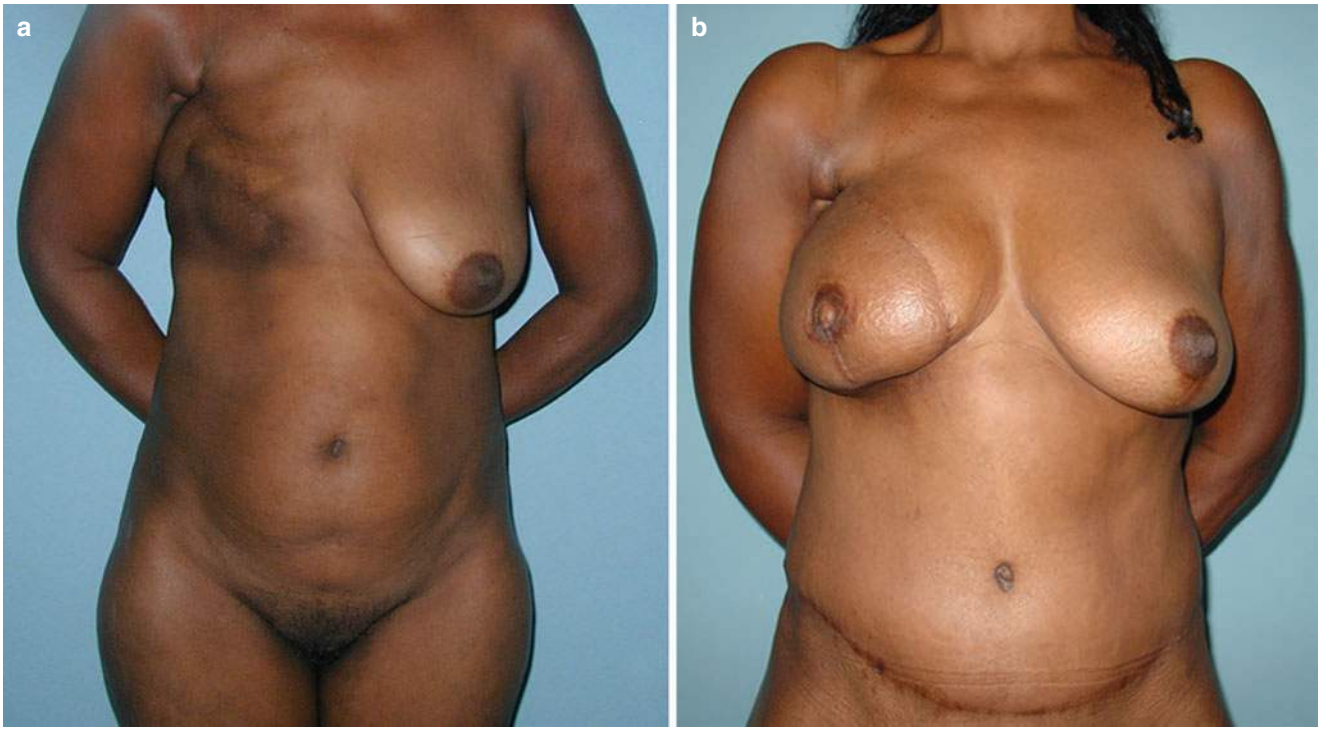

Fig. 43.2 Preoperative (**a**) and postoperative (**b**) delayed reconstruction on a patient with visible damage after radiotherapy. The bipedicled TRAM flap was a suitable option a with good outcome

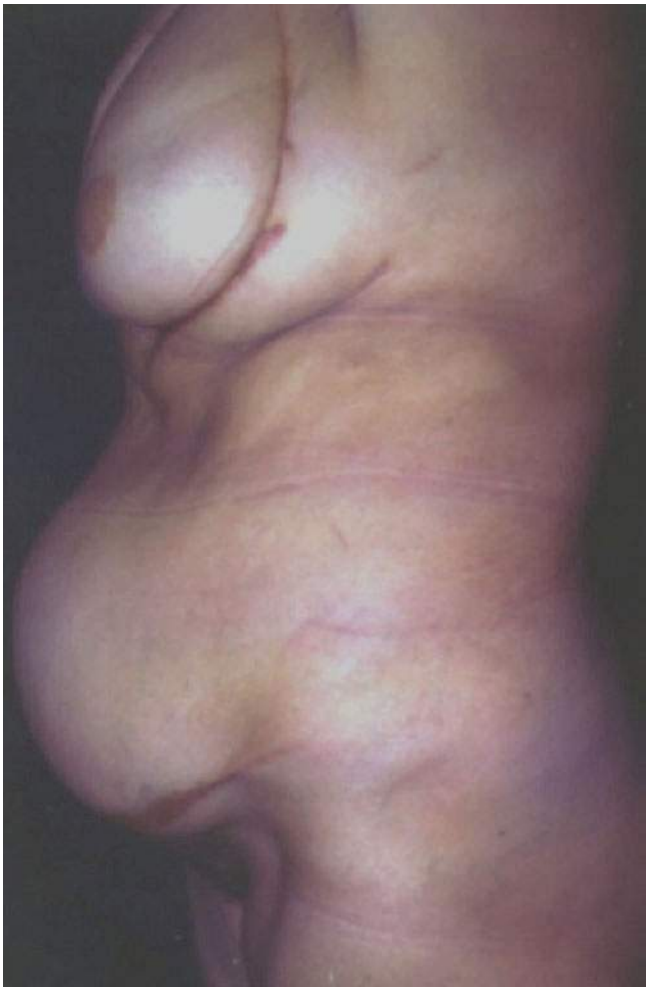

Fig. 43.3 Bulges and true hernias are more frequent with the bipedicled TRAM flap technique

single-pedicle transfers caused important impairment of the upper portion of the rectus and oblique muscles opposed to 60% of the double-pedicle series.

The muscle-sparing technique (transferring only the central portion of the muscle, which contains the vessels) based on the work of Mizgala et al. [13] has not proved the expected efficiency in reducing the morbidity to the abdominal wall of the classic pedicled TRAM flap, unilateral or bilateral. On the other hand, splitting the muscle in pedicled flaps remains controversial, and some surgeons [14] emphatically avoid doing this because of the vascular pattern of the epigastric system (choke vessels connect the superior and the inferior systems), where superficial to the rectus muscle, an important net of arteries and veins can be injured during muscular division.

Finally, a recent study by Chun et al. [15] suggests there is no significant difference in donor-site morbidity, functional outcomes, and patient satisfaction when bipedicled TRAM or DIEP flaps are used in breast reconstruction, concluding that the technique remains a good choice for many patients who will undergo postmastectomy breast reconstruction with autologous tissue.

43.5 Patient Selection

The success of the reconstruction employing the transfer of the lower abdominal tissue will ultimately depend on two factors: patient selection and the selection of the right procedure.

The patient is assessed for risk factors. Increased complication rates after TRAM breast reconstructions are associated with the following risk factors: age (over 60 years), obesity (more than 25% over ideal body weight), abdominal scars (primarily, Kocher, paramedian, or multiple abdominal surgical scars), diabetes mellitus, hypertension, previous radiotherapy applied to the chest wall, and smoking history.

I also consider it as indicated for patients who perform competitive high-impact sports or those who depend on intensive muscular dynamics at work (maids).

Anatomical assessment is also of paramount relevance, including abdominal contour and fat deposits (potbelly habitus patients are formally contraindicated for TRAM flaps).

The slender patient and those patients with poor abdominal strength or abdominal muscular laxity will not be considered for bipedicled TRAM flap reconstruction.

Preoperative testing by sit-ups is an easy and effective method to evaluate the abdominal strength. Patients who are not able to perform these movements are considered poor candidates too.

To select the right procedure, one simple question is mandatory: What are the patient's needs?

The primary indication for the bipedicled TRAM flap is the need for a large amount of abdominal tissue to replace a large breast (Fig. 43.4). The second is a need for increased vascularity. Patients who have risk factors will benefit from the technique. When we take as an example fat necrosis, a typical complication with its origin in poor vascular supply, for monopedicled flaps, patients with two or more risk factors have three times the incidence of those with no or one risk factor. Patients with two or more risk factors who had bipedicled TRAM flaps had no associated increased incidence of fat necrosis. For flap loss complications, similar findings have been noted.

43.6 Patient Education and Preoperative Care

The patient is clearly informed about the procedure. Postoperative pain and 4–5 days of hospitalization is emphasized. The presence of drains that can remain for 1 week and the need for a synthetic mesh to reinforce the abdominal wall are also pointed out.

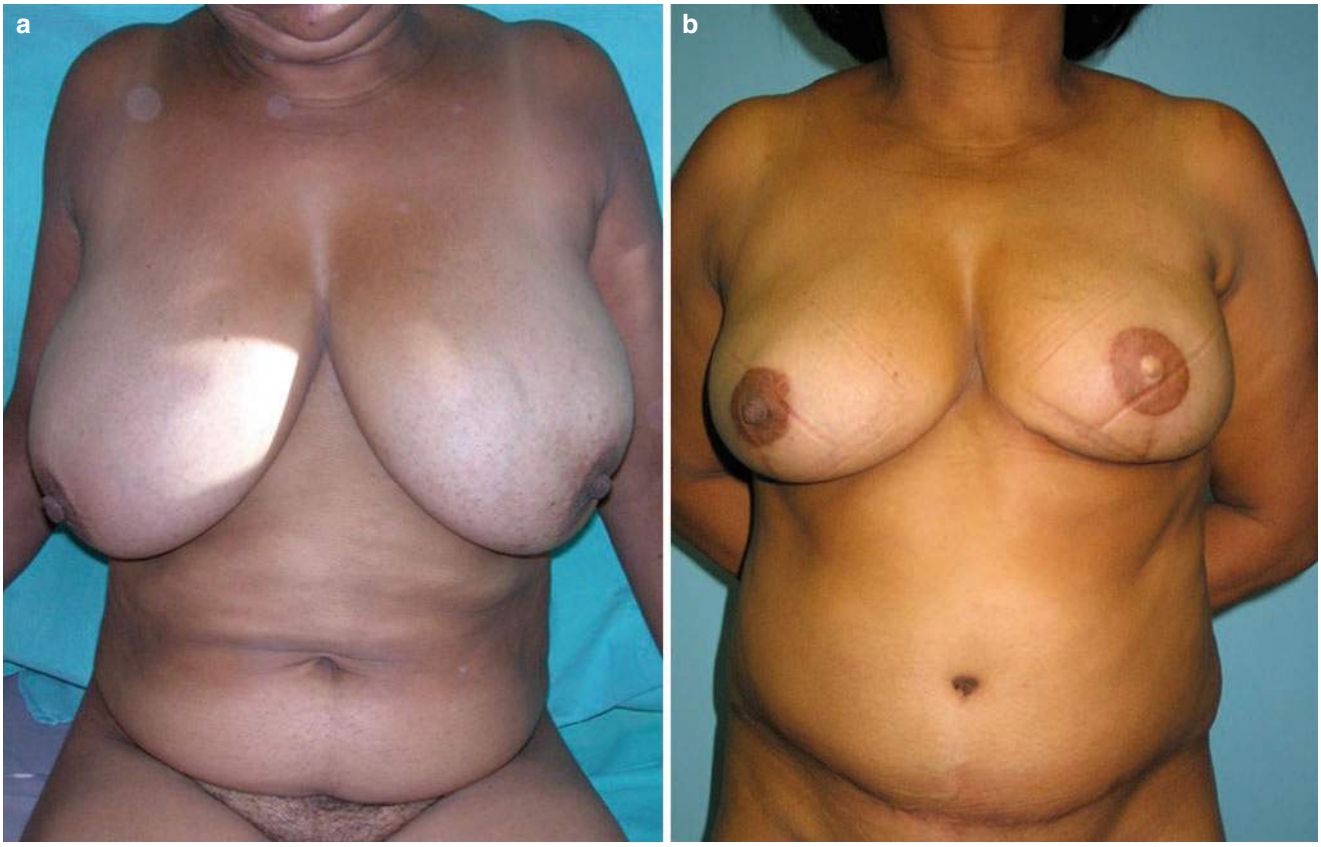

Fig. 43.4 Patients with large breasts benefit from double-pedicle harvesting. The whole abdominal flap can be safely raised

The recovery time is roughly 6 weeks, and the patient is made aware of a long-resting period of not less than 2 months. The patient is also informed of weakness of the abdominal wall, mainly patients who undergo bilateral TRAM flap reconstructions.

Finally, potential complications are discussed, and it is important that the patient is confident in the capacity of her surgeon to solve every problem related to an incidental failed reconstruction.

I rarely do immediate bilateral or free TRAM flap reconstructions. The extension of the operation added to the mastectomy procedure is not appealing. Perhaps on an institutional basis with a very well-trained team, it could be beneficial to the patient.

I frequently use a two-stage operation, performing the permanent phase after a primary expansion simultaneously with the mastectomy; therefore, blood transfusion and clinical complications have been rare in my practice.

43.7 The Importance of an Image Profile for Safe Harvesting

Since my interest in the perforator-based TRAM flap began, I have found the necessity of imaging evidence, which can give me not only the dimensions but also flow measurements of the upper and lower epigastric vessels, both breasts, and the positions of the perforators. Initially, I found the color Doppler scan very illustrative. The evolution toward angiotomography was able to detail and locate very clearly the whole system and its perforators to the lower abdominal skin-fat paddle (Fig. 43.5).

Probably this is not so important for the evaluation of pedicled flaps, but it can sharply define the circulation from the breast to the lower epigastric vessels, which can be useful in irradiated patients.

43.8 Surgical Technique

After a judicious selection of the technique and indication of the bipedicled TRAM flap, the flap is outlined on the abdominal wall. Two teams work simultaneously: one preparing the recipient site and other undermining the abdominal flap.

The concept of "breast footprint" popularized by Blondeel et al. [16] is applied here to create a pocket of the right size to receive the abdominal flap and match the remaining breast in shape and volume (Fig. 43.6).

All scar tissue must be removed. In irradiated patients, extra care is required with the mastectomy flaps in order to keep them well vascularized, avoiding any damaging maneu-

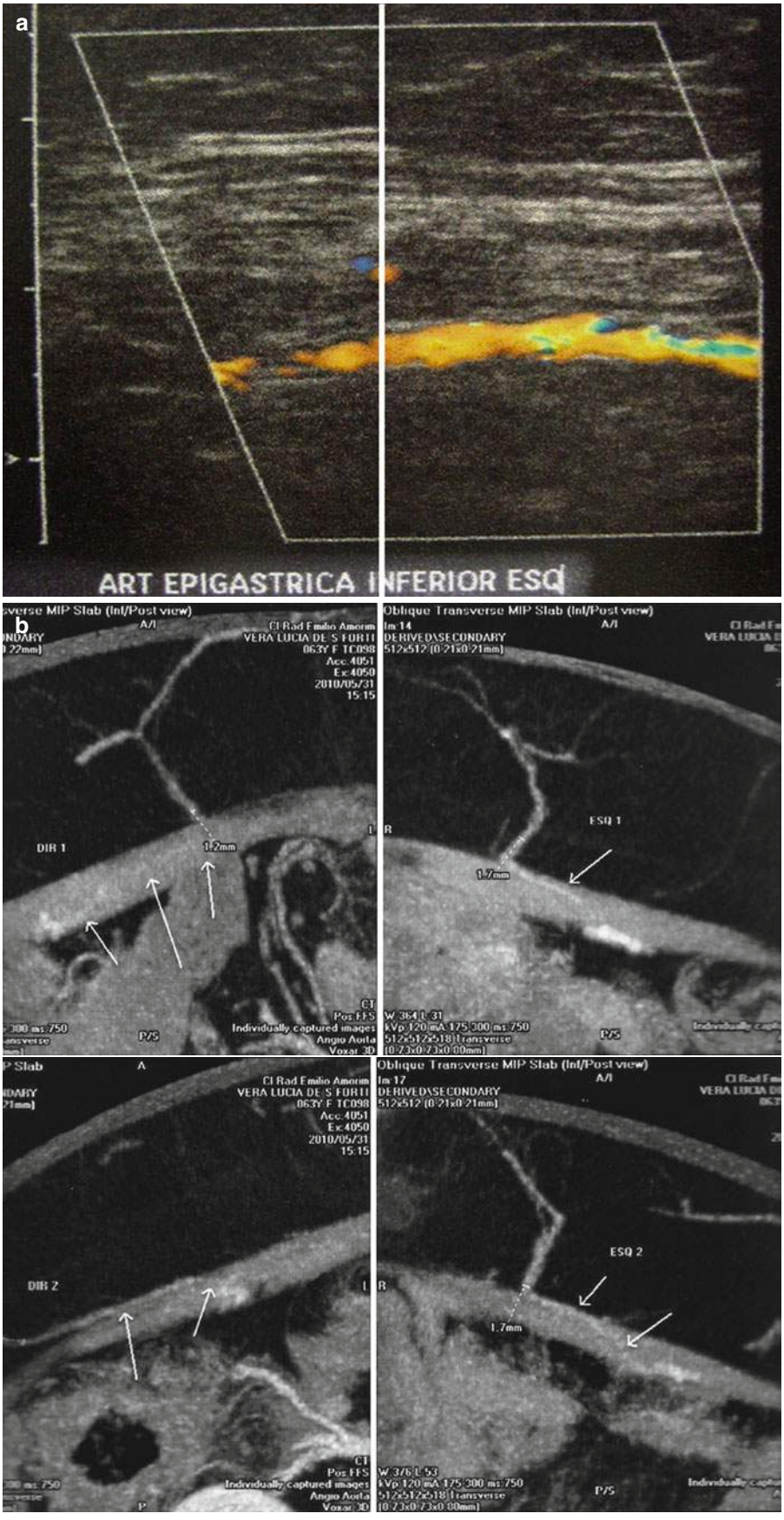

Fig. 43.5 Color Doppler scan (**a**) and angiotomography (**b**) allow the surgeon to locate very clearly the whole epigastric system and its perforators

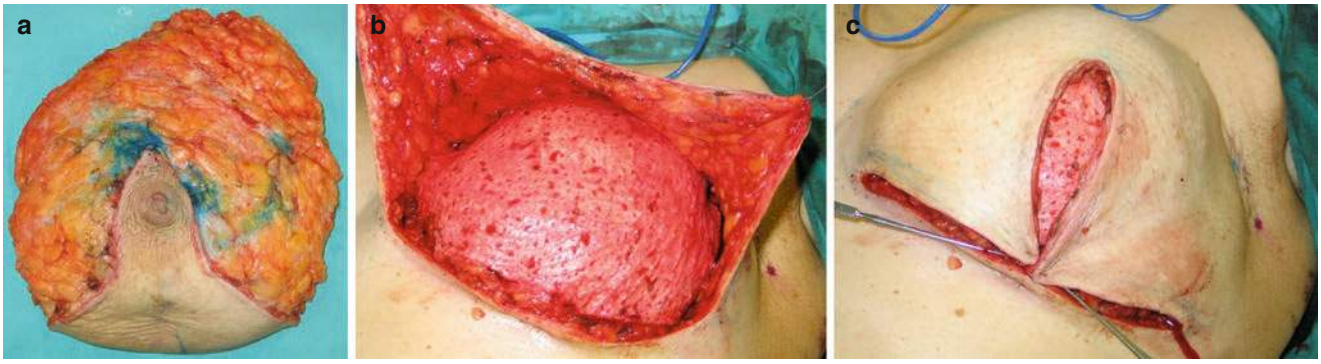

Fig. 43.6 The concept of breast "footprint" is clearly shown here: an inverted-T pattern mastoplasty is drawn over one dermal fat paddle of a TRAM flap

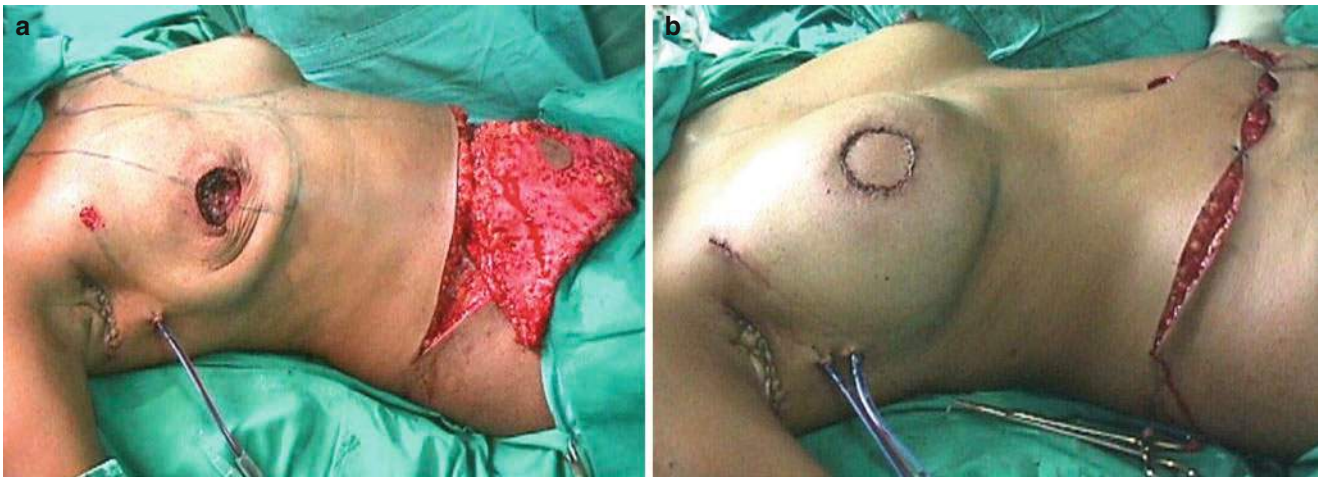

Fig. 43.7 The abdominal flap of a bipedicled TRAM flap ready to be transposed

ver. Attention has to be paid to the submammary fold, which must be kept at the same level as that of the opposite side.

The tunnel that connects both spaces should be large enough to permit the large flap to pass through. At this point gentle maneuvers are expected, and compression or constriction must be strongly avoided.

The abdominal flap is marked previously with the patient in the standing and seated position. The possibility of flap donation is rechecked and confirmed. The incision is placed in the most cosmetic position according to the principles of safety for an ideal closure (Fig. 43.7).

During the abdominal detachment, the surgeon should avoid dissecting too far laterally in order to preserve the intercostal perforators responsible for the vascular nutrition of the flap.

After the upper abdominal flap elevation, the rectus abdominis muscles are partially degloved from their sheath. A strip of fascia is kept attached to each muscle. I prefer to elevate the whole muscular unit. A better vascular supply is expected with this technique, and the damage to the abdominal wall is apparently equivalent to that with the muscle-sparing technique.

The umbilicus is then outlined and released from the lower abdominal flap, making possible its future ascent to the thoracic wall.

Next, the identification and ligation of the lower deep epigastric artery and veins is performed. Next, the lower abdominal flap is entirely separated from the abdominal wall. This dissection is done with magnification (×2.5) and a sharp scalpel, so many tiny subcutaneous vessels can be identified and preserved. The epigastric pedicle is observed, and the point it enters the muscle is used as a landmark for its section. Usually this point is located above the arcuate ligament.

Both rectus abdominis muscles are sectioned, and the whole flap is raised to its new location very carefully with gentle maneuvers.

Next, the upper abdominal flap is inset and stapled in the new site with the patient in the seated position. Now, the new breast is shaped. I have no rules for this exciting time. The skin and fat flap must fit the subcutaneous pocket in the most appropriate position according to the remaining breast "footprint," shape, and volume.

Once the surgeon feels the breast can be considered done, the patient returns to her normal decubitus position, and the

abdominal wall is repaired simultaneously to the breast suture.

I always use a Prolene mesh to repair the abdominal muscular deficit. The mesh is sutured to the remaining oblique muscles with polydioxanone 2-0 in two planes.

A vacuum drain is always used and kept in place for at least 5 days for the new breast and abdominal areas. The abdomen is finally sutured following a normal abdominoplasty pattern.

A surgical brassiere is used for the breast, and a moderate compressive dressing for the abdomen is employed for 2 days.

43.9 Complications

Specific complications of the bipedicled TRAM flap are:

Fat necrosis is a late complication. It can appear after 12 months and is associated with an ischemic mechanism. Clinically, it presents as a subcutaneous firmness that can be confused with malignancy (recurrence or a new tumor). A biopsy is mandatory to clarify the diagnosis. A more extensive fat necrosis area can definitely compromise the cosmetic outcome.

Bipedicled TRAM flap and free flap transfer have significantly reduced the incidence of fat necrosis.

Partial flap loss is a complication that occurs in more than 10% of all pedicled TRAM flaps. It can happen to different degrees. Light marginal necrosis due to venous deficiency can be revised later and does not compromise cosmetically the result. A remarkable reduction of this complication is observed when the bipedicled TRAM flap or free flap transfer is employed (Fig. 43.8).

Total flap loss can happen when free flap transfer is used, probably owing to arterial or venous thrombosis when salvage methods have failed. It is infrequent for pedicled flaps and is extremely rare when bipedicled flaps are used. In general, total flap loss corresponds to an important technical mistake.

These ischemic complications are often present in patients with more than two risk factors.

Hernias and abdominal laxity (bulges) are donor-site complications resulting from the bipedicle technique. From the mere incapacity to do sit-ups to real hernias and back pains, these are frequent complaints that afflict patients who underwent the technique.

In my personal series, I have had less than 2% of cases with abdominal laxity. I ascribe this low rate to respect for the arcuate line limits and closure in every case with only Prolene mesh.

Hematoma is minor complication. The rates of postoperative bleeding and subsequent hematoma have been lowered to practically zero thanks to the long-term drainage and changing of chemoprophylaxis for venous thromboembolism for intermittent leg compression perioperatively and postoperatively.

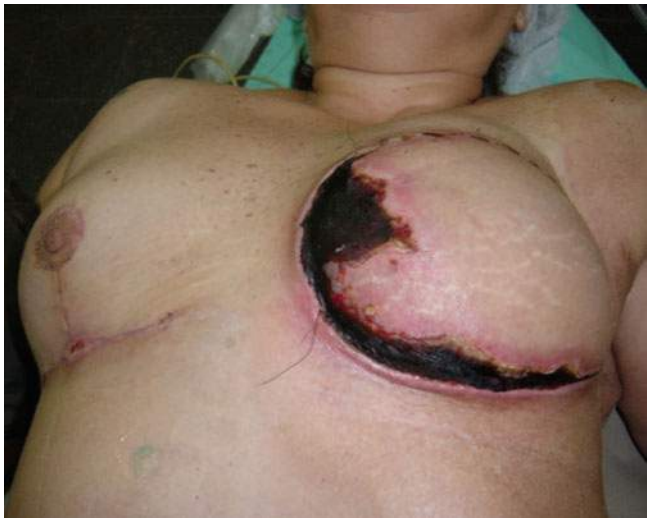

Fig. 43.8 Partial flap loss: marginal necrosis follows generally progressive venous impairment

Seroma of the abdominal flap has also dramatically improved by regular tacking of the abdominal flap to the fascia, enhancing the contact and avoiding the sliding movements associated with the seroma.

Abdominal slough and necrosis are expected complications when extensive abdominal undermining is done. Limited dissection preserving the intercostal perforators is essential to avoid such complications.

For infections, prophylactic antibiotics are always used (according to the hospital protocol).

43.10 Discussion

Since its first description in 1982 by Hartrampf et al., the TRAM flap has been considered by many as the gold standard for breast reconstruction after mastectomy.

Technically it has evolved. Two issues propelled that evolution.

First, the blood supply. The classic pattern, monopedicled TRAM flap, has been demonstrated to be unreliable or at least unsteady when harvested beyond the midline.

Moon and Taylor [2] have elegantly and definitely demonstrated that the rectus abdominis's arterial and venous territories both present the same pattern. Blood has to traverse a multiple venous valvular system before reaching the deep superior epigastric territory. These valves frequently impair the venous drainage owing to obstructions, resulting in fat and skin necrosis. Several modifications, including a more cephalad flap, primary delays, and the free TRAM flap transfer, have minimized this problem.

The bipedicled TRAM flap also increased flap perfusion because of a dual artery inflow and similar venous outflow. Basically it is indicated when a large amount of tissue is required.

Partial flap loss and fat necrosis rates have been consistently reduced by the method.

The recognition of risk patients made the technique appealing and for patients with more than two factors, for many surgeons, mandatory.

The other important and controversial issue is the injury that the pedicled TRAM flap causes to the abdominal wall. Hernias and bulges have been shown, mainly when the two rectus abdominis muscles are used. To minimize the anatomic deficit provided by TRAM flap harvesting, muscle-sparing free TRAM flap and no muscle transfer, like perforator flaps (DIEP flap and superficial inferior epigastric artery flap) have been described and popularized worldwide especially in centers where highly trained microsurgeons master the technique and perform it in a conveniently short time.

Unfortunately this is not the general rule for many services where mastectomy is responsible for severe damage that needs to be fixed fast and safely.

Nonetheless, a study has been published comparing in a large series with a long follow-up patients who have undergone reconstructions with bilateral TRAM flaps with bilateral DIEP flaps. The results showed no significant differences in donor-site morbidity, functional outcome, and patient satisfaction between bilateral TRAM flap and DIEP flap breast reconstruction.

The author's conclusion is although the perforator flap is technically an evolution, bilateral TRAM flap reconstruction is still a good option for autologous breast reconstruction.

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Free Flap Breast Reconstruction

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Peter W. Henderson and Colleen McCarthy

44.1 History of Autologous Breast Reconstruction

The most recent incremental development in the progression of autologous breast reconstruction is microvascular free tissue transfer. As such, it is considered by many the gold standard approach to postmastectomy reconstruction.

The first documented form of modern autologous breast reconstruction was the latissimus dorsi myocutaneous flap, described by Iginio Tansini of Italy in 1896 [1]. Unfortunately this technique was not rediscovered by mainstream surgeons until the 1970s. Around the same time, the pedicled rectus abdominis myocutaneous flap with a vertically oriented skin and subcutaneous tissue island was developed [2], and the first free flaps were being performed for breast reconstruction using either groin flaps or latissimus dorsi flaps [3]. The next significant advance came in 1982 with the publication by Carl Hartrampf of the pedicled transverse rectus abdominis myocutaneous (TRAM) flap [4]. This was quickly followed by the first description of a "free" TRAM by Roger Friedman in 1985 [5]. The next step in the evolution of abdominal-based breast reconstruction was the description of the total rectus abdominis-sparing free flap: the deep inferior epigastric perforator (DIEP) flap by Robert Allen in 1994 [6].

Though used less commonly than abdominally based flaps because of multiple factors (most notably the less ideal donor location), gluteal-based free flaps (first described by Fujino et al. in 1975 [7]) and thigh-based free flaps (first described by Yousif et al. in 1992 [8]) have been developed and refined over the course of the past two decades.

44.2 Advantages and Disadvantages

Regardless of exact surgical technique, the general goals of breast reconstruction are to maximize aesthetics while minimizing morbidity. Microvascular free tissue transfer allows for the transfer of donor tissue that is an excellent match for native breast tissue, both in terms of the subcutaneous tissue that reconstitutes the breast mound and the simultaneous transfer of skin, where indicated. In addition, there exists a range of donor sites (including abdomen, thigh, and buttocks, among others), and increases the options for women who may have been previously not considered for autologous tissue transfer. Similarly, by expanding the repertoire of available flaps, the advent of microvascular free tissue transfer increases the available options in case the initial attempt at breast reconstruction fails (regardless of whether it is device-based, pedicled autologous, or free autologous). And finally, microvascular reconstruction can minimize donor site morbidity in many situations.

Despite its many advantages, free tissue transfer is not without its disadvantages. Most notably, relative to both device-based and pedicled autologous reconstructive procedures, the operative time for free tissue transfer procedures is longer (and in some cases significantly longer), which leads to an increased risk of intraoperative and postoperative complications (e.g., deep vein thrombosis, surgical site infection). Additionally, compared to pedicled autologous flaps, the risk of total flap loss is increased.

44.3 Indications and Contraindications

Indications for patients to undergo microvascular free tissue transfer as means of breast reconstruction include healthy and realistic expectations. Patients should have a comprehensive understanding of the risks of the procedure, which include complete or partial flap loss, infection, fat necrosis, deep vein thrombosis or pulmonary embolism, wound healing complications, and the need for emergent reoperation.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_44

Contraindications include comorbidities that preclude a long operation, as well as anatomy that is not amenable to the procedure (either because of congenital anatomic variants or because of previous operations).

44.4 Relevant Surgical Anatomy

44.4.1 Donor Site: Abdominal Wall

The abdominal wall is comprised of skin, subcutaneous tissue, fascia, aponeuroses, and muscle. Within the abdominal wall are arteries, veins, and nerves. Below the skin is fatty tissue, which is split into "supraScarpa's" and "subScarpa's" fat by the thin but moderately strong superficial fascia known as Scarpa's fascia.

Lateral to the rectus abdominis muscles on both sides are the external oblique, internal oblique, and transversus abdominis muscles. These structures are muscular lateral to the rectus abdominis muscle and aponeurotic overlying the rectus abdominis muscles. The aponeuroses of these three muscles contribute to the formation of the rectus sheath, and the relative contributions are different above and below the "arcuate line" (of Douglas, also known as the linea semicircularis), which is about 1/3 of the way from the umbilicus to the pubis. Above the arcuate line, the anterior rectus sheath is comprised of the aponeurosis of the external oblique and the anterior leaflet of the internal oblique. At the same level, the posterior rectus sheath is comprised of the aponeuroses of the posterior leaflet of the internal oblique and the transversus abdominis. Below the arcuate line, the anterior rectus sheath is comprised of the aponeuroses of all three layers, and the posterior sheath only receives contribution from the thin, weak transversalis fascia. The intercostal neurovascular bundles run in the plane between the internal oblique and the transversus abdominis muscles.

The paired rectus abdominis muscles run from the costal margin and xiphoid to the pubis and receive blood supply from both the superior epigastric vessels and the deep inferior epigastric vessels (thus making it a Mathes-Nahai type III muscle). Each muscle has three or four tendinous inscriptions, and the muscle is innervated by multiple intercostal nerves that usually pierce the posterior rectus sheath and enter the lateral half of the muscle from the deep/posterior surface.

The overlying skin and fascia are perfused by both (1) a deep system comprised of the deep inferior epigastric artery and vein (DIEA and DIEV) and the superior epigastric vessels and (2) a superficial system comprised of the superficial inferior epigastric vessels (SIEA and SIEV). While abdominal donor tissue can be relied upon to be successfully perfused by the deep system in almost all cases in the setting of microvascular surgery, the likelihood that it can be equally well perfused by the superficial system is less.

44.4.2 Donor Site: Gluteal Region

The gluteal region potentially affords a large volume of fatty tissue (though it is usually denser and more fibrous than is abdominal or thigh tissue). The perforators that perfuse this region emerge from the gluteus maximus muscles and are branches of the superior gluteal and inferior gluteal vessels. Both vessels originate from the internal iliac vessels and exit the pelvis through the greater sciatic foramen. The greater sciatic foramen contains the piriformis muscle, and the superior gluteal vessels exit cranial to the piriformis muscle ("suprapiriformis"), and the inferior gluteal vessels exit caudal to the piriformis muscle ("infrapiriformis").

44.4.3 Donor Site: Thigh

The fatty tissue of the medial thigh is generally of smaller volume than is found in the gluteal region but is thought to be softer and more similar to native breast tissue. The medial compartment of the thigh contains the adductor muscles (magnus, longus, and brevis) as well as the gracilis muscle. The blood supply to this region is from the profunda femoris system, either as perforators directly off the profunda femoris or else off of the medial circumflex femoral system.

The greater saphenous vein runs along the medial aspect of the thigh before it joins the deep venous system at the saphenofemoral junction. This vessel can be sacrificed but should be preserved if possible.

44.4.4 Recipient Vessels: Chest

The internal mammary artery (IMA) and vein (IMV) are the primary recipient vessels in the chest. As they arise from the first part of the subclavian artery and innominate vein, respectively, the IMA and IMV run just lateral to the sternum on both sides of the body in the fatty plane superficial to the parietal pleura. The terminal branches are the superior epigastric and the musculophrenic vessels.

Each of the true ribs (first through seventh) has a cartilaginous portion that runs from the costochondral joint to the most anterior aspect of the osseous portion of each rib. Between each rib is the intercostal muscle bundle, which is comprised of three layers of muscle (the external intercostal, the inner intercostal, and the innermost intercostal). The neurovascular bundle (intercostal artery, vein, and nerve) tends to run in the plane between the inner and innermost intercostal muscles (analogous to the musculature of the abdominal wall).

A fairly well-defined plane exists between the anterior surface of the parietal pleura and the posterior aspect of the posterior perichondrium and deep surface of the innermost

intercostal muscles. This plane is comprised mainly of fatty tissue, as well as the IMA and IMV (which usually branches into two veins at approximately the level of the third rib). These vessels frequently have small branches that arise from the medial, lateral, or anterior surfaces (though rarely from the posterior surfaces) and must be ligated in a controlled fashion in order to safely utilize these vessels as free flap recipient vessels.

44.4.5 Recipient Vessels: Axilla

The axilla is conceptually thought of as a pyramid with a base (infero-laterally) and an opening at the apex (superomedially). The lateral border is the humerus, the medial border is the chest wall, the anterior border is the pectoralis major, and the posterior border is the latissimus dorsi.

There are a number of relevant arteries, veins, and nerves that are in the axilla. The axillary artery and vein and brachial plexus are obvious structures which should be preserved at all costs. The three most relevant nerves are the long thoracic, thoracodorsal, and intercostobrachial. The long thoracic nerve (which innervates the serratus anterior muscle) runs in a cranial-caudal direction on the lateral chest wall near the midaxillary line. The thoracodorsal nerve (which innervates the latissimus dorsi muscle) also runs in a cranial-caudal direction but, posterior to the long thoracic nerve, often on the deep surface of the latissimus dorsi. The intercostobrachial nerve (otherwise known as the lateral cutaneous branch of the second intercostal nerve) runs perpendicular to the course of the previous two nerves, in the upper axilla.

The thoracodorsal artery and vein are common recipient vessels for free tissue transfer and run with the thoracodorsal nerve. It is important to remember that the neurovascular bundle can be distorted and/or adherent to the lateral chest wall if the patient has previously undergone radiation treatment or an axillary dissection.

44.5 Types of Free Flaps

44.5.1 Abdominal Flaps

The abdomen usually provides a good amount of skin and subcutaneous tissue available for transfer. Furthermore, the resulting abdominal contour and resultant scar approximate very closely (though not exactly) an abdominoplasty, which many patients are pleased to undergo. Even patients who appear to have minimal tissue at the abdominal wall can successfully undergo breast reconstruction using this donor site (especially if unilateral, so that more than half of the tissue can be used for the single breast reconstruction).

44.5.1.1 TRAM (Transverse Rectus Abdominis Myocutaneous) Flap

The TRAM flap is the prototypical abdominal-based flap for breast reconstruction. It is harvested on the deep inferior epigastric artery and vein and carries some (in the case of the "muscle-sparing" TRAM) or all of the ipsilateral rectus abdominis muscle, as well as the overlying fat and skin.

The vascular connection between the DIEA/DIEV pedicle deep to the muscle and the skin and subcutaneous superficial to the anterior rectus sheath is in the form of perforators; these can be either small (and insufficient to independently perfuse and drain an entire flap) or large (and sufficient to independently perfuse the flap). The TRAM procedure does not specifically dissect and isolate these perforators but instead takes them collectively.

The potential functional consequences of sacrificing the rectus abdominis muscle include weakened abdominal wall flexion (which becomes most noticeable during "core" exercises such as sit-ups, golf, etc.) and abdominal bulges (that might or might not quality as distinct hernias). The magnitude of these consequences is variable and depends on how much of the muscle was injured and/or displaced, as well as how much of the muscle that was left in place was denervated (the innervation to the rectus abdominis muscle comes the intercostal nerves, which enter the muscle from the deep/posterior aspect of its lateral portion; even if the muscle is left in situ, disruption of its nerve supply renders it nearly as dysfunctional as if it had been removed).

44.5.1.2 DIEP (Deep Inferior Epigastric Perforator) Flap

A DIEP is technically a "total muscle-sparing TRAM," as it dissects the perforating vessels through the rectus abdominis muscle, effectively leaving the muscle in place. It represents the current state of the art in abdominal wall-based breast reconstruction and requires a very high degree of surgical skill and comfort and familiarity working around the particularly small perforating vessels. Even relatively minor injury to these vessels can render them unusable and force the surgeon to seek an alternative source of tissue for reconstruction.

44.5.1.3 SIEA (Superficial Inferior Epigastric Artery) Flap

When it is judged that the flow through the superficial inferior epigastric system is sufficient to carry a flap, then roughly the same amount of tissue as the DIEP/TRAM can be carried as a superficial inferior epigastric artery (SIEA) flap.

The greatest advantage of the SIEA flap is that the vessels usually originate from the common femoral artery and vein, and therefore never penetrate the rectus sheath or rectus abdominis muscle; instead they wrap around the rectus sheath.

This is beneficial because the dissection is both simpler and faster, which leads to a shorter operation, and by not having to at a minimum incise the anterior rectus sheath (which is done in the DIEP flap) and at most actually remove a segment of the anterior rectus sheath (which is done in the TRAM flap), the likelihood of incisional hernia is reduced nearly to zero.

The disadvantage of the SIEA flap is that the SIEA and SIEV do not always reliably perfuse the entire flap. At this point there is no definitive objective measure, though some authors have suggested that an SIEA diameter greater than 1.5 cm can give the surgeon a reasonable expectation of sufficient perfusion.

44.5.2 Gluteal Flaps

Flaps harvested from the gluteal region include the superior gluteal artery perforator (SGAP) flap and the inferior gluteal artery perforator (IGAP) flap. Neither flap requires sacrifice of any muscle, and therefore donor site morbidity can be minimal. While abdomen-based flaps are the first-line choice in most cases, there are scenarios in which gluteus-based flaps may be chosen. First, if the patient has had prior abdominal surgery or liposuction, alternative flap donor sites should be strongly considered. Additionally, the gluteal flaps have a high "fat-to-skin" ratio (in contrast to the abdomen-based flaps, which have a high "skin-to-fat" ratio), and that makes them preferable in patients in whom the need for volume is greater than the need for skin [9]. It has been said that the ideal candidate for a gluteal flap has a large amount of gluteal fat and is interested in a reconstructed breast that is approximately a "B" cup. It must be remembered, however, that harvest of gluteus-based flaps requires intraoperative repositioning to a prone position, and accordingly breast resection and gluteal flap harvest cannot occur simultaneously.

44.5.2.1 SGAP (Superior Gluteal Artery Perforator) Flap

The SGAP flap is based on perforators of the superior gluteal artery, which is a branch of the internal iliac artery and emerges from the pelvis through the "suprapiriformis" portion of the greater sciatic foramen. Theoretical advantages of the SGAP flap include possible concealment in a swimsuit and possible hip roll improvement. The SGAP flap, however, has a short pedicle (5–8 cm), and the upper buttock design can lead to a "scooped-out" appearance.

44.5.2.2 IGAP (Inferior Gluteal Artery Perforator) Flap

The IGAP flap is based on perforators of the inferior gluteal artery, which emerges from the "infrapiriformis" portion of the greater sciatic foramen; also emerging from this foramen is the sciatic nerve. The advantages of the IGAP flap include the fact that the scar can be nearly completely hidden in the gluteal crease, it can correct "saddlebags," and it has a longer pedicle than the SGAP flap (7–10 cm). The most notable disadvantage is the relative difficulty of the dissection, the closer proximity to the sciatic nerve, and tenderness with sitting in the early postoperative period.

44.5.3 Thigh Flaps

In cases in which the abdomen is not available as a donor site, the next tier of breast reconstruction donor sites includes the gluteal region and the thigh. Based on the gracilis muscle, or perforators in that vicinity, the fat of the medial thigh is considered by many to be a closer match to the soft, pliable breast fat, compared to the denser, fibrous fat of the gluteal region. Additionally, because both the dissection and the harvest are performed supine, repositioning is not needed, and thus the breast team and reconstructive team can work simultaneously.

44.5.3.1 Gracilis Myocutaneous Flaps

Gracilis muscle-based flaps can be designed with different skin paddle orientations, which have relative advantages and disadvantages in terms of reliability of vascularity, volume of tissue available, and potential donor site complications.

The transverse upper gracilis (TUG) flap optimizes vascularity by including a wide swath of tissue that maximizes the likelihood of capturing perforators. By not including distal thigh skin, the surface area of skin available is less (and thus potentially insufficient in cases in which a large amount of skin is needed), and the transverse orientation can lead to labial spreading, which is a complication that is very difficult to treat [10].

The vertical upper gracilis (VUG) flap results in a scar that is vertically oriented on the medial thigh. This decreases the likelihood of labial spreading but does increase the likelihood that the scar is visible while wearing shorts. Also, the narrower subcutaneous tissue island can be less reliable than that seen in the TUG, but this risk can be mitigated if certain measures are taken. These include beveling outward to maximize perigracilis fat and fascia and oftentimes extending into the adductor longus fascia [10].

44.5.3.2 PAP (Profunda Artery Perforator) Flap

The most recently described flap harvested from the thigh is the muscle-sparing, profunda artery perforator (PAP) flap. First described by Robert Allen in 2012 [11], the PAP flap is based on perforators from the profunda femoris artery that traverse the adductor magnus muscle before emerging in the subcutaneous tissue and dermis posterior to the gracilis muscle (and usually medial to the semimembranosus muscle). The harvested tissue has the advantages of a long pedicle (7–13 cm), soft and pliable fat, and a donor site at the far superior extent of the posterior thigh that is largely concealed.

Disadvantages include limited volume (though the possibility of stacking bilateral flaps for unilateral reconstruction is one solution in a patient with large breasts), and the potential need for prone positioning, though many now describe "frog leg" positioning that allows for successful harvesting of the flap without leaving the supine position [11].

44.6 Recipient Vessels

The two vascular pedicles that are most frequently used as recipient vessels in microvascular breast reconstruction are the internal mammary (thoracic) vessels and the thoracodorsal vessels.

44.6.1 Internal Mammary Artery and Vein

The IMA and IMV are currently the most commonly used recipient vessels. By removing the cartilaginous portion of the third rib (though a complete rib-sparing approach has been described), the IMA and IMV (which exist as either one or two veins) can be made available for end-to-end microsurgical anastomosis.

The benefits of using the IMA/IMV include their location on the medial aspect of the breast footprint, which results in a greater proportion of flap being medially (which is where cleavage is generally desired) as opposed to laterally (which has a tendency to pull the transferred tissue laterally and caudally). Also, the location and caliber of the vessels are quite reliable (especially on the patient's right side), and the surgeon and microscope positioning are consistent and straightforward.

Surgeons must be careful when isolating the IMA/IMV because they run in a variably fatty plane immediately superficial to the parietal pleura, and even small missteps can lead either to injury to the vessels or violation of the pleura.

Cardiac history is of particular importance when there is consideration of using these vessels, as a history of coronary artery bypass grafting (CABG) utilizing the ipsilateral IMA precludes its use as a recipient vessel. Also, in a patient with a cardiac history who has not yet undergone CABG but may require such a procedure in the future, the surgeon should strongly consider using an alternative site. In such a patient as the one described above with serious cardiac disease, however, consideration should be made of not performing complex, lengthy microvascular breast reconstruction—or perhaps any breast reconstruction at all—at this time.

Most patients do not report any functional consequence after having a segment of the third rib removed, though some patients (especially those who are very thin) note a cosmetic defect visible through the overlying tissue.

44.6.2 Thoracodorsal Artery and Vein

When microvascular free tissue transfer was first described for breast reconstruction, the thoracodorsal vessels were the primary vessels used. This can be attributed to surgeon's general familiarity with the axilla and its contents.

This pedicle is identified by finding the lateral edge of the cranial aspect of the latissimus dorsi muscle and then dissecting down on the deep surface of the muscle until the thoracodorsal vessels are identified. Structures to be avoided include the thoracodorsal nerve, axillary vein, and axillary lymph nodes (damage to which could lead to upper extremity lymphedema).

Benefits of using the thoracodorsal vessels include ease of dissection (especially if axillary dissection has been performed during the same procedure) and decreased likelihood of significant morbidity relative to the IMA/IMV.

Conversely, disadvantages include a tendency of the transferred tissue to settle laterally (because of the location of the recipient vessels in the axilla) and a more awkward and potentially uncomfortable microscope orientation. Also, there is the possibility that the vessels have been damaged by prior axillary dissection or radiation, and there is the theoretical concern that use of the vessels may hinder the ability to safely use the latissimus dorsi muscle as a salvage flap if the microvascular free tissue transfer was to fail (though a latissimus dorsi muscle-based flap can still be pedicled on the serratus branch of the thoracodorsal pedicle even if a main branch of the thoracodorsal pedicle is unusable).

44.6.3 Others (Lateral Thoracic, Thoracoacromial, Cephalic Vein)

A number of additional recipient vessels have been described in the literature [12], including the lateral thoracic, branches of the thoracoacromial vessels, and the cephalic vein, though each of them has disadvantages that make them less desirable than either the IMA/IMV or thoracodorsal vessels. Most notable is the potential disruption of the lymphatic system (and resulting lymphedema) that can occur following skeletonization of the cephalic vein.

44.7 Care Delivery Requirements

Free flap reconstruction after breast surgery is a complex endeavor not only in terms of the technical steps but also of both the equipment needed in order to perform it and the personnel and systems that must be in place in order to optimize the likelihood of success in the postoperative period.

In the operating room, the needs specific to the success of free flap breast reconstruction include an operating microscope

(though some surgeons advocate for performing microsurgery with loupe magnification), microsurgical instruments (including well-conditioned, fine jeweler's forceps, vessel dilators, needle drivers, scissors, and vascular clamps), fine nylon sutures (8-0, 9-0, or 10-0), and an operating table that reliably flexes at the waist (in order to facilitate abdominal closure).

Well-trained nurses in the recovery room and on the hospital floor are imperative for the early identification of signs of impending flap compromise (changes in flap color, temperature, Doppler signal, etc.). Equally well-trained residents and fellows are a valuable adjunct, but not as vitally important as the nursing care.

If flap compromise is identified, an effective and reliable system for rapid activation of personnel in order to get the patient into an operating room as quickly as possible can make the difference between a flap that is successfully salvaged and one that is not.

44.8 Long-Term Recovery

The long-term satisfaction after microvascular free tissue transfer for breast reconstruction is very high. This is most likely because the patient has undergone reconstruction with "her own tissue," and that tissue changes in sync with the rest of her body. In stark contrast to reconstruction with breast implants, donor tissue ages and will undergo fluctuations in weight along with the patient. Furthermore, because there are no foreign bodies involved in the reconstruction, the incidence of long-term infection is very low, and if infection does occur, it is usually easily treated with antibiotics alone (as opposed to reconstruction with an implant that often requires removal of the implant).

44.9 Conclusion

The introduction and refinement of microvascular free tissue transfer has revolutionized the way that breast reconstruction is performed. By increasing the number of potential donor sites, breast reconstruction can be tailored to individual patients' needs in ways that were never possible before.

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Delayed Breast Reconstruction After Mastectomy

45

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45.1 Introduction

Delayed breast reconstruction is thought to be the first technique for restoring the physical integrity after mastectomy. Until some decades ago, breast reconstruction could not be performed until 2 or even 5 years after conclusion of oncologic treatment [1, 2]. Today, immediate breast reconstruction can be indicated for most breast cancer patients, but unfortunately the majority of them remain without their breasts. And there are different well-documented reasons for that, such as disparities related to race, sociodemographic factors, and financial and some cultural barriers. Then, delayed breast reconstruction is an option for many patients [3, 4].

Implants and autologous reconstructions are the most important options. Indications for them depend on patient's anatomy, previous radiotherapy, or patient's preferences. Both magnitude of the procedure in terms of invasiveness and morbidity in each individual case are important points to considerate. Implant-based breast reconstruction is notable for its surgical simplicity, applicability, and faster recovery time, but it is not allowed in all cases [5]. Despite of that, there are some limitations for such an approach, like previous radiotherapy or Halsted's mastectomy. It is also important to take in account patient's expectations in order to better individualize the decisions.

So, the aim of this chapter was to cover the indications, preoperative evaluation, operative techniques, and complications related to delayed breast reconstruction.

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45.2 Indications and Selection of Patients

45.2.1 Timing of Reconstruction

Delayed breast reconstruction can happen at any time, given that the wound has healed and adjuvant therapy has been already completed. But postradiation acute skin lesions and hematologic effects of chemotherapy should be completely ceased [6]. At *Hospital Nossa Senhora das Graças* Breast Unit in Curitiba (Brazil), the routine is wait at least 6 months after the conclusion of adjuvant radiotherapy and 30–40 days after the end of chemotherapy. Different from the immediate approach, the delayed one can be indicated even for patients who had impaired perfusion of skin flaps after mastectomy [7]. Therefore, it is useful to be clear for patients who suffer from some medical comorbidities such as active smoking, diabetes, obesity, or cardiopulmonary disease that these conditions might predispose to some additional risks.

Delayed breast reconstructions have some facilities regarding to immediate ones because adjuvant treatment is already concluded. Moreover, there are series demonstrating that delayed has fewer complications [8]. However, the technique might entail other surgeries in order to ameliorate esthetics, thus prolonging the overall time of treatment for patients, because it provides less cosmetic quality than the immediate reconstruction [7]. Furthermore, delayed reconstruction has limited reconstructive options following radiation therapy.

45.2.2 Implant-Based or Autologous Techniques

Delayed breast reconstructions can be implant-based or autologous flap-based ones. The first one the use of silicone-filled or saline-filled implants and definitive or temporary expanders beneath the remaining mastectomy skin flaps and the pectoralis major muscle, whereas the autologous reconstructions use musculocutaneous flaps, which consist of a segment of vascularized muscle with the overlying skin and fat, which are per-

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_45

fused by perforating vessels from the underlying muscle. It can be with pedicle or free flaps, and sometimes it is also necessary the association of an implant for better volume and projection, as it is the case with latissimus dorsi flap. While for some patients the overall result is more pleasing with musculocutaneous flaps [3, 4, 7], there are some disadvantages, which include longer surgical length and prolonged postoperative recovery when compared to implant-based reconstructions. In Fig. 45.1 there is a nice example of this, in a patient with previous breast cancer and radiotherapy in the thoracic wall and neurofibromatosis. Moreover, with implants there is no donor site morbidity, reduced operative time, and more rapid postoperative recovery when compared to autologous reconstructions [9, 10]. In addition, with the new generation of breast implants, particularly the anatomical ones, it is possible to achieve good esthetic outcomes and high rates of patient's satisfaction.

45.2.3 Definitive Implants or Temporary Expanders

In patients who were not previously irradiated, the choice of the most appropriated technique requires some specific preoperative clinical evaluations: skin and musculocutaneous conditions in the mastectomy flap, size and ptosis of the contralateral breast, and patient's expectations about her breast reconstruction. For instance, the complete absence of the pectoralis muscles due to a Halsted's mastectomy is a contraindication to this approach [11, 12]. Using a definitive form-stable implant rather than a temporary expander is not frequent in delayed reconstructions. The ideal patient for this approach should have a non-tense cutaneous flap, a good quality of her pectoralis major muscle, and a small contralateral breast.

The tissue expansion with a temporary expander before to change to a definitive form-stable implant is the most frequent indication for delayed breast reconstruction for nonirradiated patients—the two-stage techniques. The expander is used to distend the cutaneous flaps in order to facilitate the insertion of definitive form-stable implant in a second surgery. The choice of the temporary expander is in a similar way of the definitive ones—basis, height, and desired volume should be considered. Older patients, those with significant medical comorbidities, and women with minimal abdominal tissue in whom the autologous technique would be unsuitable, also benefit from this technique. Besides, the expander/implant technique is to be indicated for those patients devoid

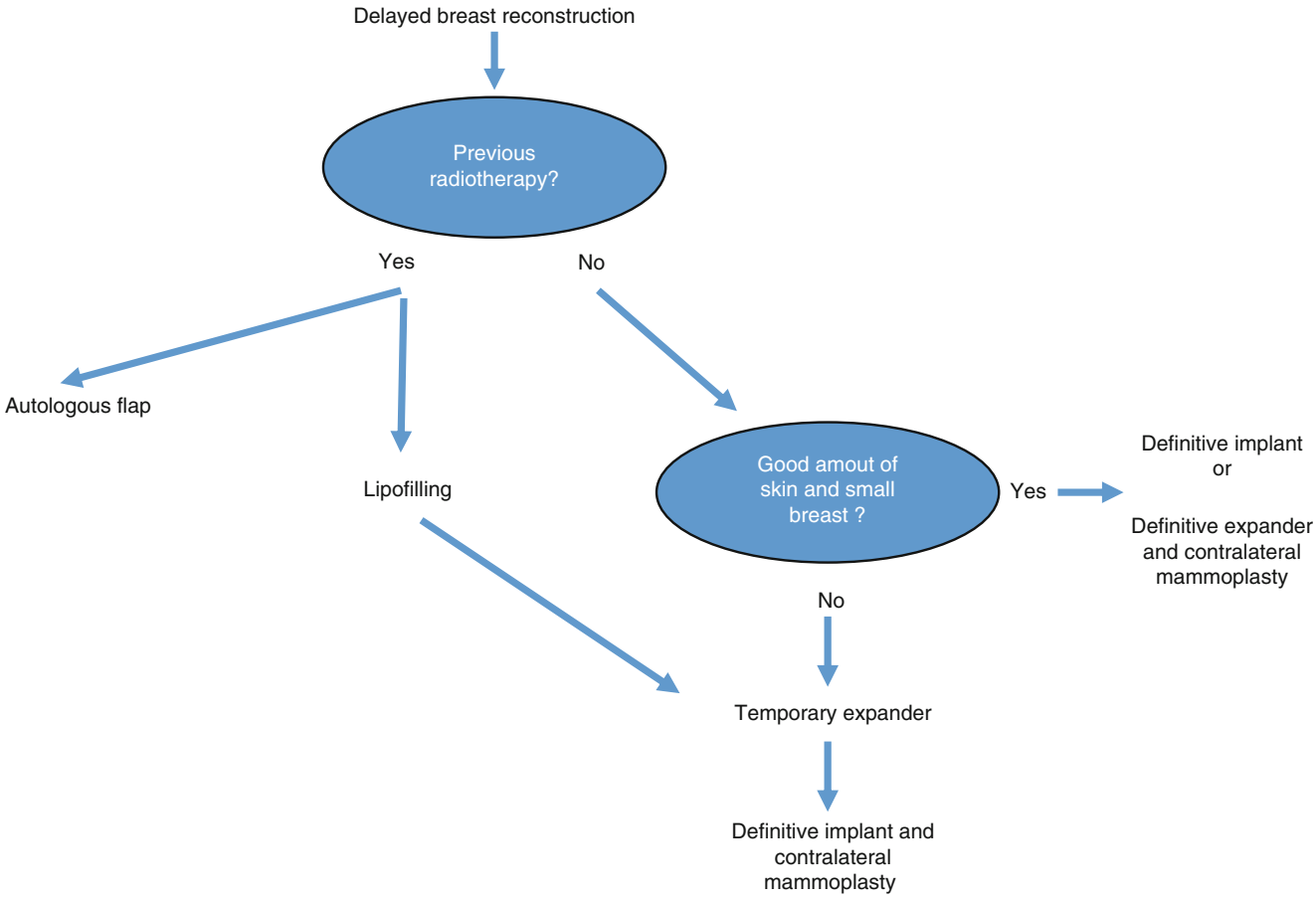


Fig. 45.1 Preoperative measurements for surgical planning and choice of the expander and implant

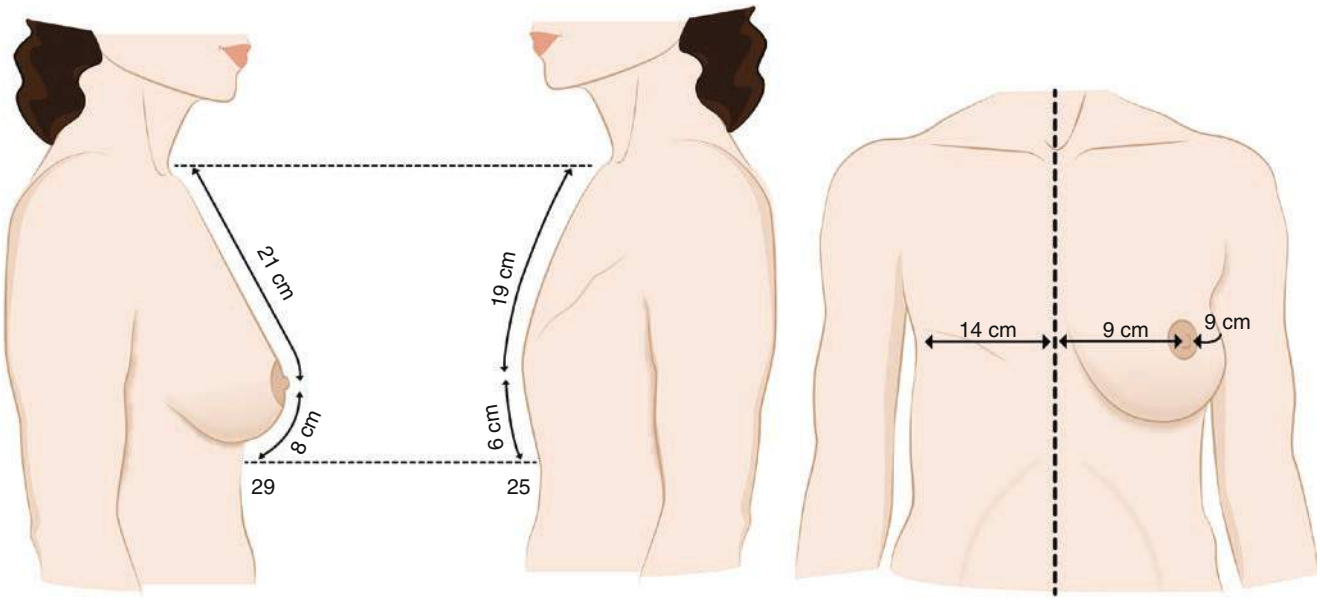


Fig. 45.2 Young patient with previous mastectomy, thoracic wall radiotherapy, and neurofibromatosis

of sufficient skin or preserved subcutaneous tissue in flaps resulting from mastectomy. This may occur when there is little elasticity of the cutaneous flaps from mastectomy or in the case of a contralateral breast presenting a rather large volume. In these situations, the two-stage implant reconstruction usually yields esthetically superior outcomes.

There are some cases where two-stage approach is contraindicated, and they are basically the same ones as those for definitive implants, with even more emphasis on the risk of expanders after radiotherapy [13]. Many authors have realized that several postoperative complications can ensue when attempting to distend previously irradiated tissues [13–16], since the radiation decreases the tissue elastic distension capacity. In these cases, the most frequent complications are painful and difficult expansion with possible extrusion of the expansion device or periprosthetic capsule. Even though one achieves the final stage of expansion, the cutaneous coverage of the prosthesis becomes too thin and fragile to protect the definitive implant. Recently, the addition of lipofilling in breast reconstruction armamentarium is allowing to expand irradiated tissues in selected cases, but it is necessary to have more data in this specific approach.

A practical flowchart for decisions in delayed breast reconstruction is shown on Fig. 45.2.

45.3 Preoperative Evaluation

The aim of breast reconstruction is to obtain symmetry [17, 18]. For this reason, it is essential to carry out a preoperative plan that includes a detailed analysis of the healthy breast's characteristics in order to make the correct choice of the most suitable technique to reconstruct the other breast [19]. It is important to remember that the reconstructed breast, most of the time, will have low projection in the upper pole and no ptosis. With these characteristics in mind, the contralateral breast should be planned to have an intervention for symmetry in the same surgery or in a second one (after the change of the temporary expander for a definitive implant).

Clinical and radiologic preoperative evaluations are crucial in order to clarify the patient's risks for the surgery. Diabetes, hypertension, obesity, and tobacco-addicted patients have higher risks for bad esthetic outcomes and for implant or expander extrusions. It is also important that a detailed oncologic evaluation be performed, surveying the following topics of the past treatment: type, localization, and size of tumor; number of positive lymph nodes; type of surgical procedure performed; chemotherapy; radiotherapy; hormone therapy; follow-up period; and the most recently performed radiologic and blood exams. Furthermore, the evaluation of the contralateral breast is also mandatory in order to exclude bilateral neoplasm and should include mammographic and ultrasound exams. In high-risk patients with hereditary breast cancer syndromes such as BRCA 1/2 mutations, it is necessary to add breast a MRI. These exams are important because contralateral breast surgery—a reduction mammoplasty, mastopexy, or augmentation mammoplasty—is frequently required to obtain a more pleasing symmetry.

45.4 The Day Before the Operation

On the day before the operation, the whole procedure is explained to the patient again, and then the informed consent form is obtained. The patient is then placed standing, and photographs are taken in profile, in partial profile, and in forward-facing position. It is useful to make precise measurements of the contralateral breast in this occasion, such as base width, thickness of subcutaneous adipose tissue, and height as well as anterior projection (Fig. 45.3).

45.4.1 Choosing the Correct Expander and Implant

Concerning the decision as to which implant one should use, it is important to compare the contralateral breast with the future implant with regard to the parameters of base, height, and anterior projection. This is done during the preoperative period in order to choose two or even more models and sizes of implants that are most likely to be used during the surgical procedure. The final decision can be made at the intraoperative stage, sometimes with the help of samples. Surgeons should pay attention to whether samples are prohibited in the country they work in. In Brazil there are some specific norms for that, and at the European Union, for instance, the re-sterilization of samples is strictly forbidden. Nevertheless, the non-sterilized implants can be thoroughly coated with a highly adherent and resistant sterile plastic envelope, therefore permitting their repeated usage. This technique for choosing the implants based on the aforementioned measures is precise and particularly useful in the cases in which it is necessary to use an expander/implant and, subsequently, perform a contralateral augmentation mammoplasty [20–22]. In cases of definitive implants with mastopexy or reduction mammoplasty in the contralateral breast, the decision as to the type and volume of the implant must also take in account the volume reduction, the change of shape, and the reduction of the breast base. These calculations can be based on augmentation mammoplasty papers [20, 23], which employ these methods to calculate the volume and shape of implants for esthetic improvement, on samples, and in surgeon's personal experience.

45.4.2 Surgical Markings

Afterward, lines are drawn on the patient's chest to assure the correct understanding of the anatomic conditions. There

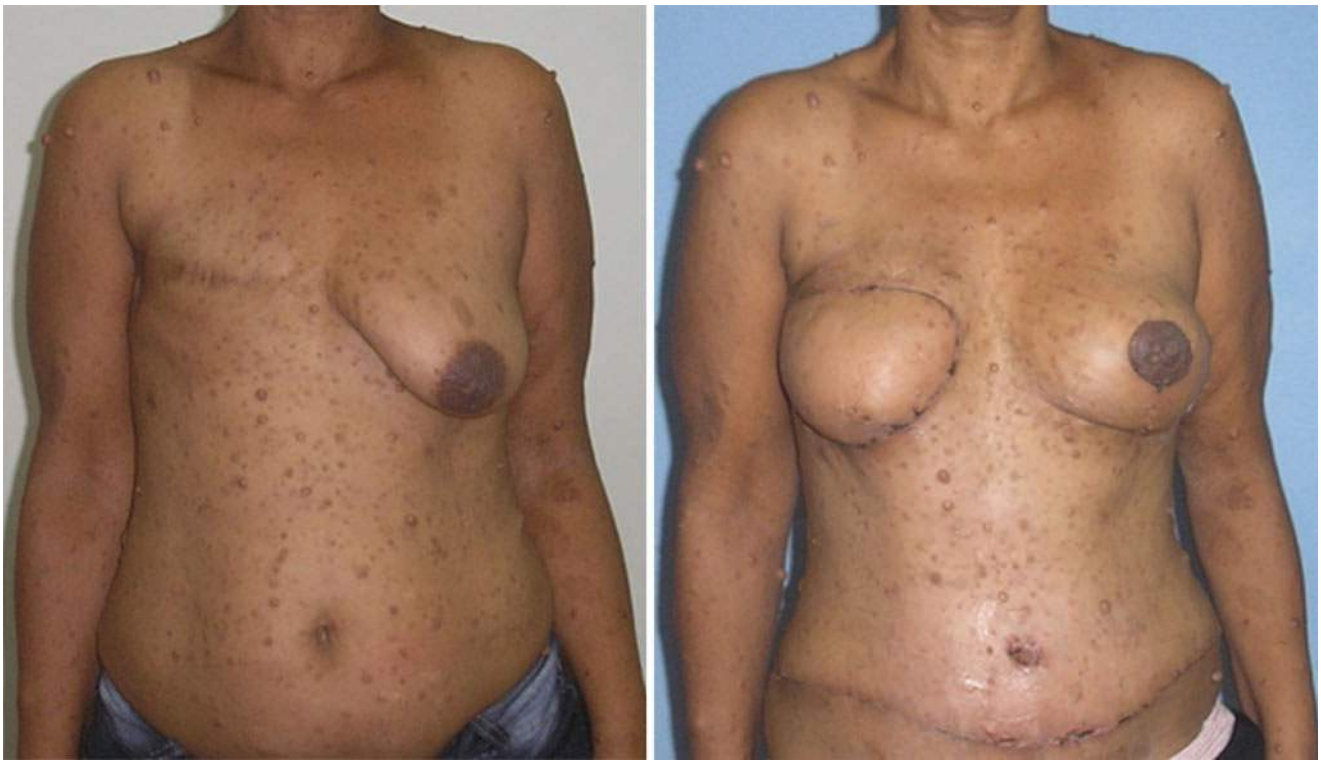


Fig. 45.3 A practical flowchart to guide decisions in delayed breast reconstruction

should be drawn a median line from the sternal notch to the xiphoid appendix, and the inframammary fold should be placed at the same height and shape of the contralateral breast. (Figs. 45.4, 45.5 and 45.6).

45.5 Surgical Technique

45.5.1 Before Skin Incision

In the operating room, patient is placed in supine position, keeping her arms parallel to the trunk. The operating table must be set in a way the patient can be placed in a 90-degree position, i.e., sitting, at the end of the procedure

45.5.2 Skin Incision and Scar Excision

In cases of autologous flap delayed reconstruction, it is possible to remove part of the mastectomy flap, in order to replace that for the flap's skin and to shape the new breast. But with implants, the incision should be most of times in the preceding mastectomy scar and, if possible, in the pectoralis major muscle. This technical detail allows for a safer suture of the pros-

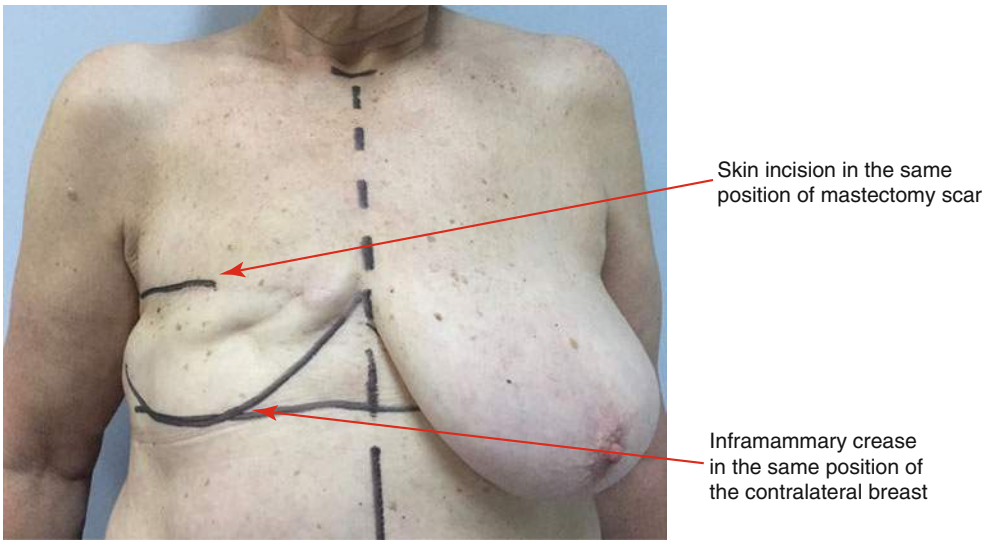
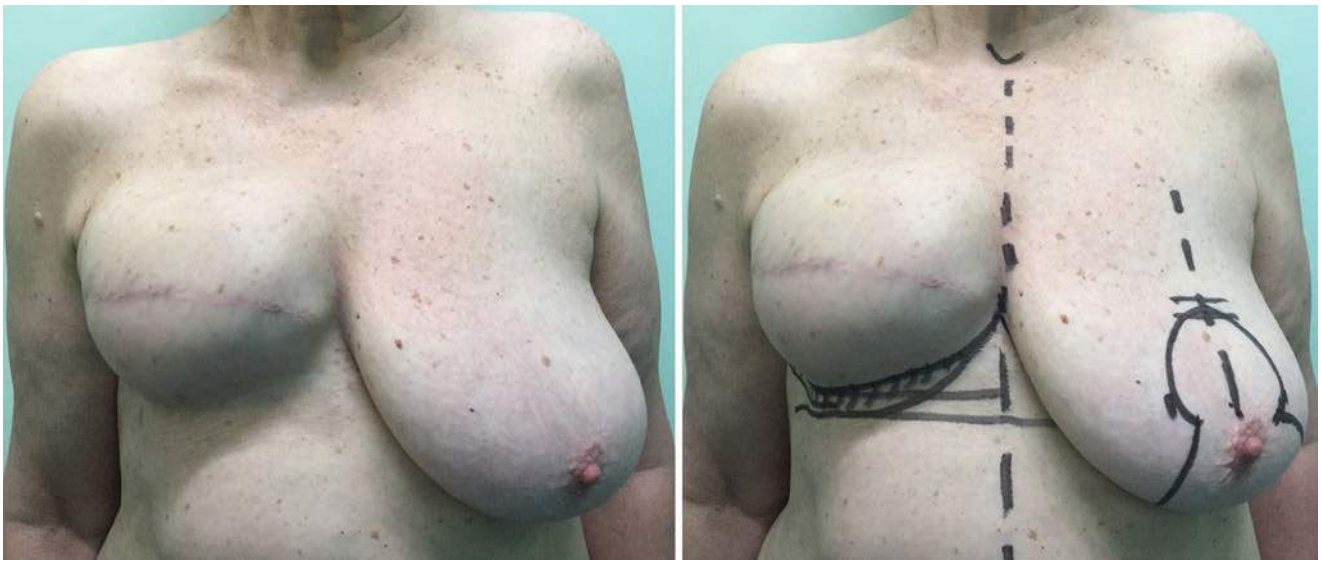


Fig. 45.4 Preoperative view with planning draws of a 70-year patient for delayed breast reconstruction with temporary expander



Final result after reconstruction with temporary expander

Pre-operatory draws for changing by definitive implant and contra-lateral breast reduction

Fig. 45.5 Preoperative view before changing temporary expander by definitive implant and contralateral breast reduction

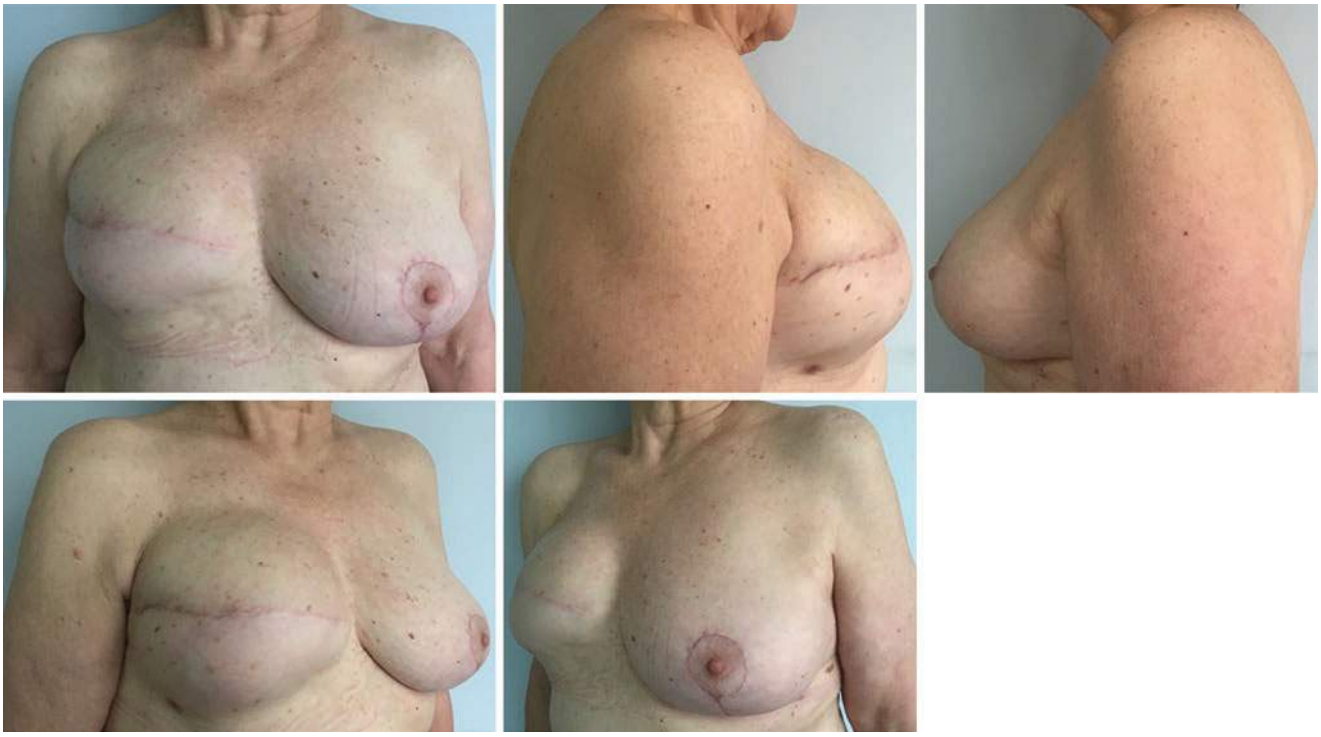


Fig. 45.6 Final outcome after definitive anatomical implant in the right breast and contralateral mammoplasty

thetic pocket in two layers, namely, the muscular and the cutaneous layers. Incision with either partial or complete removal of the scar is chosen based on three clinical situations:

- Wide scar with a good amount of skin in the mastectomy flap—in this case the exeresis of the scar is indicated.
- Narrow scar with little tense flap—here it is not necessary to remove the scar.
- Wide scars without much skin when it has already been decided to use an expander—scar can be removed completely or almost completely, but extra care must be taken when expansion is performed, as a too sudden distension could widen the scar again.

45.5.3 Operative Technique

Autologous flap reconstruction is described in other chapters in this book. After incising the skin, an inferior and lateral subcutaneous undermining must be performed in order to do the contour of the inframammary fold. This is required to set the prosthetic pocket, which can be located subcutaneously in this region or under the serratus muscle, in case the skin or the adipose subcutaneous tissue in the inferior lateral region is too fragile. As a result of this maneuver, one can see the lateral edge of the pectoralis major muscle, which is then lifted to set the submuscular pocket. This pocket can be made via a digital undermining in the upper portion, where no perforating vessels are found. In the inferior and medial regions, a light retractor is required so that the efficient hemostasis of large internal mammary pedicles found in this region is performed. The pectoralis major muscle then must be completely detached from the costal plan about 4 or 5 cm above the medial extremity of the inframammary fold. This dissecting procedure is mandatory so that a nonesthetic movement of the implant can be prevented when the pectoralis major muscle contracts. Preparation of the inframammary fold demands great technical attention, as it is an anatomic landmark crucial to the long-term esthetic result [5]. There are two possible variants:

- Without an upper abdominal skin flap—it is used in cases either when there is great elasticity of the skin, which allows the insertion of a definitive prosthesis or, if a decision has been made for a reconstruction in two surgical steps, of a temporary expander. In such cases, the subpectoral dissection must reach no more than the inframammary fold level, and then an incision into the aponeurosis of the rectus abdominis muscle must be performed to achieve a better projection of the lower mammary pole. There is no need for an undermining maneuver lower than the projection of the inframammary fold; otherwise the prosthesis might end up being placed below the inframammary crease, producing asymmetry.
- Using an upper abdominal skin flap—this autogenous tissue reconstruction technique is recommended for those

cases in which a definitive implant is applied and the skin flaps from mastectomy are not very elastic. A rectus abdominis muscle aponeurosis (made according to the projection of the inframammary fold) can be used if there is good elasticity of the skin in the upper abdominal area (just below the inframammary fold). The subpectoral dissection must reach the inframammary fold level followed by incision of the undermining of the supra-aponeurotic region 2–3 cm below the inframammary fold. A cutaneous advancement flap can be easily performed if the patient is placed in a semi-sitting position. The inframammary fold is reconstructed with spread stitches of nonabsorbable thread, suturing the superficial aponeurosis at the upper limit of the aponeurosis of the rectus abdominis muscle medially and laterally at the serratus muscle.

After the prosthetic pocket is set up, an internal irrigation is performed with either pure or with an antiseptic product-added saline solution. At this point, rigorous skin cleaning and change of gloves of the whole team before contact with the implant is mandatory. Such care helps to reduce the risk of microcontamination of the implants and therefore reduces the risk of postoperative infection or the formation and development of a periprosthetic capsule [24]. The implant, i.e., either the definitive implant or temporary expander, is carefully inserted into the prosthetic pocket.

Finally, a tubular multiperforated aspirating drain is inserted into the prosthetic pocket as a safety measure. Then, suture is done in two plans. The first one is done in the subcutaneous tissue with absorbable monofilament stitches of 3-0, and the second is an intradermal cutaneous suture with absorbable monofilaments 4-0.

45.6 Postoperative Care

Some surgeons apply a dressing with elastic straps, making a moderate compression for 3 days. Others choose a lighter dressing with no compression and also advise the patient to wear a sports-type bra, medium compression, right on the first postoperative day. This second option allows an easier control of a possible postoperative hematoma and avoids risks of allergy and cutaneous lesions that might occur when adhesive elastic straps are used. The drain is removed when the drained fluid is serous and its volume is lower than 50 cc in the past 24 h. If a temporary expander is chosen, an expansion with a variable volume of saline solution is the usually recommended each 3 weeks. The correctly instilled volume should not cause tightness or erythema or disrupt the patient's comfort or skin quality. As the aim of the expansion is to surpass the quality of a one-stage definitive implant, an augmentation of 25% is needed to achieve this purpose, with ideal skin drape and recoil [5].

45.7 Association with Fasciocutaneous Thoracodorsal Flap

This technique was initially described by Holmstrom [10], who advocates the use of a rotational fasciocutaneous thoracic dorsal flap to improve the projection of the lower pole of the reconstructed breast. This technique can be applied in those cases of an oblique mastectomy scar, and the graft must be grounded on epigastric vascular pedicles, which cross the anterior aponeurosis of the rectus abdominis muscle. The flap must be designed with two thirds of the base above the future inframammary fold and a third below. After the preparation of the fasciocutaneous flap, an upper rotation of the flap is performed, and the donor zone is covered with the inferior rotation of the lateral triangular flap together with the advancing of the upper abdominal skin flap. The implant is inserted below the pectoralis major muscle in the upper internal region and below the flap in the inferior lateral region. This technique is not routine due to the vascular fragility of the flap. It can be used when applying more complex techniques such as when the latissimus dorsi or the transverse rectus abdominis myocutaneous (TRAM) flaps are contraindicated.

45.8 Complications

Complications related to breast reconstruction of any type can be classified into immediate (until 2 months after the surgery) or secondary (after the aforementioned period) [5]. The most frequent complications comprise hematomas, seromas, infection, flap necrosis, and capsular contracture. Capsular contracture rates may be lessened by the use of implants with a textured shell rather than a smooth shell, by placement of the implant in a submuscular rather than subcutaneous location, and by avoiding use of this technique in women who need radiotherapy [25, 26]. Obesity, diabetes, age older than 65, smoking, and hypertension are risk factors for complications following breast reconstructions [27, 28].

45.9 Conclusions

Delayed breast reconstruction can achieve satisfactory cosmetic outcomes with low rate of complications. Temporary expanders and implants are surgical procedures that represent minor risks and sometimes can even be performed under day-surgery. Overall, this is the most used technique due to its practicability, lower risk of complications then musculocutaneous flaps, and satisfactory esthetic outcomes with the various anatomic implants available nowadays. Patients who were previously irradiated are better for autologous flaps or lipofilling.

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Part V

Management of Complications

Prevention and Treatment of Infections in Breast Reconstruction with Implants

46

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Breast cancer is one of the main causes of deaths among women all over the world. Its treatment has been changed dramatically over the last decades with the paradigm change from radical mastectomy to conservative surgery associated with radiotherapy [1, 2]. Nonetheless, conservative surgeries could make deformities in the breast and better strategies needed to be used for better aesthetic results [3]. The oncoplastic surgery is the answer for this matter with greater benefits, including excellent cosmetic outcomes, better local control of the margins of the tumor, and greater satisfactions from patients and surgeons [4]. The skills of the breast surgeons have been improved in conservative techniques and also in reconstruction of the breast in cases of mastectomies, with a complication rate of 15–25% [5, 6].

In 1963, silicone implants were used for the first time, and since then they have been a great option for breast reconstruction. There are several researches looking for better materials, biocompatibility, resistance, durability, less deformability, ideal shape, and smooth touch more similar to the natural breast [7].

Most breast reconstructions are based on implants or tissue expanders [8]. Some of the surgeries using those devices may have complications, such as infections, capsular rupture or contracture, distortion, fibrosis, and chronic inflammation [9].

One of the worse complications in breast reconstruction using implants is infection. In some cases, the removal of the device is necessary, and the patient could stay for a long time hospitalized [10]. This could cause psychological damages and expensive costs and postpone the adjuvant treatment of the cancer.

In the United States, a surgical site infection after breast surgery can cost approximately 4000 dollars [11]. Infection in the breast pocket of the implant can cost even more. Infections and capsular contracture are the main cause of reoperations [12].

The authors of this article made a bibliographic review using the data of the *Public Medical Literature Analysis and Retrieval System Online* (Pubmed) and Cochrane Library in seven steps (Table 46.1) using the specific citations: *infection; complications; reconstructive; risk factors; antibiotic prophylaxis, irrigation; implant; breast; salvage; capsular contracture.*

It was found that out of 1436 articles published until 2015, 40 of them were selected (39 from Pubmed and 1 from Cochrane Library) based on the topics: risk factors for complications in breast reconstructive surgery, surgical site infection in breast procedures, antibiotic prophylaxis in breast surgery, irrigation of breast implant pocket, and biofilm and capsular contracture. Articles about complications with autologous tissue reconstruction, case reports, and non-human procedures were excluded.

This paper was conducted in the Santa Casa de Misericórdia, Belo Horizonte (MG), Brazil.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_46

Table 46.1 Steps on bibliographic review

Steps	Citations	Articles found	Selected articles
1	*Infection and implant and breast*	583	08
2	*Complications and reconstructive and implant and breast*	494	10
3	*Risk factors and Infection and implant and breast*	90	07
4	*Capsular contracture and implant and breast*	104	05
5	*Antibiotic prophylaxis and implant and breast*	29	04
6	*Irrigation and implant and breast*	46	03
7	*Salvage and implant and breast*	90	03
Total		1436	40

46.1 Infection Incidence Rates in Breast Surgery with or Without Implants

Breast surgeries are classified as clean according to the surgical wound classification, and infection rates are usually less than 2%. Comparing mastectomy to aesthetic procedures, the former has 4.4% and the latter 1.1% infection [13].

Reconstructive breast surgery can be exhausting for patients because it demands more interventions, such as the use of implants, immediate and delayed contralateral symmetrization, treatment of complications, and nipple reconstruction. In 2014, the median number of procedures was 2.37 by breast [14].

Complication incidence rates differ significantly between distinct institutions. In 134 studies with 42,146 patients (8.2% of these studies were randomized trials), there has been found less than 20% of complications. The author recommends more accurate methodological criteria to determine the exact rate of complication [15].

In breast reconstruction with implants or tissue expanders, infection rates vary in 1–30%, depending on definition of surgical site infection, type of procedure, patient's comorbidities, follow-up, pre- and postoperative assessment and treatments, and proper registration in patient's data [16].

46.2 Risk Factors for Breast Implants

There are multiple and complex variables associated with surgical site infection (SSI) rates and, as a severe consequence of it, extrusion of the implant. The definition of SSI from the *Center Disease Control and Prevention (CDC)* is based on those criteria [17]:

- Purulent drainage, with or without laboratory confirmation, from the superficial incision
- Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
- At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat
- Diagnosis of superficial incisional SSI by the surgeon or attending physician

In 2009, a strong association was shown between infection and these variables: large breasts ($p < 0.001$), previous irradiation ($p = 0.007$), and repeated implant ($p = 0.008$). Additional significant covariates in this model included one surgical oncologist ($p = 0.003$) [11]. In 2012, another study with 195 women demonstrated cellulitis as an independent factor, raising more than 200 times the risk of infection [18].

In 2012, a meta-analysis with eight randomized trials described those following risk factors: increased age (OR 1.73), hypertension (OR 1.69), higher body mass index—BMI (OR 1.96), diabetes mellitus (OR 1.88), American Society of Anesthesiologist (ASA) 3 or 4 (OR 2.06), previous breast biopsy or surgery (OR 1.84), preoperative chemoradiation (OR 2.97), hematoma (OR 2.45), seroma (OR 1.65), intraoperative bleeding (OR 1.38), postoperative drain (2.84), longer drainage time (OR 2.95), and second drainage tube placed (OR 3.35) [16].

Another study with 981 Japanese women that were reconstructed with tissue expanders or implants was described: diabetes (OR 4.22), repeated expanders (OR 2.81), expanders larger than 400 cc (OR 2.52), postoperative hormone therapy (OR 2.50), preoperative chemotherapy (OR 2.36), nipple-sparing mastectomy (OR 2.30), and delayed reconstruction (OR 1.21) [19].

In a review with 14,585 patients, factors were age >55 years (OR 1.66, $p = 0.013$), class II obesity (OR 3.17, $p < 0.001$), active smoking (OR 2.95, $p < 0.001$), bilateral reconstruction (OR 1.69, $p = 0.007$), and direct-to-implant reconstruction (OR 1.69, $p = 0.024$) [20].

Using the ACS-NSQIP program in 12,163 patients from 250 institutions who made immediate reconstructions with expanders, researchers identified the following risk factors: age >55 years (OR 1.4), BMI > 30 (OR 3.4), operative time >4 h (OR 1.9), and acellular dermal matrix—ADM (4.5% versus 3.2% in the patients who didn't use ADM) [21].

A recent publication described as predictors of complication: radiation (raising infection and capsular contracture 5–48%), smoking (37.9%), BMI >30 (seven times more reconstruction failure), hypertension (twice more), and previous conservative mastectomies with radiotherapy. The material of the implant, immediate reconstruction, and fat grafting can improve the aesthetic results [22].

Summarizing, Table 46.2 shows the risk factors for infection that was found in this review:

Table 46.2 Risk factors that increase the rates of infection in breast surgeries using implants

Patient characteristics	Surgery	Clinical treatment
Diabetes (OR 4.22)	Repeated implants (OR 2.81)	Preoperative chemotherapy
BMI > 30 (OR 3.1–3.4)	Expansor larger than 400 cc (OR 2.52)	Radiotherapy
Smoking (OR 2.95)	Nipple-sparing mastectomy (OR 2.3)	Postoperative hormone therapy
Age > 55 years (OR 1.4–1.66)	Operative time >4 h (OR 1.9)	
Others: hypertension, previous breast biopsy or surgery, large breasts	Bilateral reconstruction (OR 1.69)	
	Direct-to-implant reconstruction (OR 1.69)	
	Delayed reconstruction (OR 1.21)	
	Others: drains, surgeon's experience, the absence of antibiotic prophylaxis, acellular dermal matrix, intraoperative bleeding, hematoma, seroma, cellulitis	

46.3 Capsular Contracture (CC) and Infection

Capsular contracture is the most common complication in augmentation mammoplasty. Usually aesthetic procedures have less CC than reconstruction (11% × 37.5% CC), but the rates can vary from 2% to 80% of CC in breast reconstruction with implants [23, 24].

The material and the pocket placement can influence those incidence rates. Smooth implant surfaces have higher incidence of CC than textured ones (statistical significance at 3.10; 95% CI, 2.23–4.33). Only the subglandular group had a statistically significant pooled result of 3.59 (95% CI, 2.43–5.30) [25]. Radiotherapy has an adverse impact in capsular contracture, well-described in articles and reviews. CC in patients with radiotherapy can reach 21.6% versus 3.3% in non-radiated patients [26].

Capsular contracture score is based on Baker classification (1975), which includes clinical firmness evaluation of the breast:

- Grade I—the breast is normally soft and appears natural in size and shape
- Grade II—the breast is a little firm but appears normal
- Grade III—the breast is firm and appears abnormal
- Grade IV—the breast is hard and painful to touch and appears abnormal

Capsular contracture can occur in days, months, or years after the surgery. The precise cause is still unknown, but there are theories about inflammatory and infectious etiology. Exaggerated inflammatory response was identified in patients with CC. The quantity of silicon particles associated with macrophages and myofibroblasts providing a contractile force seems to influence the severity of contracture [27].

The infectious hypothesis is based on biofilm, in which bacterial stimulus maintains inflammation and fibrosis. Some studies describe the incidence of CC four times higher with biofilm. Subclinical bacterial colonization can be found in up to 66.7% Baker III and IV CC. The microorganisms usually found in those cases are coagulase-negative staphylococcus species and *Propionibacterium acnes*, and capsular infection is more associated with *Staphylococcus epidermidis* [9].

The contamination can occur because of contaminated saline solution or implant, surgical room, skin microbiome, and mammary ducts besides bacterial invasion from other sites [26].

Some prophylactic methods can be used to diminish the probability of infection and CC, such as textured implants, submuscular pocket, inframammary incision, adequate hemostasis, and antibiotic prophylaxis [28].

46.4 Antibiotic Prophylaxis in Breast Implants

Despite of the use of antibiotic prophylaxis by surgeons in breast reconstruction, the rates of surgical site infections are still high and can reach 35% [29].

The use of antibiotic prophylaxis in breast surgery is not a consensus. Some surgeons select the cases they are going to use it, like high-risk patients for infection [30], while others use antibiotics for every patient for 7 days or during the drainage. *The National Surgical Infection Prevention Project* suggests that antibiotic prophylaxis should not last longer than 24 h, based on studies from plastic surgeries and not breast reconstructions with implants [31].

The discussion about the best option of antibiotic and for how long the surgeon should maintain the prophylaxis remains. In some institutions cephalexin is prescribed; for others vancomycin, azithromycin, clindamycin, ampicillin-sulbactam, or quinolones can be used. *Craft* indicated in his study the use of vancomycin, nasal swab evaluation to treat methicillin-sensitive and methicillin-resistant *Staphylococcus aureus* before surgery with mupirocin nasal ointment, chlorhexidine scrub to the surgical area, and breast pocket irrigation with povidone-iodine as well as a triple antibiotic solution [29].

In this review, three articles were selected to show the impact of antibiotic prophylaxis in aesthetic and reconstructive breast surgeries (Table 46.3).

Table 46.3 Impact of antibiotic prophylaxis in aesthetic and reconstructive breast surgeries

Article	Type of study	Year	Objective	Results
Once Is Not Enough: Withholding Postoperative Prophylactic Antibiotics in Prosthetic Breast Reconstruction Is Associated with an Increased Risk of Infection [32]	Retrospective	2012	• To determine whether the change in antibiotic prophylaxis regimen would affect rates of surgical site infections • To compare preoperative and postoperative prophylactic antibiotics with only a single dose of preoperative antibiotic • Breast pocket irrigation was used according to surgeon's preference	• The overall rate of SSI increased from 18.1% to 34.3% ($p = 0.004$) • 4.74 times more likely to develop a surgical site infection requiring reoperation in the preoperative antibiotic group • Infections requiring reoperation increased from 4.3% to 16.4% ($p = 0.002$)
Prophylactic Antibiotics to Prevent Surgical Site Infection After Breast Cancer Surgery [33]	Systematic review	2014	• 2867 patients • To determine the effects of prophylactic (pre- or perioperative) antibiotics on SSI after breast cancer surgery	• Prophylactic antibiotics used preoperatively reduce the risk of SSI in patients undergoing surgery for breast cancer • Further studies with patients undergoing immediate breast reconstruction are needed
Antibiotic Prophylaxis in Prosthesis-Based Mammoplasty: A Systematic Review [34]	Systematic review	2015	• To compare systemic antibiotic prophylaxis more than 24 h postoperatively with antibiotic prophylaxis within 24 h • 2438 patients • Cephalosporin was the most commonly preferred antibiotic regimen, vancomycin or clindamycin in allergic patients	• Extended systemic antibiotic prophylaxis more than 24 h postoperatively could significantly decrease infection risk • Extended antibiotic prophylaxis could significantly decrease SSI risk in implant reconstruction surgery, but not in aesthetic procedures

46.5 Pocket Irrigation in Breast Implants

Studies from 1986, 1994, and 1995 had already shown benefits of prosthesis pocket povidone-iodine irrigation in reducing capsular contracture. A review including 1244 augmentation mammoplasty patients whose surgeons prescribed intravenous cefuroxime during the procedure and have done irrigation of the pocket with a solution of cefuroxime 750 mg, gentamycin 80 mg, and povidone-iodine 10% found only 10 cases of Baker III and IV capsular contracture, which is 0.6% of the patients ($p = 0.006$) [35].

There is a 6-year prospective study with 335 aesthetic and reconstructive breast surgery patients who were submitted to pocket irrigation with povidone-iodine 50 mL, cefazolin 1 g, and gentamycin 80 mg diluted in 500 mL of saline solution. The follow-up of the study was 14 months. 1.8% of patients had Baker III and IV CC in aesthetic surgeries, no patient had it in breast augmentation and mastopexy, and 9.5% of patients had it in breast reconstruction. The researchers recommend triple solutions in breast augmentation and reconstruction [36].

A retrospective cohort study with 33 breast augmentation patients compared two different groups. The first one, group A, had a single dose of intravenous cefalotin 1.5 g intraoperatively plus cephalexin 750 mg orally for 7 days. The second one, group B, had a single dose of intravenous cefuroxime 750 mg intraoperatively and irrigation of the pocket with a solution of 25 mL of 10% povidone-iodine, cefuroxime 750 mg, and gentamycin 80 mg diluted in 150 mL of saline solution plus levofloxacin 500 mg for 5 days. The infection rates were 1.8% and 1.2%, and capsular contracture rates were 6% and 0.6%, respectively [37].

A recent systematic review of cosmetic breast augmentation analyzed three retrospective and one prospective studies. It compared the incidence of CC in a group with pocket irrigation and another one without it (control group). The median CC rate in the first group was 4.86% versus 6.81% of the control group. The odds ratio of CC was 0.472 (95% CI, 0.316–0.707, $p < 0.001$) in the irrigation group [34].

A 2015 meta-analysis of patients undergoing aesthetic breast augmentation evaluated nine studies with a total of 5153 women. Only three comparative studies achieved high methodological quality. The meta-analysis included four studies, with 1191 patients receiving povidone-iodine irrigation and 595 patients receiving saline irrigation. The meta-analysis indicates povidone-iodine irrigation for decreasing Baker class III/IV capsular contracture (2.7% versus 8.9%; OR, 0.30; 95% CI, 0.18–0.50; $p < 0.00001$; $I = 0\%$). The reported implant rupture rates for both silicone and saline implants were less than 1% [35].

The most common germs found in implant infections are *Staphylococcus epidermidis*, methicillin-sensitive *Staphylococcus aureus*, *Serratia mascescens*, *Pseudomonas aeruginosa*, *Enterococcus* sp., *Escherichia coli*, *Enterobacter* sp., group B streptococcus, and *Morganella morganii.* In this analysis, 70% of bacteria were cefazolin-resistant and sensitive to gentamycin (86%), levaquin (80%), and ciprofloxacin (63%). In those cases with skin necrosis, the surgeon should consider *Pseudomonas aeruginosa* infection resistant to ciprofloxacin, and levofloxacin is a better choice. ADM was used in 70% of the reconstructions in this group [38].

The severity of periprosthetic infection and the presence of skin necrosis are important factors to evaluate when considering salvage of prosthesis. Some protocols can reach salvage rates of 76.7%; others describe 37.3% with the following interventions: culture of the capsule, exhaustive irrigation of the pocket with antibiotic solutions, capsulectomy and capsulotomy, removal of necrotic tissue, and positioning of a new implant [39, 40].

46.6 Conclusion

The infection incidence rates in breast reconstruction are higher than in aesthetic procedures. Many factors can influence these rates such as factors related to the patient, the procedure itself, and the treatment of the disease. In the implant infection/pathology, it is included inflammatory reaction and biofilm formation. Antibiotic prophylaxis, prosthesis pocket irrigation, and intraoperative cares are essentials to protection.

Conflict of Interest There is no conflict of interest.

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Implant Exposure and Extrusion

47

Christina Garusi and Visnu Lohsiriwat

47.1 Introduction

Breast implant exposure is due to insufficient soft tissue or muscle tissue coverage. Being a foreign material, the breast implant will become infected as soon as it is exposed, and it will therefore have to be removed. There are three situations:

1. Implant exposed but not infected
2. Implant exposed and infected
3. Implant extruded

All these conditions can occur in patients who have had reconstruction after mastectomy as well as in patients who had an aesthetic breast implant.

47.2 Breast Augmentation and Implant Exposed

The situation is very rare and is difficult to explain. The reason could be an infection or the presence of very thin tissue coverage. Most cases need temporary removal of the implant and secondary breast implant reconstruction.

Among the potential complications associated with the use of a breast implant are the risks of implant infection and device extrusion, with an infection rate following breast augmentation ranging from 1% to 2% [1, 2]. There are a few reports of salvage of an infected and exposed breast device, such as the report of Gatti et al. [3], where the salvage of the infected breast cosmetic implant was obtained in a case report thanks to intravenous administration of an antibiotic, local irrigation with an antibiotic, hyperbaric oxygen therapy, and subsequent capsulotomy and implant exchange. Fodor et al. [4] described their experience treating six patients (eight breast implants) with silicone prosthesis exposure after cosmetic augmentation. In the original surgery, the implant was placed in the subglandular plane through an inframammary incision. The exposure occurred 10–14 days postoperatively through the incision line. The size of the exposure site ranged between 0.5 and 3 cm. The women were offered two options: immediate removal of the implant and reimplantation at a later stage or antibiotic treatment with an attempt to close the exposed area after the discharge stops. All patients chose the latter option. Antibiotic treatment was started on the day of exposure until 2 weeks after closure. Wound washing was performed three times per day. A sterile dressing was placed over the wound. When the discharge stopped, sterile strips were applied to keep the wound closed. Four of eight implants were saved. The authors had to remove the other four. According to this series, 50% of eight exposed breast implants could be saved with conservative treatment.

Although there are very few cases of infection and exposure of the implant in aesthetic breast augmentation, recently some surgeons have experienced this when using acellular dermal matrix especially in revision procedures [5, 6]. However, there is still a need to evaluate the benefits and complications associated with the use of implants, and the best practices for surgeons.

47.3 Breast Reconstruction and Implant Exposed

Regarding breast reconstruction, there are different reasons for implant exposure [7]:

1. Immediate breast reconstruction with mastectomy skin necrosis and partial muscle pocket reconstruction
2. Immediate breast reconstruction on previous irradiated tissue

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_47

3. High-grade capsular contraction on thin mastectomy flaps and risk of exposure
4. Skin diastasis with an underlying implant that becomes exposed

Yii and Khoo [8] proposed a combination of capsulectomy and continuous irrigation with saline and intermittent antibiotic instillation to salvage infected expanders in breast reconstruction. Spear et al. [9] developed treatment guidelines for implant infections, threatened device exposure, and actual device exposure. They submitted patients with severe implant infection and actual exposure (from both reconstruction and mammoplasty) to device removal and achieved a 0% salvage rate. Chun and Schulman [10] described the successful salvage of nine consecutive severely infected breast prostheses after mastectomy reconstruction, adopting a technique of immediate intravenous administration of antibiotics followed by early device exchange and a long course of postoperative antibiotics.

The rate of exposure has been reported to be between 0% and 0.29% for breast augmentation and between 0.25% and 8.3% for device-based breast reconstruction [11–14].

In the past, common practice was the immediate removal of the infected and exposed breast prosthesis; however, the more recent plastic surgery literature has explored options for device salvage. Methods for salvaging an infected device have included systemic antibiotics combined with conservative wound drainage, antibiotic lavage, capsulotomy and device exchange, and antibiotic lavage followed by capsule curettage and device exchange.

Despite a number of reports focusing on management of the infected or exposed breast implant, there is still disagreement regarding the wisdom of and indications for device salvage and the optimal timing, setting, or technique. Device explantation is a traumatic event and, for practical purposes, results in the loss of a breast. Successful device salvage offered to properly selected patients with the greatest possibility of success would be a highly desirable alternative to loss of an implant.

Spear and Seruya presented a single surgeon's 15 years' experience of 87 events of breast device infections and/or exposures from 69 patients [11]. Thirty-four cases involved breast prostheses with mild infection, and all of patients were treated conservatively with 100% success rate. Twenty-six cases were considered as severe infection, and in eight patients (30.8%) the implant was salvaged.

In a group of six patients, the implant was exposed but not infected and the implant was preserved, and in a group of three patients, the implant was exposed and there was mild infection, the implant being preserved in two of three cases. Further, in a group of five patients with an exposed implant and severe infection, there was a 40% salvage rate. A group of six patients had exposure of the implant and mild infection, the implant being preserved in four of six cases.

The strategy of immediate postmastectomy implant breast reconstruction with single-stage and tissue expander approaches has been compared in terms of complications. The rates of complications in 18 months are comparable; however, the approaches should be more strictly evaluated in controlled clinical studies [15].

The unfavorable effects of radiation on implant-based breast reconstruction in patients have been widely recognized. The surgeon should be aware of this issue especially in the era of increasing skin-sparing mastectomy, nipple-sparing mastectomy, and radiotherapy. Some patients should have been offered flap-based reconstruction. If the previous procedure was implant-based reconstruction, the patient can have the conversion procedure to autologous flap reconstruction to reduce the number of implant-related complications [16, 17]. However, a cohort study showed the acceptable rate of early complications in patients who have had prior breast conservation therapy who require salvage mastectomy can successfully complete with the rate for postmastectomy tissue expander/implant reconstruction [18]. There is a study showing that the ideal irradiated patient would have a BMI less than 30 and be younger than 50 years of age to maximize the likelihood of a successful tissue expander/implant reconstruction [19].

Acellular dermal matrices are increasingly being used to reinforce the lower pole of the breast during tissue expander/implant breast reconstruction. Their use is preferred by some surgeons who are undertaking a thin skin flap or revision procedure. Their use is claimed to have a low complication rate in immediate single-stage implant reconstruction [20–22]. However, a recent meta-analysis shows that the use of human acellular dermal matrix may increase complication rates. From the analysis it is also suggested to weigh this disadvantage against its advantages in enhancing cosmesis and ameliorating contracture [23].

47.4 Clinical Cases

47.4.1 Case 1: Immediate Breast Reconstruction on Previously Irradiated Tissue

The need for immediate breast reconstruction in a patient with previous conservative surgery and in actual need of nipple-sparing mastectomy is very high; therefore, complete muscle coverage is mandatory.

Irradiated tissue can have poor skin perfusion, skin atrophy, and fibrosis [24–26] with augmented risk of wound breakdown and implant exposure. As soon as the implant is exposed, we can consider it is infected and therefore needs to be removed. The patient can be offered a concomitant breast reconstruction with the use of a flap.

This is a case where an extended latissimus dorsi flap, which is the flap that has been extended the harvest area of overlying adipofascial layer more than the classical latissimus dorsi flap, was used at the time of exposed implant removal in order to preserve the mastectomy flap and start reconstructing the breast (Figs. 47.1, 47.2, 47.3, 47.4, 47.5, and 47.6).

This is not the normal practice, but the use of well-vascularized tissue can improve the irradiated tissue itself [13].

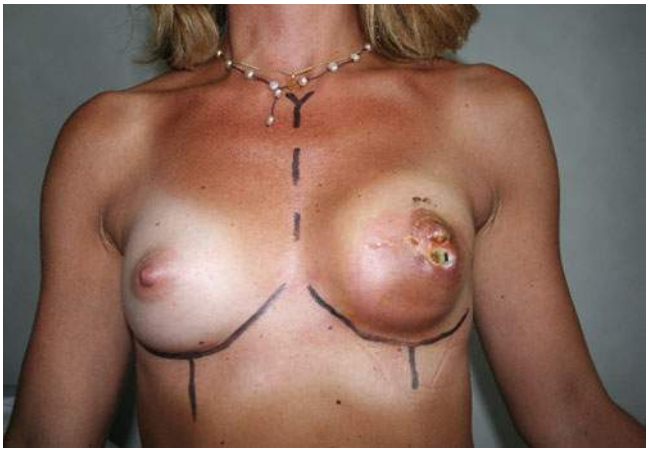

Fig. 47.1 Implant exposure in a previous irradiated breast treated with nipple-sparing mastectomy and immediate implant reconstruction and contralateral augmentation

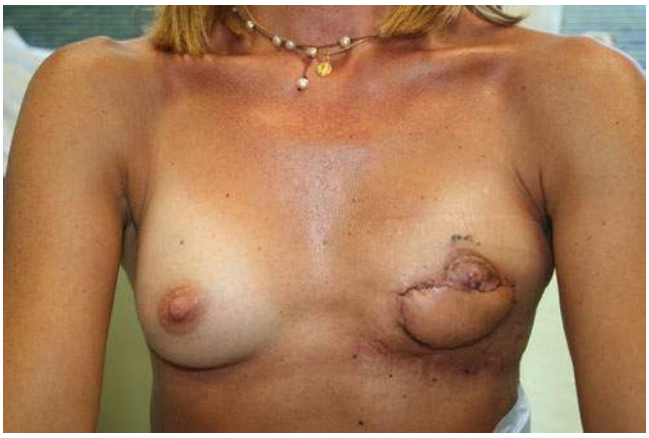

Fig. 47.2 Immediate result 15 days after surgery

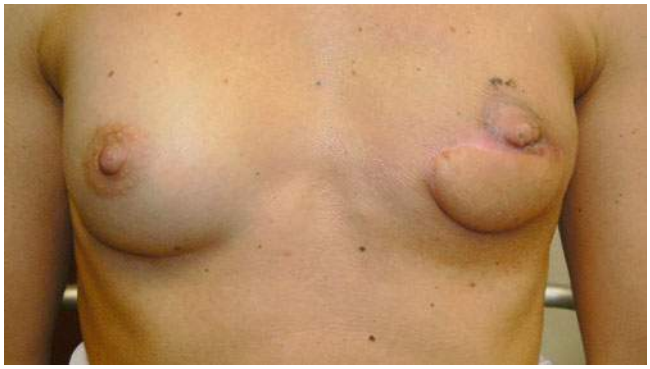

Fig. 47.3 Result 4 months after surgery

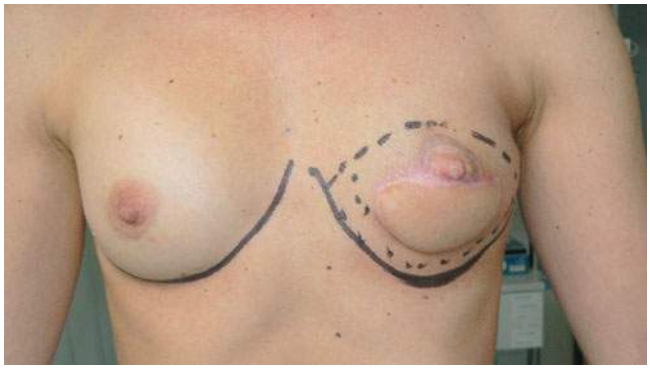

Fig. 47.4 Result 6 months from the time of the first lipofilling

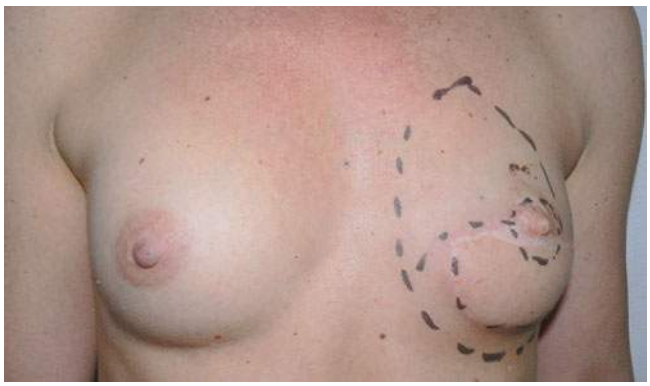

Fig. 47.5 Result at 10 months when the second lipofilling is planned

47.4.2 Case 2: High-Grade Capsular Contraction in Very Thin Mastectomy Skin Flaps

This situation needs an urgent solution. The presence of both capsular contraction and very thin tissue will require a flap in order to offer the patient an immediate solution.

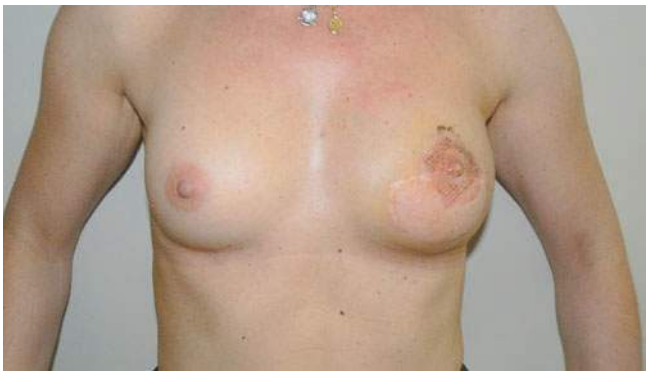

Fig. 47.6 Result 2 months from the last lipofilling at the time of the third lipofilling and tattooing

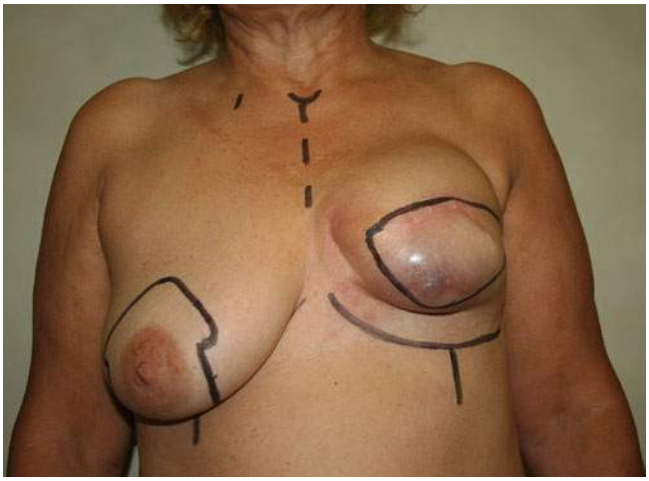

Fig. 47.7 Patient presents with high-grade capsular contraction

In this case a deep inferior epigastric perforator flap was offered to solve the problem with contralateral breast reduction at the same time (Figs. 47.7, 47.8, 47.9, and 47.10).

The final aesthetic outcome was acceptable, but there was a previous periprosthetic capsule remained at the parasternal part. So lipofilling was suggested as a possible improvement.

47.4.3 Case 3: Expander Decubitus

This is another case of a patient who originally underwent immediate reconstruction with an expander. The reason for using the expander was because of the presence of a very thin mastectomy skin flap; it can be considered an emergency reconstruction.

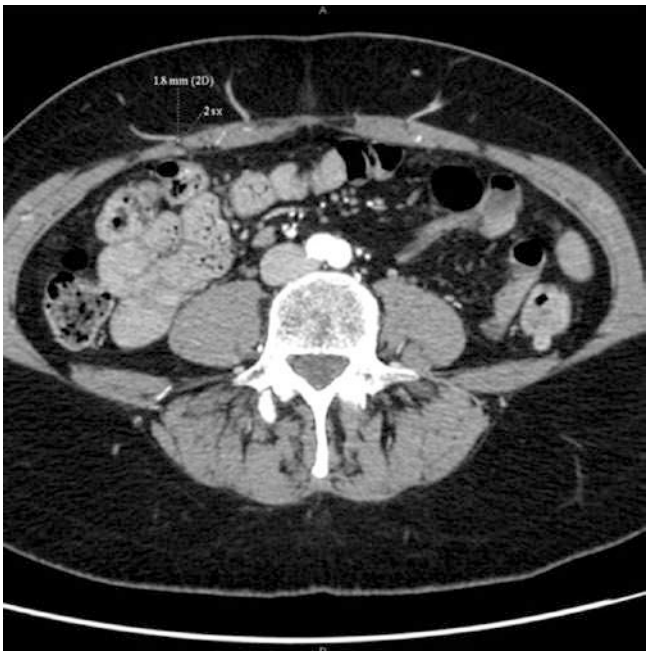

Fig. 47.8 Preoperative planning for deep inferior epigastric perforator (DIEP) flap reconstruction

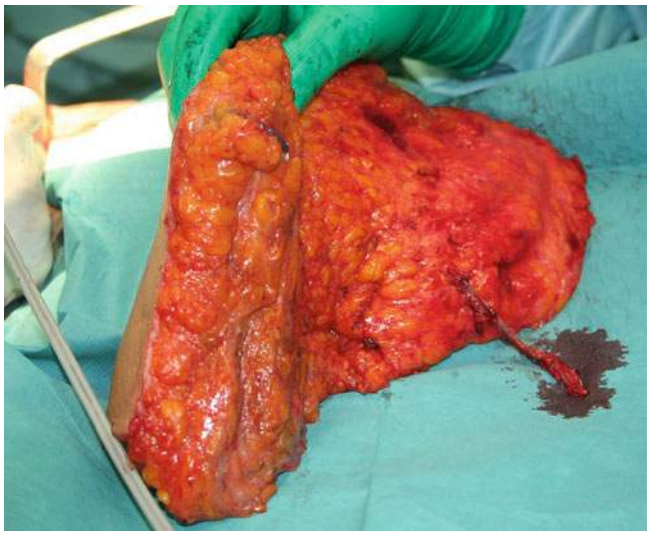

Fig. 47.9 Intraoperative assessment of the DIEP flap

During the expansion there was a decubitus of the expander, and the procedure was changed to autologous reconstruction with a deep inferior epigastric perforator flap (Fig. 47.11).

The final result at the time of nipple–areola reconstruction is shown in Fig. 47.12.

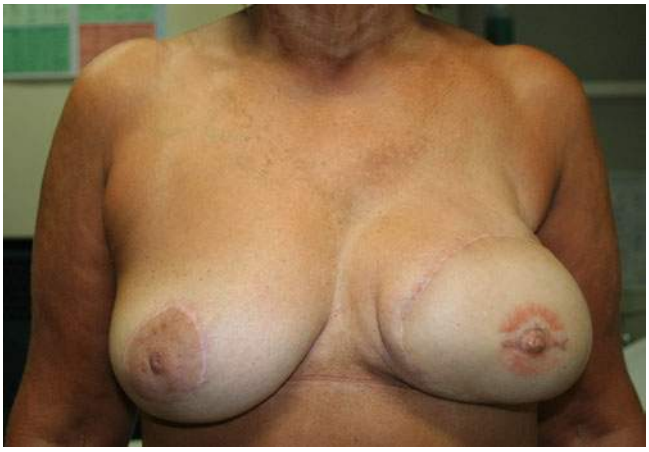

Fig. 47.10 Final result

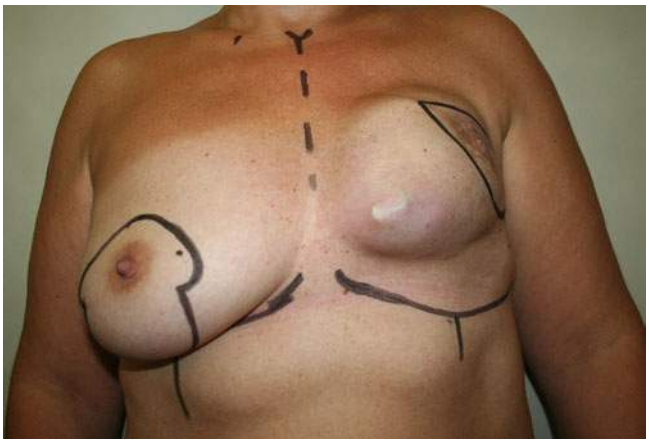

Fig. 47.11 Patient with a decubitus of the expander and planning for DIEP flap reconstruction

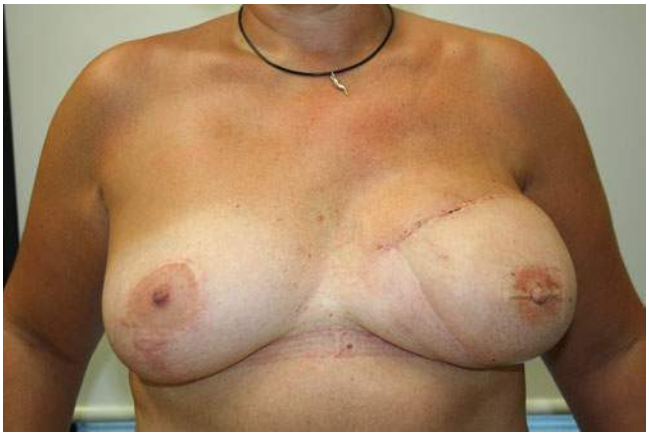

Fig. 47.12 Final result

47.5 Conclusion

The salvage of the infected and/or exposed breast prosthesis remains a challenging but viable option for a subset of patients.

Keys to success include culture-directed antibiotics, capsulectomy, device exchange, and adequate soft tissue coverage. Relative contraindications to breast device salvage include atypical pathogens on wound culture, such as Gram-negative rods, methicillin-resistant *Staphylococcus aureus*, and *Candida parapsilosis*.

Patients with a prior device infection and exposure and a history of either radiotherapy or *S. aureus* on wound culture should be closely monitored for signs of recurrent breast prosthesis infection/exposure and managed cautiously in the setting of elective breast surgery.

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Physiopathology, Prevention, and Treatment of Capsular Contracture

48

Alessia M. Lardi and Jian Farhadi

48.1 Introduction

Capsular contracture is the formation of a fibrous periprosthetic shell as a foreign body response. The capsule has a trilaminar structure. The inner layer consists of a synovial-type metaplasia from fibrocytes and histiocytes, the intermediate layer of smaller fibrils in a vessel-rich network, and the outer layer of densely packed collagen fibers. Myofibroblasts sit in the outer layer, and the capsule may constrict and cause pain and deformation of the implant. Capsular contracture despite advances in surgical technique and implant devices remains a frequent complication after breast reconstruction (2.8–15.9%) [1, 2]. With the adjunct of radiotherapy, a recognized risk factor, capsular contracture rates of 15–50% have been reported [3–8]. In 20–30%, revision surgery has to be performed because of capsular contracture [9–12]. Capsular contracture, because of the multifactorial and in part still unclear etiology, the impairment of quality of life, and the significant economic impact, is subject of greatest interest in plastic and reconstructive surgery.

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48.2 Diagnosis

Estimation of the presence and severity of capsular contracture is performed by a clinical evaluation. Baker's classification of capsular contracture is used widely for assessment and classification of capsular contracture. The modification of the Baker's classification includes classes IA, IB, II, III, and IV and has been developed to describe breast reconstruction more accurately (Table 48.1) [13, 14].

This evaluation is subjective in regard to the individual examiner, and various clinical works outline the importance of imaging techniques in the evaluation of the severity of capsular contracture. A range of imaging modalities was tested for this purpose including mammography, ultrasound, CT scans, and magnetic resonance images (MRIs). Of these, MRI and ultrasound (US) were proven as the modalities of choice [15, 16].

In clinical practice there is no consent of performing imaging to confirm capsular contracture. Many plastic surgeons still rely on clinical evaluation in planning further treatment. MRI and US might be useful to find rupture of the implant and distinguish from other causes of pain/symptoms as tumor or seroma and last but not least for legal reasons.

Table 48.1 Baker's classification

Class IA	Absolutely natural; cannot tell breast was reconstructed
Class IB	Soft, but device is detectable by physical examination or inspection because of the mastectomy
Class II	Mildly firm reconstructed breast with a device that may be visible and detectable by physical examination
Class IIB	Moderately firm reconstructed breast with a device that is readily detectable, but the result is acceptable and does not require operative intervention
Class III	Moderately firm reconstructed breast with a device that is readily detectable and that requires operative intervention
Class IV	Severe capsular contracture with an unacceptable aesthetic outcome and/or significant patient symptoms that require operative intervention

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_48

48.3 Physiopathology

The etiology of capsular contracture has been considered for many years. Potential etiologies include the hypertrophic scar hypothesis, myofibroblasts, silicone gel bleed, hematoma theory, age, and the infectious theory. Most of these theories do not have sound data to support their relevance; however, the infectious theory has accumulated a plethora of supporting data and remains the leading theory for this condition. Nevertheless, most experts feel that capsular contracture is a multifactorial problem. What we know is at the cellular level capsular contracture is most likely caused by any factor producing inflammation within the periprosthetic pocket and near the developing capsule, leading to abnormal downstream collagen or myofibroblast deposition [17–25].

While several capsular contracture studies investigated signaling pathways mediated by transforming growth factor-ß (TGF-ß) [18], tumor necrosis factor-stimulated gene-6 (TSG-6) [20], or leukotriene antagonist-mediated immunomodulation [23, 26, 27], others focused on the impact of subclinical infection or biofilms [28–35]. An association between bacteria and capsular contracture is supported by studies implementing increasingly sophisticated culture techniques [34], recently accompanied by electron and confocal microcopy and molecular biology [28, 29, 31, 33]. Techniques mitigating periprosthetic bacterial contamination that reduce the rate of capsular contracture support this association [29, 36, 37]. A prospective, blinded study showed that *S. epidermidis* was significantly associated with capsular contracture. *S. epidermidis* was present in 90% of implants removed for Baker grade III or IV contracture, compared to 12% of implants removed for reasons other than contracture [30]. Data have also suggested that capsular contracture and its relation to the infectious theory are a polymicrobial issue with multiple bacteria implicated in the formation of capsular contracture [38] (Table 48.2). Studies on biofilms and the propensity for these to attach to the silicone elastomer have further supported the infectious theory for capsular contracture, suspecting that multiple bacterial strains, both biofilm and nonbiofilm, may cause this condition [30]. Nevertheless there is still no definitive conclusion on the etiology of capsular contracture. Capsular contracture does not affect every patient; also the time lapse between surgery and clinically significant contracture development can vary greatly. In a porcine experiment, animals which were given implants and inoculated with *S. epidermidis* did show an increase in the incidence of capsular contracture when compared to those not inoculated; however, there were still incidences of capsular contracture in the non-inoculated group [31]. Some authors suspect, therefore, that infection, and the subsequent inflammatory response, while maybe increasing the rate at which capsular contracture develops does not in fact cause it and biofilm formation may be an incidental finding, rather than a cause and effect in the setting of capsular contracture [39].

Table 48.2 Polymicrobial factors in formation of capsular contracture [38]

Staphylococcus epidermidis
Diphtheroids
Propionibacterium acnes
Enterobacter cloacae
Camphoctophaga
Group D *Enterococcus*
Propionibacterium granulosum
Staphylococcus aureus
Peptococcus
Streptococcus gamma
Propionibacterium avidum
Micrococcus
Clostridium clostridia
Bacillus cereus
Clostridium cadaveris
Enterobacter agglomerans
Escherichia coli
Proteus mirabilis
Pseudomonas

Adams describes the net sum of the potentiators and suppressors that ultimately result in the pathologic state of capsular contracture. Potentiators are bacteria, tissue trauma, blood, and radiotherapy; suppressors of inflammation are antibiotic irrigations, sound surgical technique, and implant type [38].

48.4 Prevention

Different approaches have been investigated in preventing capsular contracture:

1. Filling material: Historically, the type of fill was thought to influence the development of capsular contracture. Silicone gel implants have had higher capsular contracture rates than saline implants. Older-generation silicone gel devices were characterized by higher gel bleed than current generation implants and exhibited much higher contracture rates [1, 40–46]. Current-generation silicone implants appear to have a similar risk of contracture compared to saline implants.
2. Placement: Several studies suggest that submuscular placement reduce the risk of capsular contracture [47]. Submuscular placement may protect against capsular contracture because the pectoralis muscle moves the implant in the pocket during regular activity. A second hypothesis is that the pectoralis major muscle serves as a protective barrier to bacterial contamination from the

nipple and is more resistant to infection compared to skin flaps. It may be the muscle simply disguises the capsule because it is one more tissue layer covering the implant.

3. Texturing: Texturing of the implant surface is associated with reduced capsular contracture following subglandular and submuscular placement of saline and gel-filled implants [48–50]. This finding has been supported by a recent risk analysis concluding that smooth implants resulted in increased odds of capsular contracture [51]. Polyurethane foam-covered implants by most authors are described as superior in reducing the risk of capsular contracture compared with smooth or textured implants [9, 52, 53]. Histological examination has found less fibrotic tissue and less type 3 collagen in capsules surrounding polyurethane implants than seen with textured. The role of texturing and polyurethane covering in the pathogenesis of breast implant-associated anaplastic large cell lymphomas (ALCLs) is not yet clarified [54–56]. In contrast, other authors report that texturing of implants did not have a beneficial effect in submuscular placement [49, 57], even after 10 years [9]. Currently, there is still a lack of definitive data to support a benefit of texture with regard to capsular contracture.
4. Prophylactic antibiotics: The role of systemic prophylactic antibiotics in development of capsular contracture is unknown. It does reduce the intraoperative wound microbiology [58] and may reduce the risk of early and late postoperative complications [59, 60]. From the current evidence available, it is recommended to routinely administer prophylactic antibiotics in reconstructive breast surgery to reduce surgical site infection [61, 62]. A recent study suggests a single preoperative dose of intravenous antibiotics to be sufficient to provide adequate prophylaxis against immediate postoperative wound infection in immediate implant-based breast reconstruction [63]. We follow these recommendations because infection is a well-known risk for development of capsular contracture, and preventing infection in our opinion means partially preventing capsular contracture.
5. Irrigation: In the past, antibiotic breast pocket irrigation with triple antibiotic solution was emphasized as a method of encapsulation prevention [36, 64]. Recent studies concluded that perioperative antibacterial solution may be suboptimal to prevent bacterial seeding as breast ductules likely harbor bacteria seeding the implant and antibiotic irrigation is unlikely to reach bacteria contained within breast ductules as it only bathes cells exposed by the surgical dissection [65].

   Betadine irrigation 50% was associated with a significantly lower capsular contraction rate than irrigating the pockets with saline alone [66].
6. Surgical incision: In reconstructive surgery the incision is given by the location and size of the tumor in oncological mastectomy. In aesthetic surgery inframammary incision is associated with lower capsular contracture rates then periareolar incisions [67, 68]. In prophylactic mastectomies there is no clear data comparing nipple-sparing and skin-sparing mastectomies in terms of incision and capsular contracture rates.
7. Drainage: There is a large body of clinical data showing low capsular contracture rates when no drain was placed [1, 36, 40, 41, 43]. The risk of infection is fivefold higher with the use of drains [69].
8. ADM: ADM-assisted breast reconstructions have been associated with capsular contracture rates of <5%, albeit a shorter follow-up period of 0.6–2.4 year [70–77] is reported. Mechanistic studies in animal models as well as human histopathologic studies suggest a reduction or delay in capsule formation in the presence of ADM [78–82]. A recent long-term study looked at 127 patients with a reconstruction with a porcine acellular dermal matrix and reported a capsular contracture incidence of just 0.6% at a mean follow-up of 19.6 months, suggesting this may be an effective strategy at preventing or delaying the onset of capsular contracture [83]. Again, like with other proposed management strategies, long-term studies are needed in a patient population in order to establish if acellular dermal matrices do in fact prevent capsular contracture or if they simply delay its onset.
9. Fat grafting: Placing fat grafts in the initial procedure along with a half-sized implant, or after radiotherapy to prepare for implant reconstruction, has been suggested as strategy in prevention/reduction of capsular contracture [84, 85].
10. Pharmaceutical: Recently Ruth Graf recently proposed leukotriene antagonist as a prevention option for capsular contracture in aesthetic mammoplasty [86] (see also comment in “Treatment”).

In our opinion the following measures are recommended in the prevention of capsular contracture: preoperative check for underlying infection; skin preparation with 0.5% chlorhexidine (recommended by Cochrane Review 2015 [87, 88]); precise planning; highest attention on sterility in OR; nipple shield; submammary incision; submuscular placement of the implant; sharp surgical technique – no blunt dissection and no over-dissection of the implant pocket—irrigation; change of glove before insertion of implant; “no touch” technique during implantation; no drains; use of ADM in breast reconstruction; and usage of high cohesive, textured, or polyurethane foam-covered silicone implants.

48.5 Treatment of Capsular Contracture

For the treatment of capsular contracture, we suggest to differentiate between irradiated and non-irradiated breast reconstructions, as their treatment varies.

In non-irradiated breast reconstructions, the majority of capsular contractures occur in the first year postimplantation. The timing of treatment for an early capsular contracture should allow enough time for the process to reach a homeostasis where there is not an on-going progression in the contracture. 6–9 months from the time of diagnosis is adequate for an early capsular contracture [38]. The treatment non-irradiated, Baker grade III and IV capsular contractures typically involves a total capsulectomy, removing the entire affected capsule and implant. Although reoperation with implant exchange is the most definitive measure for capsular contracture in non-irradiated breast reconstructions, with a success rate of approximately 79%, it still has a recurrence rate of 54% [47]. Due to suspected issues with biofilms, which are extremely hard to eradicate from the silicone elastomer of the implant, it is essential to use a new implant in the affected breast when treating capsular contracture.

Complete acellular dermal matrix coverage, when used as a treatment for established capsular contracture, has been described to be an option in treatment in grade III to IV capsular contracture. In one study no recurrence was seen at a follow up of 9.2 months, in comparison to earlier studies which used partial acellular dermal matrix coverage and found a recurrence rate of 6.3% [77]. Long-term studies are expected to confirm these findings.

Autologous fat transfer, by increasing the vascularity of the tissue around the implant, has been discussed as treatment strategy for capsular contracture. In a study using pigs, they found, although there was no significant difference histologically or in Baker grading of the implants, fat injection did cause the capsule to soften in the treatment group, potentially due to neovascularization in adjacent tissue [89]. This is the only study found addressing the use of autologous fat transfer as a treatment of capsular contracture. Therefore, these results will have to be replicated before broad generalizations can be made. However, it does show promise for novel surgical treatments.

Capsular contracture after radiotherapy is a well-known and frequent problem and challenge for reconstructive surgeons. Cordeiro recently published long-term data with 40.6% of grade III and IV capsular contracture after radiotherapy compared to 0.4% high-grade capsular contracture rates without radiotherapy. In these cases of severe capsular contracture after radiotherapy, the risk of recurrence is enormous. Irradiation may cause permanent damage to fibroblasts and fibroblast stem cells. Also, often there is an irreversible damage to the skin enhancing the risk for wound breakdown and at the end failure of the reconstruction [16, 88]. In our opinion, in these cases of severe capsular contracture after radiotherapy, patients profit from a procedure chance to an autologous breast reconstruction. Autologous reconstruction brings new well-perfused healthy tissue and skin into the scarred and contracted area after irradiation, and patients are released from numerous revision surgeries. According to patients' figure and preferences, the tissue is taken from the belly, thigh, or buttocks.

In the senior authors' practice, decision for reoperation in non-irradiated reconstructions is taken only in grade III and IV capsular contracture, according to patient's symptoms, and earliest 6–9 months after primary surgery. Patient's information about high recurrence rate is crucial. The same preventive measures as named before are taken. We aim for a complete removal of the implant with its capsule in one piece. Depending on different circumstances we adjunct autologous fat transfer and/or ADM to the new reconstruction.

In irradiated breast reconstruction, if a progressing capsular contracture is found, the procedure change to autologous reconstruction is proposed irrespective of time of occurrence of capsular contracture.

There has been interest in the nonsurgical treatment of capsular contracture. A variety of different modalities have been considered, including mechanical implant displacement, antibiotics, vitamin E, external ultrasound, steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), chemotherapeutics, and leukotriene inhibitors. No definitive data have been reported with a variety of anecdotal experiences presented. Several studies in augmentation mammoplasty indicate leukotriene receptor antagonists (LTRAs)—specifically Accolate (zafirlukast) and Singulair (montelukast) may be a potential treatment for capsular contracture [90–92]. No data are available for capsular contracture in reconstructive surgery. These drugs used for asthma have their pharmacologic effect along pathways thought to be related to the pathogenesis of capsular contracture. There have been some significant (mostly hepatotoxicity-related) adverse effects with these drugs, and without good scientific basis for their efficacy the off-label use of these medications is not recommended.

In aesthetic mammoplasty and symmetrization procedures, adjuncts to the surgical treatment of contracture include considering a site change, and, particularly if the implant is in the subglandular position, a site change to a subpectoral or dual-plane position may be considered or, in extreme cases, sometimes exchanging the implant to a fresh pocket: even subpectoral to a subglandular position may be considered [93]. A newer surgical management technique has been proposed which involves the formation of a so-called neopocket in which to place the implant. This involves the creation of a new subpectoral plane deep to the

pectoralis major muscle but superficial to the anterior capsule, which is left intact to avoid further tissue damage. This allows use of the existing capsule and is usually done through an inframammary incision [94]. A retrospective review of 198 patients, 69.7% of which presented with capsular contracture, who were treated using this technique, found a high success rate in reduction of contracture [95]. This could be a potential new standard of treatment for capsular contracture as it allows the use of the existing capsule but gives a new vascularized pocket in which to insert a new textured implant. However, at present this is only feasible in submuscular placement, as there is enough tissue to allow a new plane to be created.

48.6 Summary

Capsular contracture is a frequent complication in implant-based breast reconstruction (2.8–15.9%). After irradiation capsular contracture rates increase to 15–50%. Capsular contracture has great impact on patient's quality of life and economic aspects. Diagnosis is based on clinical evaluation. Baker's classification is widely accepted for grading its severity. Ultrasound or MRI might be useful to find rupture of the implant and distinguish from other causes of pain/symptoms. There is still no definitive conclusion on the etiology of capsular contracture. The infectious theory remains the leading theory, but most likely the etiology is multifactorial. Adams describes the net sum of the potentiators and suppressors that ultimately result in the pathologic state of capsular contracture. Potentiators are bacteria, tissue trauma, blood, and radiotherapy; suppressors of inflammation are irrigations, sound surgical technique, and implant type. Lots of effort is made in preventing capsular contracture. Up to date textured implants, submuscular placement, a single preoperative dose of antibiotics, irrigation with Betadine or saline, and avoidance of drains are recommended for prevention. In addition ADM and fat grafting are described to lower the risk of capsular contracture.

Treatment for non-irradiated implant-based breast reconstructions with high grade (grade III and IV) is total capsulectomy and exchange of implant and is performed earliest 6–9 months postoperative. In high-grade capsular contracture after irradiation, because of the persistent damage to the tissue and high recurrence rate, a procedure change to autologous reconstruction is recommended.

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Implant Rupture

49

Cicero Urban, Mauricio Resende,
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49.1 Introduction

Failure of a breast implant means either a deflation of a saline implant or rupture of silicone gel device. Although rupture is one of the main causes of implant removal, its real rate is difficult to quantify, especially in breast reconstruction [1]. Reported mechanisms of implant rupture include iatrogenic damage, which is the most frequent cause, trauma, seat belt contusion injury, blunt trauma, compression during mammographic imaging, severe capsular contracture, and degradation of the implant shell. Patient's age, comorbidities, smoking, medications, presenting symptoms, implant duration, and volume did not correlate with implant rupture [2, 3].

The significant contribution of iatrogenic damage to overall rupture rate suggests that rupture may be more often operator-related than device-dependent [2]. Radiation therapy in patients with breast implants does not seem to cause a significant increase in complication rates and seems to be feasible in the therapeutic management of patients undergoing implant-based breast reconstruction [4]. Most of the ruptures have no obvious traumatic origin and are silent or intracapsular, thus asymptomatic, and with difficult diagnosis with conventional exams (mammogram and ultrasound) [1–4].

Rupture is clinically defined as a breach of any size in the implant shell. All implants are susceptible to silicone bleeding. However, because of the large weight molecules of the silicone, the gel cannot diffuse through the shell, and the gel does not appear outside the implant, unless the shell has ruptured. Rupture has been suspected to occur as a result of biochemical degradation of the silicone, physical trauma to the elastomer at the time of implantation, and fold-flaw failures or as a result of mechanical injuries during mammograms, closed capsulotomies, or accidents. Loss of integrity of the implant shell is diagnosed when silicone gel is present outside the implant but within the intact fibrous capsule (intracapsular rupture). Extracapsular rupture is less common and is defined as rupture of both the implant shell and the fibrous capsule with silicone leakage into surrounding tissues and embolized tissues at a distance, a situation that although rare is possible. Both require implant removal and removal of as much of the silicon as possible [5–8] (Figs. 49.1 and 49.2).

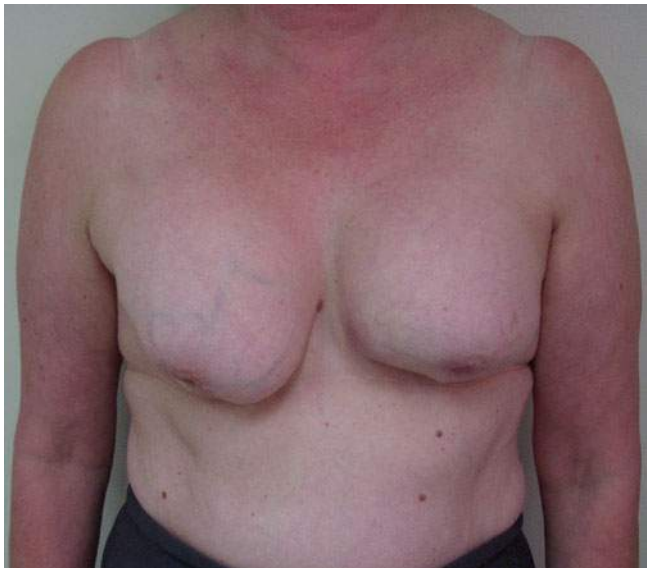

Fig. 49.1 Long-term clinical consequences of patient's negligence in ruptured implant showing bilateral breast deformity

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_49

Fig. 49.2 Silicone bilaterally infiltrating breast tissue (explanted from patient in Fig. 49.1)

Above 93,000 breast reconstructions were performed in 2010 in the United States, according to the American Society of Plastic Surgeons [9]. Aesthetic outcomes have improved with FDA's reapproval of silicone implants in 2006 and introduction of a variety of new implant types. Cohesive silicone gel breast implants are composed of a textured silicone elastomer shell and are filled with cohesive silicone gel. Cohesive gel is formed by increasing the number of cross-links between gel molecules, which results in an implant that has better retention of shape and is less likely to fold or collapse, especially in the upper pole. In consequence, implant-based breast reconstruction (IBBR) nowadays is the main technique for breast reconstruction [10].

The concentration of low-molecular-weight siloxanes in the filler may play a role in implant rupture; these compounds can produce swelling of the elastomer shell, which eventually may lead to mechanical weakening and rupture. The low-molecular-weight silicone content of current third-generation (or later) breast implants is significantly lower than for the second-generation devices [3].

The 2012, unfortunately, represented the year of the worldwide crisis with Poly Implant Prosthèse (PIP) implant and exposed the need for better evidence regarding effectiveness and safety of these devices [11]. The terms of the warranty must be carefully studied and fully explained to the patient as part of the surgical informed consent [12].

So, the aim of this chapter was to address the incidence, evaluation, and management of implant rupture in breast reconstruction.

49.2 Incidence

The incidence of implant rupture ranges widely from 0.3% to 77% and remains a controversial issue. Different methods to evaluate and diagnose rupture can explain this discrepancy [13–18]. Marotta conducted a large cohort meta-analysis for explanted silicone gel-filled breast implants (8000 explants from 35 studies) and found a statistically significant correlation between implant duration and elastomer shell failure (25% within 3.9 years and 71.6% at 18.9 years). An updated reanalysis (9774 explanted implants from 42 studies) revealed 26% failure at 3.9 years, 47% at 10.3 years, and 69% at 17.8 years [11, 18].

The fact that prevalence of rupture increases over time is not surprising since prevalence is a cumulative measure at a given moment in time. This, however, does not imply that the probability of rupture during a specified time period (incidence) increases with increasing implant age, a conclusion that cannot be drawn from the selected cross-sectional data. In addition, damage to implants during the explantation can also lead to an overestimation of in vivo prevalence. According to Slavin and Goldwyn, as many as 24% of rupture identified at time of explantation occurred as a direct result of the procedure to remove the implant [19].

So it is difficult to compare the results of many cross-sectional rupture prevalence studies, for several reasons. Studies often include women with first-, second-, and third-generation implants, saline and silicone implants, and implants made by different manufacturers. Moreover, studies show data on women with different follow-up periods, and determination of rupture has been based on different detection methods like explantation, ultrasound, mammography, MRI, and clinical survey in patient cohorts. Specific analyses in IBBR are rare. Henriksen found three cases of implant rupture (IR, 0.4 cases per 1000 implant-months) 2 years after breast reconstruction using silicone implants ($n = 1610$) [20]. Although there is limited data, less capsular contracture and implant rupture with recent generations of breast implants is expected, and the rupture rate could be between 12% and 15% [9–20]. There is no long-term conclusive data on IBBR and on influence of radiotherapy.

49.3 Diagnosis

Clinical diagnosis is difficult, being based solely on nonspecific findings such as palpable nodules (silicone granuloma), asymmetry, or tenderness. Most ruptures are silent, and the sensitivity of expert surgeons to diagnose rupture has been estimated to be approximately 30% [3]. Free silicone has, in rare cases, spread to distant body regions giving rise to symptoms. If implant rupture is accompanied by loss of the shape of the breast, the diagnosis at a physical examination is feasible. Breast pain is a strong indicator of rupture, but the absence of pain doesn't exclude rupture. Contour deformity (44%) is the most common symptom followed by displacement (20%) and mass formation (17%). Physical examination fails to diagnose implant rupture in more than 50% of cases. Rupture of silicone implant, for most of women, is a harmless condition, which does not appear to progress or to produce significant clinical symptoms [9–24].

Early diagnosis of implant rupture is important because surgical removal of extracapsular silicone in the breast parenchyma and lymphatics is difficult [25].

Ultrasound has a low sensibility to detect silicone implant rupture; about 41% of women with implant rupture have an ultrasound with no detectable changes; features considered indicative of intracapsular rupture were hyperechoic "serpentine" and silicone nodules in the axillary cords and false positive in about 40% [21, 26]. The most reliable sign of extracapsular rupture is a group of focal nodules with a generalized increase in echogenicity of the breast tissue and loss of normal parenchymal interface resulting from dispersion of the ultrasound beam, hyperechoic and hypoechoic assets (caused by a leakage of the intraprosthetic content, resulting in inflammation of the periprosthetic tissue), discontinuity of the breast implant capsule, siliconomas, and granulomas containing large silicone parts (which result in the transmission of an ultrasound beam similar to that in fluids, with minimal fibrous reaction and the appearance of complex cysts) [22, 26] (Fig. 49.3).

Mammography is of little value in the assessment of implant integrity, although it may be useful for the assessment of the surrounding breast tissue. Although there are some reported cases of implant rupture from compression during a mammogram, probably they occurred in women who had intracapsular ruptures previously [6].

Magnetic resonance imaging (MRI) is the most accurate technique in the evaluation of implant integrity. Its sensitivity for rupture is between 80% and 90%, and its specificity is between 90% and 97%. The use of contrast agents in MRI studies for assessment of breast implant integrity is not recommended. Silicone leakage progression either herniation of silicone within the fibrous capsule, migration from the intracapsular space into the surrounding tissue, or progression of extracapsular silicone can be observed by MRI. Signs of intra- or extracapsular implant rupture are already reported in literature: linguine sign, teardrop sign, keyhole sign, presence of siliconomas, and free silicone. There's no increase in autoantibody levels and no increase in reported breast hardness. Normally women do not relate breast changes and do not produce significant clinical symptoms. Thus, MRI is the gold standard to detect and follow-up breast implant ruptures, and the presence of a positive ultrasound examination requires magnetic resonance imaging before surgery to avoid an unnecessary operation and to contain costs [4, 23, 24, 26, 27] (Figs. 49.4 and 49.5).

The use of dual-energy computed tomography is promising in evaluating the extent of extracapsular rupture and nodal involvement in a single, noncontrast, breathhold scan, according to Glazebrook et al. [28].

Fig. 49.3 Bilateral rupture after 4 years of immediate breast reconstruction with form-stable anatomic breast implants

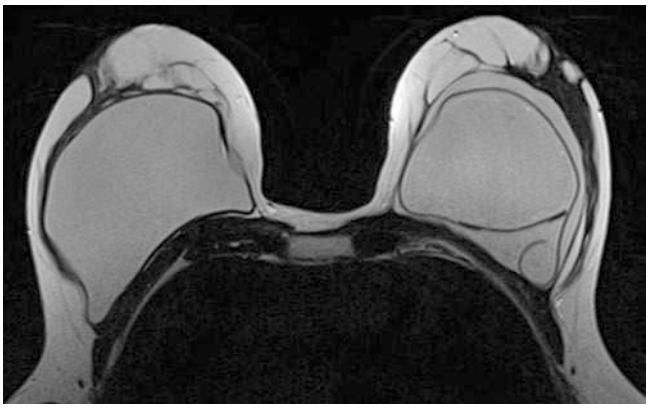

Fig. 49.4 Magnetic resonance showing intracapsular rupture in a second-generation implant in the left breast (Linguine's sign)

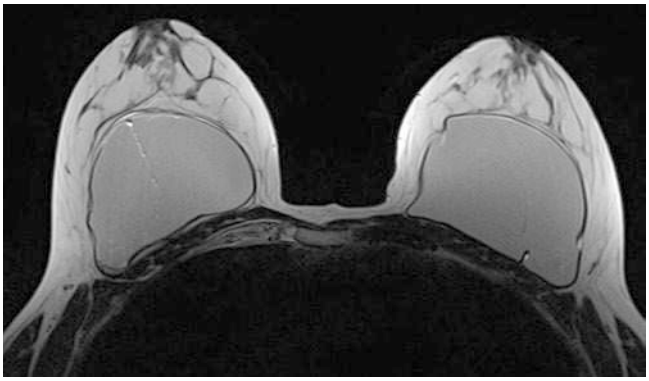

Fig. 49.5 Magnetic resonance showing intracapsular rupture in a third-generation implant in the right breast

The US Food and Drug Administration recommends that patients with silicone gel implants should undergo magnetic resonance imaging screening 3 years postoperatively and at 2-year intervals thereafter. However, the scientific basis for these recommendations has been the subject of considerable debate. Some have questioned whether magnetic resonance imaging screening of asymptomatic women leads to a reduction in patient morbidity and whether the potential benefits outweigh the risks and costs. Others have reported asymptomatic patients with a false-positive magnetic resonance imaging scan who underwent unnecessary surgery. Such information led individual members of a recent US Food and Drug Administration advisory panel to suggest eliminating the current screening recommendations from labeling [3].

49.4 Treatment

Explantation is the gold standard treatment to silicone implant rupture, with the removal of as much silicone as possible. In patients with capsular contracture, insertion of the new implant into a virgin pocket is advisable to reduce the risk of recurrent contracture. It may be advisable to place the new implant in a virgin pocket to isolate it from the field of gel contamination when all silicone material couldn't be removed [3].

Surgery isn't the single alternative. Hölmich studied 64 patients with at least one rupture at MRI. There was progress in 11% of silicone either as a conversion from intracapsular into extracapsular ruptures [15]. There was no increase in levels of autoantibodies during the study. Because of the small risk of silicone spread, women with implant rupture could be followed clinically, if not (preferentially) operated on. Residual silicone inside the breast of a breast cancer patient represents a risk for a mass in the breast that could add difficulties in differential diagnosis with recurrence.

Some authors suggest a relationship between implant rupture and fibromyalgia. But it remains an unsolved question. There's no evidence that silicone breast implant rupture can cause long-term serious diseases, like breast cancer or connective tissue diseases [9, 17].

49.5 Conclusions

IBBR is the main technique in breast cancer reconstruction. Rupture rates in these cases are not well known, although an early diagnosis and prompt surgical management are expected to avoid major local problems, and silicone is expected to not give any systemic consequence to the patient. Modern implants are constructed with more durable elastomeric shells, incorporate a barrier to gel bleed, and contain more cohesive silicone than earlier generation devices [3].

MRI is the most accurate method for implant failure diagnosis, but long-term cohort studies are necessary to evaluate integrity rates of these devices to better support their indications, follow-up, and limits in breast reconstruction and will enable patients to become active participants in making treatment decisions.

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Inframammary Fold Reconstruction

50

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The inframammary fold (IMF) is the lower boundary between the breast and the chest wall. It is usually located between the fifth or sixth intercostal space. The inframammary fold is approximately 5–7 cm distant from the areola in small to medium breasts and 7–9 cm in larger breasts [1–6].

There have been controversial opinions between anatomists and surgeons regarding the anatomy of the inframammary fold. Whereas anatomists do not see the inframammary fold as a specific anatomical structure, but as part of the superficial fascia of the breast, surgeons believe in the existence of a true inframammary ligament.

The most critical visual landmark of the breast is the inframammary fold, and creating a well-defined inframammary fold is very important for the success of breast reconstruction, regardless of the surgical technique used.

Other significant factors for defining breast aesthetics are the position of the nipple-areola complex and breast contour and projection.

The symmetry with the contralateral breast is determined not only by breast shape, volume, and degree of ptosis but also by a well-defined position of the fold.

It is important to preserve the inframammary fold in oncologic breast surgeries, whenever possible. In certain situations, the fold can be moved to a lower or upper position. Therefore, during a mastectomy, surgeons should prevent the dissection from extending far beyond the inframammary fold, thus avoiding creating an undefined fold. For this reason, special attention should be paid to the ptosis of the reconstructed breast and inframammary fold positioning in postmastectomy reconstructions (Fig. 50.1).

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50.1 When Should Reconstruction Be Performed?

In general, inframammary fold reconstruction should only be performed after the skin overlying the chest wall achieves good mobility. In surgeries initially using a tissue expander, fold reconstruction should be performed only when the expander is replaced with the prosthesis. In patients submitted to radiotherapy after mastectomy and immediate implant

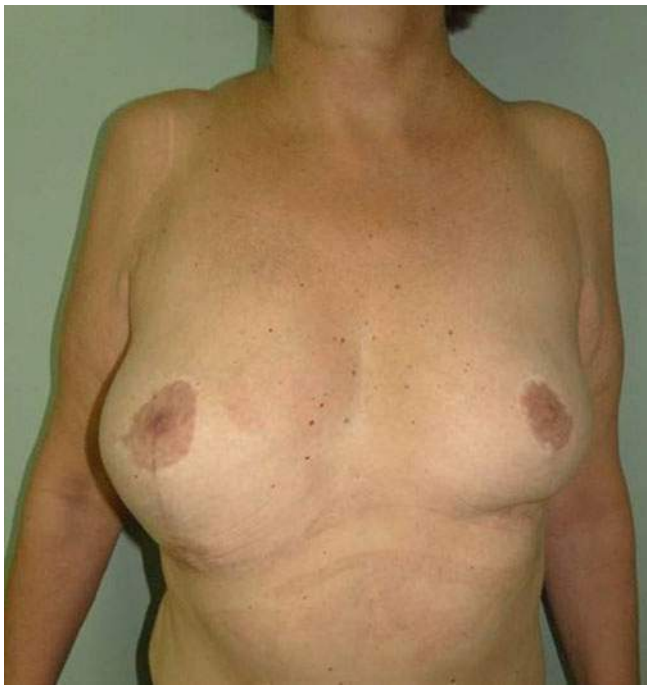


Fig. 50.1 Mammary asymmetry: 60-year-old patient, with previous breast mastoplasty, in 2003 underwent conservative surgery and radiotherapy in the left breast after the diagnosis of in situ ductal carcinoma. Weight gain and ptoses over the years reflected in different shape and breast volume, specially with the constrictive effect of radiotherapy over the left breast. Photo taken in 2012 showing asymmetric volume and position of the inframammary fold. Source: Dr. Cericatto

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_50

(tissue expander or prosthesis)-based breast reconstruction, at least 4–6 months are necessary after radiotherapy to plan the secondary surgery, when inframammary fold correction is mandatory.

50.2 Indications for Inframammary Fold Reconstruction

Inframammary fold reconstruction is mainly performed in cases of late postmastectomy breast reconstruction. Usually the anatomical landmark of the original fold site could not be preserved because of larger skin excision and upward dislocation of the IMF as the result of skin closure. Late effects of adjuvant radiotherapy may also interfere with the position and the definition of the inframammary fold. It is also worth mentioning that the main goal of the breast reconstruction should be to achieve symmetry with the opposite breast.

50.3 Surgical Planning

After defining the technique to be used for inframammary fold reconstruction, skin marking is performed with the patient in a sitting or standing position, in the preoperative setting. IMF position is located on or immediately below the sixth rib, along the breast meridian line. Contralateral IMF projection is used to delimit the correct planning (Fig. 50.2).

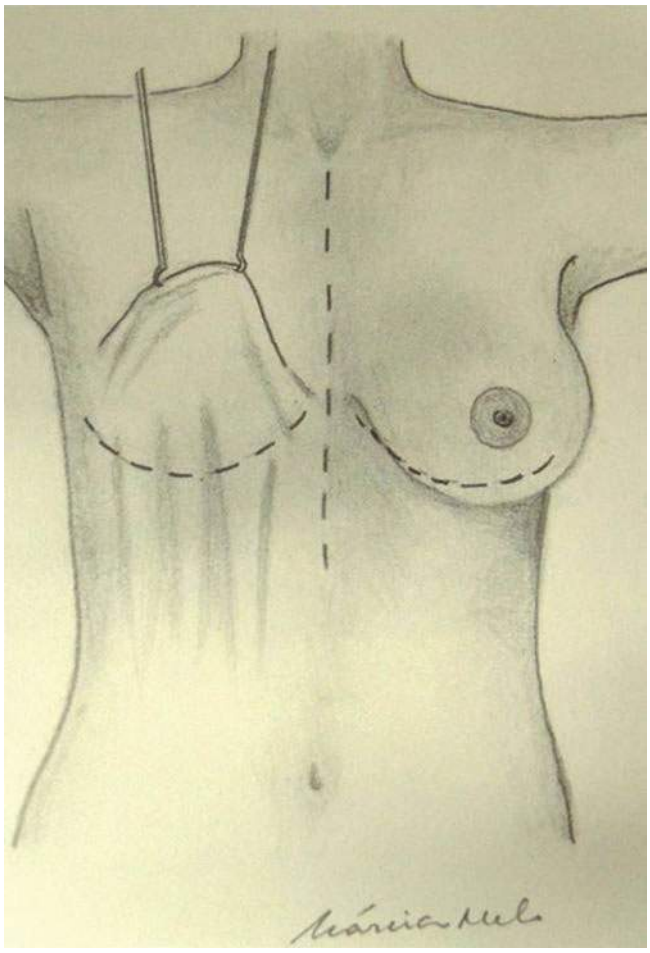


Fig. 50.2 Planning late breast reconstruction and inframammary fold projection. Source: Biazús JV et al. Cirurgia da Mama, 2011

50.4 Surgical Techniques

Several surgical techniques have been described for both creation and correction or better definition of the inframammary fold. More recently, lipofilling has also been associated with correction of poorly defined folds.

50.4.1 External Approach

This technique was described by Ryan in 1982, and it offers the possibility of using a portion of the upper abdominal skin to cover the prosthesis while defining and stabilizing the inframammary fold. It involves creating a new scar at the definite site of the inframammary fold. In cases of reconstruction involving direct prosthesis placement, a second marking is performed below the prior marking of the site where the fold should be located with the purpose of pulling a skin flap upward to cover the lower portion of the prosthesis. Usually 1 cm for each 100 ml of prosthesis is used as the measure below the fold for the new marking along the breast meridian line. A new 1-cm crescent marking is performed over this lower marking. During the surgery, this crescent is de-epithelized. An incision is made in the center of this crescent (reaching the hypodermis). Next, the skin is detached with the purpose of obtaining a skin flap and fixing the lower flap on the site of the definitive fold. This lower flap is then fixed on the chest wall. After prosthesis placement, the upper skin flap is fixed on the edge of the lower flap. This technique has been criticized for creating a new scar in addition to the mastectomy scar and for making it difficult to accurately determine the amount of tissue that needs to be moved upward. It is also more difficult to implement this technique in very thin patients or in those who have very thick subcutaneous tissue.

50.4.2 Internal Approach

This technique is especially used in two-stage breast reconstruction. Some consider the reconstruction of the inframammary fold as the major step in the exchange procedure. A capsulotomy is performed where the fold will be placed

using the same incision through which the expander is removed. After the removal of the expander, the inframammary fold is set using sutures that fix the deep dermis to the anterior chest wall. According to Cordeiro et al., it is not necessary to place the sutures into the periosteum for obtaining good results, but the suture on the chest wall should be placed in the soft tissues that overlie the chest wall and the ribs and in the capsule, avoiding the pain related to the periosteum suture. The same technique used to set the inframammary fold is also used to create an aesthetically pleasing curve inferolaterally. Several sutures are placed to precisely reconstruct the shape of the fold, and the breast envelope begins to take shape. Then, the implant is placed.

Using this technique, it is possible to reconstruct the inframammary fold to a higher position, and the prosthesis achieves some degree of ptosis without the need for a secondary incision or skin incision on the corrected inframammary fold. It is described long-term experience with this technique demonstrating that the inframammary fold will remain fixed over time.

50.4.3 Anchor Approach

Similar to the internal approach, in this technique the correction is performed through the same incision used for placing the definitive prosthesis. The inferior edge of the pectoralis major is anchored, and it partially covers the breast prosthesis by being sutured to the skin of the site where the fold will be placed. The suture is externally anchored to the skin, which is then protected with swabs (Figs. 50.3 and 50.4).

50.4.4 Allograft Approach

In the last decade, it has been frequently immediate or late breast reconstruction using implants with the use of allografts, especially to cover the outer lower quadrant of the breast implants and to define the inframammary fold. Allograft malleability makes it possible to achieve good definition of breast contour and projection, without the association of serratus anterior muscle [7–12].

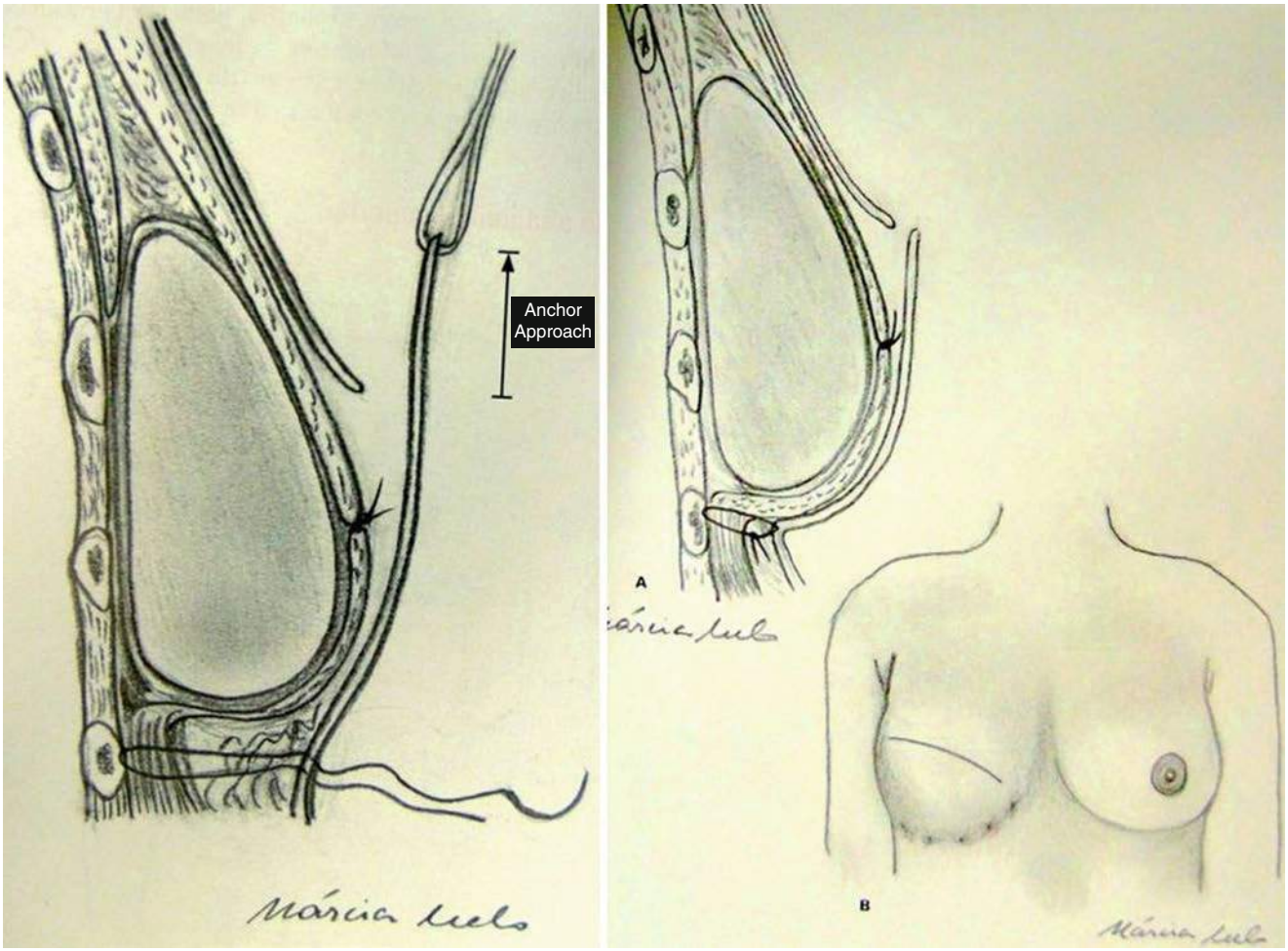


Fig. 50.3 Anchor points with abdominal flap advance. Source: Biazús JV et al. Cirurgia da Mama 2011

50.4.5 Muscle Flap Recontruction

In late breast reconstruction or failed reconstruction with implants, muscle flaps are an option to restore breast volume and projection, associated with a more natural consistency, even with the development of a natural ptosis, over the years. A concern in muscle flap technique is to preferentially set the flap at the IMF position, in order to avoid the "patchwork" effect of the transition of different skin tonalities (Figs. 50.5 and 50.6).

50.4.6 Lipofilling

The association of lipofilling with external, internal, or anchor approach techniques, to reconstruct the IMF, is a new option to breast reconstruction. In general, these techniques are used in patients who failed in previous implant-based breast reconstruction. Below are selected cases of totally breast reconstruction with lipofilling associated with infra-mammary fold definition techniques (Figs. 50.7 and 50.8).

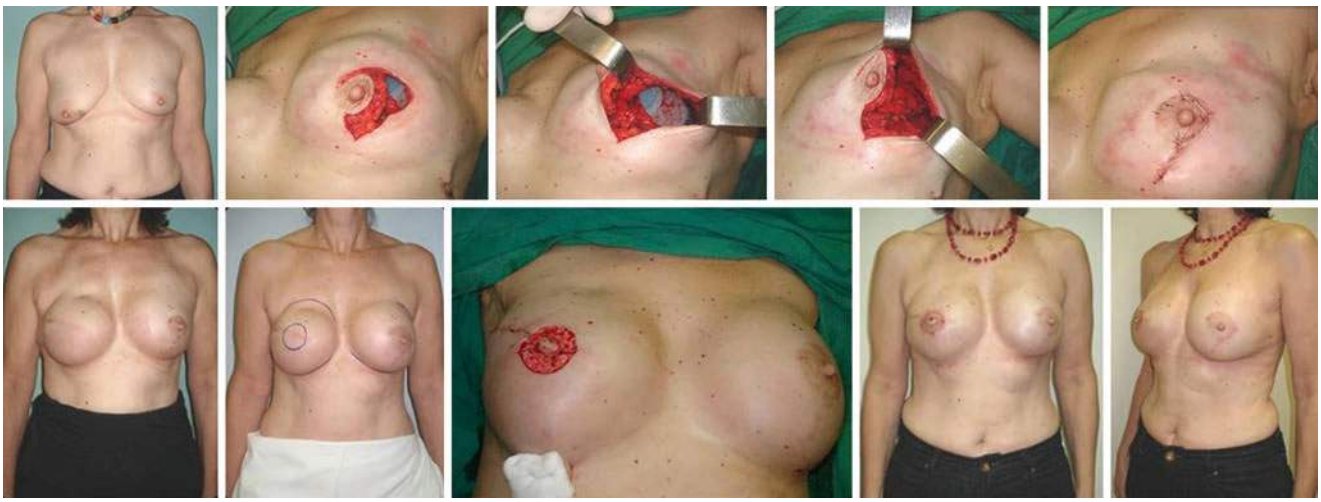


Fig. 50.4 Anchor points—bilateral mastectomy with reconstruction using tissue expanders. Asymmetric fold position. When expanders are replaced with silicone prosthesis, external anchor points recreate the new fold when they are fixed to the periosteum of the sixth rib. Source: Photos Dr. Cericatto

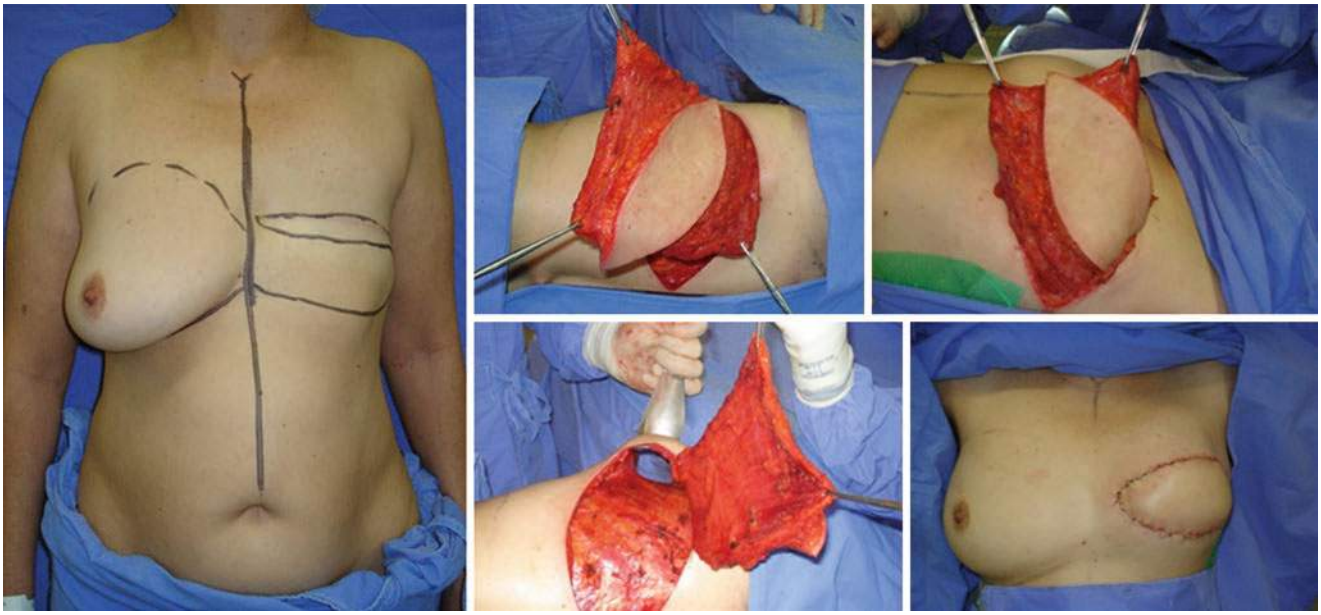


Fig. 50.5 Four-year evolution of late left breast reconstruction with latissimus dorsi flap and 280 cc prosthesis. Although there is a good symetry and development of ptosis, over time, the ideal flap position would be over the new inframammary fold position. Regarding the breast aesthetic subunit concept, flap positioning over the IMF would avoid the "patchwork" visual effect. Source: Images Dr. Cericatto)

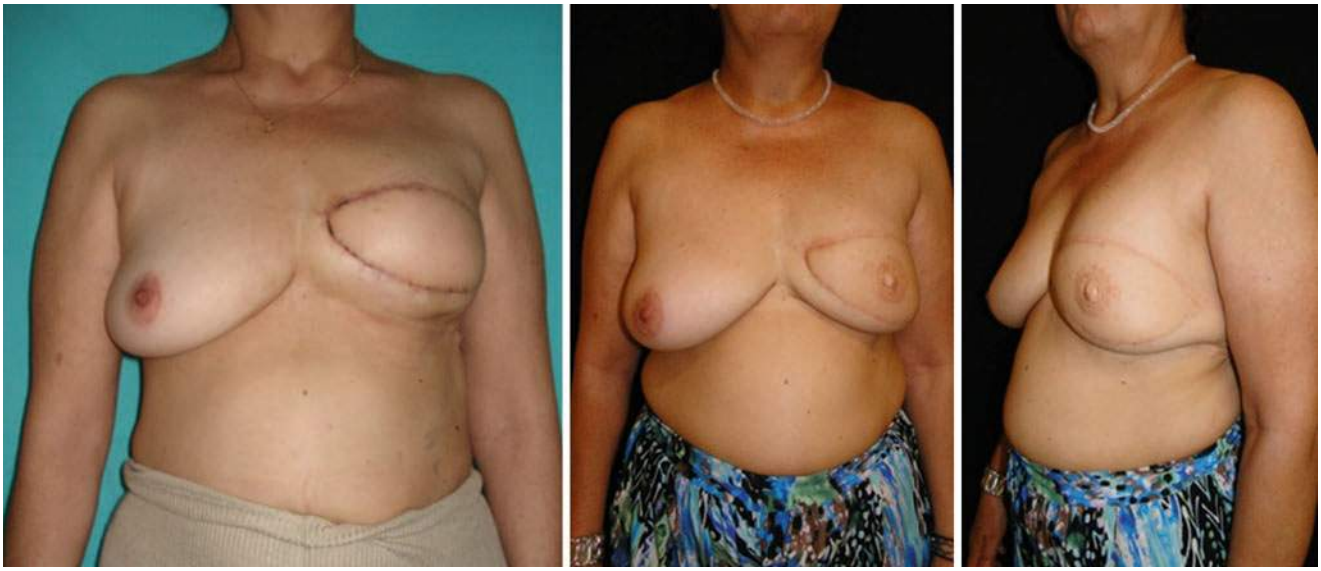


Fig. 50.5 (continued)

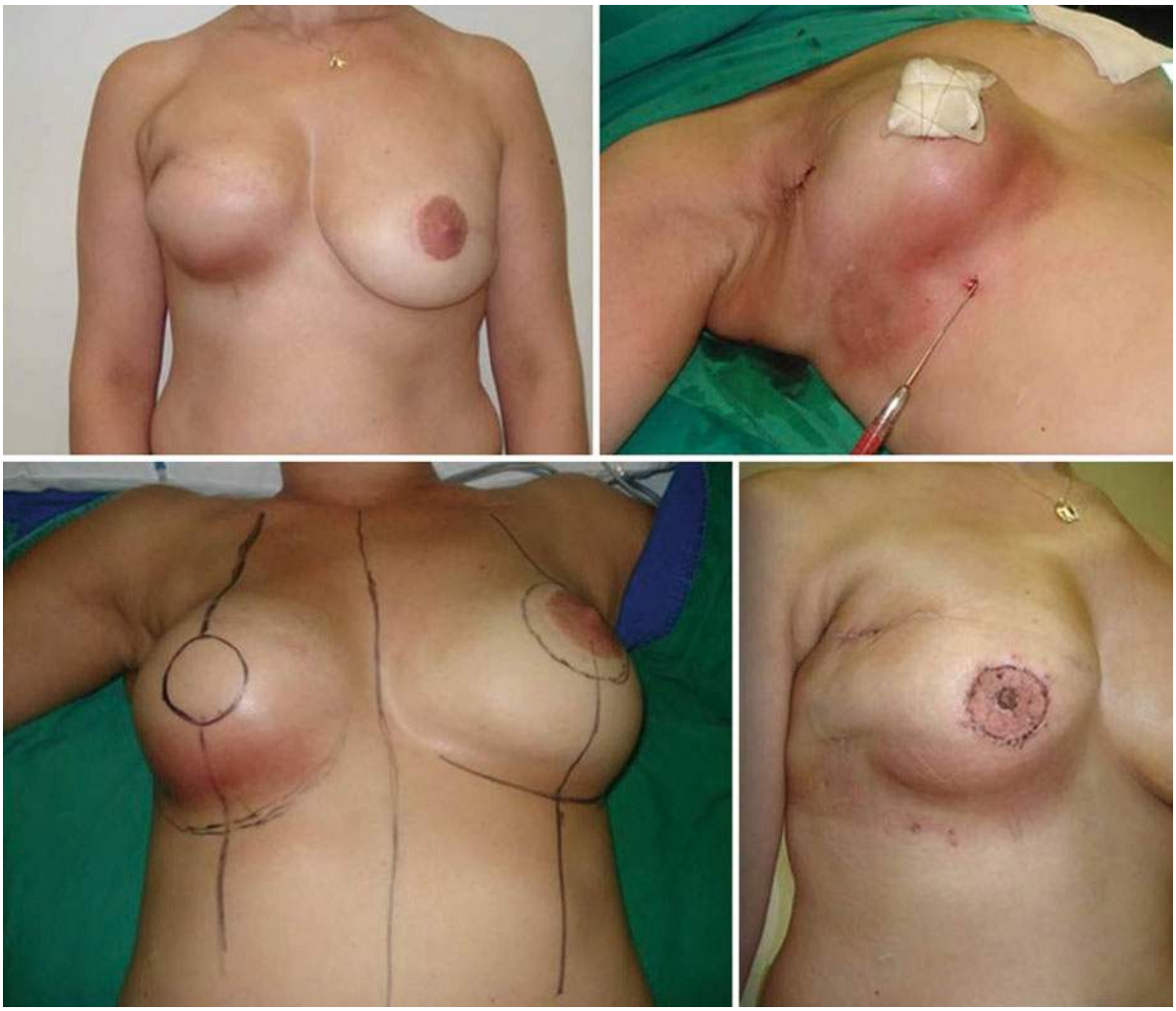


Fig. 50.6 Inframammary fold reconstruction using a latissimus dorsi flap: radical mastectomy (on the right) with tissue expander reconstruction and adjuvant radiotherapy. Expander replaced with silicone prosthesis. Significant capsular contracture, fold retraction, and thinned skin and muscle in the lower quadrants. Lipofilling was performed without success. Inframammary fold reconstructed using latissimus dorsi flap and new silicone prosthesis and left breast mastoplasty. The flap was positioned in the IMF, respecting the breast aesthetic subunit concept. Photo source: Dr. Cericatto

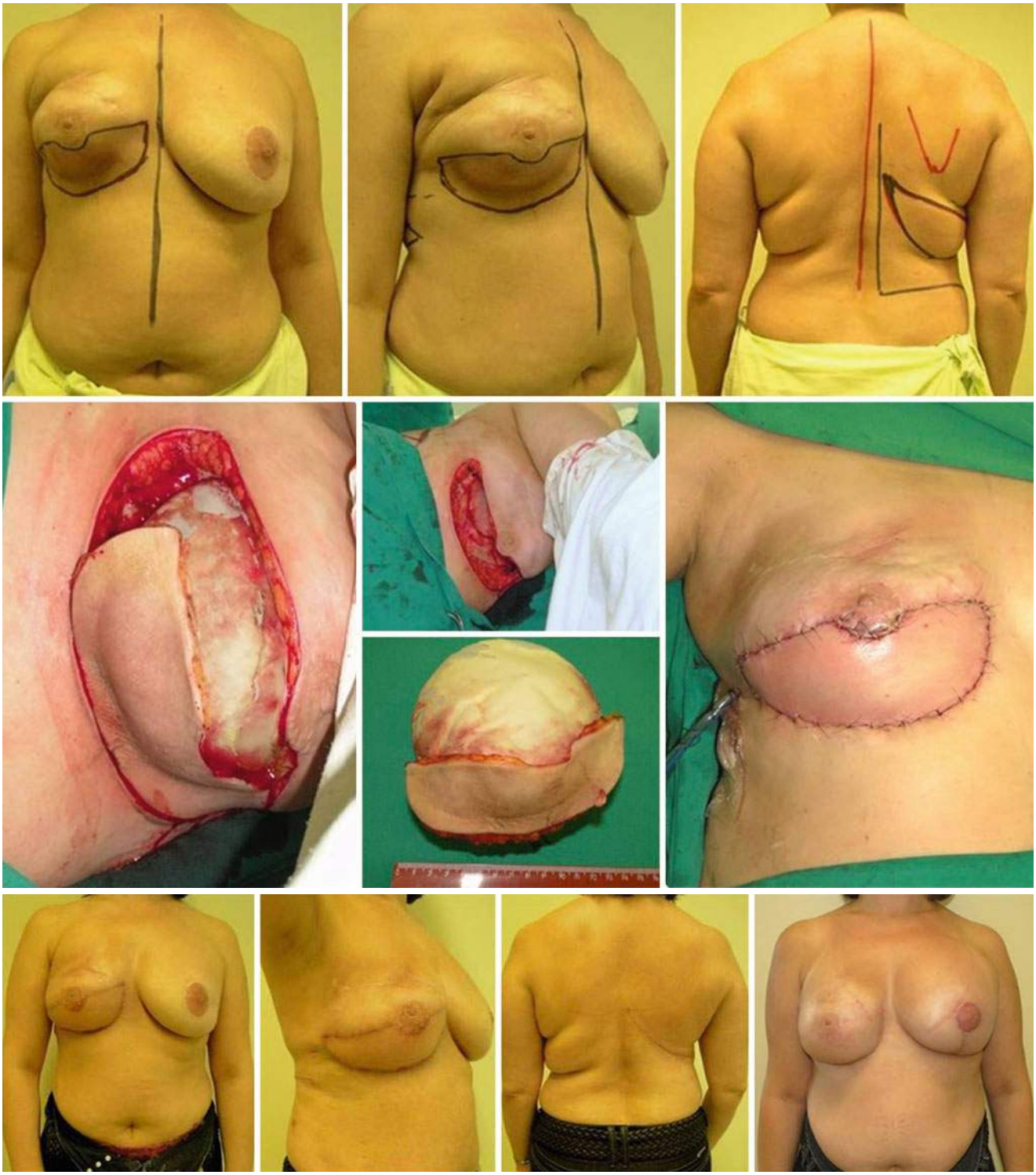
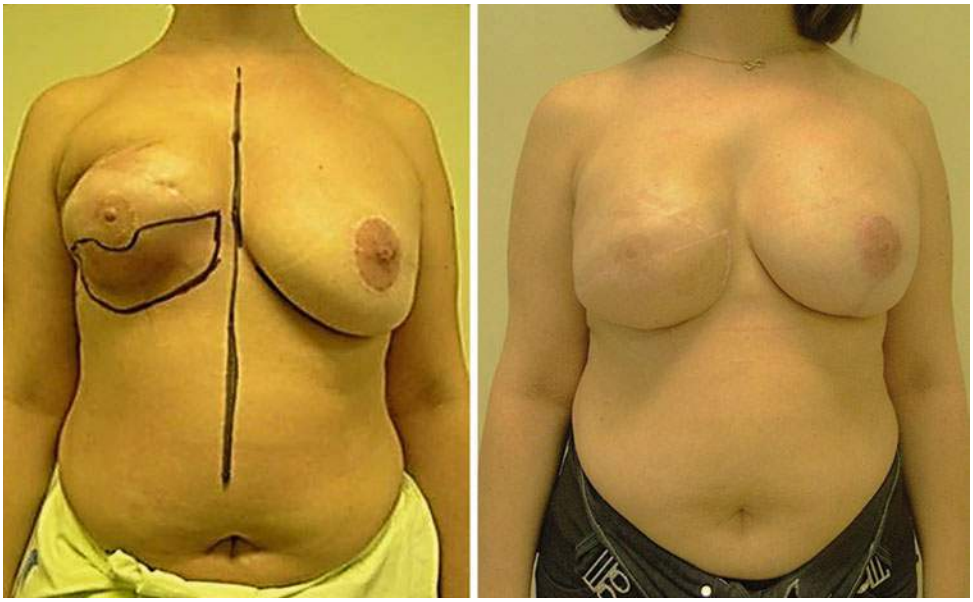


Fig. 50.6 (continued)



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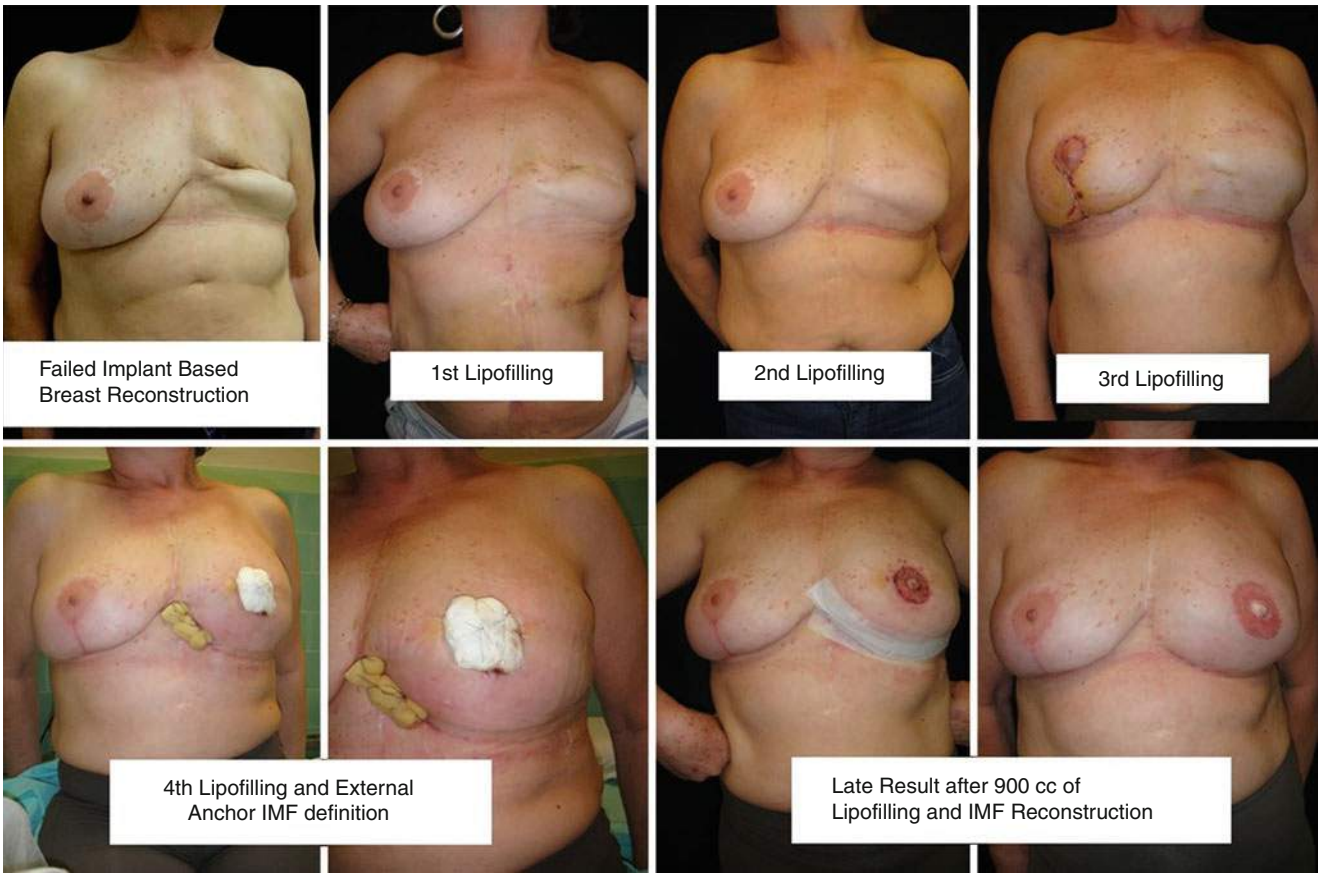

Fig. 50.7 Failed left breast reconstruction with implant. Late left breast reconstruction after four sessions of lipofilling associated with external IMF approach technique. 900 cc of lipofilling achieved an excellent result, with natural breast consistency, temperature, and projection. Source: Dr. Biazús

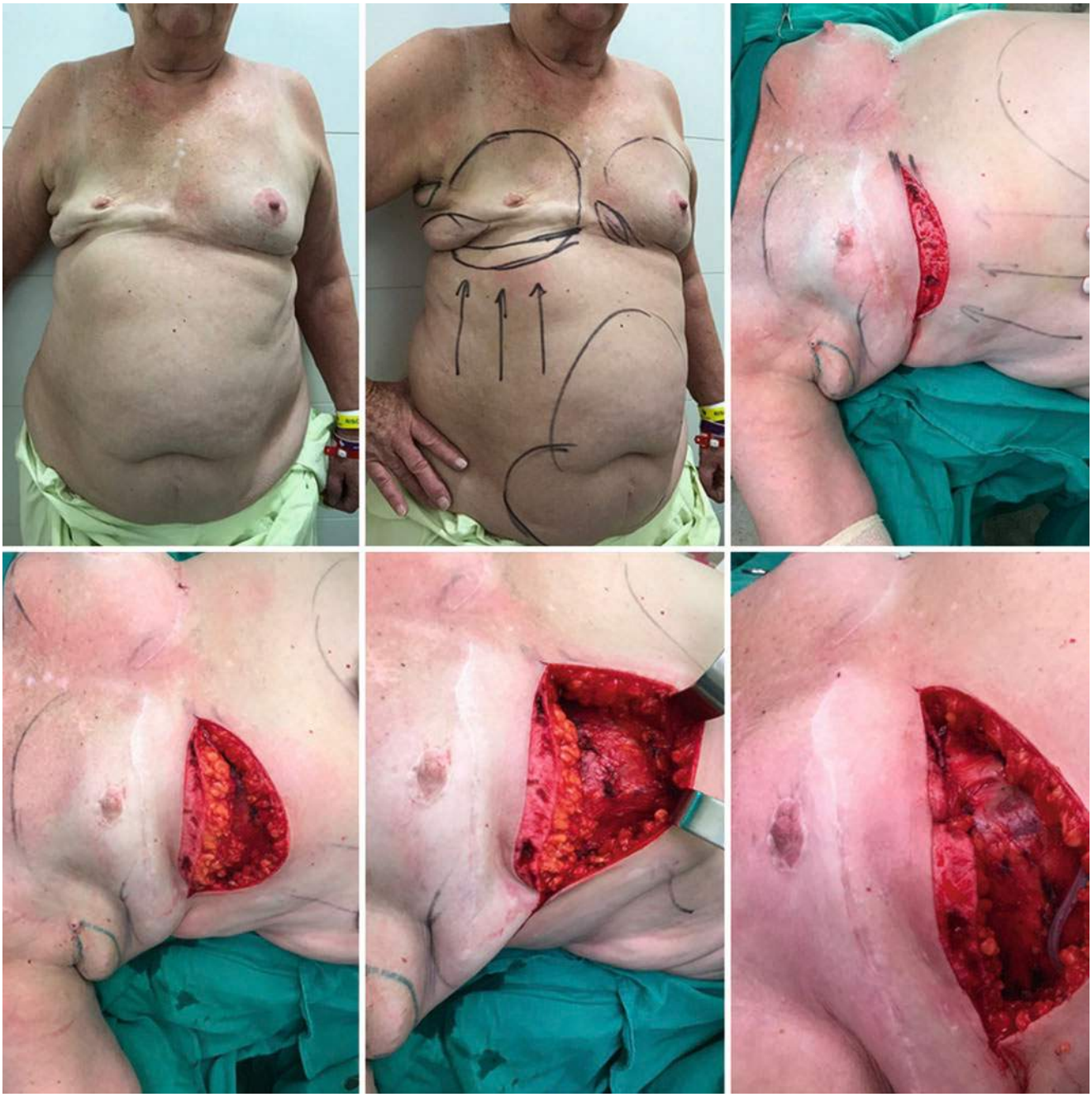

Fig. 50.8 Failed right breast reconstruction with implant. Breast was reconstructed with advancement of upper abdominal flap, associated with 300 cc of lipofilling. Follow-up of 15 days post surgery. Source: Dr. Cericatto

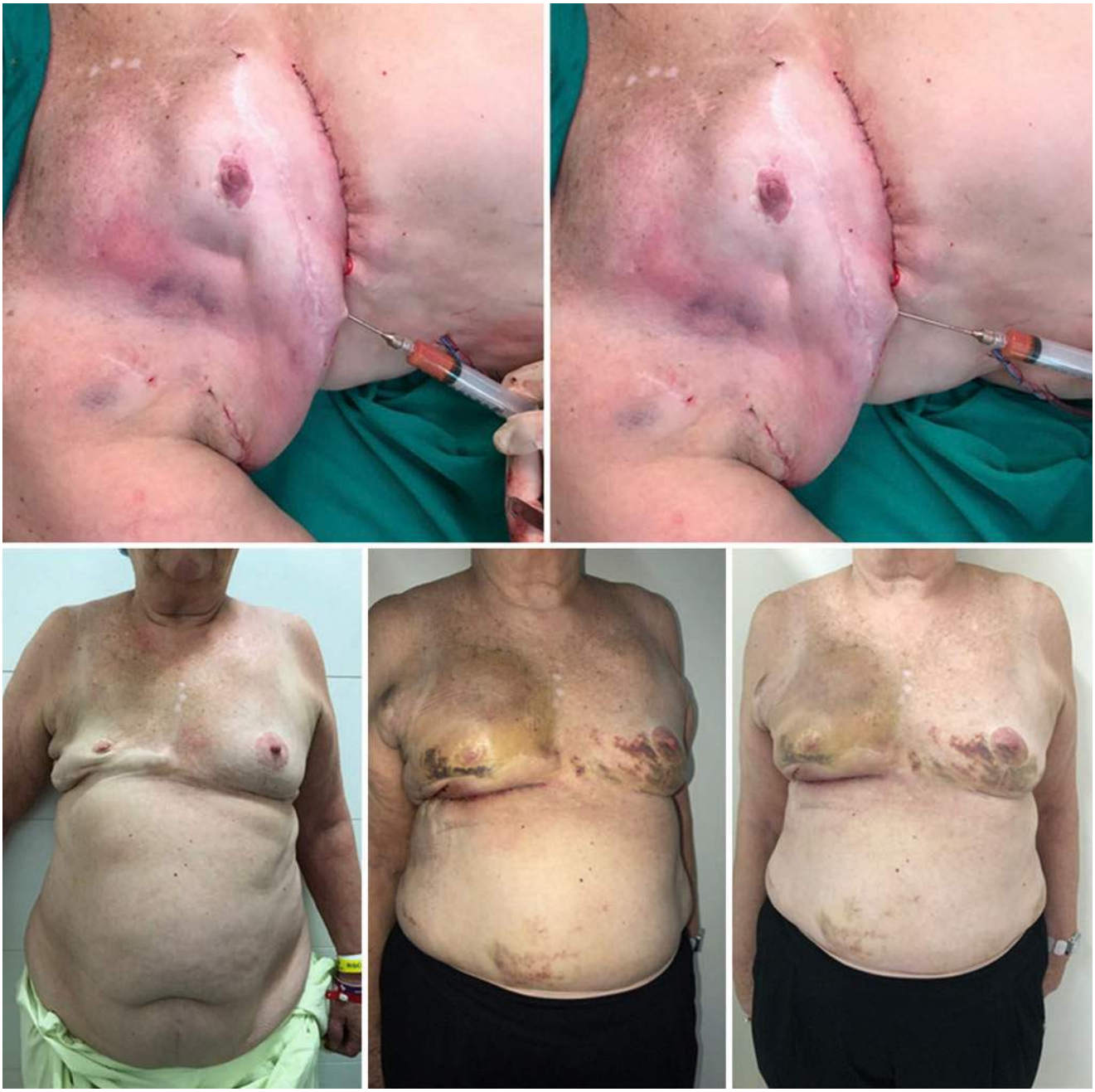

Fig. 50.8 (continued)

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Donor-Site Complications

51

Andrea Manconi, Jean-Yves Petit, and Dario Ribero

51.1 Introduction

Donor-site morbidity is a fundamental topic to take into account before surgery in order to balance benefits with iatrogenic diseases. Most common donor sites in breast reconstruction are the lower abdomen and the back. Complications can be classified in wound healing complications and functional ones.

51.2 Abdominal Flaps

51.2.1 Functional Complications

The lower abdomen is a well-known donor site used initially as myocutaneous flap (pTRAM flap) [1]. Bipedicle flaps were described in order to improve blood supply, in association with a higher risk of postoperative complications [2]. Subsequent methods applied microsurgery to use the dominant deep inferior epigastric blood supply, which led to use of the free TRAM flap [3]. The purpose of decreasing the abdominal wall morbidity resulted in a shift toward muscle-sparing techniques and the deep inferior epigastric artery perforator (DIEP) flap [4]. The advantages of the DIEP flap versus the pTRAM flap consist of functional preservation with the rectus abdominis muscle and rectus sheath sparing. This may reduce the incidence of abdominal morbidity. Other advantages include better abdominal contour [5] and decreased postoperative pain [6]. Critics of the DIEP flap cite increased flap failure and operative time attributable to the meticulous dissection required for this flap [7]. On the other hand, increase in operative time for DIEP flap is justified by reduced donor-site morbidity [8]. Knox's large retrospective review suggests that previously described benefits of the pTRAM flap may be offset by the need for surgical correction of abdominal wall complications. He found that hernia or bulge risk is described up to 20% of the cases, with 60% of these patients requiring surgery [9]. Although DIEP flaps have a longer operating time, functional morbidity rate is low, which may contribute to benefits in patient-reported satisfaction and health-related quality of life. Others, however, argue that reinforcing abdominal wall closure with mesh results in fairly low rates of hernia in pedicled TRAM and free TRAM flaps, thus putting into question the importance of muscle preservation during flap harvest. Abdominal hernias necessitating repair are not uncommon following abdominally based autologous breast reconstruction, with the amount of rectus muscle harvested correlated to the likelihood of developing an abdominal hernia (Figs. 51.1 and 51.2). A retrospective cohort study using the 2008–2012 compared pTRAM, free TRAM, and DIEP flap founding that abdominal hernias necessitating repair are not uncommon following abdominally based autologous breast reconstruction, with the amount of rectus muscle harvested correlated to the likelihood of developing an abdominal hernia.

Anyway pTRAM flap is still largely used. Rietjens described the EIO experience showing an abdominal closure technique that leaded progressive reducing of bulge/hernia formation to maximum. This technique is based on two principles: a dual-layer suture repair with mesh and a muscular dissection above the arcuate line. Posterior rectus sheath isn't represented below the arquate line, and any gap of anterior sheath repair can expose the peritoneum giving the birth to a hernia formation [10, 11]. Also bipedicled pTRAM flaps seem to have low morbidity rate if abdominal wall is repaired with a two-layer mesh closure [12]. By contrast myosonographic studies provided evidence to support the claim that, in younger patients, rectus abdominis muscle function is

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_51

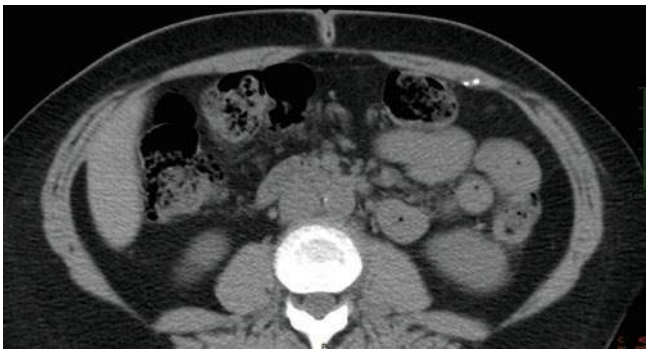

Fig. 51.1 CT abdominal scan after DIEP, original anatomy is restored; vascular clips are visible

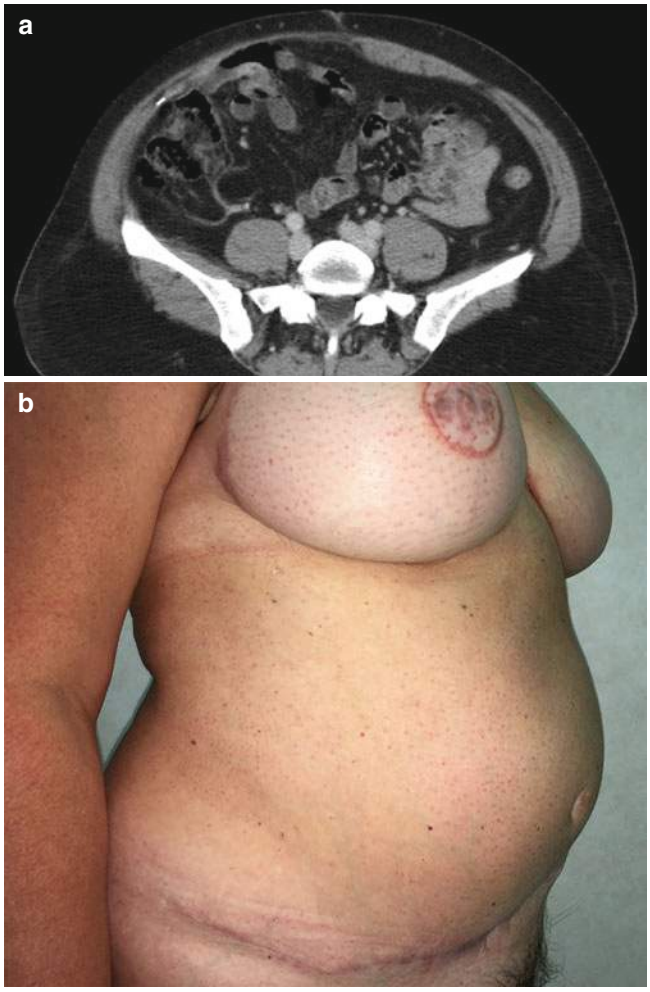

Fig. 51.2 (**a**, **b**) Postoperative view and CT scan after monopedicle TRAM flap and abdominal wall repair with mesh (**b**). Moderate bulge is noticeable. Please notice parietal sheath dilatation in correspondence of rectus abdominis lack. Surrounding muscle and navel root are displaced but abdominal wall is continent. Surgery is not strictly required

statistically better preserved after harvesting a DIEP flap compared to a TRAM flap reconstruction. Good recovery of muscle function, with complete recovery after surgery, was seen in younger women, but still hernia/bulge formation is possible although very rare [13]. Hernia repair should be meticulous in order to avoid recurrence. In the literature this topic is poorly described. Basing on literature and EIO experience, suprafascial, supramuscular, and laparoscopic approaches are possible. The types of mesh used will also vary. Mersilene mesh is most frequently used in our institution. Suprafascial and supramuscular techniques are obtained by abdominal scar opening; cutaneous undermining is performed; and bulge or hernia is exposed. Simple bulge can be reduced by suprafascial mesh positioning and suture on muscular fascia. Hernias should be exposed and intra-abdominal adhesions taken down. The surrounding muscle sheath is incised and dissected from the muscle. Muscle edges are approximated as much as possible, and the mesh is buried beneath the muscular sheath and sutured in a double-layer fashion. Laparoscopic approach is based on standard principles of triangulation. Port placement in the laparoscopic repair technique varies for each patient, depending on the hernia site, and sites for entry are based on clinical evaluation and CT scan. Entry is obtained by making a 1.5-cm incision through the skin, and electrocautery is used to incise soft tissue until anterior fascia was identified. Both the anterior and posterior fascial layers are sharply incised under direct vision to allow access into the intra-abdominal cavity and trocars are placed. Carbon dioxide was insufflated, and the camera is placed. Intra-abdominal adhesions should be taken down. Once avascular planes are established, the hernia contents are reduced, and hernia entry is closed by mesh positioning and suture (Fig. 51.3).

51.2.2 Wound Healing Complications

Abdominal wall closure is also exposed to wound breaking risk. Major risk factors are tension, obesity, smoking, diabetes, and previous surgery. Skin necrosis and seroma formation can be potential wound break causes. The use of quilting suture is controversial, and opposite founding in terms of seroma prevention is present in the literature. A rare pyoderma gangrenosum has been reported in EIO study as a donor site and flap complication causes [14]. It may cause a severe systemic infective-like disease with progressive necrosis in which diagnosis and treatment are difficult to assess. Mesh infections represent one of the most terrific complications in breast reconstruction. Late and chronic infections can lead to fistula formation (Fig. 51.4a–c).

In those cases treatment is based on antibiotic therapy, surgical debridement, VAC therapy, and mesh removal if necessary (Fig. 51.5a, b).

Synthetic immediate mesh repositioning isn't recommended, and high recurrence rate was observed after biological mesh repair of contaminated hernia. Direct

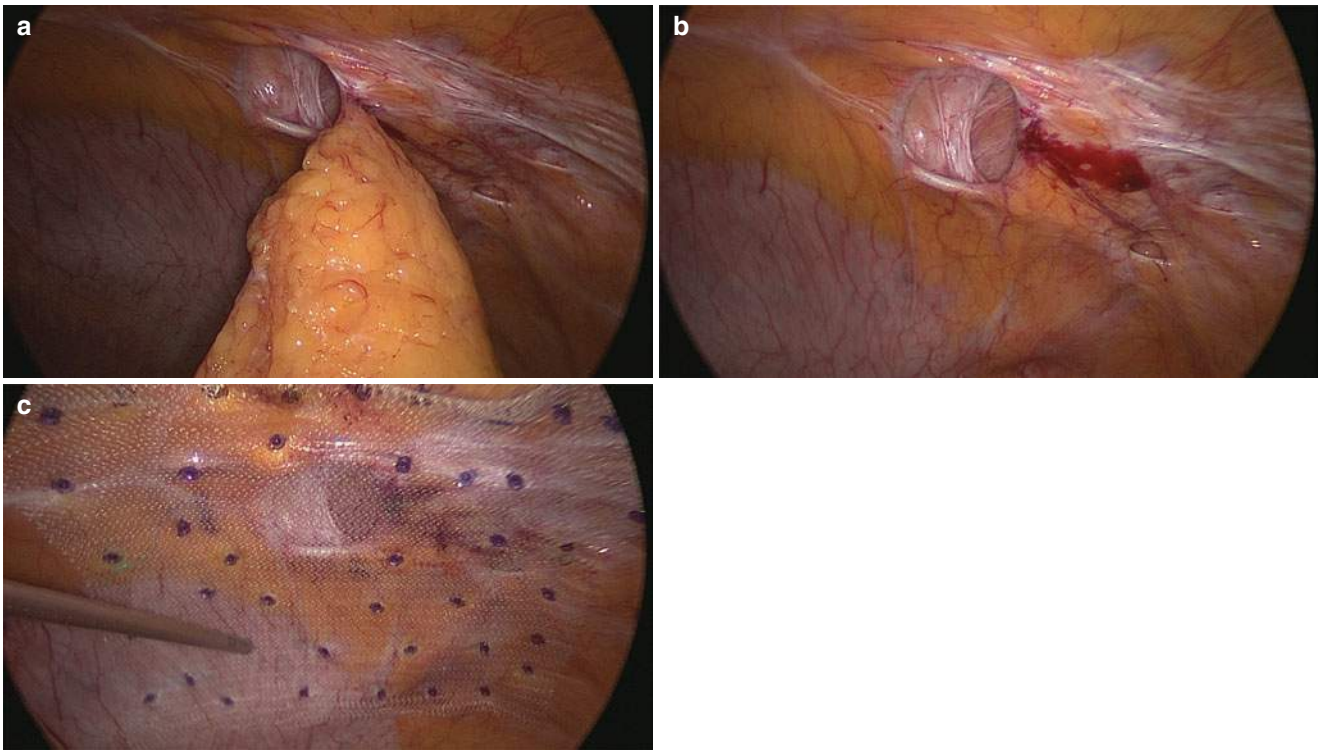

Fig. 51.3 (**a**–**c**) Laparoscopic hernia repair: intraoperative hernia view, scar release, and mesh positioning

closure is possible as hernia formation can increase. So DIEP flap presents another strong point because donor site is rarely repaired with mesh although infections are possible (Fig. 51.6).

51.3 Latissimus Dorsi Flap

51.3.1 Functional Complications

Latissimus dorsi (LD) myocutaneous flaps are well tolerated in breast reconstruction, both with implant insertion and as extended autologous flap (ELD) [3, 13]. Several previous studies have shown that LD muscle transfer can have sequelae at the ipsilateral shoulder, but the exact functional impairment has been a subject of debate. Majority of publication support the belief that muscle is expendable, and residual muscles of the shoulder joint would compensate for it [25, 26]. The topic is debated, but functional impairment and changes in daily lives after flap transfer may not be as tolerable as previously considered. Nevertheless, the patient samples for most of these studies are limited, and assessment modalities used in some of these studies were not standardized. In the literature [15], 9 out of 13 articles reported some type of limitations in shoulder range of motion after flap transfer. In the majority, the degree was not severe, while four articles reported no limitation (Clough et al.) [16]. The study states that 46% of patients had limitations in upward mobility of the hand, while 70% of patients do not show objective limitation in muscle function, and 37% have a certain functional limitation which did not significantly affect strength and mobility of the shoulder. Some weaknesses in shoulder strength have been tested for any type of motion as described in the literature [15]. Impaired shoulder extension is most frequent, in concordance with our data. Lumbar hernias are also exceptional and may be difficult to detect clinically, but the wider use of CT scans may allow their detection. Two spontaneous varieties are well described: a Petit's hernia and a Grynfeltt-Lesshaft's hernia [16]. The first one is through the inferior, and the second one is through the larger and superior lumbar triangle. The external oblique and LD muscles form the "roof" in this region, and thus, mobilization of this muscle predisposes to weakness and herniation. The rarity of this complication can be presumably due to missed reports or symptom complains. Even lumbar hernia treatment is well described in the literature, and different cases after latissimus dorsi flap had been presented of whom few surgical procedures are described both by laparoscopy

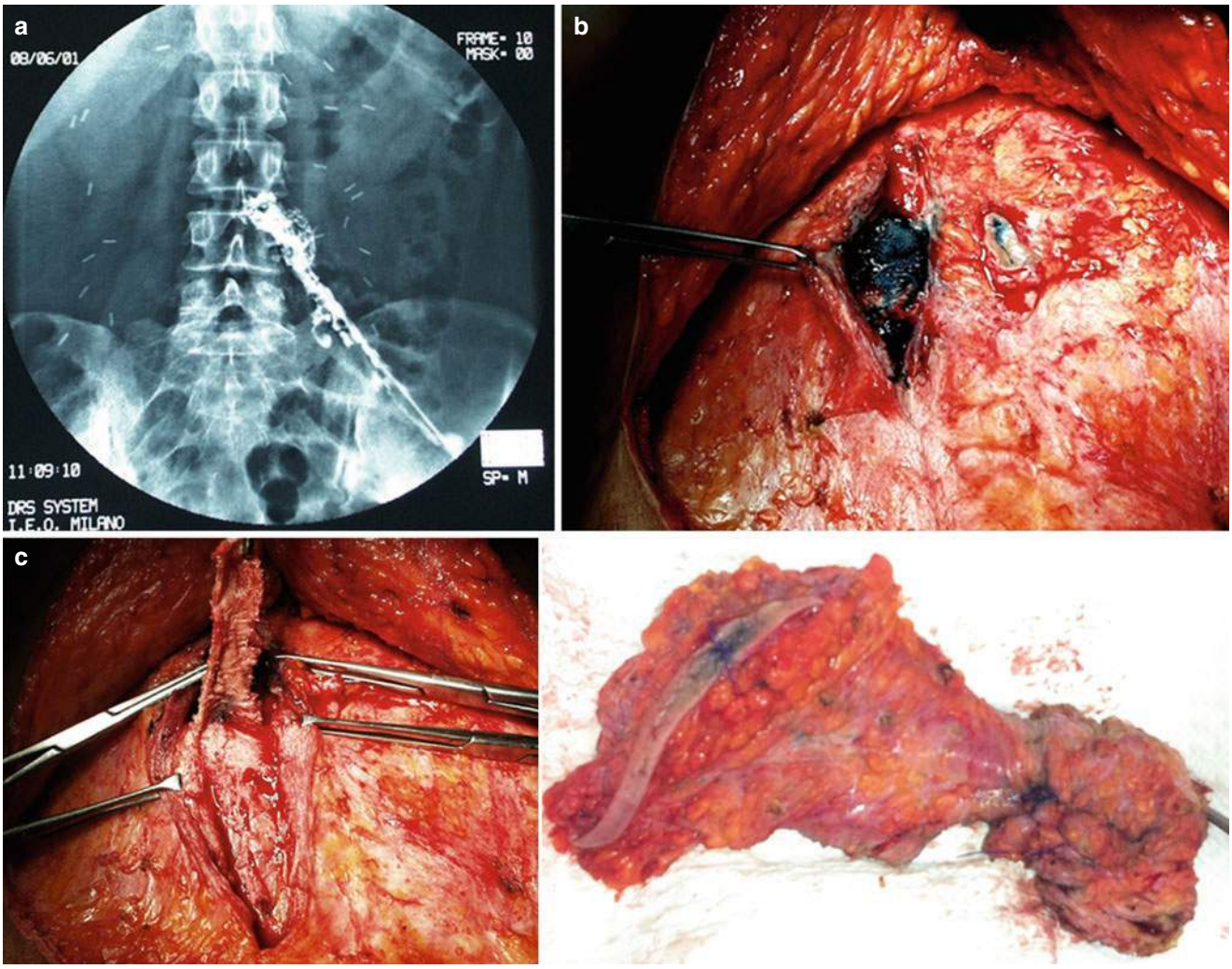

Fig. 51.4 (**a**–**c**) Infected mesh with cutaneous fistula resection: preoperative fistulography, intraoperative view, and specimen. Fistula tract is colored with blue patent to facilitate complete mesh resection

and laparotomy. Technical principle is similar to standard lumbar hernia. Of course it is important to prevent these complications; in our opinion care should be taken in order to avoid extensive muscular dissection beneath rib edge, preserving its protective function. In EIO only 1 case in more than 1000 cases has been found. Lumbar hernia has been successfully treated with back skin incision, sac exposure and incision, and repair with intraperitoneal mesh.

51.3.2 Wound Healing Complications

Seroma is a well-recognized and not uncommon complication following LD muscle transfer. The incidence of seroma after LD muscle harvest has been reported to be high, occurring in up to 80% of patients [17]. Although they have yet to be documented clearly, the suggested mechanisms of seroma formation include the development of a dead space after flap harvest, potentially causing shearing effects with inflammatory reactions, and prolonged leakage into this dead space by disrupted vessels and lymphatics as a result of surgical dissection [16]. Donor-site seroma following LD muscle transfer can lead to patient discomfort and anxiety and also may create wound problems, including wound infection due to repetitive aspiration, wound dehiscence, and overlying skin flap necrosis. Many efforts have sought to reduce the incidence of seroma formation after LD muscle harvest, including avoidance of diathermy dissection, endoscopic or robotic dissection, pressure dressings, use of quilting sutures, and instillation of fibrin sealants [18]; the latter two methods have been the strategies most commonly employed in recent years [19]. Several investigations have been conducted to determine their efficacy on the prevention of seroma formation following LD muscle transfer; however, these studies

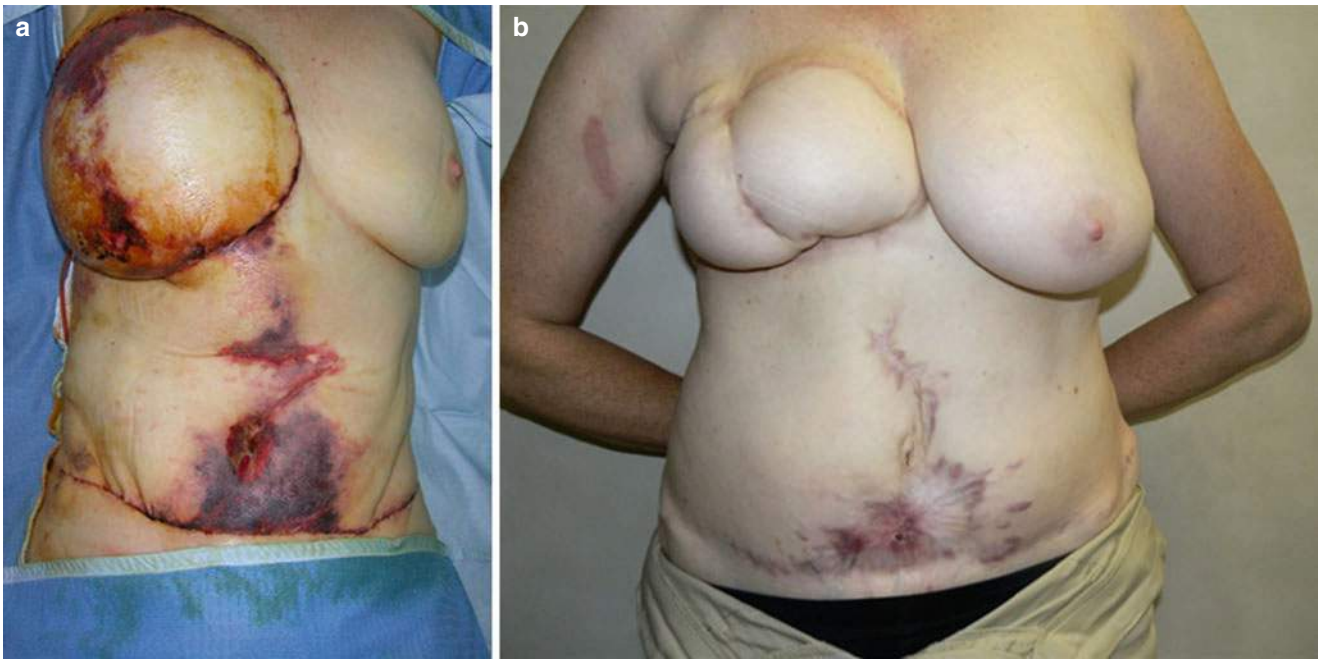

Fig. 51.5 (**a**, **b**) Bipedicled TRAM flap massive necrosis. Flap and donor site result after several surgeries

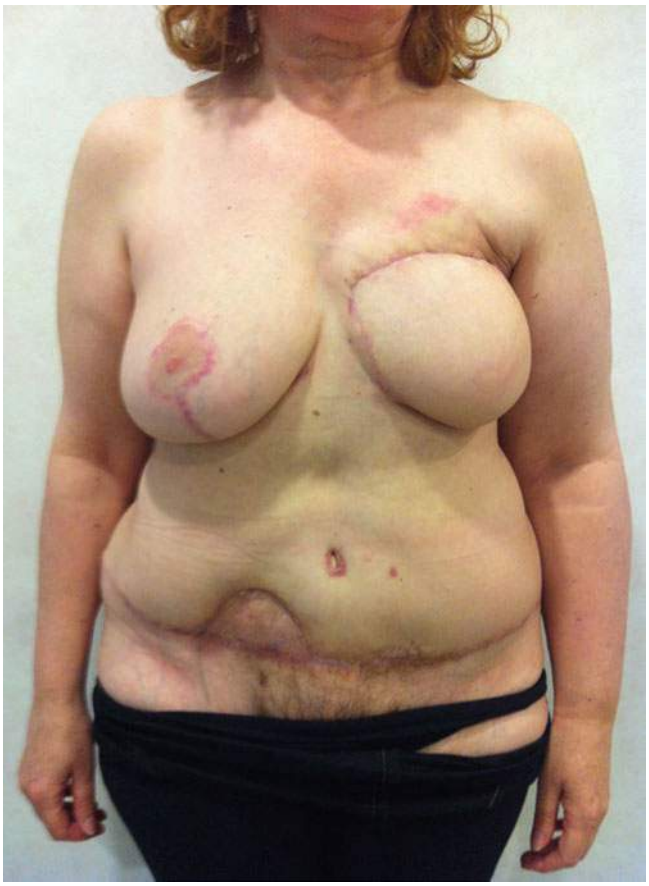

Fig. 51.6 A 6-month postoperative result of DIEP flap donor site complicated by infection. Spontaneous healing could be possible thanks to mesh absence

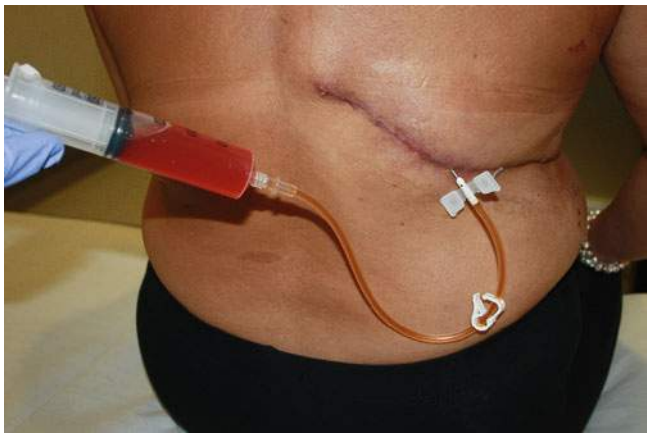

Fig. 51.7 Latissimus dorsi donor-site seromas can be easily evacuated by needle aspiration using 15-gauge butterfly needle system connected with luer lock 50 cc syringe

had contradicting results [20], and there remains no consensus regarding the efficacy of these techniques. In our institution, those techniques are rarely used, but drains are left in place for 15 days, and extensive unnecessary dissections are avoided in order to prevent seroma formation [21]. Anyway, seroma is often observed and treatment consists in percutaneous aspiration eventually repeated once a week (Fig. 51.7). Of course patient information represents a key role. Back skin necrosis is rarely observed with increased rate in ELD flap.

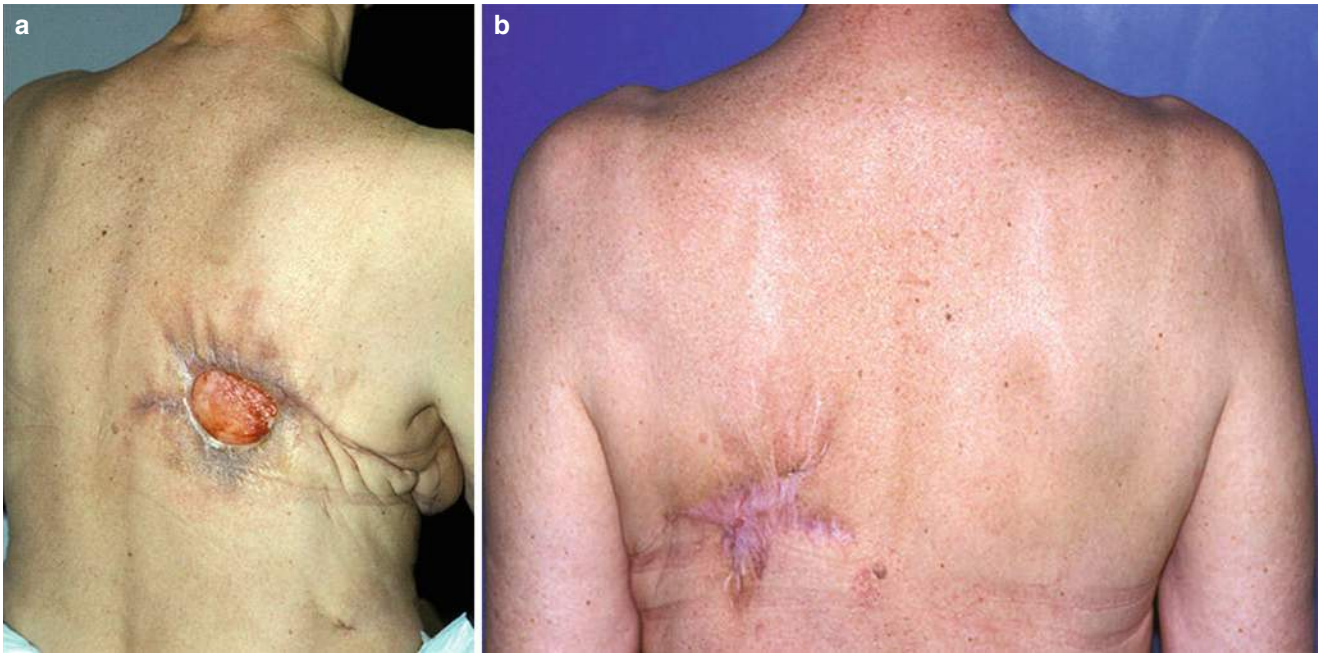

Fig. 51.8 (**a**, **b**) Latissimus dorsi donor-site skin necrosis and wound breakdown: complete spontaneous healing after several months

Additional risk factor corresponds to skin thickness, in fact subcutaneous undermining is performed very superficial in ELD flap [22]. Seromas, infections, and necrosis are potential causes of wound breaking. In that case conservative treatment is usually possible and wound suture can be easily performed in office once the wound bed is properly prepared in most of the cases (Fig. 51.8a, b).

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Complications of Unipedicled TRAM Flap Reconstruction: Treatment and Prevention (and Their Influence on the Choice of the Reconstruction)

52

Jean-Marc Piat

52.1 Introduction

After a description of the technique in 1982 [1], Carl Hartrampf was the pioneer and promoter of unipedicled transverse rectus abdominis myocutaneous (TRAM) flap breast reconstruction. The principles of pedicled TRAM flap (unipedicled or bipedicled) reconstruction with preparation of the flap by ligation of the inferior epigastric vessels (delayed TRAM flap) and strengthening of the vascularization by microanastomoses of the inferior epigastric vessels (supercharged TRAM flap) and the principles of free TRAM flap reconstruction by microanastomoses of the deep inferior epigastric vessels were quickly proposed [2, 3].

Subsequently new techniques of reconstruction with TRAM flap microanastomoses were developed in order to preserve the abdominal fascia. The deep inferior epigastric perforator (DIEP) flap reconstruction leaves the right rectus abdominis muscle totally in place the [4]. The superficial inferior epigastric artery (SIEA) reconstruction avoids a fascial incision [5]. These techniques give excellent results in referral centers for surgeons trained in microsurgery.

TRAM flap reconstruction is a technique of choice because it allows reconstructing a breast without a prosthesis, with a natural look, and which is easily improvable by lipomodeling and is very stable over time regardless of changes in the weight of the patient [6]. Specific complications are mainly necrosis of the flap and the weakening of the abdominal wall, which can cause a hernia or bulge. There are also less specific complications such as infection, which must be taken into account when choosing the technique (whether or not to use mesh at the wall).

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The TRAM technique is used routinely by many surgeons all over the world. The choice of the technique (unipedicled, bipedicled, or microanastomoses) depends largely on individual experience, but proportionally few surgeons are experienced in microsurgery. Each TRAM technique has advantages and disadvantages, with a risk of partial or total necrosis and a risk of more or less important parietal complications. The risk of complications is dominated by parietal complications for pedicled TRAM flap reconstruction and the total loss of the TRAM flap for microanastomoses [7, 8].

Since being trained in the technique of unipedicled TRAM flap reconstruction by Madeleine Lejour in Brussels in 1989, I have acquired a personal experience of more than 680 such reconstructions. The beginning was marked by an important rate of partial necrosis of 8% during the first 60 TRAM flap reconstructions without this being clearly explainable by a technical problem or a specific risk factor related to the patient. Then we became more selective with patients and improved the technology to make it more and more reliable. The use of delayed TRAM flap reconstruction has reduced very significantly the rate of partial necrosis to 3%, as it was shown by a study of 192 consecutive unipedicled TRAM flap reconstructions done between 2003 and 2009. Similarly, the rate of parietal complications of about 10% at the beginning of the study was reduced to 4.6% owing to the technical reconstruction of the wall adapted to each patient. The rate of partial necrosis went down to 1.4% (2 cases over 141 TRAM carried out), in a prospective study done between November 2012 and June 2016, for which a computed tomographic angiography was systematically done after preparation (either surgically or with embolization). Eleven patients were contraindicated due to a really poor resumption of superior epigastric vascularization after preparation.

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_52

52.2 Complications of Unipedicled TRAM Flap Reconstruction and Their Treatment

52.2.1 Necrosis

Necrosis is linked to a lack of blood supply, following an arterial ischemia, to part of the flap, resulting in peripheral venous congestion followed by thrombosis. In my experience, an important arterial flow coming from the superior epigastric artery, after having severed the lower epigastric artery on the lower part of the right rectus abdominis muscle, is a good sign of a future vascularization of the flap, even more if the flow is pulsatile.

After the surgery and in the early postoperative hours, the capillary refill is the best indirect evidence of vascularization of the flap. If it is less than 2 s in the peripheral zone, the least well vascularized, we can expect a favorable outcome. If it is more than 2 s, the flap should be monitored very carefully. If it is more than 3 s, necrosis is a concern. It is rare to observe a suffering of the flap related to a venous congestion. This may happen when the venous return is done preferably through the cutaneous network rather than the epigastric vessel. In this situation, it evolves positively within 48 h, with blood loss that may require blood transfer.

Some propose putting a temporary drain in place during the operation, intubating one of the epigastric inferior veins with an angiocatheter to drain the flap when the degree of venous congestion is very high [9].

52.2.1.1 Important Flap Loss (Greater than 25% of the Flap)

The total loss of the flap is exceptional in cases of unipedicled TRAM flap reconstruction. It may be related to a problem of notification as it has only happened once in our experience. This was a 65-year-old woman who had had two Pfannenstiel incisions (one for a hysterectomy and one for a prolapse), which were much more traumatic for perforating vessels than a Pfannenstiel incision made for a caesarean section. As the patient showed abdominal excess compatible with TRAM flap reconstruction and moreover was very adamant about having the operation, TRAM flap reconstruction was chosen, knowing that there was a risk associated with her age and surgical history. The appearance of the flap after surgery was satisfactory. The results were marked by progressive thrombosis of the flap causing extensive necrosis of more than 50%, as well as a pulmonary embolism occurring on the 15th postoperative day which required the removal of the flap on postoperative day 21 (Fig. 52.1). The patient reported spontaneous thrombosis related to a factor V Leiden anomaly in her daughter. Additional tests showed the existence in her case of a factor V Leiden anomaly, which is known to be a risk factor for necrosis of the TRAM flap [10].

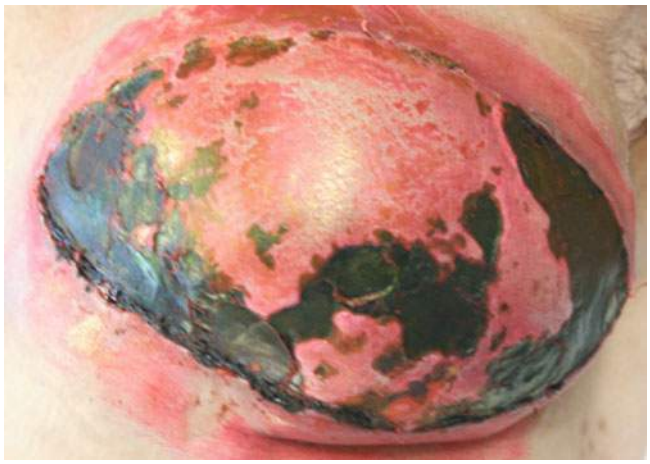

Fig. 52.1 Total flap loss

Apart from high-risk situations of poor arterial blood supply (smoking, obese, or diabetic patients, Raynaud's syndrome), which are for some only relative contraindications to unipedicled TRAM flap reconstruction, significant necrosis of the flap can occur owing to a technical error during the intraoperative harvesting injuring the superior epigastric vessels as in the following case. This was an obese patient of 52 years of age for whom unipedicled TRAM flap reconstruction was chosen despite a BMI of 31 to correct a faulty immediate reconstruction with an expander (infection). The operation was marked by a spontaneous and complete tear of one of the two pedicles of the upper division epigastric vessels before it entered the posterior face of the right rectus abdominis muscle. This occurred as a result of traction on the pedicle (which was attached to the rib cage) by the particularly heavy flap of this patient while it was being shifted upward. Microsurgical repair of the injured pedicle (artery and vein) was performed. Despite that, a necrosis occurred. Further surgery was done 48 h later to resect about 25% of skin tissue developing necrosis (Fig. 52.2a), with good progress after 1 month (Fig. 52.2b), but fat melting was recorded later (Fig. 52.2c).

52.2.1.2 Moderate Flap Loss (Between 5% and 25% of the Flap)

This complication occurs more frequently, from 3% to 15% in published series [11, 12]. Early treatment is performed to save as much as of the flap as possible, and a later treatment is proposed to correct the sequelae of this necrosis. The ischemia causes a marbled appearance of the skin, and then an aspect of venous thrombosis, well-marked after 48 h, that will develop toward necrosis.

Further surgery is indicated on the second postoperative day when the limits of the cutaneous vein thrombosis are well marked and before thrombosis spreads to a larger portion of the flap. It is generally found in patients whose blood

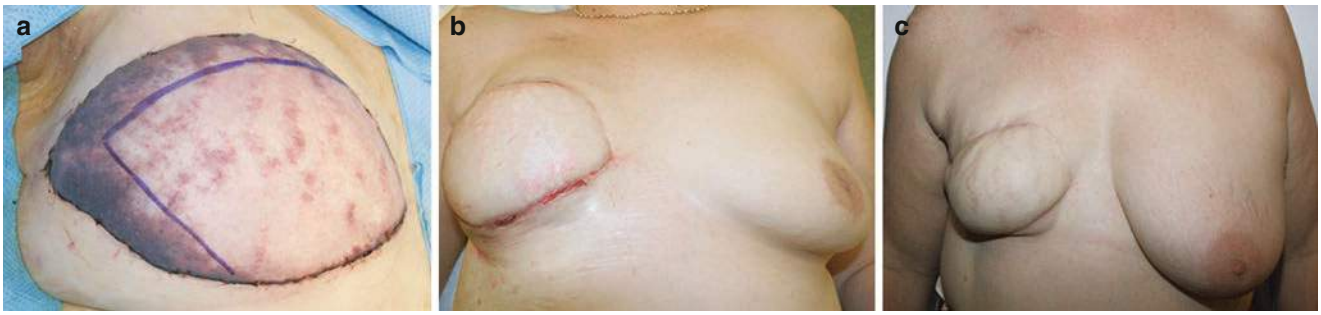

Fig. 52.2 (**a**) Resection of thrombosed tissues after 48 h. (**b**) Result after 1 month. (**c**) Result after 1 year and fat melting

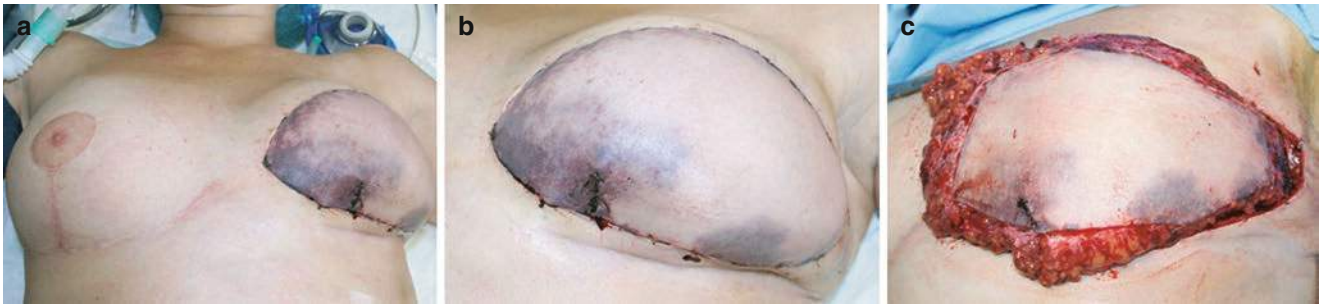

Fig. 52.3 (**a**, **b**) Images showing the thrombosed tissues after 48 h. (**c**) Removal of thrombosed tissues and complete remodeling of the flap. (**d**) Result 9 months later

supply to the flap was overestimated intraoperatively, especially in its periphery and the side opposite the pedicle muscle. In this case the removal of thrombosed tissue requires a complete remodeling of the flap, which is easy to perform on the second postoperative day before scar tissue fibrosis occurs as is shown in the case in Fig. 52.3.

It is better to intervene early rather than let necrosis evolve naturally, for several reasons:

- Early intervention saves more volume of the flap (before the necrosis spreads).
- Spontaneous evolution of the necrosis can last several months with important localized health treatment, which can lower the patient's morale.
- In some cases there is a risk of infection of necrotic tissue that may extend to the whole flap.
- The final result with a retractile fibrosis and a defect located on the edge of the flap is more difficult to correct than one treated after an early intervention leaving the residual flap smoother.

The necessary correction in the long run is made using lipofilling (Fig. 52.4).

52.2.1.3 Minimal Skin Necrosis (Less than 5% of the Flap)

This does not require early new surgery. Its boundaries are difficult to assess in the first few days after surgery and can be treated by allowing the lesion to evolve spontaneously as postoperative care is then simple and can be done by the patient herself without too much trouble. It leaves a zone of residual underlying fat necrosis. It is often associated with a small skin necrosis of the abdominal scar, reflecting a general vascular status of the patient that is not optimal.

52.2.2 Fat Necrosis

Fat necrosis is associated with skin necrosis but can also occur without evidence of skin necrosis. Its frequency ranges from 4% to 35% depending on the series [7, 13, 14]. It is troublesome if it is large and the cause of a large induration perceived by the patient. It can, as in the case shown in Fig. 52.5, be corrected by an excision followed by remodeling of the flap done in conjunction with the areolar reconstruction.

If the fat necrosis cannot be resected without distorting the reconstruction, or if it is minimal, it can be left in place and treated with a simple lipofilling.

52.2.3 The Parietal Complications

52.2.3.1 Mechanical

All types of complications can occur following a relaxation of the fascial suture in 4–29% of cases depending on the series [15–17].

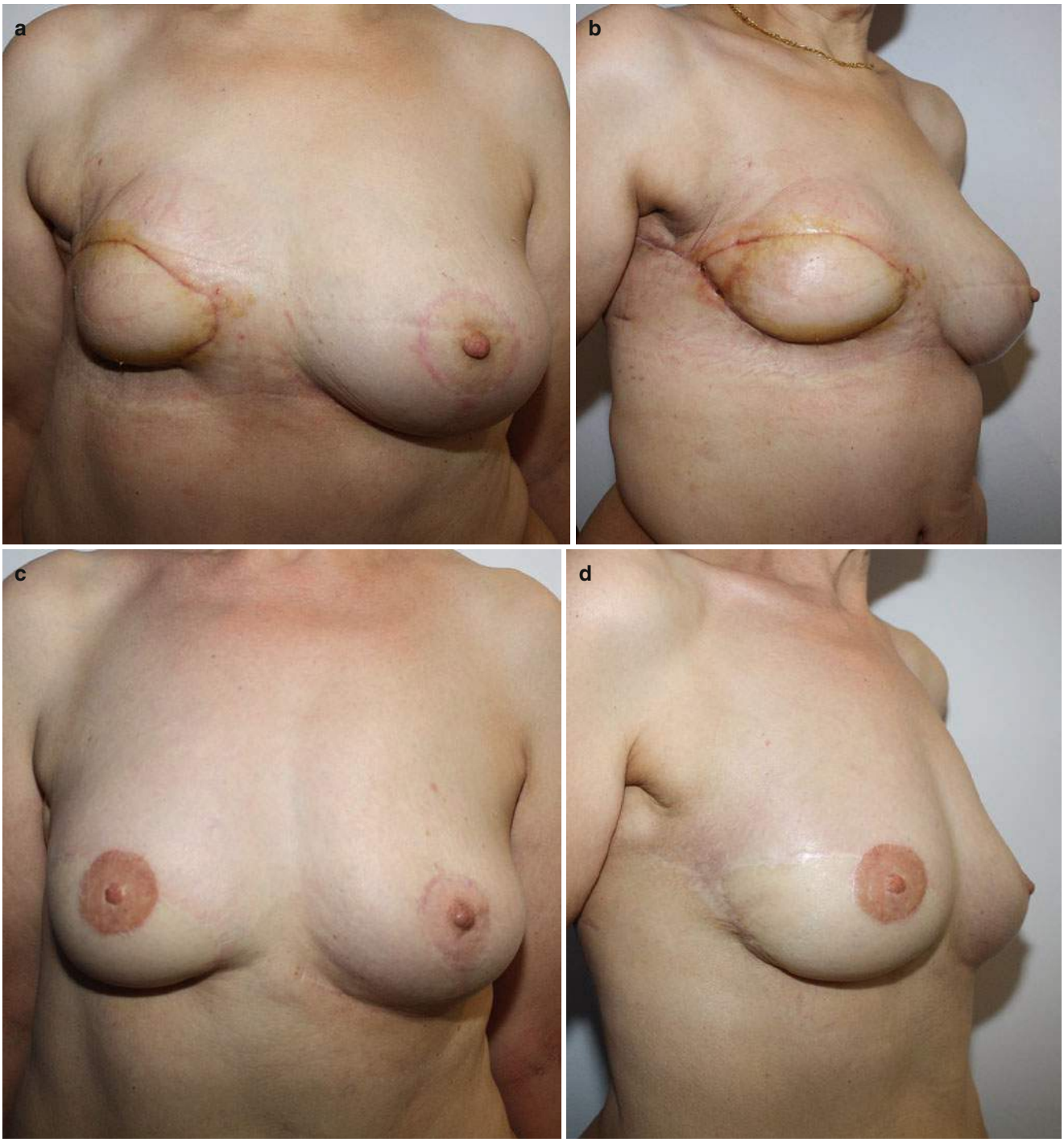

Fig. 52.4 (**a**) Frontal view and (**b**) oblique view 3 months after TRAM and flap necrosis. (**c**) Frontal view and (**d**) oblique view after correction by four lipofillings, nipple-areola reconstruction, and reduction of the contralateral breast

The most troublesome are the abdominal hernias, which can be localized in the epigastric region (transition zone of the flap) or below the umbilical region (area of weakness below the arcuate line). They should be treated as if they are symptomatic. The placement of a mesh by laparoscopy is the most elegant treatment (Fig. 52.6).

The commonest complication is weakness of the fascia in the infraumbilical region (laxity or bulge), which can be corrected later, if the patient wishes, by a complete detachment of the wall followed by plication of the fascia (for re-tension) and the establishment of a reinforcing preaponeurotic mesh.

52.2.3.2 Infections

Infections of the flap are rare outside necrosis cases.

Acute and significant postoperative infections of the abdominal wall require removal of the prefascia mesh,

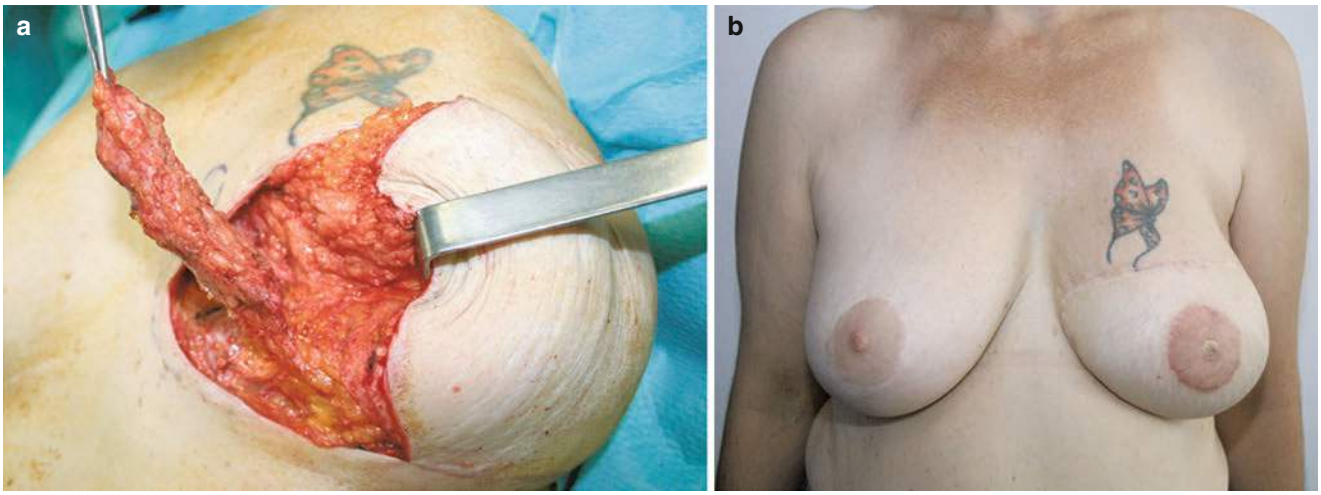

Fig. 52.5 (**a**) Removal of internal fat necrosis (10 × 2 × 1.5 cm), remodeling of the flap, and areola reconstruction 8 months after transverse rectus abdominis myocutaneous (TRAM) flap reconstruction. (**b**) Result 8 months later

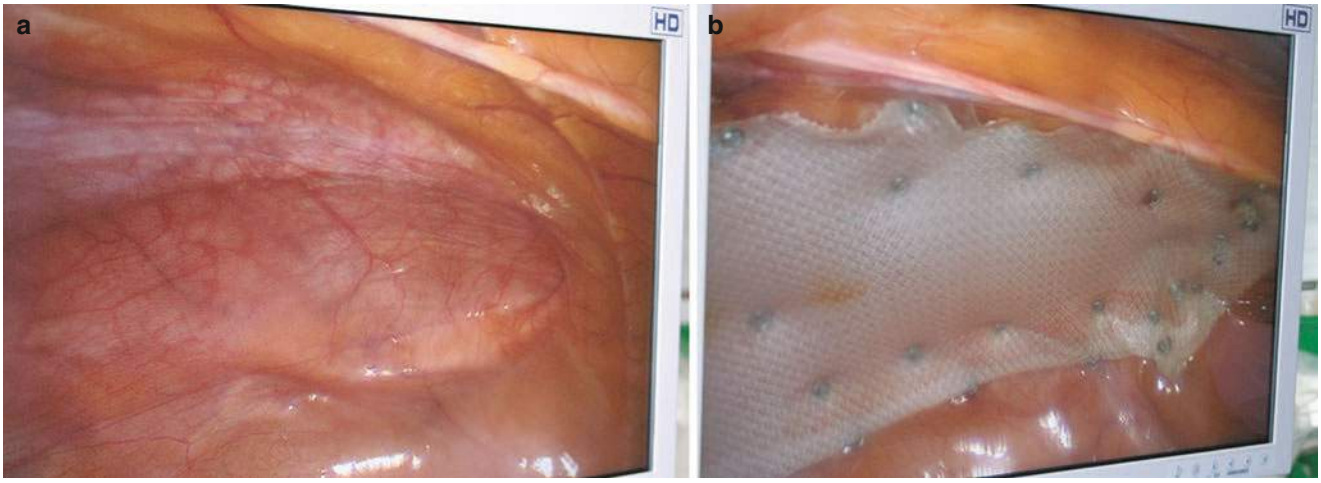

Fig. 52.6 (**a**) Laparoscopic view showing abdominal infraumbilical hernia 2 years after unipedicled TRAM flap reconstruction without preaponeurotic mesh. (**b**) Repair using intraperitoneal mesh

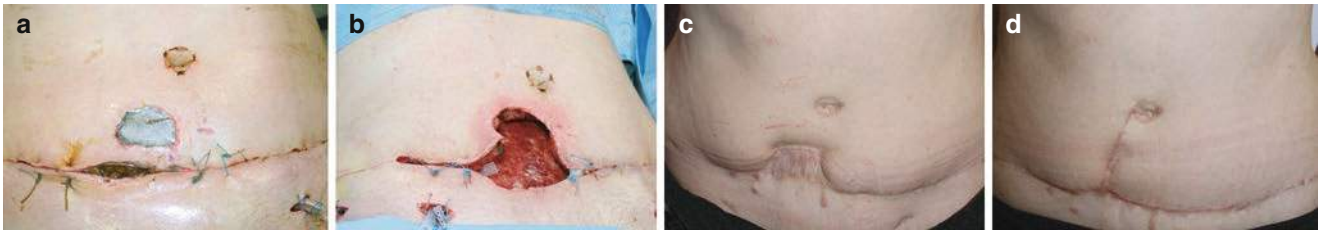

Fig. 52.7 (**a**) Drainage of acute infection with anaerobic germs of the abdominal infraumbilical skin 8 days after TRAM flap reconstruction. (**b**) Removal of the infected tissues and the prefascia mesh 15 days after TRAM flap reconstruction. (**c**) Result 6 months later, after important localized health treatment. (**d**) Result 1 year later after correction of the scarring sequelae

followed by monitored wound healing and later cosmetic correction away from the abdominal scar (Fig. 52.7).

Infections of the abdominal wall in relation to a dehiscence abdominal scar after a deficit of blood supply to the lips are handled by local treatment without removal of the parietal prosthesis.

Some infections such as those occurring away from a hematoma or seroma of the abdominal wall can cause a chronic skin fistula problem. If the prosthesis located deep in the sheath of the right rectus abdominis muscle is affected by germs, superficial debridement of the wound, even combined with appropriate antibiotic therapy, is inadequate. The final

treatment of the infection requires removal of the underlying contaminated prosthesis, which can weaken the wall, with a risk of secondary eventration. The use of a dermal matrix prosthesis can be of great help to obtain proper healing and a solid wall in a septic environment.

52.3 Our Series

Two studies have been made, using a personal experience of over 680 cases of unipedicled TRAM flap reconstructions done as main surgeon.

We performed 192 unipedicled TRAM flap reconstructions in our unit between October 2003 and October 2009. The analysis was done from medical records (hospitalization and outpatient) and also from questionnaires sent to patients (77% responded). At that time, we used the unipedicled TRAM flap by taking of the contralateral right rectus abdominis muscle. Preparation by ligation of inferior epigastric vessels is routinely performed at least 3 months before the completion of the TRAM flap reconstruction.

In this series, the rate of specific complications was low. As shown in Table 52.1, there were six cases of flap necrosis (3%), of which three cases were necroses greater than 5% requiring further surgery: one for an intraoperative problem already described (Fig. 52.2) and two related to the overevaluation of the intraoperative vascularization of the flap, treated by removal of areas of necrosis at 48 h, with subsequent correction of asymmetry.

As shown in Table 52.2, there were nine cases of mechanical complications of the wall (4.5%), of which six cases were bulges and three cases were abdominal hernia requiring further surgery by laparoscopy (1.5%).

Five infections of the abdominal wall, of which two of the more important required removal of the preaponeurotic mesh, had to be treated.

The loss of hemoglobin was on an average 2.5 g per 100 ml (between the preoperative samples and those obtained on the third postoperative day). Four patients had to be transfused, a rate of 2%.

Table 52.1 Cases of necrosis observed (among 192 cases)

Flap loss >25%	1 case
Flap loss of 5–25%	2 cases
Flap loss <5%	3 cases
Fat necrosis <10%	17 cases

Table 52.2 Cases of mechanical complications observed (among 192 cases)

Abdominal hernia	3 cases
Abdominal laxity	6 cases

Table 52.3 Prospective study with angioCT after preparation (among 147 cases)

Preparation by surgery, 49 cases, and by embolization, 98 cases
Poor vascularization on both sides, 11 cases, and on one side, 15 cases
Side of the harvest of the muscle: 58 homolateral, 76 contralateral, and 2 bilateral
Necrosis: cutaneous, 2 cases, and fat, 19 cases

This low rate of complications is explained by three factors:

1. The careful selection of patients.
2. The vascular preparation of the TRAM flap.
3. The careful refection of the abdominal wall.

A second prospective study was carried out between November 2012 and June 2016 on 147 patients (Table 52.3), for whom a computed tomographic angiography was systematically done after preparation (either surgically in 33% of cases or through embolization in 66% of cases). Both types of preparation have shown the same results. The preparation through embolization was simpler to carry out because the procedure could be done in the radiology department, as an outpatient.

A checkup by computed tomographic angiography was systematically done after a minimum delay of 2 weeks. This procedure permitted to show great variations in the upper epigastric revascularization, which couldn't have been shown otherwise (Fig. 52.8).

In fact, the angioCT before preparation usually only visualizes the lower epigastric vessels. The one after preparation reveals the upper epigastric vascularization. This one may be really different depending on cases, and when a pedicle is deficient, it must not be used, in order to avoid a very high necrosis risk (Fig. 52.9).

As shown in Table 52.3, we observe an important asymmetry, with a poor vascularization on one side in 15 cases and a poor revascularization on both sides in 11 cases. The side of the harvest muscle, homolateral (in 43% of cases) or contralateral side (in 56% of cases), was chosen according to the data collected by the angioCT. Six patients showing a really poor resumption of the upper epigastric vascularization were contraindicated. This procedure enabled to improve the vascular safety of the flap. The rate of cutaneous necrosis went down to 1.4% (2 cases over 138 TRAM), and the rate of fat necrosis went down to 13% (18 cases over 138 TRAM).

52.3.1 Selection of Patients

Apart from the classic contraindications for TRAM flap reconstruction, three factors should be discussed on the basis of the risk of complications related to them.

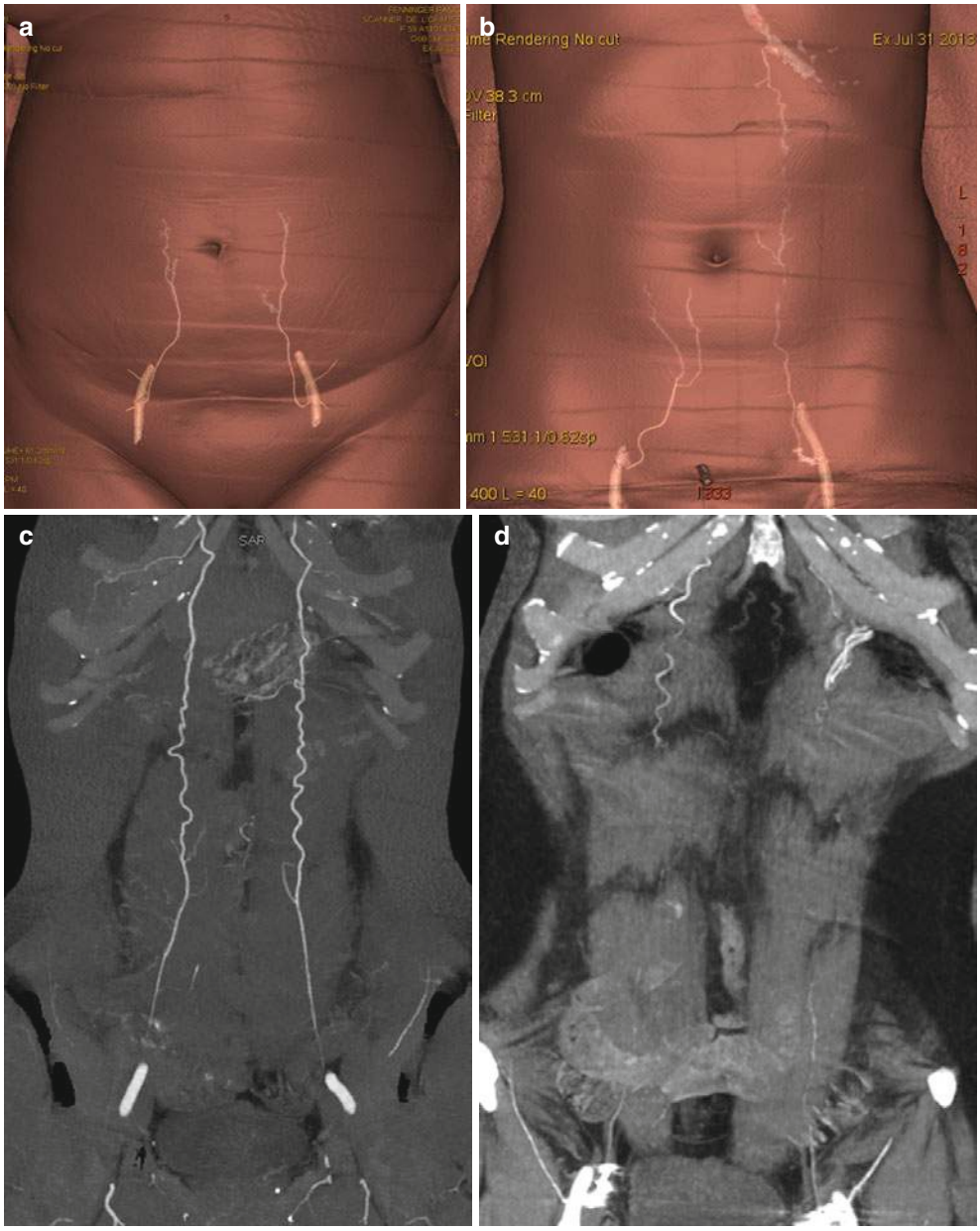

Fig. 52.8 Aspect of computed tomographic angiography. (**a**) AngioCT before preparation. (**b**) AngioCT after preparation only of left side. (**c**) AngioCT after preparation of both sides with a very good result. (**d**) AngioCT after preparation of both sides with a very poor result

52.3.1.1 Age

The average patient age was 48 years. In younger patients, the pedicled TRAM flap reconstruction is ruled out when the patient desires to become pregnant later [18]. For older patients, the theoretical upper age limit is set at 60 years but can be overturned on a case-by-case basis depending on the general condition of each patient. Our oldest patient (73 years old) had perfectly simple follow-ups.

52.3.1.2 Tobacco

We found early in our experience, and as reported throughout the literature [19], that tobacco intoxication was a major risk factor for complications owing to a decrease in the arterial supply leading to necrosis of the flap and also more complications in terms of scar abdominoplasty. These necroses can then cause infections. Because of this we operate, and this is our strict condition, only on nonsmokers or patients who stopped smoking at least 6 months before the TRAM flap reconstruction. In most cases this formal condition allows patients who want a TRAM flap reconstruction to be even more aware of the harmfulness of tobacco. Most quit smoking and are also grateful for doing so in the long run. If the patient will not stop smoking, we offer another method of reconstruction safer than a latissimus dorsi flap.

52.3.1.3 Obesity

Obesity is also a complicating factor in the type of flap necrosis, mechanical complications in the abdominal wall, and infection [20].

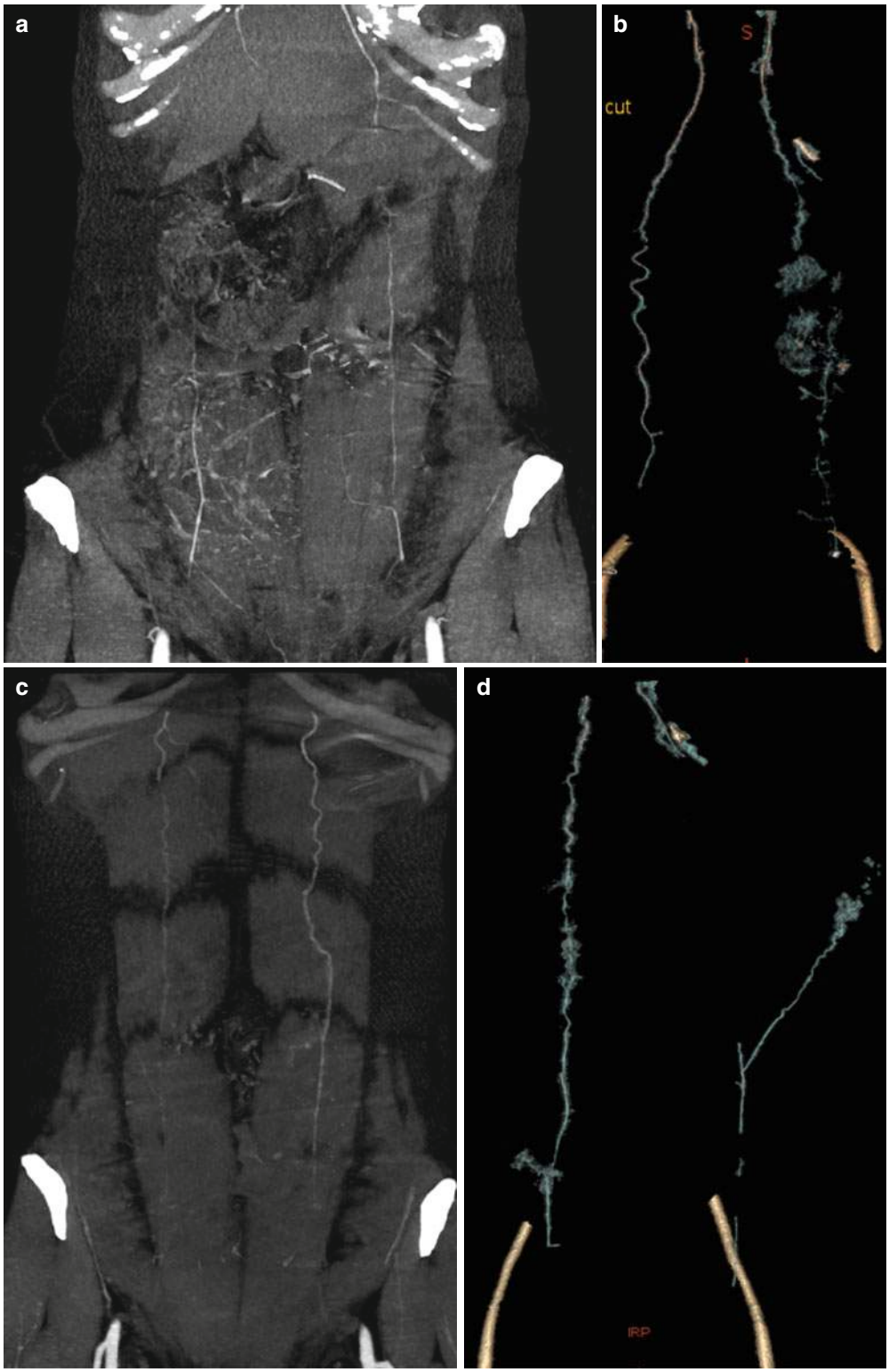

Fig. 52.9 TRAM contraindications with respect to computed tomographic angiography. (**a**) Of both sides: lack of good bilateral recovery of the superior epigastric arteries after preparation. (**b**) Of one side: lack of unilateral recovery of the superior epigastric vessels. (**c**) Another case with unilateral lack of the recovery of the superior epigastric vessels. (**d**) Revascularization through an intercostal artery

Obesity in itself is a risk factor for vascular complications. Too great a thickness of the flap results in a lower skin vascularization with an increased risk of necrosis after surgery. It is also often associated with metabolic risk of poor vascularization (high cholesterol level, diabetes, etc.), promoting arthritis, thus further increasing the risk of necrosis. Obesity also increases the mechanical complications favoring an abdominal hernia or laxity.

For these different reasons, we do not perform TRAM flap interventions in patients with a BMI higher than 30. By properly explaining these risks, and also with the help of a dietician, we can in most cases help these patients to lose weight to get to a BMI under 30. In our series, the average BMI was 24, with a range from 20 to 31.

52.3.2 Vascular Preparation (Delayed TRAM Flap Reconstruction)

Early in our experience, we observed, as have others [21], unexplained flap necrosis occurring without any risk factor. Following the first publications on delayed TRAM flap reconstruction [22, 23], and researching a method to make the results less random, we gradually began a vascular preparation in our patients. Faced with the obvious clinical improvement of the vascularization of the flap, this preparation has become a routine and was performed in the same way in all patients in the series studied. The goal is to improve the blood supply of the future flap, in particular in segments III and IV opposed to the pedicle muscle as in the classification of Ninkovic [24], segment II being adjacent to outer segment I, which remains the part of flap best vascularized, in front of the preserved pedicle muscle.

Until the end of June 2012, the procedure was done bilaterally with the patient under general anesthesia. The technique is the same on both sides. After an incision in the lateropubian fold, leaving a very discreet scar, the superficial inferior epigastric vessels which vascularize some of segments II and IV of the flap are reached at their origin and are cut between ligatures. These vessels are inconstant (especially the artery), but they are easily found, when they exist, at the bottom or at the external part of the incision. We then open the aponeurosis of the external abdominal oblique muscle in the direction of its fibers at the external inguinal ring. The internal inguinal ring is reached, and the deep inferior epigastric vessels, found after a short incision in the fascia transversalis, are linked (the vein is always present lower and below the artery).

A minimum period of 3 months is required before doing the TRAM flap reconstruction, giving time for a good healing of the preparation before the TRAM. This intervention occurred at the same time as a total mastectomy in 19% of cases and a contralateral reduction plasty in 15% of cases, thus avoiding an additional procedure.

Since 2012, we offer the patients the possibility to do this preparation through embolization. This procedure is done under local anesthesia, as an outpatient, and is very well accepted by our patients, and today most of our preparations are done this way. The angioCT is made after a minimum delay of 15 days. This enabled us to reduce the delay between preparation and TRAM and to offer more immediate reconstructions with TRAM.

52.3.3 Wall Repair

This has to be meticulous. The fascia of the rectus abdominis muscle is preserved as much as possible to reduce sidewall tension, which explains much of the postoperative pain. We leave a strip of 5 mm in the region above the umbilicus in the middle of the right rectus abdominis muscle, which is removed in its entirety. In the infraumbilical region, the quality of perforating vessels is evaluated beforehand with an angioCT, as well as during the initial dissection of the flap, which is done down to the centerline on the opposite side to the removed muscle. If these perforating vessels are numerous and consistent, especially the perforating vessels of the periumbilical and central region, the perforating vessels of the outermost side of the sample can be linked, thus preserving more fascia. Otherwise these vessels must be maintained, resulting in a higher secondary tension of the fascia in the subumbilical fascia.

A flexible polyester mesh, Parietex, is always anchored in the sheath of the rectus abdominis muscle to improve the wall tension in a longitudinal direction (to facilitate subsequent movements of flexion of the torso). The fascia of the rectus abdominis muscle is then sutured with slowly absorbable thread. Plication of the contralateral wall is performed to improve symmetry of the wall and bring the umbilicus in a more central position. Depending on the strength of the fascial suture (variable from one patient to another depending on the quality of tissue and the size of the sample taken from the fascial flap), a second mesh can be put in place in the prefascia to reduce the risk of hernia and later bulge. In our series, this was necessary in 59% of cases, and among those the mesh was placed over the entire surface of the wall in 78% of cases, only in the epigastric region in 19% of cases, and only in the infraumbilical region in 3% of cases.

52.4 Discussion

52.4.1 Delayed TRAM Flap Reconstruction

The effectiveness of the preparation is a matter of discussion. It is criticized because it involves a supplemental intervention and can cause local complications, making reconstruction more complicated later. For some it is remarkably effective to obtain a quality of vascularization of the flap similar to that of a free TRAM flap [25].

In our series, preparation has reduced our rate of partial necrosis of 8% before using this technique to 3% and later to 1.4% since the preparation is followed by an angioCT. There is an excellent sign of the indirect contribution of the preparation, during surgery, i.e., the existence of an inferior epigastric pedicle pulsatility with the flow from the superior epigastric vessels, after section of the inferior epigastric pedicle.

Excepted through the mean of a prospective study, it is very difficult to demonstrate the value of preparation because the performance criteria are mainly clinical. However, such a study is hard to conduct when one is convinced of the efficiency of preparation, because, when one is sure, one does not want to penalize the patient for whom the preparation is not done because of the framework of a study. When a classic pedicled TRAM flap reconstruction is performed, there is very good blood supply to segment I, quite good blood supply to segment II, and adequate blood supply to segment III of the flap. After preparation, the blood supply of vascular segments I and II is very good, that of segment III is quite good, and that of segment IV is inconstant [26]. In our series the entire TRAM flap including segment IV of the TRAM flap has been or could have been (without that being necessary) kept partially or completely in about 20% of cases, which is particularly interesting, mainly in flaps of moderate volume, thus enabling to increase the indications of unipedicled TRAM flap. When the volume of the TRAM flap is not sufficient, complementary lipofilling can be proposed [27].

The advantage of the surgical method we use is its simplicity for any surgeon, and there is minimal scarring, compared with a direct inguinal incision. The remote location of the incision made, relative to the incision made at the future lower flap, avoids local complications, which are the cause of fibrous scars in the future flap and also increase the risk of postoperative wall infection. This is also why we have not opted for an associated skin delay like others have [28].

One disadvantage of delayed TRAM flap reconstruction is that it requires an additional intervention. This can be avoided by making the preparations at the same time as the mastectomy or at the same time as contralateral plastic breast surgery is performed. Given the delay of 3 months that we respect between preparation and reconstruction, it is not feasible in the case of immediate TRAM flap reconstruction except for a preventive mastectomy.

Some practice delayed TRAM flap reconstruction by a laparoscopic approach [29]. After trying this method, we have not adopted it, because research of inferior epigastric vessels has sometimes been difficult, with a bleeding risk, which may be responsible for specific complications and because this technique does not allow ligation of superficial inferior epigastric vessels.

The method with embolization, which we currently practice, benefits the patient as it is simpler and leaves no additional scar [30, 31]. Although the embolization only concerns the deep lower epigastric artery, our experience hasn't shown any difference between the results of embolization and those of the surgical preparation that binds additionally the epigastric deep vein and the superficial epigastric vessels.

52.4.2 Abdominal Wall

The TRAM flap, whatever the technique, can improve the aesthetic appearance of the abdomen. In our series, 75% of patients were satisfied with the cosmetic result of the abdominoplasty with an improvement compared with their previous situation. The consequences of a unipedicled TRAM flap at the abdominal wall are both mechanical and functional.

The risk of mechanical complication in our series was small compared with the risk reported in the literature. This low rate of parietal complications can be partly explained by the relatively short time period studied and especially by the introduction of a mesh when the fascia closure is fragile. This is easily found during surgery where there is significant tension of the suture and where the sutures tend to tear the tissue. The disadvantage of this preaponeurotic mesh is the risk of compromising the treatment of a potential postoperative wall infection. In borderline cases, in front of a major abdominal skin tension with subsequent risk of dehiscence, or if poor vascularization of the skin of the abdomen is found, this risk must be taken into account by avoiding, if possible, putting in a preaponeurotic mesh.

Compared with the bipedicled TRAM flap, where use of preaponeurotic mesh is mandatory, the parietal consequences are much lower with the unipedicled TRAM flap [16]. The risk of eventration and functional consequences (going back to normal activity and residual discomfort) is much lower. The quality of the blood supply to the bipedicled TRAM flap, however, is better, which makes this technique more reliable for some, especially in borderline cases (patients who are moderate smokers, or obese patients, or reconstruction of a large volume). Because of the rigorous selection of patients and the preparation, the lack of blood supply was detrimental in our series in only three cases (1.5%) of partial necrosis of more than 5%, making

performing a bipedicled TRAM flap reconstruction unnecessary outside bilateral reconstructions.

Compared with the free TRAM flap reconstruction, preparation seems to result in the same level of vascularization. The risk of parietal complications is essentially the same after a unipedicled TRAM flap reconstruction [2]. The delayed TRAM flap reconstruction is a technique that is much simpler than microsurgery and can be performed by all surgeons. It seems to me preferable considering the duration of the intervention and the risk of total failure with the free TRAM flap, given that preparation seems to ensure the same quality vascularization.

With DIEP and SIEA flaps, without taking the muscle, the risk of complete necrosis is higher than with the unipedicled TRAM flap, ranging from 2% to 7% depending on the experience of the surgeons and the centers where they work, whereas this risk is close to zero after unipedicled TRAM flap. Although for DIEP flap reconstruction the risk of partial necrosis seems to be the same as that after delayed TRAM flap reconstruction without angioCT, the risk of fat necrosis is higher in some series [12, 13]. And the risk of partial skin necrosis seems higher than after preparation and angioCT. In contrast, the functional consequences are clearly less important in the abdominal wall [5].

In our series the functional aspect has been studied through answers to the questionnaire:

- Resuming a professional life (if not physical work) occurred on average 2 months after the unipedicled TRAM flap reconstruction.
- Sports activities were resumed after 5 months for 70% of patients who exercised before surgery; most of the other 30% had no athletic activity.
- Only two patients, i.e., 1%, later regretted having unipedicled TRAM flap reconstruction because of their inability to resume the active sports activities they had previously practiced.
- For 40% of patients, there were, however, some physical activities that were no longer feasible after the procedure.
- Residual discomfort was significant for 16% of patients. However, 95% of patients were satisfied or very satisfied with the reconstruction, thus putting the residual functional discomfort in perspective.

52.5 Conclusion

If an adequate treatment is to be implemented before any complication of unipedicled TRAM flap reconstruction, the best treatment is prevention.

The skin or fat necrosis is the main complication. Preparation followed by an angioCT brings a lot of security to unipedicled TRAM flap reconstruction with a risk of partial skin necrosis brought down to 1.4% and a risk of fat necrosis brought down to *y*%. Under those conditions, the unipedicled TRAM after preparation and angioCT seems to us safer than DIEP, let alone SIEP.

The disadvantage of surgical preparation is that it requires an additional operation. It can be avoided by doing the surgical preparation in the same time as the mastectomy or jointly with an opposite breast plastic surgery that could be necessary. The preparation through embolization simplifies the procedure that can then be done under local anesthesia, leaving no scar. Its efficiency is equal to the one of surgical preparation.

Lipofilling is the ideal solution to later correct any sequels of necrosis. Although careful closure of the abdominal wall minimizes the risk of parietal complications after a pedicled TRAM flap reconstruction, the DIEP and SIEA flaps need to be offered preferentially to patients needing the integrity of the abdominal wall: as in young women who can become pregnant later, very athletic women, and those who must carry heavy loads in their professional activities. In this situation, it is best to refer the patient to a center experienced in using this technique regularly rather than one that uses it occasionally.

In summary, unipedicled TRAM flap reconstruction, after a rigorous selection of patients, routine vascular preparation followed by angioCT, and reconstruction of the wall proper are techniques within the reach of many oncoplastic surgeons and are very reliable and suitable for most patients seeking breast reconstruction by means of a TRAM flap.

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Part VI

Refinements After Breast Reconstruction

Treatment and Care of the Scars in Breast Reconstruction

53

Christina Garusi and Visnu Lohsiriwat

53.1 Introduction

Immediate breast reconstruction or oncoplastic technique has been widely performed as an integral step in breast cancer surgery [1, 2]. The contralateral breast can be operated for symmetrical procedure or an exploration step for tissue diagnosis [3]. Besides the general consideration and management of scar tissue, breast cancer surgery-related scar also particularly depends on location of scar (breast or donor site of autologous tissue), timing of scar (immediate or delay), adjuvant therapy given to individual cancer patient (e.g. radiation and chemotherapy) and cancer prognosis. In this chapter, we would like to discuss the specific characteristic and problem of each scar. We mainly categorized scar with regard to its location of primary incision.

53.2 Location

53.2.1 Breast

Breast-related scars included both ipsilateral and contralateral breast surgery. The reason is that the contralateral scar pattern can also be categorized the same as the ipsilateral one. The incisions which frequently relate to breast conservative treatment (BCT) or total mastectomy can be divided.

53.2.1.1 Breast Conservative Treatment

- **Without Oncoplastic Technique**
  This refers to incision which uses in general tumorectomy, lumpectomy or wide excision. It usually lies corresponding to the location and quadrant of primary tumour. The overlying skin may or may not be removed depending on the distance of the tumour to the skin and the technique of the surgeon. The incision can be radial, curvilinear or circumareolar incision. The incision should be place with respect to the aesthetic unit of the breast [4].
- **With Oncoplastic Technique**
  Incision for BCT with oncoplastic procedure usually resembles to those of mastopexy or breast reduction procedure. The most common use incisions are periareolar incision, vertical incision and inverted T incision.
  Management of these scars usually has an effect from radiation therapy which is almost always integrated in BCT. However, radiation probably plays a positive role for scar remodelling and formation [5]. Despite resulting in more scars from oncoplastic technique, it makes more symmetry and better aesthetic result to the patient. Moreover if the incision for oncoplastic is well planned, it can be hidden in the less visible area. Another special consideration of scar management for BCT is when the scar develops contracture. It may lead to nipple malposition and unpleasant configuration of the entire preserved breast. Especially the contracture occurs from the scar tissue in the breast itself.

53.2.1.2 Total Mastectomy

- **Skin-Sparing Mastectomy (SSM)**
- The incisions usually performed for SSM are elliptical incision, racquet incision or circumareolar incision. The breast mould is the immediate reconstruction by expander prosthesis or autogenous base. Scar from SSM can be revised during the secondary procedure of nipple areolar complex (NAC) reconstruction.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_53

- **Nipple-Sparing Mastectomy (NSM)**
  The incisions which are recommended by the author's institute are supero-lateral radial incision, infero-lateral radial incision, superior circumareolar incision and peri-areolar incisions [6]. Regardless of the incision type, the unique concern of this procedure is the location of the NAC. Scar from radial incision can displace the NAC position towards the vector of scar contracture.
- **Scar After Conventional Mastectomy or Delay Mastectomy Scar**
  The scar from this category tends to have least aesthetic outcome. The scar usually attaches to the chest wall and lacks adjacent healthy skin and subcutaneous tissue, especially after external radiotherapy.

53.2.1.3 NAC Area

We should pay special attention to the scar in NAC area because it can affect the final outcome of the reconstruction. The scar in this area may distort the disc-shaped areolar and nipple projection.

53.2.2 Scar of Autologous Donor Site

In this chapter we would like to mention the scar in other locations other than the breast because these are common donor site for breast reconstruction.

53.2.2.1 From Abdominal Flap

Scar in this area is intended to cover under the bikini lines. The scar here is relatively long and may have the possible unpleasant appearance from abdominal bulging or poor umbilical reconstruction technique.

53.2.2.2 From Latissimus Dorsi Flap

Even scar in this area is hidden behind the back, but it probably causes impaired shoulder movement. If possible, the scar in this area should be designed in transverse plane and possible to hide under brassiere coverage [7].

53.2.2.3 Others

Gluteal flap and gracilis flap are also indicated in breast reconstruction. The scar from gracilis flap is located in the hidden area. But the scar in this area can cause disfiguration of the genital labia and upper thigh. Gluteal flap scar complication can also cause a postural discomfort in sitting or lying position, and the incision should be initially placed in gluteal crease.

53.3 Method of Scar Improvement

53.3.1 Surgery

Surgical treatments offered to the patient include scar revision, partial excision or wide excision. Sometimes the scar revision procedure can be done simultaneously with other refining procedures such as prosthesis substitution, NAC reconstruction or lipofilling. There is an option to combine the surgery with other methods such as corticosteroid injection, silicone gel sheet application or pressure compression in postoperative course as well.

53.3.2 Corticosteroid Injection

Injection of corticosteroid can be performed in any part of the breast and donor sites. The result is quite promising but may require several injections. In case of over-injection, the scar may turn to scar hypotrophy and cause difficult sequelae such as telangiectasias or depigmentation. The drawback of this method includes systemic effect from steroid especially when it relates to the menstruation and hormonal status. There are clinical trials of topical steroid cream, but the absorption is limited, and the efficacy is not comparable as in intralesional injection (Figs. 53.1, 53.2, 53.3, and 53.4).

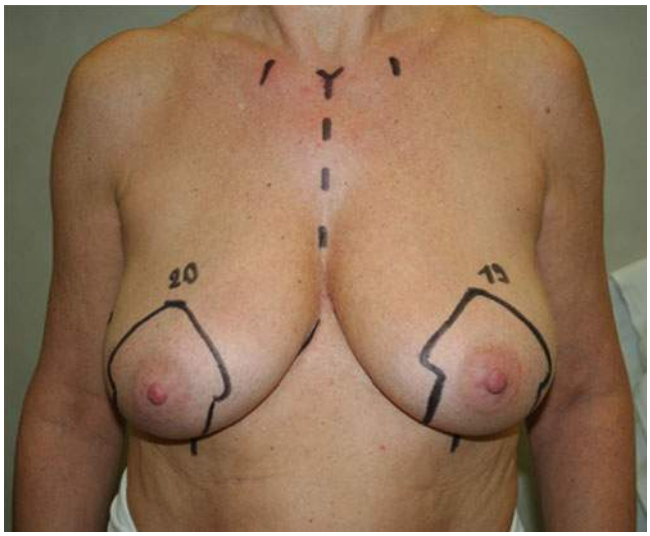

Fig. 53.1 Preoperative view of the patient before inferior right breast quadrantectomy, intraoperative RT (IORT) + bilateral reshaping

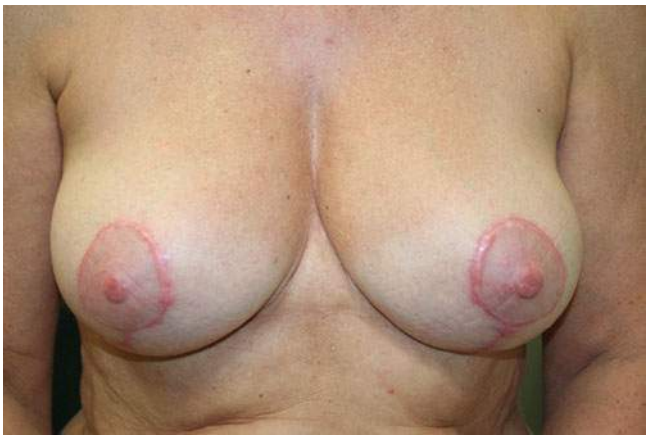

Fig. 53.2 Result at 7 months after the surgery with bilateral hypertrophic scars

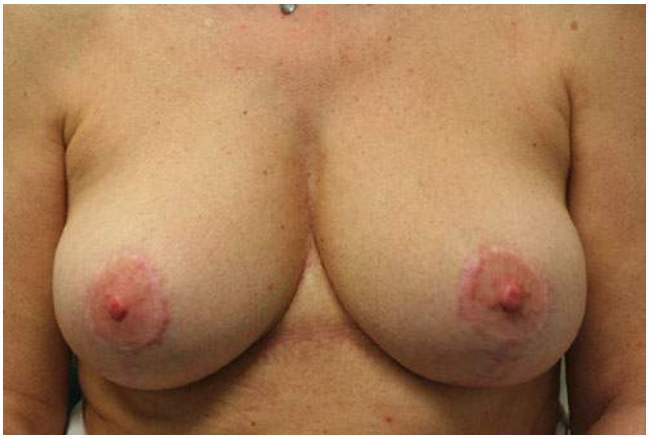

Fig. 53.3 Result at 2 years after three sessions of cortisone intralesional injections

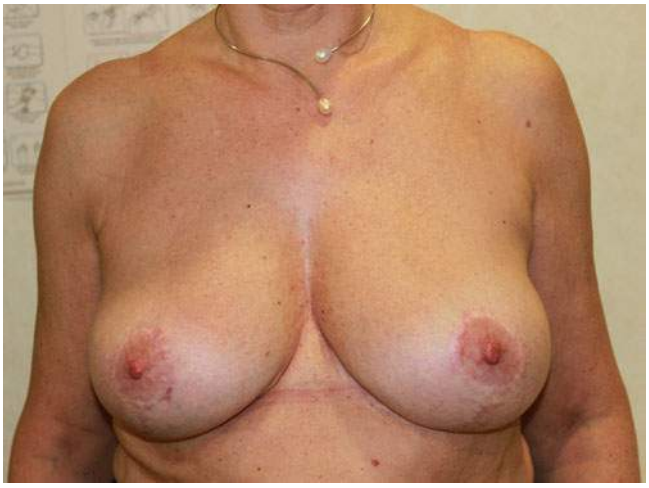

Fig. 53.4 Final result at 4 years

53.3.3 Silicone Gel Sheet

Applying silicone gel sheet is the simple method and preferred by some patients. It can be applied in the area wherein it is difficult to do pressure compression therapy such as the breast, abdomen and back. However, it takes a long time to achieve the goal and mostly to prevent the scar, so it may not satisfy all patients' expectation. There were trials to compare the formula of various types of the silicone sheet and also formulation of silicone oil gel; however, these trials had limited evidence and were too weak to draw the conclusion.

53.3.4 Pressure Compression

It has been used for scar treatment for decades; however, one of the limitations is how to maintain the constant optimum pressure on the treatment site. Pressure garment or medical kit is mostly preferable for burn and scar contracture patient, but it is rarely recommended in breast cancer surgical scar patient.

53.3.5 Other Techniques

There are other several methods for scar treatment and preventions, for example, radiation therapy, laser abrasion, cryotherapy, 5-fluorouracil injection, administration of antitumor or immunosuppressive agent, etc. [8, 9]. However, the need for machine or instrument, the possibility of interfering adjuvant cancer treatment and the surgeons' preference make these latter methods less popular in our institute.

53.4 IEO Experience

Hypertrophic scar has been treated surgically followed by brachytherapy according to two different techniques.

A total group of 51 patients have been included in the database with breast scar, and in the first period, LDR (with isolation of the patient) was used in 31 patients, while recently a group of 20 patients have been treated with HRD (on DH bases without isolation).

Recurrence rate were 8 (15.7%) with global aesthetic result considered good in 58% of the cases (Figs. 53.5 and 53.6).

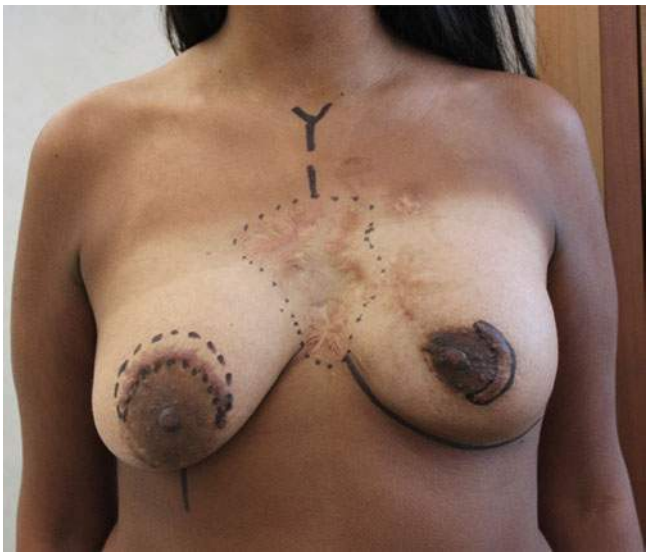

Fig. 53.5 Preoperative result with bilateral keloid scars

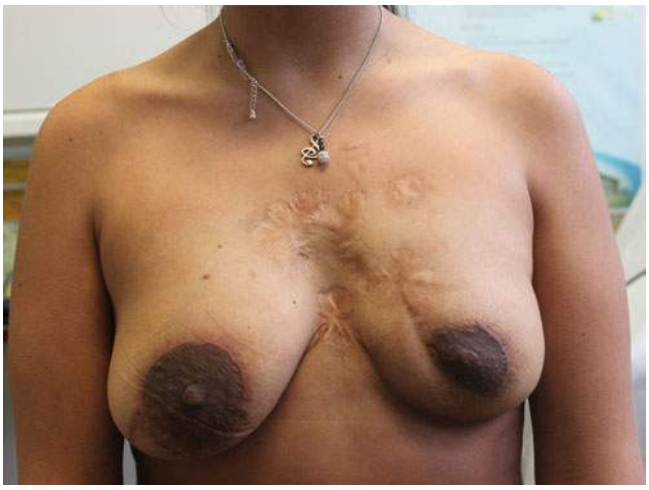

Fig. 53.6 Result 3 months after scar revision and brachytherapy treatment

53.5 Conclusion and Future Trends

In conclusion, several methods even single or combination can be used for scar treatment and prevention. The position and risk of scar development should be planned ahead of making the choice of incision. Biology of cancer and the postoperative adjuvant related to breast cancer treatment are obligated to be considered when offering scar management. In the future, genetic therapy and tissue engineering may play roles in primary scar management, treatment and prevention, which may lead the clinician and patient to achieve maximum satisfactions.

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Fat Grafting in Breast Reconstruction

54

Mario Rietjens, Visnu Lohsiriwat, Cicero Urban, and Andrea Manconi

54.1 Introduction

Lipofilling is an autologous technique used in breast reconstruction. It is also known as "fat transfer," "lipotransfer," "fat injection," or "fat transplantation," as well as many other terminologies. The procedure consists of two major steps which are liposuction and lipoinjection of the patient's own fat tissue and other tissue elements, either with or without specific preparation processes before lipoinjection. It is considered as a minimally invasive procedure which can be effectively performed under local or general anesthesia.

This technique was initially introduced for aesthetic and scar correction purposes especially for the face and hands [1–6]. Recently, it has also been widely applied for breast indications including micromastia, postaugmentation deformity, tuberous breast, Poland's syndrome, postlumpectomy deformity, postmastectomy deformity, deficits caused by conservative treatment or reconstruction with implants and/or flaps, damaged tissue from radiotherapy, and nipple reconstruction augmentation [7].

Despite various indications related to breast reconstruction after breast cancer treatment, there are different strategies of performing lipofilling procedures in different countries without international consensus [8]. Up to now, the literature provided evidence of only expert experience and clinical series trying to demonstrate the oncological safety and efficacy of lipofilling for the breast cancer patient [9–12]. So, in this chapter it will be presented the technique, indications, and limits of this procedure.

54.2 Biology of the Lipoaspirated Specimen

The fat specimen when injected into the breast is not just a physical filler or framework but contains significant number of cells which can survive and function. Viable and dead adipocytes, adipose-derived stromal cell (ASCs), vascular endothelial cells, fibroblasts, hematopoietic cells, blood cells, and other cells can be found in the lipoaspirated specimen [13, 14]. The laboratory research from the European Institute of Oncology in Milan also found that adipose tissue is a very rich reservoir of vascular progenitor cells. Current literature provides data on the endocrine, paracrine, and autocrine activities of the transplanted fat tissues. It is also interesting that in the future of medical bioengineering, stem cell culture and expansion may alter the composition and biology of the fat injection specimen. There is a specific chapter about stem cell biology in this book.

54.3 Fat Grafting and Oncological Concern

When lipofilling was introduced for scar correction and aesthetic indications, there was rarely a question of cancer risk or cancer incidence. On the other hand, the concern for oncological safety becomes obviously important when performing lipofilling for the breast cancer patient. Theoretically, the "tumor-stroma interaction" can potentially induce cancer reappearance by "fueling" dormant breast cancer cells in the tumor bed. Previous experimental findings at the European Institute of Oncology in Milan also suggested that purified

Electronic Supplementary Material The online version of this chapter (doi:10.1007/978-3-319-62927-8_54) contains supplementary material, which is available to authorized users.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_54

progenitor cells from liposuction specimen can stimulate angiogenesis, cell growth, and metastasis in animal models. No study on the effects of lipotransfer on human cancer breast cells in vivo proved it [10].

In our clinical experience [8, 9, 11, 12], we demonstrated that there is no increased risk of local recurrence in the invasive breast cancer patient who is treated with lipofilling. However, we recommend close oncological follow-up in this particular group, especially in the carcinoma in situ patient. If abnormal clinical or radiological signs are detected during follow-up, prompt pathological examination is highly recommended. Until now, we propose surgeons who perform lipofilling to do a complete preoperative oncological examination and create a database registration of fat grafting patients. In Curitiba, at Our Lady of Grace Hospital Breast Unit, we routinely perform MRI before lipofilling in all the patients. There is a specific chapter about it in this book.

54.4 Surgical Technique

54.4.1 Donor Site

The procedure can be performed under local or general anesthesia, depending on the patient's clinical condition and risks. Local anesthesia is our preference, while general anesthesia is recommended in cases of harvesting a large amount of fat tissue or combined multiple procedures. The preferred donor sites are the abdomen and flank areas, outer thighs, buttocks, inner thighs, and knees. The donor site selection is based on excess fat tissue in the area and then an amount of fat that can be removed without aesthetic damage of the donor site. The selected donor site is infiltrated with Klein's solution which consists of 1 cc of epinephrine diluted in 500 cc of 0.001% lactate ringer solution (LRS). Mepivacaine 2% is added in the solution if lipofilling under local anesthesia is indicated (Fig. 54.1).

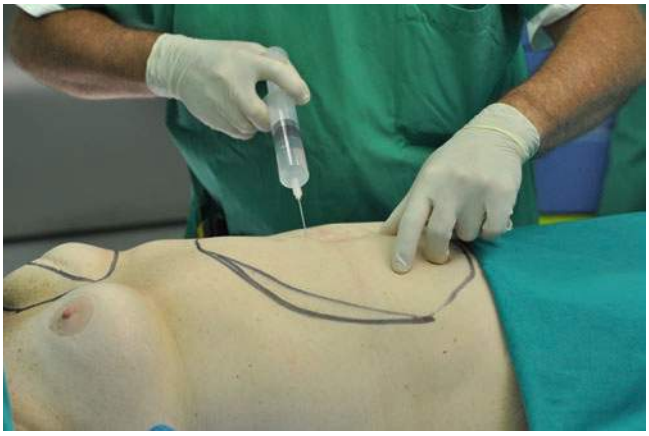

Fig. 54.1 Infiltrating the donor site with Klein solution

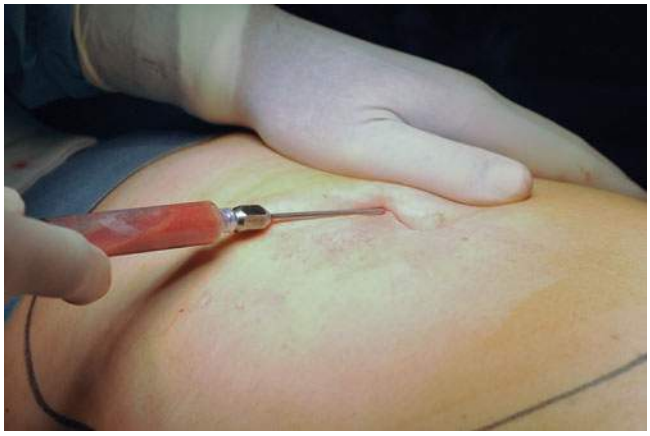

Fig. 54.2 Harvesting the fat tissue with a Coleman cannula

The amount of solution injected is double the volume of pre-estimated fat tissue requirement. The whole procedure of fat harvesting and "lipofilling" is performed according to Coleman's technique [15]. After the injection of the diluted solution, a two-hole, 3-mm diameter Coleman's cannula with a blunt tip attached to a 10-cc Luer-Lock syringe is inserted through the small incision. A combination of slight negative pressure and the curetting action of the cannula through the tissues allows fat harvesting [2] (Fig. 54.2). The method of liposuction with different machine models or manual syringe and different size and number of cannula holes is not proven to affect fat cell survival. However, the "nontraumatic" blunt cannula technique is preferred rather than a sharp cannula technique [16–19]. Other harvesting techniques such as water-assisted liposuction or body-jet system [20], Cytori Therapeutics' Celution System [21], and Adivive Lipokit system are also made available by many companies. There is an issue between open and closed system techniques, but there is no definitive conclusion in the differences of fat cell survival and clinical results in each group. At the end of the lipoaspiration procedure, the access site of the cannula is sutured with fine absorbable material, and a pressure dressing is applied.

54.4.2 Fat Processing Techniques

There are different methods to process and purify the fat before grafting. The choice depends on several factors such as surgeon's preference, costs, higher concentration of adipocyte-derived stems cells, volume requirement, and injection. Different techniques can be used:

1. No preparation—This no-touch technique allows surgeons to inject the lipoaspirate fat to the recipient site without any

preparation [22]. The advantages are that the specimen remains in a closed system and allows shorter operative time compared to other techniques. However, it is suitable only when performing lipoinjection for small volume requirements, for example, a few cubic centimeters, to make a reconstructed nipple projection or a small linear scar correction. The disadvantage is the increase risk of calcification and cyst formation, because the oil is not eliminated.

2. Mechanical preparation (centrifugation, decantation, or washing technique)—The purpose of this technique is to remove the cell debris, serum, tumescence solution, and oily component from the adipocytes and its derivative cells. Centrifugation is the current technique currently used by the authors [11, 12]. In our setting, the fat is centrifuged at 3000 rpm for 3 min until the oily and fluid parts are separated from adipose tissue (Fig. 54.3). The speed and duration of the centrifugation have no effect on adipocyte survival, but higher force seems to bebetter to clean off oil and cell debris than lower centrifugal forces as was demonstrated by some authors [23]. Other authors have preferred lower speeds and duration to avoid adipocyte damage [24] (Figs. 54.4 and 54.5). After removal of the top (oily) layer and the bottom (fluid) layer, the middle (cellular) layer which contains the adipocyte, endothelial cells, and mesenchymal stem cells is immediately transferred to a 1-cc Luer-Lock syringe and prepared for injection [11, 12, 25].
3. Other methods of preparation (enzymatical and biological preparation)—Some scientists try to enhance the fat graft survival with beta-fibroblast growth factor [26]. Some surgeons divide the lipoaspirate specimen in half and prepare each half separately before putting them together and performing lipoinjection. An example of this technique is called cell-assisted lipotransfer (CAL). This process increases adipose-derived stromal cells (ASCs) before fat injection [27, 28]. Cytori Therapeutics' Celution System also prepares the fat by separation of two equal parts of lipoaspirate specimen before mixing them together [21].

Fig. 54.3 Medical device for fat centrifugation

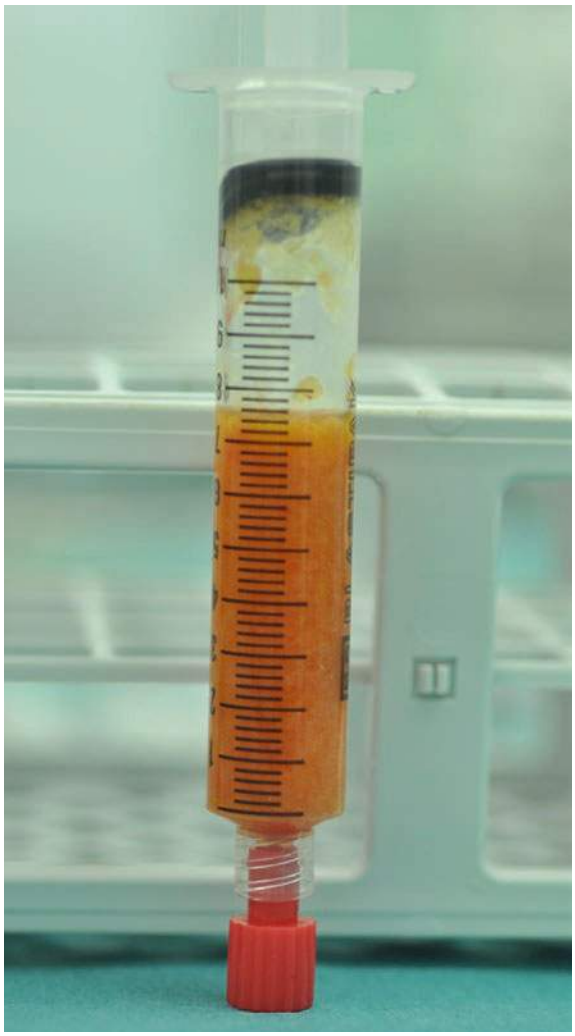

Fig. 54.4 Specimen before centrifugation

Fig. 54.5 Specimen after centrifugation

54.4.3 Recipient Site

The recipient site is prepared by preoperative marking and estimating the area which is required for lipoinjection. A proper local anesthetic agent is injected around the defect prior to the purified fat injection if the procedure is carried out under local anesthesia. Prepared cellular component is then injected into the defect area through a blunt Coleman's cannula. Retrograde injection with thin-layer, multiple-tunnel, and fan or cylindrical shape technique is performed (Fig. 54.6). We avoid placing the fat as an excessive deposit, which may result in liponecrosis and graft loss. We judge the amount of fat needed to be grafted in each individual case based on the tissue quality and shape and size of the defect. If the anatomical site allows, we try to avoid intraparenchymal injection. In the case of tight fibrosis from a surgical scar or irradiated tissue, a sharp needle is inserted to break up the fibrotic scar and create a space for lipoinjection (Fig. 54.7). In general, we overcorrect the volume deficit by approximately 30–40% depending on the reconstructive indication and recipient site tissue quality. After finishing the injection, the entrance site of the injection cannula is sutured in a conventional fashion.

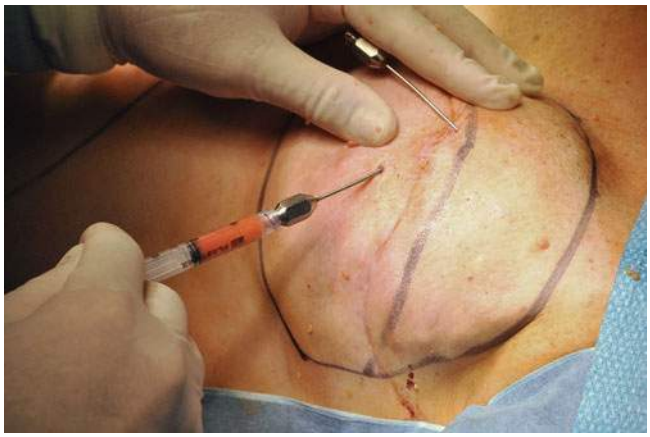

Fig. 54.6 Fat injection in the recipient site

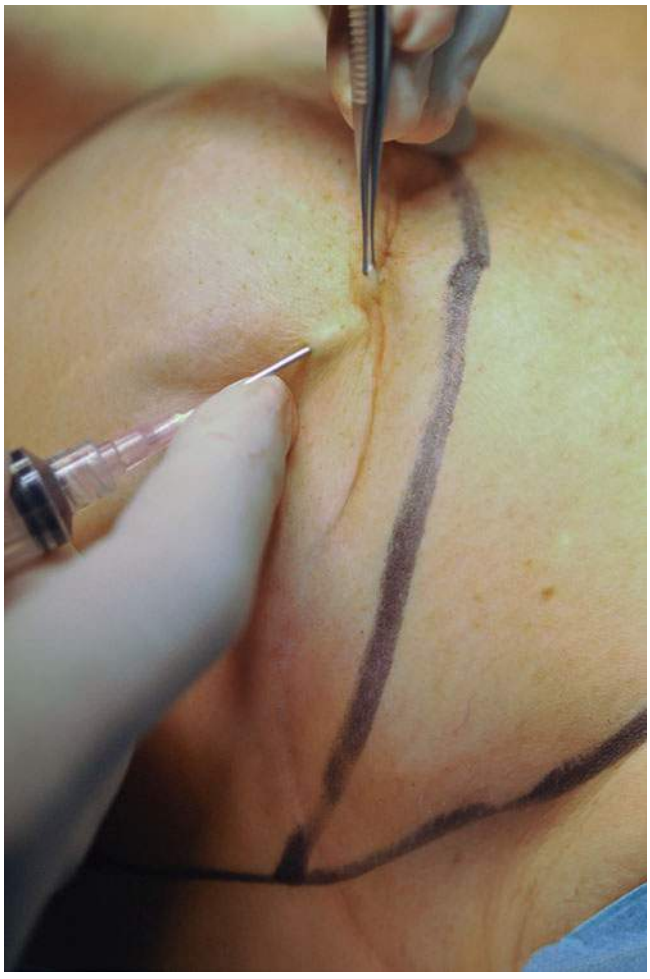

Fig. 54.7 A sharp needle is used to release fibrotic scars

Some authors have proposed the use of an external suction machine on the donor site to produce subcutaneous tissue expansion and allow for a larger volume of fat that can be harvested and injected. This machine (the Brava

system) is not comfortable for patients and needs to be used during the night 1 month before and after the procedure [29].

54.5 Indications

54.5.1 Defects After Breast-Conserving Surgery

A patient with BCT usually receives conventional radiotherapy and therefore leads to difficulty in selecting a reconstructive procedure. However, lipofilling offers a simple and reliable method which does not increase the complication rates in the BCT patient.

- Immediate reconstruction after BCT—Lipofilling can be used for reshaping of the breast immediately after conservative surgery as a sole procedure or in combination with other oncoplastic procedures. A good indication would be in the case of a small breast and an upper quadrant tumor. A quadrantectomy can be performed, and the defect can be closed with glandular sutures. The defect created by these sutures can be repaired by fat grafting in the subcutaneous space [30]. Circumcavity injection is recommended, and intracavity injection should be avoided.
- Delayed reconstruction after BCT—This is one of the main indications for lipofilling in practice. It is possible to correct the defects and also increase the skin quality after radiotherapy damage. Depending on the defect dimensions, the correction can be done with one or more sessions. The procedure can be performed under local anesthesia in case of a monolateral procedure and under general anesthesia in cases that need a contralateral procedure, as a reduction mammaplasty (Figs. 54.8 and 54.9).

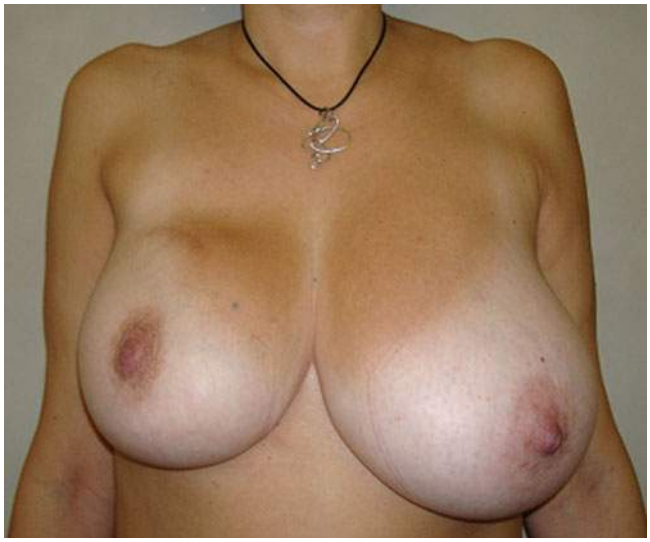

Fig. 54.8 Patient with huge asymmetry after right breast conservative surgery and radiotherapy

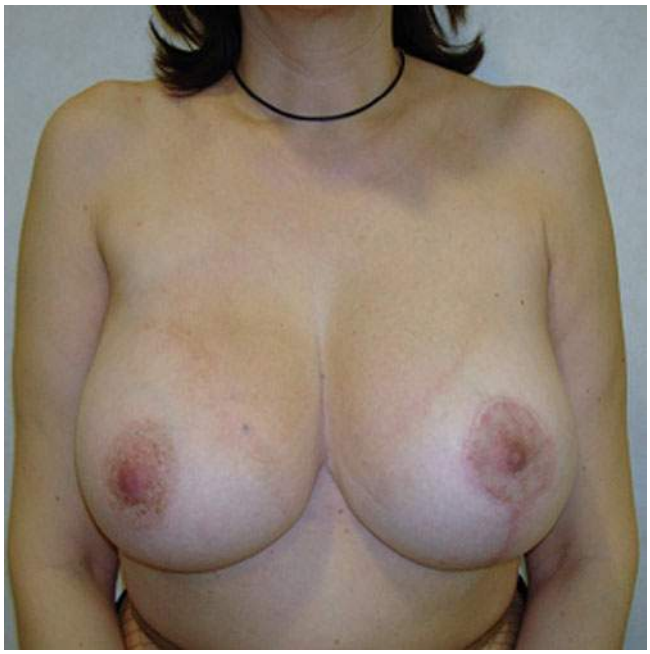

Fig. 54.9 Postoperative view after 250 cm^3 of fat grafting in the *right side* and *left* reduction mammaplasty

54.5.2 Defects After Mastectomy

Lipofilling is actually one of the main techniques in breast reconstruction after mastectomy, and it is indicated in the following situations:

- Immediate breast reconstruction: Lipofilling in immediate reconstruction is very difficult due to the lack of a surgical plane for fat implantation. In special cases with a small breast and huge flank lipodystrophy, an implant can be positioned at the same time as the mastectomy. After complete expansion, the reconstructive steps start with deflation of the expander and fat grafting to twice *the* volume deflated. After two or three fat grafting sessions, the expander can be removed and the nipple and areola reconstructed to achieve the final result without implant (Figs. 54.10, 54.11, and 54.12).
- Secondary total breast reconstruction using lipofilling as primary reconstructive procedure: This is still an early procedure done in a few surgical centers and usually performed with pre-expansion or vacuum systems [29, 31–33]. It allows

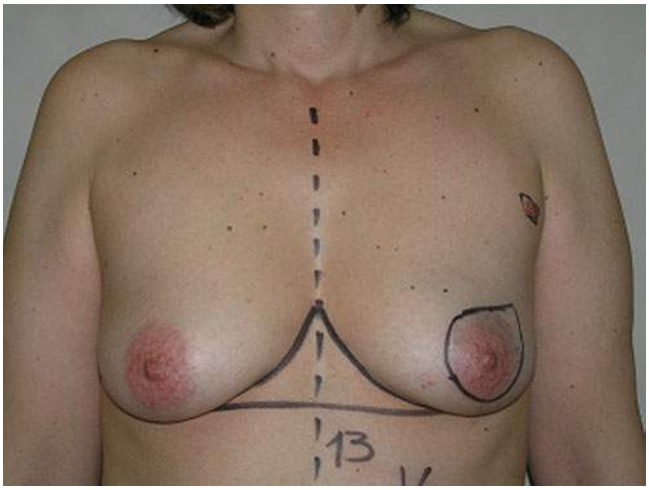

Fig. 54.10 Preoperative view before mastectomy and immediate breast reconstruction with a tissue expander

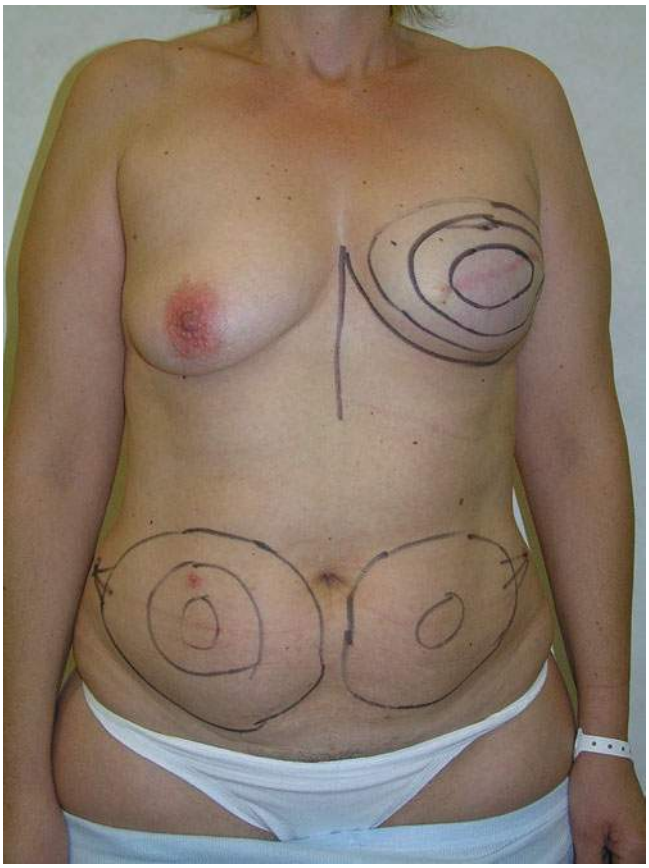

Fig. 54.11 Preoperative view before 280 cm^3 of fat grafting and deflating the expander

delayed total breast reconstruction with autologous fat tissue; however, the procedure can rarely be completed in a single stage. It is also difficult to obtain a good skin envelope, definition of the inframammary fold, and breast mound.

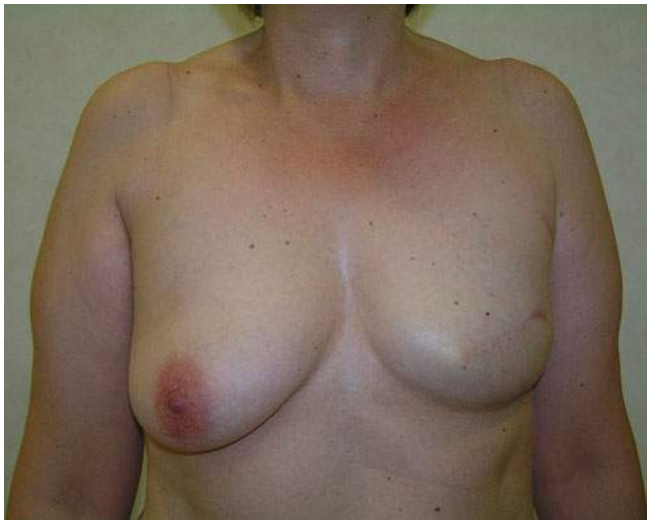

Fig. 54.12 Postoperative view after expander removal and a second session of 250 cm^3 of fat grafting without any implant

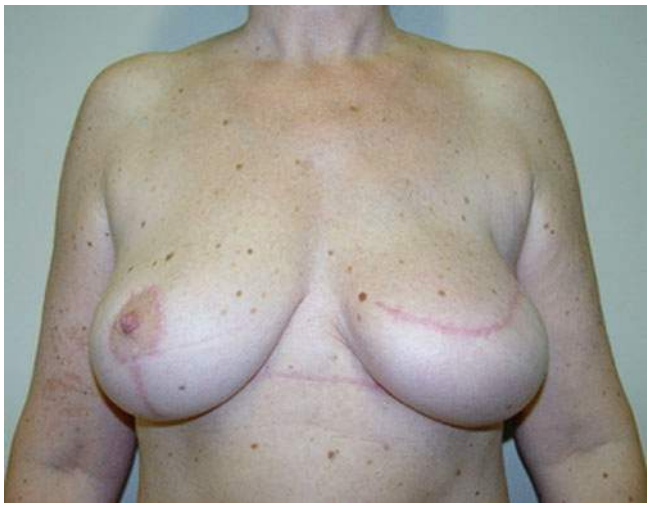

Fig. 54.13 *Upper* breast fullness after immediate *left* breast reconstruction with an anatomical implant

- Secondary defect corrections after breast reconstruction with implants or autologous flaps: Lipofilling can be used to correct upper breast fullness in cases of anatomical implant defect or also correct the lower pole fullness (Figs. 54.13 and 54.14). It can also be used for secondary defects of reconstructions done with autologous flap procedures [34]. When an autologous flap reconstruction develops early or delayed complications such as partial flap necrosis or delayed flap atrophy, especially for extended latissimus flap reconstructions, lipofilling can replace volume deficit without requiring flap or microvascular procedures (Figs. 54.15, 54.16, 54.17, and 54.18).

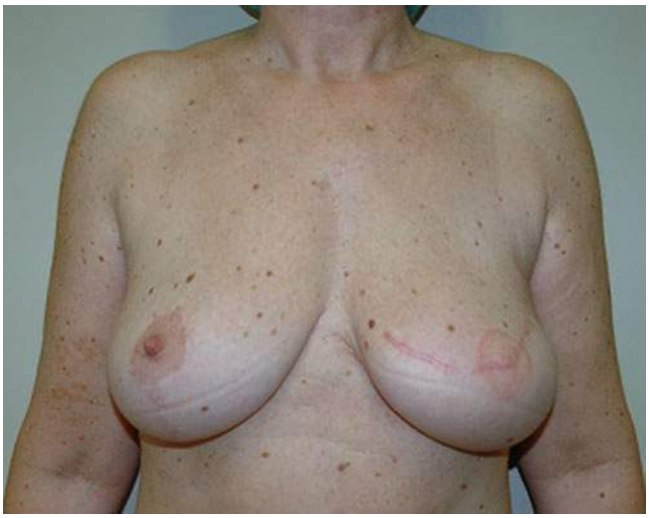

Fig. 54.14 Postoperative view after 80 cm^3 of fat grafting in the upper pole of the left breast

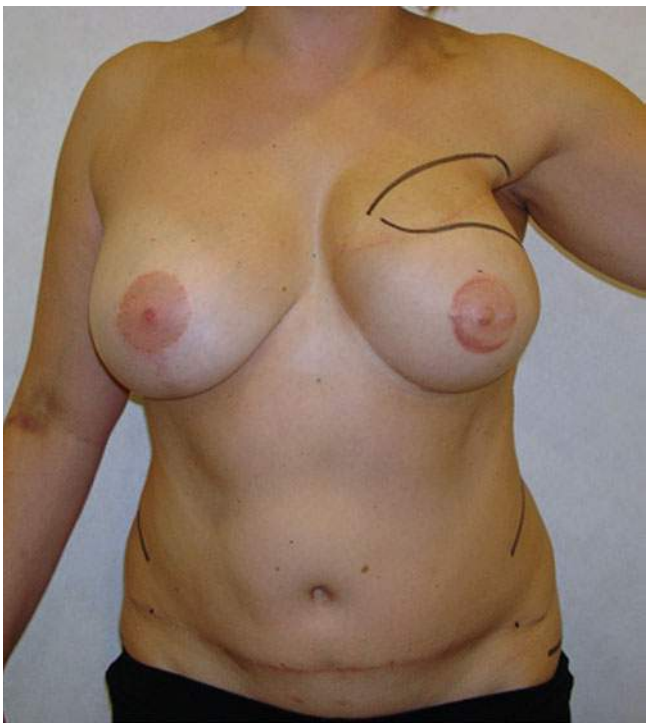

Fig. 54.15 Upper outer defect after delayed reconstruction with a monopedicled transverse rectus abdominis myocutaneous flap

54.5.3 Unusual Indications

- Rippling correction—To correct visible rippling after implant-based reconstruction (Figs. 54.19 and 54.20).
- Capsular contracture—Fat grafting around the implant and especially around the capsule can correct a visible

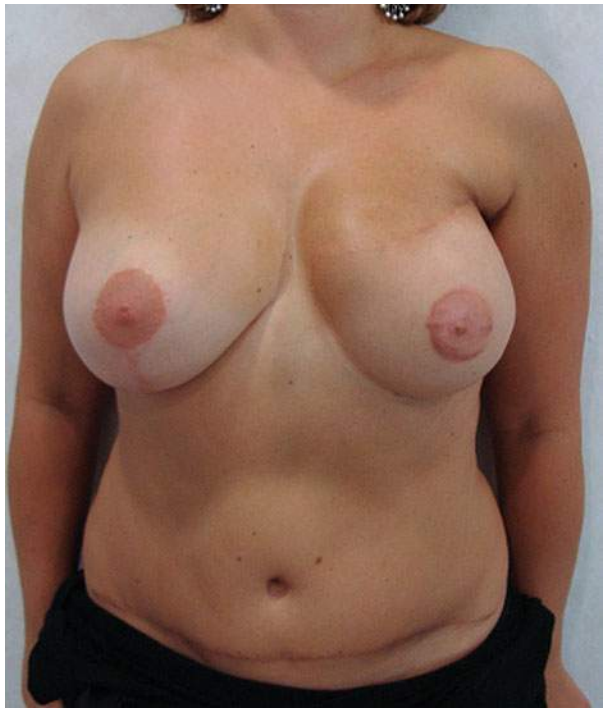

Fig. 54.16 Cosmetic results 6 months after lipofilling

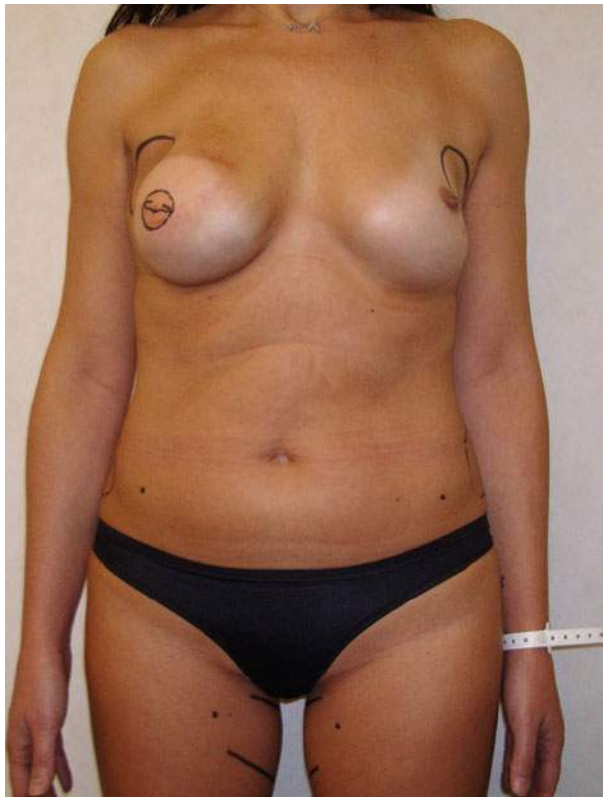

Fig. 54.17 Cosmetic results 6 months after immediate *right* breast reconstruction with a latissimus dorsi flap plus an implant and prophylactic mastectomy of the *left* breast and immediate breast reconstruction with a definitive implant. A bilateral upper outer lipofilling was performed with the inner thighs as the donor site

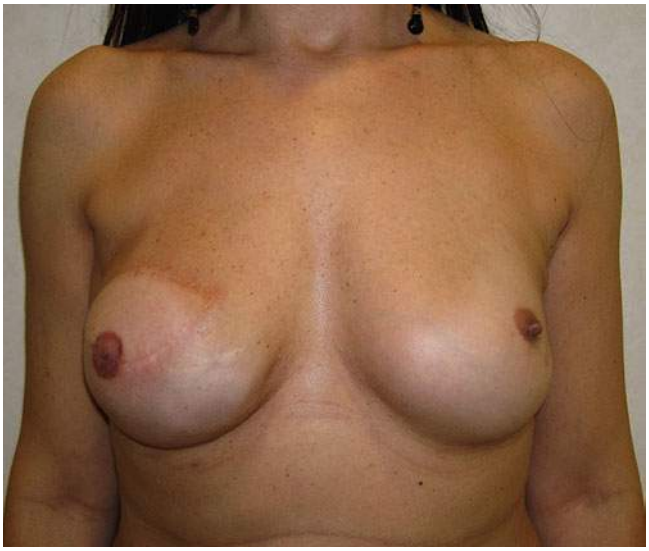

Fig. 54.18 Final cosmetic results after 6 months

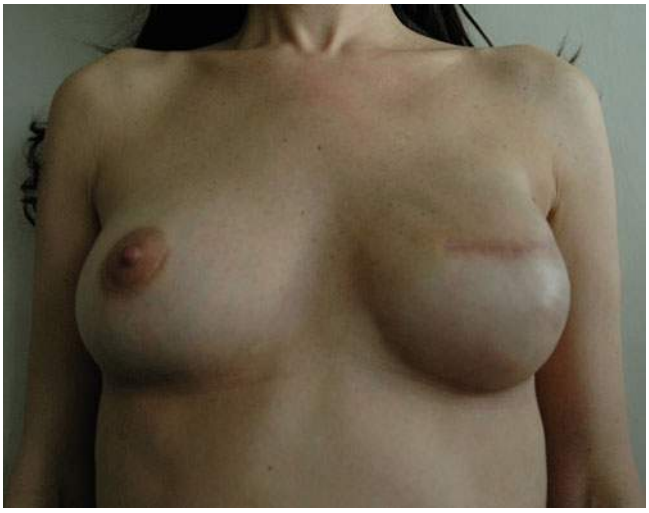

Fig. 54.19 *Upper* pole rippling after immediate *left* breast reconstruction with ab implant

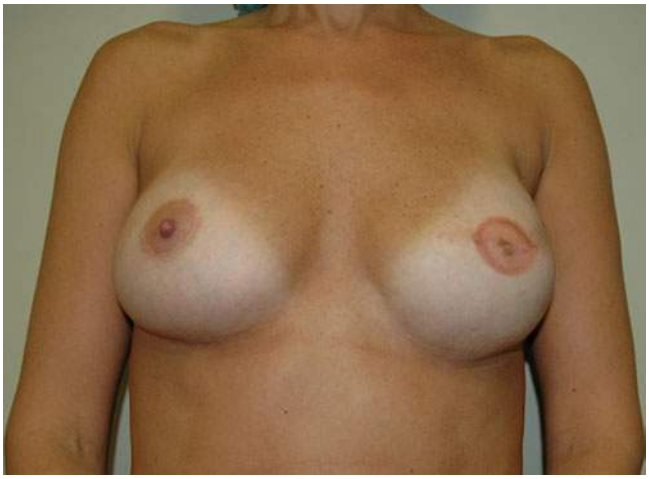

Fig. 54.20 Cosmetic results at 6 months after injection of 50 cm^3 of fat in the upper pole of the *left* breast

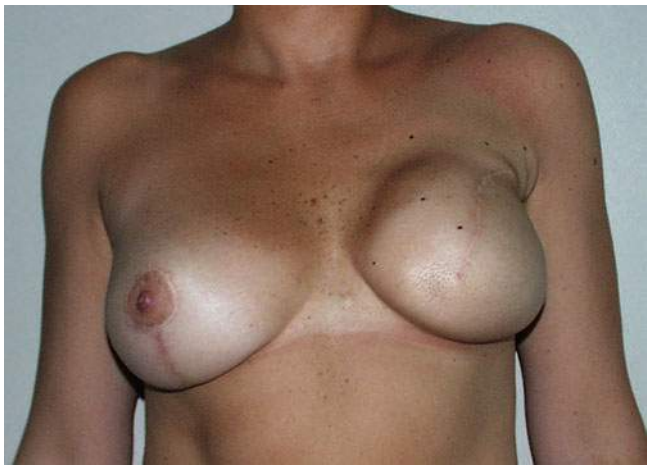

Fig. 54.21 Patient with Baker IV capsula contracture after mastectomy and immediate breast reconstruction with a definitive implant

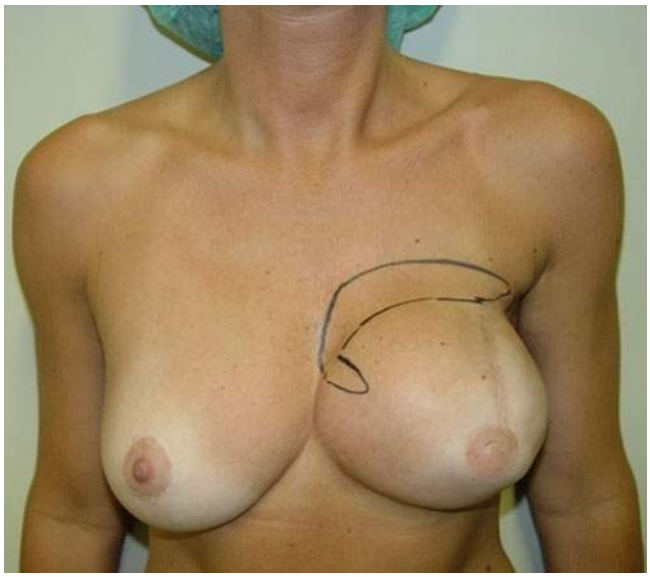

Fig. 54.22 Cosmetic result after four sessions of *left* breast lipofilling

rippling appearance by increasing the thickness of the capsular wall. Moreover, the effect of ASCs in the cellular component of the lipoinjection may cause biological tissue remodeling of the cellular structure in the contracted capsule (Figs. 54.21 and 54.22).

- Nonspecific pain therapy—There is still no clear explanation for this mechanism of action. Adipose tissue is a rich source of various types of progenitor, endothelial, and mesenchymal stem cells. Some of them have angiogenic potential which may resolve the nonspecific pain pathway.
- Improvement of irradiated local tissue damage (including post-radiotherapy ulcer)—The cellular component in the lipofilling specimen has angiogenic potential and is able to generate new stromal and cellular matrix which benefits the chronic wound healing process and irradiated tissue.

- Contralateral symmetrical procedure—Lipofilling can also be used on the contralateral side to produce symmetry either immediately with the oncological procedure or later after reconstruction.

54.6 Complications and Sequelae

54.6.1 Immediate Complications

Immediate complications include seroma, hematoma, cellulitis, abscess, and liponecrosis. In a previous published data from the European Institute of Oncology in Milan, we reported a range of 2.8–3.6% rate of complication [11, 12]. Types of oncologic resection, types of reconstruction, and types of radiation do not affect the occurrence of immediate complications.

54.6.2 Late Complications

Late complications include fat reabsorption, scar retraction, and donor site deformity. Donor site deformity can be avoided by the selection of the proper donor sites, obtaining the optimum volume of lipoaspiration, and avoiding superficial planes of lipoaspiration. Fat reabsorption is an expected sequela after lipoinjection and is estimated at 30–60% in the first year [35]. However, a stable result may start to be observed at 6 months. The reabsorption also depends on the technique of injection, recipient tissue quality, volume of injection, and methods of preparation. We prefer to perform more than one session of lipofilling in case of large volume defects.

54.7 Conclusions

Lipofilling has been attracting the interest of many surgeons who want to improve aesthetic results after breast cancer treatment. It has a low rate of complications, and there are many series proving its safety [36]. Especially in the tissue engineering era, adipose tissue is being experimented upon and utilized by many scientists and companies worldwide. Some novel products and machines may need approval and well-done clinical studies before being accepted in surgical practice.

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Nipple-Areola Complex Reconstruction

55

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55.1 Introduction

The reconstruction of the nipple-areola complex (NAC) is an integral part of breast cancer treatment after mastectomy or central quadrants, transforming the reconstructed mound into a breast. The final result becomes pleasing and natural. NAC reconstruction has a positive psychological impact on breast cancer patient; it may cover part of the mastectomy scar [1]. However, not all women desire to complete the reconstruction, and generally older patients do not.

55.2 When to Perform the NAC Reconstruction?

NAC reconstruction is generally planned at least 3–6 months after breast reconstruction either with definitive implants or flaps or after the contralateral symmetry procedure (if not performed simultaneously with the reconstruction). In fact, it should be delayed after breast reconstruction settled down to its final shape and position. In the earlier period, it is probably not possible to determine the right position of the new areola, resulting in disturbing asymmetries.

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55.3 Where Is the Position of NAC?

The planning of the new NAC should be performed with the patient in the upright position, being the opposite healthy breast used as a guide. Specific anatomical landmarks help to determine the proper position, such as the sternal notch, the midline, or the imaginary intersection line through the healthy nipple. The distance between the healthy spared areola (if present, not in bilateral reconstructions) and the sternal notch, inframammary fold, and midline can be measured to reproduce the ideal position on the reconstructed mound. More often, the new areola simply looks right, depending on the so-called a glance visual. Proper appearance takes precedence over measurements, which can merely confirm the accuracy of the visual positioning.

Other advises regard the distance between the two nipples, which is maintained between 18 and 22 cm on average, therefore avoiding unaesthetic medial areola position. Moreover, the NAC should be positioned on the maximum projection of the reconstructed breast.

55.4 How to Reconstruct the NAC?

Several surgical techniques have been described over the past 30 years for the reconstruction of the NAC. The new NAC tissue can be harvested from local or distant tissues. There is also a combination of different methods, and it can be even combined with alloplastic material or filler injection. Each of these methods has its own advantages and limitations; most of them yield good results transiently, but in few cases nipple definition and projection are guaranteed with time. For these reasons no method has become the favorite. The decision between different methods depends both on the anatomical local conditions both on surgeon and patient's preferences.

Schematically, we will consider separately the reconstruction of the areola and nipple.

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_55

55.4.1 The Reconstruction of the Areola

55.4.1.1 The Grafts

Skin grafts have been used for a long time as the method of choice before the introduction of "tattooing." Currently the technique of tattooing is more popular than the traditional grafting.

Dermoepidermal full-thickness grafts could be harvested from the inguinal region, the retroauricular area, and the vulvar region according to the natural color of the healthy areola. The procedure consists of skin harvesting from donor area to the recipient one. The diameter and shape depend on the size and features of the contralateral areola. If the skin of the reconstructed breast is under tension, we have to consider that when performing de-epithelialization of the new areola, its diameter will increase in size of about 5–10% from the original areolar plan. It is due to the lack of its epidermis.

If the healthy areola is large enough, we can perform "areola sharing" [2] with the concentric circle method, which involves removing a strip of the outer portion of the areola and transferring to the recipient site. This method results in symmetrical small areolas (Fig. 55.1). Generally, the areolar graft strip is quite thin and it must be placed in a spiral form.

Mostly the upper thigh is selected as a donor site. The graft from this region turns color to light brown when it cooperates into the recipient site. The grafts harvested from the major labia are more pigmented. In cases of pale pink color areola, it is better to harvest grafts from retroauricular region.

The disadvantages of this method include the donor site morbidity (infection, wound dehiscence, unpleasant scar, etc.) and the risk of partial/total necrosis of the graft. Clinically, there is a lack of nipple projection as the areolar area is completely flat.

More recently, the reconstruction of areolar projection using a purse-string suture has been described. Evenly spaced stab incisions are made in a circular pattern, approximately 5 mm outside of the boundary of the proposed areola. Using these incisions, a nonabsorbable purse-string suture is placed in the deep dermis. Finally, the diameter is cinched down to the desired measurement, providing areolar projection [3].

55.4.1.2 The Tattooing

The widening indication of this method is mainly due to the simplicity of procedure, the absence of donor site scar, and the availability of several colored pigments to have similar color of the natural areola [4–8].

The basic equipment needed for tattooing includes the tattoo machine, generally running 10,000 rpm, sterile pigments, and the needles. We advise to use a needle assembly that uses nine points to accelerate the proper application of pigments. This extremity can be made sterile. By rotating the cap of the needle assembly, it can be regulated how deep the needles penetrate (Fig. 55.2).

Permanent and semipermanent sterile pigments are available; they can be mixed together to achieve the desired tone. The selected color is typically one or two shadows darker than the native areola because it tends to fade and discolor with time. The needles are dipped into the pigment and applied in a radial and circular pattern.

Postoperative care of tattooing includes a dressing with vaseline oil and gauzes. The patient may remove her dressing at 1 week/10 days and shower. She is instructed to remove the dressing carefully and not to peel off scabs because this will remove the tattoo pigment. Sunscreens are suggested for 6 months after tattooing.

Dermabrasion before tattooing has been recently described to improve the quality of dermopigmentation while reducing its completion time [9]. Dermabrasion allows better penetration of the pigments inside the dermis and thus offers a more durable result over time and reduced operation time by reducing the number of passing of the machine tattoo.

Finally, three-dimensional nipple-areola tattooing has been proposed [10] creating a lighter inner circle with a dark border. This border is thickened inferiorly to have a shadow effect and mimicking nipple projection. Satisfactory result can be achieved with standard medical tattooing equipment; however, a professional tattoo artist with specialized equipment and ink can produce an outstanding result, including tattooing of Montgomery glands.

55.4.2 The Reconstruction of the Nipple

Different methods have been described for the reconstruction of the nipple, including the use of external prostheses, the simple tattooing, or surgical reconstruction. Nowadays the use of external prostheses is completely abandoned since glue adhesion problems and allergy have been described [11–13]. Tattooing alone gives no projection and therefore unsatisfactory results. The surgical reconstruction is definitely the most used and schematically involves the use of grafts or local flaps.

55.4.2.1 The Grafts

If the nipple of the contralateral breast is large enough, the method of choice is "nipple sharing" which transfer a part the opposite healthy nipple on the reconstructed breast. It is ideal in color and bulkiness, it can be employed satisfactory only when the native nipple is large in size. Sharing can be performed by "decapitation" (Fig. 55.3a). The decapitation method can also be performed with "starred resection" (Fig. 55.4a–f). Another possible method of harvesting the nipple is the "vertical bipartition," especially indicated if the

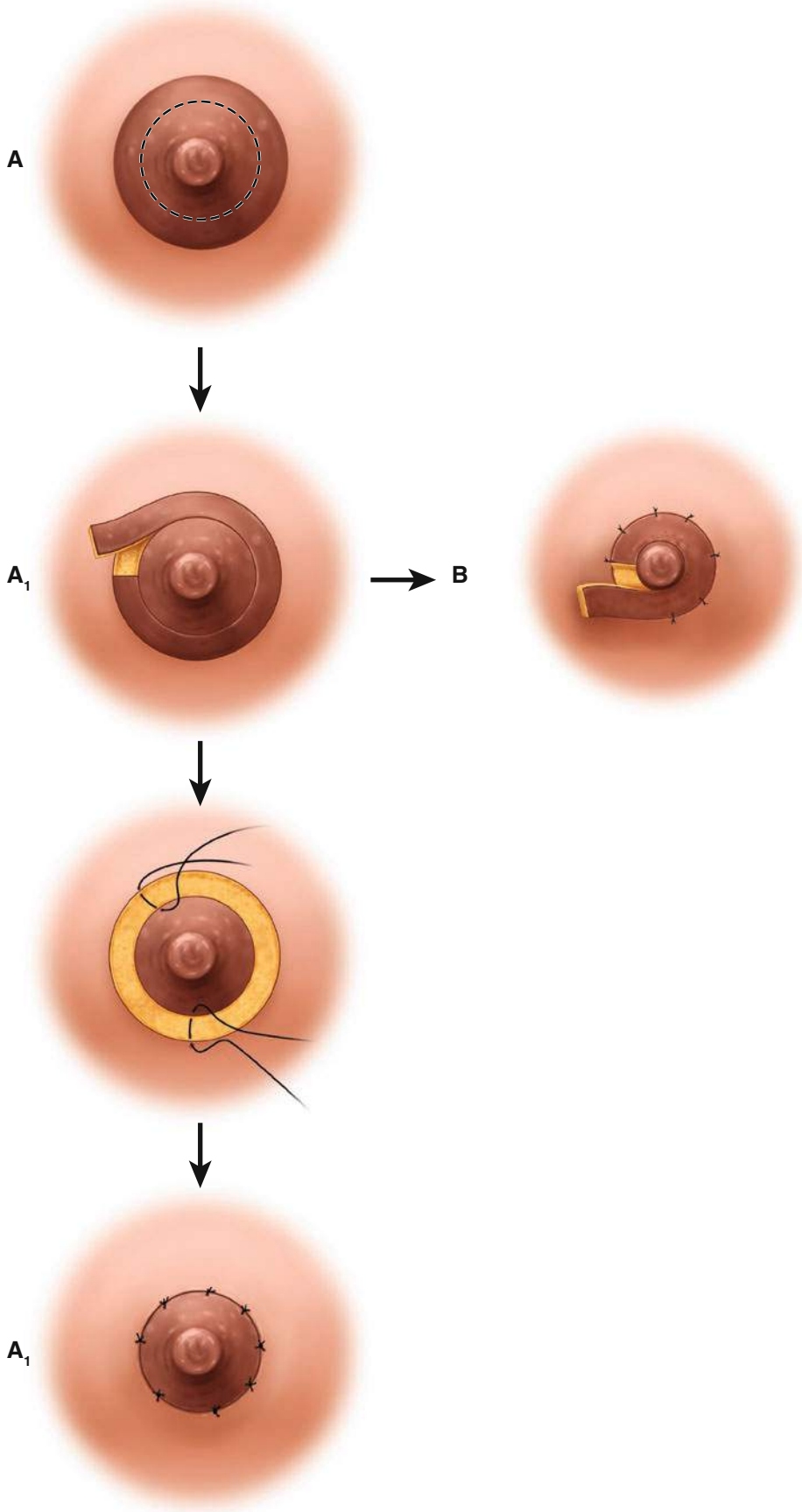

Fig. 55.1 Areola grafting (**a**) with the technique of the concentric circle (**a1**), obtaining two equal-sized areolas (**b** and **a1**)

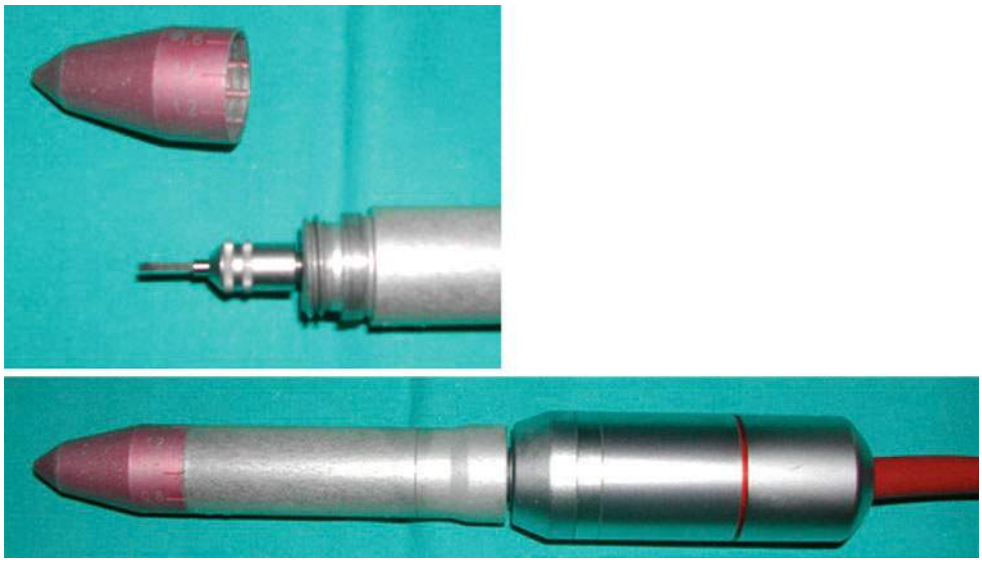

Fig. 55.2 The needle assembly with nine points for tattooing

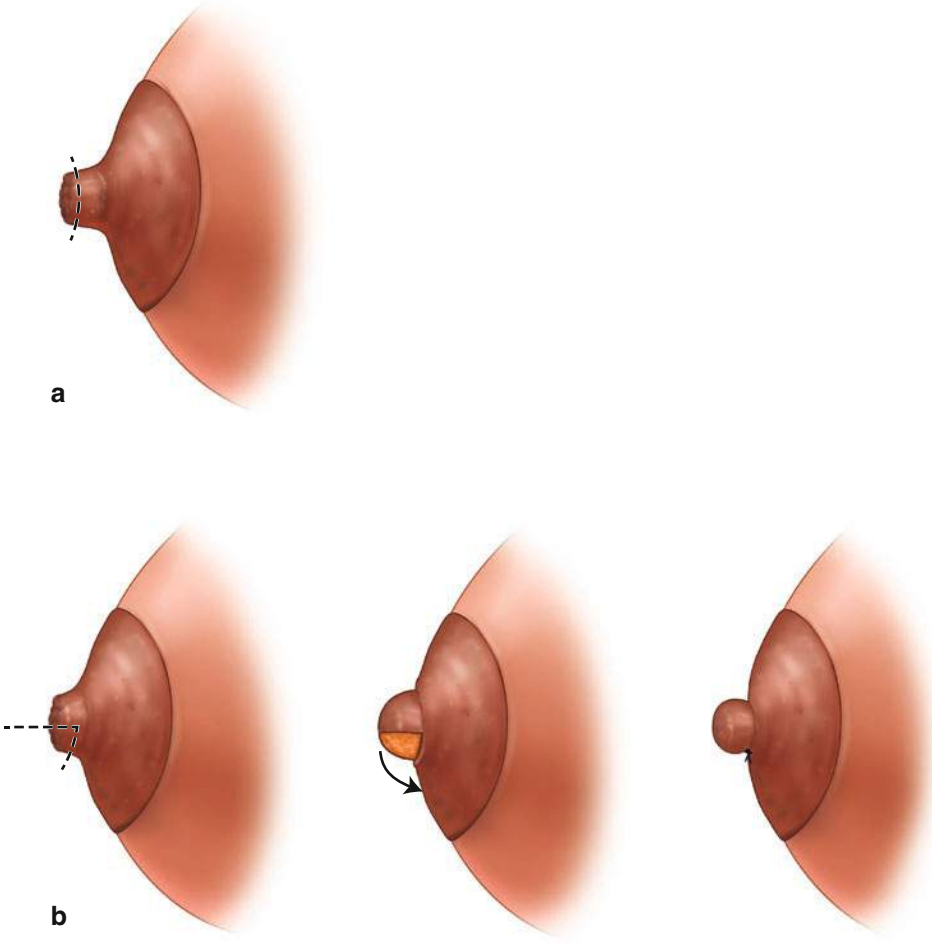

Fig. 55.3 Decapitation (**a**) and bifurcation (**b**) of the natural nipple and grafting on the reconstructed breast

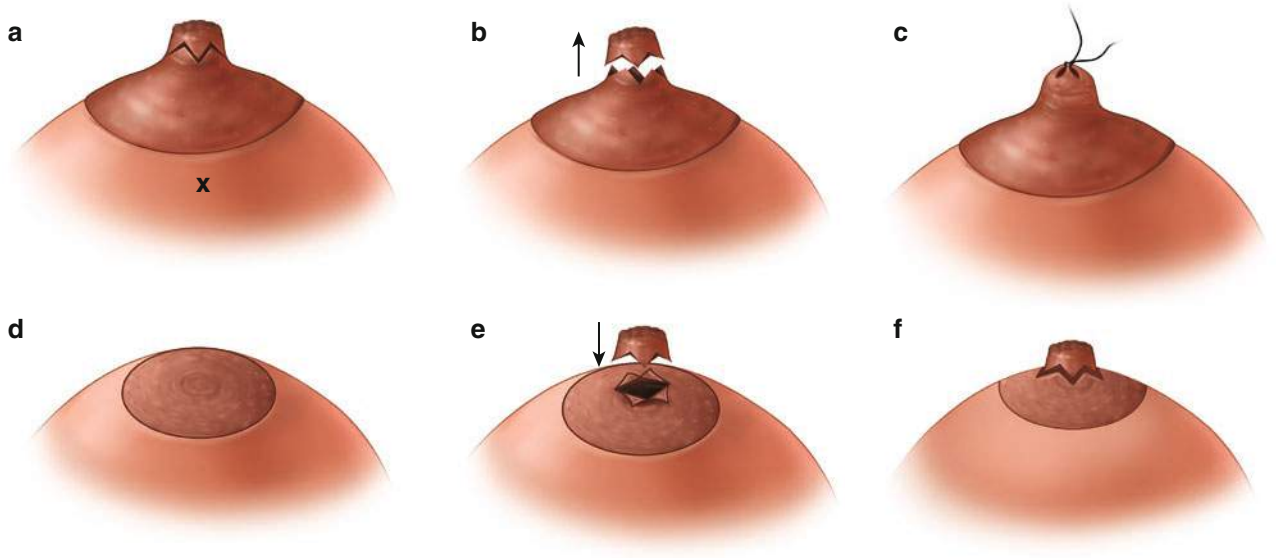

Fig. 55.4 Decapitation of the natural nipple as a starred resection (**a**, **b**), primarily closure of the donor area (**c**) and grafting in the receiving region (**d**, **e**, **f**)

diameter of the nipple exceeds its height. In all cases the donor nipple is directly closed with a simple suture (Fig. 55.3b).

The perfect tissue matching with regard to color and texture between the two nipples is definitely the main advantage of nipple grafting [14–17]. On the contrary, the disadvantage includes the fact that any composite graft has an inherent risk of incomplete revascularization, which can lead to loss of tissue and projection. The structural distortion and sensation of the nipple is also found as less frequent complications [18].

If patients are reluctant to disturb the healthy opposite nipple or the native nipple is not large enough, other possible donor sites of composite grafts are the toe pulp or auricular tissue [19–21]. In both areas, there is a skeletal part similar to the fibrofatty nipple tissue, but the color is much lighter. Even the skin graft from the minor labia has been used in the past but now completely abandoned due to the morbidity of the donor site and the very satisfactory result from the surgical reconstruction [22].

Cartilage graft is also harvested to obtain the projection of the nipple [23]. It can be positioned under a skin graft in the same surgical setting or afterward. However, the survival of the skin graft overlying cartilage cannot be secured and due to the ongoing skin graft contraction can gradually minimize the projection of the cartilage graft [24–26].

55.4.2.2 The Local Flaps

More frequently, the nipple is reconstructed with local flaps. Different techniques have been described, but for all of them, at least 50% loss of the nipple projection has been observed within 1 year after surgery. For this reason, the new nipple should be planned larger and more project than the expected endpoint [27–38].

The flattening of the reconstructed nipple is due to the lack of the natural anatomic infrastructure of the normal nipple as well as the existence of centrifugal forces on the superficial surfaces on the reconstructed eminence. Projection is also influenced by local tissue characteristic such as thickness of the dermis and amount of local scarring. Those nipples created over previous scar had minimal loss of projection, whereas those performed on an individual with a tightly expanded breast mound and a thin dermis lost the most projection.

Nipple reconstruction with local flaps depends on local availability of soft tissue to achieve nipples of desired size. Previous local scars (such as mastectomy or central quadrant scars) influence flap design and may interfere with flap vascularization.

The surgical techniques can be divided into two main groups: the "pull-up techniques" [39–41], based on deep dermal and adipose flaps, and the "traction techniques" [42–44], based on local skin advancement flap.

Pull-up techniques based on a central subcutaneous core require a deep dermal and adipose tissue dissection. They produce an irreducible hernia of the central core local flaps. They are preferably applicable to autologous tissue breast reconstruction. For breast mounds with a thin subcutaneous layer, as commonly associated with the implanted breast, local flaps using a central subcutaneous core can have strong advocates. Evolution of these techniques includes the tripods and mushroom flap, the Maltese crosses, quadrapods, and H-flap.

The double-opposing tabs, the bell flap and the star flap, belong to the "traction techniques" based on subdermal pedicled flaps.

The Quadrapod Flap

It is known as one of a central subcutaneous core pedicle techniques previously described by DiPirro and later modified by Little [45, 46]. After designing the position of the nipple and the diameter of the areola, four opposing skin flaps are dissected with the preservation of the central fat core (Fig. 55.5a–d). The radial length of the flap is according to the new nipple height projection. The dissection starts from the outer part toward the central core. The central fat core is then raised and covered by the four opposing flaps. However, the color of the new nipple is not matching the contralateral one, so secondary tattooing is needed and the surrounding areolar area must be grafted. Despite the promising immediate result, there is still a loss of projection later on.

The H-Flap

It has been described by Hallock as a cylindrical nipple reconstruction with the similar principle of central subcutaneous core pedicle technique [47]. The design is based on purpose to maintain the central core projection by wrapping with counteracting of cylindrical flaps. The flap is designed in the round diameter as the diameter of the areola. The lateral rectangular shape is designed as the "H" shape

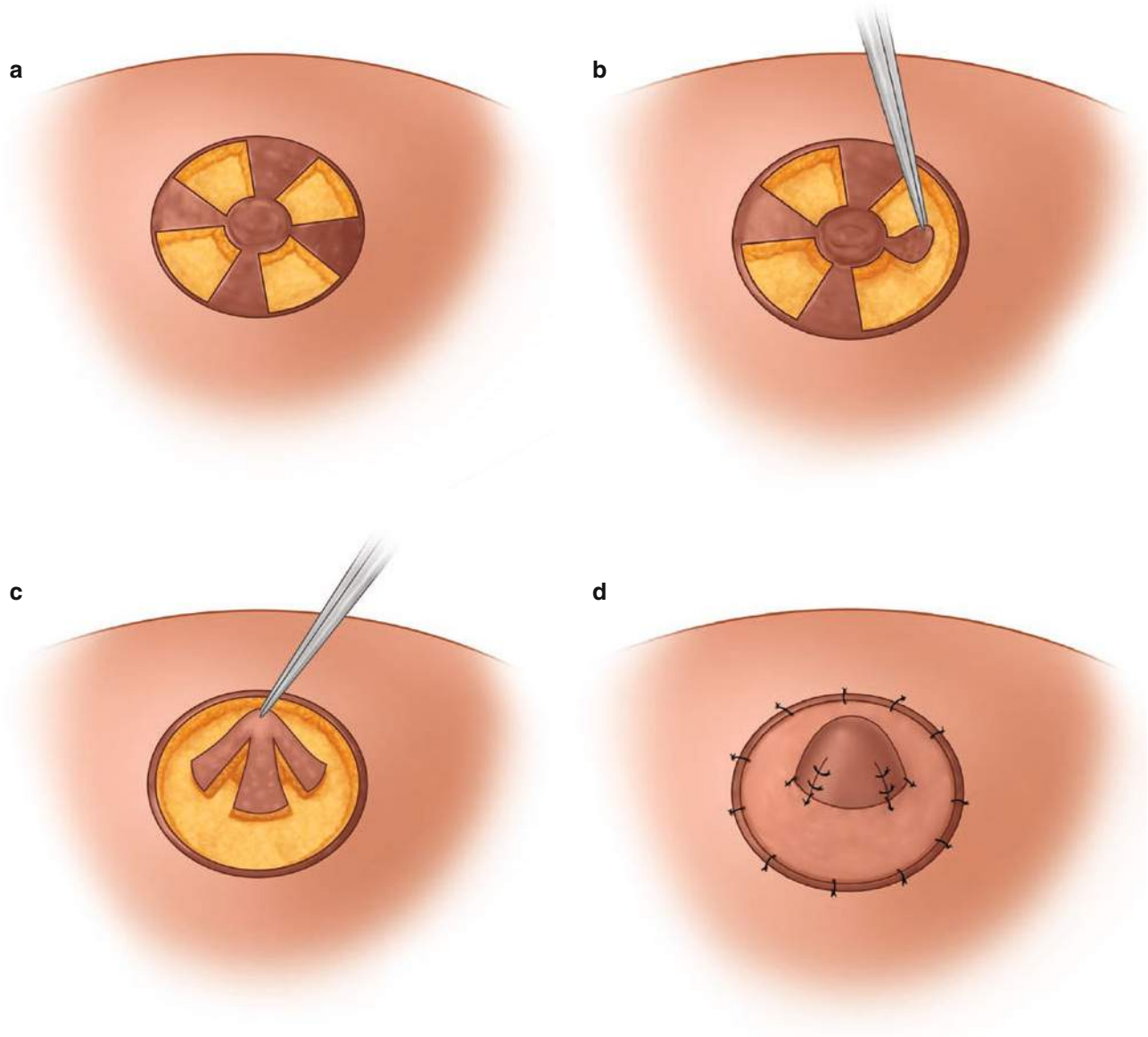

Fig. 55.5 (**a**–**d**) Schematic drawing of the quadrapod flap for nipple reconstruction

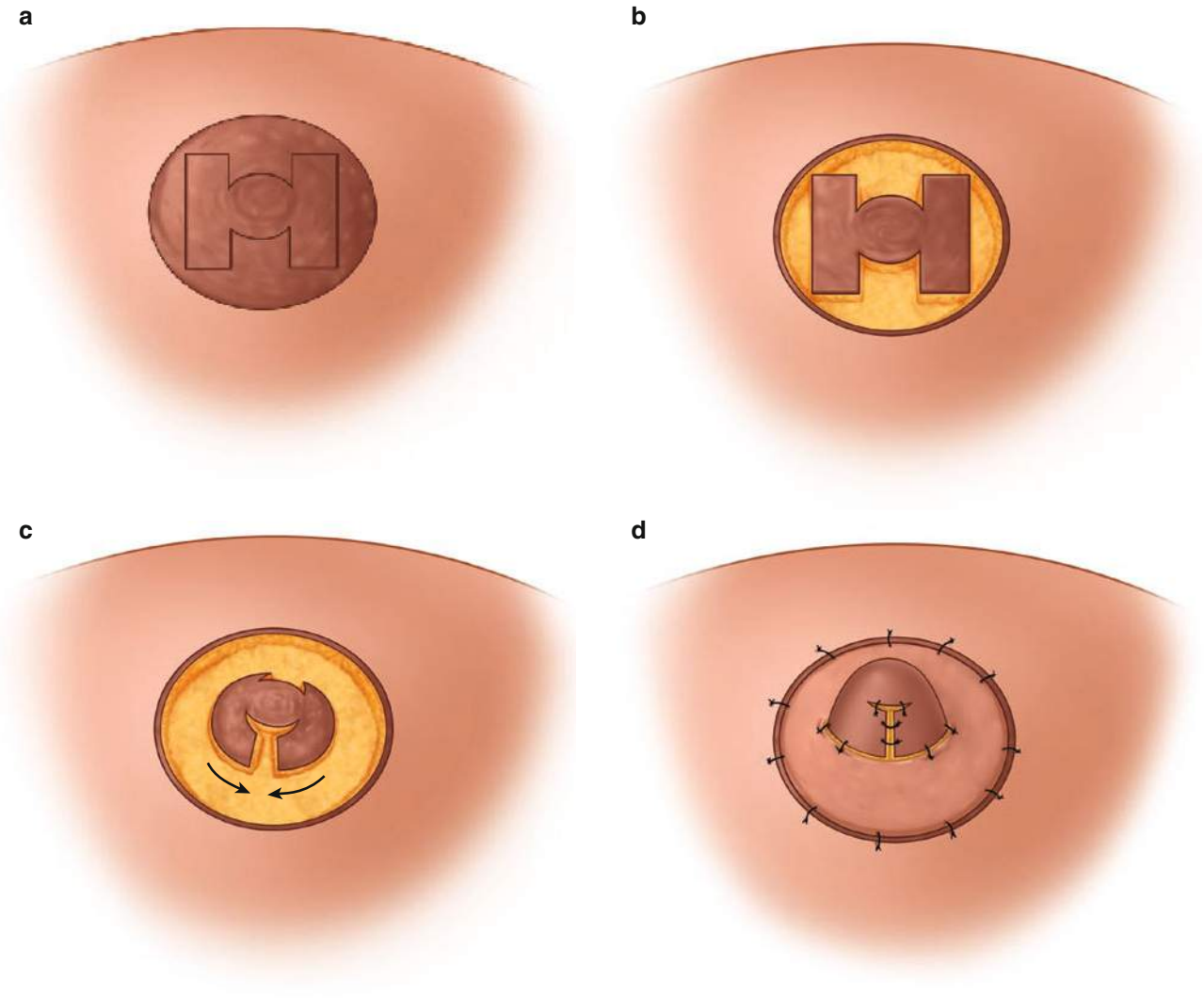

Fig. 55.6 (**a**–**d**) Schematic drawing of the H-flap for nipple reconstruction

(Fig. 55.6a–d). The width of each leg is according to the new nipple projection design, and the length of each side is matched to half circumference of the new nipple. If there is the scar present in the area, the flap can be designed in a different direction. The dissection is performed preserving subdermal vessels. However, the long-term result is still disappointing for scar contracture and the need of secondary nipple tattooing and grafting for areola reconstruction.

The Modified Star Flap

The modified star flap belongs to a second group of flaps, based on the subdermal plexus, and it is very frequently used [48]. Its evolution is the C-V flap and modifications [49, 50]. The flap can be based superiorly, laterally, or inferiorly as local scarring dictates, although a more natural projection and appearance to the patient are obtained by basing the flap superiorly. The "wings" of the flap will determine nipple height (Fig. 55.7a–e). Their height should be bigger than the ultimate desired height, allowing decrease in projection over time. The nipple flap is tattooed prior to flap elevation. The wings are raised containing dermis and subcutaneous fat, getting thicker toward the base. The donor incisions are closed directly around the base of the nipple. The wings are wrapped together, being one wing placed at the base of the nipple and one partially overlapping. Afterward, the areola diameter is remarked and tattooed (Fig. 55.8). The most common problem is the variable loss of projection of the nipple over time.

The Modified "Arrow Flap" with Immediate Tattooing: Author's Experiences [51, 52]

From the previous technique of Rubino et al. [52], we agree with the principles that nipple projection and volume are obtained by increasing the amount of dermis within the flap without enclosing any excess subcutaneous fat. The dissection of the flap can be performed effectively with the preservation of the dermal plexus. However the necessity of

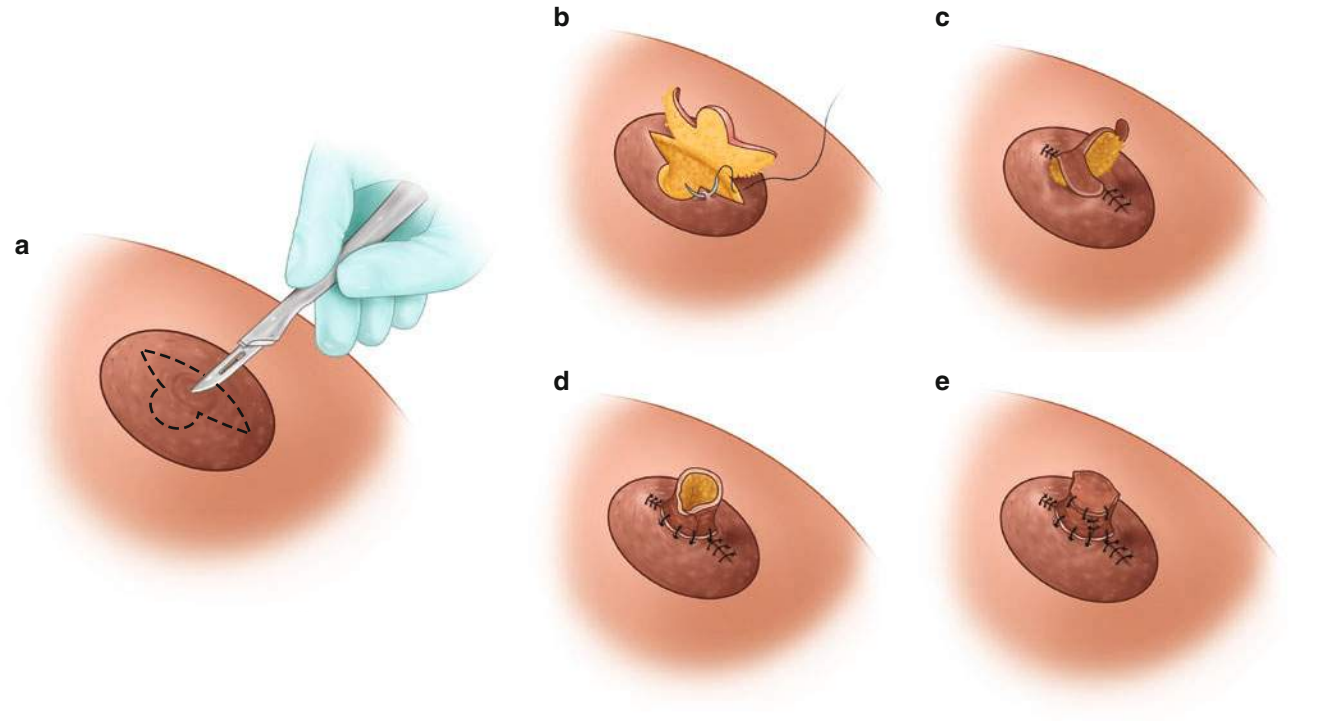

Fig. 55.7 (**a–e**) Schematic drawing of the modified star flap for nipple reconstruction

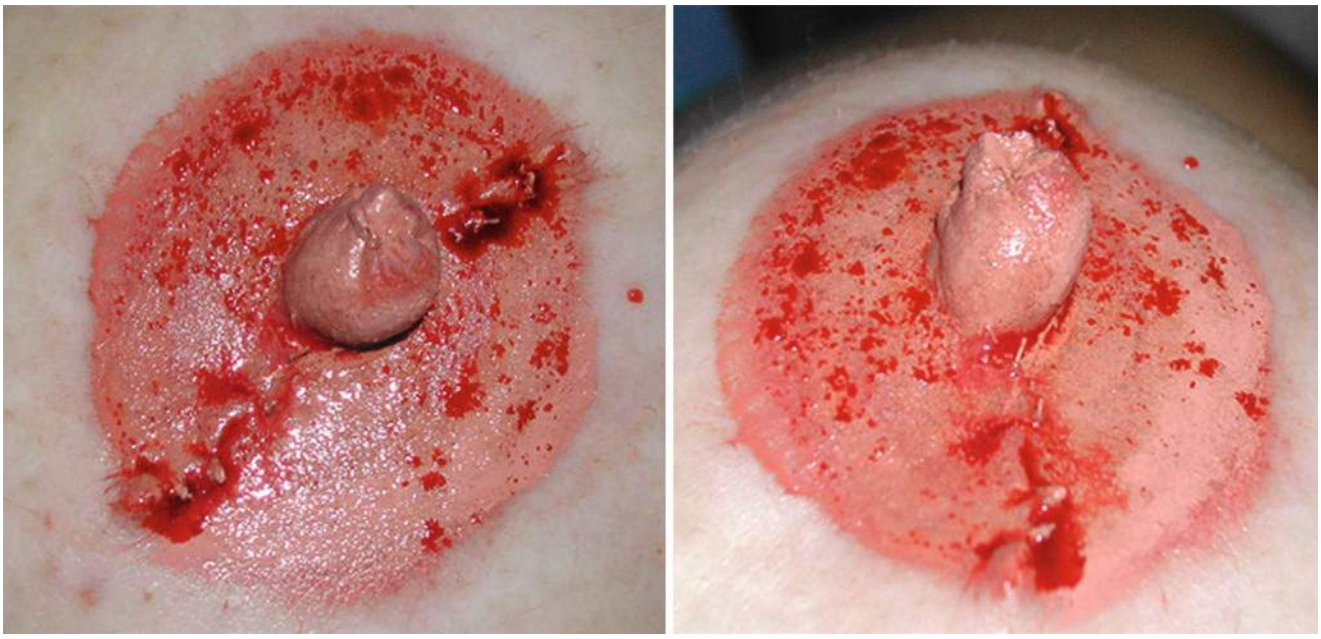

Fig. 55.8 Early postoperative results of the nipple reconstructed with the modified star flap and tattooing

skin grafting is a drawback of the original technique. Therefore, we suggest the immediate tattooing simultaneously with the arrow flap procedure.

The flap can be designed in any position, superior-, inferior-, lateral-, or medial-based, depending on the previous scar if existent. The width of the flap wing is matched to the new projection of the nipple. We recommend to design it wider because the final result of the flap will shrink down in 6 months. Pre-tattooing is recommended before flap harvesting. Finally, additional tattooing is required to adjust the shape of the areola to the contralateral healthy one. We expe-

rienced no increased local complication rate by combing the two procedures.

The advantages of pre-tattooing are the following:

- The reconstructed nipple has more similar pigmentation of the areola, and it is not lighter than the native nipple.
- Tattooing can be performed easier on a flat surface than on a projected nipple papule, resulting in a more uniform color.
- There are no more disadvantages related to donor site harvesting.
- No further second procedure is necessary.

55.5 Conclusion and Future Trends

In conclusion, there are many options and techniques for nipple and areola reconstruction. Each of these techniques has its own advantages and disadvantages. There is no one unique method available for every patient, but we have to individualize and discriminate for the most benefits in each patient. Meticulous surgical methodology should be strictly followed to achieve maximum aesthetical outcomes. In the future, there will be probably different types of tissues and materials available for NAC reconstruction. Tissue engineering, tissue banking, and genetic tissue culture which have already been tested in the animal laboratory may play roles in the future of NAC reconstruction [53].

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Revisions After Breast Reconstruction

56

Eduardo Gonzalez and Gastón Berman

Breast reconstruction (BR) is currently considered an integral part of breast cancer treatment. Various oncologic factors, such as tumor size and lymph node status as well as the type of sequelae in already operated patients, determine the approach that should be taken and the technique to be used after preparing a detailed report of the procedure and considering the patient's preferences.

Women's need to minimize the psychological impact of the potential physical change as a result of the disease and their willingness to maintain or improve their body image pose a challenge to surgeons. Quality of life is no longer considered a secondary endpoint; it is currently a key issue, and its variables can be measured through outcome assessment instruments such as BREAST-Q [1]. Regardless of the technique used (pediculated flaps, microsurgical flaps, expanders/prostheses, or a combination of several techniques), many patients decide to undergo re-interventions to optimize the cosmetic outcomes through the refining of the techniques used. Lipofilling (LF) has a prominent role at this stage since it is a simple, hardly exhaustible technique, with low morbidity and good esthetic results.

For different reasons, revision surgeries have recently been gaining popularity in breast reconstruction (BR). On the one hand, outcome expectations have changed over the years, and patients currently "demand" that the reconstructed breast or, actually, the general reconstruction outcomes be similar to those obtained in esthetic breast plastic surgery (augmentation, reduction, and mastopexy). At this point, we must mention the complex issue of "symmetry" and of producing long-lasting stable results. As we know, there are currently several techniques available to optimize those results, but the utopia of perfection cannot be achieved, not even with the best surgeons. In order to balance these factors, surgeons should be very careful when giving information to patients and should not promise unrealistic results. This is important not only when primary breast construction is indicated but also, and especially, in the case of a revision procedure, where expectations, if not met, may cause disappointment as a result of a discrepancy between what was interpreted in the pre-surgery discussion and the final outcome [2].

On the other hand, we should define the concept of "revision surgery" (RS), for which there is not much agreement. In our experience, the term "revision" not only includes "correcting bad results" of treatments or sequelae of reconstructive procedures secondary to other treatments (particularly, radiotherapy) or changes in patients' body structure (weight changes, skin elasticity differences between the reconstructed and the remaining breast, etc.). It also entails correcting outcomes of unsatisfactory primary procedures, resulting from choice of wrong technique due to either lack of knowledge or over-indication of a preferred procedure by the acting surgeon, bad execution due to lack of expertise or criterion, and/or as a result of complications.

The approaches and procedures to indicate in complications of surgeries using any of the known techniques that resulted in total loss of the reconstructed breast will not be included in this chapter. We consider those cases are not revision surgeries but actual secondary reconstructions with a higher level of complexity than primary procedures, which therefore need to be dealt with in another context.

According to our line of thought, we consider that there are different scenarios for surgical revisions after BR, which can be classified into three groups:

- Correction of conservative surgery sequelae with or without previous oncoplastic surgery.
- Correction of defects after BR with expanders/prostheses.
- Correction of defects after BR with autologous tissue.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_56

56.1 Correction of Conservative Surgery Sequelae with or Without Previous Oncoplastic Surgery

Breast-conserving surgery (BCS) is now considered a treatment option for breast cancer patients after various studies showed equivalent long-term survival rates in comparison with mastectomy [3, 4]. Although it is the ideal technique to preserve body image, between 20 and 30% of the patients have an unsatisfactory cosmetic outcome, and in some cases, they have to resort to major surgery for correction [5]. Expertise in glandular modeling basic techniques and more complex oncoplastic techniques prevent most of these bad results, which adversely affect patients "qualify of life" [6].

The degree of sequelae after BCS varies considerably, ranging from volume asymmetry with conserved shape to severe shape alteration with displacement of the nipple-areolar complex, radiation-induced fibrosis, and skin retraction [7].

The type of RS chosen will depend on the degree of the deformity, the quality of breast skin, and the symmetry alteration.

Our classification of these sequelae and the approaches we took in these situations are addressed in detail in Chapter 19 of this book.

56.2 Correction of Defects After Breast Reconstruction

Current trends in breast cancer treatment include an increased number of bilateral and risk-reducing mastectomies, skin and nipple-areolar complex conservation, and the extension of indications for radiotherapy [8].

Such extension has had a series of therapeutic implications in the decision-making process and the technical considerations taken into account by surgeons.

In general, autologous tissue is better than implants in patients who have undergone post-mastectomy radiotherapy [9, 10]. It produces fewer complications and has a higher rate of satisfactory cosmetic outcomes in the long term.

However, innovation in implant quality, the use of acellular dermal matrices (ADM) [11], and LF have enabled the optimization of the cosmetic results obtained with techniques using heterologous materials.

Although there is a growing number of professionals and teams trained in breast reconstruction, the abovementioned considerations show that there are general factors as well as surgeon-related technical factors which may cause the results not to be the expected ones, as shown in Tables 56.1 and 56.2.

It is important to know what to do in these cases. Revisions are usually a challenge for the reconstruction surgeon due to the tactical and technical difficulties faced to obtain an excellent result in a single-stage procedure. Although the evaluation surgeons perform depends on the kind of cosmetic expectations from each patient, it is always advisable to inform the patients about the complications that may appear, the hypotheses of solution, and the need in most cases for several reconstruction stages in order to optimize cosmesis.

Table 56.1 General factors that may result in poor outcomes and the need for revision surgeries

Factors	Consequence
Choice of wrong surgical technique resulting from lack of experience or over-indication of a technique due to lack of knowledge of other techniques	Bad outcomes in relation to structure and symmetry
Underestimation of previous morbidity Obesity, smoking, diabetes, etc.	More complications and poor outcomes
Adjuvant treatments or recidivism Radiotherapy, chemotherapy	More complications and poor outcomes

Table 56.2 Surgeon-related individual factors which may result in poor outcomes and the need for revision surgeries

BR technique	Factors
Common to all techniques	Error in clinical or anatomical evaluation and in the preoperative design and marking of the patient
Expanders/ prostheses (BR-EP)	Insufficient or excessive pocket dissection with wrong positioning of the implant. Mismanagement of capsulectomies or capsulotomies
	Mismanagement of inframammary fold. Unnecessary disinsertion, incorrect height
	Partial or complete mismanagement of muscular pocket or in the biological or synthetic mesh placement technique (Alloderm, Stratice, Seri, Vicryl, etc.)
	Wrong choice of expander size and/or shape
	Wrong choice of permanent prosthesis size and/ or shape
	Incorrect evaluation of the reconstructured breast before closing. Failure to sit patient down to evaluate symmetry
	Incorrect evaluation and selection of symmetry correcting technique
Flaps—TRAM-DIEP-CLD	Wrong choice of pedicle with inadequate rotation (pedunculated flaps)
	Wrong choice of donor vessels for microsurgical anastomosis which constrain proper positioning of the flap
	Incorrect flap modeling. Modeling performed without sitting the patient to evaluate symmetry
	Failure to consider the height of the inframammary fold in the design of the surgery
Lipofilling ((BR-EP) modeling)	Accidental prosthesis rupture in BR with expanders or prosthesis as a result of a bad technique or use of inadequate surgical instruments
NAC reconstruction	Wrong positioning due to design error

56.3 Patient Evaluation, Attempt on Systematization of Procedures, and Algorithm

Even though there is not a model to determine the ideal reconstruction procedure for patients with an indication for revision surgeries, it is always advisable to try to unify evaluation criteria.

In the interview with the patient, it is always important to analyze their surgery history, any oncologic treatments received, the time elapsed since they were performed/given, and the patient's expectations. It is also important to evaluate their body mass index (BMI) and smoking history as well as other chronic pathologies.

Physical examination is essential and it must always be performed with the patient sitting up, with good lighting, and the observer should sit opposite the patient at the height of the thorax. The patient's arms must hang relaxed at the sides of the body and must then be lifted at 180° in order to expose any potential retraction or alteration. First, breast anatomy should be analyzed (quality of the skin of the reconstructed breast, radiotherapy sequelae, presence of pectoralis major muscle, and type, location, and elasticity of scars) together with body anatomy to evaluate possible flap or LF donor areas. Then, the result of the reconstruction must be evaluated by analyzing the technique used, any defects, and the possible etiology of those defects in the reconstructed breast, in the remaining breast, and also in symmetry. A hypothesis must be made with the information obtained from the surgery plan, including the number of necessary procedures to achieve a good result, and this should be informed to the patient, who should be invited to participate in the decision and in the steps to follow. Iconography of the patient should always be obtained without marking and after marking when the plan has been decided (Figs. 56.1 and 56.2).

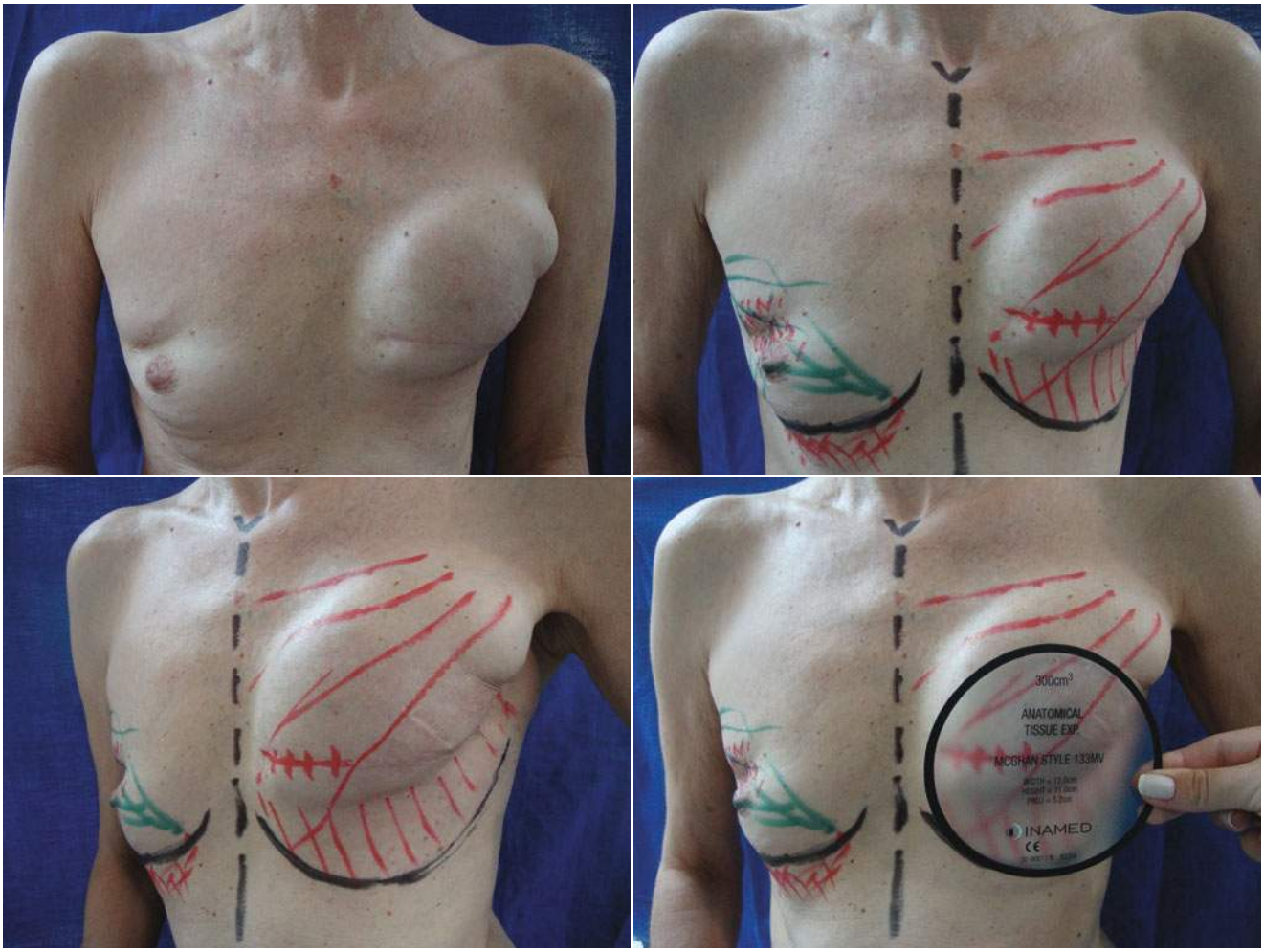


Fig. 56.1 Patient evaluation. Immediate left breast reconstruction with temporary expander and radiotherapy. Malpositioning, rotation, displacement to the armpit, and severe capsular contracture. History of conservative surgery and radiotherapy in right breast with sequelae in the 12 o'clock position (top left). Bilateral planning in two stages. Reconstructive first stage. Lipofilling in right breast, lipoaspiration with correction of the inframammary fold. Replacement of expander with another temporary expander in the left breast adequate to the patient's anatomy with lowering of the inframammary fold, lower pole reconstruction, and lateral breast expansion. Safety approach with incision to be covered by pectoralis major fibers (top right, bottom)

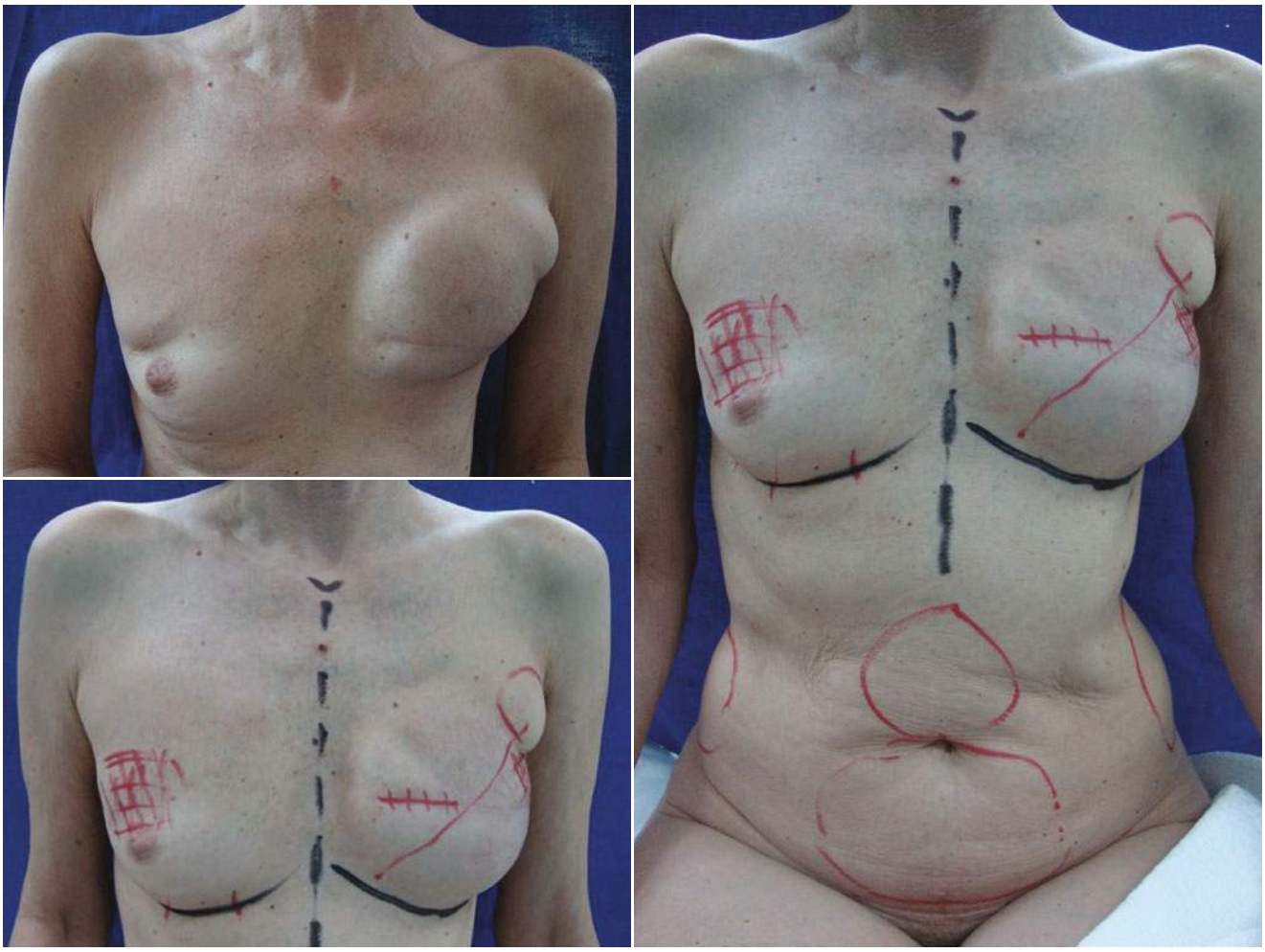


Fig. 56.2 Continued. Patient evaluation. Second reconstructive stage (8 months later): second lipofilling procedure in the right breast and replacement of expander with a prosthesis in the left breast, lipoaspiration in left armpit extension. Lipofilling of upper pole and upper-inner quadrant. Donor sites of adipose tissue in abdomen and flanks are marked (bottom left, right)

Since we have evaluated numerous cases of patients obtaining unsatisfactory results with the different reconstruction techniques available, it is possible, after years of experience, to classify different types of sequelae into subgroups and to simplify the indication for revision and secondary reconstruction procedures.

At the Mastology Department of the University of Buenos Aires Oncology Institute "Ángel H. Roffo," we developed a simple guiding algorithm to manage these situations. The algorithm first analyzes the type of sequelae and the primary reconstruction technique used. Then, the most frequently used techniques are divided into three branches (expanders/prostheses, latissimus dorsi flap (LDF), TRAM flap and its variants) and for each of them the patient's history of radiotherapy is evaluated as well as the quality of the skin regardless of whether it was irradiated or not. We give priority to this clinical evaluation and indicate the revision surgery tactic as shown in the algorithm in Fig. 56.3. The techniques in this algorithm appear in a decreasing order according to their frequency of use. However, on many occasions there are several alternatives for the same patient, in which case we choose the one that offers perspectives of good results with the lowest possible morbidity and the lowest number of surgical interventions. Surprisingly, and many times contrary to popular belief, many patients who had bad results with expanders or prostheses can obtain a successful reconstruction with the same technique, whether it is complemented with LF or not. In addition, LF may constitute a simple and not so aggressive procedure for the correction of defects secondary to prosthetic reconstruction, subsequent radiotherapy, and capsular contractures [12, 13]. Autologous tissue, particularly pediculated TRAM flaps, DIEP flaps, and, to a lesser extent, LDF, is indicated for severe sequelae in bad quality tissues which have scarce possibilities of obtaining good results with less aggressive techniques.

Symmetry correction is considered in all cases without exception, taking into account that, in general, the correction of the remaining breast must be adjusted to the reconstructed

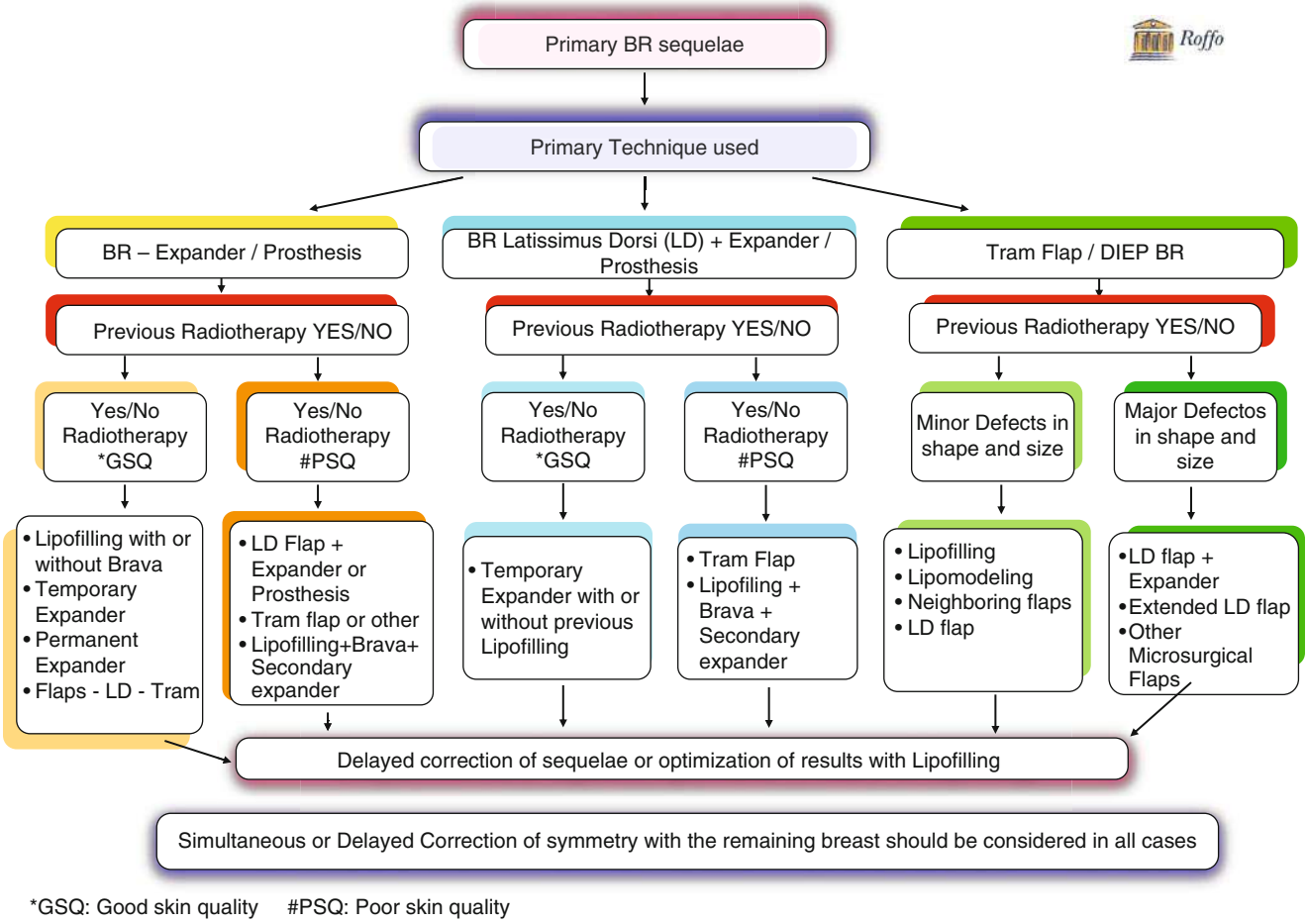


Fig. 56.3 Revision surgery algorithm—breast reconstruction

breast, since the latter has more reconstruction limitations (Fig. 56.3).

Finally, as shown in this algorithm, the addition of LF is considered very useful for the correction of small sequelae and for the optimization of the result regardless of the secondary technique used [13] (Fig. 56.3).

56.4 Revisions After Breast Reconstruction with Expanders and Prostheses

When we see patients with bad results after reconstruction with expanders or implants, we must evaluate and analyze the sequelae and the possible reasons for those results. This evaluation guides the approach to be taken and the technique to be used. Table 56.3 summarizes the most frequently observed defects, and Table 56.4 shows the techniques that can be used.

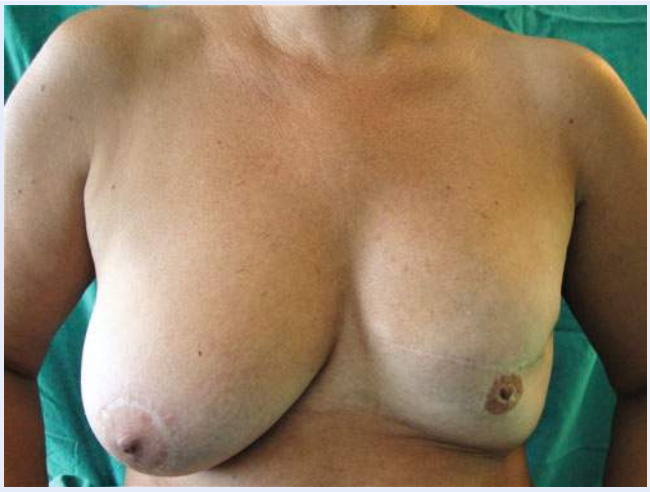
It is clear that each of these patients poses an individual problem not only from the technical but also from the psychological and emotional points of view and also in relation to the expectations they have. Therefore, despite the use of algorithms, it is difficult to accurately systematize the procedures or include all the possible options in this chapter. Below, we present some clinical cases showing the most illustrative examples of sequelae that we observed in our practice and how we solved them.

The first case is a patient who underwent skin-reducing mastectomy (SRM) sparing the nipple-areolar complex with immediate reconstruction using anatomical prosthesis. A post-surgery infection resulted in implant extrusion and loss of implant. She had a secondary reconstruction with expander plus anatomic implant in two stages, which evolved with rotation, downward and outward displacement, and lowering of the inframammary fold (Fig. 56.4).

Figure 56.5 shows the design of the reconstruction with pocket correction, adjusting it to the volume of the prosthesis, which was not replaced to prevent rotation, using the periareolar and vertical scar approach and raising of the inframammary fold through the previous scar with suture of the cutaneous adipose flap to the rib cage using slowly reabsorbing material.

The second case is a patient who underwent a mastectomy and immediate reconstruction with a temporary anatomical

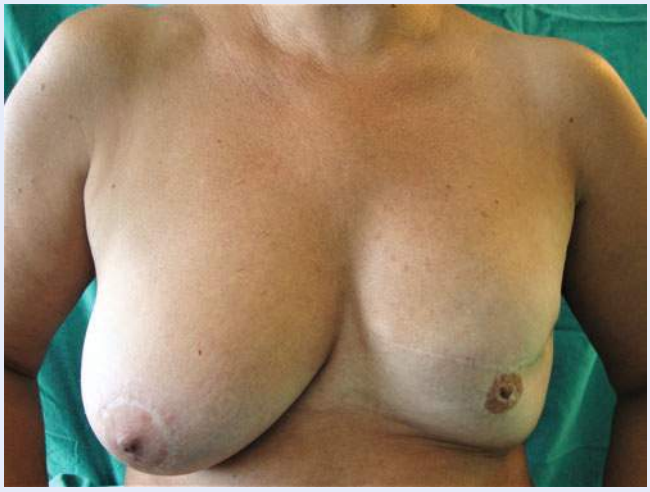
Table 56.3 BR with expanders/prostheses



Prosthesis or expander rotation
Poor lower pole expansion
Excessive filling of upper pole
Implant lateralization or centralization
Lack of projection
Defects in breast base width, too wide or too narrow
High, low, or asymmetrical inframammary fold in relation to the remaining breast
Poorly defined inframammary fold
Bad scar expansion. Presence of "dog ears"
Lower or upper pole tissue hypotrophy with or without rippling
Different grades of capsular contractures with or without previous radiotherapy
Asymmetry due to poor outcome of the reconstructed breast, the remaining breast or both
Incorrect placement of nipple-areolar complex

Analysis of most frequently observed sequelae

Table 56.4 BR with expanders/prostheses. Techniques



• Correction of pocket and IMF
• Secondary two-stage BR with exp-prost
• Secondary BR with permanent expander
• BR with autologous tissue
• Lipofilling
• Secondary correction of the remaining breast
• Correction of prosthesis rotation
• Secondary reconstruction of NAC

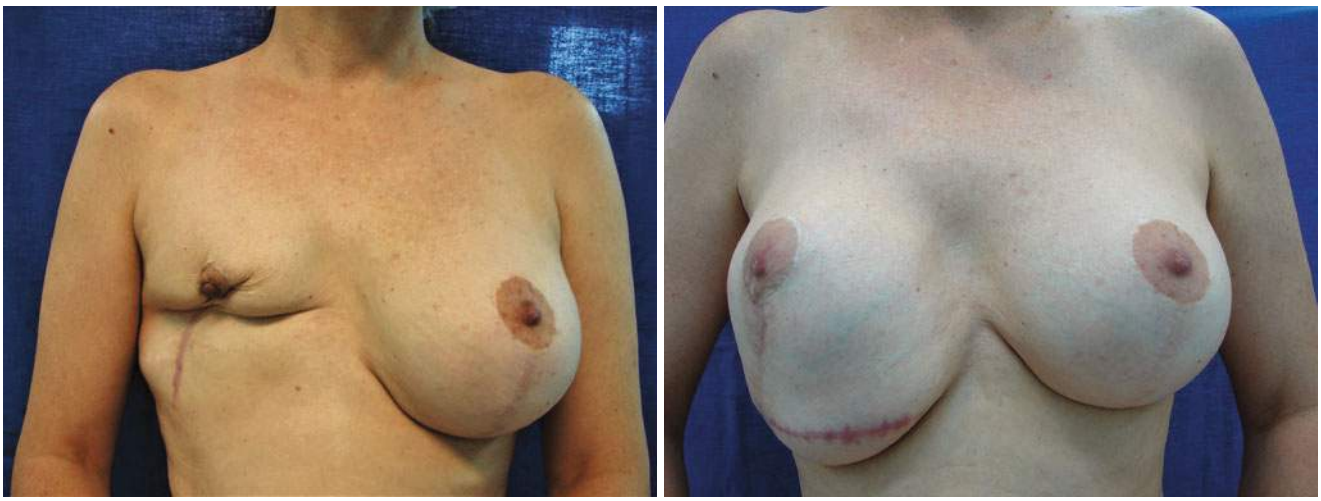


Fig. 56.4 BR with expanders/prosthesis. Secondary breast reconstruction. Prosthesis rotation, implant lateralization, and lowering with asymmetry in relation to the reconstructed breast

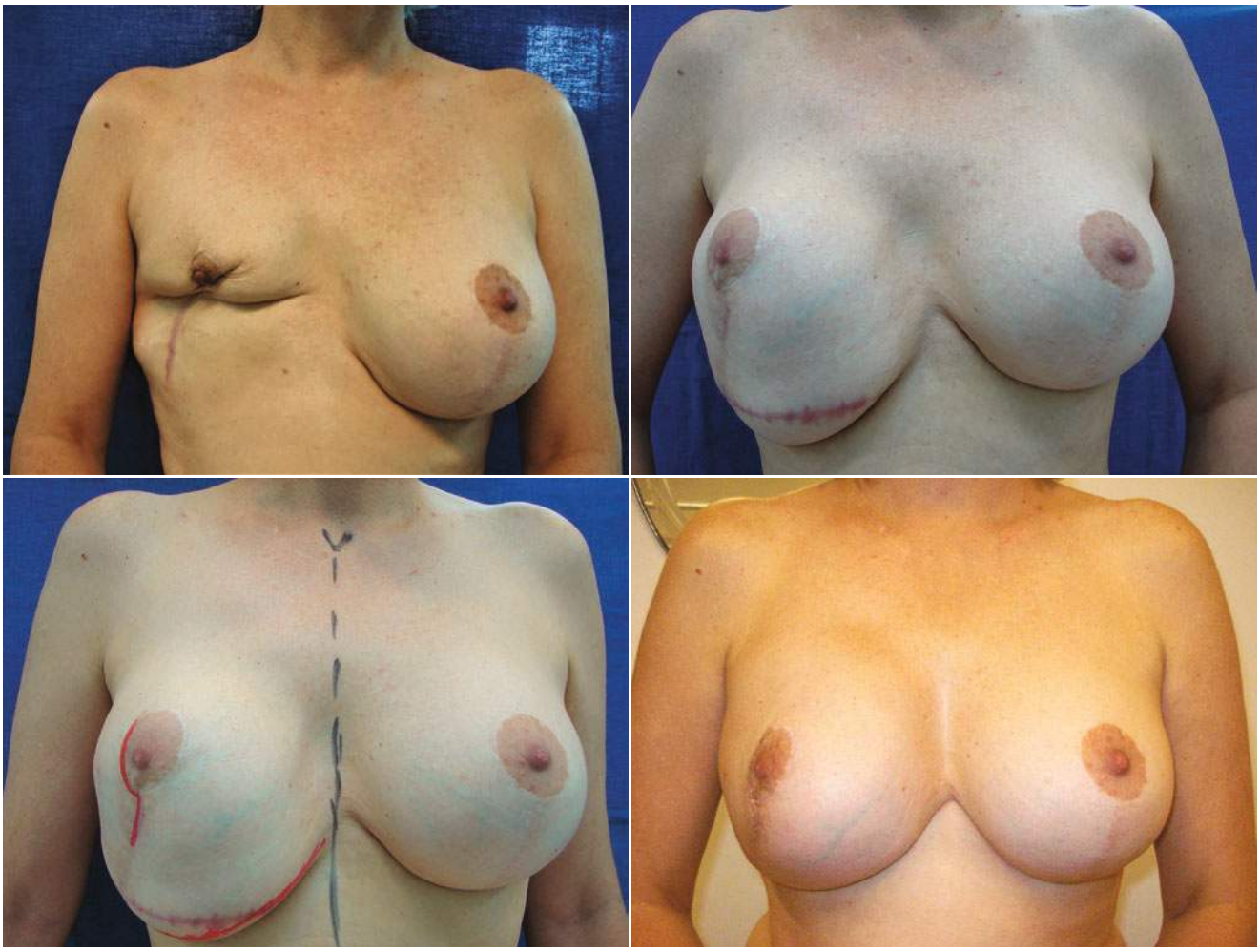


Fig. 56.5 Continued. BR with expanders and prosthesis. Secondary breast reconstruction. Prosthesis rotation, implant lateralization, and lowering with asymmetry in relation to the reconstructed breast (top). Design of reconstruction with correction of pocket (reduction) through periareolar and vertical approach and raising of inframammary fold with suture to the rib cage (bottom left). Final result (bottom right)

expander. She did not receive adjuvant radiotherapy. Due to personal issues, she did not complete the expansion properly and made an appointment 18 months later presenting with severe capsular contracture and marked asymmetry with raised inframammary fold and volume and shape alteration (Fig. 56.6). Figure 56.7 shows the design of the pocket correction through the previous incision in the pectoral muscle and upper, lower, anterior, and concentric capsulotomies. An anatomical prosthesis was placed and adjusted to thorax anatomy and to the structure of the remaining breast. Symmetry correction was performed simultaneously with a pexy of the left breast, with a good final outcome.

The patient in the third case underwent reconstruction with expander and prosthesis in two stages, nipple reconstruction and reduction of the remaining breast. An unfavorable result was obtained, with capsular contracture and implant medial and upper displacement, nipple lateralization, and marked asymmetry (Fig. 56.8).

Secondary reconstruction with expander and anatomical prosthesis was performed in two stages, with concentric, inferior and anterior capsulotomies, and resection of the reconstructed nipple. Secondary reduction of the remaining breast and secondary nipple reconstruction with star flap (Fig. 56.9).

The fourth case is a patient who underwent single-stage prosthetic reconstruction, with no correction of the remaining breast. An unfavorable outcome was obtained, with capsular contracture, medial and upward displacement of the implant, retractile scar in the lower pole, and marked asymmetry (Fig. 56.10).

The first stage consisted in replacing the prosthesis with a temporary expander with capsulotomies and lowering of the inframammary fold. The expander was replaced by a permanent prosthesis, and secondary reduction of the remaining breast was performed. In the final outcome, correction of the lower pole of the right breast with LF is still pending (Fig. 56.11).

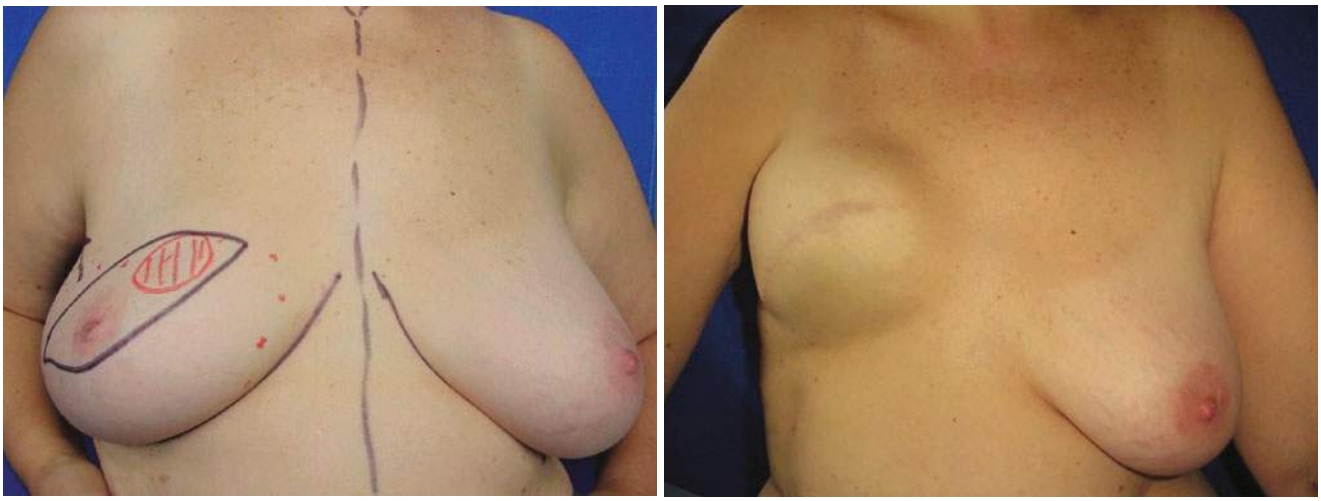


Fig. 56.6 BR with expanders/prosthesis. Immediate breast reconstruction with temporary expander. Severe capsular constracture without radiotherapy. Marked asymmetry with raised inframammary fold, shape, and size alteration

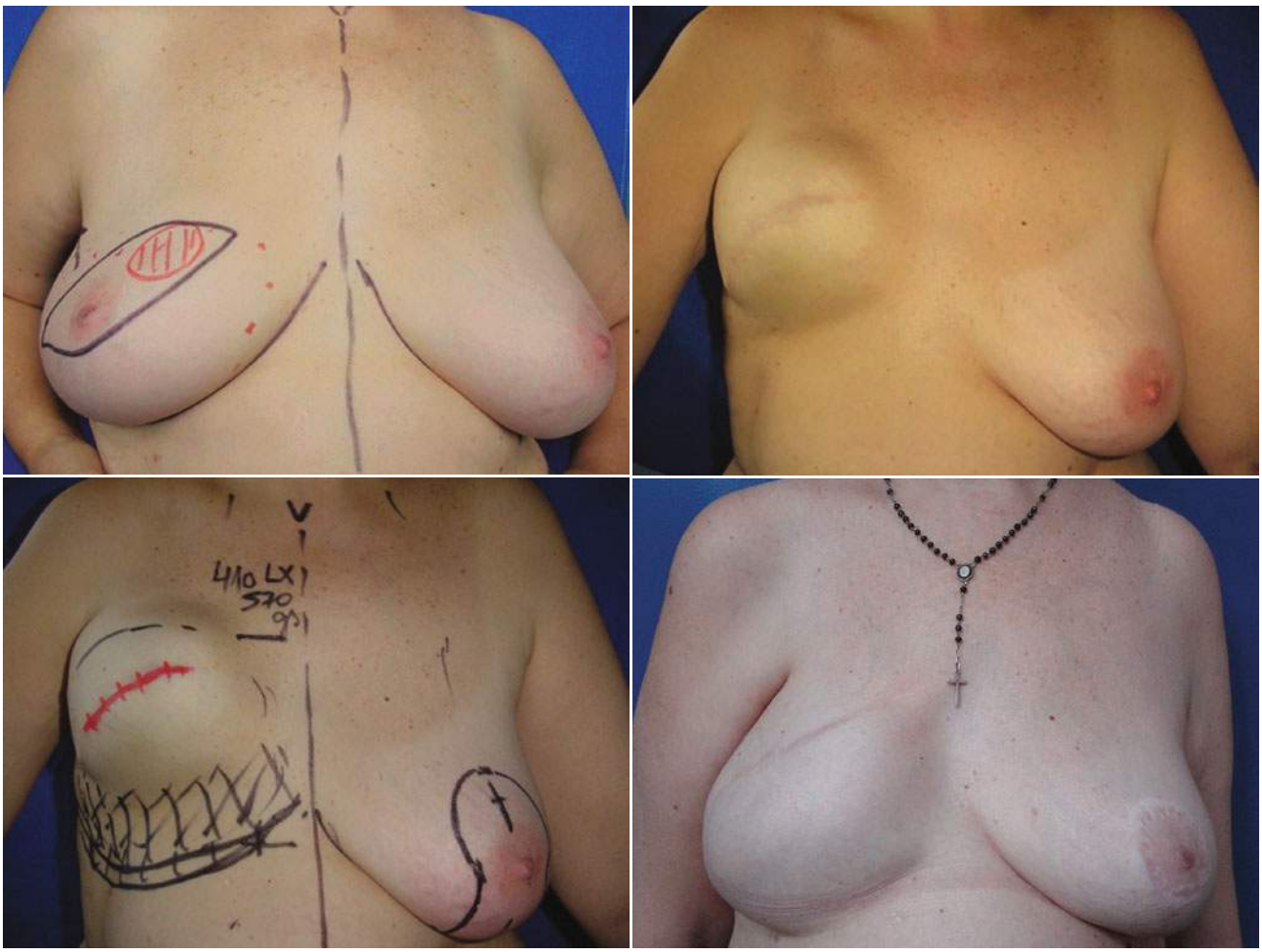


Fig. 56.7 Continued. BR with expanders/prosthesis. Immediate breast reconstruction with temporary expander. Severe capsular constracture without radiotherapy. Marked asymmetry with raised inframammary fold, shape, and size alteration (top). Design of the pocket correction through the previous incision in the pectoral muscle and capsulotomies. Placement of anatomical prosthesis adjusted to thorax anatomy and to the structure of the remaining breast. Symmetry correction performed simultaneously with a pexy of the left breast. Long-term final result (bottom)

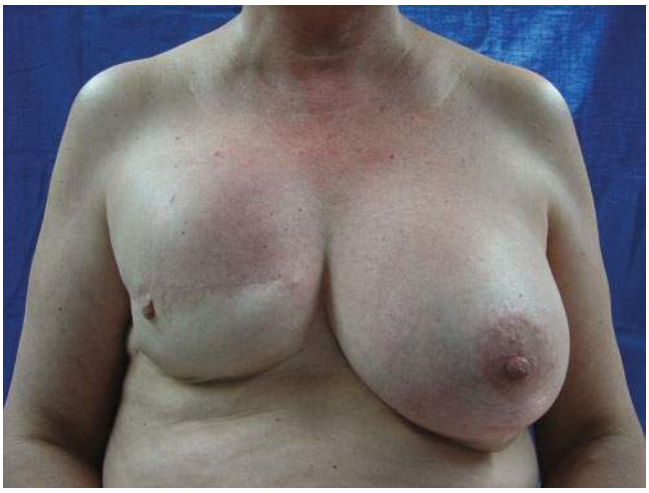


Fig. 56.8 BR with expanders/prosthesis. Patient underwent two-stage reconstruction with expander and prosthesis, nipple reconstruction, and reduction of the remaining breast. Unfavorable results with capsular contracture and implant medial and upper displacement, nipple lateralization, and marked asymmetry

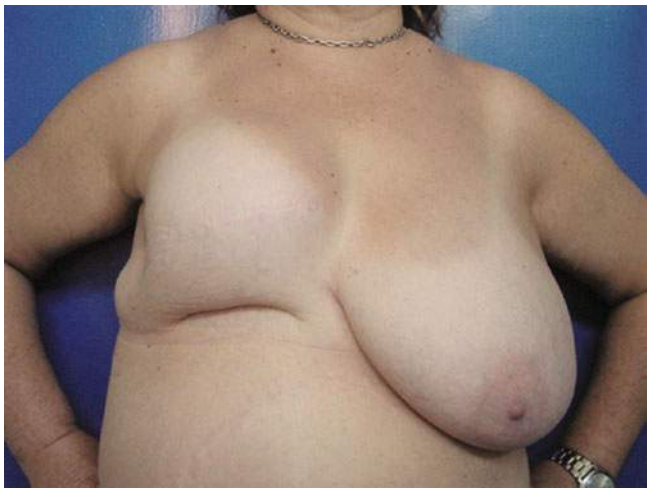


Fig. 56.10 BR with expanders/prosthesis. Patient underwent a single-stage prosthetic reconstruction. Unfavorable result with capsular contracture and implant medial and upper displacement, retractile scar in the lower pole, and marked asymmetry

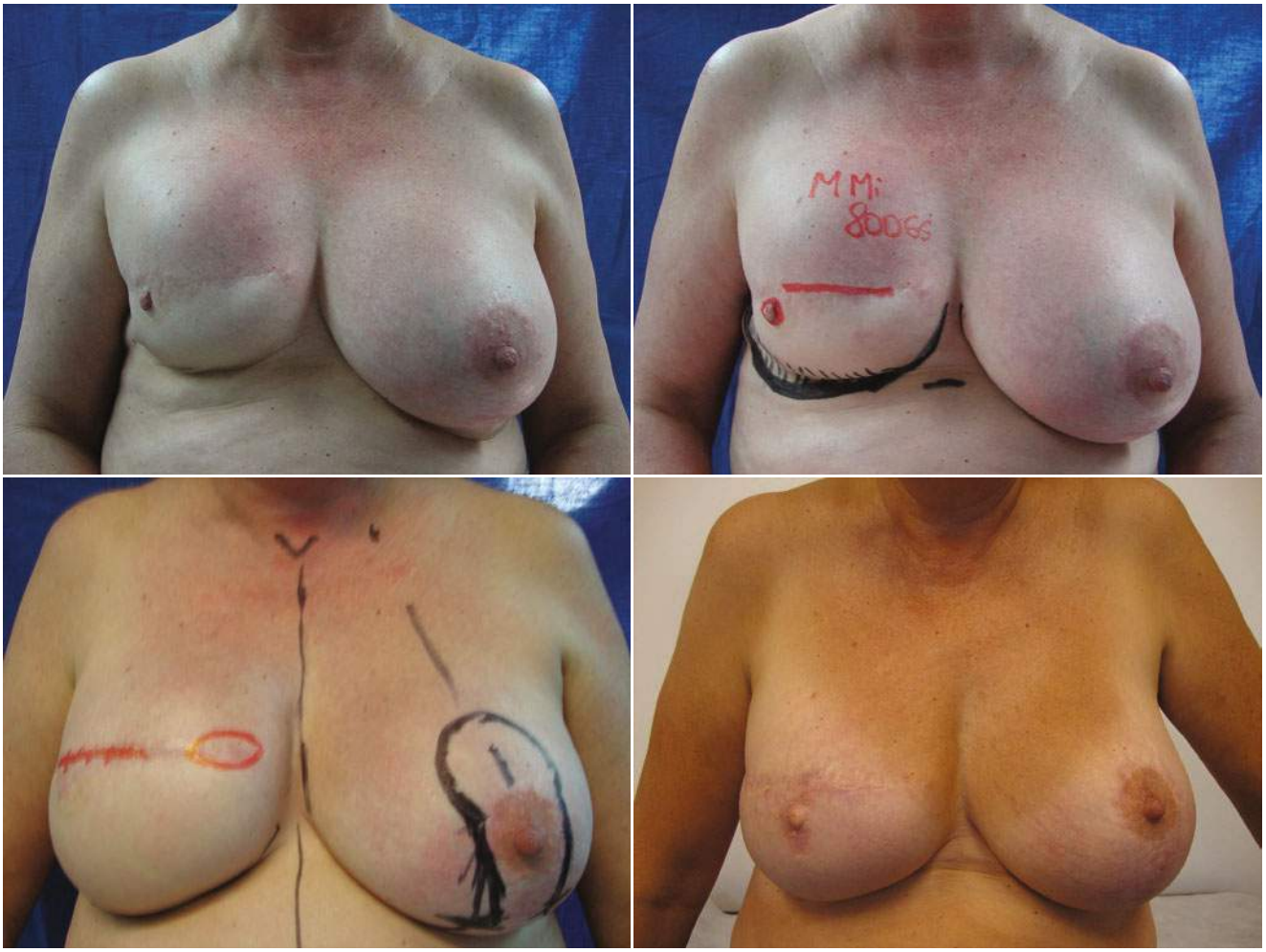


Fig. 56.9 BR with expanders/prosthesis. Patient underwent two-stage reconstruction with expander and prosthesis, nipple reconstruction, and reduction of the remaining breast. Unfavorable results with capsular contracture and implant medial and upper displacement, nipple lateralization, and marked asymmetry (top left). First stage consisted in nipple resection and replacement of prosthesis with temporary expander, performing capsulotomies, and lowering the inframammary fold (top right). Replacement of expander with prosthesis and secondary reduction of the remaining breast (bottom left). Final result after secondary reconstruction of the nipple prior to the tattoo (bottom right)

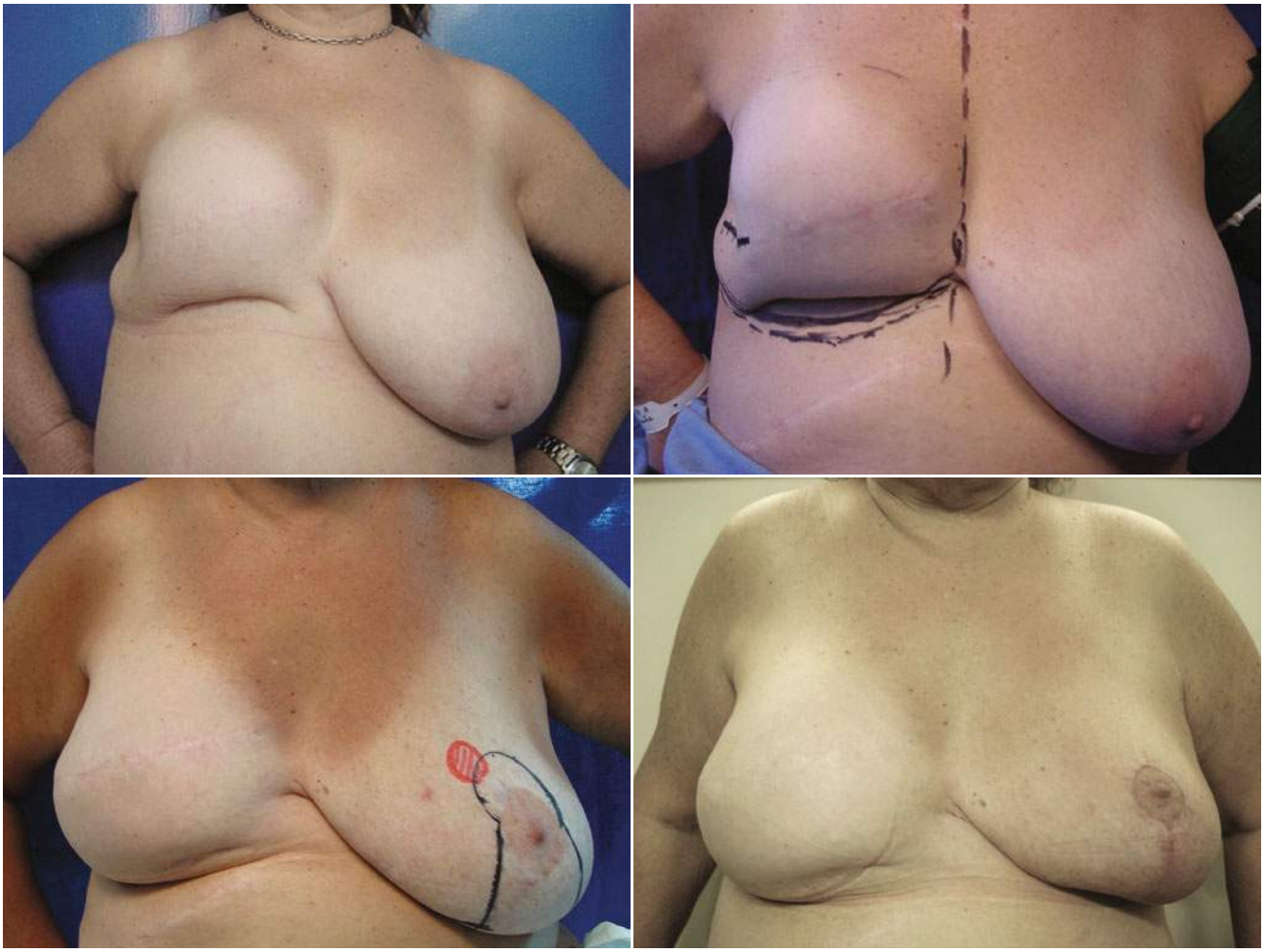


Fig. 56.11 BR with expanders/prosthesis. Patient underwent a single-stage prosthetic reconstruction. Unfavorable result with capsular contracture and implant medial and upper displacement, retractile scar in the lower pole, and marked asymmetry. First stage consisted in replacing the prosthesis with a temporary expander, performing capsulotomies, and lowering the inframammary fold (top right). Replacement of expander with prosthesis and secondary reduction of the remaining breast (bottom left). In the final outcome, correction of the lower pole of the right breast with lipofilling is still pending (bottom right)

The fifth case is a patient with a history of right breast mastectomy, breast prosthetic reconstruction, NAC reconstruction, and radiotherapy. She evolved with severe capsular contracture with intra- and extracapsular implant rupture and marked asymmetry. The right breast skin had good elasticity with no marked sclerosis (Fig. 56.12).

The first stage consisted in the replacement of the prosthesis with a temporary expander with capsulotomies and lowering of the inframammary fold. The expander was replaced with a prosthesis and then LF was performed (Fig. 56.13).

The sixth case is a patient with a history of right breast mastectomy, breast prosthetic reconstruction, and radiotherapy. She had elastic skin with mild actinic sclerosis and marked asymmetry (Fig. 56.14).

The defect was corrected by replacing the prosthesis with a double-lumen permanent expander following multiple capsulotomies and simultaneous pexy of the remaining breast (Fig. 56.15).

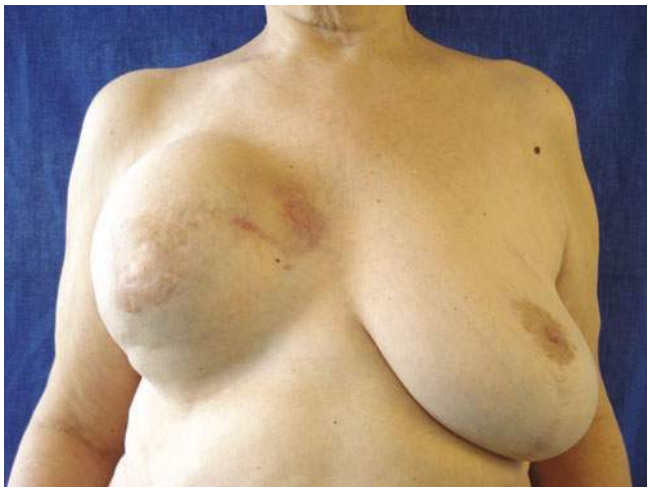


Fig. 56.12 BR with expanders/prosthesis. Patient with a history of right breast mastectomy, breast prosthetic reconstruction, NAC reconstruction, remaining breast reduction, and radiotherapy. Severe capsular contracture with intra- and extracapsular implant rupture. Marked asymmetry. Right breast skin with good elasticity and no marked sclerosis

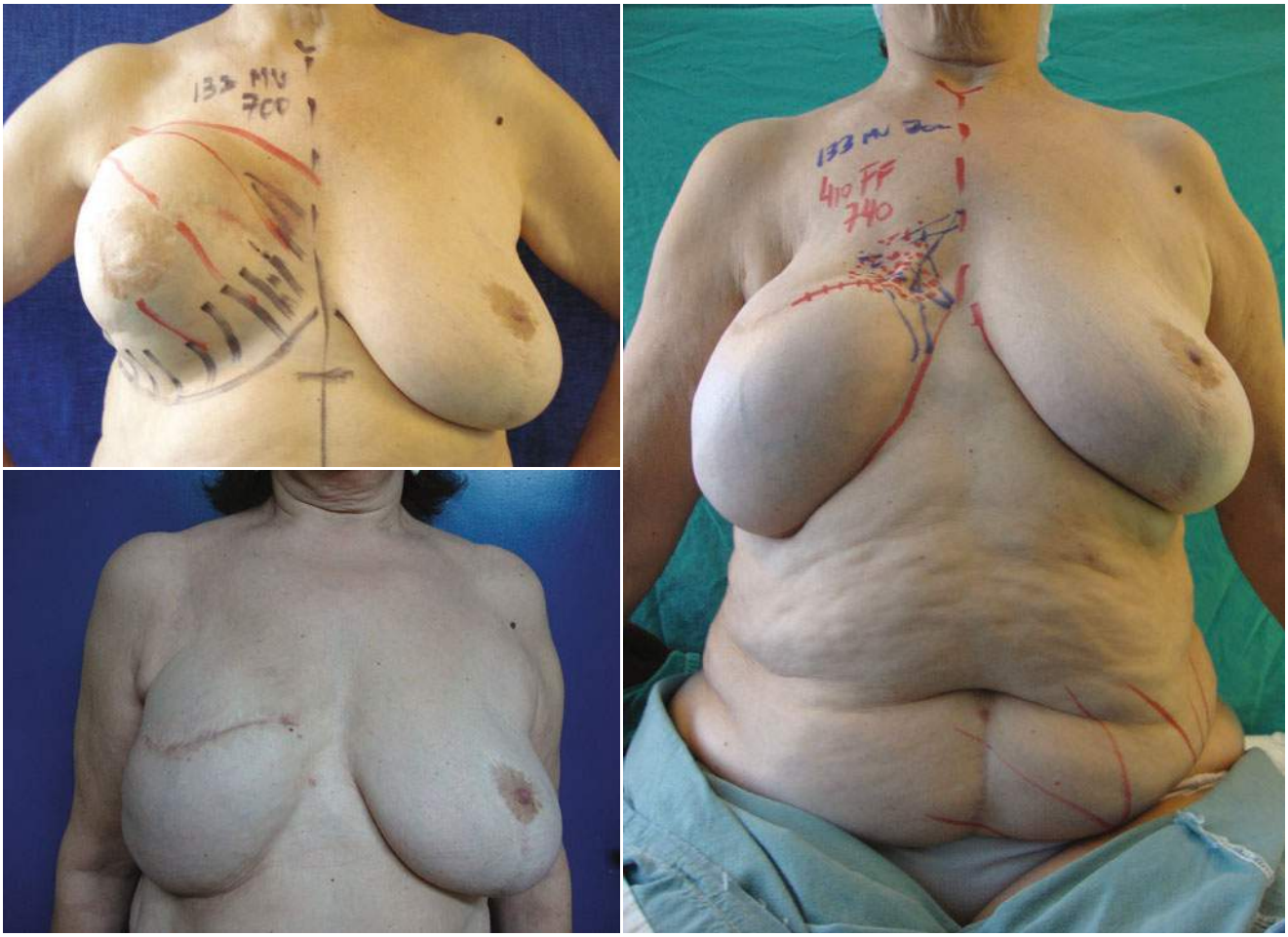


Fig. 56.13 BR with expanders/prosthesis. Patient with a history of right breast mastectomy, breast prosthetic reconstruction, NAC reconstruction, remaining breast reduction, and radiotherapy. Severe capsular contracture with intra- and extracapsular implant rupture. Marked asymmetry. Right breast skin with good elasticity and no marked sclerosis. First stage consisted in replacing prosthesis with temporary expander, performing capsulotomies and lowering the inframammary fold (top left). Replacement of expander with prosthesis and subsequent lipofilling (right). Final result (bottom-left)

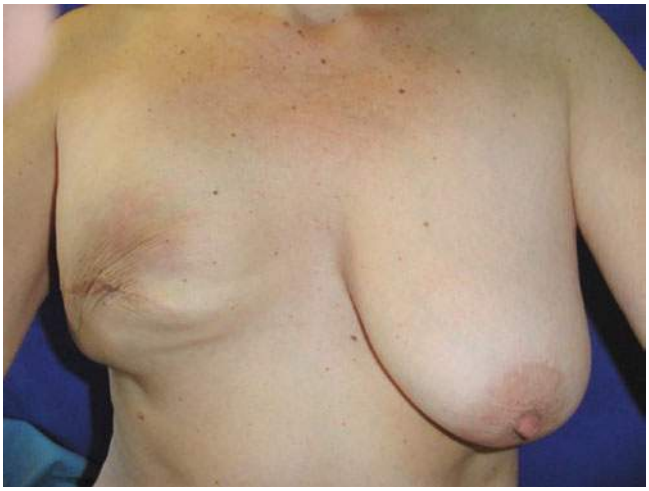


Fig. 56.14 BR with expanders/prosthesis. Patient with a history of right breast mastectomy, breast prosthetic reconstruction, and radiotherapy. Elastic skin with mild actinic sclerosis. Marked asymmetry

The seventh case is a patient with left breast neoplasia, who underwent a mastectomy, sentinel node biopsy, and immediate reconstruction with temporary anatomical expander. She developed an infection during treatment with adjuvant chemotherapy and residual capsular contracture (Fig. 56.16).

The sequelae was evaluated, and since the skin had not been irradiated and had good elasticity, placement of a permanent double-lumen anatomical expander was indicated, with concentric, inferior, and anterior capsulotomies and simultaneous reduction of the remaining breast (Fig. 56.17).

In some cases, depending on the sequelae and the biotype of the patient, it is not possible to perform a secondary prosthetic reconstruction and flaps must thus be indicated. This was required in the eighth case. This is an obese patient who received radiotherapy of the mastectomy site and underwent single-stage prosthetic reconstruction with simultaneous reduction of the remaining breast. A sequela with severe

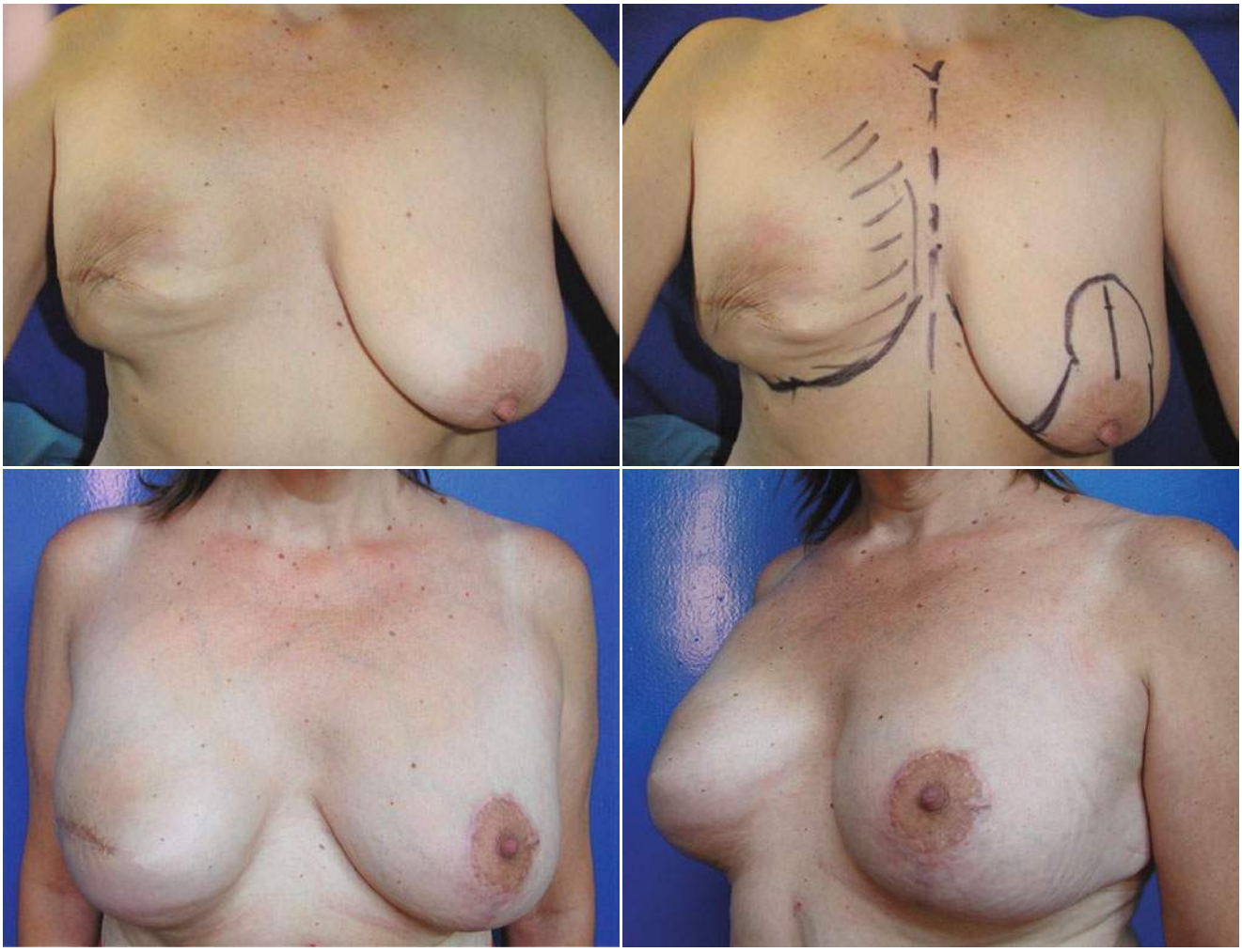


Fig. 56.15 BR with expanders/prosthesis. Correction of defect with replacement of prosthesis with a double-lumen permanent expander after performing multiple capsulotomies and simultaneous pexy of the remaining breast

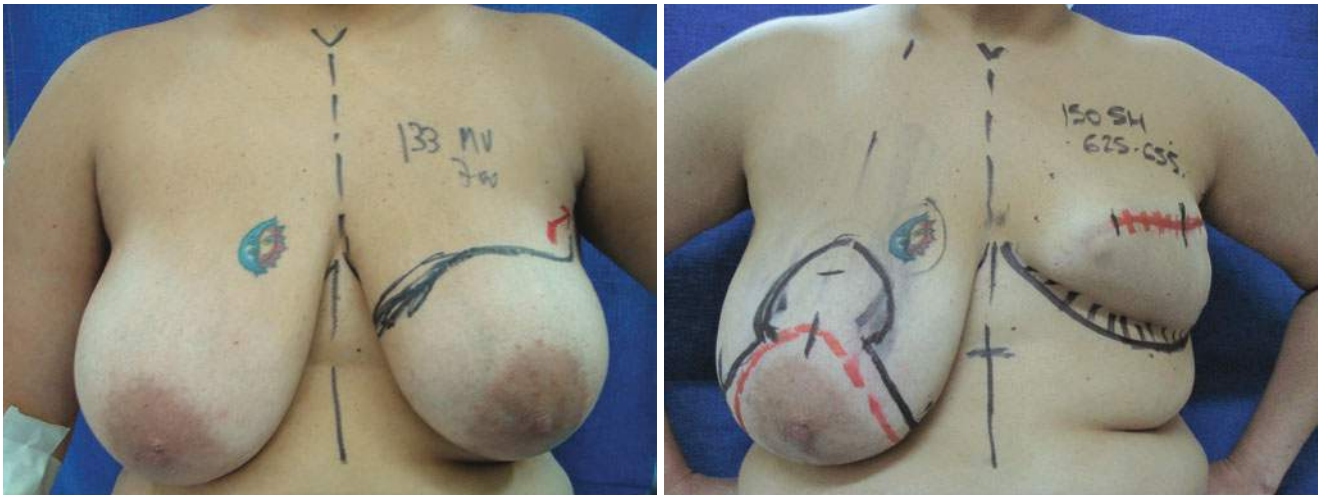


Fig. 56.16 Patient with left breast neoplasia, who underwent a mastectomy, sentinel node biopsy, and immediate reconstruction with temporary anatomical expander. She developed an infection during treatment with adjuvant chemotherapy and residual capsular contracture with raised inframammary fold. Marked asymmetry

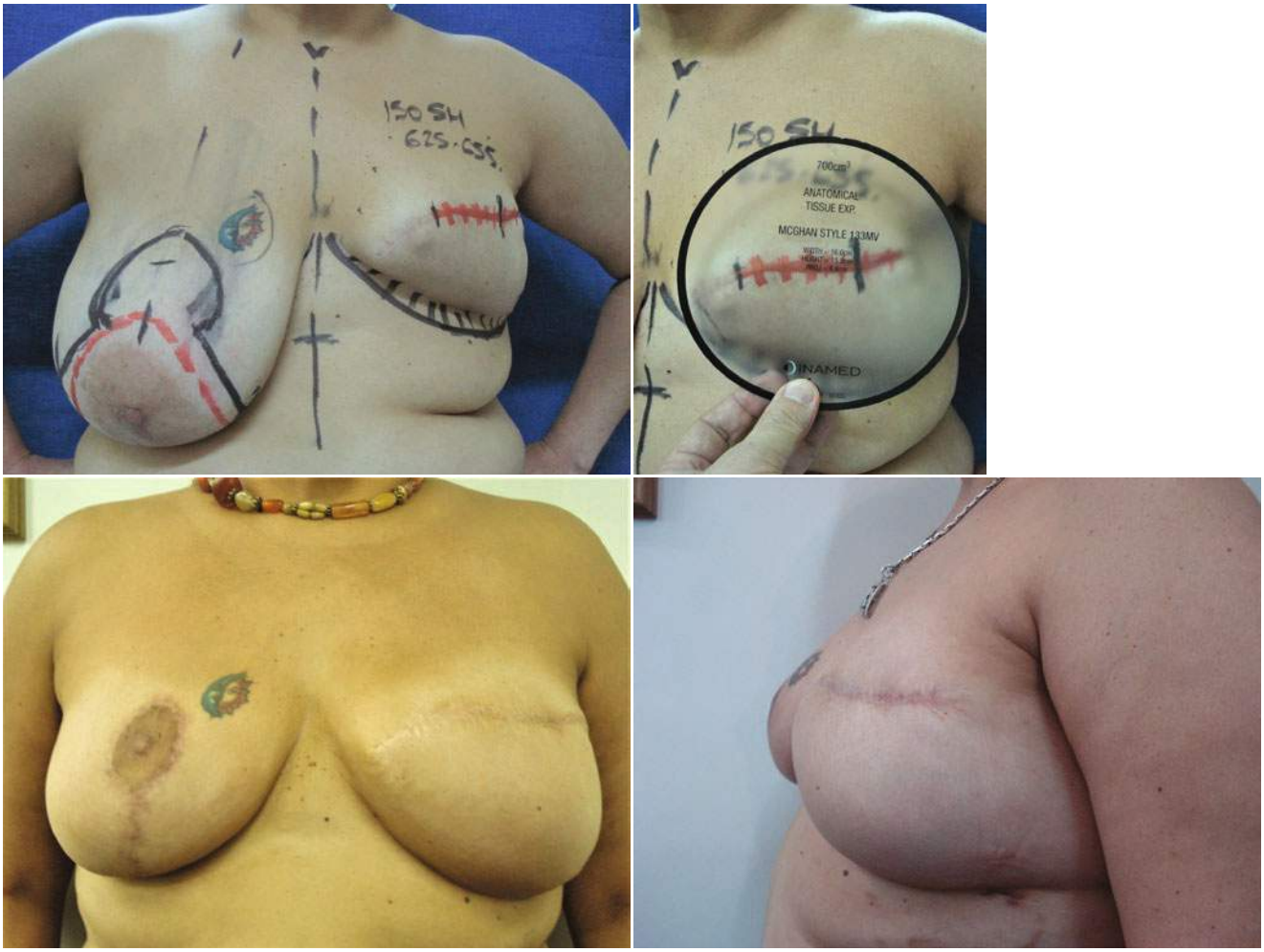


Fig. 56.17 BR with expanders/prosthesis. The sequelae was evaluated, and since the skin had not been irradiated and had good elasticity, placement of a permanent double-lumen anatomical expander was indicated, with concentric, inferior, and anterior capsulotomies and simultaneous reduction of the remaining breast

capsular contracture of the left breast is observed, with moderate to severe actinic sclerosis and marked asymmetry (Fig. 56.18).

Secondary reconstruction was indicated to remove the prosthesis with a DIEP flap with an anastomosis of the internal mammary vessels and secondary reduction of the right breast (Fig. 56.19).

LF indication: Ninth case. A patient with right breast neoplasia. A mastectomy, sentinel node biopsy, and immediate breast reconstruction were performed placing a temporary anatomical expander and then a prosthesis. She underwent adjuvant radiotherapy and involved with cutaneous retraction and alteration in breast size and shape, moderate capsular contracture, and breast asymmetry (Fig. 56.20). It was corrected with LF and Rigottomies (transcutaneous subcisions). The last step was nipple reconstruction with the star flap technique and pexy of the remaining breast (Fig. 56.21).

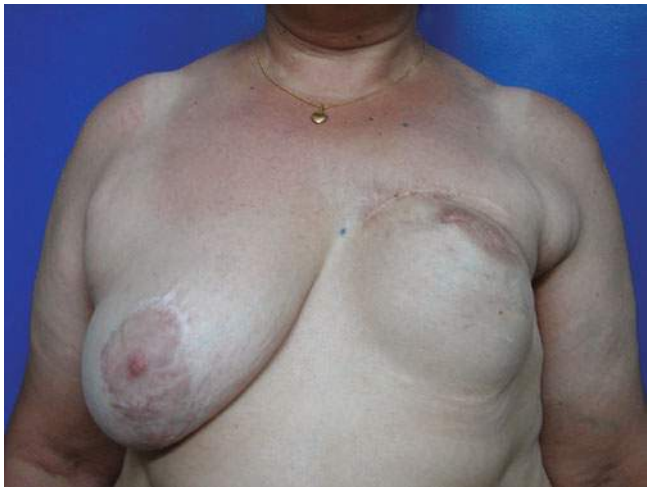


Fig. 56.18 Patient with left breast neoplasia, who underwent a mastectomy, radiotherapy, and immediate reconstruction with round prosthesis. She developed capsular contracture with raised inframammary fold. Marked asymmetry

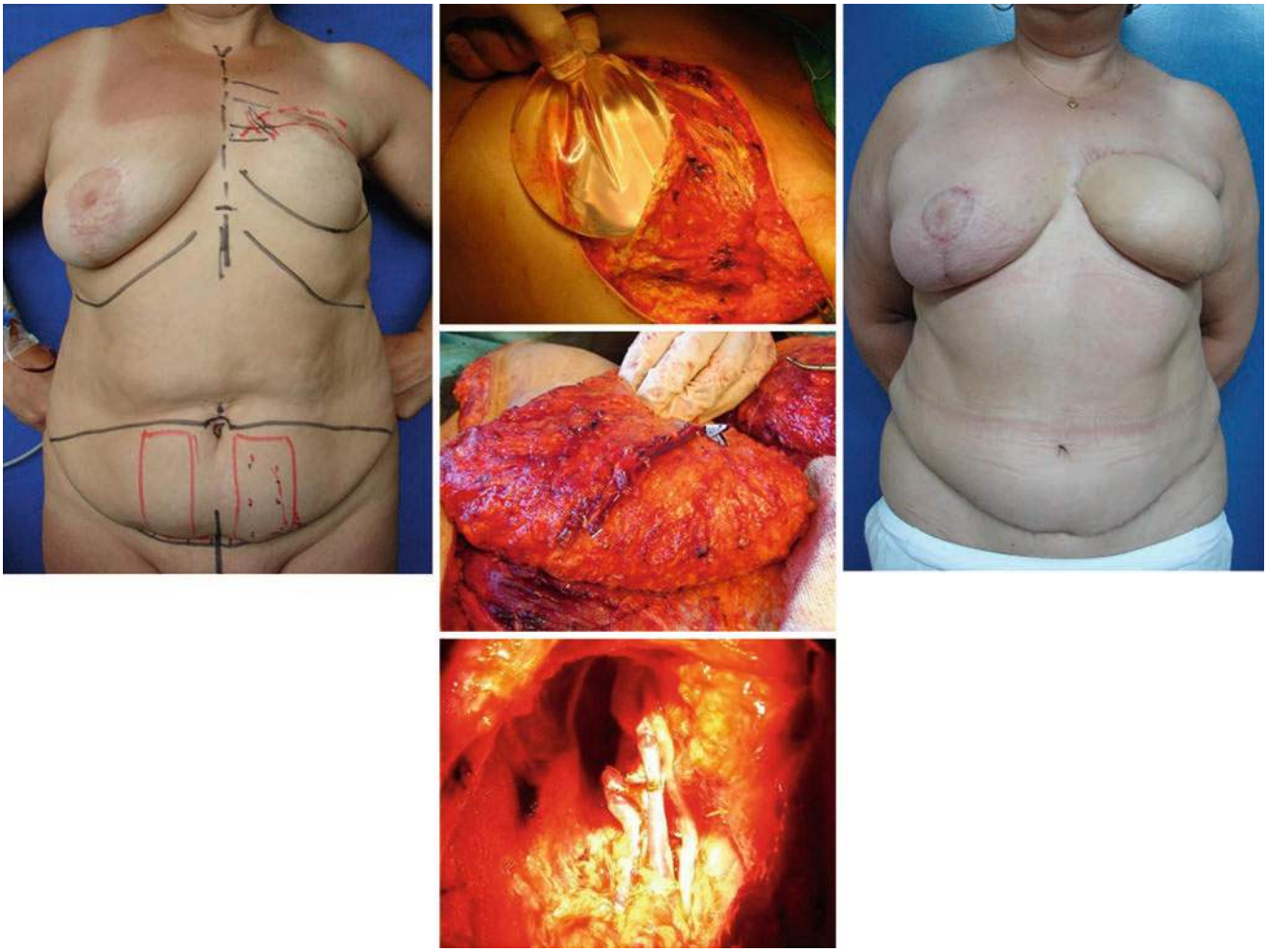


Fig. 56.19 BR with prosthesis. Secondary reconstruction is indicated to remove the prosthesis with a DIEP flap, with anastomosis of the internal mammary vessels and secondary reduction of the right breast

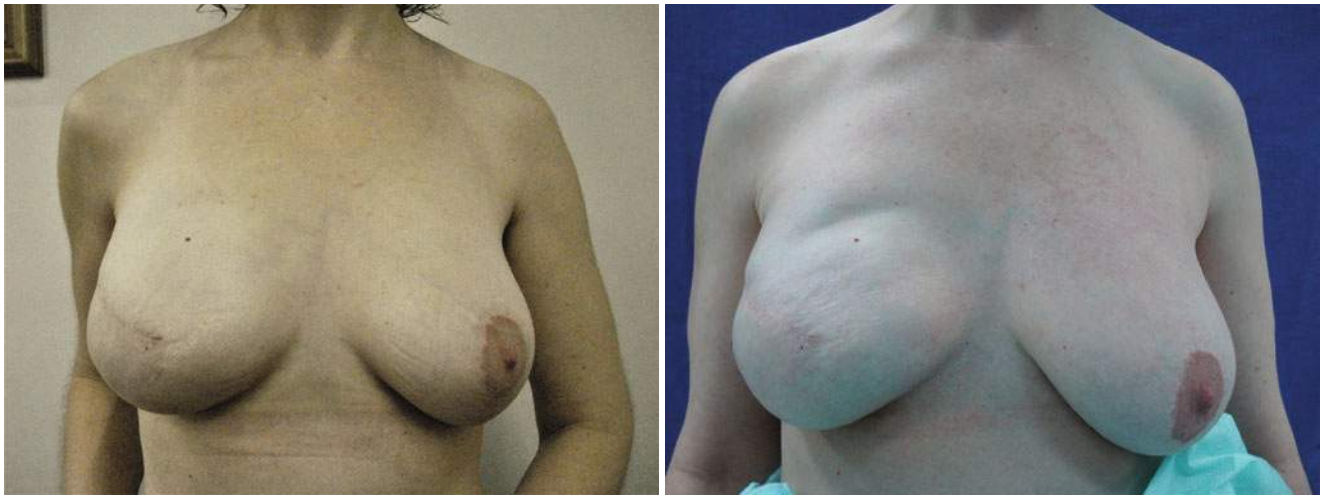


Fig. 56.20 Patient with right breast neoplasia underwent a mastectomy, sentinel node biopsy, and immediate breast reconstruction with placement of a temporary anatomical expander and then a prosthesis. Adjuvant radiotherapy with cutaneous retraction and alteration in breast volume and shape. Moderate capsular contracture. Breast asymmetry

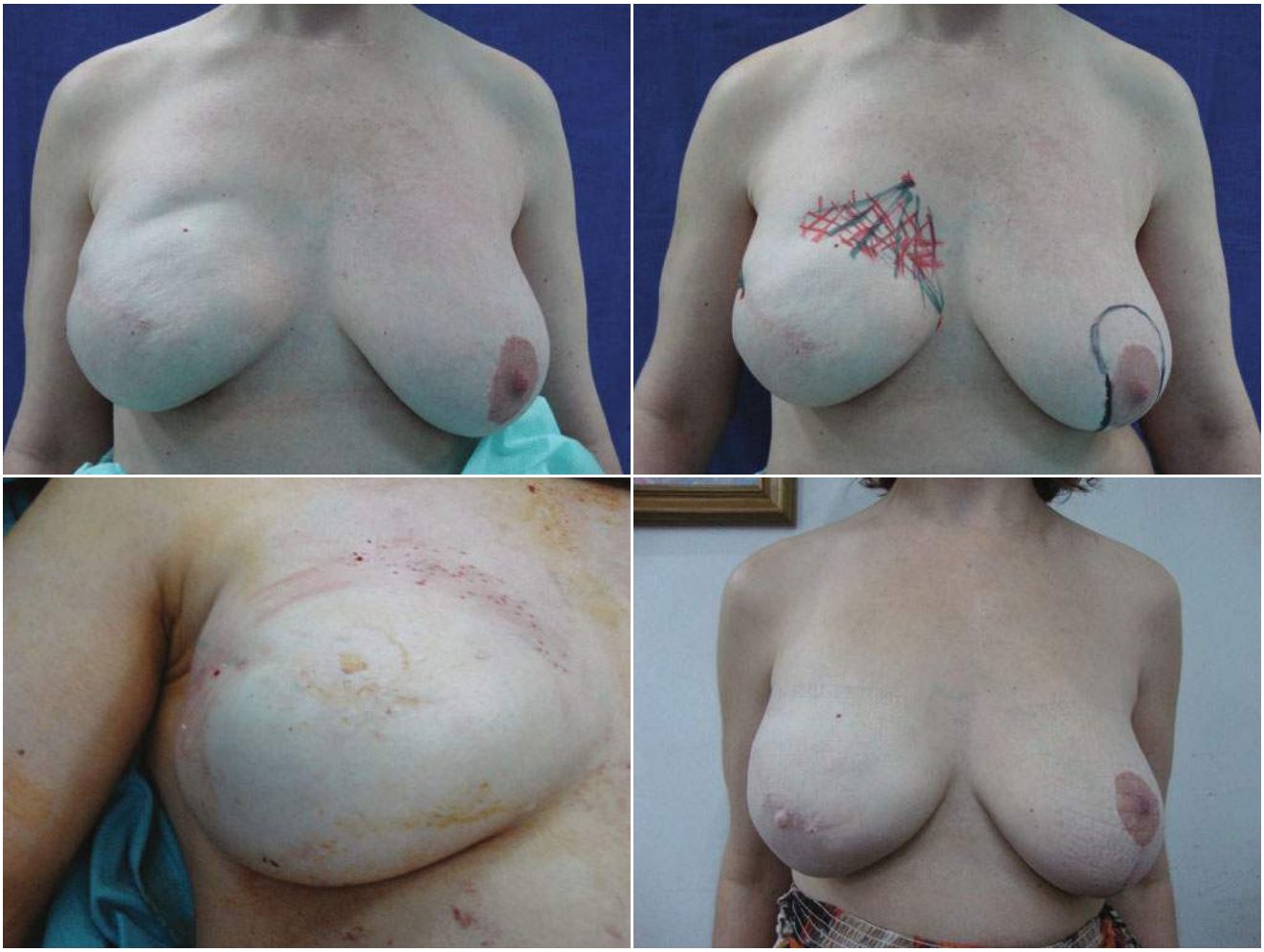


Fig. 56.21 Continued. BR with expanders/prosthesis. Shape and size sequelae in the right breast secondary to radiotherapy. Moderate contracture. Correction with lipofilling and Rigottomies. Nipple reconstruction with the star flap technique and pexy of the remaining breast

56.5 Revisions After Breast Reconstruction with Autologous Tissue

When patients present with poor results of reconstructions with autologous tissue, we must, as we do with other techniques, evaluate and analyze the sequelae and the possible reasons for those results. This evaluation guides the approach to be taken and the technique to be chosen. Table 56.5 summarizes the most frequently observed defects and Table 56.6 shows the techniques that can be used.

As with revisions of patients with expander and prostheses, it is difficult to accurately systematize the procedures or present all the possible alternatives. The algorithm presented above (Fig. 56.3) shows the usefulness of the various techniques and our preferences depending on the magnitude of the defect to be corrected (major or minor). We present some clinical cases of the most illustrative examples of sequelae we observed and how we solved them.

The tenth case is a patient with right breast neoplasia, mastectomy, radiotherapy, and delayed BR with pedunculated TRAM flap with pexy of the remaining breast. Flap with no projection of the lower pole and lowered and undefined inframammary fold, defect in upper pole volume (Fig. 56.22).

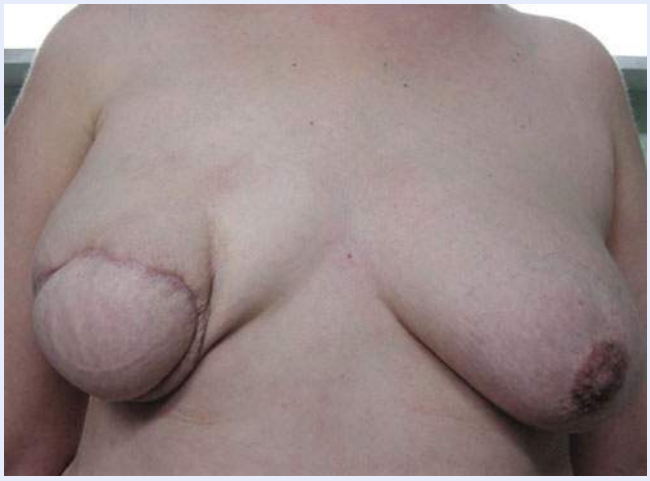
The defect was corrected through reconstruction and raising of the inframammary fold with a polypropylene mesh and lipofilling for the correction of the upper pole deficit and reconstruction of the nipple-areolar complex (Fig. 56.23).

The eleventh case is a patient with left breast neoplasia, who is a smoker and had received radiotherapy. She had had a skin-conserving mastectomy and immediate BR with microsurgical free TRAM flap. She developed extensive cutaneous necrosis as a complication (Fig. 56.24).

It was decided to adopt a watchful waiting approach with periodic dressing changes, and healing of the defect was observed. Then, flap modeling correction was performed by drying the scar and sequelae fibrosis with a very good result after NAC reconstruction (Fig. 56.25).

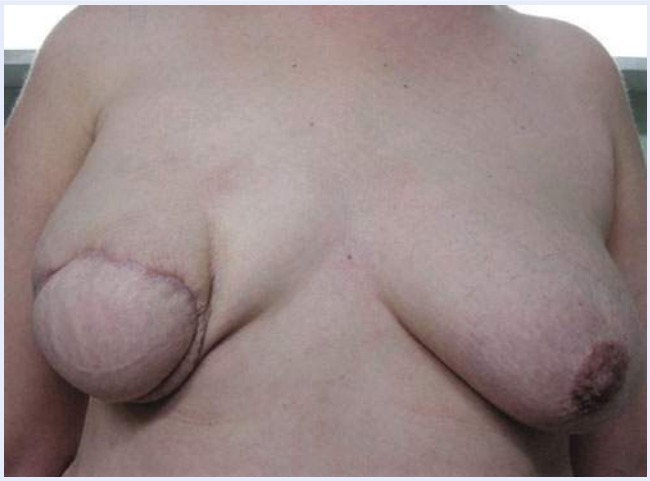
The twelfth case is a patient with left breast neoplasia, mastectomy, and adjuvant radiotherapy. Delayed reconstruction was performed with pediculated TRAM flap. As a result, the

Table 56.5 BR with autologous tissue



Analysis of most frequently observed sequelae
Shape alteration
Size alteration (excess or defect)
High, low, or asymmetrical inframammary fold in relation to the remaining breast
Poorly defined inframammary fold
Asymmetry due to poor outcome of the reconstructed breast, the remaining breast or both
Incorrect placement of nipple-areolar complex

Table 56.6 BR with autologous tissue. Techniques



• Flap modeling
• Inframammary fold reconstruction or modeling
• Secondary BR with neighboring flaps
• Secondary BR with autologous tissue
• Lipofilling
• Secondary correction of the contralateral breast
• Secondary reconstruction of NAC

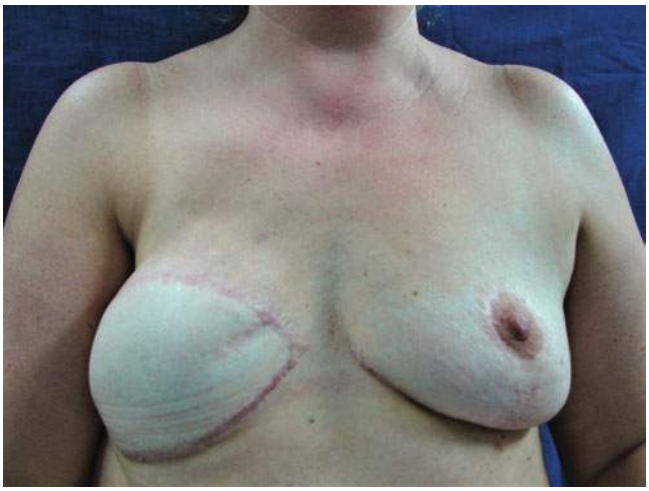


Fig. 56.22 Patient with right breast neoplasia, mastectomy, radiotherapy, and delayed BR with pedunculated TRAM flap, with pexy of the remaining breast. Flap with no projection and lowered and undefined inframammary fold. Defect in upper pole volume

flap exceeded the breast margins with a bigger size than the remaining breast, lowering of the inframammary fold, and asymmetry (Fig. 56.26).

The defect was corrected by modeling the flap and drying the scar and excess external tissue and modeling of the rectus abdominis muscle pedicle by inverting it in order to mark the inframammary fold, achieving a good result after NAC reconstruction (Fig. 56.27).

The thirteenth case is a patient with right breast neoplasia, mastectomy, and radiotherapy. Delayed reconstruction with pedunculated TRAM flap was performed. The flap exceeded the margins of the breast outward and downward in size, with lowered inframammary fold and asymmetry (Fig. 56.28) [14].

The right breast defect was corrected by modeling the flap with a surgical tape mold of the remaining breast (S Kroll) [15] and resection of excess external tissue. Result after NAC Reconstruction (Fig. 56.29).

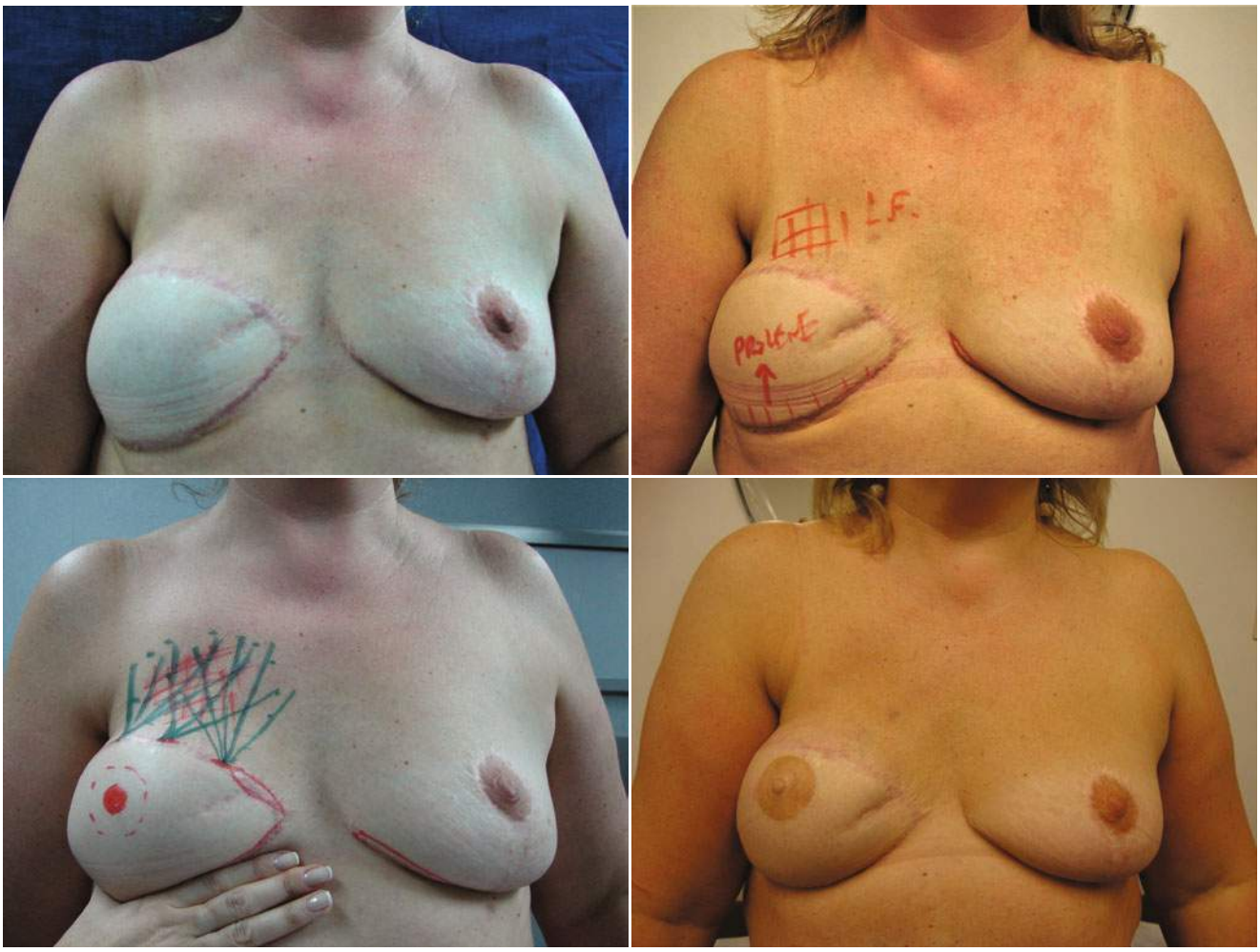


Fig. 56.23 Continued. BR with autologous tissue. Right breast defect correction through reconstruction and raising of the inframammary fold with a polypropylene mesh and lipofilling for the correction of the upper pole deficit

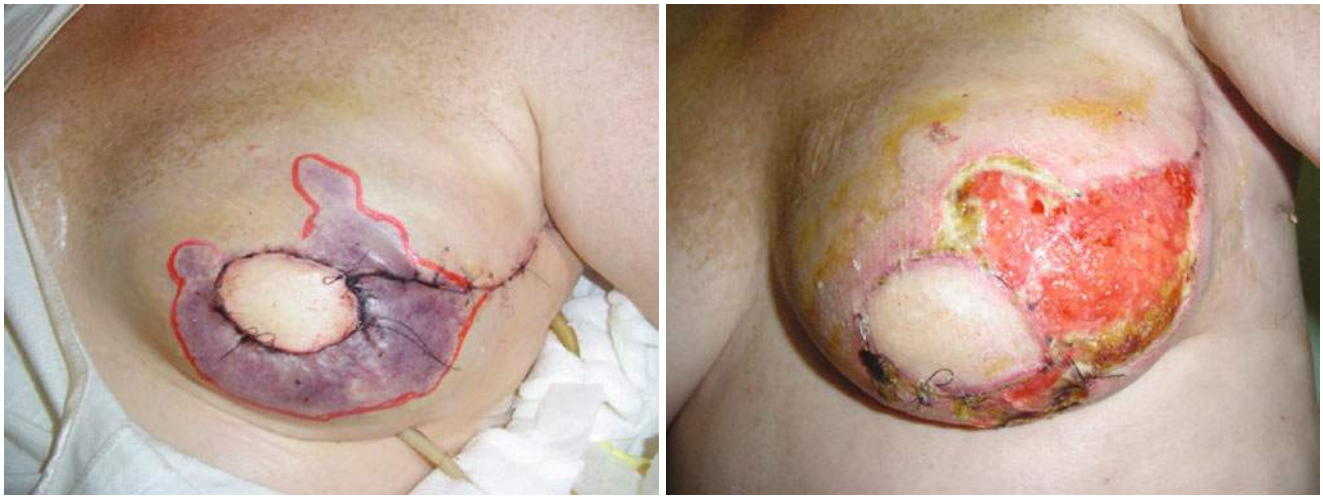


Fig. 56.24 Patient with left breast neoplasia who had received radiotherapy. She underwent a skin-conserving mastectomy and immediate BR with microsurgical-free TRAM flap. Extensive cutaneous necrosis

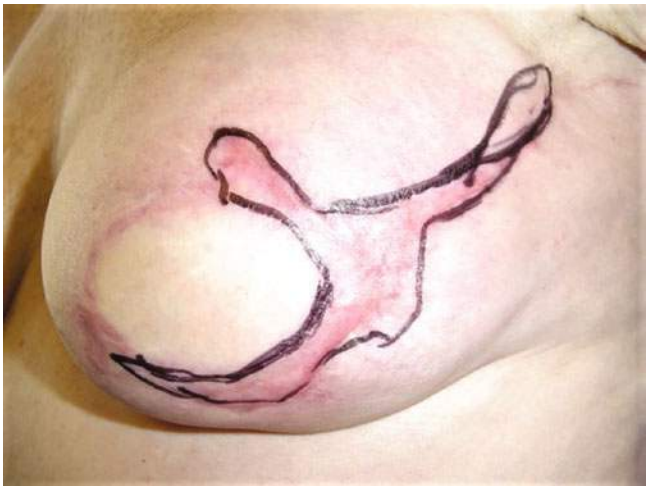


Fig. 56.24 (continued)

56.6 Conclusions

RS success is achieved by obtaining a breast with normal anatomical appearance, dynamically and with good symmetry after unsatisfactory initial results.

To reach this goal, it is crucial for professionals to have vast experience in all breast reconstruction techniques, conduct a critical analysis, and evaluate the defects and their probable etiology in order to customize the procedure in each case. In addition to the experience needed and the fulfilling of all these requirements, the use of the guiding algorithms and satisfactory results, although difficult to achieve, is possible, if we also consider a fundamental concept described by Steve Kroll many years ago, which stated that breast reconstruction is an interesting combination of engineering and art. Probably, art is paramount here in order to achieve these goals.

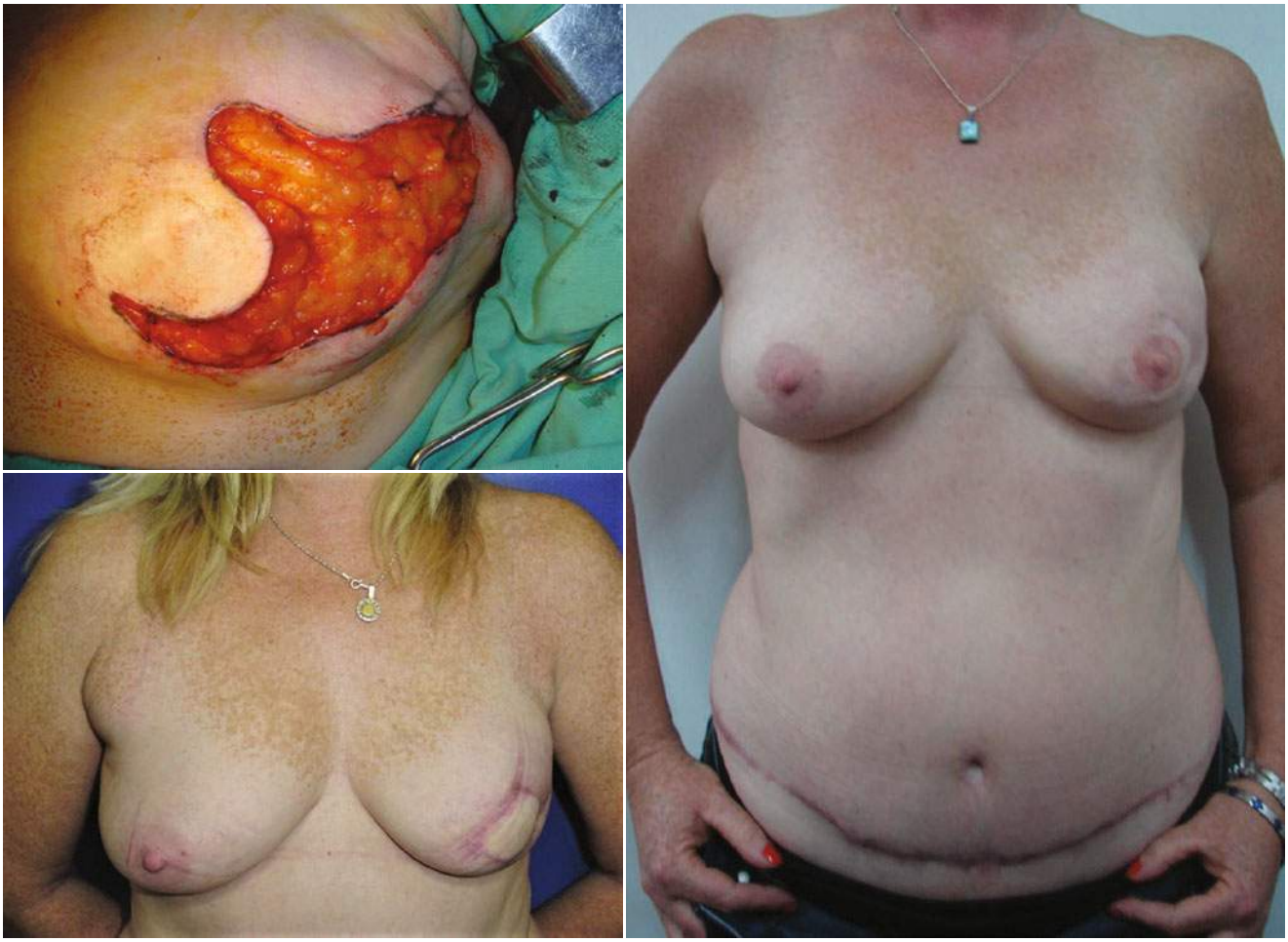


Fig. 56.25 Continued. BR with autologous tissue. Correction of left breast defect with flap modeling by drying the scar and sequelae fibrosis (top left). Immediate result (bottom left). Result after NAC reconstruction (right)

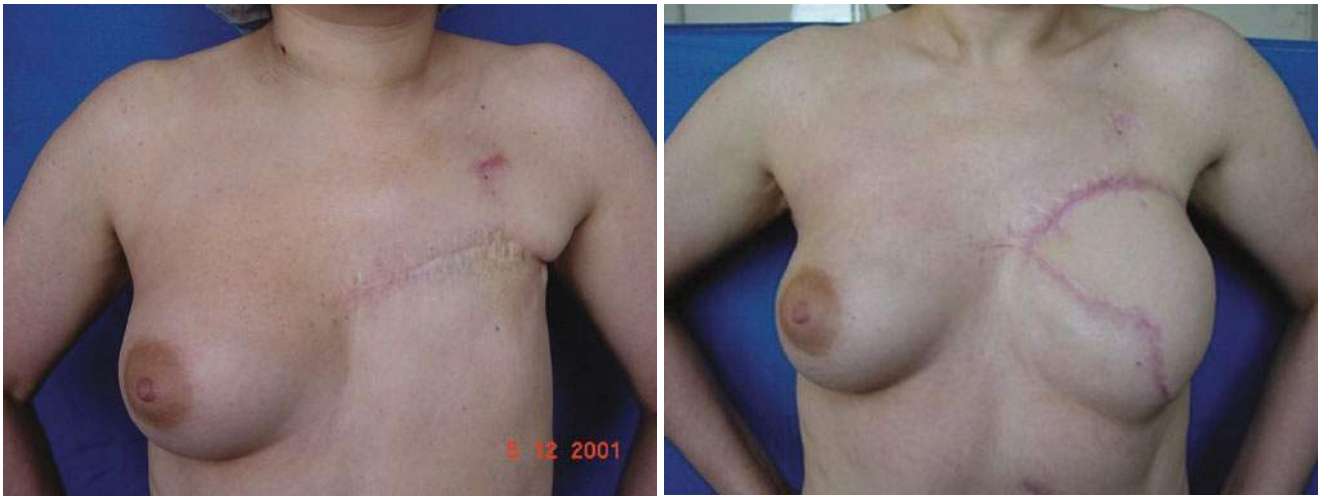


Fig. 56.26 Patient with left breast neoplasia, mastectomy, and radiotherapy. Delayed reconstruction with pedunculated TRAM flap. Flap exceeding the breast margins with a bigger size than the remaining breast, lowering of the inframammary fold, and asymmetry

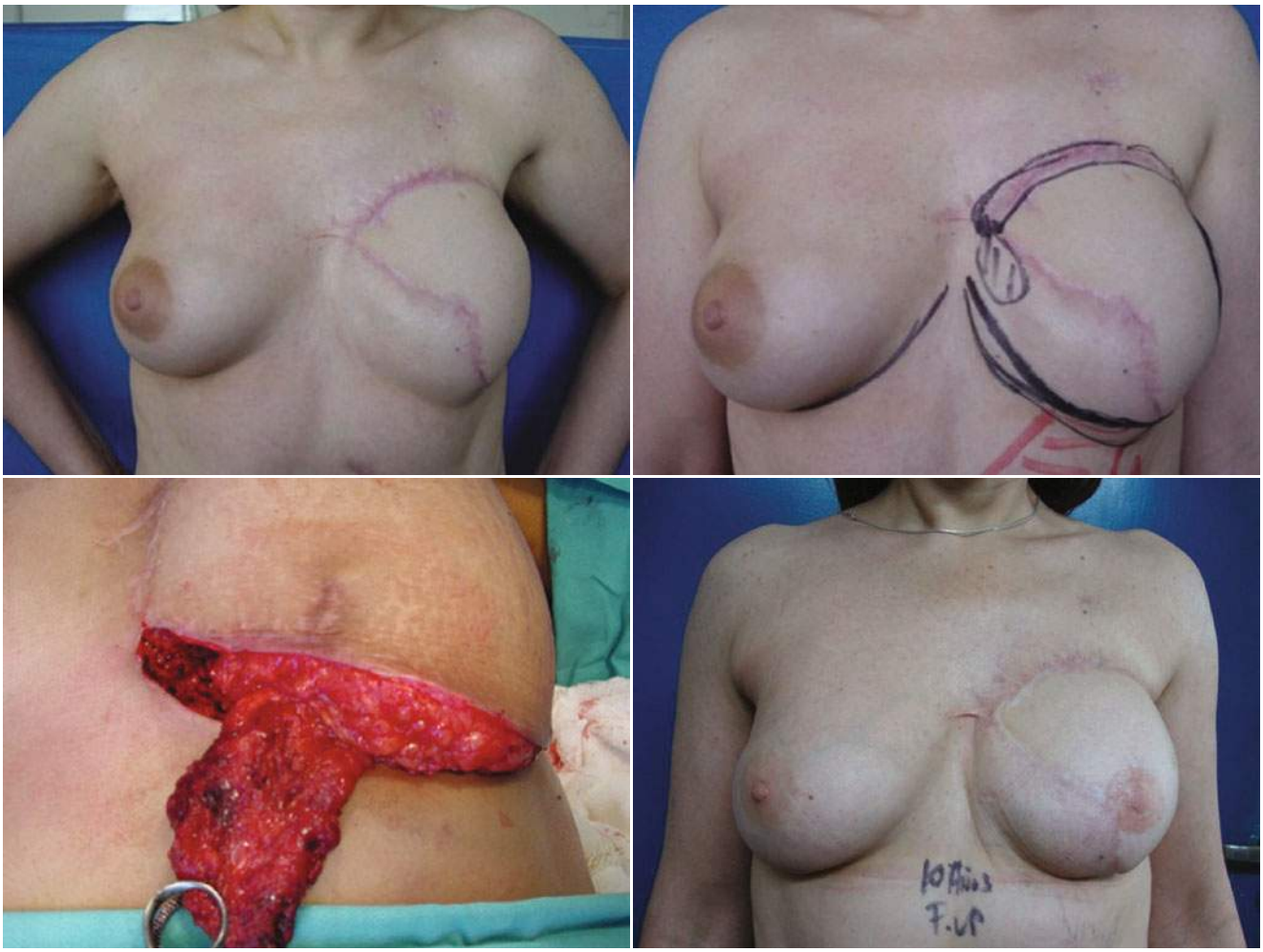


Fig. 56.27 Continued. BR with autologous tissue. The defect was corrected by modeling the flap and drying the scar and any excess external tissue and modeling the rectus abdominis muscle pedicle by inverting it in order to mark the inframammary fold (bottom left). Result after NAC reconstruction (bottom right)

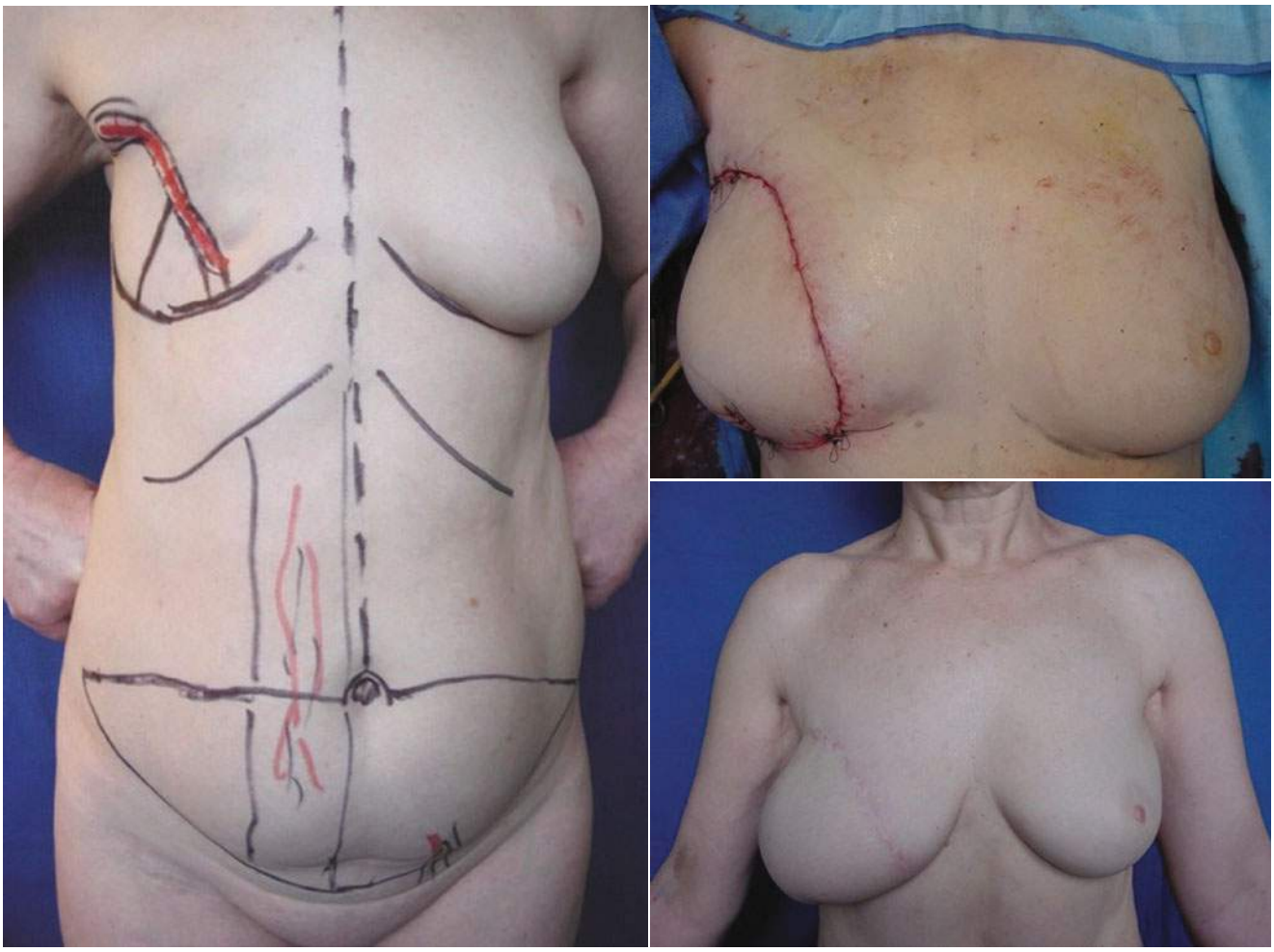


Fig. 56.28 Patient with right breast neoplasia, mastectomy, and radiotherapy. Delayed reconstruction with pedunculated TRAM flap. Flap exceeded the margins of the breast outward and downward in size, with lowered inframammary fold and asymmetry

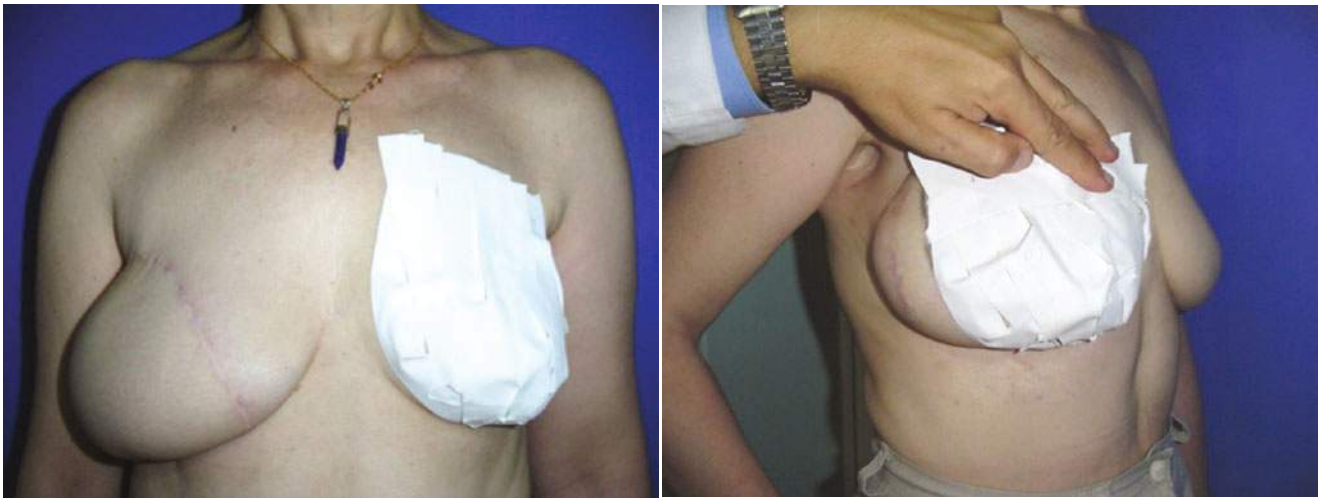


Fig. 56.29 Continued. BR with autologous tissue. Correction of right breast defect by modeling flap with a surgical tape mold of the remaining breast. Resection of excess external tissue. Result after NAC reconstruction (bottom right)

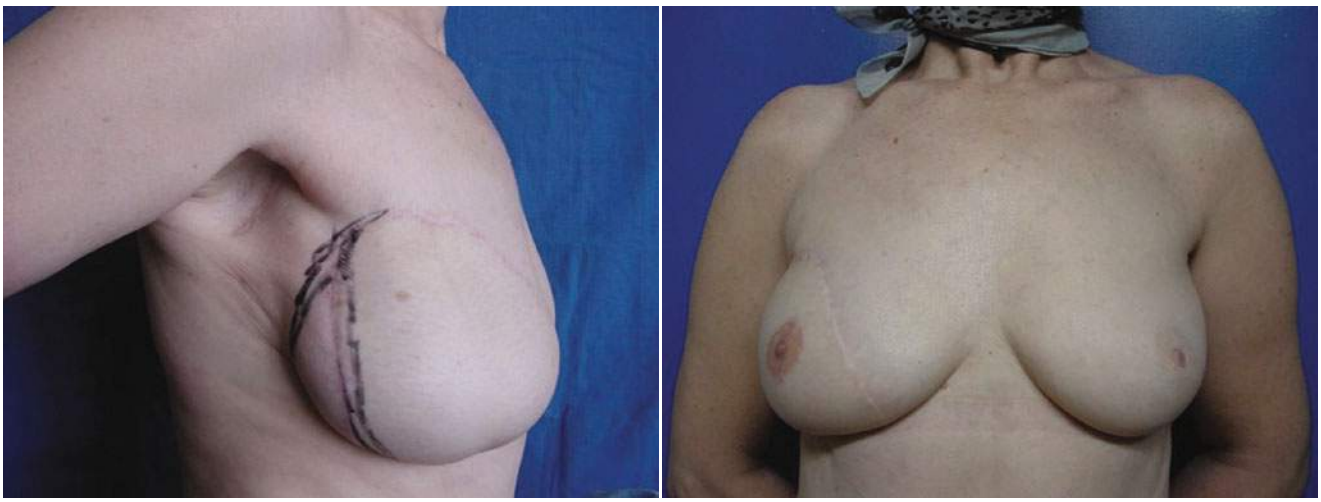


Fig. 56.29 (continued)

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Part VII

Breast Reconstruction in Special Populations

Immediate Breast Reconstruction in Pregnancy and Lactation

57

Cicero Urban, Cléverton Spautz, Rubens Lima, Eduardo Schünemann Jr, and Vanessa Amoroso

57.1 Introduction

The definition of pregnancy-associated breast cancer (PABC) includes breast cancer diagnosed during pregnancy and within a year after pregnancy, or any time during lactation [1–3]. Although the prevalence of PABC is relatively low (1:3000 deliveries), it puts the medical team in a complex setting, because two individuals are involved: the mother and the unborn child. It is estimated that 3% of all breast cancers may be diagnosed in pregnant women, and its incidence is expected to increase due to worldwide postpone childbearing [4–6]. Or, putting in another way, at least 10% of patients with breast cancer who are younger than 40 years of age will be pregnant at their diagnosis [7, 8], with PABC constituting approximately 7% of all breast cancers in women less than 45 years of age [9]. Breast cancer in pregnancy will continue to increase, and standardized treatment strategies are required to be developed [10].

Clinical examination of the breasts during pregnancy is difficult because breast presents an increased density and firmness. About 80% of women with a palpable painless lump during pregnancy have a benign mass. Any palpable lump persisting for more than 2 weeks should be deeper investigated with further specific workup. Nipple discharge and "milk rejection" sign are not frequently present [11–14]. Diagnostic delays of 2 months or longer are common in women with gestational breast cancer. Patient denial and, potentially, physician reluctance to intervene during pregnancy may also lead to delayed diagnosis [14]. Such delays may adversely impact oncological outcome, since even a 1-month delay in diagnosis can increase the risk of nodal involvement by 1–2% [15–18], leading to a diagnosis in more advanced stage in regard to tumor size (T3–4 tumors represented 31% of the PABC tumors vs. 13% of the control tumors, $p = 0.006$) [9]. The majority of breast cancer is an infiltrating ductal carcinoma with high grade and lymph vascular invasion, and in around 70% of cases estrogen and progesterone receptor negative and a higher expression of Her2/neu [7, 13, 19].

The management of these young women represents a challenge to all those involved in their care. In contrast to other areas of breast oncology, there are no large randomized trials to guide surgical and clinical practice. Most of treatment recommendations are based on case reports and retrospective cohorts. In consequence of that, until now there is no standardized treatment for PABC. But the options should be always influenced by the need to give optimal treatment to the mother while minimizing risks to the fetus [19–22].

Its prognosis and underlying therapeutic strategy for affected patients are currently subjects of debate [9]. PABC patients experienced more local recurrence than the control patients, and this was observed for smaller initial tumors, which usually have a good prognosis [9]. As PABC patients with T0–T2 tumors have a poor prognosis, they must be considered at high risk of local relapse and must be treated appropriately [9].

The Hartman et al. meta-analyses demonstrated that women who are diagnosed with breast cancer during or after pregnancy are at an increased risk of both death and recurrence compared to those diagnosed with nonpregnancy-related breast cancer. On the other hand, women with a history of breast cancer who subsequently become pregnant have improved survival rates compared to those who do not become pregnant [23]. In addition, several studies have demonstrated improved survival outcomes for women conceiving after treatment for breast cancer. These findings, however, may be a result of the "healthy mother" effect, a selection bias whereby women who have had favorable outcomes are

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more likely to conceive than those who have relapsed thereby skewing the true effect [23].

Gestational age is the most important factor affecting treatment. Treatment of an oncologic patient needs to be discussed within a multidisciplinary tumor board setting, which includes obstetrical and pediatric input. Eventually, the therapeutic strategy needs to be determined with the patient [6, 10].

Surgery under anesthesia is safe at any stage of pregnancy [10]. The concerns of sentinel lymph node biopsy (SLNB) in pregnancy are the fetal effects of exposure to radiation and/or blue dye [14]. Lymphazurin blue is generally avoided because of the risk of allergic reactions and anaphylaxis, while methylene blue is avoided because it is associated with jejunal atresia during the first trimester, but according to Gropper et al., that described a 47-patient cohort with node-negative breast cancer in pregnancy, it is feasible and appears safe [14].

A decision between breast-conserving surgery and mastectomy must be made as in nonpregnant patients [10]. Therefore, breast anatomy is completely altered and no data exists about how it can affect the decisions on the best technique to reconstruct the breast in PABC. Consequently, some authors defend that breast reconstruction should be delayed until after delivery and after the end of oncologic treatment, when all reconstructive options can be available [20].

Mastectomy is sometimes preferred for breast cancer in pregnancy since follow-up radiation therapy is typically not required postoperatively [24].

Neoadjuvant chemotherapy allows, in some cases, postpone surgery after delivery and oncoplastic surgery helps to avoid mastectomy in these patients [19, 25].

In case of mastectomy, the immediate reconstruction must be weighed against the overall medical situation. Reconstruction following mastectomy during PABC is usually delayed until after delivery because achieving symmetry is considered difficult due to pregnancy-associated breast engorgement, as well as to fetal and maternal concerns [14]. As delayed reconstruction (either autologous or heterologous) remains an easy option, it should be considered. Implants should be used if immediate reconstruction is required [10].

Lohsiriwat et al. described reconstruction in pregnancy in 78 patients: 22 underwent unilateral mastectomy; 13 of 22 had immediate reconstruction (12 with a tissue expander and one with immediate implant). There was no infection, hematoma, capsular contraction, or flap necrosis, and 75% of patients completed expansion intrapartum. Eleven of 12 patients continued their pregnancy; one had a termination at 9 weeks. With a median follow-up of 32 months postpartum, one patient had expander leakage after external radiation and one had a local recurrence 19 months postmastectomy. This study suggests intrapartum reconstruction is a feasible option warranting further investigation [14, 26]. The same was found in the Meisel et al. retrospective chart review with 74 patients. Immediate reconstruction was utilized without apparent complication [22].

Chemotherapy during the first trimester is not recommended, because of the highly teratogenic potential of all antiproliferative drugs, specifically during organogenesis (weeks 4–12). As long-term data are only slowly accumulating, the data on systemic chemotherapy during the second and the third trimesters remain limited [10, 14]. Hormonal treatment with tamoxifen is not indicated during pregnancy, as it is associated with many serious fetal side effects. The start of treatment can be delayed until childbirth. The aforementioned descriptions also hold for anti-HER2 treatment, as existing evidence indicates severe fetal side effects such as oligohydramnios and renal failure associated with poor neonatal outcome. Only very limited data exist regarding anti-HER2 therapy, which has a particularly higher effect in a poor prognosis subgroup. Precisely, anti-HER2 therapy should not be recommended during pregnancy [10].

A 2- to 3-week temporal duration between the last chemotherapy and childbirth is ideal for both mother and child. Breast-feeding during treatment is not recommended [10].

So, the purpose of this chapter was to present a model that allows immediate breast reconstruction in this complex group of patients, and not compromising oncologic treatment and fetus evolution.

57.2 Surgical Algorithm

Most PABC patients underwent mastectomy. Breast reconstruction can be performed following a specific model designed in our Breast Unit since 2008, where these patients are divided in three distinct groups (Fig. 57.1):

- *First trimester*: Immediate reconstruction in one-step surgery with breast implants and contralateral symmetry with breast reduction or mastopexy or two-step surgery with temporary expanders (Fig. 57.2).

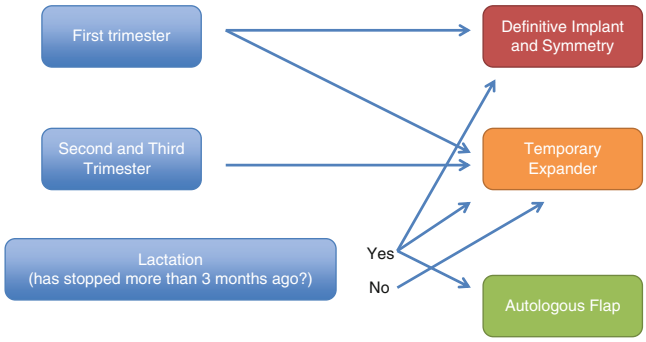


Fig. 57.1 Immediate breast reconstruction decision algorithm in pregnancy and lactation

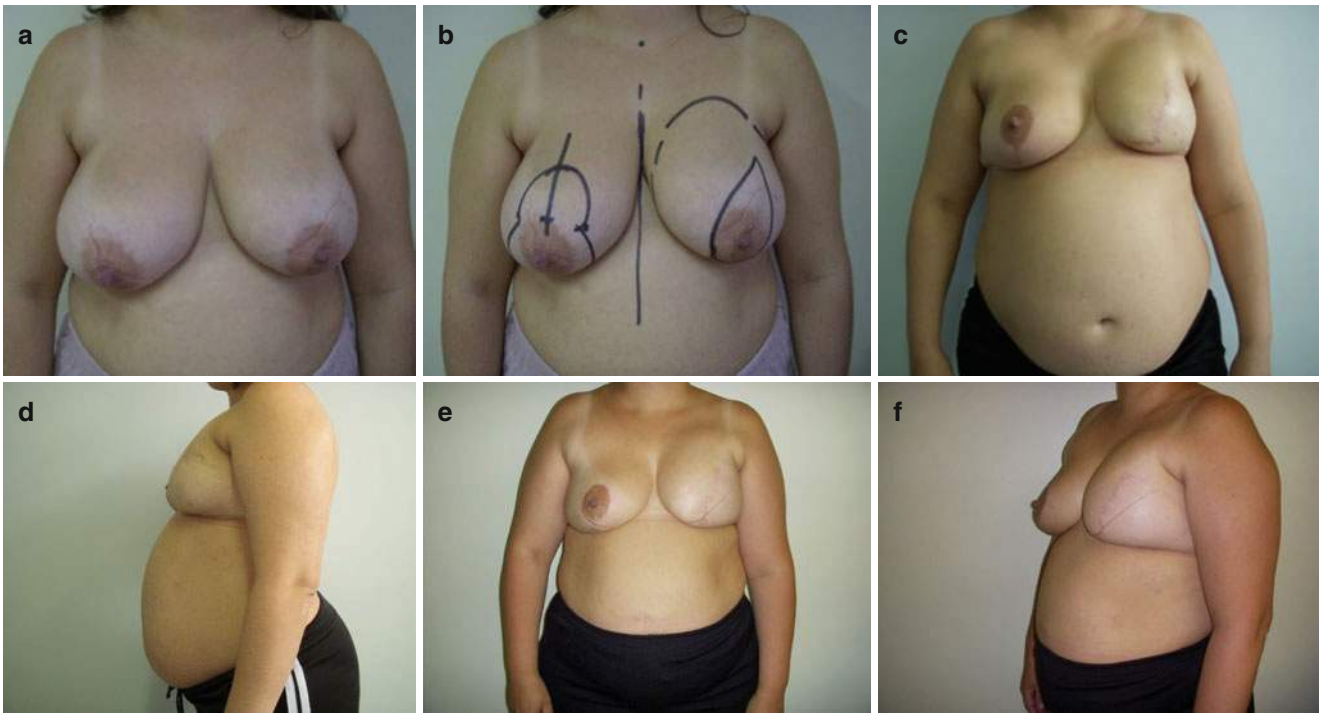


Fig. 57.2 (**a**, **b**) Pre-operatory view of a 32-year-old patient, with 8 weeks of pregnancy and a diagnosis of an invasive ductal carcinoma on left breast, G2, T2N1, ER/PgR positive, and HER2. (**c**, **d**) 8 months after left skin-sparing mastectomy, axillary dissection, immediate breast reconstruction with form-stable implant, and contralateral breast reduction for symmetry. (**e**, **f**) Results 4 months after delivery

- *Second and third trimester*: Temporary expanders.
- *Lactation*: Temporary expanders, autologous flaps, or breast-conserving therapy (BCT). If the lactation had ceased at least 3 months ago, it is possible to perform one-step surgery with definitive implant and contralateral breast symmetry (Fig. 57.3). In this situation, an approach with a breast conservative surgery is possible too.

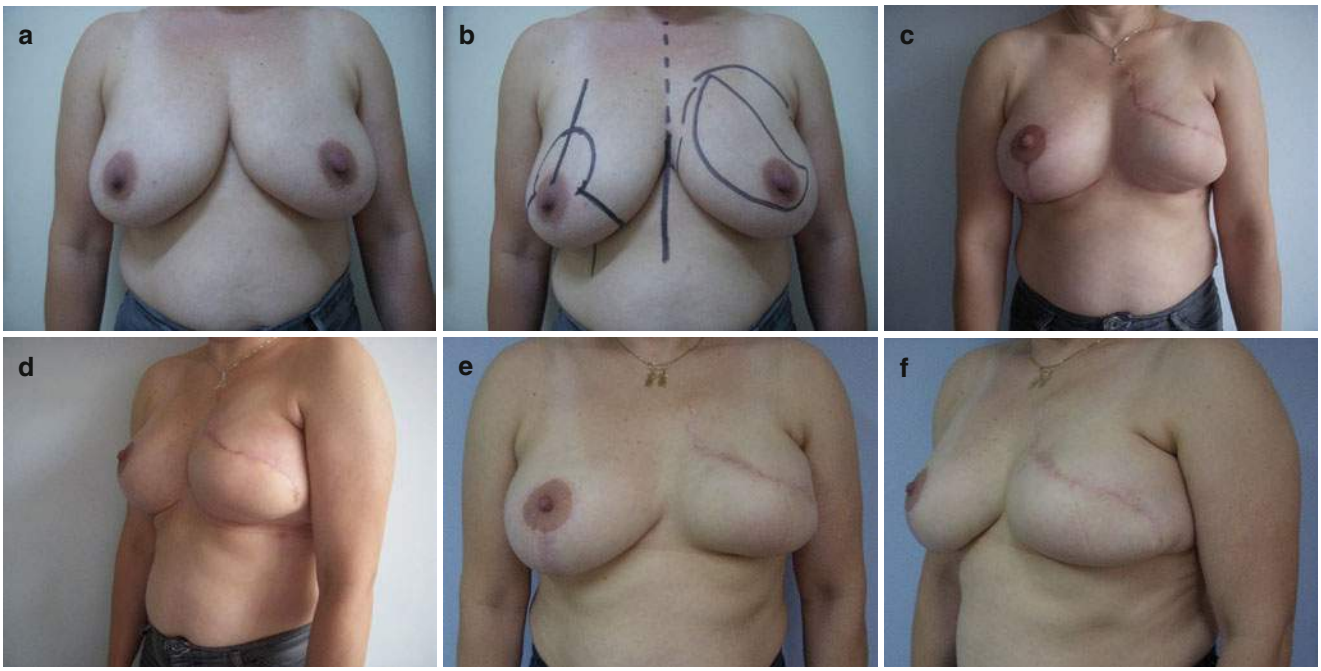
57.3 Rationale

Although BCT is a good alternative in selected cases of PABC, higher tumors than those found in nonpregnant patients, associated to the fact that radiotherapy should be avoided until after delivery, result in low rate of this kind of surgery in this group of patients [21]. In our Breast Unit there were no BCT in pregnant patients, since the dominant tumors were pT2 and pT3. Therefore, sentinel node biopsy was not yet consolidated in PABC until some years ago, and all the patients underwent to axillary dissection.

Pregnancy affects all the body. Physiological changes particularly associated with pregnancy include increased cardiac output, decreased peripheral vascular resistance, increased blood volume, physiological dilutional anemia, increased oxygen consumption, increased renal plasma flow, increased coagulability, decreased lung capacity, supine positional hypotension, and slow gastric emptying [19, 20]. They impose special care from anesthesiologists and surgical team (Table 57.1). So there are limits to be considered in the extension of surgeries in pregnancy.

With regard to breast reconstruction, pregnancy affects particularly the breasts, resulting in glandular hyperplasia and hypertrophy (mean breast weight normally doubles in pregnancy), increasing ptosis, areolar enlargement, nipple hypertrophy, and increasing pigmentation of the nipple and areola. At the end, breast anatomy is completely altered (Fig. 57.4). Unfortunately no data exists about the changes in breast structure, as well as volume and shape, and how it can affect the decisions on the best technique to reconstruct the breast in PABC. Due to that, some authors defend that breast reconstruction should be delayed until after delivery when all reconstructive options can be available (especially autologous tissue flaps) and when symmetry could be easier to achieve.

However, nowadays, immediate breast reconstruction is widely preferred and does not have a negative influence on breast cancer survival rates or recurrences. It has innate advantages in terms of quality of life and aesthetic outcomes, if compared to delayed reconstruction, especially for young women [27]. So our reconstructive approach to these patients in this series was to divide them in three different categories, according to the phase of their pregnancy and body and breast modifications:



Figs. 57.3 (**a**, **b**) Pre-operatory view of a 37-year-old patient with a multicentric invasive ductal carcinoma on left breast, T2N0, ER/PgR-, HER2-, and lactation has been interrupted 3 months ago. (**c**, **d**) 3 months after left skin-sparing mastectomy, sentinel node biopsy, immediate breast reconstruction with definitive form-stable implant, and contralateral breast reduction for symmetry. (**e**, **f**) Long-term result: 2 years after surgery

Table 57.1 Physiological changes in pregnancy that can potentially interfere in breast reconstruction decisions and outcome

Physiological change	Pregnant
Blood volume	Increase by 30–50%
Hematocrit	30–35% normal
Heart rate	Increase by 10–15 bpm
Clotting factors	Increase factors II, VII, VIII, IX, X, fibrinogen
White blood cells	10,000–14,000
Platelets	Low to normal

- *First trimester*: Breast and body are less modified by pregnancy. The result of the reconstructed breast is more predictable than in the other two phases. Then immediate reconstruction could be performed in a one-step surgery with breast implants and contralateral symmetry with breast reduction or mastopexy or in a two-step surgery with temporary breast expanders (Fig. 57.2). Autologous tissue flaps, especially those abdominal wall techniques (pedicled or free TRAM flaps), are contraindicated. Latissimus dorsi flap could be indicated in well-selected cases, but it increases both surgical time and clinical complications. In this series there were two patients who underwent to immediate breast reconstruction through one-step surgery with definitive implant and contralateral symmetry, resulting in a good aesthetic result. There were no significant modifications in their breasts over the time (Figs. 57.5 and 57.6).
- *Second and third trimesters*: The breast and body modifications are more evident and the final result of the reconstructed breast is less predictable. So temporary expanders are the best choice in this group. The second surgery should be done at least 3 months after delivery (considering the impossibility of most patients in lactation due to oncologic treatment), or 3 months after lactation, when the breast achieves the normal shape, ptosis, and volume.
- *Lactation*: The breast modifications are more evident and the body modifications are progressively less important than before delivery. Temporary expanders are the best choice. The second surgery should be done at least 3 months after lactation has ceased, when the breasts will achieve their definitive volume, shape, and ptosis. Autologous flaps could be indicated as primary surgery in selected cases, considering that the risks are the same as those in non-lactating and nonpregnant patients. But in the decision, it is necessary to consider the unpredictability of breast modifications after lactation. It could be a negative influence to breast symmetry. In fact, most of the patients in our series were in this category. All of them underwent to temporary expanders with good long-term results. After the end of lactation, it was easier to achieve symmetry by changing the temporary expander for a definitive implant and by performing contralateral mammoplasty. There were no additional complications due to lactation. In cases where lactation is ceased at least 3 months, it is possible to do one-step reconstructive sur-

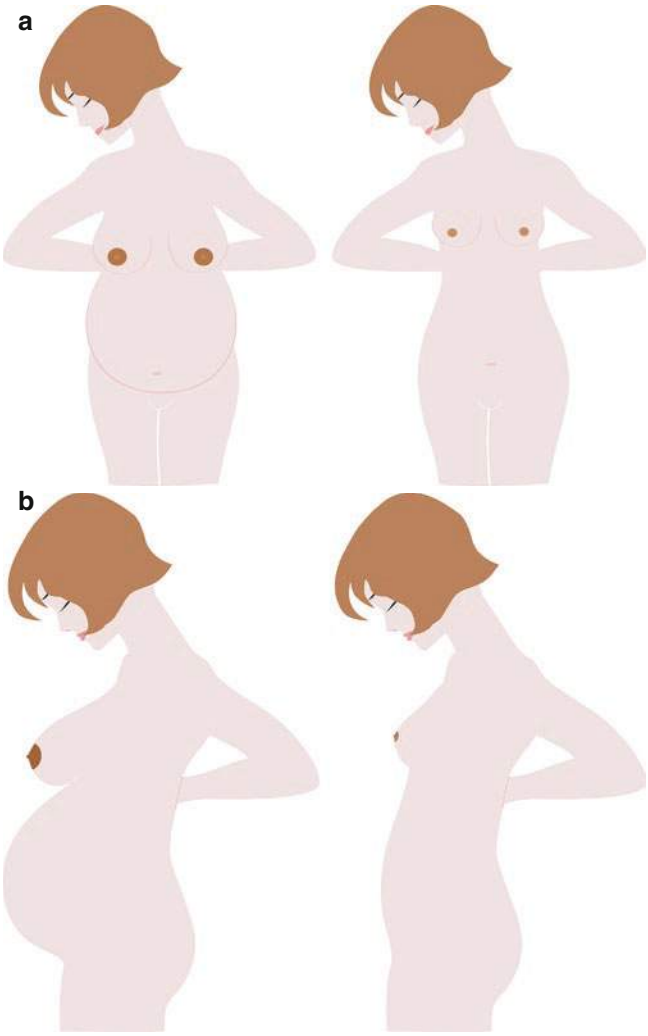


Fig. 57.4 (**a**, **b**) Aesthetic modifications in breast and body during pregnancy

gery with definitive implant (Fig. 57.3) or a BCT with an oncoplastic approach.

Since PABC is a group of patients usually with a more aggressive disease (Table 57.1), it is expected that some of these patients will undergo postmastectomy radiotherapy and a more aggressive adjuvant therapy [28]. It is necessary to consider it in the decision process. Therefore, it is expected no delay in the beginning of chemotherapy due to breast reconstruction in this group. In a previous study carried out as retrospective and prospective analysis of consecutive PABC patients who had undergone mastectomy, axillary dissection, and immediate breast reconstruction in our Breast Unit from March 2004 until July 2008, in a total number of 598 cases of invasive breast cancer, 10 PABC cases (1.7%) were selected (Table 57.2). These patients were younger and with more aggressive tumors than nonpregnant ones. Breast reconstructions were performed following the decision model presented here. First trimester patient ($n = 2$) underwent to immediate reconstruction in one-step surgery with breast implants and contralateral symmetry. Second and third trimester patients ($n = 2$) underwent to temporary expanders. Lactation patients ($n = 5$) underwent to temporary expanders, or one-step surgery with implants in cases of lactation had ceased at least 3 months ago ($n = 1$). No surgical complications or delay in adjuvant therapy were observed in this group of patients. Only one patient needed postoperative radiotherapy, resulting in Baker 2 capsular contracture. All the patients were alive without disease and the fetus evolutions were not compromised by the surgery [29]. We have one patient that is receiving chemotherapy since 20 weeks of pregnancy.

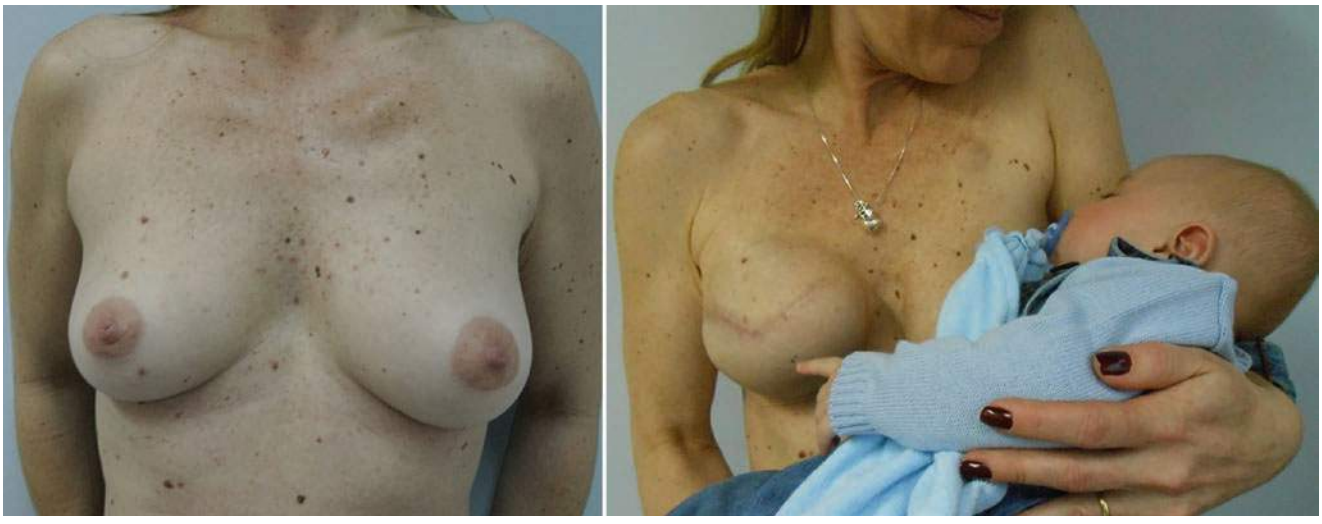


Fig. 57.5 29 years patient with 6 weeks of pregnancy and right breast cancer: pre and post operatory view

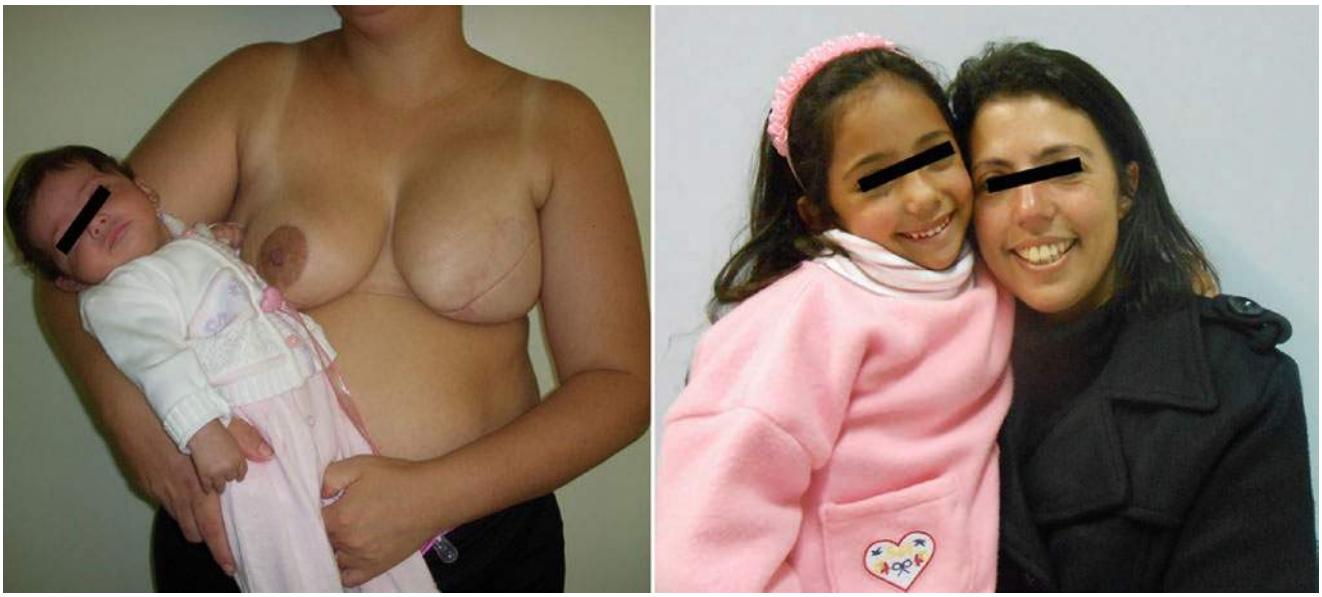


Fig. 57.6 4 months after delivery and after 5 years of follow up in the patient of the Figure 57.2

Table 57.2 Comparison between pregnant and nonpregnant patients with invasive breast cancer at Hospital Nossa Senhora das Graças Breast Unit, Curitiba, Brazil 2004–2010

Characteristic	Nonpregnant (n = 598)	Pregnant (n = 10)	Statistical analysis
Age	56.6	33	
T2 and T3	20.1%	90%	p = 0.0001
ER/PgR+	78.7%	30%	p = 0.0008
HER2+++	22.4%	20%	p = 0.456
Axila+	15.1%	80%	p = 0.001
Mastectomy	45.8%	100%	p = 0.0002

Modified from Urban et al. [22]

So, if the patient has no oncologic contraindication for immediate breast reconstruction, the key point in this model for the decision process of the best technique for immediate breast reconstruction is the lactation. First trimester patients and those patients where lactation had ceased at least 3 months ago are more predictable in terms of shape, volume, and ptosis, so one-step surgery could be a good option. In cases where effects of lactation in the breast are present, temporary expanders could be the best choice, because it is not possible to achieve symmetry due to accentuated breast modifications. When neoadjuvant chemotherapy is necessary, the surgical treatment can be postponed after delivery or lactation. In this case, both immediate breast reconstruction with definitive implants or oncoplastic surgery are possible indications.

Finally, with this reconstructive approach to PABC patients, it is possible to minimize the effects of mastectomy. It is a transversal model, which considers all aspects: oncologic, obstetric, and reconstructive, with both the patient and the fetus in the center of decisional process.

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Breast Reconstruction in Elderly

58

Francesca De Lorenzi, Benedetta Barbieri,
and V. Lohsiriwat

58.1 Introduction

Almost two-thirds of solid tumors occur in elderly patients [1]; between them, breast cancer is largely represented, and women aged 70 years and over have the highest incidence and mortality from breast cancer of any age group.

Unfortunately, in the past breast reconstruction has been not always been offered to elderly population due to the reluctance by clinicians concerned about attendant serious comorbidities. Elderly are often considered unfit for reconstruction due to an inaccurate estimation of operative risk. Moreover, no consensus exists on therapy of elderly cancer patients. Treatments are influenced by unclear standards and are usually less aggressive both for surgical and medical options. Finally, it has been demonstrated that many older women with breast cancer are receiving treatments that are not generally considered to be appropriate care [2]. Nowadays the behavior is changing, as people are living much longer and are healthier. Old age is becoming more prevalent; older people remain in the workforce; there is an increased emphasis on caring for grandchildren, children, and partners; and attitudes to marriage and sexual activity are adjusting. Surgical techniques and anesthesia are becoming safer. In addition, the survival rate of breast cancer is improving also in elderly patients, so a larger proportion of patients are living with the long-term consequences of their treatment. For these reasons, the consideration of breast reconstruction should be offered to elderly patients in order to improve their quality of life.

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58.2 Definition and Characteristic of Elderly

Conventionally, "elderly" have been defined as those with a chronological age of 65 years or more, being those from 65 through 74 years old referred as "early elderly" and those over 75 years as "late elderly" [3].

There are several major physiologic changes of aging affecting the central nervous system, the cardiovascular system, the respiratory system, and many others. Quantifying the general risk of anesthesia with the ASA classification (scored from I to IV), most of the elderly patients fall in ASA class II or III. Elderly patients also have poor Karnofsky Performance Status [4, 5]. The elderly should have more careful preoperative and postoperative assessment and probably require more often intensive care management to reduce the surgical risk. They are also vulnerable to the adverse effects of anesthesia because of their reduced margin of safety. Acute and chronic medical conditions, nutritional status, and level activity are needed to be taken in consideration (Figs. 58.1, 58.2, 58.3, and 58.4).

58.3 Psychological Benefits and Quality of Life

In general, there is a clear psychological benefit and quality-of-life benefit for breast reconstruction regardless of any age group. However there are only few reports focusing on quality-of-life assessment and mostly utilized general health questionnaires rather than specific ones [6, 7]. Girotto et al. reviewed 316 consecutive women older than 65 years of age (400 reconstructions) with breast cancer undergoing mastectomy with reconstruction. Their outcomes were assessed with the use of a self-reported questionnaire (SF-36) addressing health-related quality of life, body image, and physical functioning. Concerning the overall quality-of-life issues after reconstruction, older patients with breast reconstruction had better outcomes than age-matched general population and

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_58

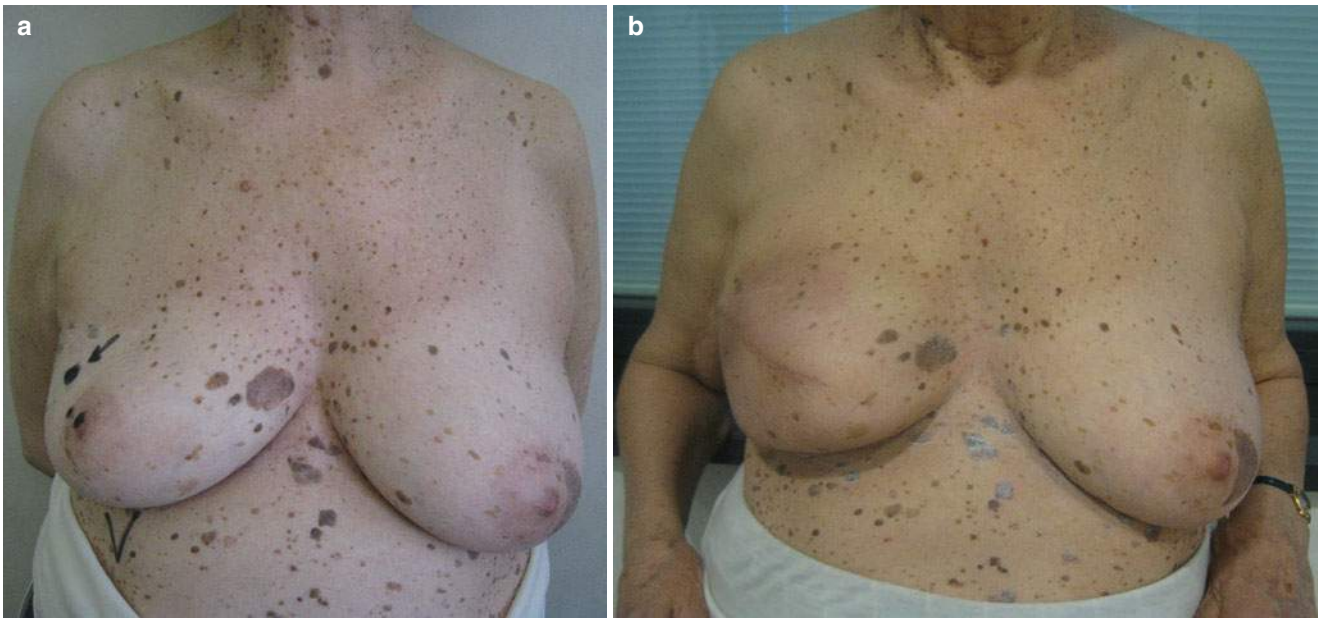

Fig. 58.1 (**a**) An 86-year-old woman with a multifocal tumor of the right breast. Preoperative view. (**b**) Postoperative results after right skin-sparing mastectomy and immediate reconstruction with a definitive silicone gel implant

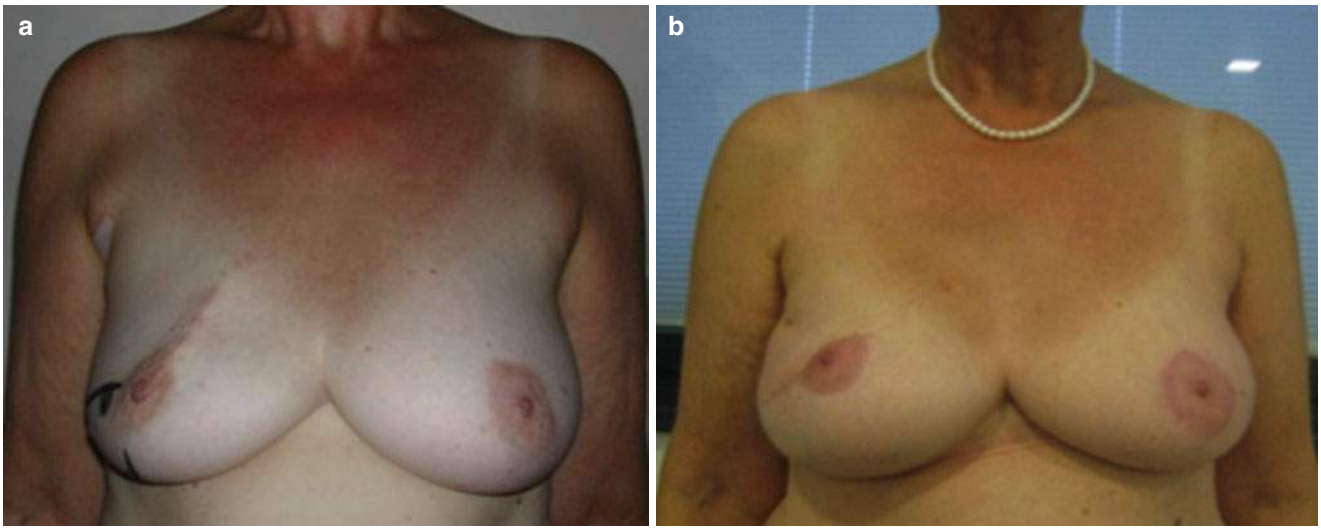

Fig. 58.2 (**a**) A 67-year-old woman previously treated with breast conservation for carcinoma in situ of the right breast. Final histology revealed positive margins requiring mastectomy. Surgical scar at the superior quadrants. (**b**) Postoperative results after right nipple-areola-sparing mastectomy and immediate reconstruction with a definitive silicone gel implant and simultaneous periareolar mastopexy of the left healthy breast

previously reported mastectomy-only patients (>55 years). Specifically, elderly patients had better outcomes in the subscales that are strongly influenced by one's mental health. However, when compared with prior data for younger patients undergoing mastectomy and reconstruction, the older patients had worse outcomes in the areas related to physical function.

Aneja et al. specifically investigated health-related quality of life in elderly breast cancer patients undergoing breast reconstruction [8]. They observed that although mastectomy with breast reconstruction is associated with a transient mental health-related quality-of-life benefit compared to breast conservation and irradiation within the first 2 years of treatment, it also is associated with decreased physical health-related quality of life within the first 2 years of treatment and in the longer follow-up.

Recently, a literature research aimed to find out an evidence-based algorithm regarding breast reconstruction in the elderly [9]. The authors conclude that if reconstruction is oncologically plausible and comorbidities and frailty are formally assessed, older women should be actively informed about breast reconstruction, receive support, and engage in "shared decision-making."

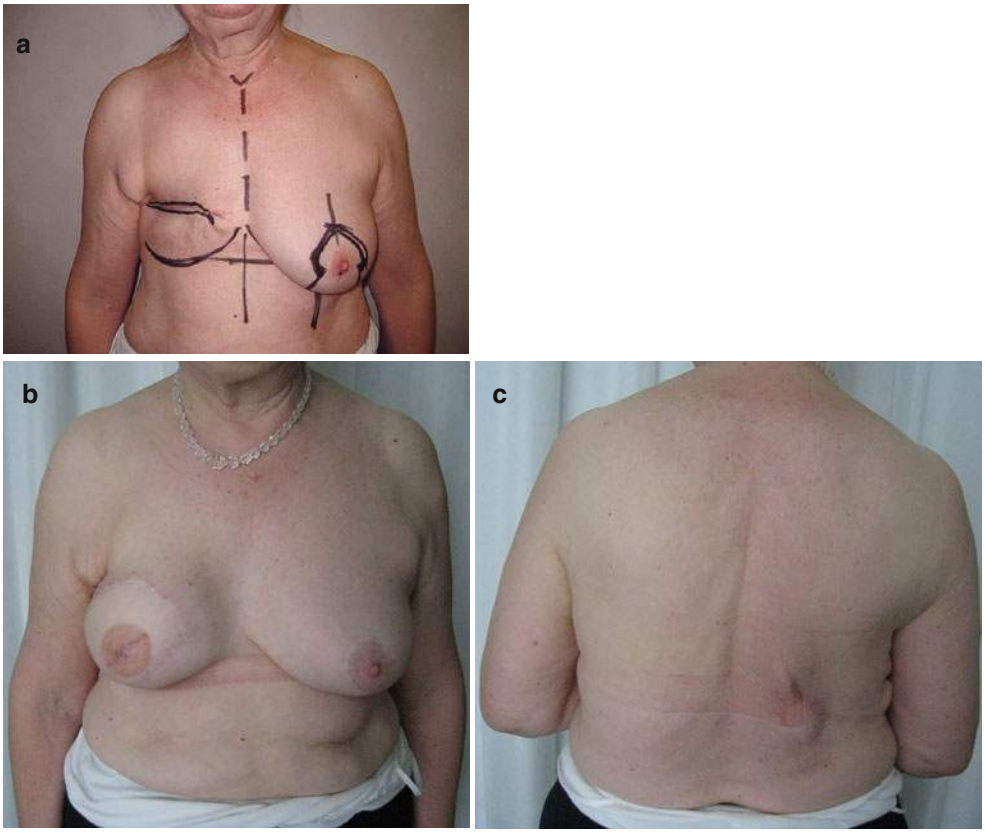

Fig. 58.3 (**a**) Preoperative view of a 73-year-old woman who underwent right modified radical mastectomy and locoregional irradiation. (**b**) Postoperative results after delayed reconstruction of the right breast with latissimus dorsi flap and definitive implant and simultaneous left mastopexy. Right nipple-areola complex has been reconstructed with tattooing and local flaps. (**c**) Postoperative results of the donor area

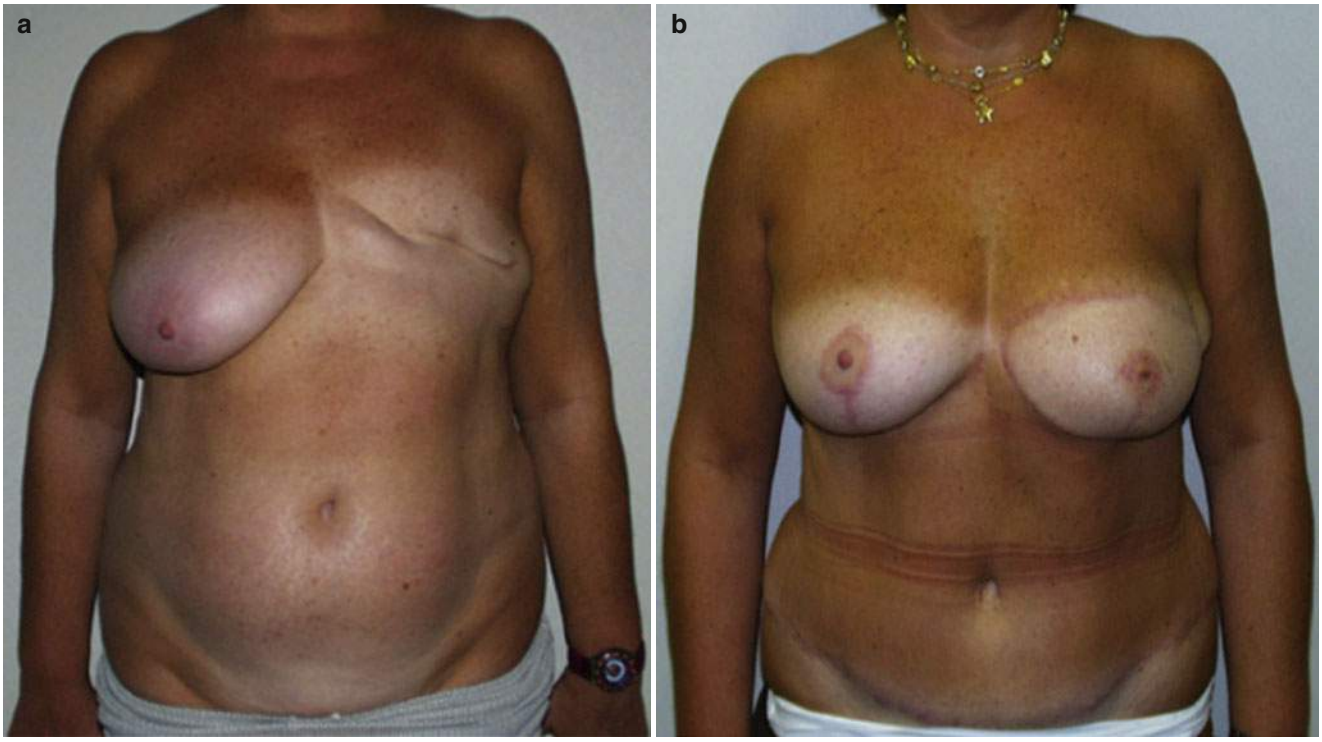

Fig. 58.4 (**a**) A 66-year-old woman after left modified radical mastectomy and no reconstruction. Preoperative view. (**b**) Postoperative results after delayed reconstruction of the left breast with a pedicled TRAM flap and simultaneous right mastopexy. Left nipple-areola complex has been reconstructed with tattooing and nipple sharing

58.4 Oncologic Safety

Breast cancer surgery is associated with a low risk of operative morbidity and mortality if compared to more difficult and longer surgeries. Wherever feasible, older women with a reasonable life expectancy should be treated with standard surgical procedures applicable to younger patients, including the choice of breast conservation or mastectomy where appropriate; breast reconstruction or oncoplastic procedures should be included in the options available.

Unfortunately, the review study by Kiderlen et al. [10] noted that the proportion of elderly patients that received radiotherapy after conserving treatment decreased with age in all countries. Moreover, in all countries the proportion of patients who do not receive axillary surgery increased with age. They observed large international differences in the treatment of elderly early stage breast cancer patients, with the most surprising result consisting in the large proportion of elderly who did not undergo surgery at all.

Smith et al. [11] demonstrated that breast cancer outcomes have preferentially improved in women aged less than 75 years. Focused research is needed to improve outcomes in older women. However, this conclusion might be the consequence of elderly undertreatment resulting in poorer survival. Better screening tools and programs and more effective adjuvant chemohormonal and target therapy with lower toxicity are being developed and should be researched in elderly for achieved significant improvement in survival rate [12].

58.5 Type of Reconstruction

58.5.1 Breast Conservative Treatment (BCT)

BCT is largely indicated for elderly patients since the favorable tumor bio-histology characteristics in the elderly cohort make the local recurrence rate lower than the general population. Although the large majority of quadrantectomies does not require any oncoplastic approach, in about 10–15% of cases, it is required to improve the cosmetic result [13, 14]. In fact, wide glandular resections can induce deformities and volume and shape asymmetry between the two breasts, such as glandular defects or scar retraction as well as nipple-areola complex (NAC) dislocations. An oncoplastic approach may avoid these asymmetries and the difficulties of glandular reshaping after breast irradiation justify an immediate partial reconstruction. Most of the deformities can be avoided using simple tricks without any specific training in plastic surgery: optimal positioning of the scar, transposition of the NAC to avoid dislocation, and better evaluation of the symmetry. In the other cases, a specific knowledge of reconstructive techniques is mandatory. Schematically, there are two fundamentally different approaches: volume displacement and volume replacement procedures.

Volume displacement procedures combine resection with a variety of different breast reduction and reshaping techniques, according to the location of the tumor. Volume replacement procedures combine resection with immediate reconstruction by using local flaps, as glandular, fasciocutaneous, and mini-muscle flaps. Glandular flaps are feasible and safe in case of glandular and very dense breasts. In cases of fatty breast with low radiologic density, as elderly patients usually do have, a really careful evaluation is mandatory, and glandular flaps are more often contraindicated since there is a very high risk of necrosis after fat undermining and mobilization. Implant replacement is indicated only in selected cases, when intraoperative exclusive irradiation is delivered [15]. In case of fatty breasts and large resection, mammoplasty procedures should be preferred if simple closure of the lumpectomy cavity is not feasible. Surgical reshaping after quadrantectomy for wide glandular excisions (oncoplastic techniques) can be offered in elderly patient [16, 17]. Oncoplastic surgery increases the oncological safety of breast-conserving treatment as a much larger volume can be excised and wider surgical margins can be achieved [18].

In cases of poor results after conserving treatment, an easy and simple technique to correct and replace the defects is fat grafting. Fat grafting is largely used also in the elderly cohort; it can be performed in a second operative time, after the external irradiation is delivered, usually in local anesthesia with minimum scarring. Different studies are in the process demonstrating the safety of lipotransfer in cancer patients [19–21].

Fat grafting in elderly patients has been specifically investigated by Chirappapha et al. [22]. They didn't observe any surgical complication at the donor area in their series of 153 consecutive patients. Complications occurred at the recipient area in 8% of the patients, being liponecrosis the more frequent one (7%). Thirty-three percent of the patients received more than one grafting procedure. The authors conclude that the relatively low early complication rate confirms fat grafting as a good option for small defect correction after breast conservation even in older patients.

58.5.2 Mastectomy

Many type of mastectomies can be safely offered to elderly patients, such as total mastectomy with immediate or delay reconstruction, skin-sparing mastectomy, or nipple-areola-sparing mastectomy with immediate reconstruction [23]. Reconstruction includes implant-based of flap-based techniques.

Implant reconstruction is easy, with a short operative time, no donor site morbidity, and relatively quicker recovery.

Respecting and evaluation of vascularity of the mastectomy flaps are mandatory in the immediate setting, to prevent marginal flap necrosis, wound dehiscence, secondary healing, and implant exposure. Additional operations after the primary procedure are usually necessary since aesthetic outcomes deteriorate over time, but most of the time these procedures can be performed under local anesthesia, including implant change and removal and nipple and areola reconstruction.

In our experience, flap reconstructions are generally limited to those patients who had received preoperative radiotherapy, since radiation adversely affects the outcomes of implant-based reconstructions, and in those cases of wide mastectomies requiring flap repair. In the future, in the era of perforator flaps reducing donor side morbidity for strength and function, the number of elderly patients requiring this kind of reconstruction will probably increase.

Elderly alone should not be considered as a sole factor when selecting type of reconstruction for patients. Nevertheless, comorbidities, patient's condition, and concomitant factors, together with the patient's opinion and tumor stage, should influence the type of reconstruction. In addition, not all of breast cancer patients will definitely require reconstruction. Some of elderly patients who have high risk for surgery refuse the reconstructive surgery, and limited social lives may prefer external prosthesis to cope to mutilation of mastectomy.

Girotto et al. [6] reported that elderly women are less likely to complete the nipple-areola complex reconstruction compared to younger cohort. Our study demonstrated that only 15.5% of elderly patients completed their reconstructions with the creation of the nipple-areola complex.

58.6 Complications

Data from the literature demonstrated that breast reconstruction is safe in elderly patients although it is well known that the risk of perioperative complications is proportionately increased because the number of comorbidities (i.e., hypertension, coronary artery disease, cerebrovascular disease, chronic lung disease, diabetes, congestive heart failure) [24] and the relative risk of severe complications and death are significantly greater in the geriatric population than in the younger cohort. It is mandatory to address the overall status of the elder patient when reconstructive options are being considered. Certainly, the overall health condition, comorbidities, patient expectations and motivations, and tumor stage clearly affect the decision of reconstruction.

In our series [24], the majority of our elderly patients had an implant-based reconstruction with a low percentage of postoperative complications: no adverse events were observed in the postoperative period. Infection occurred in 6.34% of patients, partial necrosis of the mastectomy flap in 5.5%, and total implant removal in 12.24% due to infection (5.8%) or exposure (1.9%) or capsular contracture (4.2%).

On the contrary, Lipa et al. [25] reported a series of breast reconstruction in older women with majority of autologous flap reconstructions. They described a remarkably high complication rate associated with implant-based reconstructions. Fewer complications resulted from autogenous tissue reconstruction than from prosthetic reconstruction.

Howard-McNatt et al. reported on 89 women older than 60 years having mastectomy and reconstruction (both implants and flaps). They concluded that age should not be a contraindication for breast reconstruction in elderly women [26].

58.7 Conclusion

Advanced age (in itself) is not a contraindication to breast reconstruction and it can be successfully performed on well-selected patients. The safety of reconstruction together with improvements in life expectancy increases the incentive to allow older women with breast carcinoma to be reconstructed without major barriers related to age, functional status, and social support. Future cancer research should be conducted in the elderly to provide more confidence in cancer treatment and decrease undertreatment in elderly patients.

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Breast Reconstruction and Radiotherapy

59

Sophocles H. Voineskos, Christopher J. Coroneos, and Peter G. Cordeiro

59.1 Introduction

Postmastectomy radiotherapy (PMRT) has become an essential component in the treatment of a subset of patients with invasive breast cancer. Since 1997, when Ragaz et al. [1] and Overgaard et al. [2] originally described the indications for radiotherapy, a considerable number of patients now receive PMRT. Breast reconstruction has also become more frequent [3]. Reconstructive surgeons are faced with the challenge of performing breast reconstruction before radiotherapy or for patients requesting breast reconstruction in a previously irradiated field. When providing care for patients with advanced disease, the timing and sequence of chemotherapy, mastectomy, reconstruction, and radiotherapy are not established. Our preferred algorithm to help guide the complex decision-making process is illustrated in Fig. 59.1. If radiation is anticipated, we advocate immediate two-stage prosthetic reconstruction; this provides the patient with a breast mound and still maintains the option of salvage reconstruction with a flap [4].

59.2 Radiotherapy

The therapeutic use of ionizing radiation, or radiotherapy, is a fundamental component of the multidisciplinary approach in treating breast cancer. In patients with advanced breast cancer, radiotherapy reduces the locoregional recurrence rate and prolongs breast cancer-specific survival [5]. Additionally, it has been shown to reduce the overall death rate after breast-conserving therapy [2]. Radiotherapy is delivered via external beam radiation to the chest wall and, when indicated, to supraclavicular, infraclavicular, and axillary apical lymph nodes.

59.2.1 Indications for Radiotherapy

The ASCO PRMT guidelines [6], published in 2001, state that PMRT is recommended for the following patients with:

1. Four or more positive axillary lymph nodes
2. T3 tumors (i.e., more than 5 cm diameter) with positive axillary nodes
3. Patients with operable stage III tumors

Although the benefit of PMRT in patients with less than four positive nodes has traditionally been much less certain [7], the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) demonstrated radiotherapy to reduce both recurrence and breast cancer mortality in patients with axillary dissection to at least level II, with one to three positive nodes [8]. The ASCO guidelines are currently being updated, and thus the recommendations may change.

59.2.2 Effect of Radiotherapy at the Cellular Level

Radiotherapy is used to control or destroy malignant cells through two mechanisms. Damage is caused by either direct or indirect ionization of DNA molecules, producing tissue toxicity. Direct ionization disrupts protein and DNA molecules. Indirect ionization is thought to be more important; surrounding water molecules are ionized, producing free radicals that cause secondary damage to DNA. Radiation injury triggers multiple stress and apoptotic pathways, inducing a response of DNA repair, senescence, or cell death.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_59

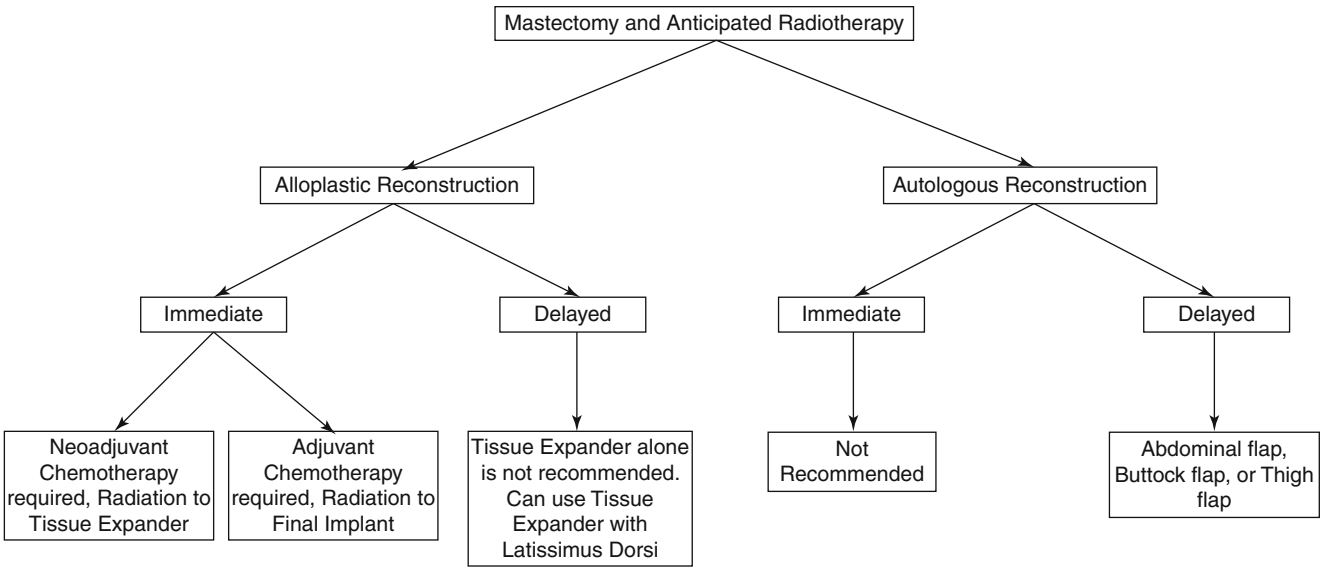

Fig. 59.1 Decision algorithm for mastectomy and anticipated radiotherapy

59.2.3 Pathophysiology of Radiotherapy

Tissue injury following radiotherapy has classically been thought to result from microvascular occlusion via a depletion of parenchymal and vascular endothelial cells. A secondary reactive process occurs potentially in response to microvascular occlusion and stem cell death. The specific cellular mechanisms are poorly understood; however they are thought to result from a loss of stem cells and involve inflammatory mediators leading to fibrotic processes [9]. Long-lasting fibroblast changes may inhibit wound healing through alterations in angiogenesis, collagen production, and decreased stem cell activity [9, 10].

59.2.4 Sequelae of Radiotherapy

The pathological process of radiation injury occurs immediately after irradiation; however the clinical and histological features may not appear for weeks or months [11]. Radiation injury is classified as acute, within a few weeks or late months to years after exposure. Acute damage is seen in tissues with rapidly proliferating cells, such as the skin or salivary glands. Skin initially becomes erythematous, followed subsequently by hyperpigmentation and dry desquamation that may progress to moist desquamation. Late changes may develop gradually or suddenly and tend to occur in tissues with slow cell turnover, such as nervous tissue. Potential long-term risks of PMRT include lymphedema, brachial plexopathy, radiation pneumonitis, rib fractures, cardiac toxicity, and radiation-induced second neoplasms [6]. ASCO guidelines suggest the risk of these long-term toxicities to be low enough that they should not influence the use of radiotherapy when it is indicated [6].

59.2.5 Impact of a Reconstructed Breast Mound on the Ability to Delivery Radiotherapy

The exact impact of a breast mound on the ability to effectively deliver radiotherapy, and the subsequent oncologic outcomes, is not universally agreed upon. Immediate breast reconstruction, in the form of a tissue expander, implant, or autologous flap, results in breast contours that might hinder the treatment planning of PMRT [12, 13]. The altered design of effective radiation fields can lead to increased total radiation dosage or to exclusion of radiation to areas that may harbor breast cancer. A metallic port, contained in most models of tissue expander, has been a particular point of concern [14] as it can scatter or block the radiation beam. On the other hand, the presence of an implant does not seem to impact the efficacy of radiotherapy on local control of the treated chest wall and nodal regions [15]. If radiotherapy is carefully planned and delivered, excellent local control with acceptable heart and lung doses can be achieved for patients undergoing immediate reconstruction [15, 16].

59.3 Breast Reconstruction Before Radiotherapy

59.3.1 Effect of Radiotherapy on an Alloplastic Reconstruction

The most common breast reconstruction technique is a two-stage prosthetic reconstruction [3]. Long-term reconstructive failure rate of a two-stage implant reconstruction is significantly lower in patients who do not undergo PMRT [17]. In the largest prospective study to date, Cordeiro et al. reported

implant loss to occur in 9.1% of irradiated implants and only 0.5% percent of non-irradiated implants [18]. Similarly, high-grade capsular contracture (grade IV) was significantly more common in irradiated implants than non-irradiated implants, 6.9% and 0.5%, respectively [18]. Patients not receiving radiotherapy also had significantly higher health-related quality of life and satisfaction, measured using the BREAST-Q, when compared to patients undergoing radiotherapy to either their tissue expander or implant. On the other hand, PMRT is increasingly common for patients with advanced breast cancer. If these patients desire an expander/implant reconstruction, or are high-risk surgical patients unable to tolerate autologous reconstruction, they will either receive radiotherapy to the tissue expander or to the permanent implant following the exchange procedure.

59.3.2 Memorial Sloan Kettering Protocol for Immediate Alloplastic Reconstruction with Mastectomy and Anticipated Radiotherapy

Timing of radiotherapy is determined by the need for neoadjuvant chemotherapy. When neoadjuvant chemotherapy is required, radiotherapy is delivered before the exchange procedure for a permanent implant. When patients require adjuvant chemotherapy, radiation therapy is delivered after the exchange procedure. Timing of radiotherapy is illustrated in Fig. 59.2.

In patients receiving radiation therapy to the tissue expander, total mastectomy with immediate placement of a submuscular tissue expander with complete musculofascial coverage is performed 3–4 weeks after completion of chemotherapy. Sentinel lymph node biopsy and/or axillary lymph node dissection is performed as necessary. Intraoperatively approximately 50% of tissue expansion is performed. Subsequent expansions are performed weekly, starting 10–14 days postoperatively. The final volume is achieved, through rapid expansion, by 6 weeks postoperatively. Radiotherapy commences at 8 weeks postoperatively and is administered to both the chest wall and regional lymph nodes with the tissue expander fully expanded. 15 MV photons are used for the reconstructed chest wall to minimize "scatter" dose off the magnetic tissue expander valve. A daily bolus of 1 cm is placed over the chest wall fields to ensure an adequate dose to the skin surface and mastectomy scar. Six months after radiation therapy is completed, aggressive capsulotomy is performed and the permanent implant is inserted (Fig. 59.3).

For patients receiving radiotherapy to the permanent implant, expansions are performed weekly, starting 10–14 days postoperatively, and are continued during chemotherapy. Four weeks after completion of chemotherapy, the exchange for the permanent implant is performed. Radiotherapy to the permanent implant commences 4 weeks after the exchange procedure. The paraclavicular nodal region is always included in the radiation field. The internal

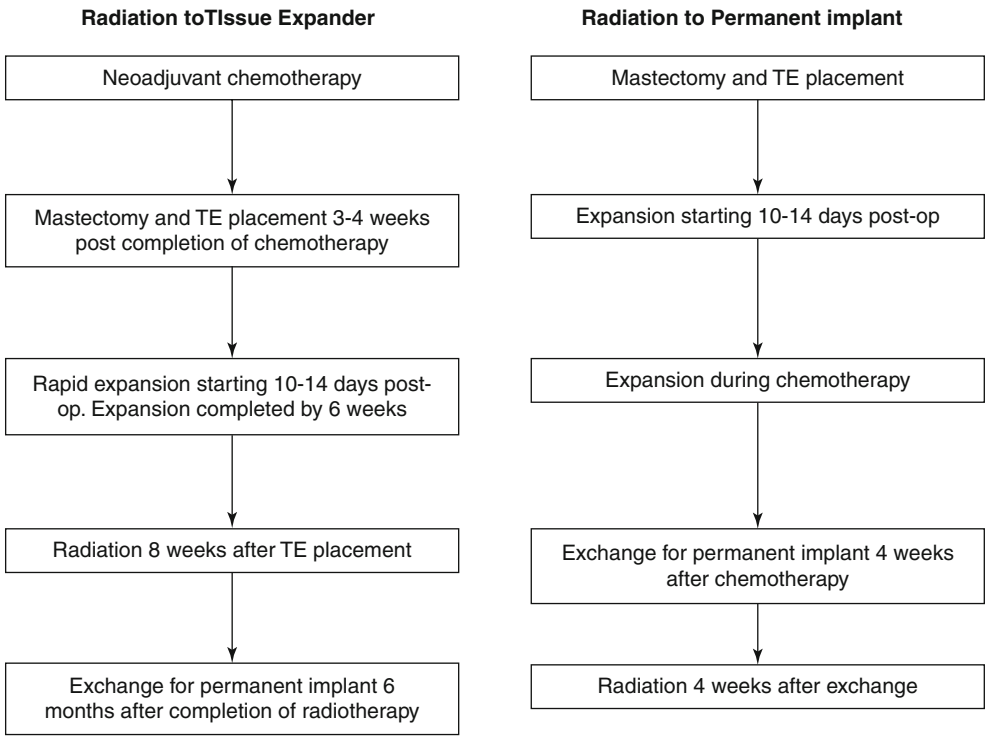

Fig. 59.2 Memorial Sloan Kettering protocol for immediate alloplastic reconstruction with mastectomy and anticipated radiotherapy

TE, tissue expander

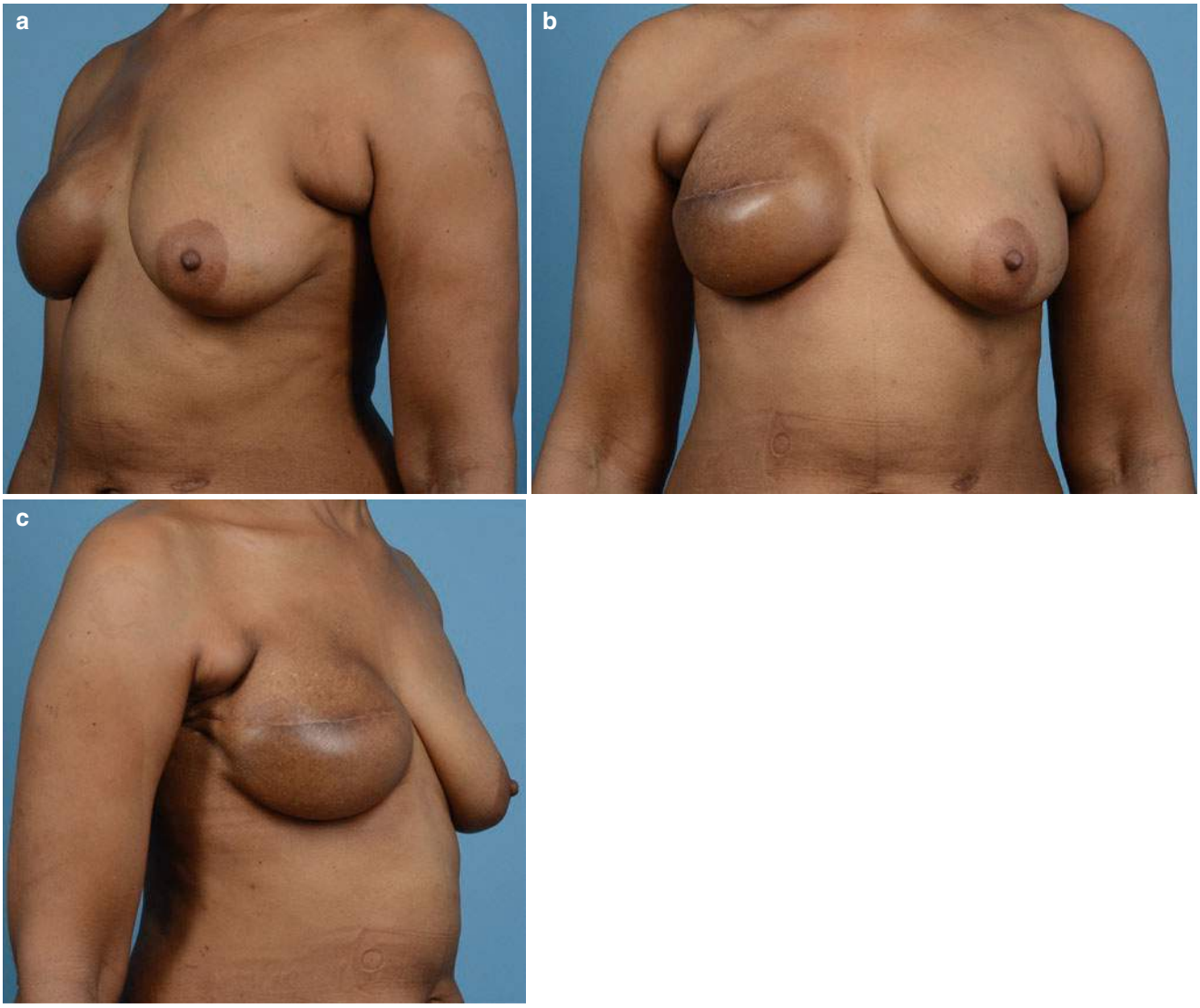

Fig. 59.3 Patient with postoperative radiotherapy to tissue expander. (**a**) Lateral, (**b**) frontal and (**c**) Oblique views showing early postoperative results

mammary chain and axillary nodes are irradiated based on preoperative imaging or pathologic evaluation. The prescribed energy for the radiation therapy to the permanent implant patients is 6 MV photons unless the patient is very large breasted. A daily bolus to the chest wall fields of 0.5 cm is administered. Irradiation of the permanent implant can cause both acute (Fig. 59.4) and late changes to the appearance of the breast (Fig. 59.5).

59.3.3 Radiotherapy to the Tissue Expander Versus the Permanent Implant

Patients who undergo radiation therapy of the tissue expander followed by the exchange procedure have a two times greater 6-year predicted failure rate than those receiving radiation therapy to the permanent implant after the exchange procedure, 32% versus 16%, respectively [17]. Patients with tissue expander radiation are significantly more likely to lose their expander than those with permanent implant radiation [19]. Therefore, to minimize reconstructive failure, it is recommended to irradiate the final implant.

Data on long-term aesthetic outcomes in irradiated two-stage expander/implant reconstruction is sparse. Nava et al. found subjective evaluations of shape and symmetry, assessed by surgeons, and patient opinion of the final reconstruction to be favorable toward irradiating the final implant [19]. However, data published by Cordeiro et al. suggest that patients with tissue expander radiation have better aesthetic outcomes as evaluated by the surgeon and lower rates of severe capsular contracture (grades III and IV) than patients with permanent implant radiation [17]. Irrespective of the timing of radiotherapy, expander/implant reconstruction can have a good result, with minimal scarring or capsular

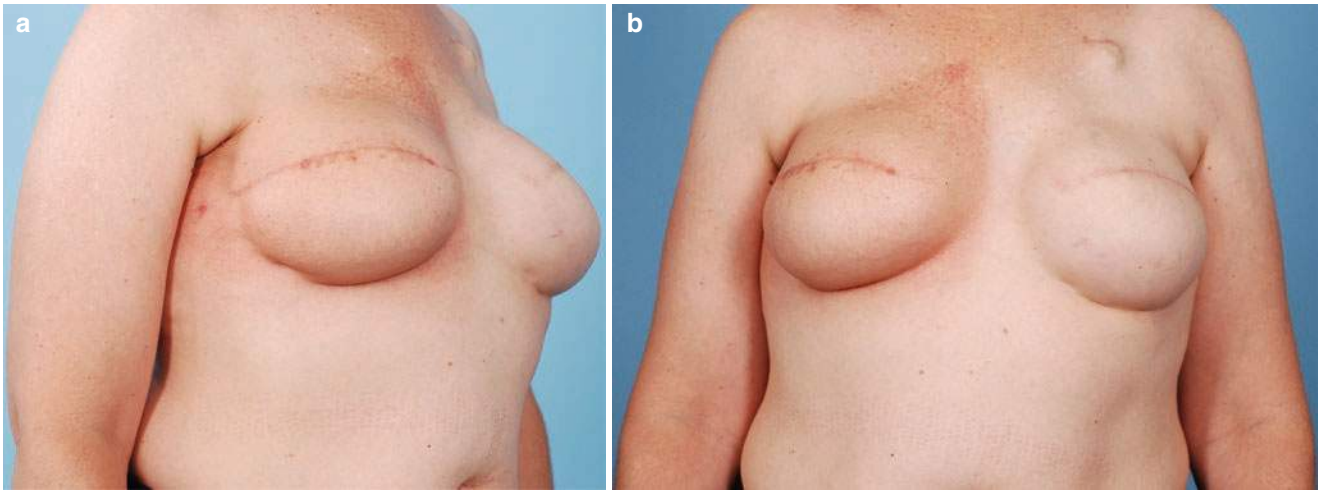

Fig. 59.4 Patient with postoperative radiotherapy to implant: acute changes. (**a**) Lateral, (**b**) frontal, and lateral views showing postoperative results

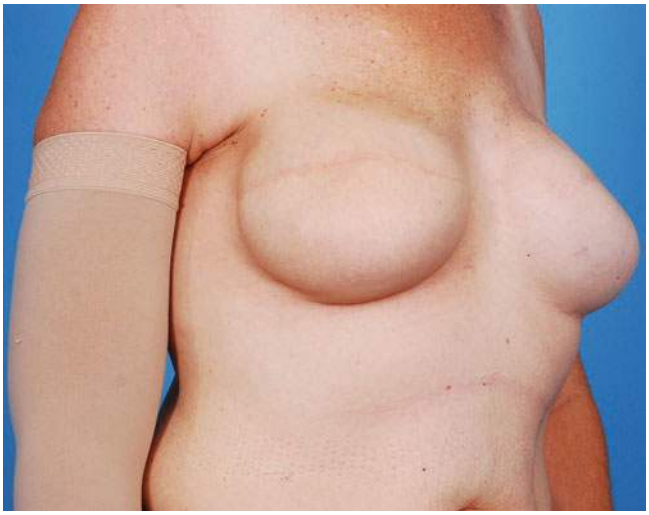

Fig. 59.5 Patient with postoperative radiotherapy to implant: late changes

contracture (Fig. 59.6), or a poor result, with distortion of the breast and a grade 4 capsular contracture (Fig. 59.7). Patients with tissue expander radiation can benefit from extensive capsulotomy at the time of the implant exchange, allowing the skin envelope to redrape over the implant, potentially contributing to a better aesthetic result. Patient-reported outcomes, as measured using the BREAST-Q, in patients with different radiation timings appear to be similar [17].

The reconstructive surgeon is faced with a predicament when a patient who desires a two-stage prosthetic reconstruction requires adjuvant radiotherapy. Should the surgeon recommend radiation therapy to the tissue expander, accepting a higher rate of reconstructive failure to potentially achieve a better aesthetic result? Or is a successful reconstruction a priority for the patient, understanding they will likely have an inferior aesthetic result? This judgment decision-making should be shared between the physician and patient. The senior author's current approach is to have this discussion with patients and review their goals and expectations. Patient-reported outcomes may be informative in this scenario.

59.3.4 Effect of Radiotherapy on an Autologous Reconstruction

Immediate autologous breast reconstruction for patients planning to receive PMRT is controversial and traditionally has been not recommended [20–22]. Conventionally, the risk of deleterious effects from PMRT on a flap is thought to be too great, and patients are exposed to a higher rate of long-term complications, fat necrosis, volume loss, flap contracture, and inferior aesthetic outcomes [20, 21, 23] (Fig. 59.8). Despite a successful free-flap transfer, consistent results of breast volume and symmetry are difficult to achieve. These complications could require revision surgery. Unfortunately, the additional operations may not adequately address these radiation-induced changes.

Common autologous options include abdominally based flaps (transverse rectus abdominis myocutaneous (TRAM), deep inferior epigastric perforator (DIEP), and superficial inferior epigastric artery (SIEA)) and thigh- or buttock-based flaps (transverse upper gracilis (TUG), superior gluteal artery perforator (SGAP), inferior gluteal artery perforator (IGAP), and profunda artery perforator (PAP)). The TRAM flap, either pedicled or free, is the most common method for autologous breast reconstruction [24, 25]. The pedicled TRAM is naturally less robust than a free TRAM since the

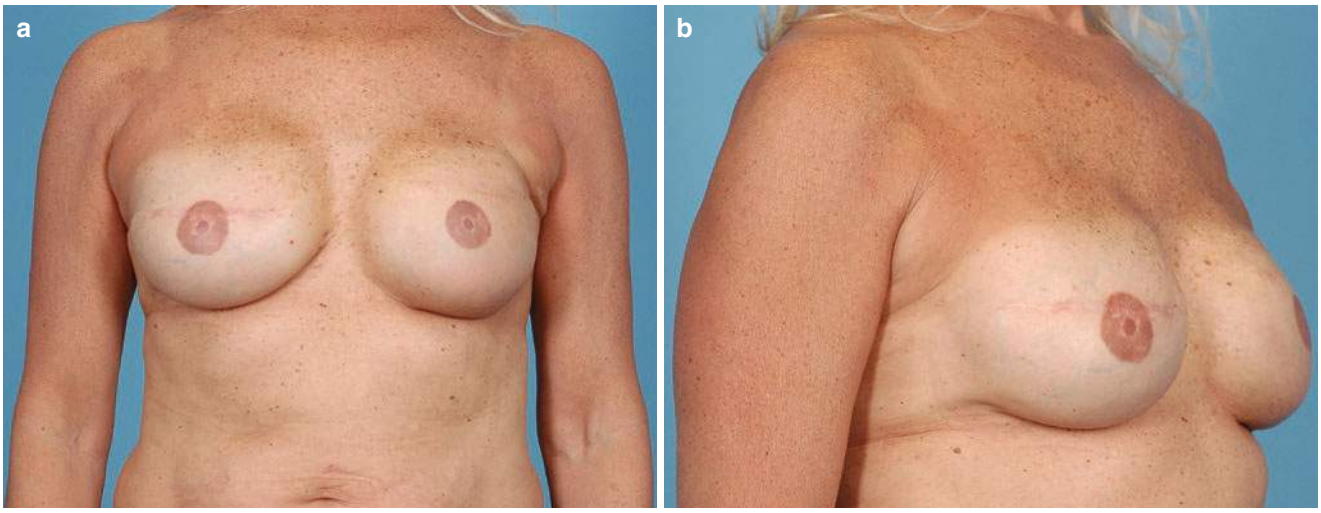

Fig. 59.6 Radiotherapy to TE/implant grade 1 capsular contracture (good result). (**a**) Frontal and (**b**) lateral views showing postoperative results

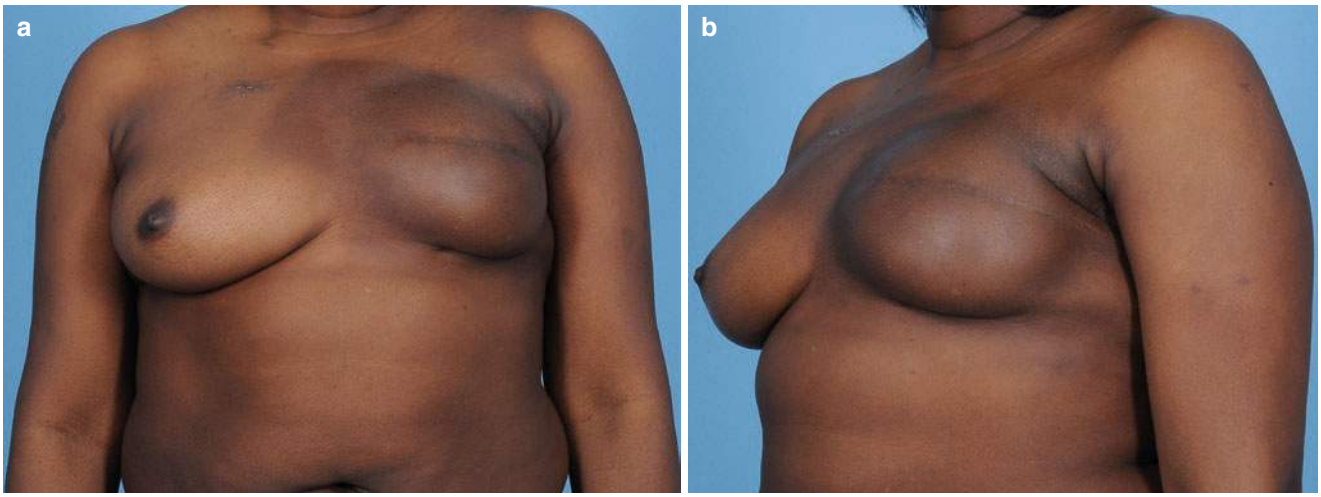

Fig. 59.7 Radiotherapy to TE/implant grade 4 capsular contracture (bad result). (**a**) Frontal and (**b**) lateral views showing postoperative results

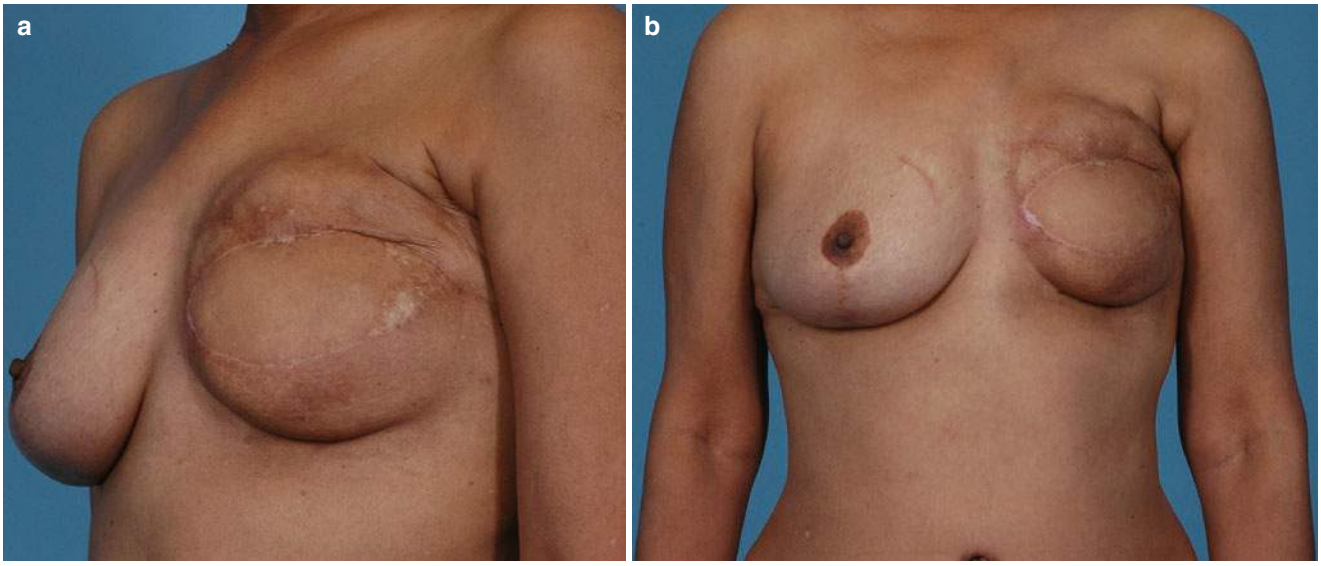

Fig. 59.8 Patient with postoperative radiotherapy to TRAM flap. (**a**) Lateral and (**b**) frontal views showing postoperative results

dominant blood supply to the TRAM tissue is the deep inferior epigastric artery. It is understandable that a pedicled TRAM is more affected by radiotherapy and associated with more complications [26].

Studies investigating the susceptibility of various free flaps to radiotherapy changes are beginning to emerge. Myocutaneous free flaps (e.g., free TRAM, muscle-sparing TRAM) contain muscle tissue bulk and multiple perforating vessels, which could theoretically help to minimize the consequences of radiotherapy. The DIEP flap, which uses fewer perforating vessels, is a modification of the free muscle-sparing TRAM flap. In non-irradiated patients, the DIEP flap can reduce abdominal wall morbidity but is associated with an increased risk of fat necrosis and flap loss [27]. Interestingly, in irradiated patients the superior vascularity of a muscle-sparing TRAM flap does not appear to protect the reconstructed breast mound from perfusion-related complications and does not result in lower rates of fat necrosis than with a DIEP flap [28, 29].

Recently, studies assessing outcomes and complications in free-flap breast reconstruction with PRMT argue that not offering patients this option denies an increasing number of women the benefits of immediate reconstruction [23, 30, 31]. Conflicting outcomes of flap fibrosis, flap contractures, and aesthetic outcomes are being reported for patients undergoing radiotherapy pre- or post-autologous reconstruction. Similar rates of total flap loss, wound healing complications, infection, hematoma, seroma, and fat necrosis are being reported between the two groups [31]. Proponents of this approach are suggesting that immediate autologous reconstruction not be overlooked as a viable option in patients who are likely to require postmastectomy radiotherapy, as this would deny them the benefits of an immediate reconstruction. Nevertheless, the utility of immediate autologous reconstruction for advanced disease remains controversial and is not recommended routinely in guidelines [32]. Some surgeons are able to provide an autologous reconstruction with good aesthetic outcomes [33] and acceptable complication and revision procedure rates [23, 29], in patients uncertain to require PRMT. In general, for patients known to require PMRT and who desire an autologous reconstruction, we do not recommend immediate breast reconstruction due to the detrimental effects of radiation on the newly created breast mound. Furthermore, these patients should be counseled that postoperative complications might postpone the opportunity to initiate PMRT.

59.4 Delayed-Immediate Technique

Delayed-immediate breast reconstruction is a treatment approach for patients with invasive breast cancer who are at an increased risk of requiring PMRT and who desire breast reconstruction [34]. Specifically, at MD Anderson, patients found preoperatively to have a T2 tumor, invasive disease with extensive ductal or lobular carcinoma in situ, multicentric breast cancer, or one positive axillary lymph node are considered candidates [35]. As mentioned above, delaying breast reconstruction until after mastectomy and pathology results reveal that PMRT is not needed, or until after PMRT is completed, denies patients the aesthetic and psychological benefits of immediate reconstruction. Delayed-immediate reconstruction is viewed as a possible solution.

In stage 1, a tissue expander is placed at the time of mastectomy and is filled to as great a volume as the vascularity of the mastectomy skin flaps will safely allow [35]. This prevents skin retraction and maintains breast shape. The permanent sections are reviewed, and the necessity of PRMT is assessed. In stage 2, if radiotherapy is not required, definitive breast reconstruction is performed 2 weeks after mastectomy [35], either with autologous tissue or by using a permanent implant with or without a latissimus dorsi flap. In the event that PMRT is recommended, the expander is deflated for treatment and reinflated no longer than 2 weeks after completion of PMRT [35]. Delayed reconstruction, with either autologous tissue or a permanent implant, should be completed no longer than 3 months after PMRT [35].

For patients in whom PMRT is not indicated, the second operative stage provides the opportunity to debride nonviable mastectomy skin if present and revise the inframammary fold if necessary. On the other hand, the long-term benefit of these revisions is uncertain and might not merit committing these patients to an extra operation.

The advantage for patients requiring PRMT is related to maintaining breast shape [36] and skin requirements for autologous reconstruction. A preserved breast skin envelope considerably decreases the amount of skin necessary for autologous reconstruction [35]. A skin-preserving delayed-immediate patient could potentially require only half of the abdominal flap to create a single natural-appearing breast. This affords the opportunity to use the other half of the abdominal tissue to reconstruct the contralateral breast if the patient desires a contralateral prophylactic mastectomy, possibly providing a more symmetrical result [35]. Conversely, when planning a standard delayed autologous reconstruction after PMRT, the surgeon may need to use a significant portion of the available abdominal tissue to recreate a ptotic breast.

For patients in whom PMRT is indicated, the need to perform the reconstruction "no longer than 3 months after the completion of PMRT" [35] might actually risk greater complications in the perioperative period than a standard delayed autologous reconstruction after PMRT. Patients who undergo free-flap reconstruction with a recent history of radiation therapy may have higher rates of intraoperative vascular complications, overall flap loss, and additional technical risk [23, 37].

59.5 Breast Reconstruction After Radiotherapy

59.5.1 Alloplastic Reconstruction in a Previously Radiated Field

The faster recovery, avoidance of a donor site, and relative simplicity of an alloplastic reconstruction can be appealing to many patients. Historically, studies reported high complication rates in patients undergoing tissue expander/implant-based reconstruction in a previously irradiated field and recommended alloplastic reconstruction be avoided in this setting. Tissue expansion in an irradiated chest has been associated with problems of underexpansion, infection, extrusion, and pain [10]. Radiated tissue is often unyielding, unpredictable, and predisposed to breakdown. Aesthetic outcomes are inferior when compared to alloplastic reconstruction in patients without a history of radiotherapy [38]. The reconstructed breast can be asymmetric, has decreased projection, and requires more secondary procedures, especially due to the increased rate and severity of capsular contractures [10] (Fig. 59.9). Pooled data from studies of alloplastic reconstruction either with pre- or post-reconstruction radiation did not show markedly different rates of minor complications, major complications, capsular contracture, and failed reconstructions (i.e., need for a flap) [39]. However, there was considerable variability in the results of the studies included, and the confidence intervals of the pooled estimates were wide. In their review, Momoh et al. noted that complication and failure rates of recent studies were lower than those of older reports [39]. The variability in results could have been due to a combination of advances in expander technology, differences in surgical technique between institutions, alterations to radiation dosing regimens, and the delivery of radiotherapy [39, 40].

Successful outcomes can be achieved in highly selected patients undergoing salvage mastectomy and immediate tissue expander/implant reconstruction following breast conserving therapy (lumpectomy/irradiation). Cordeiro et al. selected patients based on their tissue quality, location of previous scars, timing of radiotherapy, and patient expectations [40]. In the assessment of skin and soft tissue quality, the authors recommend choosing patients whose skin still exhibits some elasticity and has minimal to no discoloration from the irradiation [40]. Large or multiple scars are usually a contraindication, and the breast tissue must be soft or only slightly firm [40]. The mastectomy flaps should be elevated and handled carefully to minimize complications. Their early complication rate was greater in irradiated than non-irradiated patients, with the most common complication being mastectomy flap necrosis [40]. On the other hand, these patients could complete their breast reconstruction with a similar incidence of grade III or grade IV capsular contracture and be satisfied with their final result (Fig. 59.10). The authors acknowledge that the overall outcome is, to some extent, usually aesthetically inferior to non-irradiated, but it is a safe and reliable option in highly selected patients [40].

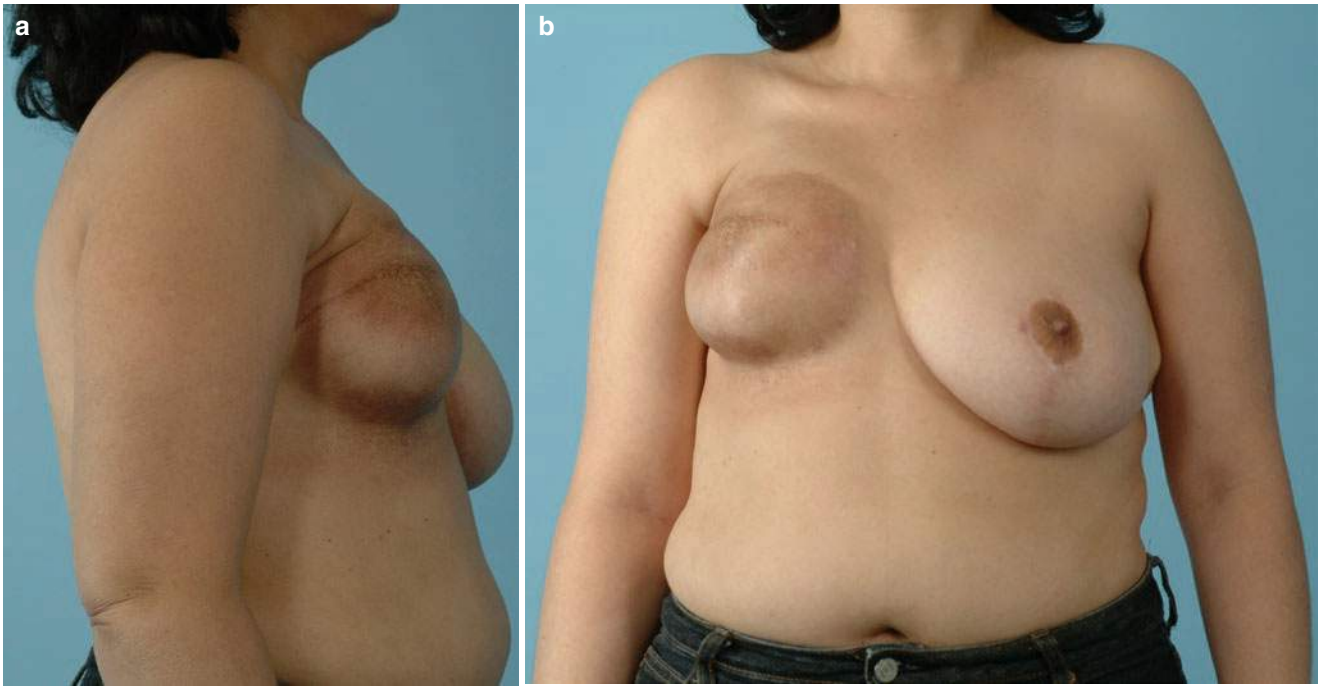

Fig. 59.9 Capsular contracture and poor aesthetic result in a previously irradiated patient who underwent delayed tissue expander/implant reconstruction. (**a**) Lateral and (**b**) frontal views showing postoperative results

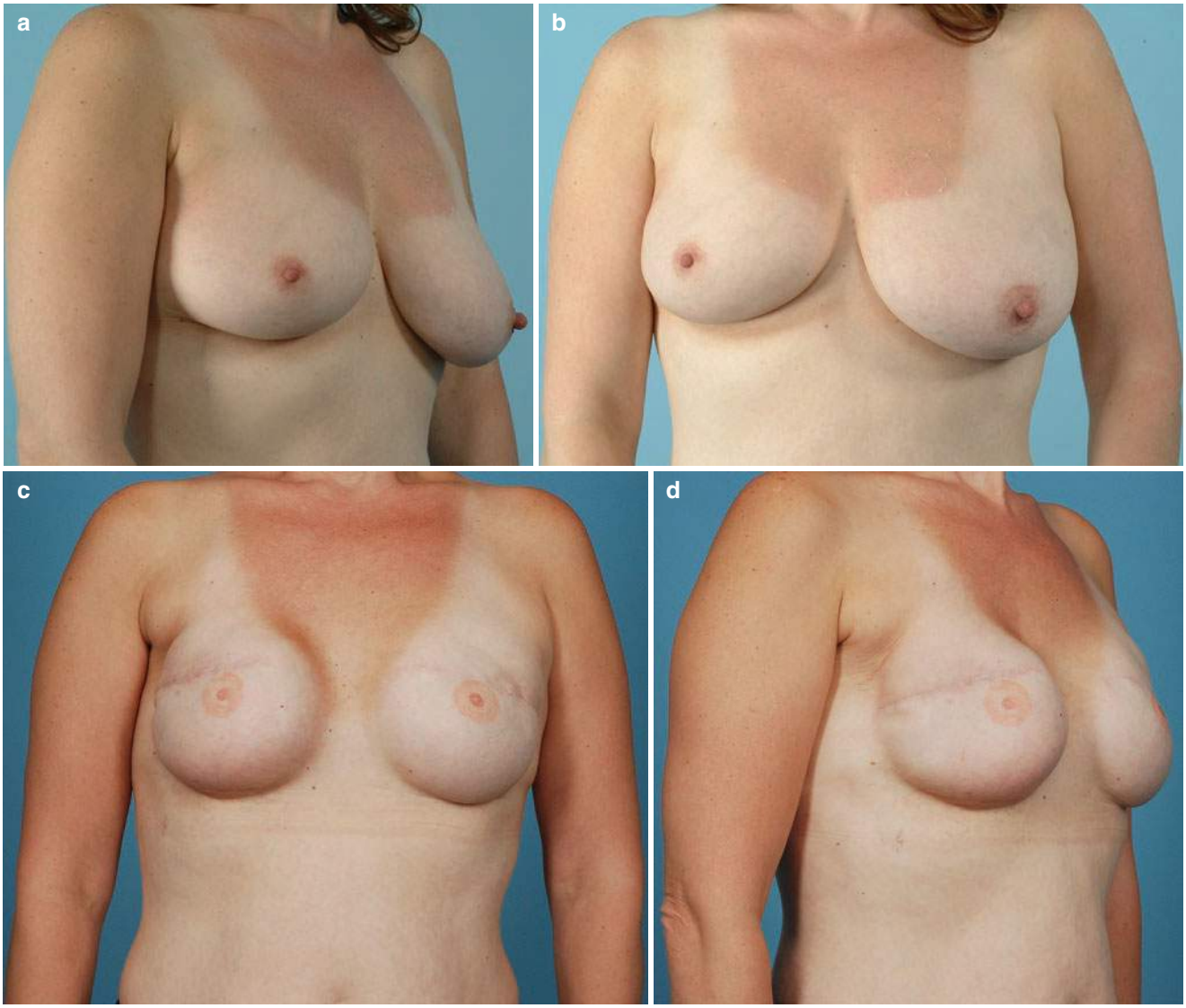

Fig. 59.10 Good aesthetic result in a previously irradiated patient who underwent salvage mastectomy and immediate tissue expander/implant reconstruction for cancer recurrence following breast conservation therapy (lumpectomy/irradiation). (**a**) Lateral and (**b**) frontal preoperative views. (**c**) Lateral and (**d**) frontal views showing postoperative results

We rarely recommend using a tissue expander alone in previously irradiated tissue. Although often technically possible, it is associated with higher complication rates. In particular, patients with questionable skin and soft tissue quality, unfavorable scars, or radiation in the past 2 years are unlikely to have a successful reconstruction using a tissue expander alone. For these patients, providing well-vascularized, soft tissue coverage of the tissue expander with a latissimus dorsi flap is a means to achieve very good to excellent aesthetic results and an acceptable rate of capsular contracture [41]. The latissimus muscle is able to cover the expander and is compliant, nonradiated tissue that will more readily expand. The skin island on the flap is used to replace as much damaged tissue as the flap donor site can safely accommodate [10].

59.5.2 Autologous Reconstruction in a Previously Radiated Field

The timing of autologous breast reconstruction in relation to administration of radiotherapy is important and can considerably affect the final outcome. Tran et al. compared the effects of radiotherapy in immediate and delayed free TRAM breast reconstruction [21]. They found late complications of fat necrosis, volume loss, and flap contracture to decrease dramatically when the breast was reconstructed after radiotherapy [21]. When evaluating the effect of pre- or post-reconstruction radiation on pedicled TRAM flaps, Spear et al. proposed that TRAM reconstruction should be postponed in patients expected to receive postoperative radiation

[22]. They found risks of serious flap and/or donor-site complications to be similar between groups. However, hyperpigmentation, symmetry, contracture, and aesthetic outcomes all had better scores in patients undergoing reconstruction after radiotherapy [22]. Due to the detrimental effects of PMRT on both chest wall tissue and autologous flaps, we prefer to perform delayed rather than immediate autologous reconstruction in women "known or expected" to require radiotherapy.

The autologous reconstructive options mentioned previously, abdominal- (TRAM, msTRAM, DIEP, SIEA), thigh- (TUG, PAP), and buttock-based flaps (SGAP, IGAP), are all potential options to recreate a breast mound in an irradiated mastectomy defect. Usually an abdominal-based flap is preferred; this tissue is best able to mimic the ptosis, shape, and feel of a breast mound. In the irradiated chest wall, a free TRAM is favored over a pedicled TRAM [10, 42]. Flaps from the buttock often result in a firmer, less supple breast due to the innate skin and subcutaneous tissue qualities from this region [24].

Overall flap survival is not affected by the fibrotic skin and soft tissue of the chest, though the probability of a successful breast reconstruction is decreased due to complications related to the local tissue's impaired ability to heal. Important technical details include excising the previous mastectomy scar completely [24] and replacing the scarred, noncompliant lower mastectomy flap using the new, healthy soft tissue from the abdomen, thigh, or buttock. Even in a previously irradiated field, autologous tissue can be used to reconstruct a breast mound with similar shape and ptosis of a natural breast and to recreate the inframammary fold (Fig. 59.11).

The optimal amount of time to wait between completion of radiotherapy and autologous reconstruction is contentious. Many reconstructive surgeons recommend waiting 6 months before delayed reconstruction to allow the radiation-damaged tissue to heal. Some advocate to wait at least 1 year [37], yet others see no significant benefit to waiting longer than 6 months [43]. By and large, in delayed autologous reconstructions not requiring radiotherapy, reconstruction is suggested to be performed no sooner than 6 months after mastectomy because of immature scar formation [24].

59.5.3 Microvascular Surgery in a Previously Radiated Field

Early experimental studies of microvascular anastamoses in radiated femoral vessels of rats did not show an impact on arterial anastamotic patency rates but demonstrated a significant decrease in patency rates of the venous anastamoses [44, 45]. In irradiated vessels, the fibrosis of the arterial media and intima have actually been described to improve the ability to handle arteries, though veins are thought to become more friable [10]. In head and neck reconstruction, prior radiotherapy as an independent risk factor for vascular complications in free tissue transfers is debated [46]. In breast reconstruction, clinical studies are beginning to quantify the outcomes and complications, such as anastamotic failure, specific to microvascular surgery in the setting of previous radiation therapy [37, 46, 47]. While radiation is known to impair the quality of recipient vessels, the relevant clinical effects are likely related to perivascular fibrosis, which along with anastamotic and flap failure is more commonly observed with the thoracodorsal vessels [47]. In a retrospective review, where most recipient vessels (>95%) were internal mammary vessels, Fosnot et al. isolated previous radiation therapy as an independent risk factor for vascular complications in free autologous breast reconstruction [46]. The majority of vascular complications occurred intraoperatively [46], which may be a result of the increased technical difficulty and additional dissection that is usually more common. Temporal proximity to postmastectomy radiation may influence the success of microvascular surgery. Baumann et al. demonstrated decreased rates of microvascular thrombosis and total flap loss with delayed free abdominal flap breast reconstruction 12 months or more after the completion of radiotherapy [37].

In an immediate breast reconstruction, thoracodorsal vessels are often well-exposed following axillary dissection and have consistent anatomy. These vessels used to be the standard recipient for most reconstructive surgeons recreating a breast using a TRAM flap [48]. However in the setting of delayed breast reconstruction post-radiotherapy, a difficult dissection is required in the scarred, fibrotic axillary field. The positioning needed to perform a microvascular anastomosis in the axilla is unfavorable and sometimes technically challenging. In contrast, internal mammary vessels are now often the first-choice recipient site, especially in cases of delayed microvascular breast reconstruction [48]. Internal mammary vessels are in a consistent location, of large caliber, and are seldom in a scarred recipient bed, allowing more reliable flow across the anastamoses in delayed post-radiotherapy reconstructions [49, 50]. In this setting, when internal mammary recipient vessels are deemed "unusable," it is more often due to an inadequate vein or artery, whereas thoracodorsal vessel are usually deemed "unusable" because of excessive scarring [50]. Individual surgeons have their preference between recipient sites, and success can be achieved with either option [50]. Ultimately, a microsurgeon should remain capable and comfortable enough to use either the internal mammary or thoracodorsal recipient vessels.

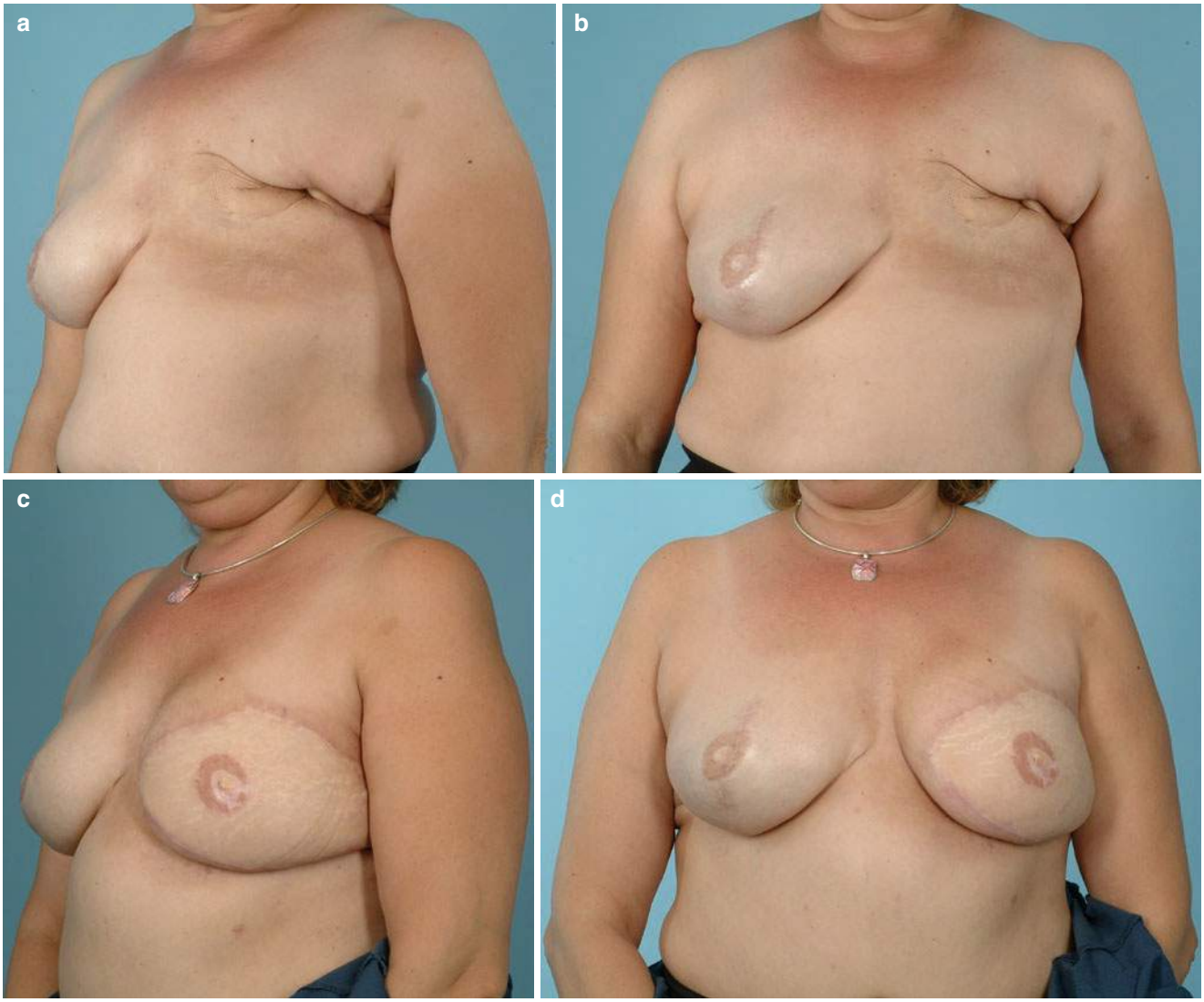

Fig. 59.11 Patient with delayed TRAM flap in a previously irradiated field. (**a**) Lateral and (**b**) frontal preoperative views. (**c**) Lateral and (**d**) frontal views showing postoperative results

59.6 Radiotherapy and Nipple-Areolar Complex Reconstruction

Nipple-areolar complex (NAC) reconstruction is a safe procedure subsequent to breast mound reconstruction in patients who have not received radiotherapy. Conversely, NAC reconstruction is considered by some to be contraindicated in the setting of expanded and irradiated skin. The postoperative complication rate after NAC reconstruction has been shown to be significantly higher in an irradiated field (41%) than the non-irradiated setting (6%) [51]. Some of these complications are potentially devastating, involving revision surgery or even implant loss.

We believe that NAC reconstruction, in the setting of PMRT with implant-based reconstruction, can be performed in carefully selected patients. Attempting this procedure for patients with thin mastectomy skin flaps, a history of infection at the surgical site, or a history of delayed healing/necrosis of the mastectomy flaps is not recommended [52]. The presence of moderate to severe late radiation changes of the mastectomy flap skin is a poor prognostic indicator [52]. At Memorial Sloan Kettering, good candidates are thought to have the following qualities: (1) resolution of acute radiation changes, (2) no evidence of late radiation changes, and (3) adequate thickness of the mastectomy skin flaps [52]. Patients should be assessed on a case-by-case basis, and the comfort level of the individual surgeon determines what is an

"adequate thickness." Reconstruction of the nipple can be achieved using various local flaps in both autologous and alloplastic reconstructions. It is best to avoid attempting areolar reconstruction with a full-thickness skin graft, specifically in patients with an underlying prosthesis as one risks losing the implant. Therefore we suggest tattooing to recreate the areola for implant-based reconstructions. We emphasize that patients with a history of radiotherapy should be carefully selected for NAC reconstruction, an important final step in the recreation of a natural-appearing breast.

59.7 Authors' Viewpoint

Patients receiving PMRT have stage 2 and 3 breast cancer with advanced disease. They often have a poor prognosis and might not be appropriate candidates for, or might not desire, autologous reconstruction. Immediate alloplastic reconstruction provides the simplest surgical solution for the group of patients who will need neoadjuvant/adjuvant chemotherapy and PMRT. We believe that motivated patients can achieve good outcomes, particularly if the approach we have outlined is followed carefully. Breast reconstruction in this scenario can be exceptionally worthwhile from the patient's perspective. Although alloplastic reconstruction in the setting of radiotherapy is fraught with higher, but often acceptable, complication rates and lesser aesthetic outcomes, it should not mean it is an absolute contraindication. A majority of these patients are extremely grateful and remain satisfied with their results despite potentially marginal aesthetic outcomes [53]. If the patient prefers autologous reconstruction, we recommend delaying breast reconstruction until after PMRT is completed. Despite significant hurdles imposed by oncologic therapies, reconstructive plastic surgeons must strive to provide solutions for their patients and be prepared to rise to the challenge as treatment modalities continue to evolve.

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Immediate Breast Reconstruction in Previously Irradiated Patients

60

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60.1 Introduction

The oncologic benefit of radiotherapy is very well established in breast-conserving therapy (BCT), and it becomes an important cornerstone in breast cancer treatment, not only due to the decrease of local recurrence rate but also due to the reduction of mortality [1]. Despite the benefits of radiation to the oncologic treatment, it is well recognized that radiation induces damages not only to the target cells but also to neighboring normal tissues as a result of either direct exposure to radiation or the so-called bystander effect, which refers to biological effects in non-irradiated cells caused by signals from irradiated cells. Then radiotherapy changes the normal architecture of breast tissue, and offers additional risk to any subsequent reconstruction surgery, especially when a local recurrence occurs and a salvage mastectomy is necessary [2].

Radiotherapy can also cause endarteritis, which leads to a less vascularized bed. It is potentially damaging if further intervention is necessary because ischemia alters the local resistance to infection. Furthermore, the reduced lymphatic drainage, resulting from the actinic lymphangitis, favors the accumulation of fluids. Finally, many patients develop a certain degree of breast fibrosis a few months after the end of radiotherapy, which prevents the expansion of the tissue with temporary or definitive expanders. Due to these factors, autologous flaps are generally indicated for previously irradiated breast cancer patients.

Although autologous breast reconstruction with myocutaneous flaps is usually the first option in the irradiated breast, in the last years the use of implants in this situation has considerably increased. In 2015, Agarwal et al. evaluated a total of 5481 female patients from the Surveillance, Epidemiology, and End Results (SEER) database from 2000 through 2010, who underwent radiation and breast reconstruction. The authors showed that the percentage of specified reconstructed patients in the United States who were reconstructed with implants only increased from 29% in 2000 to 52% in 2010 ($p < 0.001$), while over the same time period, the percentage of reconstructed patients reconstructed with autologous tissue generally decreased from 55% to 32%. Combined autologous tissue with implant techniques reconstruction remained stable at an average of approximately 13% [3].

After BCT, the use of implants is controversial due to the damaging effects of radiotherapy on soft tissues. An increased risk of reconstruction failure, wound complications, and severe capsular contracture when radiotherapy accompanies breast reconstruction was reported in previous series [4, 5].

The purpose of this chapter is to establish an algorithm for breast reconstruction after recurrence of breast cancer in patients previously exposed to BCT and irradiation.

60.2 Implants

A high percentage of capsular contractures and postoperative complications in reconstruction with implants when adjuvant radiotherapy is used have been reported. Due to a more intensive inflammatory response, there are reports of pain, distortion, and capsular contracture in approximately 30% of

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_60

the patients during long-term follow-up. There are also reports of implant displacement, implant exposure, poor aesthetic outcomes, and high rates of implant removal [6–12].

More recently this paradigm—to not use implants when radiotherapy is present or planned—had been challenged by reports of good to excellent results in breast reconstruction despite the previous use of radiotherapy or its application after reconstruction [7, 13], and the use of an implant-based reconstruction in a previously irradiated breast has dramatically increased [3]. However, as long as some authors describe favorable experiences of reconstruction after radiotherapy, others are still opposed to that procedure due to the higher rates of complications in this group.

Cagli et al. analyzed surgical outcomes, complications, satisfaction, and well-being in 10-year experience of two-stage implant breast reconstruction after salvage mastectomy in previously irradiated breast. The patients were divided into two groups: group A (study group) included 30 patients submitted to salvage mastectomy after local recurrence in previously irradiated breast. Group B (control group) included 53 patients who were submitted to primary radical mastectomy. The median follow-up time was 36 months (12–144 months). In the group A, the median time from RT to reconstruction was 24 months (9–192 months). The overall rate of complications was not different between the two groups (66.6% vs 58.5%). However, the major complications occurred mostly in the irradiated group (53.3% vs 32%, $p = 0.07$). The group A patients had a significantly higher risk of grade III–IV capsular contracture (RR 3.75, $p = 0.02$) and of autologous salvage reconstruction (RR 10.4, $p = 0.02$). In the analysis of postoperative satisfaction with BREAST-Q postoperative module, psychosocial well-being, sexual well-being, physical well-being, satisfaction with breast, satisfaction with outcomes, and total satisfaction achieve a higher score in the control group. The total satisfaction results were 65 ± 9, in the group A, and 83 ± 10, in the group B [14].

In 2014, a total of 26 studies were selected for a systematic review of complications of implant-based breast reconstruction in order to compare the results from patients submitted to radiotherapy prior to reconstruction surgery, predominantly for breast conservation therapy, to patients submitted to radiotherapy post-reconstruction surgery either after placement of tissue expanders or after implant placement. Complication rates were not significantly different between patients submitted to radiotherapy before or after reconstruction. Reconstruction failures were considered if implants have to be taken out, replaced with flaps, or revised with the addition of a flap, and there was no difference between the pre (19%)- and post (20%)- reconstruction radiation. The incidence of severe capsular contraction was high in both groups and also not significantly different between the groups (25% in the pre-reconstruction radiation group versus 32% in the post-reconstruction group). Thus although the complication rates were elevated in both groups, there were no difference if the radiotherapy was done before or after the breast reconstruction [15].

In a previous series from the Our Lady of Grace Hospital Breast Unit in Curitiba (Brazil), it was reported three cases of one-stage breast reconstruction in patients who previously underwent a quadrantectomy followed by radiotherapy and presented with local recurrence. All of them underwent skin-sparing mastectomy followed by one-stage immediate breast reconstruction with anatomic profile implants. After an average follow-up of 16 months, no evidence of capsular contracture was noticed, the aesthetic results were stable, and the patients did not present with early or late complications. The authors suggest that the success in these patients could be due to the association of a selection of the patients with no breast fibrosis after radiotherapy and the use of anatomic implants smaller than the original size of the irradiated breast. Immediate breast reconstruction with implants in this well-selected group of patients needs to be tested in a large series in order to confirm these preliminary results [12] (Fig. 60.1).

To improve the results with the implant-based reconstruction after radiotherapy, a good muscular coverage of the prosthesis is necessary. Acellular dermal matrix (ADM) has been employed to create an inferior pocket for the tissue expander and allow for quicker tissue expansion with better coverage and definition of the lower pole of the breast, in the two-stage

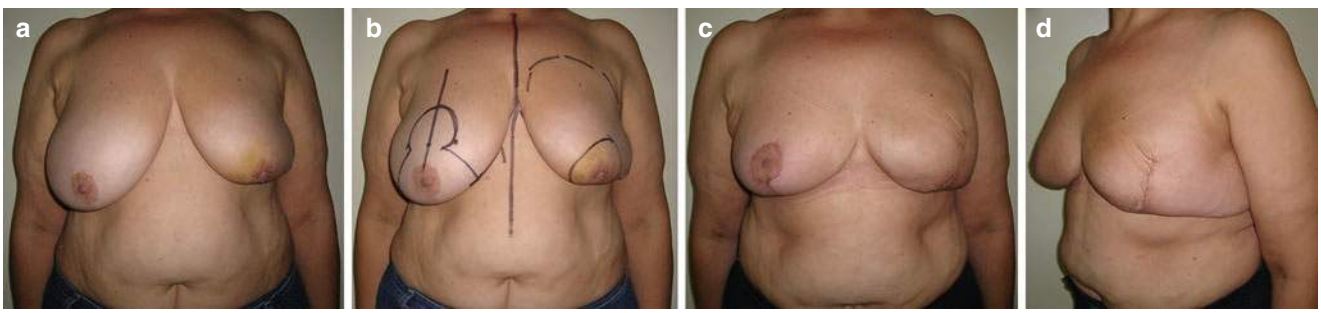

Fig. 60.1 Preoperative (**a** and **b**) and postoperative (**c** and **d**) views of a 62-year-old patient with a local recurrence after breast-conserving therapy 8 years earlier in the left breast. 12 months of postoperative surgery with one-stage breast reconstruction with implant and contralateral breast reduction for symmetry

reconstruction, but the cost of this material still limits its use [16, 17]. The use of ADM has resulted in decreased time to second-stage reconstruction, decrease number of expansions necessary, and increased total expander volume at initial operation. Other benefits include the decrease in inflammation, resulting in less capsular contracture.

In 2016, at the Our Lady of Grace Hospital Breast Unit, it was first described the use of bovine pericardium in an 82-year-old patient previously submitted to radiotherapy and now submitted to skin-sparing mastectomy who was referred to implant-based reconstruction but during the surgery did not have a suitable pectoral muscle to cover the prosthesis. Then a bovine pericardium from Braile Biomedica was used to protect the prosthesis [18]. A previous study has described the use of Veritas® bovine pericardium in a retrospective analysis of 54 patients in 93 immediate breast reconstructions with a complication rate of 21.5% [19]. The bovine pericardium from Braile Biomedica is normally used in cardiac surgery but has never been used for breast reconstruction before. There was no complication nor capsule contraction observed in a period of 18 months of follow-up of this patient.

60.3 Flaps

The description in 1977 of the latissimus dorsi musculocutaneous (LD) flap for breast reconstruction introduced another important option for autologous tissue reconstruction in patients after mastectomy [20]. Until the description of the transverse rectus abdominal muscle (TRAM) flap in 1982 [21], the use of autologous tissue for reconstructions was closely linked with breast implants. TRAM flap provided a relatively easy technique for acquiring ample tissue for shaping and skin coverage in most reconstructions. When a large amount of skin replacement is required, it is the preferred technique.

Previously irradiated patients ranged from a mastectomy defect with minimal radiation changes to frank skin necrosis. The coverage is the primary purpose for the latter group, and the reconstructive operation becomes an aesthetic procedure in the former. For the reconstructive surgeon, there are two major areas of concern after radiation treatment:

- The recipient bed
- The flap's vascular pedicle

Breast reconstruction with a TRAM flap after radiation therapy is reasonable and should remain as the first choice for most patients, although multivariable logistic regression analysis showed both obesity and prior radiation to be associated with an increased risk for fat necrosis [22].

The bipedicled flap should be used when possible to allow for sufficient tissue for reconstruction after resection of the radiated recipient site and provide improved blood supply to a vascular impoverished recipient bed [22]. However, using a bipedicled flap in the irradiated patient does not prevent the incidence of fat necrosis. The rate of fat necrosis suggests some compromised blood flow to the subcutaneous fat, possibly from partial obstruction of the internal mammary artery.

The largest review of irradiated patients undergoing TRAM flap reconstructions supports previous histologic studies that large vessel damage from radiation is rare and not prohibitive for using pedicles for flaps [22]. Moreover, Kroll et al., using four independent observers, compared 82 patients with a history of previous chest wall irradiation to 202 non-irradiated patients, in order to determine whether prior irradiation was associated with more frequent complications. Both groups underwent LD and TRAM flap breast reconstruction. Complications in the irradiated group were 39% versus 25% in non-irradiated one ($p = 0.03$). In the irradiated group, complications were more frequent with LD flap group (63%) than those in TRAM flap (33%; $p = 0.063$), but it was not statistically significant [23].

Although only irradiated groups were evaluated, Schuster et al. in a study with patient questionnaires had shown higher satisfaction rates with TRAM flap reconstructions than with LD flaps or implants in previously irradiated patients [24] (Fig. 60.2).

60.4 Effects of Radiation in Immediate Breast Reconstruction Decision

Issues concerning breast reconstruction in patients who have had or may potentially require radiation therapy include:

- Effect of radiation therapy on soft tissues
- Timing of irradiation in the patient presenting with breast cancer
- Choice of a breast reconstruction option that will produce optimal long-term cosmetic outcome

The effects of radiation on wound healing are extensive and well known, although the specific causes remain a matter of speculation. Early response is characterized by dry or moist desquamation, dependent on the dose-response of the host. The chronic phase is characterized by fibrosis, loss of elasticity, and in some circumstances a susceptibility to breakdown and ulceration [25].

A recent analysis was published of 277 consecutive LD breast reconstructions performed in 243 patients, with one-third being immediate reconstructions. The mean age at reconstruction was 50.4 years. Mean follow-up was 47 months, and 3.6% of patients developed Baker grade III

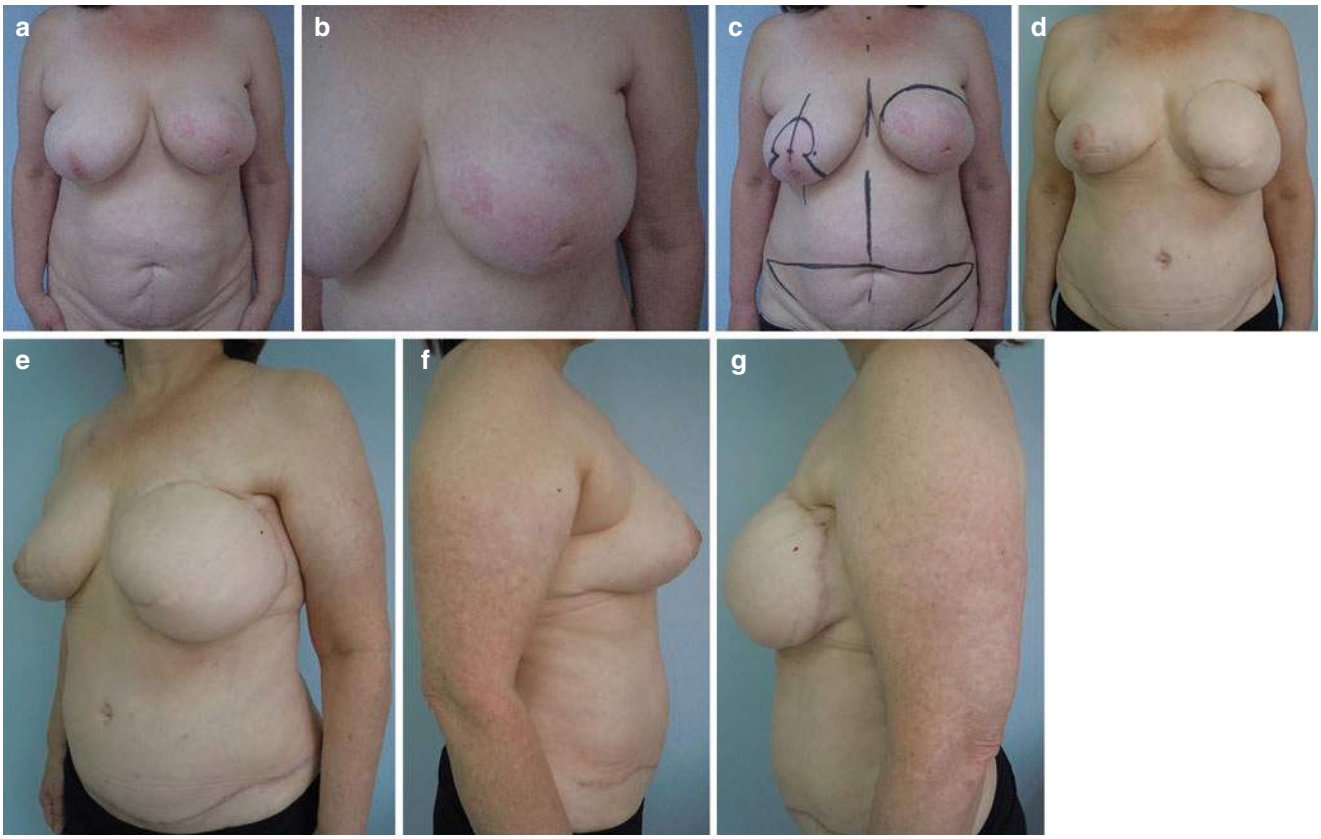

Fig. 60.2 Preoperative (**a**–**c**) and postoperative view (**d**–**g**) of a 59-year-old patient with an extensive local recurrence after breast-conserving therapy 4 years earlier in the left breast. 12 months of postoperative surgery with one-stage breast reconstruction with a bipedicled TRAM flap and contralateral breast reduction for symmetry

capsular contracture requiring capsulotomy. Chemotherapy provided a protective effect ($p = 0.0197$) against capsular contracture formation. Previous radiotherapy had no significant influence on symptomatic capsule formation. Therefore their conclusion was that the use of textured, cohesive gel silicone implants, combined with a standardized surgical approach, could reduce complications in the short- and long-term postoperative period, independent of radiotherapy [26].

On the other hand, Garusi et al. [27] evaluated the use of LD breast reconstruction after radiotherapy. They performed 63 LD flaps with implant reconstructions between 2001 and 2007. All of them were performed in breast cancer recurrence cases after breast conservative treatment and then preceded to total mastectomy. The capsular contraction Baker's grade III was observed in two cases (3.1%). The rest were grade I–II, and there were no grade IV contractures. They proposed that LD flaps with implants can be performed in irradiated breasts with a low capsular contracture rate.

The same European Institute of Oncology group [28] performed an interesting study addressing whether there is any difference in the evaluation of cosmesis according to the gender and specialization of the observer. Fifty-two photographs of the patients who had undergone TRAM reconstruction for breast cancer were divided into three groups according to treatment (TRAM alone, TRAM → RT, RT → TRAM) and were evaluated by 21 specialists, 10 males and 11, females from different areas: radiotherapy, breast surgery, and plastic and reconstructive surgery. A significantly worse score was registered in the TRAM → RT group compared with the other groups.

In the last few years at the Department of Mastology and Breast Reconstruction of the Hospital de Cancer de Barretos, 45 cases of autologous flaps with or without radiotherapy were performed. The LD flap was indicated in 29 cases, 10% of them before radiotherapy, aiming to reshape large quadrantectomies. The comparison between the cases reconstructed before and after the radiotherapy revealed unsatisfactory results in 66% for the first group. TRAM flap was performed in 16 patients. The poor results with flaps and implants occurred in 26.66% of cases, the rate of capsular contracture being 52.2% in irradiated patients versus 16% in non-irradiated ones.

Regarding flap reconstruction, the quality of the skin at the recipient bed is important in the final decision, and it must be explained to the patient. One suggestion is to avoid flap reconstruction before radiotherapy due to a progressive loss of aesthetic results related to fibrosis. Complications after TRAM and LD flaps were more frequent in previously irradiated than in non-irradiated patients, probably because of irradiation-induced damage to the chest wall skin. These differences would be not enough to suggest that previous irradiation is a contraindication to breast reconstruction, instead of that it is necessary to consider flap reconstruction as the first choice in most cases.

A meta-analysis in 2011 selected 11 studies and a total of 1105 patients examining postoperative morbidity following immediate or delayed breast reconstruction combined with radiotherapy. Autologous flaps resulted in less morbidity than implant-based reconstruction. Although they did not address the specific case of previous radiotherapy in BCT, comparing immediate versus delayed reconstruction with autologous flaps in irradiated patients after mastectomy, they did not find statistically significant morbidity differences [29].

Cordeiro et al. [30], from Memorial Sloan-Kettering Cancer Center, in a timely paper, retrospectively describe their experience with immediate two-stage implant-based reconstruction in 121 patients who had previously undergone radiation therapy to a breast-conserving treatment. They compared complications, aesthetic outcomes, and patient satisfaction with 1578 patients who had undergone the same surgery, but not undergone radiation therapy. It was reported a significant higher incidence of postoperative early (29% versus 15%; $p \leq 0.001$) and late complications in the irradiated group and a poorer aesthetic outcome. The most frequent early complication in both groups was mastectomy flap necrosis (18% versus 7.7%; $p < 0.01$). But they concluded that with a careful selection of the patients, implant-based breast reconstruction is acceptable, with a slightly higher incidence of capsular contracture grades III and IV (10.6% versus 6.3; $p = 0.2$) and despite a higher incidence of postoperative complications. Patient satisfaction did not differ between the two groups, and most of irradiated patients had good or very good results, whereas most non-irradiated patients had excellent results ($p = 0.04$).

In 2016, a systematic meta-analysis addressed the benefit of the use of the LD flap to coverage the prosthesis in the irradiated field. Thirty-one studies involving 1275 breast reconstruction were included. Six studies compared implant loss rates for LD-assisted implant reconstruction versus implant-only reconstruction. The LD-assisted reconstruction presents the lowest incidence of implant loss (5%), comparing with a 15% implant loss with submuscular-only reconstruction ($p < 0.001$). Subgroup pooled incidences of complications by the different reconstructive techniques demonstrated statistically lower rates of wound infection with LD-assisted reconstruction (4%) versus implant-only reconstruction (6%, $p = 0.007$). Reoperation rate was also significantly lower in the LD-assisted reconstruction group versus implant-only (15% vs 33%, $p < 0.001$) [31].

In 2017, Chetta et al. compared the morbidity associated with implant and autologous breast reconstruction in 4781 patients submitted to radiotherapy and breast reconstruction. Each patient has a 15-month follow-up to enable the identification of complications and reconstruction failure. Eighty percent of the sample (3846) was submitted to implant-based reconstruction, and 20% (935) underwent autologous reconstruction. The implant-based reconstruction group presents a much higher rate of overall complications (45.3%, $p < 0.001$), with reconstruction failure in 29.4% of patients, while the autologous reconstruction had a 30.8% overall complication rate, with failure of reconstruction in just 4.3% of patients. The highest probability of reconstruction failure was among patients with implant-based delayed reconstruction and pre-reconstruction irradiation (37.2%). The lowest probability of failure was among patients with immediate autologous reconstruction with post-reconstruction irradiation (3.5%). This study shows that although the implant-based reconstruction in patients previously exposed to radiotherapy has become much more common, it is still associated with significant morbidity, and failures of reconstruction with this technique are still high and approach 30% in the short term [32]. Thus the implanted-based reconstruction is associated with higher risk of complications that varies considerably between the studies and is still controversial in the radiotherapy setting. It is important to further identify the best profile of patients who will benefit from this technique.

A decision flowchart used in the Hospital Nossa Senhora das Graças Breast Unit to this group of previously irradiated patients is shown on Fig. 60.3.

60.5 Conclusions

Breast reconstruction in previously irradiated patients represents a difficult challenge to the surgeon due to the higher rates of complication and reconstruction failure that occur in this group of patients, especially with implants. Flaps remain the primary option, although for some very well-selected patients, implants can achieve satisfactory results with low rates of short- and long-term complications.

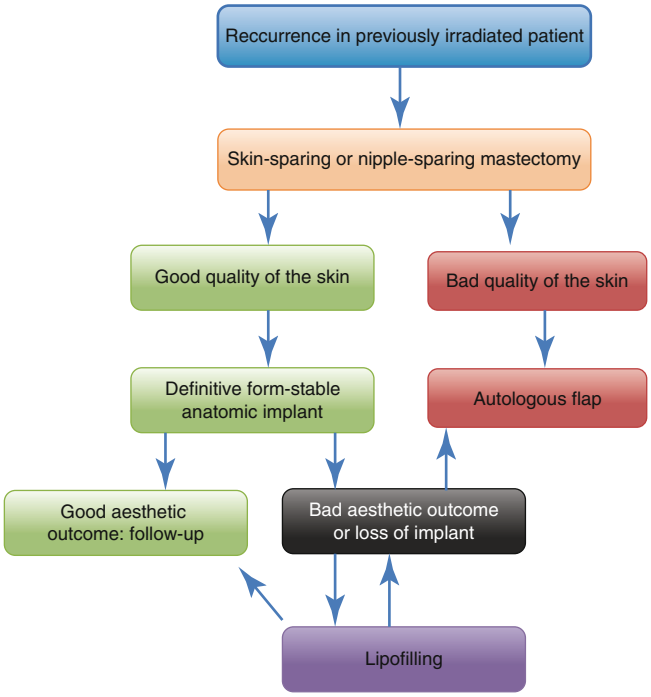

Fig. 60.3 Procedure flowchart in previously irradiated patients

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Breast Reconstruction After Aesthetic Surgery

61

Fabricio Palermo Brenelli and Natalie Rios Almeida

Breast cancer is the most common type of cancer affecting women in the world with an estimated 1.67 million new cancer cases diagnosed in 2012, representing 25% of all cancers, and causing slightly more deaths in less developed countries (883,000) than in more developed (794,000), according to the World Health Organization [1]. The Surveillance, Epidemiology, and End Results (SEER) Program of the US National Cancer Institute estimated 246,660 new cases of breast cancer in the USA in 2016, representing 14.6% of all new cancer cases and 40,450 deaths, and between 2006 and 2012, the percentage of surviving patients was 89.7% [2].

On the other hand, breast aesthetic surgery is the most popular cosmetic intervention in the USA, representing 19.6% of worldwide breast procedures in 2015 (546,260 cases) and probably in many other countries as well [3]. The breast augmentation based on implant insertion is among the top five cosmetic surgical procedures in the USA (290,467 procedures), with an increase of 4% compared to 2015 and 27% compared to 2000, according to the American Society of Plastic Surgeons [4].

Statistics suggests that 12.4% of women will be diagnosed with female breast cancer at some point during their lifetime [2]. Women who previously had breast aesthetic surgery will obviously be at risk for breast cancer. It has been estimated that 45,000 women receiving breast augmentation each year and a smaller number of women undergoing reduction mammoplasty will develop breast cancer in their lifetime [5].

Therefore, breast reconstruction after breast aesthetic surgery is at the forefront of discussion. It is a challenge for both the plastic and oncoplastic breast surgeon. Nevertheless, little is known about this topic, and a good level of evidence is lacking in the literature. Knowledge has been mostly acquired from the author's experience rather than gained from prospective studies.

Breast augmentation and breast reduction procedures are registered as aesthetic breast surgeries. However, these procedures are quite different in terms of breast tissue manipulation (skin and glandular parenchyma). Therefore, distinct implications for breast cancer and breast reconstructive surgery arise from both types of surgery, and evaluation should be performed separately.

For this reason, this chapter has been divided into two parts: breast reconstruction after breast augmentation and breast reconstruction after reduction mammoplasty. Each technique will thus be evaluated and discussed in a separate manner.

61.1 Breast Reconstruction After Breast Augmentation

As previously discussed, breast augmentation has rapidly become the most frequent type of cosmetic surgery since the approval of silicone implants by the US Food and Drug Administration (FDA). In the USA, since 2006, breast augmentation is the top cosmetic procedure, and silicone implants were used in 80% of the procedures in 2015 [4].

The development of breast cancer is expected in some women with breast implants, but they are not associated with an increased risk [6]. Although some studies in rodents had associated the presence of foreign bodies with sarcomas, subsequent studies refuted this association. Indeed, many other studies confirmed the safety of implants regarding

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_61

breast cancer. The use of these implants has been currently cleared after many publications proved their safety in breast augmentation [7–10].

In several retrospective cohorts, the standardized incidence ratio, computed as the number of observed breast cancer events divided by the expected number of events, was less than one, showing that there was no increased risk for cancer in augmented breast [11]. Besides that, the tumor characteristics do not vary among prior breast augmentation and non-breast augmentation patients, and palpability of tumor was more frequent in operated breasts [12].

In 2012, a large Canadian cohort has suggested that women with breast implants were associated to a reduced rate of breast cancer compared to other surgical women. It can be explained by a lower risk profile in augmented women and their presurgical screening and maybe because the higher-risk women are not the preferential population for aesthetic procedures. Other studies showed that the increased proportion of palpable tumors in augmented patients must be a consequence of higher breast/body awareness in this group, such as decreased breast volume, and the palpability did not influence the overall stage and outcome compared to non-augmented patients [13, 14].

Therefore, many patients with breast cancer in previously augmented breasts will be seen at outpatient clinics. In a patient without any previous surgery, the decision as to surgical treatment should be made differently. Reconstruction can be tailored to the patient, dependent on the oncologic approach. If breast-conserving therapy is indicated, a partial reconstruction will be required. In contrast, if mastectomy is indicated, total breast reconstruction will be necessary.

61.1.1 Partial Breast Reconstruction

Considering that recent studies have described lower nodule detection in augmented breasts and that the treatment with conservative surgery is the gold standard for patients with early breast cancer and good proportion between breast and tumor sizes, it is necessary to evaluate which patients would benefit from the conservative surgery and also from an aesthetic point of view [11].

Breast-conserving therapy involves quadrantectomy associated with radiation therapy. Despite some publications about a small number of patients with augmented breast and good cosmetic results [15, 16], this procedure has been correlated with poor outcome in many series, resulting in pain, implant exposure, and even rupture in retained breast implants. Guenther et al. [16] published that 85% of the patients undergoing quadrantectomy and radiotherapy after augmentation surgery had good cosmetic outcome. The authors suggested that capsular contracture is less common when the implant is positioned in the submuscular space.

On the other hand, capsular contracture was a very frequent finding in this patient group, according to many authors, resulting in poor cosmetic results. More than half of the patients required a second or third surgical correction or even mastectomy. These complications usually resulted from radiotherapy. Tumor size and location, in addition to scarce remaining glandular tissue, may have contributed to an unnatural result [15–17]. Complications are shown in Figs. 61.1 and 61.2.

Patients who are candidates for partial breast irradiation (PBI), especially those who are candidates for intraoperative radiation therapy (IORT), could benefit from lumpectomy and implant maintenance [18]. Despite the paucity of evidence, this could be a good option for resection alone and local glandular flap partial reconstruction (Fig. 61.3).

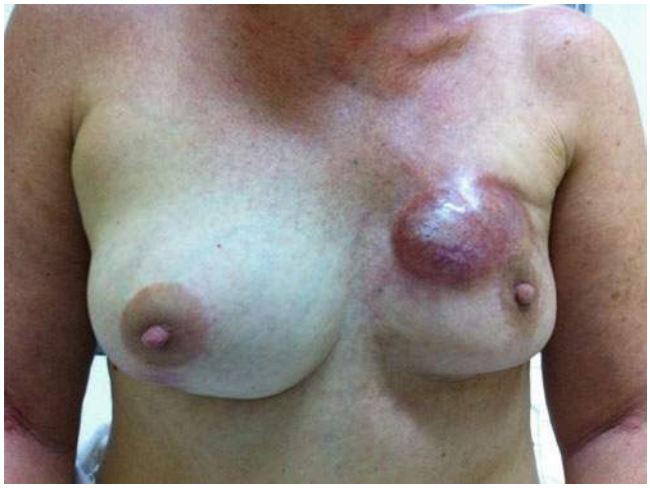

Fig. 61.1 Capsular contracture and skin alteration after augmented breast treated with lumpectomy and radiotherapy

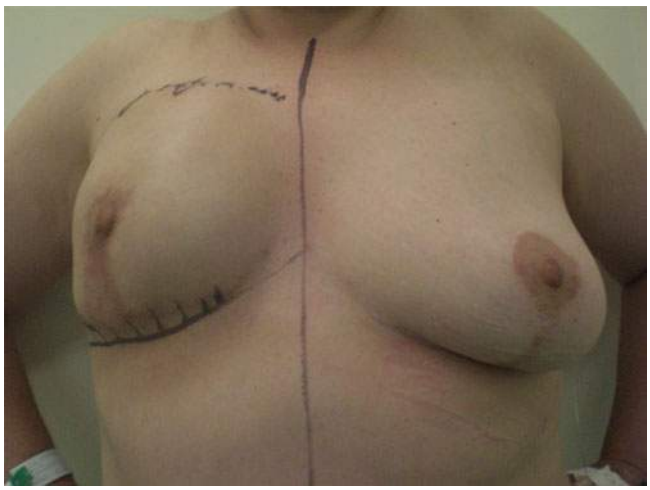

Fig. 61.2 Capsular contracture and asymmetry after mammoplasty with implant and radiotherapy

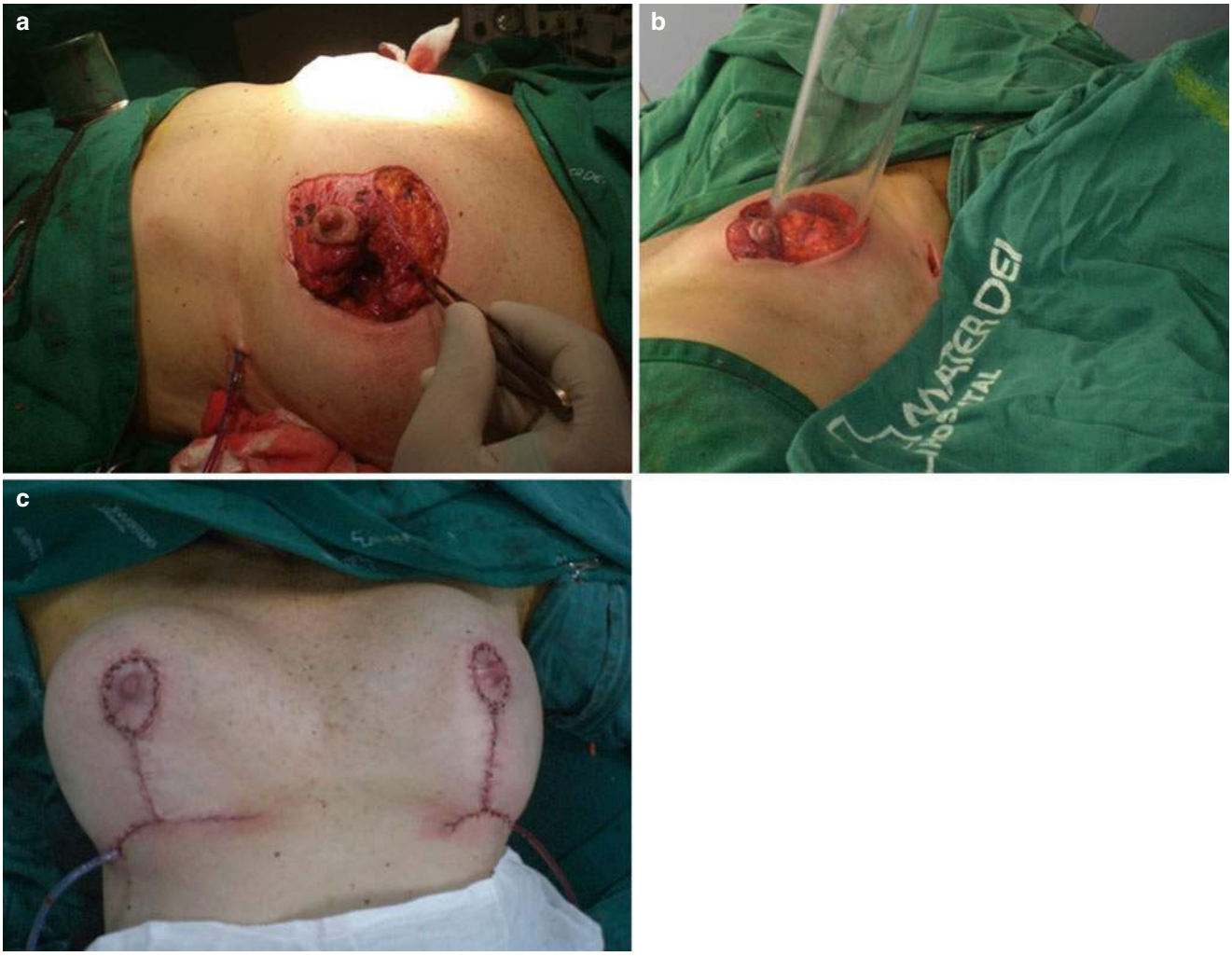

Fig. 61.3 (**a**) Lumpectomy after implant removal and inferior pedicle mammoplasty. (**b**) IORT at tumor bed. (**c**) Final result after lumpectomy and implant reinsertion (new implant)

In a single institute experience (European Institute of Oncology), in case of augmented women, all of the subglandular implants were removed during the quadrantectomy, and, after the IORT, they were replaced at the submuscular plane. When augmentation was done at the same time of the oncological surgery, the implant was directly positioned behind the pectoralis major muscle. Comparing capsular contracture in the irradiated breast after replaced implant and contralateral breast with implant and no irradiation, there was no significant increase of contracture after targeted irradiation and 0.76% of local recurrence rate and death, showing oncological safe with IORT in selected patients [11].

Breast-conserving therapy with implant removal is a less desirable option. Women receiving breast augmentation often have scarce breast tissue, which is actually why many undergo this procedure. In addition, it has been shown that the presence of an implant results in thinning of the stretched overlying breast tissue over time. One study reported that native breast tissue comprised 50% of overall breast volume [19, 20]. Therefore, this is a suitable option only for a very small group of patients who have a considerable amount of remaining tissue. In these cases, mammoplasty techniques should be used such as a T-/Wise-pattern or vertical scar technique (Lejour's technique) to adjust excess skin when necessary. Figure 61.4 shows a flowchart for decision-making regarding augmented breast surgery and oncologic surgery.

61.1.2 Total Breast Reconstruction

As previously discussed, mastectomy and immediate reconstruction seems to be the best treatment for breast cancer patients with preexisting breast augmentation [21–23].

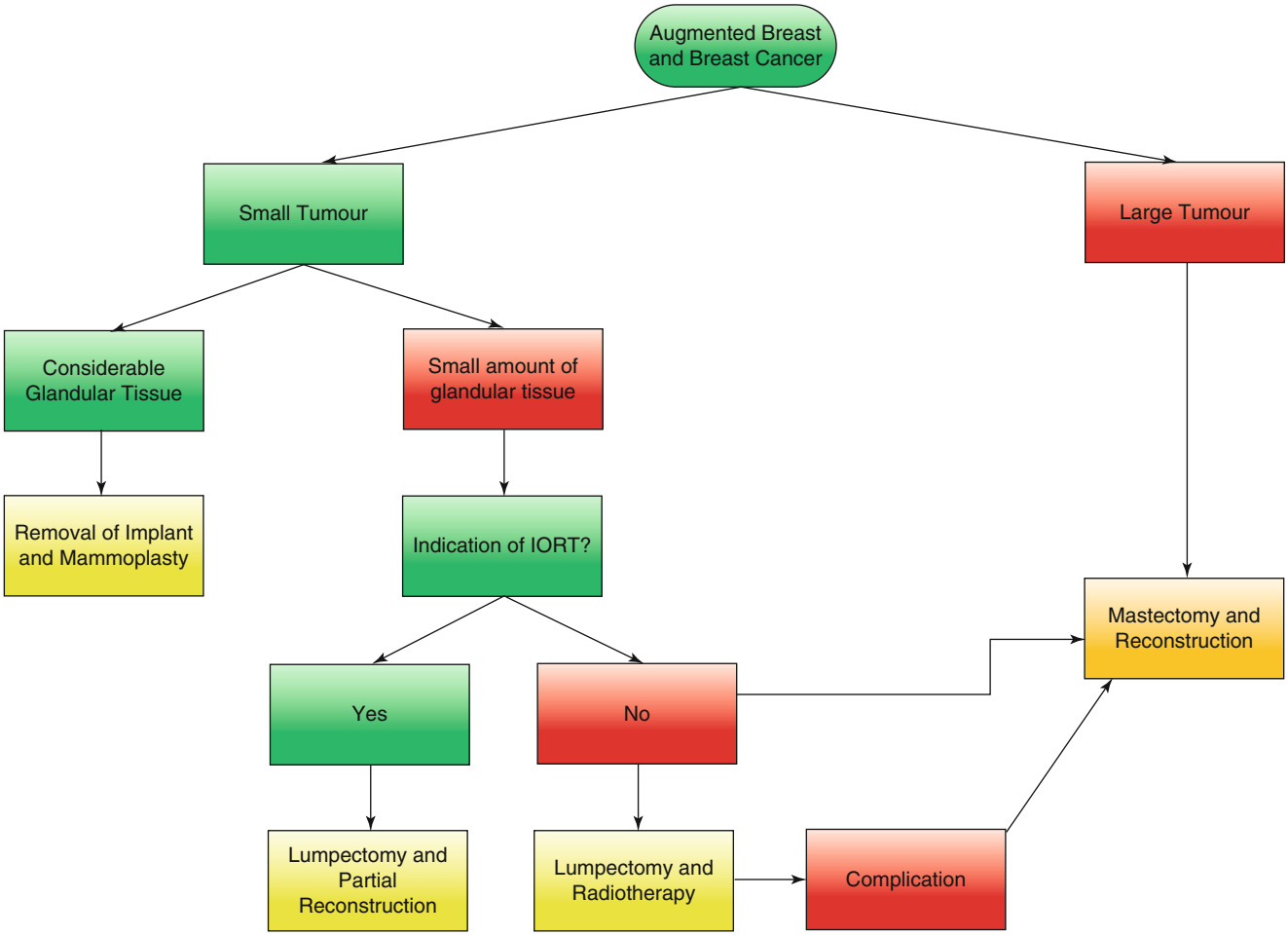

Fig. 61.4 Flowchart on surgical decision of augmented breast and lumpectomy

Decisions on the type of reconstruction should be made according to local conditions following mastectomy and patient's shape. If a large amount of skin needs to be removed, reconstruction with autologous tissue is more suitable, e.g., a TRAM or DIEP flap. Latissimus dorsi (LD) flap with an implant is also a good option for these cases. Extended LD without an implant would probably not be a good option, since patients usually hope for a reconstructed breast that is the same size as before. Employing this technique, it is difficult to achieve the desired result. However, the choice of technique can be challenging, because the majority of augmented women have lower body index mass and may not have the necessary tissue for flap-based reconstruction [24].

In contrast, if the native skin can be preserved, a skin-sparing mastectomy (SSM) or nipple-sparing mastectomy (NSM) is performed. Reconstruction can easily be performed with a single-stage implant (implant or definitive breast expander) or a two-stage implant (tissue expander plus implant exchange). When choosing implant-based reconstruction, it is critically important to evaluate the quality of both the skin and muscles (pectoralis major and serratus).

As shown in previous chapters, adequate implant reconstruction is performed with a good muscular pocket that partially or completely covers the implant. In a partially covered implant where the skin is compromised, the implant can be exposed and should be removed. The possibility of inferior pole coverage with the capsule formed by the implant in augmented breast, like a pectoralis major muscle extension, can improve the new implant pocket. More recently, the use of acellular dermal matrices (ADM) can also provide a better coverage for the implant and a lower capsular contracture grade with better outcomes [24, 25].

Definitive implant reconstruction is desirable in patients requiring a large amount of skin removal. The reason is that it is a faster technique with no donor site complications [26, 27]. In a previously augmented breast, skin coverage is rarely a problem, and good cosmetic results can be achieved.

The need for adjuvant radiation therapy may play an important role in reconstruction preference. Although some authors strongly contraindicate reconstruction due to a high complication rate (up to 70–90%) [28], good results have been achieved by many other authors, showing up to 80% of

patient satisfaction [29]. Indeed, we recommend implant reconstruction whenever feasible, even in a scenario of adjuvant radiation therapy. Figures 61.5, 61.6, and 61.7 show the results of breast reconstruction, with and without radiation therapy.

Tumor location and skin incision are of major importance to surgical outcome. Skin or nipple areola complex (NAC) necrosis can translate into reconstruction failure, if there is exposure of the implant. There is no study addressing the use of a preexisting augmentation mammoplasty incision to perform mastectomy. When choosing an incision, the surgeon must consider oncologic outcome and preexisting scarring

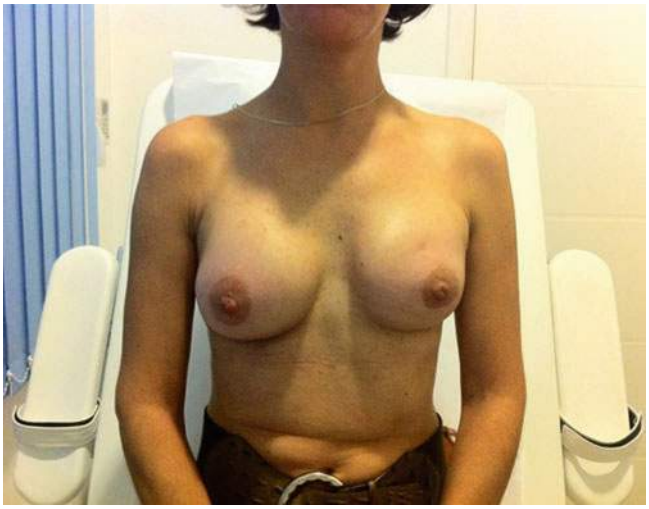

Fig. 61.5 Left breast capsular contracture after mastectomy and implant reconstruction in a breast augmented patient followed by radiotherapy (Rtx)

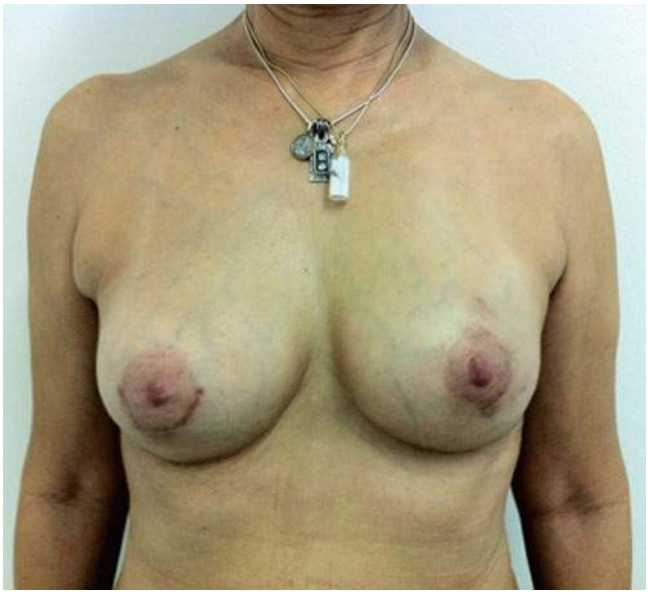

Fig. 61.6 Left breast implant-based reconstruction after left nipple-sparing mastectomy (NSM) in an augmented patient with RTx

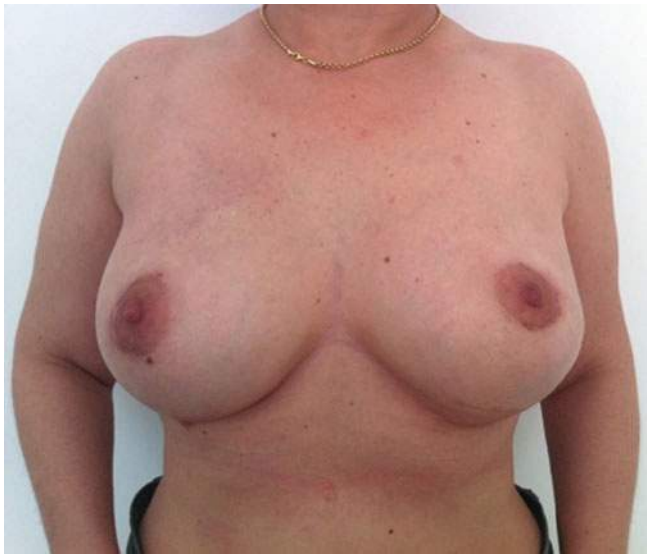

Fig. 61.7 Bilateral implant-based breast reconstruction after bilateral NSM in an augmented patient with no RTx

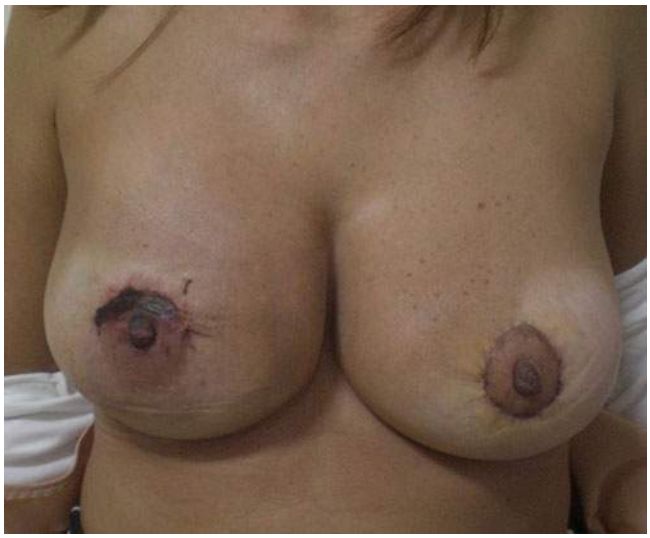

Fig. 61.8 Periareolar mastectomy and reconstruction in previous augmented patient with NAC partial suffering

which can translate into abnormality of the skin and NAC irrigation. Figures 61.8 and 61.9 show a periareolar approach, in which a preexisting scar from breast augmentation is used.

Preexisting breast surgery is a well-known factor related to postoperative complications. Skin incisions for augmentation mammoplasty are periareolar (complete or partial) in the inframammary fold or in the axillary line, when it is not associated with mastopexy (vertical or inverted "T" pattern). SSM is performed with removal of the NAC, so the incision must be made in the central portion of the breast. However, when NSM is indicated, the incision can be made in any part of the breast (periareolar, inframammary, etc.). Therefore, the surgeon can attempt to use the preexisting scar to perform NSM.

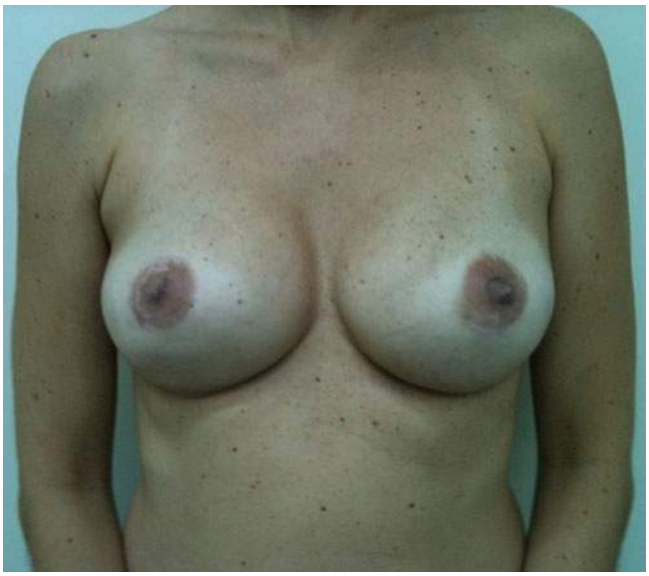

Fig. 61.9 Periareolar bilateral mastectomy and reconstruction in previous augmented patient with no complication

To predict surgical outcome relative to surgical access for mastectomy and reconstruction, an analogy was made between studies evaluating NSM incisions according to outcome. Wijayanayagam et al. showed that a radial incision and inframammary fold incision (in not overly large breasts) are good options with a low risk of NAC or skin necrosis [30]. Algaithy et al. showed a low risk of necrosis with superolateral radial incision and a high risk of complications with circumareolar and periareolar incision [31]. Figure 61.10 shows a radial approach to mastectomy and reconstruction in a patient with periareolar breast augmentation.

Therefore, a complete periareolar incision or large circumareolar incision should be discouraged. Inframammary fold incisions should be performed in selected cases and only in patients with small breasts. A periareolar 180° incision can be performed, although the risk of wound dehiscence and skin necrosis is higher due to direct skin traction during surgery. Table 61.1 shows the risk of skin and NAC necrosis, according to incision and breast size.

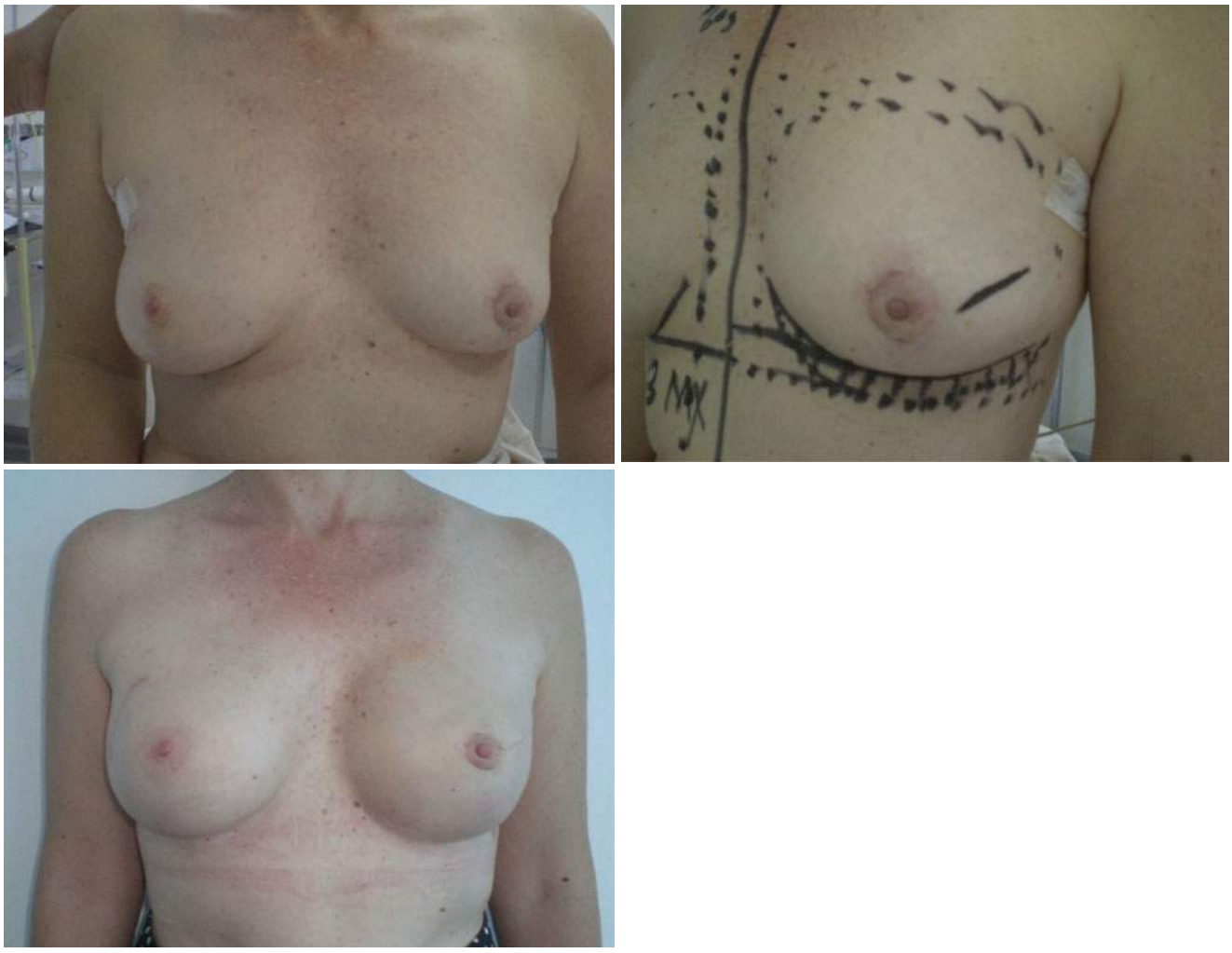

Fig. 61.10 Patient with periareolar breast augmentation and capsular contracture in the preoperative period and postoperative period of left breast mastectomy and reconstruction using radial scar and right breast implant exchange

Considering the previous augmented breast, some authors describe that these patients may have a lower risk of skin flap necrosis after mastectomy because the vascularity is improved after the prior disruption of some vascular perforators from the pectoralis and breast tissue [24].

Table 61.1 Risk of skin and NAC necrosis according to skin incision pattern in mastectomy and breast volume, based on published data [30, 31]

Incision	Large breast	Medium/small breast
Complete periareolar	High risk	High risk
Periareolar 180°	Moderate risk	Moderate risk
Circumareolar	High risk	High risk
Radial	Low risk	Low risk
Inframammary fold	High risk	Low risk

Another issue that should be opened for discussion is whether the implant should be exchanged during surgery or the old implant maintained. Many authors consider that implant exchange is mandatory when the implant is located in the subglandular space because it must be removed for adequate patient treatment. Other considerations that are clearly in favor of implant exchange are implant rupture, capsular contracture, infection, and poor cosmetic result [21, 22]. Few publications have advocated the possibility of maintaining a preexisting implant in case of a new generation implant located in the submuscular space [32]. Actually, this should be an exception rather than the rule, applied only to strictly selected cases. Figure 61.11 shows a flowchart of decisions on augmented breast and total breast reconstruction.

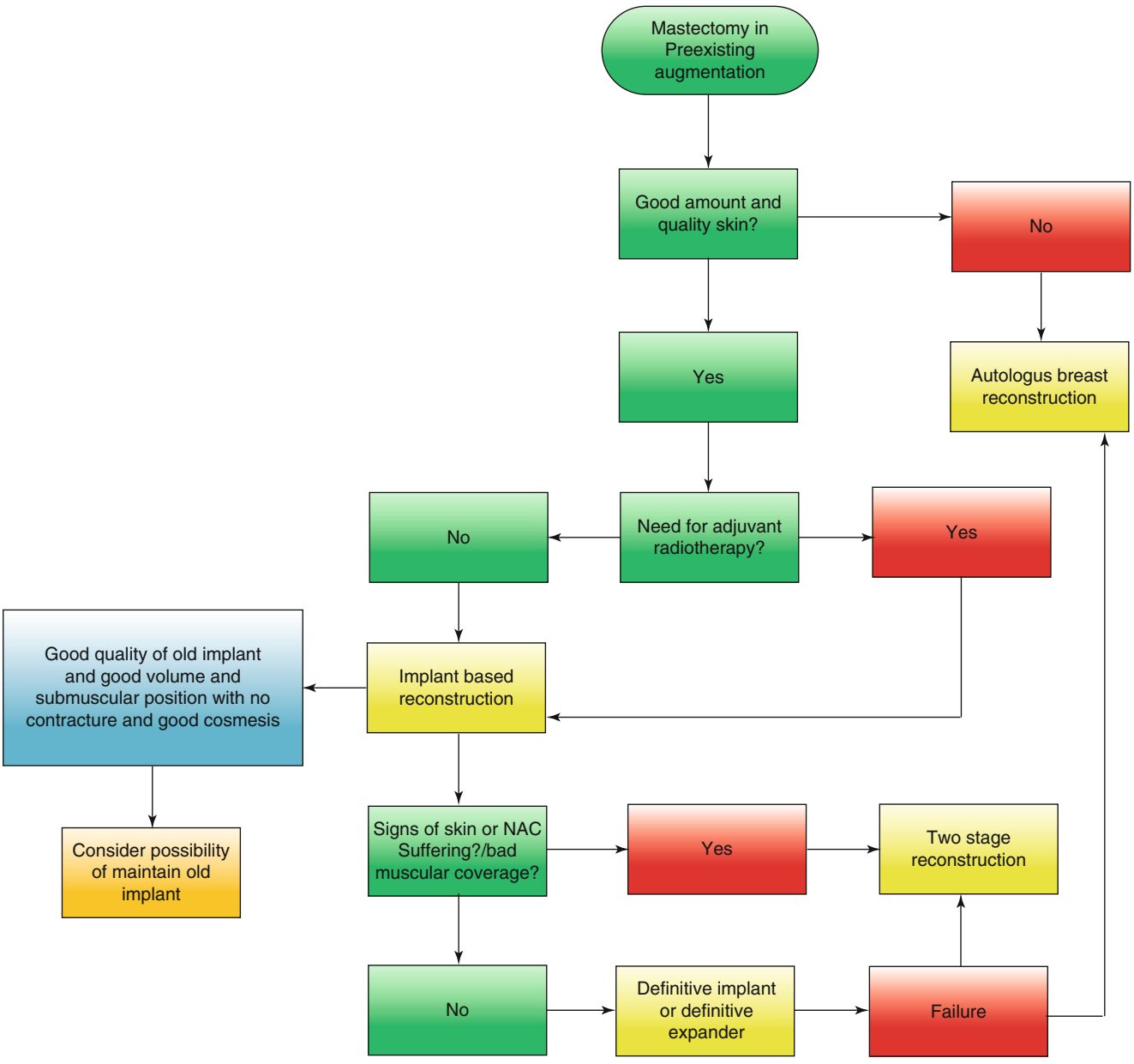

Fig. 61.11 Flowchart of indications of breast reconstruction after mastectomy in augmented patients

61.2 Breast Reconstruction After Breast Reduction Mammoplasty

As previously discussed, breast reduction mammoplasty is the fifth most common cosmetic intervention in the USA. A considerable number of patients undergoing this procedure will develop breast cancer at some time in their lives. The procedure per se already reduces the risk for breast cancer. Some studies have shown up to 50% reduction in breast cancer risk [33].

Considering the high prevalence of breast reduction surgery, a likely scenario encountered by the oncoplastic surgeon is breast cancer in a glandular parenchyma subject to many changes and skin scarring that may lead to vascular pattern abnormality. Despite the lack of specific studies concerning these abnormalities, it is a well-documented fact that previous mammoplasty is associated with minor and major postoperative complications, e.g., wound breakdown, fat and glandular necrosis, skin necrosis, and loss of the NAC [34, 35]. Although mammoplasty is a widely accepted procedure, it is associated with up to 42–50% of complications in some series. Major complications include skin and NAC necrosis, leading to reoperation ranging in rate from 5% to 15% [35].

Therefore, patients with preexisting mammoplasty and breast cancer undergoing large resections or mastectomy for cancer who require reconstructive surgery should be particularly and conscientiously evaluated. Counseling should be offered to these patients regarding the most common postoperative complications.

61.2.1 Partial Breast Reconstruction

Partial breast reconstruction can be performed with local glandular remodeling or major remodeling, including dermal-glandular flaps with mammoplasty techniques. In the first situation, a low complication rate is found, unless large undermining has occurred and fatty tissue has more likely suffered necrosis (Fig. 61.12). Therefore, fatty breasts should be treated with minor undermining for the correction of defects, especially in patients with previous breast reduction.

If a large resection is required or the tumor is located in a quadrant where the aesthetic outcome can be unnatural, i.e., the internal or inferior quadrants, then a mammoplasty technique will be necessary. Studies with substantial evidence correlating preexisting mammoplasty with oncoplastic surgery are lacking. However, it is known that consecutive breast surgery may lead to an increased risk of complications. Therefore, we used data from studies evaluating risk factors for mammoplasty to estimate the risk of complications in partial breast reconstruction. Table 61.2 shows the risk factors for mammoplasty. In these patients, preexisting breast reduction per se raises the complication risk. Cumulative risk factors increase the rate of these complications.

Irrespective of whether mammoplasty or mastopexy is the technique of choice for correction of the breast defect, it is crucially important to know which technique was previously used. Despite the lack of evidence, we strongly discourage the use of different patterns of mammoplasty in oncoplastic

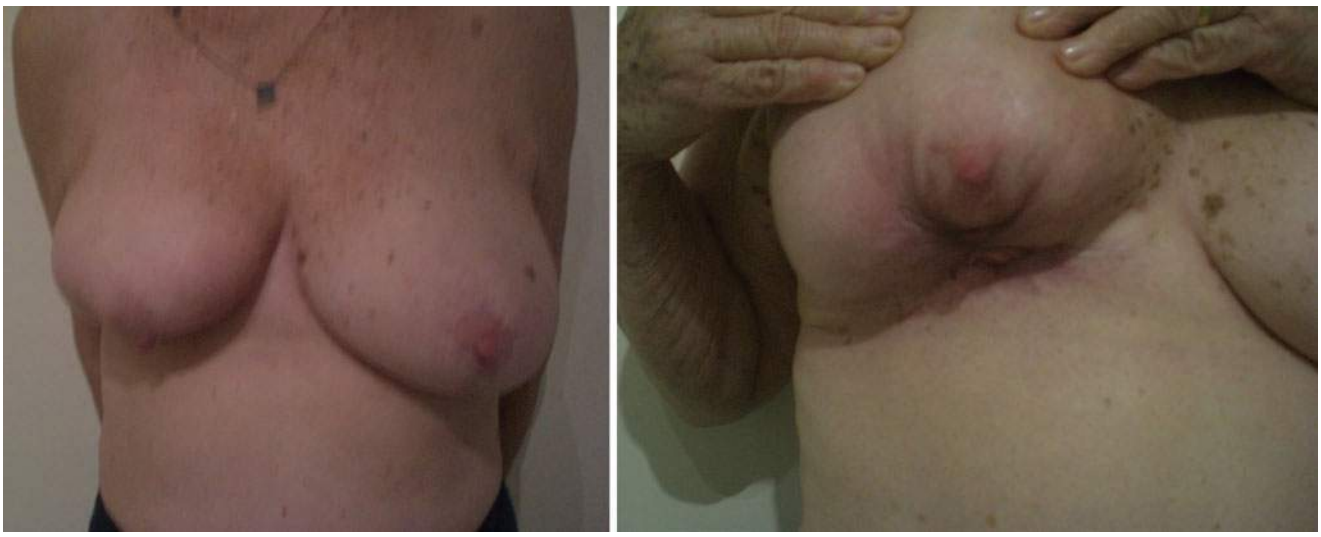

Fig. 61.12 Fat necrosis of the breast after extensive glandular undermining in oncoplastic partial reconstruction, in a patient with previous mammoplasty and tumor in the infero-lateral quadrant

reconstruction than those used in the previous surgeries, i.e., use of an inferior pedicle after a superior pedicle mammoplasty. Although the vascular autonomization phenomenon occurs, NAC vascularization may be compromised when a different pedicle pattern (inferior pedicle after a superior pedicle) is used. Necrosis is a proclaimed complication that affects aesthetic and oncologic outcome. Delayed healing can postpone adjuvant therapy.

Table 61.2 Risk factors for complications after mammoplasty

Risk factor	Risk of complication
Previous surgery	Medium/high
Heavy smoker	High
Obesity (BMI > 35)	High
Large resections (>1000 g)	High
Diabetes (uncontrolled)	High
Age (>50 years)	Low/medium

Figure 61.13 shows a satisfying result after mammoplasty and partial reconstruction with a new mammoplasty.

Figure 61.14 shows a patient that underwent three mammoplasties for aesthetic reasons and a bad outcome with NAC necrosis after mammoplasty for cancer.

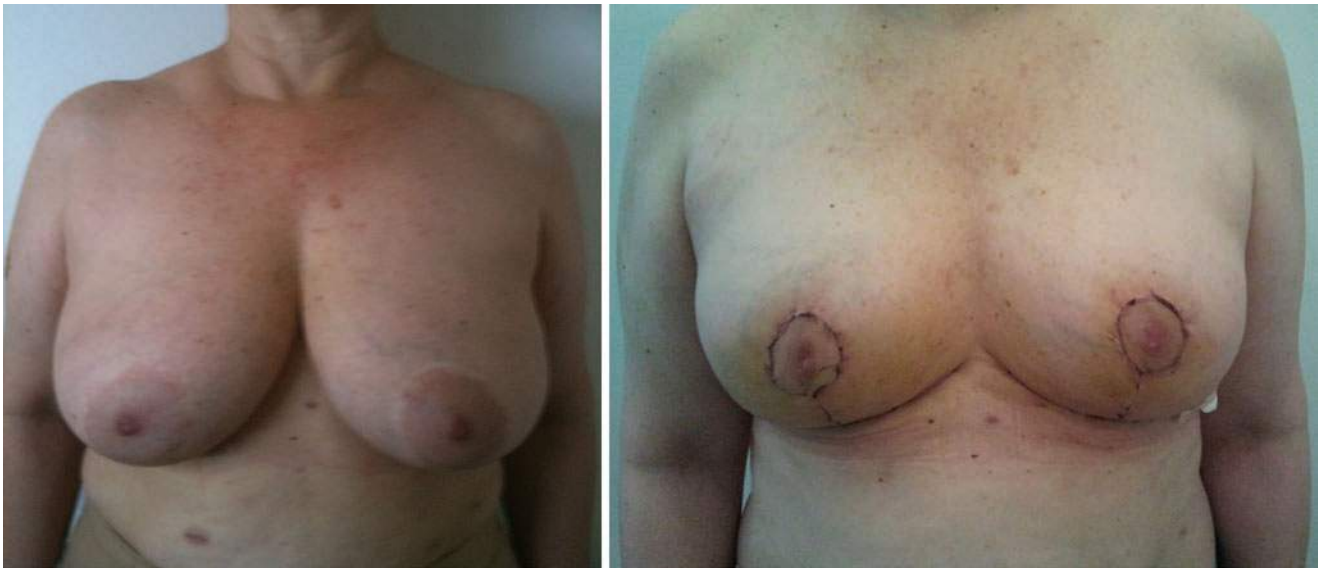

Fig. 61.13 Oncoplastic mammoplasty (superior pedicle breast reduction with excision of the tumor in the lower quadrant and SNB) in a patient with previous mammoplasty

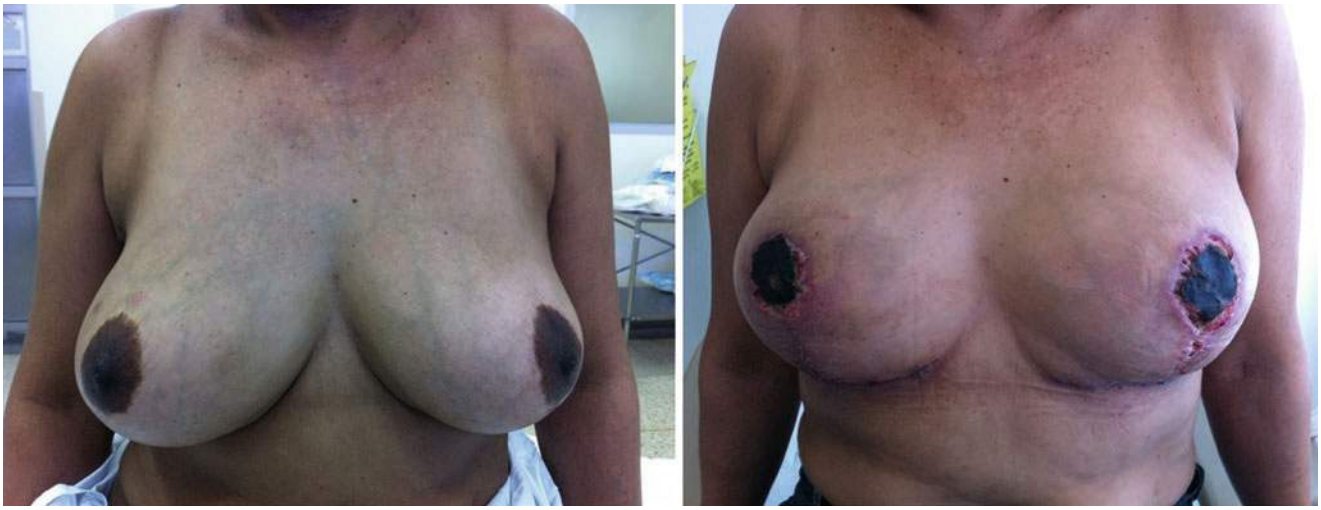

Fig. 61.14 Bilateral NAC necrosis after oncoplastic mammoplasty for a tumor located in the upper quadrant of the left breast. Patient had undergone three mammoplasties before this procedure

Therefore, a good medical history and discussion with the patient are critically important for outcome prediction. The obligation of a surgeon is to choose the most suitable technique for oncoplastic surgery. If a high complication risk is expected (Table 61.2) and the lesion is located in the quadrant where the NAC vascular pedicle was previously based, or if the previous technique is unknown, minor surgery should be performed, or another technique should be applied. A free NAC graft or even mastectomy with reconstruction should be considered in these cases. Figure 61.15 shows the deciding steps in partial breast reconstruction after mammoplasty.

61.2.2 Total Breast Reconstruction

The principles of total breast reconstruction in patients with previous reduction mammoplasty are quite similar to total reconstruction after augmentation mammoplasty described in this chapter.

On the other hand, the choice of mastectomy reconstruction technique should be based on particularities of previous reduction mammoplasty. As already discussed, previous scars can lead to a higher risk of complications, especially in NSM and reconstruction [26, 28, 31]. Therefore, NSM and SSM may pose a higher risk for these patients, owing to larger and multiple skin scars caused by reduction mammoplasty.

Despite the paucity of evidence, we recommend obtaining a very good medical history, considering NSM in low-risk patients (Table 61.2). Incision must preferably be made in a preexisting scar, e.g., a periareolar, periareolar extended to a vertical scar, or a horizontal scar in the inframammary fold. The risk of complications according to scar position is listed in Fig. 61.11 and could be used for preoperative risk analysis.

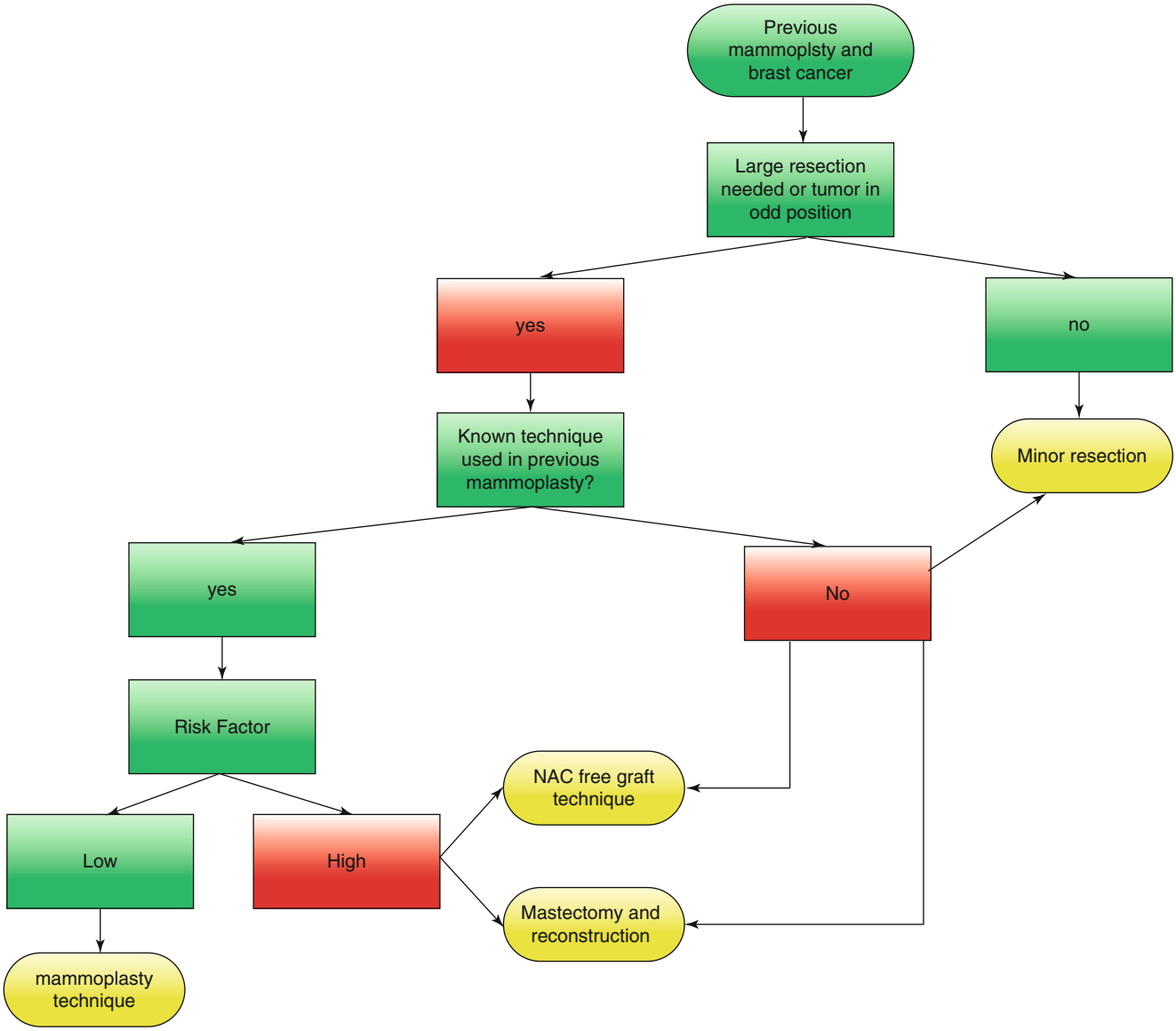

Fig. 61.15 Flowchart of surgical decision about partial breast reconstruction in patients with previous mammoplasty

Reconstruction technique will once again depend on patient's choice, the amount of viable skin available, and preservation of the pectoralis major and anterior serratus muscle. In addition, adjuvant treatment can also influence decision about the technique. If radiation therapy is indicated, delayed reconstruction or autologous reconstruction can be a choice instead of an implant-based reconstruction (definitive or temporary implants).

A good alternative for this patient group is skin-reducing mastectomy with anatomic implant reconstruction, initially described by Nava, MB [36]. Since many patients undergoing reduction mammoplasty still have large breasts after surgery with ptosis frequently recurring over time, this technique reduces excess skin and corrects ptosis. Therefore, it is possible to use a definitive anatomic implant. With this technique, previous mammoplasty scar is removed since a Wise skin pattern resection is used.

Figures 61.16 and 61.17 show breast reconstruction with implant after mammoplasty using a preexisting mammoplasty scar, with and without the compromised areola. Figures 61.18 and 61.19 show a skin-reducing mastectomy after reduction mammoplasty with good results and one with postoperative complications.

61.3 Conclusion

Breast aesthetic surgery is the most popular plastic surgery performed in the USA and probably in many other countries as well. As the technique becomes easier and technology is used to spread knowledge, more skilled surgeons can offer this treatment to patients. With cost reduction, an increasing number of women will be able to afford the procedure.

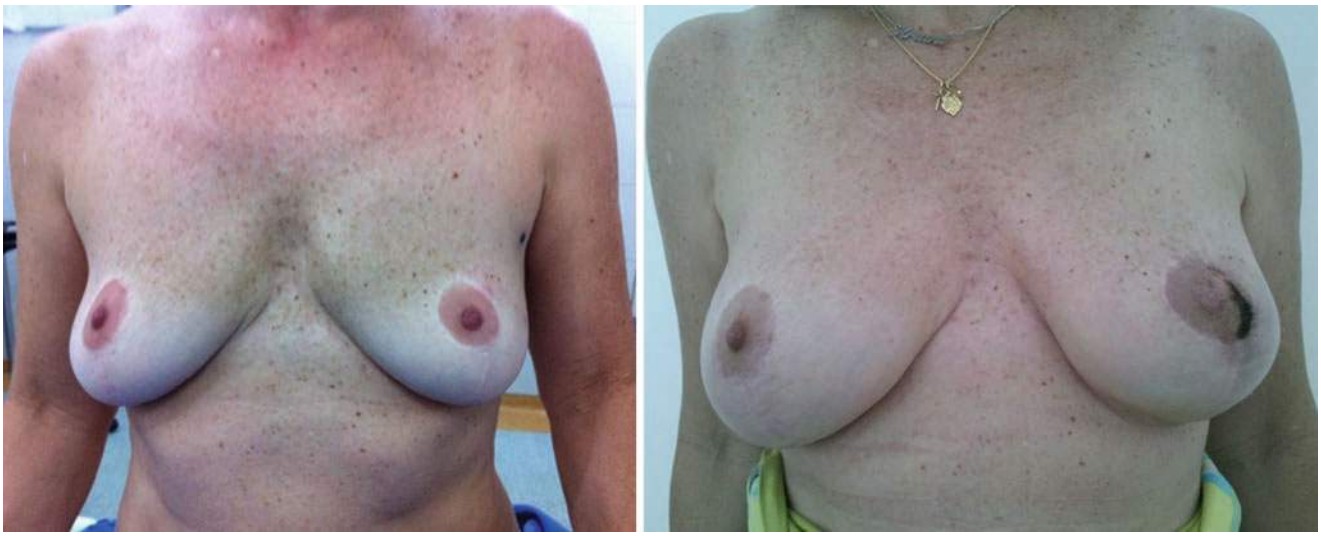

Fig. 61.16 Left NSM and reconstruction with implant using periareolar incision in a previous reduction mammoplasty. Note the partial areolar necrosis

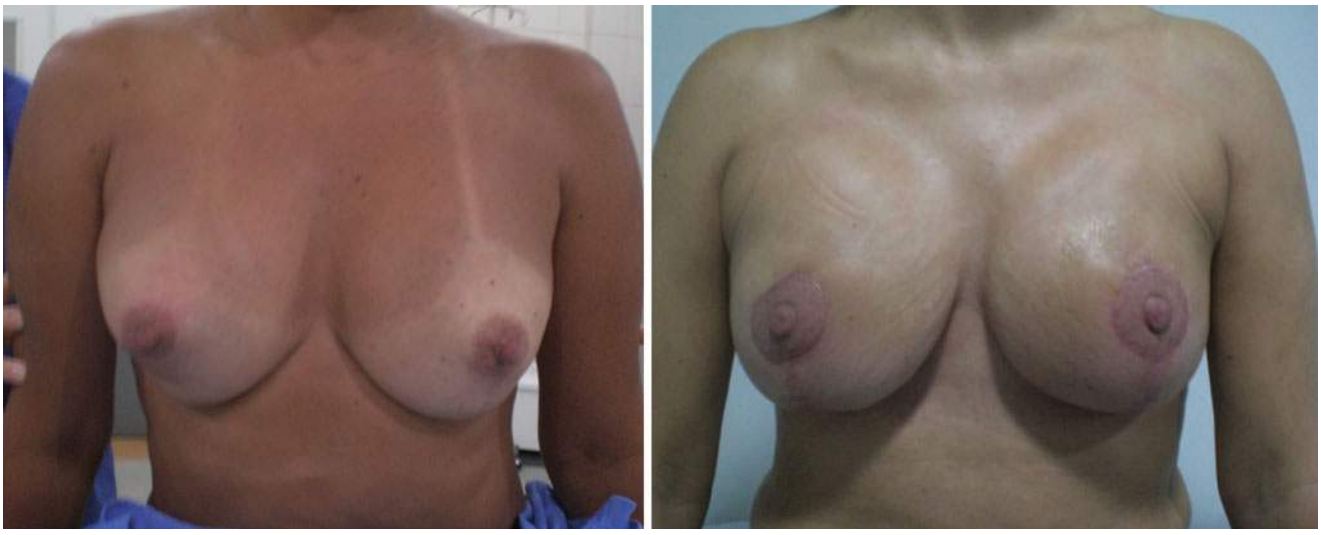

Fig. 61.17 Bilateral NSM and reconstruction using the preexisting reduction mammoplasty incision. Patient had a history of breast reduction and posterior implant insertion

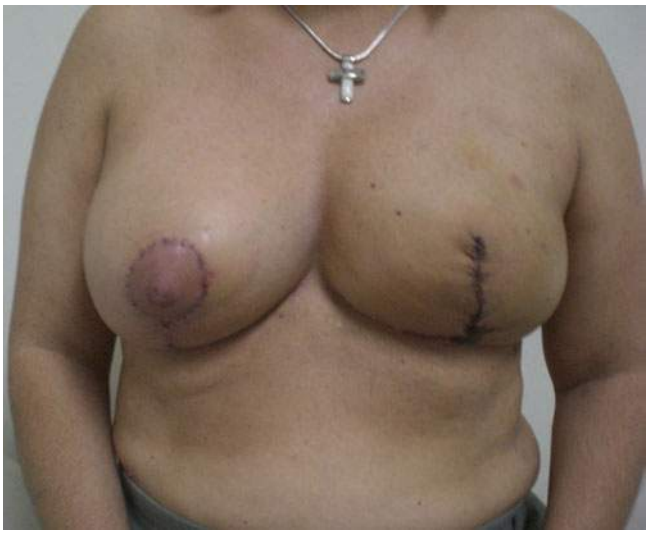

Fig. 61.18 Left skin-reducing mastectomy and implant reconstruction in a previous mammoplasty

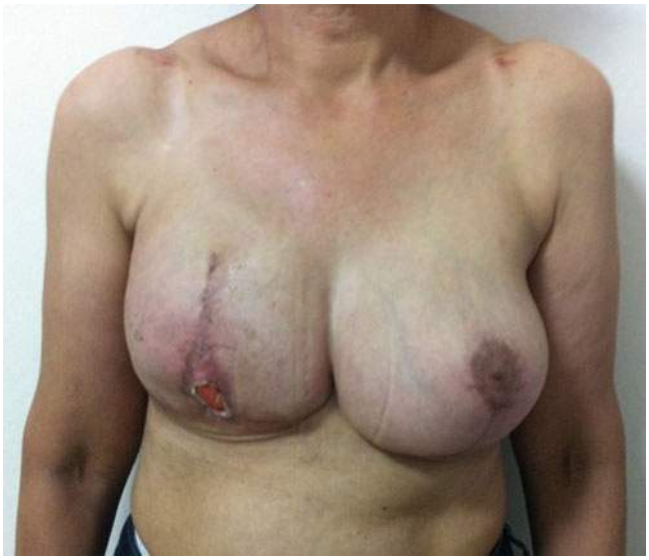

Fig. 61.19 Right skin-reducing mastectomy and implant reconstruction in a previous mammoplasty with skin necrosis

Breast, plastic, and oncoplastic surgeons will increasingly evaluate patients with breast implants or breast reduction and cancer. As previously discussed, this type of patient is different from a regular patient and deserves closer attention. In addition to optimal oncologic control, these patients expect good cosmetic results from the oncologic and reconstructive surgical team. Surgeons and patients must discuss indications, outcome, and complications thoroughly.

Patients should gain informed knowledge about surgical options and how to cope with good and bad results.

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Thoracic Wall Reconstruction in Local Recurrences and Advanced Cases

62

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Alessandro Pardolesi, and Piergiorgio Solli

62.1 Introduction

The incidence of local recurrences after mastectomy and breast-conserving therapy ranges between 5% and 40%, depending on risk factors and primary therapy [1].

The first-line treatments in recurrent breast cancer are endocrine therapy for patients with estrogen or progesterone receptor-positive cancer and chemotherapy for patients with receptor-negative cancers [2–4].

However, local therapies such as radiotherapy or surgery may be required in selected cases for local disease control and palliation of disabling symptoms like pain, bleeding, ulceration, malodorous secretion, infection, and fungating lesions [5, 6].

On the one hand, locoregional recurrence of breast cancer following breast surgery may be a systemic disease, and in many patients it tends to occur at the same time as distant metastases, making the indication for surgical resection questionable [7, 8]. On the other hand, although the primary goal of chest wall resection is to achieve local tumor control, it may lead to long-term palliation and even cure for a small subset of patients with isolated chest wall recurrence of breast cancer after multimodal treatment failure [9].

We argue that although the primary goal of chest wall resection is to achieve local control of the tumor, potentially leading to long-term palliation, another result may be cure in a small subset of patients with isolated chest wall recurrence of breast cancer [10].

62.2 Oncologic Aspects

Despite major therapeutic advances, recurrent breast cancer is still a lethal disease in most patients. Isolated local recurrences are thought to represent about 20% of all recurrences, while local disease, in combination with either regional or distant recurrences, represents a further 3% [11]. The majority of locoregional recurrences occur as isolated chest wall disease, and only a small proportion present with concurrent systemic disease or following distant metastases [12, 13].

Although palliation rather than prolongation of survival is usually the main aim of chest wall resection, some studies found that a small subset of patients would have a long disease-free interval and possibly cure after chest wall resection and reconstruction [14, 15].

Our results confirm existing evidence that surgery is indicated in patients who have isolated breast cancer recurrence, even when surgery means chest wall resection [16]. Moreover, adjuvant radiotherapy and e for estrogen

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_62

receptor-positive tumors e adjuvant hormone therapy is indicated [17].

In a correctly selected group of patients undergoing chest wall resection after local recurrence of breast cancer, the primary goal is to regain local control regardless of the extent of disease. Some of these patients, in fact, will present with painful, infected, ulcerated, or fungating lesions that cause a great distress to the patients [18]. Treatment with radiotherapy, systemic therapy, and surgery, alone or in combination, can help to achieve local control [10].

On the basis of the existing literature, we may argue that complete resection with free margins is recommended as the first choice for treatment in recurrent breast cancer. In fact, local recurrence has to be regarded as a repeated episode of a disease with an increased risk of subsequent metastases and not vice versa [10] (Table 62.1).

The curve of metastatic incidence might be flattened or reduced markedly by a radical resection with sufficient safety margins [18].

Risk factors affecting long-term survival are a diameter of the local recurrence greater than 1.5 cm, disease-free interval of less than 2 years, skin incision, initial tumor stage, and positive lymph nodes [19].

Table 62.1 Literature review

Authors	Years	Number of patients	Five-year survival (%)	Country
Miyauchi et al. [20]	1992	23	48	Japan
Dahlstrøm et al. [21]	1993	98	56	Denmark
Mora et al. [22]	1996	69	72	USA
Faneyte et al. [14]	1997	44	45	Netherlands
Downey et al. [23]	2000	38	18	USA
Henderson et al. [24]	2001	61	24	Australia
Moran et al. [25]	2002	53	55	USA
Friedel et al. [26]	2005	51	41	Germany
Veronesi et al. [5]	2007	15	19	Italy
Friedel et al. [18]	2008	63	46	Germany
Santillan et al. [9]	2008	28	18	USA
Petrella et al. [16]	2014	40(26)	68[a]	Italy

[a]Considering only patients with local radical resection (n. 26)

62.3 Technical Aspects

Here we report the case of a 77-year-old patient who submitted to left radical mastectomy and radiotherapy 35 years earlier, presenting with a recently infected and ulcerated left parasternal lesion (Fig. 62.1). Preoperative computed tomography confirmed soft tissue involvement as well as sternal plane deep contact, although no clear neoplastic tissue was obtained by preoperative biopsy (Fig. 62.2).

Operative plan considered soft tissue wide excision and deep sternal tissue biopsy: in case of neoplastic disease, complete sternectomy and prosthetic reconstruction would have been performed; in case of infection and necrosis—without neoplastic involvement—sternal shaving without the need of reconstruction would have been offered to the patient; in both case muscular reconstruction would have been performed to close chest wall defect.

Circular incision including all the infected tissue was performed, reaching the sternocostal plane (Figs. 62.3, 62.4, and 62.5).

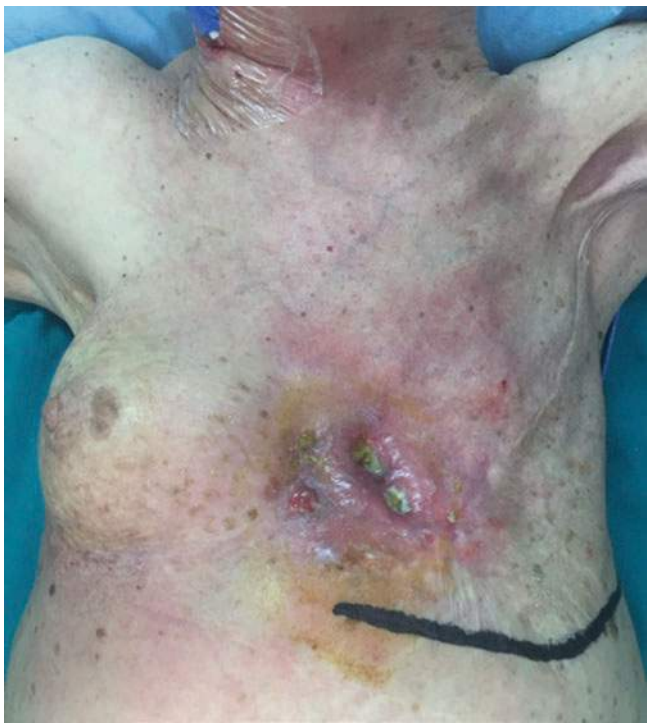

Fig. 62.1 Clinical presentation of a recently infected and ulcerated left parasternal lesion

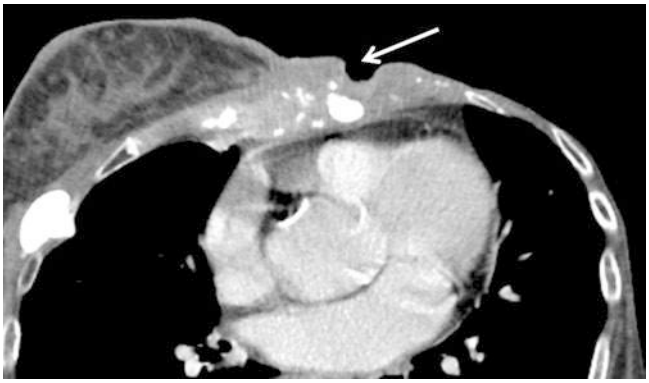

Fig. 62.2 Computed tomography disclosing soft tissue involvement as well as sternal plane deep contact

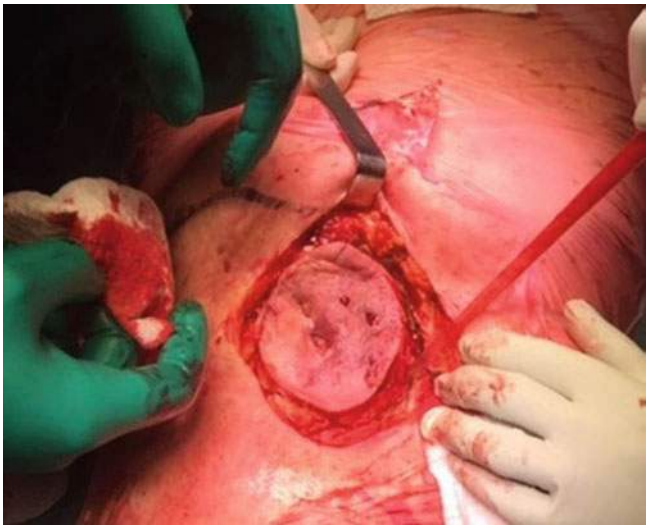

Fig. 62.3 Circular incision including all the infected tissue was performed, reaching the sternocostal plane

Shaving of the external and middle plane of the sternum was performed without any neoplastic tissue finding; thus full thickness sternal resection was skipped (Figs. 62.6 and 62.7). Left pleural cavity was open and then drained (Fig. 62.8). Rotation abdominal flap was used to close the defect (Fig. 62.9).

62.4 Conclusion

Chest wall resection and reconstruction for locally recurrent breast cancer is a feasible and safe procedure providing adequate local disease control and an excellent palliation of very disabling symptoms. This approach may be advocated as an effective palliative procedure in selected patients [16]. In locally

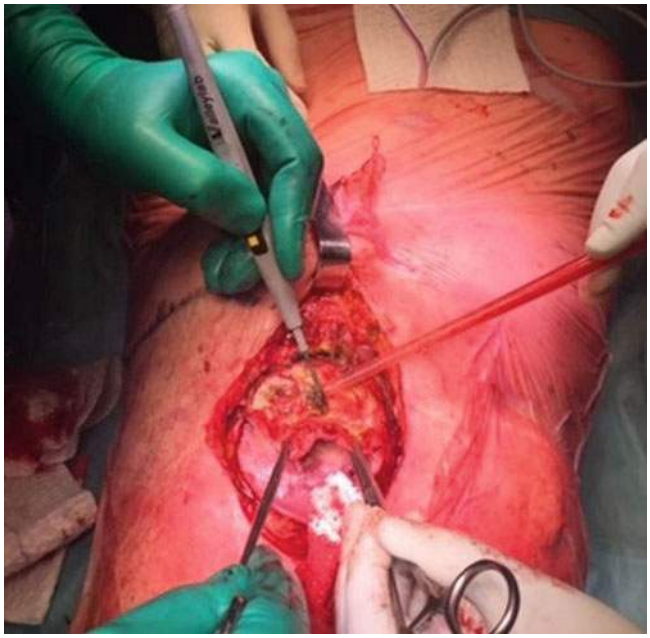

Fig. 62.4 Circular incision including all the infected tissue was performed, reaching the sternocostal plane

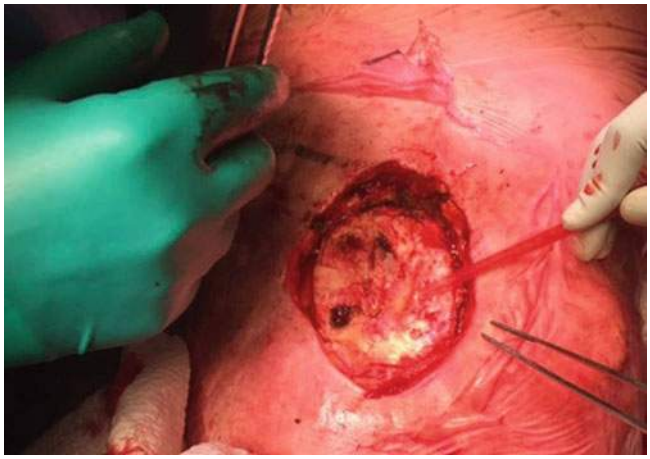

Fig. 62.5 Circular incision including all the infected tissue was performed, reaching the sternocostal plane

recurrent breast cancer, complete chest wall resection may offer radical control of the disease if it is performed with sufficient tumor-free safety margins (2–5 cm). In fact, it may offer a cure for a significant proportion of patients with isolated chest wall recurrence [10]. Patients with a long disease-free interval from their initial treatment and a slow clinical course may be ideal candidates for surgical treatments; to facilitate surgical therapy and to cover large chest wall defects, cooperation between thoracic and plastic surgeons plays a basic role [10].

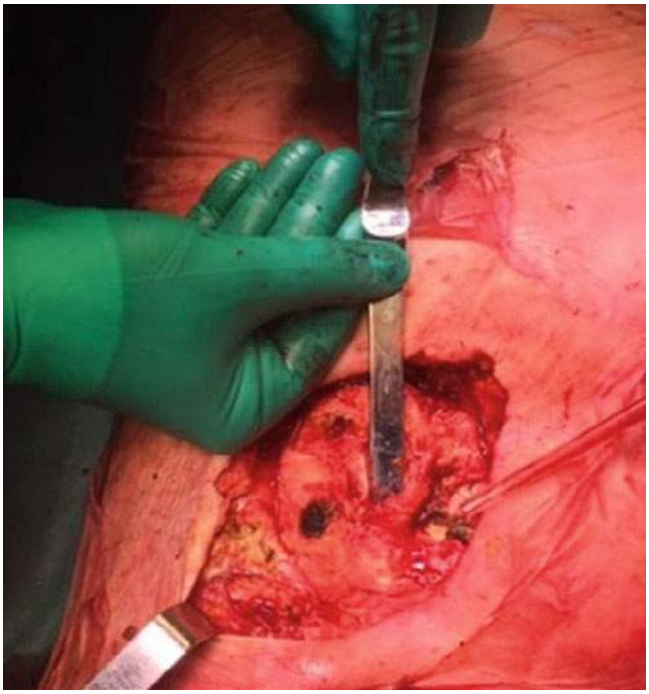

Fig. 62.6 Shaving of the external and middle plane of the sternum

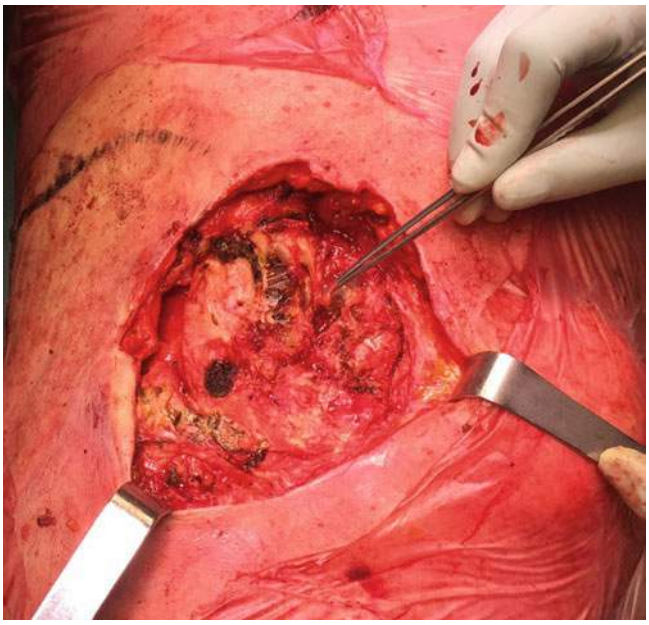

Fig. 62.7 Shaving of the external and middle plane of the sternum

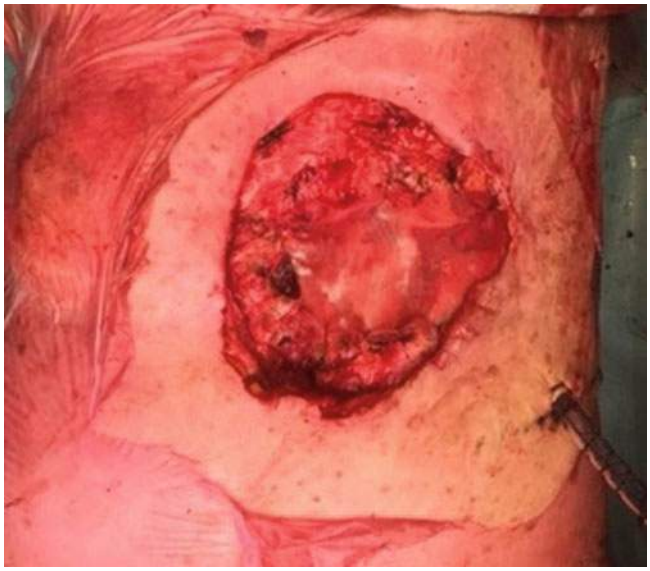

Fig. 62.8 Left pleural cavity was open and then drained

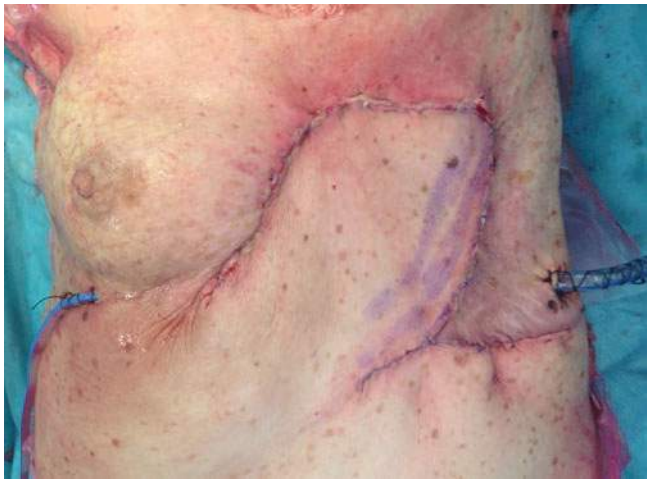

Fig. 62.9 Rotation abdominal flap was used to close the defect

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Part VIII

Other Special Considerations

Stem Cells in Oncoplastic Breast Surgery

63

Premrutai Thitilertdecha and Visnu Lohsiriwat

63.1 Introduction

There are many types of stem cells including embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), and tissue-specific stem cells; however, clinical applications of ESCs and iPSCs are limited due to ethical consideration and cell regulation. Tissue-specific stem cells are also not really accessible and still in controversial for their therapeutic potential. These, hence, make MSCs of great interest to the field of stem cell therapy. This chapter establishes fundamental knowledge of MSCs, particularly adipose-derived stem cells (ADSCs), and extensive information of isolation methods and surface antigenic profiling of human ADSCs as well as their multilineage differentiation capacity for potential utility in cell-based therapy. These comprehensive contents with scientific supports will help surgeons to better understand the basis of ADSCs and their functions before implementation into clinical practices.

63.2 Basic Knowledge

63.2.1 Nomenclature for MSCs

Mesenchymal stem cells (MSCs) have been widely recognized as a promising cell therapy in several diseases, mainly for tissue repair and regeneration. A great amount of work has been dedicated to isolate the stem cells and investigate their phenotypic characters, differentiation capacity, and possible functions for clinical application. MSCs can be obtained from various sources including adipose tissue, bone marrow, tendons, peripheral blood, cord blood, and fetus. However, any plastic-adherent cells isolated from those sources were widely called MSCs without concerning biologic properties of their unfractionated population, leading to scientifically inaccurate name and public confusion. The key characteristics of stem cells, therefore, were defined by the Mesenchymal and Tissue Stem Cell Committee of International Society for Cellular Therapy (ISCT). Stem cells have to possess plastic-adherent ability together with a specific functional connotation including long-term self-renewal (i.e., replication into many generations without losing original characteristics) and multipotency (i.e., differentiation potential to multiple cell lineages, such as adipogenic, chondrogenic, myogenic, and osteogenic cells) [1].

63.2.2 BMSCs and ADSCs

Of all stem cells, bone marrow- and adipose-derived stem cells (BMSCs and ADSCs) are most considered as tentative therapeutic agents because of safety and accessibility. Although MSCs isolated from bone marrow have been massively studied and accepted as a gold standard for adult stem cells, there is still a limitation of implementing these MSCs into real clinical practices due to the cell harvest. A procedure for BMSC collection is relatively painful, and a yield of MSCs from bone marrow is significantly low when compared to the harvest of ADSCs. MSCs from bone marrow yielded only 0.001–0.01% of isolated cells [2], whereas those from adipose tissue yielded 0.5–1.25 × 10^6 cells/g adipose tissue [3, 4]. The stem cell number from bone marrow is then insufficient for *in vitro* expansion to reach a target number required for cell therapy. ADSCs thus become alternative adult stem cells focused for therapeutic potential because of their less invasive, less expensive, and more practical procedure as well as availability in greater amounts.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_63

ADSCs have also been confirmed for their multidifferentiative capacity by numerous studies [3–6].

63.2.3 Sources of Adipose Tissue

Adipose tissue can be acquired from several sites of the body (i.e., abdomen, hip and thigh region, and mamma) and from different surgical procedures (i.e., resection and tumescent and ultrasound-assisted liposuction). Mechanical and enzymatic digestion of adipose tissue can be used to obtain stromal vascular fraction (SVF) which composes vascular endothelial cells, infiltrating cells of hematopoietic lineage, and ADSCs. Oedayrajsingh-Varma *et al*. found that there were no differences in yield of stromal vascular cells among those sites of the body (approximately 0.7×10^6 cells/g adipose tissue). Likewise, frequencies and cell viability of stromal vascular cells among those three surgical procedures were similar with approximately 0.7×10^6 cells/g adipose tissue and 81% viability. There was also no effect on growth kinetics of expanded ADSCs from the type of surgical procedure [3]. However, Cuevas-Diaz Duran *et al*. studied ADSCs from other sites of the body including inner thigh, trochanteric, lower back, and abdomen, from volunteers aged 30–65 years with the same rage of body mass index (BMI = 23 in average). Mononuclear cell count from inner thigh was the highest (1.3×10^4 cells/mL initial fat sample) followed by lower back, abdomen, and trochanteric [7]. It was also noted that there was no impact of age on cell yield.

63.2.4 White and Brown Adipose Tissues

In terms of morphology and physiology, white and brown adipose tissues are dissimilar and can be distinguished. White adipose tissue (WAT) comprises a single lipid droplet and presents in white to yellow appearance. Brown adipose tissue (BAT) is composed of multiple small vacuoles containing a large number of iron-containing mitochondria, resulting in brown color. The function of BAT is to burn lipids for heat production, whereas that of WAT is to store lipids for excessive energy. BAT is abundant in newborns and decreases with age and BMI which is contrary to WAT. In adult humans, BAT is located around cervical, supraclavicular, axillary, paravertebral, mediastinal, and upper abdomen regions [8]. Although BAT is currently considered as a potential pharmacological target to combat obesity and associated diseases, human BAT in adult is almost inaccessible due to small quantity and inconvenient body area (i.e., vital regions). In this case, WAT found predominantly in both subcutaneous and visceral depots is more reasonable as a sufficient source of ADSCs.

63.3 Isolation, Characterization, and Differentiation of Human ADSCs

63.3.1 Cell Isolation

Many well-established protocols are available for isolation and characterization of human ADSCs as adipose tissue composes a heterogeneous stromal cell population. Zuk *et al*. initially identified and described a fibroblast-like cell population or processed lipoaspirate cells (PLA cells) isolated from SVF of human adipose tissue [5]. Raw lipoaspirate from liposuction was washed with phosphate-buffered saline (PBS) and then digested with collagenase enzyme before centrifugation to obtain SVF pellet. After that, red blood cells (RBCs) in the SVF pellet were lysed and discarded by using ammonium chloride (NH_4Cl). The collected SVF was filtered to remove cellular debris and incubated overnight at 37 °C/5% CO_2 in culture medium before washing with PBS to remove residual nonadherent RBCs. The remaining adherent cell population was defined as PLA cells (Fig. 63.1). The yield of PLA cells was approximately $0.7–2 \times 10^6$ cells/mL of liposuctioned tissue. Identification of PLA cells showed that the population contained the majority of tentative mesenchymal stem cells and low levels of pericytes, endothelial, and smooth muscle cells. When culturing these PLA cells with lineage-specific differentiation media *in vitro*, they were also able to differentiate into adipocytes, chondrocytes, myocytes, and osteocytes. Taken all data together, these PLA cells were speculated to be comparable with MSCs. Zuk *et al*. then confirmed that PLA cells were unique from MSCs in terms of surface marker expression and gene profiles, although multiple CD antigens of PLA cells were expressed similar to those of MSCs [9]. These PLA cells with unique characteristics and their clonal isolates were able to differentiate toward multilineages, suggesting multipotent stem cells, termed ADSCs.

After that, there have been several studies developing techniques of isolation and characterization of ADSCs [4, 6, 10]. Each isolation method offered different yield of ADSCs even if using equal amount of adipose tissue. For example, Aust *et al*. reported the yield of ADSCs with 4×10^5 cells/mL lipoaspirate [6], whereas Zhu *et al*. claimed to get 20-fold higher number of ADSCs from their improved protocol [4]. This improvement resulted from (1) using a combination of collagenase and trypsin for tissue digestion instead of using either collagenase or trypsin alone and (2) exchanging

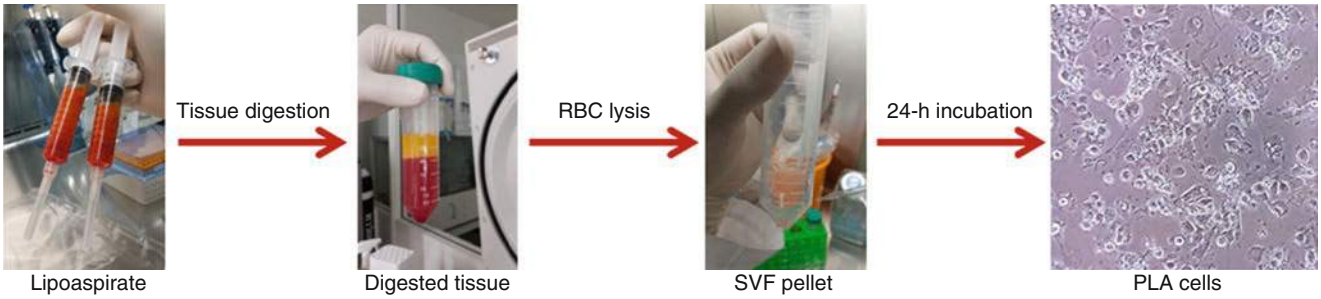

Fig. 63.1 Isolation of human ADSCs

medium for RBC removal instead of using NH_4Cl or Krebs-Ringer bicarbonate (KRB).

63.3.2 Phenotypic Characterization

As PLA cells are heterogeneous in nature, identification and quantification of ADSCs therein are detected through their specific surface marker expression by flow cytometry and immunohistochemistry. Gronthos *et al*. initiated to define the phenotype of human ADSCs in both undifferentiated and differentiated states. Expressed proteins including CD9, CD10, CD13, CD29, CD34, CD44, CD49d, CD49e, CD54, CD55, CD59, CD105, CD106, CD146, and CD166 were found in ADSCs [11]. Yoshimura *et al*. further investigated on phenotypes of ADSCs and other cells in SVF, finding that SVF was composed of ADSCs ($CD31^-CD34^+CD45^-CD90^+CD105^-CD146^-$), blood-derived cells ($CD45^+$), endothelial cells ($CD31^+CD34^+CD45^-CD90^+CD105^{low}CD146^-$), pericytes ($CD31^-CD34^-CD45^-CD90^+CD105^-CD146^+$), and other unknown progenitors [12]. Martin-Padura *et al*. studied a $CD34^+CD45^-$ population which was rich in WAT and found two subsets of dimly and brightly positive expressions of CD34 (i.e., $CD34^{low}CD45^-$ and $CD34^{high}CD45^-$, respectively) [13]. Those two subsets were further characterized by CD13, CD44, CD90, and CD140b markers, indicating that a $CD34^{low}CD45^-$ subset was endothelial cells (or endothelial progenitor cells, EPCs) and a $CD34^{high}CD45^-$ subset was ADSCs. These ADSCs were also predominant with 79–96%. It was noted that although both ADSCs and EPCs expressed CD34, their intensity levels of expression were different. Furthermore, many attempts have been made to investigate phenotypic profiles of ADSCs in order to distinguish ADSCs from the other cells, and most common surface markers are summarized in Table 63.1. The example of phenotypic characterization of human ADSCs using only CD31, CD34 and CD47 is also presented in (Fig. 63.2).

63.3.3 Multilineage Differentiation

ADSCs are generally located in their own niche (i.e., specialized environment) that influences their behaviors of proliferation, differentiation, and apoptosis. To confirm multidifferentiative potential of human ADSCs, numerous studies have been conducted both *in vitro* and *in vivo* by using different supplementation and induction media to mimic such niche and control ADSCs' differentiation ability to lineages of interest. With this strategy, ADSCs have been proved for their multipotency to differentiate toward mesenchymal (e.g., adipogenic [18, 22, 23], chondrogenic [24–26], osteogenic [27–30], myogenic [31, 32], and cardiomyogenic [33] cells), neurogenic [34–36], angiogenic [37–40], and hepatic lineages [41]. These abilities are associated with clinical application.

Although cultured ADSCs at passages 3–5 are generally used in medical treatment, changes in biologic functions and differentiation properties throughout serial passaging of ADSCs remain ambiguous. Wall *et al*. examined the effects of serial passaging of human ADSCs and indicated that ADSCs were capable of both adipogenic and osteogenic differentiation through ten passages, but the osteogenic differentiation tended to dominate at later passages [42]. It is then worth suggesting that cultured ADSCs at early passages, retaining adipogenic potential, may be most suitable to use in autologous soft tissue augmentation.

In general reconstructive practices, autologous fat transfer for soft tissue augmentation has problems in unpredictability and poor long-term graft retention that are required to be solved. Adipogenic differentiation ability of ADSCs is then highly conceivable for resolution. Matsumoto *et al*. performed fat graft transplantation by using a combination of human aspirated fat and freshly isolated SVF cells (i.e., ADSC-rich aspirated fat). This novel technique was termed cell-assisted lipotransfer (CAL) [43]. The CAL was helpful to maintain transplanted graft volume and improve graft survival rate via paracrine support rather than adipogenesis of ADSCs alone.

Table 63.1 Phenotypic profiles based on surface marker expression of human ADSCs

Markers	Expression	References
Positive expression		
CD13	+	Orecchioni *et al*. [14], Martin-Padura *et al*. [13], Zhu *et al*. [4], Traktuev *et al*. [15], Mitchell *et al*. [16], Aust *et al*. [6], Gronthos *et al*. [11]
CD29	+	Francis *et al*. [10], Zhu *et al*. [4], Mitchell *et al*. [16], Katz *et al*. [17], Aust *et al*. [6], Gronthos *et al*. [11]
CD34	+	Orecchioni *et al*. [14], Martin-Padura *et al*. [13], Francis *et al*. [10], Zimmerlin *et al*. [18], Zhu *et al*. [4], Lin *et al*. [19], Traktuev *et al*. [15], Oedayrajsingh-Varma *et al*. [20], Oedayrajsingh-Varma *et al*. [3], Yoshimura *et al*. [12], Mitchell *et al*. [16], Gronthos *et al*. [11]
CD44	+	Martin-Padura *et al*. [13], Zhu *et al*. [4], Zannettino *et al*. [21], Mitchell *et al*. [16], Aust *et al*. [6], Gronthos *et al*. [11]
CD49d	+	Katz *et al*. [17], Gronthos *et al*. [11]
CD54	+	Oedayrajsingh-Varma *et al*. [20], Gronthos *et al*. [11]
CD73	+	Francis *et al*. [10], Mitchell *et al*. [16]
CD90	+	Cuevas-Diaz Duran *et al*. [7], Martin-Padura *et al*. [13], Zimmerlin *et al*. [18], Zannettino *et al*. [21], Traktuev *et al*. [15], Oedayrajsingh-Varma *et al*. [20], Oedayrajsingh-Varma *et al*. [3], Yoshimura *et al*. [12], Mitchell *et al*. [16], Katz *et al*. [17], Aust *et al*. [6], Zuk *et al*. [9]
CD140a	+	Traktuev *et al*. [15], Katz *et al*. [17]
HLA-ABC	+	Oedayrajsingh-Varma *et al*. [20], Katz *et al*. [17], Aust *et al*. [6], Gronthos *et al*. [11]
Negative expression		
CD11a	–	Katz *et al*. [17], Gronthos *et al*. [11]
CD11b	–	Katz *et al*. [17], Aust *et al*. [6], Gronthos *et al*. [11]
CD11c	–	Katz *et al*. [17], Gronthos *et al*. [11]
CD14	–	Francis *et al*. [10], Zannettino *et al*. [21]
CD31	–	Orecchioni *et al*. [14], Martin-Padura *et al*. [13], Francis *et al*. [10], Zimmerlin *et al*. [18], Zannettino *et al*. [21], Lin *et al*. [19], Traktuev *et al*. [15], Oedayrajsingh-Varma *et al*. [20], Oedayrajsingh-Varma *et al*. [3], Yoshimura *et al*. [12], Gronthos *et al*. [11]
CD45	–	Cuevas-Diaz Duran *et al*. [7], Orecchioni *et al*. [14], Martin-Padura *et al*. [13], Francis *et al*. [10], Zimmerlin *et al*. [18], Zhu *et al*. [4], Zannettino *et al*. [21], Traktuev *et al*. [15], Oedayrajsingh-Varma *et al*. [20], Oedayrajsingh-Varma *et al*. [3], Yoshimura *et al*. [12], Aust *et al*. [6], Gronthos *et al*. [11]
CD144	–	Traktuev *et al*. [15], Mitchell *et al*. [16]
Controversial expression		
CD105	+	Cuevas-Diaz Duran *et al*. [7], Zhu *et al*. [4], Zannettino *et al*. [21], Oedayrajsingh-Varma *et al*. [20], Oedayrajsingh-Varma *et al*. [3], Zuk *et al*. [9], Gronthos *et al*. [11]
	–	Martin-Padura *et al*. [13], Yoshimura *et al*. [12]
CD106	+	Zannettino *et al*. [21]
	–	Oedayrajsingh-Varma *et al*. [20], Katz *et al*. [17], Zuk *et al*. [9]
CD140b	+	Orecchioni *et al*. [14], Martin-Padura *et al*. [13], Traktuev *et al*. [15]
	–	Lin *et al*. [19]
CD146	+	Zannettino *et al*. [21], Mitchell *et al*. [16], Gronthos *et al*. [11]
	–	Zimmerlin *et al*. [18], Oedayrajsingh-Varma *et al*. [20], Yoshimura *et al*. [12]
CD166	+	Zhu *et al*. [4], Zannettino *et al*. [21], Oedayrajsingh-Varma *et al*. [3], Mitchell *et al*. [16], Gronthos *et al*. [11]
	–	Oedayrajsingh-Varma *et al*. [20]
SMA	+	Traktuev *et al*. [15]
	–	Zimmerlin *et al*. [18], Lin *et al*. [19], Zuk *et al*. [9]
HLA-DR	+	Oedayrajsingh-Varma *et al*. [20]
	–	Zhu *et al*. [4], Katz *et al*. [17], Aust *et al*. [6], Gronthos *et al*. [11]

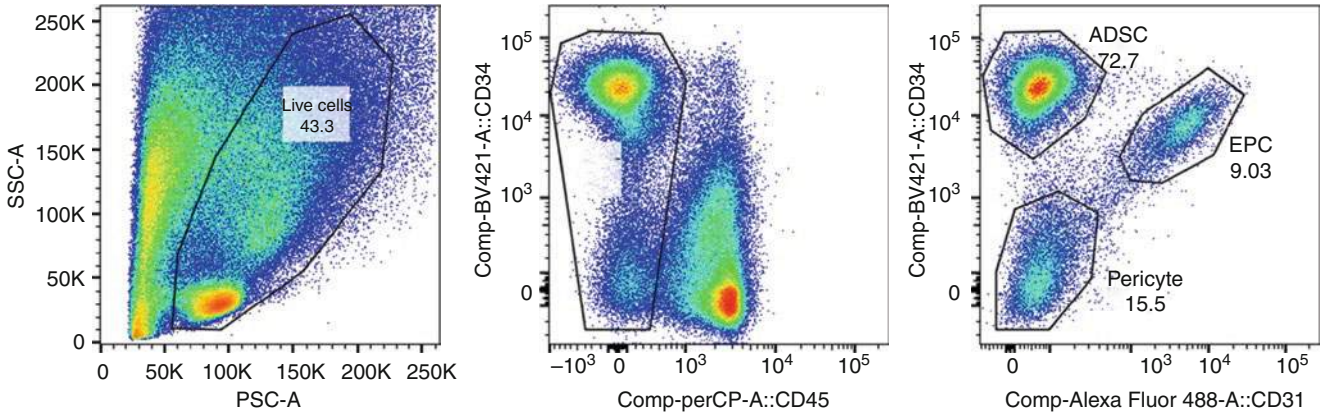

Fig. 63.2 Phenotypic characterization of human ADSCs

Besides the usefulness of ADSCs in fat graft improvement, ADSCs also play role in *de novo* fat formation. Vermette *et al.* cultured human ADSCs with an adapted self-assembly method producing a three-dimensional adipose tissue for soft tissue reconstruction [44]. ADSCs were induced by ascorbic acid supplementation to generate their own bio-extracellular matrix as supportive stroma, resulting in recreation of an adipose substitute similarly to subcutaneous fat. The three-dimensional spheroid culture of ADSCs has been further studied by Naderi *et al.* They demonstrated that ADSCs were able to grow as floating micro-tissue spheres through several passages and the adipogenic differentiation of ADSCs was able to be accelerated in the three-dimensional spheroid culture [23]. These can possibly lead to a novel micro-tissue preparation of ADSCs for soft tissue regeneration in the future.

63.4 Application of ADSCs in Breast Reconstructive Surgery

First report on fat autografting in humans is from Doctor Gustav Adolf Neuber in 1893. Since then the fat and its component had been reluctant and had deliberate evolution due to limitation of cellular mechanism and experimental model. In 2009, the American Society of Plastic Surgery deployed five broad-based questions, which are:

1. What are the current and potential applications of fat grafting (specifically breast indications and, if data are available, other cosmetic and reconstructive applications)?
2. What risks and complications are associated with fat grafting?
3. How does technique affect outcomes, including safety and efficacy, of fat grafting?
4. What risk factors need to be considered for patient selection at this level of invasiveness?
5. What advancements in bench research/molecular biology potentially impact current or future methods of fat grafting?

Gutowski *et al.* [45] attempted to address these concerns from scientific evidences. Although not all questions were clearly encountered, this task force brought the ADSCs to the attention of plastic society around the world.

The ADSCs has long been introduced to reconstructive surgery, the application has been broadened in many organs. In particular, the soft tissue and skin are main targets for reconstructive surgeon.

The advantages and benefits of ADSCs are as follows:

- ADSCs contain high content of multipotential mesenchymal progenitor cells for regenerative therapy.
- ADSCs are abundant throughout the human body.
- ADSCs can be easily harvested with technically simple in surgical accessibility (Figs. 63.3 and 63.4).
- ADSCs are a source of patients' preference as there is a minimal donor site morbidity.

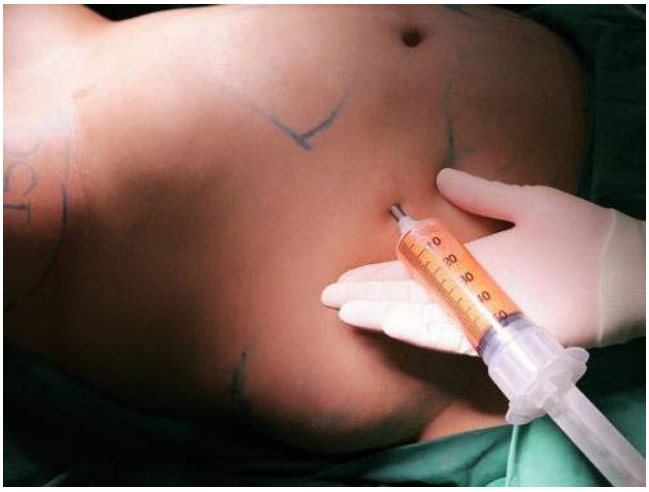

Fig. 63.3 Fat harvesting

Fig. 63.4 Specimen contains ADSCs

The applications of ADSCs in breast surgery can be listed in major categories as follows [46–50]:

63.4.1 Oncoplastic Breast Surgery

Breast reconstruction is a dynamic process where several factors can influence the final outcome, for example, adjuvant treatment, patient weight, gravity, and patients' satisfaction. So, ADSCs play a role in both partial and total mastectomy reconstructions. The application of ADSCs ranges from minor retouch and revision surgery to total breast reconstruction.

For partial mastectomy, after simple lumpectomy, the ADSCs can serve as biologic tissue filler as part of volume replacement oncoplasty procedure. Post-therapeutic mammaplasty with minor asymmetry or volume deficit can also enhance the volume by ADSCs application.

For total mastectomy, ADSCs are being applied as retouching procedure after implant base or autologous base reconstruction. ADSCs can improve several implant complications such as lack of upper pole fullness, capsular contracture, rippling, and volume deficit. ADSCs also help surgeon to avoid major autologous flap surgery revision by slightly improve the flap atrophic change or correct the necrotic area after debridement.

63.4.2 Aesthetic Breast Surgery (Contralateral)

The contralateral breast symmetric procedure including augmentation mammoplasty, reduction mammoplasty, or mastopexy might be performed simultaneously with indexed breast reconstruction. However, it is very challenging for surgeons to achieve a perfect outcome as the contralateral breast is usually native and has no adjuvant treatments. In order to improve the surgical outcome, ADSCs show a promising result for symmetrical procedure as a sole therapeutic procedure or along with other surgical corrective procedure.

63.4.3 Congenital Breast and Chest Wall Deformity Correction

Not only in cancer surgery, but many other conditions resulting in breast deformity might benefit from ADSC application. Poland's syndrome, pectus excavatum, and tubular breast are not uncommon congenital conditions which necessitate surgical correction. ADSCs may improve upper pole fullness in Poland's syndrome, rib bony contouring defect in pectus excavatum, and lower pole fullness with double bubble correction in tubular breast surgery. Moreover, hypoplastic and constricted lower pole breasts are suitable conditions for ADSCs.

63.4.4 Postmastectomy Pain Syndrome Treatment and Irradiated Tissue Improvement

These conditions are not definite breast reconstruction, but ADSCs can be initial steps toward total breast reconstruction especially with implant base reconstruction. Postmastectomy pain syndrome (PMPS) usually occurs in rarity after external radiation to the chest wall. It can develop over several years after treatment completion. The treatment modalities are somehow ineffective and might require autologous flap procedure or regional nerve analgesia.

ADSCs have been widely accepted in richness of progenitor cell and clinical reports confirm theirs improvement in surrounding tissue conditions. The stromal matrix and cellular function can be proven from translational research studies. Postmastectomy pain syndrome patients experience symptom improvement due to soft tissue softening which releases the tightness over their irradiated tissue area (Fig. 63.5).

63.4.5 Scar Correction

Abnormal wound healing leads to unpleasant aesthetic scar, in particular, for patients who are at risk of developing keloid, hypertrophic scar, widening scar, or hyperpigmented scar. As the ADSCs and their derivatives from lipoaspirated specimen contain significant amount of biological active cells and function substance, they can play a role in wound healing process. So, ADSCs not only act as static volume filler, but they can also exploit a biodynamic role for surrounding tissue interaction.

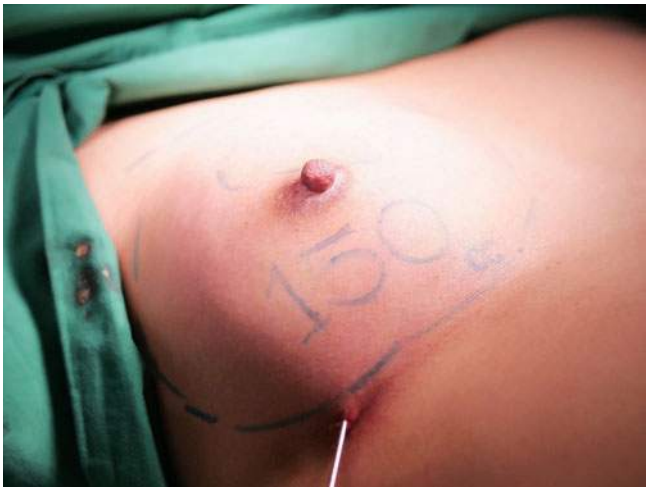

Fig. 63.5 Lipofilling is performed to improve the irradiated breast tissue

63.5 Future Trend and Research

The better knowledge from fundamental and translational researches brightens the advanced clinical application of ADSCs [13, 51, 52]. Nowadays, in vitro cell manipulation and expansion are being performed in only some particular institutions due to limited laboratory tools and scientists. In some countries, the law, medical society, and FDA still do not approve of in vitro cell manipulation and only restrict it in academic or research purposes. In the near future, when clinicians and scientists successfully proved the outcome and safety of in vitro ADSC manipulation, then ADSCs will become more widespread in medicine.

63.6 Summary

White adipose tissue is suggested to be an alternative source of stem cells which is rich of ADSCs. As several isolation procedures and phenotypic profiles of ADSCs are established, purified ADSCs can be obtained to examine their biologic functions and to prepare for clinical utilization. Differentiation capacity of ADSCs can also suggest therapeutic potentials for many diseases (e.g., bone/cartilage defects and myocardial ischemia) as well as for cosmetic purposes (e.g., breast enlargement and correction of facial deformities). Application of ADSCs is a promising future for oncoplastic breast surgery as it is does not only bring static volume enhancement but also dynamic active function to improve irradiated tissue and abnormal wound healing or scarring. ADSCs thus are promising agents for cell therapy, even though, efficacy of ADSCs needs to be proved and cell production under good manufacturing practice (GMP) is concerned.

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Systemic Treatment of Breast Cancer and Breast Reconstruction

64

Sergio D. Simon

Since the early 1970s, the concept that breast cancer is a systemic disease—and therefore needs systemic treatment—gained wide acceptance among the oncologic community. The pioneering clinical trials by Fisher [1] and Bonadonna [2] confirmed that the adjuvant treatment of women with breast cancer improves disease-free survival and overall survival. Four decades later, systemic treatment has become an integral part of the treatment of women with invasive breast cancer and has been responsible in great part for an impressive decrease in mortality over the last 25 years.

Recent understanding of the complexities of the molecular biology of breast cancer has shed new light on the systemic treatment of breast cancer. Although the presence of estrogen receptor (ER) and progesterone receptor (PR) has been regularly studied in tumor specimens since the 1970s and the presence of the HER-2/neu protein has been measured since the 1990s, it was only after seminal works in the early 2000s [3, 4] that gene expression profiles of breast cancer ("gene signatures") were identified through microarray techniques. Since then, breast cancer has been divided in the so-called molecular subtypes. Studies have demonstrated that "breast cancer" is indeed a heterogeneous group of diseases that have in common their origin in the mammary gland but have wide variations in biology, clinical presentation, prognosis, and treatment. It is now accepted that breast cancer is subdivided in five major molecular subtypes, of which four subtypes are of clinical relevance:

(a) Luminal A tumors: These tumors have high expression of steroid hormone-mediated signaling pathways, resulting in high expression of the ER protein. Luminal A tumors tend to be of low grade, have low proliferation markers, and usually have a very indolent clinical course and therefore good survival. They tend to respond well to endocrine manipulation (tamoxifen, aromatase inhibitors, ovarian ablation, fulvestrant, etc.) and less well to conventional chemotherapy. About 40% of the cases of breast cancers fall into this subtype. Adjuvant treatment of these tumors is frequently done with hormonal treatment alone, although chemotherapy can also be used for more advanced stages.

(b) Luminal B tumors: Despite the presence of ER, these tumors are different from the Luminal A due to less defined gene expression and genomic alterations. They tend to be of higher grades and to have relatively high expression of proliferation genes and cell cycle-related genes. The expression of ER and PR is usually less exuberant than in Luminal A tumors. Mutation of the p53 is not infrequent in this group, and many tumors present overexpression of the HER2 protein. The prognosis of Luminal B tumors is distinctly poorer than the Luminal A tumors, and they are usually associated with some degree of endocrine resistance. They comprise about 25% of cases of breast cancer. Adjuvant treatment of these tumors usually comprises chemotherapy and endocrine treatment, with the monoclonal anti-HER2 antibody trastuzumab reserved for the HER2-positive patients.

(c) HER2-enriched tumors: Some 20% of breast tumors belong to this subtype, which is characterized by amplification of the HER2/neu gene in the 17q chromosome region. This gene amplification results in overexpression of the HER2 protein at the cell membrane, which can be detected by routine immunohistochemistry (IHC). In cases of questionable results on IHC, fluorescent in situ hybridization (FISH) or similar techniques can be used to actually measure the number of gene copies in the tumor cells. These HER2-enriched tumors tend to be of high grade and a high proportion of them present p53 mutations. The prognosis of HER2-enriched tumors is poor, with short disease-free interval after initial diagnosis and with aggressive visceral metastases (liver, lung, brain) developing through the clinical course of these patients. With the introduction of anti-HER2 agents (trastuzumab, used both in the adjuvant and metastatic settings, and the

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_64

antibodies pertuzumab and ado-trastuzumab (T-DM1), used for metastatic disease, as well as the oral tyrosine-kinase inhibitor lapatinib), the disease-free survival and the overall survival of these patients have improved dramatically. Typically, adjuvant treatment of these tumors combines chemotherapy and trastuzumab.

(d) Basal-like tumors ("triple negative breast cancer" or TNBC): About 15% of breast tumors fall into this category. These tumors have high expression of basal epithelial markers, such as cytokeratins 5/6, c-KIT, laminin, and p-cadherin. Some express EGFR. These tumors do not express ER, PR, or HER2 protein on IHC (hence the "triple negative" name). They are usually high-grade tumors, with high proliferation index (as measured by the Ki67 antigen) and frequent p53 mutations. TNBC is usually an aggressive disease, with high incidence of visceral and brain metastasis and a very poor prognosis. Patients with familial breast cancer with BRCA1 germline mutations usually present with this subtype of breast cancer. TNBC tumors are sensitive to chemotherapy, especially to DNA-damaging agents such as anthracyclines and platinum salts. Adjuvant treatment of these tumors is usually done with aggressive and intensive chemotherapy. It has been recognized that these basal-like tumors are actually a group of at least six different subtypes, with different gene expression and different biology [5].

A fifth molecular subtype, called "normal breast-like," has been less well characterized, and its clinical correlations are not clear at this time.

Although initially defined by DNA microarray techniques, the molecular subtypes of breast cancer are usually classified by pathologists through the use of routine IHC, which is readily available to most pathology laboratories. It has been demonstrated that IHC is a reasonable surrogate marker for subtype classification and the results of estrogen receptor, progesterone receptor, HER2, and Ki67 are routinely used for this classification by most clinical oncologists.

Based on these considerations, the systemic treatment of breast cancer has been tailored to each individual patient, according to anatomical IHC (and/or gene expression patterns) of their specific tumors. Therefore, Luminal A and Luminal B tumors will include endocrine therapy as part of their treatment, while HER2-enriched or TNBC will not receive hormonal therapy. Typically, hormonal therapy is done for 5 years, with some patients receiving up to 10 years of endocrine treatment. Anti-HER2 therapy (in the form of the monoclonal antibodies trastuzumab, pertuzumab, and T-DM1 and the oral inhibitor lapatinib) has been reserved for patients whose malignant cells overexpress this protein in the cell membrane. Adjuvant trastuzumab has typically been used for 1 year. Chemotherapy, on the other hand, has been applied to most cases of breast cancer irrespective of their molecular subtypes although, as mentioned before, some subtypes are more resistant and other types are more sensitive to this type of treatment. Typically, adjuvant chemotherapy treatment will last between 3 and 6 months.

In many cases, however, inoperable/locally advanced breast tumors are treated initially with neoadjuvant (also called "primary") chemotherapy. The purpose of this type of treatment is to render these tumors operable or, in some cases, to make breast-conserving surgery possible in a case initially treatable only by radical mastectomy. The same principles that guide the choice of adjuvant treatment are applied in the choice of neoadjuvant treatment: chemotherapy, trastuzumab, and hormonal manipulation can be used, depending on the molecular subtype of the tumor.

Each of these forms of systemic treatments, causing changes in the cell cycle and the hormonal milieu of the patients, can potentially influence the final outcome of plastic surgery. Furthermore, chemotherapy is known to increase the chance of developing infection by means of causing leukopenia and decreased immune function. Therefore, the systemic treatment of breast cancer can potentially have direct implications on breast reconstruction by impairing wound healing, by increasing microthrombotic events, and by facilitating local infection.

64.1 Tamoxifen and Breast Reconstruction

Tamoxifen is a nonsteroidal selective modulator of the estrogen receptor. Its active metabolites, 4-hydroxytamoxifen and endoxifen, bind to the estrogen receptor protein in tumor cells, normal breast, and other target tissues, blocking the DNA synthesis of the estrogen-dependent genes. Because of its strong antiestrogenic and antitumoral effect, tamoxifen has been used since the 1970s in the treatment of breast cancer.

In the adjuvant setting, tamoxifen has been used mostly in premenopausal patients, since several studies have shown that aromatase inhibitors (anastrozole, letrozole, and exemestane) are more effective in postmenopausal women. When used in the adjuvant setting for 5 or 10 years, tamoxifen significantly diminishes the risk of recurrence and improves overall survival in patients with Luminal A and Luminal B tumors [6].

Side effects of tamoxifen include, among others, hot flashes, amenorrhea, sexual dysfunction, endometrial hyperplasia, and increased risk of endometrial cancer. In addition there is an increased risk of thromboembolic events, especially during and immediately after major surgical procedures or periods of immobility. Women with previous history of varicose veins, deep vein thrombosis, pulmonary

thromboembolism, myocardial infarction, and cerebral vascular accidents should be given tamoxifen with great caution.

History of hypercoagulability is also a contraindication for the use of tamoxifen, especially during surgical procedures. Factor V Leiden, a mutation of factor V which affects about 5% of the Caucasian population in the United States, is the most frequent cause of hypercoagulability. Cases of flap loss following microsurgical perforator flap breast reconstruction have been reported, with cases of recurrent arterial thrombosis both intraoperatively and postoperatively in patients with factor V Leiden using tamoxifen [7].

Tamoxifen has also been associated with the increased risk of microvascular flap complications in patients undergoing breast reconstruction. Preclinical studies [8] in Wistar rats demonstrated that animals receiving tamoxifen for 2 weeks and submitted to terminoterminal anastomoses of the femoral artery had significantly higher measurements of the thickness of intimal and total arterial wall when compared to animals not receiving tamoxifen, although no significant differences in thrombotic complications were noted. Kelley et al. [9] retrospectively compared rates of microvascular complications and pulmonary thromboembolism in patients who were and were not receiving adjuvant tamoxifen at the time of microvascular breast reconstruction. Among 670 patients, 205 were taking tamoxifen before breast reconstruction and 465 were not. Of note, patients taking tamoxifen were significantly younger, had lower body mass index, and had less comorbidities than the ones not receiving the drug. Despite this, microvascular flap complications were significantly more common in patients taking tamoxifen (21.5 vs 15%, $p = 0.04$). Patients on tamoxifen had more immediate and delayed complications, both as cardiovascular events and as surgical flap complications. Immediate total flap loss and a lower rate of flap salvage were significantly more frequent in the tamoxifen group. The authors recommend stopping the drug 28 days before microsurgical breast reconstruction.

As a practical consideration, it seems reasonable to screen candidates for microsurgical reconstruction for a history of hypercoagulability for consideration of prophylactic anticoagulation and to stop tamoxifen 28 days prior to surgery in all patients.

64.2 Chemotherapy and Surgical Outcomes

Several authors have examined the influence of chemotherapy on surgical outcomes of reconstructive surgery as well as the eventual delay in starting chemotherapy caused by immediate reconstructive surgery.

Furey et al. [10] evaluated retrospectively the rate and severity of wound complications in 112 patients who received adjuvant chemotherapy after mastectomy with immediate breast reconstruction (IBR). The rate of wound complications (20.8% in the entire group) was similar in patients receiving chemotherapy when compared with a group of patients not receiving systemic treatment. No patient had a delay in the initiation of adjuvant therapy because of wound complications secondary to IBR. There was no correlation between age, type of operation, tumor pathology, stage, number of lymph nodes harvested, type of prosthesis or chemotherapy, and wound complications. The frequency of wound complications was not increased in patients receiving adjuvant chemotherapy after mastectomy and IBR. The authors concluded that administration of adjuvant chemotherapy does not need to be delayed in patients who have immediate breast reconstruction following mastectomy for breast cancer.

Caffo et al. [11] examined the concurrent use of adjuvant chemotherapy and immediate breast reconstruction (IBR) with skin expanders after mastectomy and the acute toxicity of these treatments. Evaluating 52 consecutive patients receiving IBR with skin expanders after mastectomy and adjuvant chemotherapy and comparing them to patients undergoing IBR without adjuvant chemotherapy and to another group of patients undergoing mastectomy and chemotherapy but no IBR, these authors concluded that the interval between surgery and the start of expander inflation was similar in the groups with or without chemotherapy (median of 5 days) and that there were no statistically significant differences in complications between the groups receiving chemotherapy or not. The planned chemotherapy dose was equally delivered to both groups. They conclude that concurrent breast reconstruction and chemotherapy is safe and feasible and that no reduction in dose intensity is required.

Warren Peled et al. [12] studied the impact of chemotherapy and the timing of chemotherapy on postoperative outcomes in patients undergoing mastectomy and IBR. This retrospective study reviewed data on 163 consecutive patients undergoing mastectomy and IBR, of which 57 had received neoadjuvant chemotherapy, 41 had received postoperative adjuvant chemotherapy, and 65 received no chemotherapy. Although the adjuvant chemotherapy group had a higher rate of postoperative infections as compared to the neoadjuvant and no chemotherapy groups, the unplanned return to the operating room and the rate of implant/expander removal was the same in the three groups. Of patients who underwent expander/implant reconstruction, implant removal was not different among women in the neoadjuvant chemotherapy cohort, the adjuvant cohort, and the no chemotherapy cohort (26%, 22%, 18%, $p = 0.70$).

Evaluating the delay in starting adjuvant chemotherapy caused by breast reconstructive surgery, Alderman et al. [13]

examined 3643 patients with stages I–III breast cancer who were treated at eight different National Comprehensive Cancer Network (NCCN) institutions who followed similar treatment guidelines. Breast-conserving surgery, mastectomy with immediate reconstruction, and mastectomy with delayed reconstruction were studied, and Cox regression analysis was used to evaluate the type of surgery and the timing of chemotherapy. Of all the patients, a significant delay (>8 weeks after surgery) was observed in 5.1% of cases. Factors that favored early start of chemotherapy were younger age, lower body mass, absence of comorbidities, and non-African American ethnicity. For patients below age 60, mastectomy and immediate reconstruction was the only modality where a significant proportion of patients had a delay to start of chemotherapy >8 weeks. For women above age 60, a greater proportion had a delay in starting chemotherapy when compared to younger patients, especially in the group undergoing breast-conserving surgery. Overall, mastectomy with immediate breast reconstruction caused a modest but statistically significant delay in initiating systemic treatment. The clinical significance of this finding is unknown.

In a prospective pilot study, Giacalone et al. [14] compared the feasibility, oncological safety, and esthetic outcome of skin-sparing mastectomy + immediate breast reconstruction (IBR) with latissimus dorsi (LD) flap after neoadjuvant chemotherapy and radiotherapy ($N = 26$) with the more standard approach of mastectomy followed by adjuvant chemo- and radiotherapy and a delayed LD flap reconstruction (DBR) after completion of the systemic treatment ($N = 78$). With prolonged follow-up (median 4.1 years, range 1–8), early complications were seen in 61% of patients undergoing immediate reconstruction versus 56% seen in patients undergoing delayed reconstruction. Early implant loss was 0% in the IBR vs 12% in the DBR group. Capsular contracture, reconstruction failure, local recurrence, and cosmetic results were similar in both groups, suggesting that IBR is a safe and effective even when performed after neoadjuvant chemo- and radiotherapy.

Similar findings were reported in a retrospective study by Monrigal et al. [15], who reviewed 210 patients treated at the same institution over a period of 18 years. These patients had received neoadjuvant chemotherapy and radiotherapy prior to undergoing mastectomy with IBR (107 a latissimus dorsi flap with implant, 56 a transverse rectus abdominis musculocutaneous (TRAM) flap, 25 an autologous latissimus dorsi flap, and 22 a retropectoral implant). 46/210 events were seen (20 necrosis, 9 surgical site infections, and 6 hematomas), leading to a second surgery in 23 patients. Necrosis was especially more frequent with the TRAM flap technique. Late complications (capsular contracture, infection, dislocation, deflation) were recorded in 23.6% of patients, leading to 14 new interventions. The 5-year overall survival and disease-free survival were excellent (86.7 and 75.6%, respectively), and 30.5% of patients had recurrent disease (5 local, 9 locoregional, and 54 distant relapses). Despite the small numbers of these series of patients and the lack of randomized studies (which would probably be impossible to run), the evidence points toward satisfactory results of IBC after neoadjuvant chemo- and radiotherapy.

Immediate breast reconstruction after neoadjuvant chemotherapy was also recently reported by Azzawi et al. [16]. These authors studied the influence of neoadjuvant chemotherapy on surgical outcomes of patients operated on by the same surgeon in a 7 year period. They were compared to patients undergoing breast reconstruction without prior neoadjuvant chemotherapy. A total of 171 patients received 198 IBR procedures with different types of reconstructions (free tissue transfers, pedicled flaps, and implant-only procedures). Fifty-three patients received neoadjuvant therapy, and 118 received no primary chemotherapy. IBR failed in 2% of each group, and the rate of reoperation for major complications was 9% in each group. Differences in minor complications were not statistically different, and delay in time to commencement of adjuvant radiotherapy was the same in both groups.

Gouy et al. [17] reviewed the experience of a single institution in order to determine whether reconstruction after neoadjuvant chemotherapy and mastectomy can affect the interval between surgery and adjuvant treatment and if survival was in any way affected by this sequence of treatment. These authors conclude that immediate breast reconstruction does not delay the starting of adjuvant therapy, has no significant effect on local or distant relapse-free interval, and does not delay the commencement of radiotherapy.

Tanaka et al. [18] evaluated the impact of preoperative chemotherapy on outcomes of breast reconstruction. They reviewed 128 patients, 29 of whom received preoperative chemotherapy and 99 of whom received no chemotherapy. Wound complications were seen in 17% of patients undergoing preoperative chemotherapy versus 12% among patients with no chemotherapy. These findings are statistically nonsignificant, and the authors conclude that healing will not be impaired by chemotherapy.

Finally, Harmeling et al. [19] performed a systematic review of the delay in time to adjuvant chemotherapy caused by immediate breast reconstruction. Fourteen studies with a total of 5270 patients were examined, of which 1942 underwent IBR and 3328 underwent mastectomy only. One of these studies showed a shorter mean time to adjuvant chemotherapy after IBR (12.6 days), while four studies showed a delay of 6.6–16.8 days and seven studies showed no difference in time to chemotherapy after surgery. This systematic review of the literature suggests that IBR does not delay the start of chemotherapy to any clinically significant extent.

In conclusion, several series of patients reported in the literature raise no major concern regarding the association of

chemotherapy and breast reconstruction. The time to starting chemotherapy has not been significantly delayed by reconstructive surgery, there have been no reports of increased risk of infectious or surgical complications caused by neoadjuvant chemotherapy, and survival end points do not seem to be affected by the association of chemotherapy and reconstructive surgery. However care needs to be taken when chemotherapy and major breast surgery are performed at close intervals, since both treatments have potentially dangerous complications for patients with breast cancer.

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Systemic Impact of Breast Reconstruction

65

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65.1 Introduction

Treatment for early breast cancer usually involves some combination of surgery, radiation therapy, chemotherapy, hormone therapy, and/or targeted therapy. Surgery is still the main curative therapeutic modality for breast cancer and may be considered both frontline and sequential to a neoadjuvant treatment. Breast reconstruction (BR) following mastectomy or lumpectomy/quadrantectomy (breast-conserving surgery) represents a fundamental step in the treatment of breast cancer and has been widely studied in the few last decades. From our best knowledge, reconstruction techniques may alter the normal tissue environment with effect that may be exerted either locally or systemically. Feature, extent, and duration of surgery could influence the magnitude of systemic effect through the release of pro-angiogenic mediators [1–4]. Angiogenesis plays a key role in both wound healing and tumor survival and growth. Thus, investigations about angiogenic response after surgical interventions may help in guiding surgical approaches [1]. Normal wound repair process generates an angiogenic response to deliver nutrients and inflammatory cells to injured tissue. The angiogenic response enables the removal of debris and has a central role for the development of a granulation tissue framework, the web underlying wound closure [2]. The mediators of wound angiogenesis include soluble factors such as vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF), transforming growth factor beta (TGF-beta), b-fibroblast growth factor (bFGF), and platelet-derived growth factor (PDGF) identified in several wound models [3]. Angiogenic agonists (e.g., VEGF) and antagonists (e.g., thrombospondin-1) have been described at various stages of repair [4–6], suggesting that the neo-angiogenic stimulus may be the result of a balance of factors favoring either vessel growth or regression [7]. Previous studies have shown that surgical wound fluid collected within a few hours after a surgical operation is potently angiogenic. In a cohort of patients with early breast cancer, a transient increase in circulating levels of VEGFA was documented 3 days after the surgical procedure [1]. Similarly, bFGF levels have been shown to peak immediately after surgery and then fall by the second postoperative day [1, 8]. This immediate release has been suggested to function as an initiator of wound angiogenesis. In later wound repair stages, VEGF is the predominant angiogenic mediator [4]. VEGF expression is almost negligible in normal skin; however, response to tissue injury induces an upregulation of VEGF, thus supporting keratinocyte motility for wound re-epithelialization through a paracrine cell signaling [9]. TGF family is involved in several steps of wound healing: monocyte chemoattraction, formation of granulation tissue and fibroblast stimulation, neovascularization, wound contraction, and extracellular-matrix reorganization.

The response of the body to a cancer is not a single mechanism but goes in parallel with inflammation and wound healing: *cancer is a wound that never heals*. It has been suggested that inflammatory infiltrating cells and cytokines found in tumors are more likely to contribute to tumor growth, progression, and immunosuppression than to exert an effective antitumor host response [10]. If genetic damage is the *match that lights the fire* of cancer, some types of inflammation may provide the *fuel that feeds the flames*. Moreover cancer susceptibility and severity may be

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_65

associated with functional polymorphisms of inflammatory cytokine genes; accordingly, it is demonstrated that the deletion or inhibition of some inflammatory cytokines may inhibit the development of experimental cancers. Scientific works on the production of proangiogenic cytokines in early human wound fluid have been performed using drain fluid from patients undergoing cancer surgery [4, 8]. These studies are based on the principle that wound fluid would be generally representative of the growth environment of the wound. It would be important to study if feature, extent, type, and duration of surgery could affect systemic perioperative levels of angiogenic cytokines in patients with breast cancer. A better understanding of the time interval during which the sequelae of events in wound healing occur may be the basis for defining new therapeutic strategies that can interfere with tumor outgrowth, sparing wound healing processes. After surgical resection of a tumor, the microenvironment of the wound site differs from that of normal tissue in several ways. Hypoxia, fibroblast activation, and various growth factors released after the surgical procedure make the wounded site different from non-wounded tissue. Major oncological resections might bring to cytokine dysregulation and subsequent postsurgical immunosuppression, especially when the operation is of long duration.

Furthermore, the use of "autologous fat transplantation" in BR is getting more and more utilized; interestingly, numerous observations of adipocyte, pre-adipocyte, and progenitor cells as potential actors in breast cancer tumorigenesis have been reported, thus defining another possible concern regarding BR and tumor growth promotion [11].

65.2 Pro-angiogenic Cytokines

Tumor growth is angiogenesis dependent. Perioperative levels of endogenous stimulators (bFGF, VEGF, PDGF, angiopoietin cathepsin, copper, interleukin 1, 6, and 8), inhibitors (thrombospondin, angiostatin, endostatin, plasminogen activator inhibitor-1, tissue inhibitor of metalloprotease, zinc, interleukin 10 and 12), and modulators of angiogenesis (TGF-b, tumor necrosis factor alpha) may indicate the switch to the angiogenic phenotype of neoplasia that depends on a net balance between positive and negative angiogenic factors released by the tumor [1]. In particular, there is evidence of an alteration in the circulating levels of acute phase reactants in the perioperative period, possibly enhancing the release of malignant cells into the circulation, with an increased risk of metastasis spreading. Vascular endothelial growth factors (VEGF) have a cell mitogen effect and act as regulator of vascular permeability. Several retrospective studies reported that VEGF plasmatic level is significantly associated with relapse-free survival and overall survival. Patients with early-stage breast cancer who have tumors with elevated levels of VEGF, TGF-b, or bFGF show a higher likelihood of recurrence than patients with low-angiogenic tumors, even if treated with conventional adjuvant therapy [1]. Preoperative levels of VEGF, bFGF, and TGF-b described in our experience are similar to previously reported ones [12–14]. Other studies reported a correlation between clinical pathological features of disease and preoperative levels of angiogenic factors [15]. To better understand the mechanism of wound angiogenesis and its significance in tumor biology and surgical intervention, we reported an experience that specifically evaluated the temporal profile of serum VEGF, bFGF, and TGF-b in breast cancer patients who underwent minimal, moderate, or heavy surgery [16]. Blood samples were collected prospectively from 84 consecutive pre- and postmenopausal patients presenting with primary (T1–T4) node negative/positive (N0–N2) or locoregional relapsed breast cancer amenable to a surgical radical resection. Forty-three (52%) patients underwent minimal (lumpectomy, quadrantectomy), 18 (22%) moderate (mastectomy without reconstruction), and 21 (26%) heavy surgery (mastectomy followed by reconstruction with transverse rectus abdominis myocutaneous (TRAM) flap). The preoperative median values ($n = 82$) of serum VEGF, bFGF, and TGF-b levels were 84.50 pg/ml (range 14.97–573.66 pg/ml), 10.21 pg/ml (range 0.44–74.70 pg/ml), and 21.45 pg/ml (range 6.34–135.94 pg/ml), respectively, for each type of surgery. In our study, no relationship has been observed between age, stage, biological features, and levels of preoperative angiogenic factors. Median values of VEGF, bFGF, and TGF-b usually have a dropout at 24–48 h after surgery. Reduction of TGF-b levels from preoperative to postoperative time was statistically significant.

Kong et al. [14] showed that plasma TGF-b levels were elevated preoperatively in 81% of the patients. The mean plasma TGF-b level in breast cancer patients was showed to be normalized after surgery (19.3 ± 3.2 versus 5.5 ± 1.0 ng/ml, $p < 0.001$) in the majority of subjects; TGF-b serum levels were persistently elevated in case of lymph node metastases or overt residual tumor. No data are reported on bFGF in correlation to timing or extent of surgery in patients with breast cancer. An overall percentage change with 23% reduction after surgery has been described for VEGF. In a previous report [17], a significant change in serum VEGF levels compared with preoperative values has been described with time with an initial drop over the first 3 days; thereafter levels recovered. In this study, an analysis of the local wound response has been also performed, showing that VEGF levels in the wound environment are much higher than the serum equivalent from as early as the first postoperative day. Then, VEGF levels peak at day 2 and remain at a higher level thereafter for several days. This observation fits well with wound vascular mechanisms in animal models.

Interestingly, acute wound response could act as a "molecular trap" for angiogenic factors so that the reduction of serum levels of VEGF, TGF-b, and bFGF observed in our patients could be the result of an angiogenic molecule "trapping."

Moreover, another explanation for reduction of angiogenic factors, especially for VEGF, may be related to platelet count drop after surgical injury. Since platelets are the main source of serum VEGF as well as other anti-angiogenic factors like PDGF, it is reasonable to suppose that trapping in wound healing could explain VEGF level drop after surgery.

Indeed, the surgical wound itself is a unique extravascular compartment with increased vascular permeability and a high surface area/volume ratio. If reabsorption occurs freely from the surgical wound site, changes in local VEGF concentrations should be reflected in the circulation. Subsequent increase of VEGF (specifically in patients who underwent TRAM surgery) should be related to massive local wound VEGF production. TRAM surgery creates a wound with a larger surface area than wide local excision. This effect may mark an interaction between residual tumor-derived local inhibitors resulting in an initially depressed normal stromal angiogenic response that recovers over time. This would be in keeping with the evidence that tumor cells secrete factors that provide negative "feedback" regulation and serve to suppress vascular growth, restraining the growth of secondary tumors or metastases [18–20].

Surgical clearance of cancer involves regional extirpation, and residual tissues may still be under the influence of tumor-derived inhibitors delaying the normal angiogenic wound response. The mechanisms underlying these observations require additional investigation and may be related to the half-life of angiogenic stimulators, to a local effect on the stroma when the pro-angiogenic tumor stimulation is removed, or to an impairment of blood influx and platelet release reaction at the time of surgical injury. This muted response in cancer patients may represent an opportunity to complete surgical treatment while minimizing stimulation of metastatic disease, a biological argument in favor of immediate reconstruction after breast cancer surgery. Experimental evidence suggests that an environment rich of growth factors enables the survival of cancer cells left in an area of cancer extirpation or in the circulation (i.e., residual postoperative microscopic tumor remnant, [18–20]). However, as wounds age, the surgical site becomes less favorable to tumor implantation, and when healing process is complete, injected tumor cells do not localize to the surgical site [19]. Thus, local recurrence found in conjunction with widespread metastatic disease is likely to have been established by perioperative seeding rather than as a late phenomenon. Furthermore, a growth factors-stimulated microenvironment may affect neoplastic postsurgical remnant growth as showed in vivo and in vitro cell lines [21]. However, our experience indicates that high local concentrations of angiogenic molecules may need to be antagonized in order to reduce the possibility to create an environment prone to be seeded by tumor implants. Thus, in vivo quantification of tissue damage response may facilitate the design of "wound healing" experimental models in order to represent a paradigm of response to surgical stress. Vascular and lymphatic drainage systems may offer an opportunity to manipulate the early wound environment and reduce local cancer recurrence rates in the future. A better understanding of the time interval during which the *sequelae* of events in wound healing occur may be the basis for redefining new therapeutic strategies that can interfere with tumor outgrowth, differentiating physiological wound healing processes and tumor-promoting mediators thus sparing normal wound healing processes.

65.3 Adipocytes and Progenitor Cells

Lipotransfer, a surgical intervention of transferring adipose tissue from a body district to another, can be considered a technical revolution in plastic surgery and widely performed for aesthetic purpose. Lipofilling has been indicated in breast reconstruction and deformity correction after breast conservative treatment. However, the possible interactions between tumor beds and the lipoaspirate grafts are currently poorly understood. Scientific literature underlines the efficacy of the technique as well as its safety. Nevertheless, many experimental studies provide data on the endocrine, paracrine, and autocrine activities of the transplanted fat tissues. Adipocyte, pre-adipocyte, and progenitor cell secretions can stimulate angiogenesis and cell growth. The "tumor-stroma interaction" can potentially enhance cancer recurrence by "fueling" dormant breast cancer cells in the tumor bed. There is a lack of translational research that proves this concern in clinical setting. More recently, a cell-assisted lipotransfer technique has been proposed; in this technique, the transplant is enriched with stem cells from adipose tissue. This kind of approach opens up some concerns about graft-tumor interactions, possibly enhancing tumor growth and implant consolidation: indeed, transplanted fat survival results increased when the graft is exposed to angiogenic and growth factors such as insulin and VEGF, known to be pro-tumorigenic molecules [11]. Most studies published in the literature focus on technique, complications, fat graft survival, and cosmetic results. Several studies are focused on breast cancer patient safety. They are mainly dealing with the risk of microcalcifications observed on the mammogram in the follow-up. No data are available on the risk of recurrence due to the endocrine, paracrine, and autocrine fat activity. In 2007, the French Society of Plastic Surgery addressed the question of cancer safety for the lipofilling technique in breast cancer patients. The Society sent a recommendation to the French plastic surgeons to postpone the

lipofilling in the breast with or without breast cancer history unless it is performed under prospective controlled protocol. One year later, the American Society of Plastic Surgeons (ASPS) gathered eight important American plastic surgeons in "The ASPS Fat Graft Task Force" to assess the indications and the safety and efficacy of autologous fat grafting [22]. Five major end points were identified: (1) What are the current and potential applications of fat grafting? (2) What risks and complications are associated with fat grafting? (3) How does technique affect outcomes of fat grafting? (4) What risk factors need to be considered for patient selection? (5) What advancements in bench research/molecular biology should potentially impact current or future methods of fat grafting? The task force also stated that "based on a limited number of studies with few cases. No interference with breast cancer detection has been observed; however, more studies are needed." Despite the fact that post-lumpectomy and postmastectomy are clearly included in the indications of fat graft, the task force did not discuss the issues of adipocyte-stroma interaction and the risk of development of local recurrences.

Subcutaneously or peritoneally co-transplantation of murine mammary carcinoma cells into adipose tissue-rich environment regions can lead to tumor growth and metastasis [23]. This is the main interesting concept of local effect acting via paracrine, autocrine, or "tumor-stroma interaction" pathway that can also happen in lipofilling procedures to the breast. We have evidence that both stimulatory and inhibitory effects can be observed in the experimental researches. Some of the studies tried to validate single type of cell or type of adipokine which may be responsible for some particular stages of breast cancer cell line development. However, the majority of those studies are from fundamental research and in vitro study and somehow difficult to link with the clinical model. Indirect data that support safety of fat transfer are based on reconstruction using an autologous flap technique such as transverse rectus abdominis myocutaneous (TRAM) flap and deep inferior epigastric perforator (DIEP) flap. Despite the large amount of fat tissue transferred with the flap, no increased risk of cancer recurrence has been published in the literature. However both techniques should be distinguished. Autologous flap is made of a complex tissue with its own vascular system; the composition or ratio of the fat tissue in the flap is not altered. Lipotransfer fat composition is altered from original donor site ratio. After conservative treatment, the fat tissue is injected through the glandular tissue. Such injection of adipocytes are able to produce adipokines and several secretions which can potentially induce cancer reappearance by "fueling" dormant breast cancer cells in the tumor bed through the "tumor-stroma interaction." We cannot conclude that the flap transfer does not have any tumor-stroma interaction. Illouz et al. reviewed a personal series of 820 patients with lipofilling; only 381 patients were cancer patients; other indications were for congenital breast asymmetry and cosmetic augmentation without cancer history [24]. However, they could not make the conclusion in terms of oncological safety because almost half of the patients were lacking oncological data and follow-up. Rietjens et al. reported one of the biggest series focus on lipotransfer in breast cancer treatment and reconstruction. They followed 158 patients and found that postoperative complication rates are very low and there is little alteration in follow-up mammograms. Although they found only one recurrence in 18 months, they concluded that the potential risk of local "dormant" tumor cells being stimulated to induce a local recurrence is still unclear [25]. Another study based on cancer evolution by Rigotti compared the number of LRR of the same group of patients in the pre- and post-lipofilling [26]. Such methodology should be criticized, because the risk of locoregional recurrence (LRR) decreases with time and cannot be considered as equivalent in the pre- and post-lipofilling period. The authors excluded 104 breast conservative treatment patients from the whole study populations which breast conservative treatment patients could be the group at most risk of LRR.

Petit et al. reported a match cohort study (n = 321) of patients operated for a primary breast cancer with breast-conserving surgery or mastectomy and reconstructed with lipofilling at the European Institute of Oncology in Milan [27]. A comparable cumulative incidence of LRR was showed with a HR of 1.11 for lipofilling- vs non-lipofilling-matched cohort (p = 0.792). Interestingly, lipofilling reconstruction resulted in a worse outcome when executed in patients operated for intraepithelial neoplasia [28] with a 5-year cumulative incidence recurrence of 18% and 3% for lipofilling and non-lipofilling groups, respectively ($p = 0.02$). The recurrence occurred close to the lipofilling injection in more than 90% of cases, supporting the concept of an angiogenic-promoting process in the site of fat grafting, particularly for younger patients (less than 50 years) and less differentiated histology (high-grade neoplasia or Ki-67 $\geq$ 14).

There is increasing evidence that the stroma is important for driving tumor growth. When performing a fat transfer procedure, we should consider the potential adipokine downstream effects on breast cancer tumorigenesis. Adipokines can potentially increase the interaction between tumor and stromal cells rather than conferring self-sufficiency to the tumor. Adipocytes, pre-adipocytes, and adipokines can promote or inhibit breast cancer cell tumorigenesis through autocrine and paracrine mechanisms, thus enhancing tumor-stroma interactions, representing a major concern in proposing this technique of reconstruction, particularly for patients with a precancerous breast lesion like DCIS (ductal carcinoma in situ).

Since November 2007, the French Society of Plastic Surgery (SOFCPRE) recommends not to use adipose tissue in breast surgery until its safety has been proved incontrovertibly. Moreover, the authors underline that the

autologous fat grafting to the breast is not a simple procedure and should be performed only by well-trained and skilled surgeons. The major complications can be observed when this procedure is performed by untrained and untutored physicians and the role of education in the lipofilling technique is of paramount importance.

We cannot state that lipofilling procedure is dangerous or should not be done in patients with breast cancer, since available data are balanced on suppressive or promoting effects of fat transfer on breast cancer progression. Therefore, we should promote translational research to evaluate the role of fat grafting in the development of breast tumor, to evaluate if fat grafting may induce cancer recurrence (especially after radiotherapy) and to evaluate whether cancer induction or recurrence depends on angiogenesis mediated by cytokines produced by the lipofilling-related fat grafting process. Clinical studies based on an accurate follow-up of patients with breast cancer who underwent lipotransfer are required to definitively address all relevant questions. A prospective clinical registry including high-volume multicenter collaborative data is warranted.

65.4 Conclusion

The alteration in the circulating levels of proangiogenic cytokines may play an important role in the perioperative period, for a possible risk of systemic metastasis spreading. However, high local concentration of growth factor may need to be antagonized. A better understanding of the precise molecular sequelae of events in wound healing may pose the basis for the definition of new therapeutic strategies that can interfere with tumor outgrowth, sparing normal wound healing processes.

Moreover, there is increasing evidence that the adipocyte, pre-adipocyte, and progenitor cell can promote breast cancer cell tumorigenesis. Clinical studies with control group based on accurate follow-up are so required to confirm the safety of lipotransfer in breast cancer patients. Accordingly, surgical trial of breast reconstruction after breast cancer primary treatment is addressing the question of oncological safety (NCT02339779).

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Fat Transfer Safety in Breast Cancer Patients

66

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Although lipotransfer is not a new technique [1], it can be considered a technical revolution in plastic surgery and widely performed all over the world for aesthetic surgery [2, 3]. More recently the fat grafting has been indicated in breast cancer patients to improve the results of breast reconstructions and to correct deformity after conservative treatments [4–7]. Current literature underlines the efficacy of the technique as well as the safety of the procedure in cancer patients. But experimental studies provide data on the endocrine, paracrine, and autocrine activity of the transplanted fat tissue. Adipocyte, pre-adipocyte, and progenitor cell production of adipokines and several other secretions can stimulate angiogenesis and growth of breast cancerous cells through endocrine, paracrine, and autocrine pathways. The "tumor-stroma interaction" can potentially induce cancer reappearance by "fueling" dormant breast cancer cells in the tumor bed [7–10]. In order to confirm the safety of fat grafting procedure in breast cancer patients, clinical studies based on an accurate follow-up of patients with breast cancer who underwent fat grafting are required using relevant statistical methods to demonstrate with a control group that the local recurrence rate as well as any cancer event is not increased in the fat grafting group.

66.1 Biological Considerations

There is increasing evidence that obesity, an excess accumulation of adipose tissue occurring in mammalians when caloric intake exceeds energy expenditure, is associated with an increased frequency and morbidity of several types of neoplastic diseases, including postmenopausal disruption of the energy homeostasis results in obesity, inflammation, and alterations of adipokine signaling that may foster initiation and progression of cancer [11–15]. Other recent studies, some of which are based on endogenous WAT expressing a transgenic reporter, showed a significant level of adipose cell contribution to tumor composition. However, WAT contains several distinct populations of progenitors, and these data were obtained using crude or mixed cell populations. We therefore decided to purify by sorting the two quantitatively most relevant populations of WAT progenitors (endothelial cells and adipose stromal cells; ASC) and to investigate in vitro and in vivo their role in several orthotopic models of local and metastatic breast cancer. Compared with bone marrow-derived $CD34^+$ cells mobilized in blood by granulocyte colony-stimulating factor (G-CSF), purified human WAT-derived $CD34^+$ cells were found to express similar levels of stemness-related genes and significantly increased levels of angiogenesis-related genes and of FAP-α, a crucial suppressor of antitumor immunity. In vitro, WAT-$CD34^+$ cells generated mature endothelial cells and endothelial tubes. In vivo, the coinjection of human WAT-$CD34^+$ cells contributed to orthotopic tumor vascularization and significantly increased tumor growth and metastases in models of human breast cancer in non-obese, diabetic, severe combined immunodeficient (NOD/SCID) interleukin-2 receptor γ (IL-2Rγ)-null (NSG) mice.

66.2 Oncologic Safety

Fat transfer should not be considered only as a neutral biological material able to restore the body contour [16]. Several studies underline the power of the transferred fat to regenerate the blood supply of the skin disorders after radiotherapy [17]. Such active regeneration of the tissue can be explained by the presence of a high percentage of progenitor cells included in the fat tissue. Several recent papers have generated new hope about the use of white adipose tissue (WAT)-derived progenitor cells for soft tissue reconstruction in a variety of diseases including breast cancer, a procedure that is increasingly used worldwide (in the breast cancer field,

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_66

however, we believe that the hype for the exciting results in terms of WAT progenitor cell engraftment and tissue augmentation should be tempered when considering the recent and abundant preclinical studies indicating that WAT progenitors may promote breast cancer growth and metastasis). In two different studies, we showed at the IEO an increase of the locoregional recurrences in the in situ breast cancer patients associated with fat grafting when compared to a match control group of patients who did not received a fat grafting in their follow-up [18, 19]. However, the review of the statistical results of our study shows that with a longer follow-up the locoregional recurrence difference is no more significant.

Gale and collaborators published a control study on 328 patients with previously treated malignant breast disease who underwent fat grafting, matched to the double of patients treated for breast cancer without fat grafting [20]. After a mean follow-up of 88 months after breast cancer and 32 months after fat grafting, no significant excess oncologic events were observed with regard to local (0.95 versus 1.90%; $p = 0.33$), regional (0.95% versus 0%; $p = 0.16$), and distant metastasis (3.32% versus 2.61%; $p = 0.65$).

As breast conserving treatment (BCT) provides a higher risk of remaining cancer cells in the breast tissue, as compared to mastectomy, we set up a new match control study on fat grafting after 322 invasive breast cancers treated by BCT.

We collected 322 consecutive patients operated for a primary invasive breast cancer between 1997 and 2008 who subsequently underwent fat grafting for breast reshaping. All the patients were free of recurrence before the fat grafting. For each patient, we selected one patient with similar characteristics who did not undergo a fat grafting.

Results: Eighty-nine percent of the tumors were invasive. Median follow-up was 4.8 years from what seems to be a safe procedure after BCT for breast cancer patients (PRS (in press)).

No difference between the local events (14 lipo vs 16 controls $p = 0.49$). Axillary nodes metastasis (3 lipo vs 6 controls $p = 0.23$). Distant metastases (14 lipo vs 15 controls $p = 0.67$). Contralateral BC (4 lipo vs 5 controls $p = 0.51$).

Recently, Kronowitz et al. published a large study of lipofilling performed after breast cancer treatment [21]. They compared 719 patients in the study group to 670 controls. The matching criteria were less rigorous than in the Gale or in the Milan study, but the number of patients was much more important. After a mean follow-up time of 60 months after mastectomy, 44 months for controls, locoregional recurrence was observed in 1.3% of cases (9 of 719 breasts) and 2.4% in the group of controls (16 of 670 breasts). The cumulative 5-year locoregional recurrence rates were 1.6% and 4.1% for cases and controls. Systemic recurrence occurred in 2.4% of cases and 3.6% of controls ($p = 0.514$). Kronowitz concluded that lipofilling in a breast cancer patient does not increase the risk of locoregional or systemic recurrences.

66.3 Conclusion

Although several clinical studies do not show an increasing risk in terms of safety of breast cancer patients, the biological analysis together with the experimental research underlines the activity of fat tissue on cancer cells. It is still mandatory to set up randomized trials on delayed or immediate fat grafting to reassure definitely the patients.

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Oncologic Safety of Oncoplastic Surgery

67

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The use of oncoplastic breast surgery has increased substantially in recent years and has many benefits for the patient, including those related to cosmesis, quality of life, and avoidance of mastectomy. However, surgical oncologists have expressed concern regarding the oncologic safety of these procedures. There has been speculation, due to a variety of reasons, that oncoplastic procedures may compromise oncologic outcomes. Oncoplastic surgery has been associated with a higher complication rate than standard breast-conserving surgery, and this has raised concerns that commencement of adjuvant therapy may be delayed in these patients. Mobilization of glandular tissue in oncoplastic surgery leads to displacement of the tumor bed, posing challenges for re-excision of margins and also for delivery of radiation boost. These issues will be discussed in detail in this chapter.

67.1 Oncologic Outcomes

Several of the issues that we will discuss in this chapter have caused concern that patients receiving oncoplastic surgery may receive suboptimal cancer treatment and, therefore, have worse oncologic outcomes.

The largest analysis to address this concern was a systematic review, published in 2016 [1]. The authors included 40 studies that described oncologic outcome in patients undergoing oncoplastic breast surgery. The majority of the included studies looked specifically at patients who had volume displacement oncoplastic surgery procedures. Others examined those who had volume replacement procedures, and the remainder of the studies included patients who had a variety of oncoplastic procedures. The quality of studies included in this analysis was strikingly poor, with only two studies having a median duration of longer than 60 months and only seven studies analyzing cohorts of more than 100 patients. Overall, the studies had median follow-up periods of 10–74 months. The margins were reported to be involved in 0–36% of patients. Local recurrence rates ranged from 0 to 10.8%, and the rate of distant recurrence ranged from 0 to 18.9%. There were six studies in the systematic review with a follow-up of 48 months or more and cohorts of more than 50 patients [2–7]. Among these studies, the local recurrence rates ranged from 1.6% to 6.8%. Distant recurrence was only reported in two of these studies, and was 10% and 13%.

The European Institute of Oncology in Milan reported their long-term experience with oncoplastic procedures [8]. The study evaluated 454 patients who underwent glandular mobilization, mastopexy, or round block procedure between the years 2000 and 2008. Each patient undergoing an oncoplastic procedure was matched with two patients who had undergone a standard breast-conserving operation. The patients were matched for age, year of surgery, and pathological tumor size. All patients received whole-breast radiation therapy and boost to the tumor bed. Patients who had intraoperative radiation were excluded. The median follow-up was 7.2 years. The majority of patients in the study (66%) were 50 years of age or younger. The majority had T1 tumors (55%) with node-negative disease (54.4% of the oncoplastic breast surgery group and 56% of the standard breast-conserving surgery group). The incidence of multifocality was higher in the oncoplastic breast surgery cohort (25.8% versus 13%, $p > 0.001$). Negative margins were achieved in 88.3% of the oncoplastic breast surgery group and 90% of the standard breast-conserving surgery group. Overall survival was similar in the two groups. There was a difference in disease-free survival, however (10-year disease-free survival 69% with oncoplastic breast surgery and 73.1% with breast-conserving surgery, $p = 0.049$). When local recurrence, regional recurrence, and distant recurrence were examined individually, there was no difference between the two groups (10-year local recurrence 6.7% versus 4.2%, 10-year regional recurrence 3.1% versus 2.8%, 10-year distant recurrence 12.7% versus 11.6%).

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_67

The same group published a similar study looking specifically at T2 tumors and included 193 patients who had oncoplastic procedures, from 2000 to 2008, with a median follow-up of 7.4 years [9]. They were compared with 386 patients who had mastectomy for T2 tumors, who were matched for year of surgery, age, tumor subtype, and number of positive nodes. The estimated 10-year overall survival was 87% for both groups. Projected 10-year disease-free survival was 60.9% following oncoplastic breast surgery and 56.3% following mastectomy ($p = 0.69$). Local recurrence, as one might expect, was higher in the oncoplastic breast surgery group (7.3% versus 3%), but this was not statistically significant ($p = 0.082$).

The rate of regional recurrence was higher in the mastectomy group (8% versus 2.2%, $p = 0.04$), which may be accounted for by the higher rate of radiation therapy following oncoplastic breast surgery and a slightly larger tumor size in the mastectomy cohort. The rate of distant recurrence was comparable (18.9% after oncoplastic breast surgery and 19.6% postmastectomy).

Overall, there is no compelling evidence to support fears that oncoplastic surgery leads to inferior outcomes in breast cancer patients.

67.2 Delay in Adjuvant Treatment

Oncoplastic breast surgery, by definition, is more complex than standard breast-conserving surgery, and this, along with the increased length of surgery and increased incidence of contralateral procedures, has led to an assumption that the complication rate is higher for oncoplastic surgery. Complications of breast surgery may lead to delays in the commencement of adjuvant therapy, and these delays have been shown to have a negative impact on outcome. Klit et al. studied a cohort of 1798 women undergoing surgery for breast cancer in Denmark from 2011 to 2012 [10], of whom 445 had oncoplastic surgery, 529 had mastectomy, and 824 had standard breast-conserving surgery. The mean age and body mass index were lowest in the mastectomy group. The mean tumor size was largest in the mastectomy patients and smallest in the patients who underwent standard breast-conserving surgery. Axillary node dissection was most frequently performed in the mastectomy group (29%) followed by the oncoplastic breast surgery group (14%). The standard breast-conserving surgery group had the lowest rate of axillary node dissection at 8%. None of the patients who had breast-conserving surgery had a contralateral procedure, as compared with 12% of those who had oncoplastic breast surgery and 1% of those who had mastectomy. There was no difference in mean time from surgery to commencement of adjuvant chemotherapy (34.3 days postmastectomy, 34.9 days after breast-conserving surgery, 34.2 days after oncoplastic breast surgery). A similar study carried out in the United Kingdom comprising 169 patients reported 29 days (range 16–58) to initiation of chemotherapy following oncoplastic breast procedures ($n = 31$) compared to 29.5 days (range 15–105) after standard breast-conserving surgery ($n = 66$), 29 days (range 15–57) after mastectomy without reconstruction ($n = 56$), and 31 days (range 15–58) after mastectomy with immediate reconstruction ($n = 16$) [11].

So far, there is no evidence that oncoplastic breast surgery is associated with a significant delay in commencement of adjuvant therapy.

67.3 Margins

There is concern that the rearrangement of tissue in oncoplastic procedures may compromise the ability to accurately identify margins that need to be re-excised. However there is compelling evidence that oncoplastic surgery reduces re-excision rates. A study from the Virginia Mason Medical Center looked at the effects of implementation of an oncoplastic program at the institution [12]. They found that the mastectomy rate decreased from 34% to 15% ($p < 0.001$) and the re-excision rate decreased from 32% to 18% ($p < 0.001$). The complication rate remained low, at approximately 5%.

Clough et al. published their experience of the management of positive margins following oncoplastic surgery [13]. A total of 277 patients who underwent level II oncoplastic surgery for breast cancer from 2004 to 2013 were retrospectively analyzed. Lateral mammoplasty was the most commonly performed procedure (42.6%), followed by superior pedicle mammoplasty (14.8%) and J-mammoplasty (9.4%). The definition of a positive margin was "no tumor at the inked margin." The margins were positive in 11.9% of patients. This rate was slightly higher in patients who had received neoadjuvant chemotherapy (13.4%). Of the 33 patients with a positive margin, 11 had re-excision and 22 proceeded to mastectomy. In previous studies, the incidence of positive margins has also been found to be low, but in many of these studies, re-excision was not attempted in patients who had undergone oncoplastic surgery, and the patients had mastectomy to achieve clear margins [6, 14–17]. It is important to note that these patients may have been undergoing oncoplastic surgery because their tumors were too large for standard breast-conserving surgery, and this may be why re-excision was not attempted. However, it is also possible that the surgeons may have not been confident in their ability to identify the area to be re-excised.

Several solutions have been proposed to address this perceived reluctance to attempt re-excision of margins in patients who have had oncoplastic breast surgery. The

concept of staged oncoplastic surgery is in its infancy, and concrete data have yet to be published in its support. This involves delaying the reconstructive component of the procedure for several days until the final pathological report is available, in case re-excision of margins is needed. The obvious drawback of this is that the patient must have an additional anesthetic. A small case series on intraoperative frozen section reported a positive predictive value of 0.62; the negative predictive value was 0.97, however, for a final accuracy of 0.94. These data have yet to be replicated [18].

67.4 Radiation Therapy

The European Organisation for Research and Treatment of Cancer (EORTC) 22811-10882 randomized controlled trial of 5318 patients found that among patients who had undergone breast-conserving surgery, those who received whole-breast radiation and also a local boost had fewer ipsilateral breast tumor recurrences compared with patients who received whole-breast radiation alone (16.4% versus 12%) [19]. Those younger than 40 years of age derived the most benefit. Patients undergoing oncoplastic breast surgery tend to be younger and tend to have larger tumors, and so radiation boost is of particular importance to them. With oncoplastic surgery, complex parenchymal rearrangement may result in the tumor bed being located distant from the skin incision and even in a different quadrant than the original tumor site. Therefore, the traditional ways of identifying the area to boost, such as identification of scar or seroma cavity, or boosting the quadrant of the tumor, are not reliable for these patients. A systematic review of papers reporting radiation techniques in patients who had undergone oncoplastic surgery identified 24 studies comprising 1933 patients [20]. They found that the use of a boost was only reported in 11 studies, and in two of these studies, it was only reportedly administered to patients with incomplete margins. Clipping of the tumor cavity was only mentioned in eight studies. This indicates that there may be a reluctance to administer a boost to patients who have undergone oncoplastic surgery, and that clipping the cavity in these patients is possibly under-used.

Thomas et al. surveyed breast surgeons in the United States, and only 33.1% stated that they "always" place clips at the time of oncoplastic reduction surgery or complex tissue reorganization. Radiation oncologists were also surveyed, and 38.7% responded that they only deliver a boost if clips have been placed. This highlights the importance of placing clips to mark the tumor bed during oncoplastic breast surgery, in order to guide the delivery of radiation boost, and also highlights the need for clear communication between surgical and radiation oncologists.

67.5 Conclusions

In conclusion, there is no evidence to suggest that oncoplastic surgery is associated with adverse cancer outcomes or delays in initiation of adjuvant therapy. With clear documentation of surgical technique, re-excision of margins is feasible in these patients. Clipping of the tumor bed and clear communication with the multidisciplinary team are essential to facilitate radiation boost after oncoplastic breast surgery.

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68 Preoperative and Postoperative Nursing Considerations for the Oncoplastic and Reconstructive Patient

Liza L. Lagdamen, Maeve O. Benitez, Jennifer Fox, and Marian Fitzpatrick

The diagnosis of breast cancer is challenging emotionally and physically. Nursing care must encompass all the dimensions of the patient [1]. The nurse must educate sensitively, in accordance with each individual patient's learning preference. Breast cancer diagnosis can cause stress, anger, fear, denial, and frustration. It is therefore essential for nurses to be able to recognize these feelings and to educate in a manner that is beneficial to the patient and her overall postoperative outcome.

Kessels [2] theorizes that about 40–80% of the medical information provided to patients by healthcare professionals is forgotten immediately and that the more information provided, the less the patient retains; Kessels also theorizes that half of that which is remembered is incorrect. Barriers to learning include the use of difficult medical terminology, the manner in which the information is provided (written versus verbal), and patient-related factors, such as education level. Additionally, age and anxiety can affect memory recall [2]. Assessing and addressing the needs of the individual patient will foster a caring relationship that allows for developing trust between nurse and patient. Nurses, nurse practitioners, and clinical nurse specialists play a vital partnership role with patients in this context through preoperative and postoperative teaching, meaningful communication at concurrent visits, and becoming a support system for patients.

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68.1 Oncoplastic Surgery

Breast-conserving therapy (BCT) using an oncoplastic approach has been receiving widespread attention due to cosmetic results and the convenience of having same-day surgery. Same-day surgery is defined as admission, surgery, and discharge on the same day. One of the key components to a successful ambulatory surgery is preoperative education. In many instances, patients who appear to understand their nurse's explanations regarding the ambulatory patient process, pain management, and postoperative care are not fully comprehending what is being explained to them because of the anxiety they are experiencing [3]. There are different types of oncoplastic procedures applied for breast reconstructions. These procedures fall under two broad categories—the glandular displacement and mastopexy with or without breast reduction. In glandular displacements, the local breast tissue is mobilized and approximated to close the lumpectomy defect. With major oncoplastic procedures, the oncologic defect is closed by mobilizing the breast tissue while using a mastopexy or breast reduction techniques.

68.2 Reconstructive Surgery

Breast reconstruction can help patients regain physical and emotional wholeness [4]. Immediate breast reconstruction has a positive influence on patient satisfaction and health-related quality of life at the conclusion of treatment [5]. There are many positive psychological implications for women who choose reconstruction after mastectomy. These include improved body image and self-esteem, decreased anxiety and depression, and improved feelings of sexual attractiveness and satisfaction [6–8]. There are various immediate or delayed breast reconstruction options following mastectomy, including tissue expander insertion, immediate reconstruction with implant, autologous reconstruction using pedicle flap, autologous tissue transfer with muscle, or transfer of skin and muscle with expander or implant recon-

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_68

struction of the breast following mastectomy [9]. Meticulous nursing care and proper patient education in the perioperative period is essential to prevent complications and ensures positive postoperative outcomes.

According to the American Society of Plastic Surgeons, 102,215 breast reconstruction procedures were performed in 2014. Reconstruction with a tissue expander and implant accounted for about 73% of those reconstructive procedures. Reconstruction using a tissue expander with implant is the most common breast reconstructive option and offers the shortest surgical time with the easiest recovery compared to autologous intervention [9]. This approach requires two separate surgical procedures. The advantages of this method are simple operation, no morbidity at distant donor site, no additional scars, reduced operating time, and faster postoperative recovery [10]. The expander can be filled with sterile saline at the time of surgery, or can be filled on an outpatient basis when adequate skin healing has occurred, typically beginning 10–14 days after mastectomy. The number of expansion visits is variable and depends on the amount of fluid instilled at time of surgery, the amount of fluid the woman can tolerate at expansion, and the final volume desired [9]. Although this type of procedure is one of the most common reconstructive options, patients are often not fully aware of the two-step process. It is important to reinforce the need for a second procedure to complete reconstruction. After tissue expanders are inserted, an MRI cannot be done until the temporary expander is removed [9].

The objective of postmastectomy reconstructive surgery is to restore the appearance of a natural breast mound. Limitations of alloplastic (implant) breast reconstruction include a generally more rounded and less ptotic breast mound, which consequently requires a contralateral breast procedure for symmetry [11]. In autologous breast reconstruction, the patient's own available tissue is utilized to rebuild the breast, thereby providing a more natural shape, a softer consistency that mimics that of a natural breast, and a long-lasting aesthetic result [12].

Tissue flap reconstruction describes the removal of skin, fat, muscle, and blood vessels from one area of the body for the reconstruction of another [13]. Autologous breast flaps can be designed as pedicled or free flaps. In a pedicled flap, the tissue remains attached to its original blood supply as it is rotated, tunneled under the skin, and reattached to vessels in the chest wall. A free tissue transfer describes a tissue flap that is completely severed from its blood supply. Circulation is then restored when the blood vessels are reconnected to vessels in the chest wall by microsurgery [13]. There are various flap-based reconstruction types and the size of the patient's natural breast, her desired breast size, her lifestyle (i.e., involvement in sports), her medical/surgical history, her desire for unilateral versus bilateral breast reconstruction, the timing of cancer-related treatment, and the quantity and quality of donor tissue will all be taken into consideration by the plastic surgeon during the consultation [14]. Some surgeons will require magnetic resonance or computed tomographic angiography for preoperative planning to determine if the perforators are adequate for reconstruction using a deep inferior epigastric perforators (DIEP) flap.

In 1982 Hartrampf et al. introduced the pedicled transverse rectus abdominis muscle (TRAM) flap as an option for breast reconstruction [11, 15]. The TRAM flap's greater ability to achieve a more natural-looking breast without necessitating an implant and secondary aesthetic improvements in the donor site helped to make it a popular choice among plastic surgeons [11, 15]. Pedicled flaps continue to be the preferred flaps in community medical centers without access to intensive perioperative monitoring and/or highly specialized equipment required for microsurgery [11].

68.3 Preoperative Teaching

Prior to surgery, the nurse will review general preoperative teaching with the patient. At most institutions, patients will be instructed to shower with an antibacterial soap. Hibiclens (chlorhexidine), the agent used at our institution, is a topical skin cleanser that is used to clean the skin to prevent infections that may be caused by surgery, injection, or skin injury. Patients are instructed to purchase this at any local pharmacy and to use it the night before surgery and the morning of surgery. In areas with limited resources, the use of a generic antibacterial soap (e.g., Dial) may be an option. A clinical study performed by Rao et al. [16] suggests that a preoperative decolonization that includes mupirocin and chlorhexidine bathing is a safe way to significantly reduce *S. aureus* surgical site infections in patients undergoing total joint arthroplasty.

68.4 Supportive Bra

It is important to remind patients to bring a good supportive bra, such as a sports bra, to wear after breast-conserving surgery. If patients are having an axillary node dissection, a surgical bra will be provided to accommodate the drains. During the first 2 weeks, patients are encouraged to wear this bra both day and night to minimize any movement that could cause pain. Laura et al. [17] have undertaken a randomized controlled study to compare a breast binder with a bra postoperatively for patients undergoing lumpectomies and total mastectomies. There is good evidence from this study that postoperative discomfort can be decreased by using a well-fitting bra rather than by using the traditional breast

binder. It has been found that a well-fitted cotton bra is cooler, less irritating, and generally more comfortable both in the first 24 h after breast surgery as well as beyond. Most women also found it to be more easily applied and more attractive.

Those patients undergoing breast reconstruction with tissue expander or implant and following major oncoplastic procedures will be fitted for a bra in the operating room. The bra should be worn at all times for the first 10–14 days for compression in the postoperative period. The bra will accommodate the drains in this case as well. The surgeon will decide if a bra is to be used following nipple-sparing mastectomy. Blood flow to the nipple could be compromised in this case, so it may be avoided.

Patients undergoing autologous tissue transfer are advised not to wear any clothing items that could put pressure on the flap and therefore occlude perfusion. In most flap-based reconstructions, patients are prohibited from wearing a bra for the first 2–4 weeks after surgery.

68.5 Postoperative Considerations

68.5.1 Pain/Arm Sensations

Patients often tolerate breast surgery quite well and have minimal pain during the postoperative period. This is particularly true of less invasive procedures such as BCT with sentinel lymph node biopsy (SLNB). Medications such as hydrocodone bitartrate with acetaminophen (Norco®) often work well in the immediate postoperative period. Patients having more invasive procedures, such as axillary lymph node dissection (ALND) or mastectomy with immediate breast reconstruction, may have considerably more pain and may require stronger narcotics in addition to nonsteroidal anti-inflammatory drugs (NSAIDS). One of the most common complaints patients will describe postoperatively is soreness and numbness to the axilla. These sensations generally result from injury to the intercostal-brachial nerve. They may also experience sensory changes in the inner aspect of the upper arm, breast, or chest wall. Common sensations also include tenderness, tightness, pulling, twinges, and hypersensitivity. These sensations usually persist for several months and then begin to diminish. Baron et al. [18] conducted a study to evaluate the prevalence, severity, and level of distress of 18 sensations at baseline (3–15 days) and 5 years after breast cancer surgery and compared sensations after SLNB with those after SLNB plus immediate or delayed ALND. They concluded that the prevalence, severity, and level of distress of sensations were lower after SLNB compared with ALND, but that some morbidity existed after SLNB. Certain sensations remained highly prevalent in both groups for up to 5 years, including tenderness and twinges after SLNB and tightness and numbness after ALND. It is important to properly educate patients prior to surgery on what to expect postoperatively in order to decrease patient anxiety and manage patient expectations. Furthermore, informing the patient preoperatively that some of these sensations may not be controlled with pain medication, particularly the sensation related to transection or injury to the intercostal-brachial nerve, is important. For those patients undergoing reconstruction, the expanders are filled by injecting a self-sealing magnetic port that is under the skin. It is common for women to report tightness and fullness following a tissue expansion. This is treated with over-the-counter analgesics, such as acetaminophen or ibuprofen, and warm showers and by the performance of range-of-motion exercises. Symptoms often improve 48–72 h after expansion.

68.5.2 Monitoring Tissue Perfusion with Autologous Reconstruction

Operative time can vary from 4 to 10 h depending on the type of flap, whether the flap is unilateral or bilateral, and the complexity of the patient's anatomy. Once the surgery is complete, the patient will be transferred to an intensive care unit where close monitoring of flap perfusion can be performed. Pedicled and free tissue flaps will have different requirements for observation. Flaps may be monitored every 30–60 min while in the intensive care unit.

Clinical monitoring of a flap includes assessment of the skin for appropriate color, turgor, capillary refill, pinprick, and temperature. In addition to clinical monitoring, the surgeon may utilize certain technologies, such as Doppler ultrasonography or surface temperature probes, to monitor flap perfusion. In a review of microvascular complications over 11 years, Bui et al. found that most breast microvascular complications occurred within 48 h of surgery; they therefore recommend inpatient monitoring for 3–4 days [19].

The free flap survival rate is quoted to be about 95–99% [20]. Complications leading to flap failure include thrombosis, bleeding, hematoma, and seroma formation. Cervenka et al. report that approximately 17% of free flaps will experience some form of vascular compromise with salvage rates at 70–80% [20]. Decreased perfusion must be reported to the surgeon immediately, as it may indicate a compressed blood vessel or clot formation and will require urgent re-exploration for possible salvage [20, 21]. If early clinical detection of decreased perfusion is delayed, the likelihood for potential salvage decreases. Flap failure can be a physically and emotionally devastating setback for the patient. Patients with failed flaps may require hospitalization, additional surgeries to rebuild a breast mound, and longer

recovery. Flap failure can also delay chemotherapy and radiation impacting the treatment goals. The study by Haddock et al. of 26 microvascular centers found that in 90.9%, the nursing staff were primarily responsible for monitoring the flap [1], thus highlighting the critical role nurses play in the immediate postoperative period.

Upon discharge, patients with visible skin islands are educated to observe the flap for changes in temperature, color, and size. They must call the surgeon and present for evaluation if the flap or skin paddle feel abnormally cool to touch, if they turn bluish, or if swelling is noted.

68.5.3 Other Postoperative Considerations for Autologous Reconstruction

Motakef et al. [22] performed a systematic review to guide the management of patients undergoing microsurgical free tissue transfer. Their recommendations include maintaining fluid balance and hydration, as this ensures adequate blood flow and oxygen delivery to the transferred tissue. Nurses administer intravascular fluids as ordered until the patient is able to take fluids orally [13]. Care must be taken to manage patient oral intake and urinary output. Oral intake must be advanced slowly to prevent nausea and vomiting. Severe vomiting can cause wound dehiscence [13] and can strain the anastomosis made. Lastly, patients may be prescribed an anticoagulation regime to prevent anastomotic thrombosis. Motakef et al. [22] recommend either aspirin 325 mg orally or heparin 5000 IU subcutaneous daily. Nurses caring for a microvascular patient should be aware of the anticoagulation protocols in their hospital so that they may best be able to anticipate patient needs.

68.5.4 Drain Care

Patients are familiarized with the drain process during their consent appointment, but patients are often still uncomfortable and will need reeducating at time of discharge. It is important for the nursing staff to show a sample of the drain to both patient and care providers, so they can familiarize themselves with the drain process. Educational handouts and/or video links should be provided ahead of time to help decrease the level of anxiety and manage expectations regarding the drain process.

At time of breast reconstruction, drains are placed to collect fluid under the skin for 1–2 weeks. For patients undergoing autologous reconstruction, drains are also placed at the donor sites, such as the abdomen. Stripping the drains is reviewed to maintain patency and prevent obstruction of the drains. After the drains are removed, the patient should be educated on monitoring for seroma formation.

68.5.5 Seroma

A seroma is a serous fluid collection that may occur after breast cancer surgery. It may develop under the skin flaps of a mastectomy or in the axillary free space after axillary node dissection. Seromas are often noted to be more of an inconvenience rather than a postoperative complication; however, seromas that form near a tissue expander or implant can cause infection if left untreated. They can be uncomfortable for the patient, and oftentimes patients will have to make multiple postoperative clinic appointments to have the seroma evacuated. This is done using a percutaneous needle to aspirate the fluid.

There have been several methods used to address seromas, such as mechanical pressure, use of fibrin sealant, restriction of shoulder movement, and use of drainage devices. Pogson et al. [23] conducted a systemic review of these methods and found that none provided a solution to the problem. Conversely, Kontos et al. [24] concluded that pressure dressings are an effective, cheap, and easy-to-apply means of reducing the time with drains in situ after MRM, the number of patients developing seromas, and the number of seromas aspirated. Patients should be educated on the signs and symptoms of a seroma and when to report findings. This will decrease patient anxiety levels and help facilitate the postoperative recovery phase.

68.5.6 Surgical Site Assessment and Monitoring for Cellulitis Post Reconstruction

After breast-conserving surgery, the surgeon will apply Steri-Strips and a transparent impermeable dressing, such as an Opsite™ or a Tegaderm™. Patients are informed that showering is allowed after the first postoperative day. We advise patients to remove the clear dressing after 72–96 h and to leave the Steri-Strips in place until the post-op appointment. It is important to stress to patients that showering with soap and water is beneficial to the healing process. Often, patients are reluctant to touch the incision or apply water to the area. Postoperatively, there is a loss of sensation in part of the breast in patient undergoing BCT and in the totality of the skin overlying the tissue expander. To avoid skin burns, the patient should test any heat source (e.g., hot water, warm compresses, etc.) on a skin surface with intact sensation prior to applying it to the operative site.

Periprosthetic infection following breast reconstruction using tissue expanders poses a significant problem and complicates the course of postoperative recovery [25]. The repercussions of cellulitis are widespread. Infection can delay adjuvant treatment, require implant removal, and have emotional and psychological effects on the patient. There

also may be a need for additional surgical procedures that require hospital admissions and thereby increase costs. Infection rates for the surgical treatment of breast cancer are documented between 3% and 15% [26].

Involvement of the nursing team is essential to ongoing education and support for the patient and her family. The nurse or advanced practice nurses must provide personalized care that accounts for individual differences, needs, and intended outcomes [9]. The importance of monitoring incisions for any changes or signs of infection is essential in proper postoperative care. When the initial surgical dressing is removed postoperatively, the nurse should assist the patient in looking at the incisions for emotional support, as well as to begin the education process of incision care and daily assessment. Teaching women to immediately report signs and symptoms of infection, such as fever, chills, malaise, erythema, induration, or incisional separation, can allow for early detection and treatment of infection. In addition, nurses must provide proper aseptic technique and skin preparation when performing expansions to prevent infection. Repeat visits for ongoing expansions allow the nurse to develop a relationship with the patient and ample time to provide patient education. Ongoing education provides the patient with the tools necessary to play an active role in the recovery and prevention of complications.

Specific risk factors place some women at higher risk for developing complications postoperatively. McCarthy et al. found that smoking, obesity, hypertension, and age >65 years were among these risk factors following postmastectomy tissue expander/implant reconstruction [27].

Jones et al. found that the use of preoperative prophylactic antibiotics significantly reduces the risk of surgical site infections [26]. Patients can be placed on antibiotics for a short period postoperatively to decrease the risk of infection. The nurse must educate the patient about antibiotic administration, possible adverse reactions, and side effects of antibiotic therapy.

68.5.7 Lymphedema

Lymphedema remains a potential side effect from breast cancer surgery despite the increase in use of SLNB procedures. Signs and symptoms of lymphedema may include heaviness, tightness, or swelling of the breast, arm, hand, or fingers. Patients who undergo SLNB have a 0–7% risk of developing lymphedema compared to patients who undergo an axillary node dissection, who have a 15–25% risk of developing lymphedema [28]. In a meta-analysis study, Kell et al. [29] compared the short- and long-term morbidities associated with axillary node dissection vs sentinel lymph node biopsy. They found that patients who undergo SLNB are significantly less likely to develop postoperative morbidity relative to ALND (Table 68.1) [29, 30]. Higher body weight, higher BMI, infection, and injury to the ipsilateral side are significant risk factors for developing lymphedema. It is important to educate the patient on the signs and symptoms of lymphedema along with self-care measures. In 2011 Armer et al. performed a study to examine patients' perceptions of limitations related to self-care measures to reduce lymphedema risk following breast cancer surgery [31]. Their findings indicated a need for nurses to be cognizant of the patient's needs for personal support to engage in result-achieving self-care. This personal support includes affirmation, comfort, tangible aid, empathy, clarification, and the provision of information. Education alone on self-care measures to reduce the risk of lymphedema is not likely to be sufficient for all patients. Patients should be assessed on their knowledge of self-care measures, which can include manual lymphatic drainage and deep breathing, and on the importance of exercise, healthy diet, and proper skin care. A study performed by Lee et al. [32] concluded that some women receive conflicting information about the extent to which they may use their arm after surgery, with some advice recommending women to avoid strenuous arm activity and other advice encouraging the opposite. This can be very confusing to the patient and cause frustration. Healthcare professionals should be educating patients on the newest evidence so that patients can receive accurate and consistent information regarding arm use after surgery.

Table 68.1 Short- and long-term morbidities associated with axillary node dissection vs sentinel lymph node biopsy

	N	SLNB	ALND	OR (95%CI)	*P*
Node positive	8928	27.6%	28.8%	1.0 (0.86–1.17)	0.916
Wound infection	2781	Low	Higher	0.58 (0.42–0.8)	0.0011
Seroma	2125	Low	Higher	0.40 (0.31–0.51)	0.0071
Arm swelling	2154	70% lower in SLNB		0.30 (0.14–0.66)	0.0028
Numbness	3265	Low	Higher	0.25 (0.1–0.59)	0.0018

Note: NSABP B-32 reports the superiority of SLNB compared to ALND relative to postsurgical morbidity outcomes over a 3-year follow-up period

SLNB sentinel lymph node biopsy, *ALND* axillary lymph node dissection, *OR* odds ratio, *CI* confidence interval

68.5.8 Cording

Cording, also known as axillary web syndrome (AWS), is a complication that can occur after breast surgery. Cords are rope-like structures that develop mainly under the axilla, but that can extend to involve the medial aspect of the ipsilateral arm down to the antecubital fossa [33]. The incidence of cording following breast cancer surgery is reported to range from 6% to 72% [34, 35]. Lymphatic cording can be associated with

pain and limitation of shoulder movement. In a study by Moskovitz et al. [35], 74% of patients with AWS had shoulder abduction restricted to less than 90°. Treatment for cording is typically self-limiting; however, interventions, including range-of-motion exercises, nonsteroidal medications, and heat-compressive therapy, have been suggested [36]. It is important to educate patients on the signs and symptoms of AWS to prevent delayed range of motion and possible frozen shoulder. Early intervention with effective treatment is vital to long-term mobility.

68.6 Physical Activity

68.6.1 BCT/Oncoplasty

It is recommended that patients abstain from applying heavy pressure over the operated breast and refrain from physical activities that result in heavy bouncing of the breast (such as jogging and heavy cardiovascular exercises) for a period of 6–8 weeks so as not to disrupt the repair [37]. Wearing a sports bra during light activities is recommended to help alleviate pain and decrease swelling. Other forms of physical activities are strongly encouraged, particularly those related to rehabilitating the shoulder motion of the operated side. Arm stretches with full shoulder motion, yoga, Pilates, and weight lifting are all encouraged, provided no pressure is applied to the operated breast to avoid disruption of the repair of the breast defect.

68.6.2 Reconstruction

Following breast reconstruction, patients are given surgeon-specific guidelines regarding physical activity. For at least 6 weeks following surgery, patients should avoid lifting objects more than five to ten pounds and vigorous exercise. Activities involving pushing or pulling should be limited. The surgeon will recommend range-of-motion exercises, which can begin in the hospital and should continue after discharge [13]. In alloplastic-based reconstruction, these exercises are started on post-op day 1, but may be limited to 90° until the final postoperative drain is removed. In autologous reconstruction, these exercises may not be initiated until 2 weeks after surgery to avoid straining the anastomotic connections made. Range-of-motion exercises should be started once it is deemed safe to do so. If range of motion is hindered and there is limited improvement with these exercises, patients can be referred to physical therapy. Nurses should assess range of motion at each visit and educate the patient to stretch the affected arm slowly, to the point of discomfort but not pain. Each position should be held as long as possible [13]. Wearing clothing that opens in the front, such as button-up shirts that are easier to put on, is recommended while range of motion is limited in the immediate postoperative period. Clothing choices can also improve self-esteem during the expansion process. Loose-fitting, printed blouses, tops, sweaters, and scarves can mask asymmetry in unilateral reconstruction or until optimal size is achieved. Patients are instructed to avoid submerging incisions in bath, pool, or jacuzzi environments following surgery to avoid infection. Patients are sometimes asked to avoid showering above the waist until Jackson Pratt drains are removed. In addition, it is common to have decreased sensation following mastectomy; therefore, the importance of avoiding hot packs or cold compresses must be communicated to avoid skin breakdown and burns on mastectomy skin flaps.

Patients are encouraged to ambulate after surgery to prevent other complications such as blood cloths or pneumonia. In autologous-based reconstruction, patients are advised to avoid activities that might stretch or strain the donor sites. In abdominal-based free flaps, for example, patients may be asked to lean slightly forward to decrease tension over the abdominal incision.

68.7 Conclusion

The diagnosis of cancer is life altering and can be devastating for patients. Patients are often confronted with a variety of emotions, such as anger, denial, fear, and hopelessness. Nurses are usually the first members of the healthcare team who patients will see following diagnosis. A majority of patients require surgical intervention, which is usually scheduled within a few weeks. During their consultation, patients are asked to process and comprehend a great deal of information in a short amount of time. They are then expected to make decisions regarding their care with that information just provided.

Patients often require the expertise of different specialties. Some patients will meet with a breast surgeon, a plastic and reconstruction surgeon, a medical oncologist, and a radiation oncologist during the course of their treatment. As a result, nurses and the other specialties must collaborate, and each plays a critical role in helping patients understand all of the information. Moreover, navigating through different specialties and deciding on treatment options can be an overwhelming and frightening experience. Nurses are entrusted with the responsibility to educate, advocate, and become resources for patients throughout the continuum of their care. Open and ongoing patient-nurse communication is facilitated through telephone conversations, follow-up visits, and the use of electronic communication. It is essential in this context for nurses to provide patients with adequate information, both preoperatively and postoperatively, to keep

patients well informed and enable patients to become their own health advocates.

Patients should be encouraged to have family members or care providers present during their consultations. Most patients are unable to comprehend all the information that is provided during these consultations, and having family members or care providers present can give patients additional information-processing support and can help patients by their asking of appropriate questions on a patient's behalf. Providing patients and care providers with set expectations can help to decrease the anxiety and fear that accompanies a diagnosis of breast cancer.

Cancer has no boundaries; it affects people at any point in their lives. Along with our colleagues, we hope to ease the journey for patients and family members in this difficult situation by providing sufficient education and continued support, which, in turn, will lead to better outcomes and an improved patient experience.

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Aesthetic and Quality of Life After Breast Reconstruction

69

Gabriela dos Santos and Cicero Urban

69.1 Introduction

There are many gaps concerning satisfaction and quality of life of patients undergoing breast cancer treatment. Some authors report high levels of satisfaction with their outcomes, although the findings are limited by the use of different methods and small series [1]. Patient satisfaction is the result of the care and attention given as well as some subjective opinions. The levels of satisfaction also depend on other factors, such as socioeconomic factors, clinical conditions, and the treatment as a whole, including adjuvant therapy, preservation of the nipple and areola complex (NAC), and contralateral symmetrization [1].

The development of oncoplastic surgery is one of the greatest achievements for the treatment of breast cancer, where better aesthetic outcomes, less psychological damage, and better quality of life are expected. By use of reductive mammaplasty techniques, large areas can be resected for the treatment of large tumors, preserving the breast and keeping the symmetry with the contralateral breast, therefore resulting in satisfactory oncological and aesthetic results.

Subcutaneous mastectomy, preserving or not preserving the NAC and preserving the inframammary crease, is also an excellent option, as it can produce aesthetic outcomes that are better than those achieved with partial resections for some specific cases. When radical mastectomy is indicated, it is important to consider the following procedures: immediate reconstruction with a myocutaneous flap from the abdominal wall (transverse rectus abdominis myocutaneous flap or TRAM flap) or from the latissimus dorsi, or even implants, all of which help improve the physical and psychological well-being of the patient, having a positive impact on quality of life.

The aim of this chapter is to analyze the criteria for aesthetic and quality-of-life evaluation after breast reconstruction.

69.2 Aesthetic and Oncological Results

Randomized trials have shown that conservative breast surgery achieves the same oncological results as for mastectomy in small tumors [2, 3]. Rietjens et al. [4] demonstrated a rate of around 8% of exiguous margins or compromised ones in patients with T1–T2 tumors undergoing conservative surgery with oncoplastic techniques, a lower percentage compared with the 10% for patients with T1 tumors from the NSABP B-06 study. Therefore by using oncoplastic techniques it is possible to achieve wider margins and lower risk of of compromised margins, which means better control of local recurrence.

A satisfactory oncological result is the most important aim of conservative surgery. Indications for conservative surgery have been reviewed and have included patients with large tumors, who would undergo mastectomy in the past. Nowadays, such patients can undergo conservative procedures using concomitant plastic remodeling techniques and contralateral symmetrization.

Immediate breast reconstruction after mastectomy, preserving or not preserving the NAC, using implants or myocutaneous flaps, associated with surgery of the contralateral breast contributes to better outcomes and patient satisfaction as to her body image, preserving the woman's self-esteem.

Among other things, the aesthetic outcome depends on the size and shape of the breasts, tumor location, and the experience of the person who performs the evaluation. The existing scales do not cover all of these individualized aspects or the patient's opinion (Table 69.1).

The panel evaluation method (PEM) remains the most common and accepted approach to subjective evaluation of cosmetic results [5, 6]. Vrieling et al. suggest that a panel

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_69

Table 69.1 Examples of methods for the evaluation of aesthetic results

Methods	Parameters used	Scores	Conclusion
Harris's scale [9, 38]	Fibrosis, breast retractions, changes in the skin and the matchline effect	0 = none 1 = slight 2 = moderate 3 = severe	Excellent, good, fair, or poor
Breast Cancer Conservative Treatment. cosmetic results (BCCT.core) [12, 13]	Asymmetry, skin color change, and scar visibility		Excellent, good, fair, or poor
Breast Analyzing Tool (BAT) [11, 13]	Asymmetry		Good, fair, and poor
Garbay et al. [20]	Volume and shape of breasts, symmetry, position of the sulcus and scar	Ranging from 0 (worst result) to 10 (best result)	
Calabrese et al. [21]	Shape, volume, and symmetry	Ranging from 1 (worst result) to 3 (best result)	8–9 = excellent 6–7 = good 4–5 = fair 3 or below = poor

should consist of at least five members considering that significant variation between observers is common, including both professionals and nonprofessionals from diverse backgrounds [7]. On the other hand, Haloua et al. suggest that it may contain only three observers [8].

In 1979, Harris et al. [9] evaluated the aesthetic outcomes considering fibrosis, breast retractions, changes in the skin, and the matchline effect. The scoring system was as follows: score 0 for none, 1 for slight, 2 for moderate, and 3 for severe. In addition, other classifications were also used: scar unapparent (0), scar apparent (1), and major tissue loss (2). As a whole, the aesthetic results were classified as 1 for excellent (treated breast nearly identical to untreated breast), 2 for good (treated breast slightly different from untreated breast), 3 for fair (treated breast clearly identical to untreated breast but not seriously distorted), and 4 for poor (treated breast seriously distorted).

Two objective methods were described to assess aesthetic results in breast conservative surgery, Breast Cancer Conservative Treatment. cosmetic results (BCCT.core) [10] and the Breast Analyzing Tool (BAT) [11]. Both methods evaluate photographic records of the patients. BCCT.core analyzes parameters related to asymmetry, color change, and scar, whereas BAT focuses only on asymmetry.

The BCCT.core program automatically evaluates several indices used for the aesthetic evaluation of breast cancer conservative treatment (asymmetry, skin color change, and scar visibility). BCCT.core then uses artificial intelligence techniques to translate these measures into an overall objective classification of aesthetic results reported to the user as excellent, good, fair, or poor [12, 13]. A former analysis showed that the BCCT.core aesthetic status agreed fairly with the patient perspective, measured by the breast conservation surgery treatment outcome scale (BCTOS) aesthetic status [14–16].

Haloua et al. studied the strengths and weaknesses of the BCCT.core software with a ten-member panel from various backgrounds, assessing patients after breast conserving therapy [8]. Mean overall BCCT.core score and mean overall panel score substantially agreed (weighted kappa: 0.68). By contrast, analysis of the evaluation of scar tissue revealed large discrepancies between the BCCT.core software and the panel [8]. Analysis of subgroups formed from different combinations of the panel members still showed substantial agreement with the BCCT.core software (range 0.64–0.69), despite personal background [8]. Therefore, although the analysis of scar tissue by the software shows room for improvement, the BCCT.core represents a valid and efficient alternative to panel evaluation [8].

Two other studies, recently published, evaluated aesthetic results in oncoplastic surgery and in immediate breast reconstruction with implants, comparing a specific software program with a specialist's opinion and the patient's opinion. There was no agreement between them [17]. In the first series, this piece of software was applied for the first time in OP. Concordance between the specialists and the software was considered poor ($K = 0.12$). This result, in part, was due to the use of Garbay's scale instead of Harris's scale. Although Harris's scale is a good methodology for aesthetic evaluation in breast conserving surgery, in this study Garbay's scale seemed to be more appropriate, since it takes more account on some specific details in relation to symmetry; this could be better for evaluation in OP. Another important point that could explain this result is that the software evaluation analyzed the breasts in a single position, whereas specialists analyzed in three positions [18]. In the second series, in which the patient underwent immediate breast reconstruction with implants, there was a significant difference between the aesthetic results evaluated by patients and those evaluated by specialists and software ($p < 0.001$). In contrast to that, this difference was not observed between software and specialist's evaluation [19].

The BAT program uses well-defined landmarks (jugulomamillary distance and distances from the nipples to the edge of the breast) and calculates the difference between left and right breasts. This difference in length is multiplied by the

difference in surface area and is noted as a percent difference and as a difference factor. The values obtained can be converted to a simplified three-point Harris's scale (good, fair, poor) [11, 13].

The BCTOS aesthetic status, constructed by Stanton et al. [16], contains 22 items. It was designed to assess women's subjective evaluation of both the aesthetic and the functional outcome after breast cancer treatment. Patients are instructed to rate each item of the BCTOS questionnaire on a four-point scale evaluating the differences between the treated and the untreated breast (1 for no difference to 4 for large difference). The English version produced a coherent factor structure on 18 items and 3 internally consistent scales, which are defined as functional status (e.g., shoulder and arm movement, stiffness or pain), cosmetic status (e.g., breast size and texture, breast shape, scar tissue), and breast-specific pain (e.g., breast pain, breast tenderness, and sensitivity) [16].The value of the score of each scale is the mean of the ratings over all the items belonging to this scale [15].

Another method described to evaluate the aesthetic results and modified by Garbay et al. [20] considers the volume and shape of the breast, symmetry, the position of the inframammary crease, and scars (Table 69.2). This instrument seems to be the most complete one from the objective point of view for the evaluation of aesthetic results by experts.

Another scale reported in the literature, developed by Calabrese et al. [21], uses a scoring system that ranges from 1 to 3 and the values of parameters that can be easily identified and quantified by the researcher: shape, volume, and symmetry of the operated on breasts (Table 69.3). A sum of the scores of the three parameters between 8 and 9 was considered excellent, between 6 and 7 was good, between 4 and 5 was fair, and 3 or below was poor. This scoring was reduced by one point every time the following elements were identified: visible scar, NAC badly placed, and visible cutaneous effects from radiotherapy.

Table 69.2 Scale modified by Garbay et al. [20]

Subscale	Category 0	Category 1	Category 2
Volume of breast	Marked discrepancy relative to contralateral side	Mild discrepancy relative to contralateral side	Symmetrical volume
Shape of breast	Marked contour deformity or shape asymmetry	Mild contour deformity or shape asymmetry	Natural or symmetrical contour
Placement of breast	Marked displacement	Mild displacement	Symmetrical and aesthetic placement
Inframammary fold	Poorly defined/ not identified	Defined, but with asymmetry	Defined and symmetrical
Breast scars	Poor (hypertrophy, contracture)	Fair (wide scars, poor color match, but without hypertrophy, contracture)	Good (thin scars, good color match)

Table 69.3 Scale for evaluation of aesthetic results

Parameters	Score		
Shape	1	2	3
Volume	1	2	3
Symmetry	1	2	3
Rough and visible scar	−1		
NAC badly placed	−1		
Cutaneous effects from radiotherapy	−1		

Source: Calabrese et al. [21]

BREAST-Q, a patient-reported outcome instrument, was developed with strict adherence to recommended international guidelines to address the lack of instruments for breast surgery patients [22]. It has been translated into 30 languages, and it quantifies the impact of cosmetic and reconstructive breast surgery, pre- and postoperatively, on health-related quality of life (including physical, psychosocial, and sexual well-being) and patient satisfaction (including satisfaction with breasts, outcome, and care) [23].

There are currently four modules (breast reduction, augmentation, reconstruction, and mastectomy without reconstruction), each of which includes a core of independent scales assessing six domains (satisfaction with breasts, satisfaction with overall outcome, psychosocial well-being, sexual well-being, physical well-being, and satisfaction with care). For each item, the use of response categories scored with successive integer scores (e.g., 1 for very dissatisfied to 4 for very satisfied) implies a continuum of increasing satisfaction, from less (very dissatisfied) to more (very satisfied).

Since its inception in 2009, the number of publications incorporating the BREAST-Q has increased each year [23]. From the 49 publications, a total of 22,457 patients completed at least one subdomain of the BREAST-Q. Of these participants, 20,390 patients completed one or more scales from the breast reconstruction module. The breast reconstruction module was utilized in 39 references; the augmentation module was reported in seven references, the reduction module in four, and the mastectomy module in three [23].

69.3 Quality of Life

In 1947, the World Health Organization defined quality of life for the first time as "a state of complete physical, mental and social well-being, not merely the absence of disease or infirmity."

Quality of life is the result of a combination of subjective factors, such as the overall level of satisfaction of an individual with his/her own life, and objective factors, such

as material well-being, good family relations, promptness to undergo cancer treatment, and reliability on the medical care, to sum up, various items that provide one with peace, reliability, confidence, and well-being. Quality of life needs to cover all human needs, concerning their physical, psychological, social, and spiritual aspects.

Quality of life must be considered throughout all phases of the treatment of a cancer patient. In fact, all symptoms and problems intrinsically related to cancer and its treatment may affect the patient, and they include limitations in daily activities and toxicity resulting from chemotherapy. Many patients still experience changes concerning their jobs, social relations, physical capability, and role within the family.

As a whole, the findings demonstrate that physicians tend to underestimate functioning incapability, the severity of symptoms, psychological afflictions, and psychiatric morbidity among their patients [24, 25]. So, the use of questionnaires that evaluate quality of life has been a way to discover the functioning, psychological, and social needs of patients.

In the past decade, the psychosocial impact of cancer has become a central aspect concerning both the care of patients and the research on this disease. Much research focuses on specific aspects of quality of life that were formerly neglected, such as body image and sexuality [26, 27]. However, there are still few data taking into consideration the period of the end of the primary treatment and extended life [27]. Some researches suggest that problems involving sexuality are usual [26, 28–30], but there is also a decline in the quality of life, body image, humor, and family relations [30, 31].

Several instruments have been used to evaluate quality of life, but we have noticed that they are general questionnaires that do not assess the specific changes realized and experienced by patients undergoing breast cancer treatment (Table 69.4). We have realized that there are changes concerning the self-esteem, sexuality, and femininity that are not properly and satisfactorily assessed in the questionnaires already described and validated. These general instruments aim to evaluate, in a global way, important aspects related to quality of life (physical, social, psychological, spiritual), for instance, the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) [32], the World Health Organization Quality of Life (WHOQOL) [33], the European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23) [34], and Functional Assessment of Cancer Therapy-Breast (FACT-B) [35], and during the climacteric the most relevant ones are the Menopause Specific Quality of Life Questionnaire (MENQOL) [36], the Menopause Rating Scale (MRS) [37], and the Women's Health Questionnaire (WHQ) [38]. These questionnaires have proven reliable.

Recently a systematic review evaluated manuscripts which contained information regarding either the development

Table 69.4 Examples of instruments for the evaluation of quality of life

Instruments	
SF-36 [40, 42]	Consisting of 11 questions, in a total of 36 items, divided in eight components: functioning capacity (10 items), physical aspects (4 items), pain (2 items), overall health condition (5 items), vitality (4 items), emotional aspects (3 items), mental health (5 items), social aspects (2 items), and a question that compares the current health condition with that of 1 year before
WHOQOL-100 [33]	Comprising 24 facets scored in six domains: physical health, psychological health, levels of independence, social relationships, environment, and spirituality, religion, and personal belief
EORTC QLQ-C30 [34]	The domains of the functional scale include overall quality of life, physical functioning, role/performance, cognitive functioning, emotional functioning, and social functioning The three domains of the symptom scale are fatigue, pain, and nausea/vomit And the six simple items are dyspnea, insomnia, loss of appetite, constipation, diarrhea, and financial problems
EORTC QLQ BR-23 [34]	Consisting of 23 questions, incorporated to multi-items to measure side effects of chemotherapy, symptoms related to the arm and the breast, body image, and sexuality. There are simple items to expose the sexual satisfaction, disturbance due to hair loss and future perspectives
EORTC trial 10,801 [43]	10 questions, related to body image, fear of recurrence, satisfaction concerning the treatment and the aesthetic results
FACT-B [35]	Includes physical, social, emotional, functional subscales plus the breast cancer subscale (BCS)
Rosenberg self-esteem scale [44, 45]	10 questions, with four options for each answer: strongly agree, agree, disagree, or strongly disagree
STAI (State-Trait Anxiety Inventory) [42]	20-item scales for measuring state anxiety and trait anxiety
CES-D (Center for Epidemiologic Studies Depression scale) [42]	20-item self-report scale designed to measure the presence and degree of depressive symptoms
RAND 36-Item Health Survey 1.0 [41, 46]	Divided in eight dimensions: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, general mental health, social functioning, vitality (energy/fatigue), and general health perceptions. In addition, it includes a single item providing an indication of perceived changes in health

process or the metric properties of health-related quality-of-life instruments used among breast cancer patients. Each instrument was evaluated independently by two researchers, and occasionally a third one, using the Evaluating Measures of Patient-Reported Outcomes (EMPRO) tool. An overall score and seven attribute-specific EMPRO scores were calculated (range 0–100, worst to best): concept and measurement model, reliability, validity, responsiveness, interpretability, burden, and alternative forms. The FACT-B scored the highest on overall in our EMPRO evaluation of instruments measuring health-related quality of life among breast cancer patients. However, depending on the purpose of the study, several instruments (EORTC BR-23, IBCSG, SF-36, and WHOQOL BREF) have shown good performance in some of the specific individual dimensions included in the EMPRO [39].

SF-36 is a multidimensional questionnaire that consists of 11 questions, with a total number of 36 items, divided into eight components: functioning capacity (ten items), physical aspects (four items), pain (two items), overall health condition (five items), vitality (four items), emotional aspects (three items), mental health (five items), social aspects (two items), and a question that compares the current health condition with that of 1 year before. Each component corresponds to a value that ranges from zero to 100, for which zero represents the worst and 100 the best health condition [40, 41]. Nevertheless, this questionnaire has some limitations, such as not including questions concerning sexuality.

WHOQOL-100 is an instrument that covers 24 facets, assessed by 96 questions, and one general health and overall quality of life facet. Each facet is measured with four items with a five-point Likert scale. Twenty-four facets were initially scored in six domains of overall quality of life: physical health, psychological health, levels of independence, social relationships, environment, and spirituality, religion, and personal beliefs [33]. Nowadays, it is well accepted to convert these 24 facets into four domains as described by the WHOQOL group [40]. High facet scores indicate good quality of life, except for the facets pain and discomfort, negative feelings, and dependence on medication or treatments, which are negatively framed. The timeframe of reference is the previous 2 weeks. The reliability and validity [40] are adequate, and the sensitivity of the instrument is high [42].

EORTC QLQ-C30 and BR-23 is a questionnaire translated and validated in 81 languages, and it is used in over 3000 studies all over the world. QLQ-C30 3.0 is the most recent version, and it must be used in all new studies. It consists of 30 questions that define five functioning scales, three symptom scales, an overall quality of life item, and six simple items. The scales comprise a single question. EORTC QLQ-C30 is supplemented by specific disease modules, for instance, breast (QLQ BR-23), lung, head and neck, esophageal, ovary, gastric, and cervical cancer and multiple myeloma. The domains of the functioning scale are overall quality of life (items 29 and 30), physical functioning (items 1–5), role/performance (items 6 and 7), cognitive functioning (items 20 and 25), emotional functioning (items 21–24), and social functioning (items 26 and 27). The three domains of the symptom scale are fatigue (items 10, 12, and 18), pain (items 9 and 19), and nausea/ vomit (items 14 and 15). The six simple items are dyspnea (item 8), insomnia (item 11), loss of appetite (item 13), constipation (item 16), diarrhea (item 17), and financial difficulty (item 28). Module BR-23 consists of 23 questions incorporated in multi-item scales to measure side effects from chemotherapy (items 31–34 and 36–38), symptoms related to the arms (items 47–49) and the breast (items 50–53), body image (item 39–42), and sexuality (items 44 and 45). There are simple items to evaluate sexual satisfaction (item 46), disturbance due to hair loss (item 35), and future perspectives (item 43) [34].

EORTC Trial 10,801 is a study that evaluated the quality of life of 278 patients, 127 undergoing radical modified mastectomy and 151 undergoing conservative surgery, using a questionnaire with 10 questions concerning body image, fear of recurrence, and satisfaction with both the treatment and the aesthetic results [43]. Although this questionnaire has not been validated yet, it seems to be the most adequate to evaluate the satisfaction level of patients undergoing breast cancer treatment (Table 69.5).

Table 69.5 EORTC trial 10,801: quality of life questionnaire [43]

	All of the time	Most of the time	Some of the time	Little of the time	None of the time
1. I feel self-conscious about my appearance	1	2	3	4	5
2. I am bothered by thoughts about the recurrence of cancer	1	2	3	4	5
3. I feel ashamed of my body	1	2	3	4	5
4. I believe that the difficulties with my illness are over	1	2	3	4	5
5. I feel self-conscious about being seen nude by husband/ partner	1	2	3	4	5
6. I don't feel like myself	1	2	3	4	5
7. I feel uneasy about my future health	1	2	3	4	5
8. I don't feel as if my body belongs to me	1	2	3	4	5
9. If I should have to be treated again, I should like to have the same therapy	1. Certainly 2. Probably 3. Probably not 4. Certainly not				
10. The treated breast resembles the other one	1. Very much 2. Quite a bit 3. A little 4. Not at all				

FACT-B is designed for self-administration by patients with breast disease and has been widely used since 1997. FACT-B consists of FACT-General (FACT-G) plus the breast cancer subscale, which complements the general scale with items specific to quality of life in breast cancer. FACT-G includes physical, social, emotional, and functional subscales. Subjects are required to choose the most suitable answer according to each item of each subscale: "not at all," "a little bit," "somewhat," "quite a bit," and "very much." All subscale items are summed to a total, which is the subscale score. All subscales are scored so that a higher score is correlated with a more favorable quality of life, i.e., the higher the score, the better the quality of life [35].

In the past few decades, some scales have been used to measure the patient's level of satisfaction, such as the Rosenberg Self-Esteem Scale, which is widely accepted among the international scientific community [44, 45], through which the patient evaluates herself. The scale is composed of ten questions, with four options for each answer: strongly agree, agree, disagree, or strongly disagree. The scale produces a score that ranges from 0 (best possible self-esteem) to 30 (worst possible self-esteem) [45] (Table 69.6).

Other scales are also reported in the literature are the State-Trait Anxiety Inventory (STAI) and the Center for Epidemiologic Studies Depression Scale (CES-D).

STAI consists of two 20-item scales for measuring state anxiety and trait anxiety [42]. This scale assesses how people feel at a particular moment in time and has a four-point rating scale ranging from 1 (not at all/almost never) to 4 (very much so/almost always).

CES-D is a 20-item self-report scale designed to measure the presence and degree of depressive symptoms over the past week. The rating scale ranges from 1 (seldom or never) to 4 [(almost) always]. Scores can range from 0 to 60; scores above 16 are suggestive of depressive symptoms [42].

The RAND 36-Item Health Survey version 1.0 is practically identical to SF-36 [41] and evaluates health in eight dimensions: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, general mental health, social functioning, vitality (energy/fatigue), and general health perceptions. In addition, it includes a single item providing an indication of perceived changes in health. The rationale for these dimensions is that the health concepts are most frequently included in widely used health surveys. The items used to measure the scores per dimension were adapted from instruments that have been used for 20–40 years or longer [41]. Subscale scores are represented on a scale from 0 to 100. A high score indicates a good health status. The timeframe for evaluation of functioning is the previous 4 weeks. RAND-36 has good reliability and validity [46].

69.4 Clinical Cases

The aesthetic results were evaluated for three cases (Figs. 69.1, 69.2, and 69.3) using two models: the scale modified by Garbay et al. [13] (Tables 69.7, 69.9, and 69.11 for cases 1, 2, and 3, respectively) and the Calabrese scale (Tables 69.8, 69.10, and 69.12 for cases 1, 2, and 3, respectively).

In case 3, there was a difference in the results using the two instruments, which draws our attention to the difference between the methods and the need for a wider and more uniform scale.

Table 69.6 Rosenberg-EPM self-esteem scale [44, 45]

1. On the whole, I am satisfied with myself
2. At times I think I am no good at all
3. I feel that I have a number of good qualities
4. I am able to do things as well as most other people
5. I feel I do not have much to be proud of
6. I certainly feel useless at times
7. I feel that I'm a person of worth, at least on an equal plane with others
8. I wish I could have more respect for myself
9. All in all, I'm inclined to feel that I am a failure
10. I take a positive attitude toward myself
Choices of answer:
(a) Strongly agree (b) Agree (c) Disagree (d) Strongly disagree
The scale produces a score that ranges from 0 (best possible self-esteem) to 30 (worst possible self-esteem)

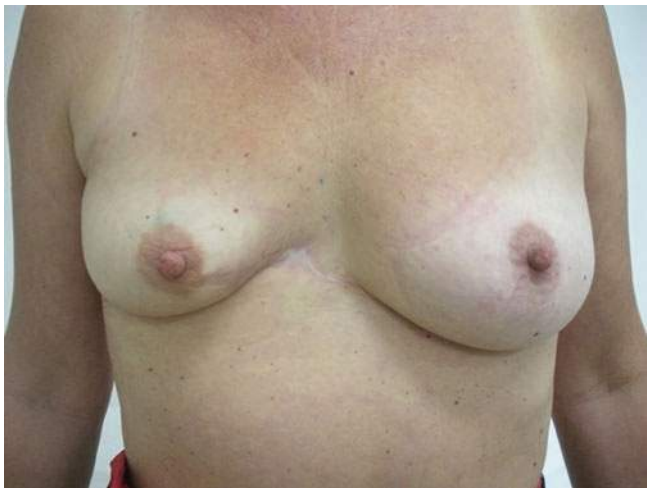

Fig. 69.1 Scales for the evaluation of aesthetic outcomes after breast cancer surgery

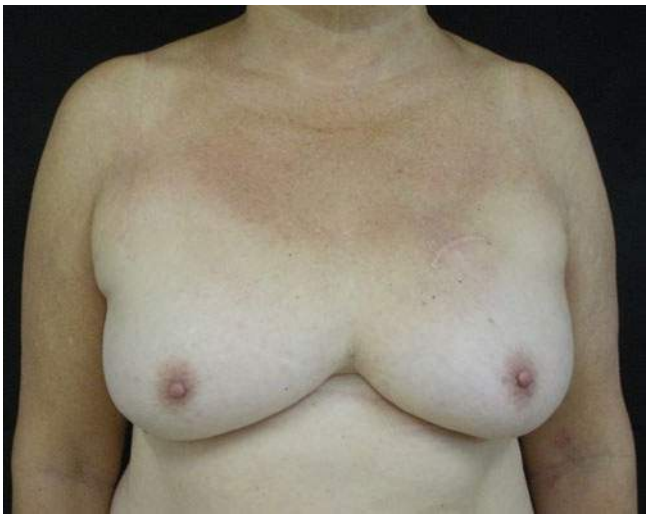

Fig. 69.2 Garbay' scale for evaluation of aesthetic outcome after breast cancer surgery

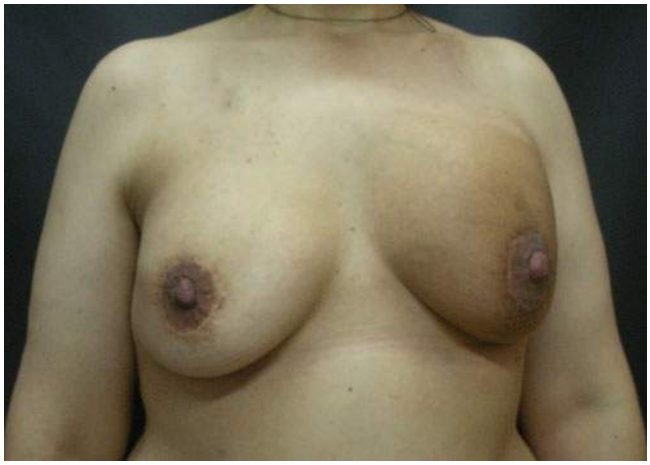

Fig. 69.3 Calabrese' scale for evaluation of aesthetic outcome after breast cancer surgery

Table 69.7 Case 1: scale modified by Garbay et al. [13]

Subscale	Category 0	Category 1	Category 2	Example
Volume of breast	Marked discrepancy relative to contralateral side	Mild discrepancy relative to contralateral side	Symmetrical volume	0
Shape of breast	Marked contour deformity or shape asymmetry	Mild contour deformity or shape asymmetry	Natural or symmetrical contour	0
Placement of breast	Marked displacement	Mild displacement	Symmetrical and aesthetic placement	0
Inframammary fold	Poorly defined/not identified	Defined, but with asymmetry	Defined and symmetrical	1
Breast scars	Poor (hypertrophy, contracture)	Fair (wide scars, poor color match, but without hypertrophy, contracture)	Good (thin scars, good color match)	1
Total score				2
Conclusion				Poor

Table 69.8 Case 1: Calabrese scale [14]

Parameters	Score			Example
Shape	1	2	3	1
Volume	1	2	3	1
Symmetry	1	2	3	1
Rough and visible scar	−1			−1
NAC badly placed	−1			0
Cutaneous effects from radiotherapy	−1			0
Total score				2
Conclusion				Poor

Table 69.9 Case 2: scale modified by Garbay et al. [13]

Subscale	Category 0	Category 1	Category 2	Example
Volume of breast	Marked discrepancy relative to contralateral side	Mild discrepancy relative to contralateral side	Symmetrical volume	2
Shape of breast	Marked contour deformity or shape asymmetry	Mild contour deformity or shape asymmetry	Natural or symmetrical contour	2
Placement of breast	Marked displacement	Mild displacement	Symmetrical and aesthetic placement	2
Inframammary fold	Poorly defined/not identified	Defined, but with asymmetry	Defined and symmetrical	2
Breast scars	Poor (hypertrophy, contracture)	Fair (wide scars, poor color match, but without hypertrophy, contracture)	Good (thin scars, good color match)	1
Total score				9
Conclusion				Excellent

Table 69.10 Case 2: Calabrese scale [14]

Parameters	Score			Example
Shape	1	2	3	1
Volume	1	2	3	1
Symmetry	1	2	3	1
Rough and visible scar	−1			−1
NAC badly placed	−1			0
Cutaneous effects from radiotherapy	−1			0
Total score				9
Conclusion				Excellent

Table 69.11 Case 3: scale modified by Garbay et al. [13]

Subscale	Category 0	Category 1	Category 2	Example
Volume of breast	Marked discrepancy relative to contralateral side	Mild discrepancy relative to contralateral side	Symmetrical volume	1
Shape of breast	Marked contour deformity or shape asymmetry	Mild contour deformity or shape asymmetry	Natural or symmetrical contour	1
Placement of breast	Marked displacement	Mild displacement	Symmetrical and aesthetic placement	1
Inframammary fold	Poorly defined/not identified	Defined, but with asymmetry	Defined and symmetrical	1
Breast scars	Poor (hypertrophy, contracture)	Fair (wide scars, poor color match, but without hypertrophy, contracture)	Good (thin scars, good color match)	1
Total score				5
Conclusion				Fair

Table 69.12 Case 3: Calabrese scale [14]

Parameters	Score			Example
Shape	1	2	3	1
Volume	1	2	3	1
Symmetry	1	2	3	1
Rough and visible scar	−1			−1
NAC badly placed	−1			0
Cutaneous effects from radiotherapy	−1			0
Total score				2
Conclusion				Poor

69.5 Conclusions

To date, the selection of the most valid method to evaluate aesthetic outcome remains challenging.

Future prospective studies should be performed in women submitted to oncoplastic surgery and breast conservative surgery as well as to mastectomy with or without reconstruction to permit comparison of different techniques of breast reconstruction, including TRAM flap, latissimus dorsi flap, free flaps, and breast implant reconstruction [47].

The models described for the evaluation of aesthetic results do not take into consideration the shape of the breasts and the location of the tumor, which are determining factors for the final result. Morbidity, postoperative limitations, and scars in the reconstructions with a TRAM flap, for instance, are not evaluated as well, and they are determining factors for the quality of life of these patients.

Another important aspect that must be highlighted is the importance of the patient's perception of her own body image and satisfaction.

The subjective and objective methods are complementary, and it is important to consider patient's opinion as well. Objective methods might be more useful for the choice of surgical technique itself, evaluating symmetry between the breasts [18].

There is a need to systematically and objectively evaluate the aesthetic outcome of different surgical and radiotherapy techniques. Therefore, we need to further develop valid approaches to define third-party objective consensus on aesthetic outcome and to promote real objective assessment on this basis [14].

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Psychological Aspects of Breast Reconstruction

70

Barbara Rabinowitz

70.1 Background

Understanding the psychological aspects of breast reconstruction really begins with seeking understanding of the psychological impact of a breast cancer diagnosis and the ensuing treatments and therapies. Much research has focused on reactions to surgery and to adjunct therapy, rather than to the reaction women have to the diagnosis alone [1], though clearly breast cancer specialists have borne witness to the person-dependent range of emotions that can surface as women face the breast cancer diagnosis. Women's reactions can be said to fall along a continuum from what may appear as equanimity (e.g. their proceeding through life "as normal" during the period of decision-making and awaiting treatment) to feeling completely undone emotionally and in some instances almost unable to move forward with life's general tasks and the decisions regarding treatment choices.

Early understanding of the emotional impact of a breast cancer diagnosis can be found in a rather unique 1952 article by Renneker and Cutler [2]. These two physicians wrote with great early understanding of the multiple ways that this diagnosis and ensuing treatment could impact women. With mastectomy the only surgical option for women at that time, they spoke in depth regarding the range of emotions women may experience which included anxiety, depression, as well as feelings of shame and fear. Though treatment options have greatly broadened during the decades since that seminal article, women continue to report a great range of emotional sequelae to hearing the diagnosis and to the treatments that also include loneliness, distress over cognitive deficits they may perceive, sleeplessness, and cancer-related fatigue. Ahead of their time, Renneker and Cutler focused also on the importance of physicians caring for women with breast cancer to consult with specialists from the psychological domain to aid cancer specialists in offering patients comprehensive care not just of the breast, but of the whole woman as she seeks to recover from her treatments and to reclaim all of life. Many domains of psychosocial and psychological research have blossomed from that first acknowledgement by Renneker and Cutler (Fig. 70.1).

Research in the evolving decades has shown that women experience problems living with uncertainty, with changes in communication patterns with friends and family, and in confusion about what to tell their children [3]. As cancer does not exert its negative psychosocial aura over the woman alone, impact on the family has been studied with findings noting that family distress, including mood swings, anxiety and depression, is found with some frequency [4]. A more recent report of companion studies has shown evidence that a patient's perceptions of their partner's positive involvement with them post-diagnosis has a salutary impact on three domains of recovery (marital satisfaction, emotional distress, and psychosexual adjustment) [5]. Ganz et al., well known for research furthering understanding of the psychosocial impact of a breast cancer diagnosis and ensuing treatments, have shown that there are frequent deficits that women experience in how they regard themselves, in health-related quality of life, and in their sexual lives [6, 7]. It has become evident that the skilled practitioners working to aid the woman with breast cancer must become sensitive to the potential for a negative impact of the breast cancer experience on any one of many domains of quality of life and responsible to refer women on to work with psychosocial specialists to aid women in their quest for comprehensive recovery.

70.2 Breast Reconstruction

The plastic and reconstructive surgeon may meet the woman with breast cancer early in her experience (particularly if immediate reconstruction is a consideration) or may not, unfortunately, meet her until she has completed her initial ablative surgery and adjunct therapies. Clearly, the opinion of the author is that an early meeting (prior to surgical decision) with a plastic and reconstructive specialist leaves the

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_70

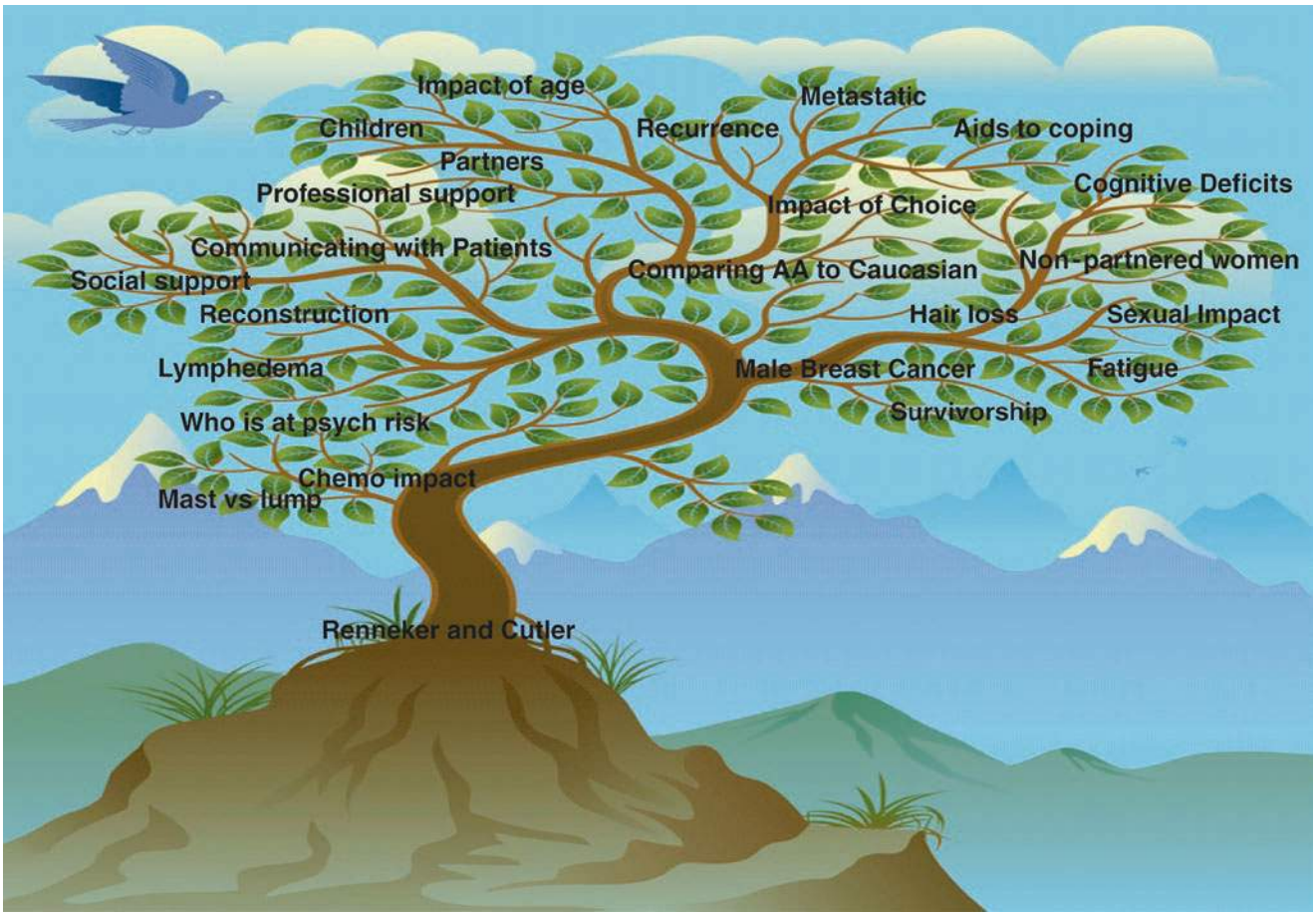

Fig. 14.1 Author's 'tree of knowledge' depiction of depth and breadth of breast cancer psychosocial research domains that have grown since Renneker and Cutler 1952 JAMA article acknowledging the importance of emotional issues for those facing breast cancer

woman best placed to be a true partner in the informed decision-making process, as well as best placed to have her psychosocial issues addressed and supported by the full range of specialists with whom she will work over her time of breast cancer treatment and recovery.

Women who are in a clinical position to be a partner in the choice between breast conserving surgery, mastectomy alone, and mastectomy with either immediate or delayed reconstruction have much to consider. Breast centers, in which each woman is seen by a variety of specialists before choices are finalized, can be a real aid to women moving through her decision-making process as there is the expectation that many members of the breast center team will review best options for the woman and that breast reconstruction will receive a "fair hearing" early in the decision-making process. This can be so both in breast centers where practitioners are located in one setting and in colloquially named "breast centers without walls" in which a group of breast cancer specialists work in separate private practices, but who come together to multidisciplinary treatment planning meetings. Even in settings without a designated breast center, solid collegial and collaborative relationships between breast cancer surgeons and their plastic and reconstructive surgery colleagues can help secure the inclusion of the reconstructive option early on.

Research regarding the benefits and limitations of breast reconstruction has been less prolific than research seeking to understand women's emotional and psychological reactions to breast cancer, to breast cancer surgery and to the impact of psychosocial interventions that can mitigate the emotional burdens women frequently endure. Nevertheless there is a body of literature that aids in understanding the psychological issues related to the breast reconstruction experience and in helping to inform plastic and reconstructive surgeons regarding how to enhance the positive effect of their role as women seek to make a best decision for themselves.

Seeking to understand the "psychosocial and psychopathological" outcome for women with breast reconstruction, Rubino et al. [8] studied women with mastectomy alone, women with breast reconstruction, and healthy women and, interestingly, found no difference in social, sexual, relationship, and quality of life issues at 1 year between the group with breast reconstruction and healthy women. While anxiety was not different between the women with mastectomy alone

and the women with breast reconstruction, importantly, depression in the reconstruction group was less than those women who had mastectomy alone. Similarly, Hartcourt et al.'s earlier work had found that though women in all three groups (mastectomy, mastectomy with immediate reconstruction, and mastectomy with delayed reconstruction) reported a reduction in psychological distress at 1 year post-surgery, it's important to note that women in all groups still reported feeling conscious of altered body image [9]. Indeed, Metcalfe et al.'s later study including all three groups found that there were not significant differences on psychosocial functioning measures between the three groups at 1 year. Noteworthy, however, is the fact that all three groups showed some remaining psychosocial distress with the study authors suggesting that women need psychosocial support after a breast cancer diagnosis, even if they elect and receive breast reconstruction [10]. Noting a perception that postmastectomy breast reconstruction is less beneficial to older women and the fact that older women rarely receive postmastectomy breast reconstruction, Sisco et al. conducted a comparison study that included 215 women 65 or older and a group of 101 women less than 65 years of age. They found that there was no correlation of age to breast satisfaction and psychosocial well-being nor satisfaction with the outcome. Older women who received breast reconstruction had better breast-related quality of life than those who did not have reconstruction, and even more interesting, the psychosocial outcomes for older women with postmastectomy breast reconstruction were similar to those outcomes seen in the younger women [11].

Evaluating satisfaction as a worthy emotional endpoint, one prospective study of women who underwent delayed reconstruction found that preoperative expectations were met in 90% of the patients with a hearty majority stating their satisfaction with the outcome [12]. Negative to psychological peace post-reconstruction for some women is the experience of "decision regret." While seeking to understand the role of information satisfaction and personal variables on regret, one study found that the majority of women in their study reported no decision regret but that for those who did experience mild to moderate or strong regret, it was associated with low satisfaction with preparatory information [13]. Questioning whether women were making high-quality decisions about breast reconstruction, Lee et al.'s small study found that women who chose not to have breast reconstruction were not well informed about breast reconstruction and suggest that "breast cancer patients would benefit from interventions to support their decision making" [14]. The value of meeting and speaking with the reconstructive specialist before surgery was clearly reinforced in these findings.

Emphasizing that there are psychological/psychosocial benefits for breast reconstruction, it has been noted in an evaluation of the overall role of plastic surgery as a component of comprehensive care of cancer patients that "the most convincing data for improved psychosocial well being through plastic surgery is in the setting of breast reconstruction after mastectomy" [15]. Yet the evidence in the research literature is mixed. Evidence for the value of breast reconstruction can be seen in a study comparing women with breast reconstruction to women with breast conservation which found no difference between the two groups in overall psychosocial adjustment to illness, body image, or satisfaction with relationships or sexual life [16]. However, some studies have shown no difference on psychosocial parameters between women with and without reconstruction following mastectomy. Seeking to broaden the comparison, many authors have sought psychological comparison between those with breast conservation, mastectomy alone, and mastectomy with reconstruction [17–20]. Two studies comparing the three groups found that the groups did not differ significantly in the psychosocial domains measured [17, 18]. The general capacity for women, irrespective of surgical option, to adjust and return to a good quality of life was further supported by Parker et al.'s prospective study in which those three groups showed differences in adjustment and adaptation at different time points along the study's trajectory, with no significant differences in psychosocial adjustment by the study's end [19]. Likewise, Collins et al. found there were differences between groups at different points along the trajectory of the study, with women with breast reconstruction faring less well on body image than those women having breast conserving surgery at "Time 2." However, by end of study (2 years), there were no significant differences in body image based on surgery type between any of the groups [20]. While it is good news that a statistically significant amount of women, independent of which surgery they choose, will return to a good psychosocial state within a reasonable period after surgery, none of this research seems to show that breast reconstruction offers a better return to psychological health than mastectomy alone. If left without further studies, one could postulate that women who do not feel the need for reconstruction are in some measure emotionally prepared to live without a breast, while those women who choose breast reconstruction know the need they feel for this enhancement and would do less well psychologically were it not available to them. In clinical practice, this author has certainly experienced those distinctions. One study does lend credence to this theory as the researchers sought to isolate psychological outcome for those with and without good cosmetic outcomes and did find a significant correlation between good cosmetic scores and good psychological adjustment [18]. Also of note is one recent study evaluating patient satisfaction and health-related quality of life specifically for those women whose breast reconstruction was conducted as autologous tissue reconstruction [21]. Using a newly available Breast-Q research tool and validating with findings of two other

frequently used tools employed for this study (Hospital Anxiety and Depression Scale and Impact of Event Scale), the authors found that these women enjoyed significantly higher scores on measures of psychosocial well-being, satisfaction with breast, and sexual well-being as early as 3 weeks postsurgery, compared to their baselines on these measures.

70.3 Immediate Versus Delayed Reconstruction

Relatively few investigators have sought to understand the possible psychological distinctions for women with immediate reconstruction vs. those with delayed reconstruction. An early study by Wellisch et al. found women with immediate breast reconstruction less often reporting "high distress" in recalling their mastectomy surgery (25%) than those women with delayed reconstruction (60%) [22]. Another early and small study found that those with immediate reconstruction experienced significant advantages that included a sense of freedom with attire as well as improved self-image as compared to women with delayed reconstruction [23]. Adding to these salutary findings on behalf of immediate breast reconstruction, a retrospective analysis of the psychological advantages of immediate reconstruction found that anxiety and depression were less and body image, self-esteem, feeling sexually attractive, and satisfaction were all higher for the immediate reconstruction group as compared to their delayed reconstruction counterparts [24]. Seeking subjects from the Michigan Breast Reconstruction Outcomes Study, an analysis by Roth et al. [25] identified that women awaiting their mastectomy with immediate reconstruction showed "higher prevalence of psychosocial and functional morbidity" (e.g., depressed emotional well-being and increased anxiety) compared to the women awaiting reconstruction for a previous mastectomy. It would be important not to assume, however, that immediate reconstruction is a poor choice with regard to emotional outcome, but rather to await further studies in which those with immediate reconstruction could be assessed again at a time further distant from their receipt of a diagnosis of breast cancer, to assess whether their time for emotional adjustment to the cancer diagnosis would compensate for this reported finding. The authors do note that those awaiting the surgery for a previous mastectomy had likely been through the adjustment to their breast cancer diagnosis, while those awaiting immediate reconstruction concurrent to their mastectomy were likely dealing with "the apprehension and fears related to a recent diagnosis of breast cancer." Lending credibility to this theory are two other studies, one prior to the above and one later, following women from this same data base finding that women with immediate reconstruction showed significant improvement on all of the psychosocial outcome subscales (this newer study evaluating them further from their time of diagnosis), other than on body image (having come from intact breasts to the surgically produced breasts) and that women with delayed reconstruction showed improvement only on the subscale for body image (having come from having no breast tissue to now having surgically produced breasts), but not on the other psychosocial measures (having already had time for adjustment to psychosocial issues before their breast reconstruction) [26, 27]. The Wilkens et al. [26] analysis and the latter by Atisha et al. [27] also showed little to no difference on psychosocial well-being based on reconstructive procedure type.

70.4 Prophylactic Mastectomy

In addition to women for whom the breast reconstruction was in follow-up to a cancer diagnosis generated mastectomy in the breast(s) scheduled for reconstruction are those women whose breast reconstruction followed either a contralateral prophylactic mastectomy or those at "high risk" who chose bilateral prophylactic mastectomies. While the circumstance driving the need for reconstruction is different, there is an interesting body of literature to inform our understanding of the psychological issues for women with reconstruction either post-contralateral or post-bilateral prophylactic mastectomies. McGaughey, in an integrative review of 13 studies evaluating the impact of prophylactic mastectomies on women's body image and sexuality, found that up to half of the women experienced a negative impact on body image and sexuality [28]. Unfortunately, many studies found likewise. Payne et al. [29] following women who had registered in the Memorial Sloan Kettering Cancer Center National Prophylactic Mastectomy Registry found women reporting negative impact on body image and sexual function as well. Following in that tradition, a smaller and more recent study with a 93% response rate found 75% of the women post-bilateral prophylactic mastectomy reporting that enjoyment of sex was negatively impacted [30]. Evaluating the experience of women with contralateral prophylactic mastectomy, Boughey et al. [31] found that women in their study who were on average 20 years post-contralateral prophylactic mastectomy frequently noted negative impact on sense of femininity, body appearance, and sexual relationships. Further validation of impact on sexuality comes from a more recent prospective study evaluating impact of bilateral prophylactic mastectomy on body image, sexuality, emotional reactions, and quality of life for "high-risk" women. Brandberg et al. [32] analyzed responses from women preoperatively, at 6 months and at 1 year postsurgery.

Sexual pleasure decreased significantly from assessment presurgery to assessment at 1 year postsurgery, though, interestingly, frequency of sexual activity remained stable through all assessment points. Though the latter might seem counter-intuitive in the face of the former, it is beyond the scope of this paper to theorize, but only to note that this prospective work supports the findings of previous retrospective studies that these women do experience a negative impact on their sexuality. This frequently reported negative impact on sexuality is not difficult to understand given the change in body image and the loss of this part of a woman's anatomy that is often pivotal to women's experience of sexual pleasure.

One of the major drivers of the decision for bilateral prophylactic mastectomy is an anticipated decrease in anxiety [33]. Happily, this was born out in Brandberg et al.'s [32] prospective study with women reporting decreased anxiety over time. This was further supported by the findings in an early study that offered bilateral prophylactic mastectomies to 143 women considered to be high risk for breast cancer [34]. Assessing preoperatively and then following both the "acceptors" and "decliners" for 18 months postoperatively, on psychological and sexual domains, the study found that the 79 acceptors showed decreased psychological morbidity over time, while no such changes were observed for the "decliners." Counter to other studies cited herein, and interestingly, this study found no changes over time in sexual comfort nor of sexual pleasure for either group. Noteworthy that those who accepted and received prophylactic mastectomies as well as those who declined and kept both breasts intact were both able to continue to enjoy sexual comfort and sexual pleasure with no significant differences between the groups.

70.5 Regrets Versus Satisfaction with Prophylactic Mastectomy

Boughey et al. reported on long-term satisfaction for women who had undergone contralateral prophylactic mastectomy (CPM) [31]. In spite of the also reported adverse impact on body image, sense of sexuality, and sexual relationships found in this study, the majority of women both at an average of 10 years and then again surveyed at an average of 20 years post-CPM reported satisfaction with their decision to have CPM. Reporting on women who had had bilateral prophylactic mastectomy (BPM), Gahm, Wickman, and Brandberg reported that feelings of regret were almost nonexistent [30]. Likewise, with a mixed CPM and BPM group, only 21 of the 370 women who had registered in the Memorial Sloan Kettering Cancer Center National Prophylactic Mastectomy Registry registered regrets about their decision to have a prophylactic mastectomy [29]. It is illuminating that while there were relatively few women reporting regrets in the registry, those regrets covered a somewhat broad range. Psychological distress and the distress over the unavailability of psychological and rehabilitation support were the most common regrets noted. Among other noted regrets were those regarding cosmesis, surgical complications, residual pain, and lack of education about the procedure. It seems that better preparing women for the potential sequelae might mitigate the impact of some of these outcomes.

70.6 The Plastic Surgeon as Communicator and Educator

The range of decisions with which women are faced as they contemplate breast reconstruction have become ever more complex. Beyond the basic decision to have or not have reconstruction lie decisions about timing (immediate vs. delayed), reconstruction method in the face of the clinical options available to that particular woman, and weighing in of personal preferences. The plastic surgeon's role in the education of these patients is deep and broad. Certainly it is essential that the plastic surgeon provides each woman a great deal of information regarding the types of reconstructive options open to her while also being sensitive to listening for her preferences, ascertaining goals and being tuned in to concerns. Lee et al. [35] afforded women in their study an opportunity to comment on what drove their decision for reconstruction, their experience with reconstruction, and how they felt about their decision. Overall, they found that women who felt they had been well prepared and understood what the recovery process would entail seemed most satisfied with their decision. However, women in this study strongly advised that future women be well informed on all matters of recovery beyond the basic issues of difficulty of the operation, the length of surgery, the risks, and the potential problems with flaps. They felt they were far less well informed on such matters as the impact of any possible loss of muscle strength, potential numbness and tingling, potential amount of scarring and of umbilical asymmetry, and potential hernia and advised through their study responses to have surgeons cover these matters routinely as well. It is important to note that while women in this study expressed satisfaction with their decision to proceed with reconstruction, many expressed needs for more information. Following the analysis of the study generated data, Lee et al. suggest that plastic surgeons routinely ask their patents to state their concerns and encourage plastic surgeons to specifically ask patients for their preferences for reconstructive method, as many women in the study stated that their choice was solely

based on what their plastic surgeon recommended without voicing their own preferences. They encourage a frank discussion on such issues their patients may have concerning how they will look both in clothes and out of clothes and whether both are equally important so surgeons are better positioned to ascertain if they will be able meet their patients' expectations.

It would appear that not only must plastic surgeons be good educators for their patients but to their physician colleagues as well so that women are referred for a discussion of breast reconstruction options before their ablative surgery. Ananian et al. [36] identified that women in their study who chose reconstruction more frequently recognized the importance of discussing this decision with a surgeon than those choosing mastectomy alone. Alderman et al. [37] found that of the women in their study who had not had breast reconstruction following mastectomy, only just over 59% of them felt that they were adequately informed of the breast reconstruction options. Lantz et al. [38], seeking to understand the impact of the ability to be involved in this decision found that increased involvement played a significant role in satisfaction and avoidance of decision regret. In another study, likewise seeking to understand decision regret, the authors were able to identify that for the almost 50% of their sample who experienced some level of decision regret that it was associated with low satisfaction with "preparatory information" [13]. In addition to the women who were having their breast reconstruction in follow-up to their breast cancer surgery, it appears that women having their reconstruction as a part of their prophylactic mastectomy process have shown a need for robust information and education as well. A study by Rolnick et al. [39] specifically asked women what they wish they had known before coming to conclusion on their decision. Two thirds of the women reported wishing that they had more information with most of the comments regarding insufficient information related to longevity of implants, look and feeling of the implants, and possible complications (e.g., pain, numbing, and scarring). Women specifically noted that they wish they had known about the rate of implant failure and the possibility of the need for replacement in a shorter than anticipated time frame. Though it may seem that women might have anticipated the loss of breast sensation, a number of women voiced that they were not prepared for this loss. It would seem that the imperative for robust discussions offering in-depth information has been established. And while the American Society of Plastic Surgeons has published a well-written booklet for women considering breast reconstruction (*Choices*), it seems clear that it will take meaningful discussions between the surgeon and the woman contemplating reconstructive surgery to assure that women's informational and educational needs have been met.

70.7 Summary

Research to date seeking to further our understanding of the psychosocial issues related to breast reconstruction has been evaluated to beg increasing scientific rigor [40]. Winters et al. note there are inherent limitations in the large group of research studies they reviewed. It appears that there may be some missed opportunities in the way the research questions are asked, in the timing of the queries (prospective vs. retrospective), in the design and in the power of the research they evaluated. To date, we may be missing some of the important and enlightening nuances.

Nevertheless, we have learned from prevailing studies, and from clinical practice, that breast reconstruction is an option that meets the needs of and enhances the quality of life for a subgroup of women facing mastectomy. We do not know definitively for which women breast reconstruction feels more necessary to their recovery than others, in part, because it is clear that some women are not offered this option nor offered any information in this domain. It part perhaps due to methodological issues such as those raised by Winters et al. it has been difficult to perceive the positive psychosocial impact of breast reconstruction between women who have this surgery compared with women with mastectomy alone and compared with women with breast conservation surgery. Yet, we can learn something about the positive psychological impact of breast reconstruction from the distinctions of the experience of women with immediate breast reconstruction versus delayed reconstruction. Therein we see a group of women who are all self-identified as desirous of breast reconstruction. Women with immediate breast reconstruction have reported better body image, self-image, self-esteem, and feelings of attractiveness than the women who must wait. In addition the women in the immediate reconstruction groups report less anxiety and depression.

As current research shows, independent of surgery type, it may take up to 2 years or more for women who have faced a breast cancer diagnosis and treatments to reclaim their previous level of psychosocial comfort. We in the psychosocial/psychological community must partner with our surgery and plastic surgery colleagues and ask they seek us out as well so that together we avail our patients of psychosocial support throughout the trajectory of their breast cancer experience.

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Training Guidelines for Oncoplastic Surgeons: Recommendations for a Standardized Approach

71

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71.1 Introduction

Breast cancer surgery has seen major progress over the past few decades. Conceptually, now it must be carried out with special attention to cosmetic results and long-term quality of life issues important to patients. Disfiguring and mutilating surgeries can no longer be biologically and oncologically justified for most patients under screening programs. In this way, oncoplastic surgery (OPS) represents a necessary evolution and a critical refinement in breast cancer surgery. It combines oncologic and plastic surgery techniques in order to improve the final aesthetic outcome. Of paramount importance, the oncoplastic (OP) approach involves appropriate oncologic surgery, immediate reconstruction using the full range of all available plastic techniques (either partial or complete reconstruction), and immediate correction of contralateral breast symmetry, whenever indicated [1–10].

The original concept of OPS and philosophy of work is already consolidated, since there are no significant changes in basic oncologic principles. Local control in terms of margins and surgical care are the same as whether for breast conserving treatment or mastectomy. This advance is now the standard practice in order to reduce deformities caused by excessively wide excisions without reshaping of the breast and/or to avoid reoperations when positive margins are encountered [1–7].

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Three important facts must be considered as the main reasons for a change in the system of breast surgery training. The first one is that most breast cancer patients are not receiving any kind of breast reconstruction at the time of cancer removal. The classic model "breast surgeon-plastic surgeon working together in all cases" works very well when this model is available. Unfortunately, for the vast majority of women around the world, this is not the case, and thus, the current model is clearly insufficient to cover the needs of all new breast cancer cases that occur. The second one is that immediate breast reconstruction (whether total or partial) with volume displacement and replacement techniques have better oncologic results in breast conserving surgery (BCS) in terms of margins, lower index of re-excisions, better local control of disease and positive results regarding radiotherapy planning, particularly for the group of patients with gigantomastia. Although there are few studies that have been done in OPS and most of them are series of cases or retrospective cohorts of patients, it is clear that the combination of plastic surgery techniques with BCS does not compromise clear excision margins nor the long-term oncological (survival) results. Moreover, immediate breast reconstruction has better aesthetic outcomes than delayed after conservative surgery and mastectomy. The third reason, and perhaps the most important of them, is the cultural and psychological representation of the breast in postmodern society. Patients with pronounced asymmetry after a breast cancer surgery are more likely to feel significantly stigmatized. They have more fear of death, increased psychosocial problems due to loss of their femininity, more depressive symptoms, and, consequently, more harm to their quality of life, independent of their chances of cancer cure [6, 8, 10].

So, this new arrangement in breast cancer surgery—with one surgery appropriately trained to approach the cancer removal while at the same time taking into consideration the aesthetic aspects of the breasts as well as the patient's personal desires and preferences—is perfectly well justified. Fellowships need to expand the current curriculum in order to create a new specialist surgeon who performs various

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_71

types of reconstructions—the so-called "oncoplastic surgeon," which is the new "breast surgeon." Of course, a single surgeon carrying both oncologic and reconstructive backgrounds requires cross-specialty training in order to master these to the highest standard, adding new responsibilities and new medico-legal implications. That is the aim of this chapter, to address the qualifications and limits in OPS training and practice.

71.2 Who Is the Oncoplastic Surgeon?

New generations of breast surgeons now should be oncoplastic surgeons. In other words, oncoplastic surgeons are specialist breast surgeons. Although the controversy whether breast surgeons or plastic surgeons should perform breast reconstruction has been a long-standing "turf" issue and this attitude is pervasive in some countries (such as the United States), the breast is an aesthetic-functional organ, and surgeons who perform breast surgeries in their practice must always consider these outcomes in all cases when performing surgery on the breast(s). Even for those breast surgeons who work together with plastic surgeons, they can perform best quality surgeries if they have broader skills in techniques related to plastic surgery of the breast. The same is true for the plastic surgeons. When they have a deeper knowledge and understanding of the oncological aspects (such as adjuvant radiotherapy), they will have a clearer understanding of the ultimate aesthetic outcome following a particular procedure. The best care is delivered with an integrated team approach, and when breast surgery work can be performed with a team effort. This holds true whether the OP approach is with two surgeons or one surgeon trained across both specialties. Moreover, there is no longer a clear division between the aesthetic and the oncologic in breast cancer surgery, no sure there be in the present time since we are confident that survival rates will remain the same.

Given the need to cross-train the upcoming breast surgeons of the future, it is necessary to develop internal and international standards for training and a special qualification for OPS. Fellows eligible for acceptance into a Comprehensive Breast Cancer Training Program for OPS can be specialists from Gynecology, General Surgery, and/or Plastic and Reconstructive Surgery. The real goal of this model is to expand the availability of high quality breast reconstruction for as many breast cancer patients as possible, and ultimately to increase the rate of breast conserving surgery around the world.

71.3 Breast Training Competencies in Oncoplastic Surgery

The standard format for an OP Fellowship training curriculum must begin with a multidisciplinary approach and include fundamental knowledge within various breast cancer correlated disciplines such as molecular biology and genetics, anatomy and physiology, epidemiology, bioethics and legal medicine, medical photography, radiology, pathology, radiotherapy, and clinical oncology. These areas across the clinical spectrum form the foundation for breast cancer treatment and surgical decisions. Figure 71.1 shows a schematic representing the comprehensive knowledge base required for a "patient-centered" OP surgical approach and the rationale behind multidisciplinary training.

In regards to the surgical aspects of OP training specifically, a greater balance between oncologic and aesthetic principles is required. Figure 71.2 depicts some of the essential

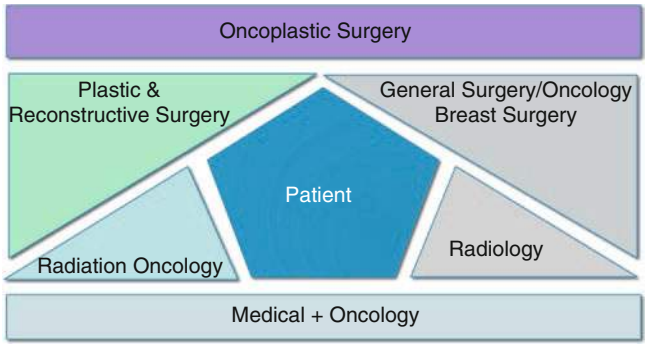

Fig. 71.1 Patient-centered oncoplastic surgery approach

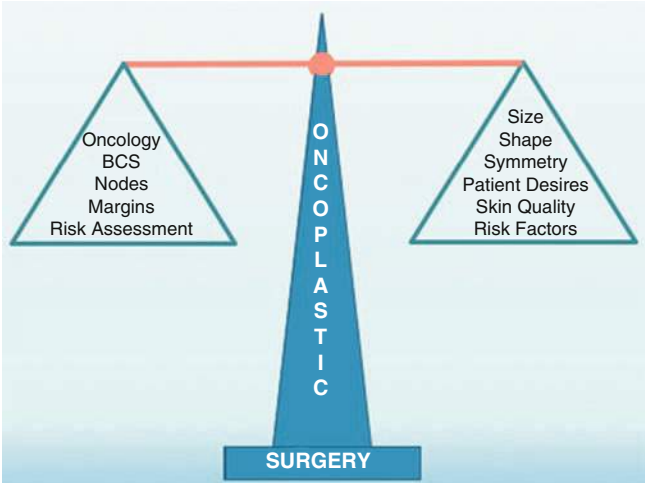

Fig. 71.2 Elements to help achieve "balance" with OPS pre-op assessment

components to be considered in the pre-operative assessment of each patient. In addition to these essential components that must be included in the training of OP surgeons, training must also focus on development of very specific surgical skills, maintaining strong ethical commitment to patients and quality care, and ongoing exploration of opportunities in research focused on improving patient outcomes with the delivery of cost-effective, quality care.

71.3.1 Developing Skills

Conceptually, "competence" is the ability of an individual who is trained adequately and is well qualified physically and intellectually for a particular activity. OP surgeons should be well trained and competent in all aspects of breast oncology and in oncologic surgery of the breast, and should have a comprehensive understanding of breast defects created by removal of tissue and their reconstructive requirements. There is also a need for an aesthetic appreciation of the breast. This is perhaps the most difficult aspect of OPS since it can be an elusive element for surgeons to grasp. The shape, contour, and overall aesthetic appearance of the breast is something that is a very subjective and a personal matter—one that has been studied and portrayed by artists since the beginning of time. The surgeon and patient may have very different opinions on what the "optimal" appearance of the breast "should" be. In general, societal influences tend toward certain characteristics being the quintessential appearance of the breast. However, events throughout the lifecycle can dramatically alter the aesthetic appearance of the breast, and this aspect of OPS can be the most difficult aspect to teach and train surgeons to appreciate and accomplish in their practice.

Therefore, in training surgeons to adopt new surgical techniques, pre-operative evaluation must take into account the changes that have occurred to the breast such as macromastia, asymmetry, post-partum atrophy and ptosis, etc. (Fig. 71.3).

The patient's input and desires of potential ways she may wish to change or "improve" the appearance of the breast must also be integrated into the surgical plan when removing abnormalities in the breast. In this manner, the surgical plan can be individualized and optimized in order to achieve the best possible outcome for each patient. Integrating the aesthetic aspects into the thought process for cancer removal is the key to OPS. After this, methods and approaches on how best to reconstitute the shape and contour of the breast whether to its original form or a new—perhaps smaller, less ptotic breast—are integrated into the surgical plan (Fig. 71.4). Thus, OP surgeons need a thorough understanding of the available methods for reconstructive techniques, and proficiency in these techniques are necessary in order to counsel patients in their pre-operative decision making as well as developing the surgical plan. As mentioned previously, if the surgeon is going to serve an area where reconstruction is not readily available, then the OP surgeon must be fully competent in these techniques for reconstruction. However, even if the breast surgeon work in collaboration with a plastic surgeon on the reconstruction, a complete and thorough understanding of these principles is necessary in order to conduct an adequate discussion with the patient offering a full compliment of surgical options. Furthermore, in-depth knowledge will help to prevent and care for potential post-operative complications [6].

Until now there has been no focused or formal training of breast surgeons in the aesthetics or reconstructive aspects of breast surgery techniques. While excellent breast training programs exist, they vary widely throughout the United States. In other parts of the world, dedicated OP surgery training fellowships have been very successful; however, these remain few and far between. In an attempt to standardize international requirements for OP surgery training, the American Society of Breast Disease and the Societe Internationale de Senologie convened with the International Steering Committee (ISC) on Oncoplastic Surgery in April 2010 and November 2012. The committee unanimously felt that competency to perform these surgeries needs to be categorized in a specific classification system in order to organize training opportunities for surgeons currently in training, but also must be applicable to those surgeons already in practice that want to broaden their abilities. Taking into consideration the input from the ISC, a classification has been developed by Urban and Lebovic in order to help standardize training in OPS. These "levels of competency" are defined by the need to acquire surgical competence with various procedures and specific skills necessary to perform OPS. Table 71.1 defines the four levels of surgical competence in OPS.

Since most breast cancer patients need Level I, II, or III techniques, it is highly recommended to conduct the basic OPS training in these competencies. Specific competence in plastic surgery techniques of the breast is not required at Level I, since general surgeons, working only in the compromised breast, do most of these procedures. Level II requires specific competence in aesthetic characteristics and appreciation of the shape and contour of the breasts, reduction mammoplasty techniques in order to repair major partial defects after breast conserving surgery, and to achieve better symmetry working on the contralateral breast, whenever necessary. Level III requires competence in indications, surgical techniques, and management of complications with breast

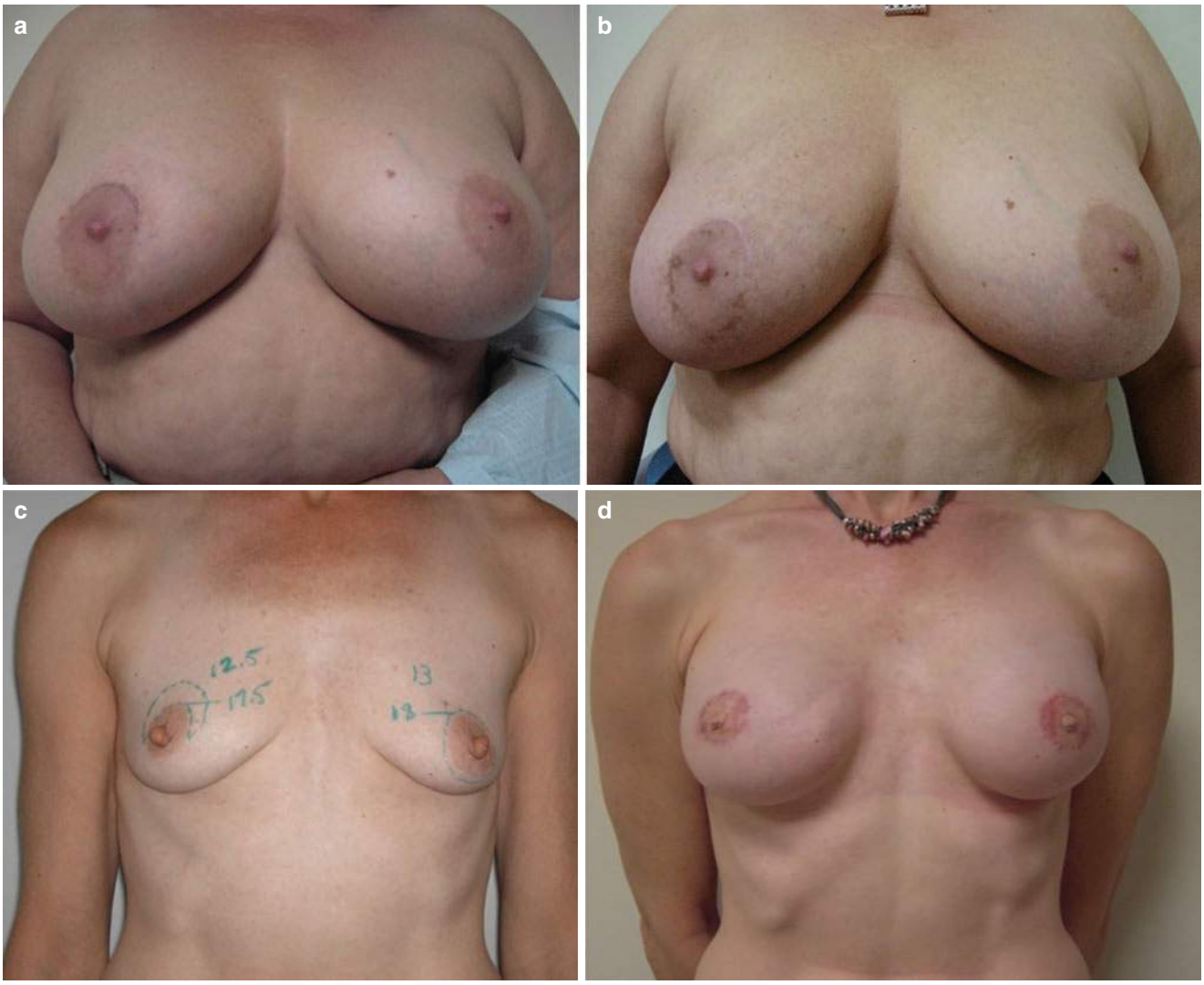

Fig. 71.3 (**a**) Patient after lumpectomy via peri-areolar incision for upper, inner quadrant tumor removed via tunneling and oncoplastic closure. (**b**) Same patient 1 year post surgery, whole breast radiation and boost. Excellent cosmetic outcome, showing only mild skin changes and no contour deformity. (**c**) Pre-op patient with 5 mm DCIS with comedo necrosis right breast, BRCA-2+, and asymmetry. (**d**) Post-op after bilateral skin-sparing mastectomies, immediate reconstructions with submuscular saline implants, and nipple/areolar reconstructions

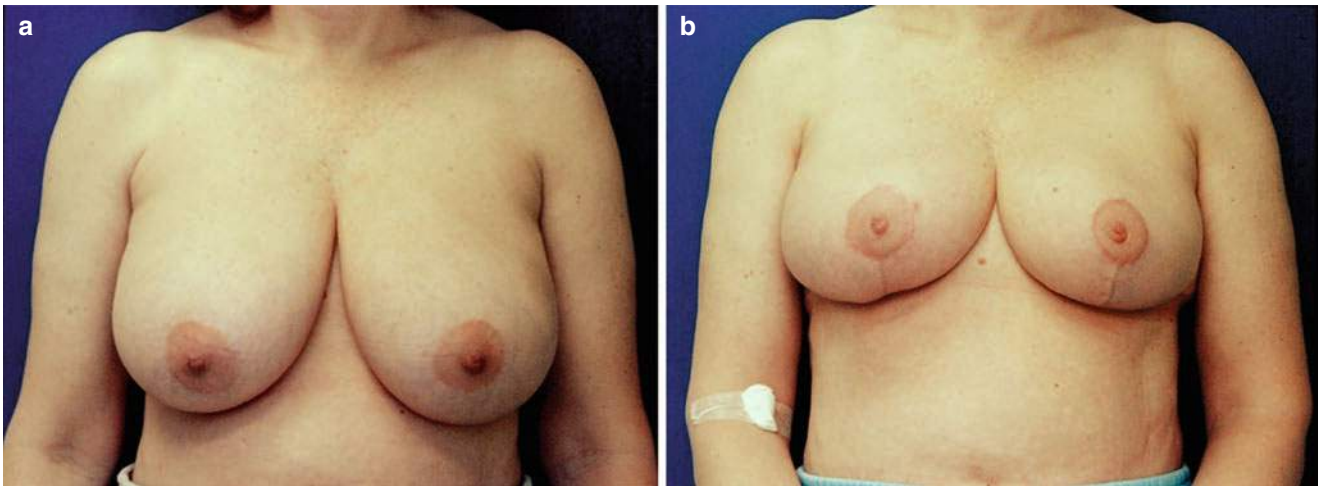

Fig. 71.4 (**a**) Patient with macromastia and 7 mm invasive carcinoma deep in right breast at 6 o'clock position. (**b**) Patient post-op superior pedicle reduction mammoplasty to remove primary tumor followed by immediate reconstruction using local tissue flaps

Table 71.1 Skill levels and guidelines for standardized training

• Level I—Multidisciplinary oncologic risk assessment, unilateral displacement techniques in breast conserving surgery including: aesthetic skin incisions, deepithelization of the areola margins, glandular mobilization, reshaping techniques, purse string sutures for central quadrant reconstruction, mobilization of glandular flaps
• Level II—Bilateral and replacement techniques: breast reduction (inferior and superior pedicles, and round block techniques), mastopexy, Grisotti flap, repositioning of the nipple-areolar complex when needed, nipple and areola reconstruction
• Level III—Expander/implant techniques: immediate and delayed breast reconstruction with temporary expanders or implants, and contralateral symmetrization procedures
• Level IV—Autologous flap techniques: pedicled or free flaps, or combination of techniques

implants. A high standard of knowledge in different qualities of implants is necessary in order to individually select which patient is better served with which implant, and specific training in surgical skills and patient management related to implants is required.

If the surgeons are well trained in immediate and delayed breast reconstruction with expanders and implants, in superior and inferior pedicled breast reductions, mastopexy and in round block techniques, they will be able to solve more than 90% of breast surgery cases in their practice. It is recommended that Level IV competencies should be undertaken as advanced surgical training with an additional, focused fellowship training program in myocutaneous flaps.

The real point to consider is how to set the limits for this new discipline, which is translational under different specialties. The challenge is to train surgeons to be competent in all these techniques in order to be able to achieve higher quality outcomes in the majority of breast cancer patients undergoing surgery, making these procedures more readily available, reducing the contrast between different centers which requires standardizing the training. Ultimately, employing these techniques has the potential for decreasing overall healthcare costs by reducing the number of surgeries as a whole (fewer re-excisions, complications, revisions, etc). Surgeons must be able to recognize their own limits using this classification system, and they must seek out training in order to advance their skills. The Dreyfus and Dreyfus five-stage developmental model of skills acquisition which is applied in health education could be useful to help determine the progress in these OP levels (Fig. 71.5).

Since there is an increasing demand for training in OP techniques, and there are different scenarios and backgrounds of breast surgeons, it is difficult to establish a minimal number of cases required per surgeon. Evidence-based training in OP surgery is more complex to build than for other new approaches such as sentinel node biopsy. In OPS, the numbers of various techniques involved and the additional unique aspects of aesthetics require training not currently offered as part of surgical training in general or breast oncologic surgery.

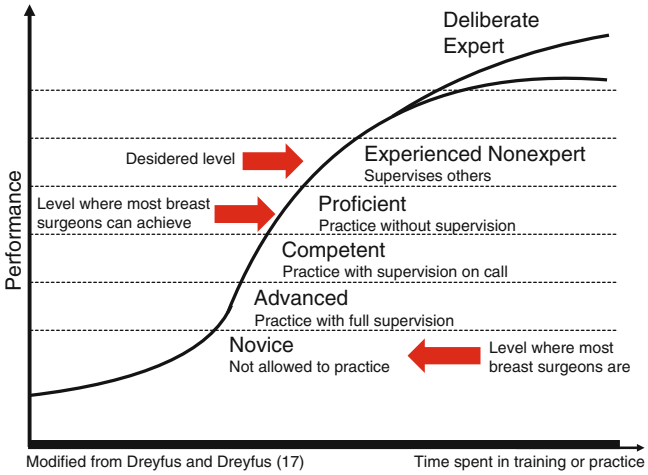

Fig. 71.5 Generic learning courve adapted from Dreyfus and Dreyfus five-staged developmental model of skills acquisition and modified from Kalet and Pusic and possible and desired oncoplastic skills to breast surgeons [11, 12]

The training of new generations of breast surgeons must include at least the first three levels of competencies in their Curriculum in order to solve most of the breast cancer cases. In this way, it is recommended that at least 15–20 cases per technique/surgeon under supervision in a credentialed Breast Unit and/or in cadavers should be used as a guide for establishing a learning curve.

71.3.2 Ethics

Demands and expectations of the patients tend to be higher with OP surgery. Although delay in diagnosis of breast cancer remains the most common reason that breast specialists are sued for malpractice in the USA, there is potential for rising issues in OP surgery. Appearance of the breast after surgery is growing as a critical component in breast cancer treatment outcomes. It is expected that medico-legal analysis will change with these advances. The essential and central element is the duty of the breast surgeon to obtain a good aesthetic outcome without compromising oncologic control. Basically, the oncologic scenario is easier to document clearly for individual analysis in a medico-legal setting as it is somewhat standardized and presented as: mastectomy versus conservative indications, local control with clear margins, and properly selected adjuvant and neoadjuvant treatments.

In contrast, the reconstructive and aesthetic aspects of OP surgery is the new and the real great difference in the medico-legal context. It is clear that OP surgery is not like purely aesthetic surgery in terms of outcomes and judgments. It is both an oncologic *and* a reconstructive procedure, not simply aesthetic or oncologic breast surgery. It has all the oncologic limits in its background and the aim is not only aesthetics.

The pre-operative discussion, decision making, and Informed Consent process must clearly outline all of these aspects considered in the final surgical plan that ultimately should be arrived in agreement between surgeon and patient based upon risks versus benefits. In order to avoid errors of interpretation and communication between surgeon and patient all aspects should be discussed in a comprehensive manner. Of course, the integration of plastic surgery techniques to oncologic breast surgery will potentially improve aesthetic outcomes, but it will add new responsibilities to the surgeon as well. Established protocols and procedures as well as the surgeon's clear understanding of their own individual competencies and limits will hopefully help to avoid both additional risks to the patients and increasing liability.

71.3.3 Research

There are many research opportunities to be explored in OP surgery such as:

1. How can training in OP be implemented and upheld to an international standard?
2. Can OP techniques help surgeons increase breast conservation rates?
3. Can OP techniques help surgeons achieve lower re-excision rates?
4. Will OP techniques lead to decreased surgical complication rates?
5. Does the use of OPS contribute to decreased recurrence rates?
6. How can a surgeon's time in the operating room be optimized?
7. In what ways can OPS help to optimize aesthetic outcomes in breast surgery?
8. Can OPS result in an overall decrease in healthcare costs associated with the treatment of breast surgery patients?
9. How can new technologies help advance the field of OPS?
10. Aesthetic and psychological benefits of OPS in breast cancer patients.

These and many other areas of research are well worth exploring in order to better understand the overall impact that OPS will have on improving patient outcomes.

71.4 Surgical Mentoring

Mentoring, according to Rombeau, Goldberg, and Loveland-Jones, is the provision of personal and professional guidance, usually to younger surgeons. Education and growth in surgery are highly dependent on this old process, perhaps more so than in any other discipline in Medicine. The complete concept of mentoring, according to these authors, has three basic characteristics related to the mentor's personality and ability to teach and evaluate technical skills of a trainee: experience, trust, and commitment [13]. Recent changes in breast surgery with the advent of OP techniques in the past two decades is bringing different methods of mentoring and requires new strategies in teaching and limit setting to the surgeon acquiring new skills.

Leaders in OP have an important role, and they represent an essential component in shaping the future of breast surgery. There is a worldwide interest in the career benefits of breast surgery with these new OP opportunities. At the same time, there are also challenges completely different from the traditional surgical mentoring process. There is no standard, no consensus nor agreement between Breast Societies and Plastic Surgery Societies in various countries around the world regarding how to establish standardized training programs. At the same time, there are a growing number of surgeons, both young and old, now interested in learning these techniques so as to be able to offer better outcomes to their patients [14]. So, it is time to revisit our pedagogical way of teaching and lack of formal guidelines in OPS mentoring.

There are three generations of OP surgeons. The first were the few pioneers who formulated this philosophical approach to breast cancer surgery and began to do these surgeries between 1980 and 1990 in the face of great opposition. Most of these surgeons were from European countries; however, there were a few scattered in the USA, South America, and as far as New Zealand. After increasing use and acceptance of breast conserving treatment and increasing success with early detection and improved survival rates, a wave of young breast surgeons embraced this approach. These surgeons were inspired and trained with the pioneers or enrolled in fellowships with progressive Plastic Surgery Departments in order to obtain specific training in plastic and reconstructive techniques. The third generation is the new breast surgeons and those of the future. These breast surgeons are fortunate to receive comprehensive OPS training within the context of their fellowships. These specialty programs exist in Brazil, France, Austria, UK, and now India. OP breast surgeons may have a primary specialty in general surgery, plastic surgery, or gynecology which represents the most likely requirements for OPS of the future as well. Between the second and the third generations of breast surgeons lies the gap in patient care.

This group of surgeons caught in the "gap" currently perform most of the breast cancer surgeries around the world and they lack specific training in OP techniques or are not able to offer breast reconstruction to most of their patients due to difficulties or unavailability of plastic surgeons in their communities to partner with. Many of these surgeons

are now looking for training opportunities with short or intensive courses, in order to learn techniques that can help them with their patients. They are not young residents or fellows, but rather, they are already specialized surgeons out in practice, with varying degrees of experience and technical skills in breast surgery. How do we provide practical guidance for OP mentors to guide these colleagues? What is the philosophy behind OP surgery and its implications for mentoring? What are the limitations for these different courses? How do we set the limits? How can we provide educational certification? These questions remain unresolved, though fundamental questions for breast surgery in the next few years.

The basic question is: "What is OP surgery and what is the philosophy behind it? Werner Audretsch, the German surgeon who originally coined the term "Oncoplastic Surgery," describes it as "tumor specific immediate breast reconstruction" [15]. So, it is not considered a new specialty. It is a gray zone between Plastic Surgery and Breast Surgery, a common area of interest for both specialties. It does not make sense anymore to discuss who should do OPS (and consequently who should not do it), because even plastic surgeons who have training in all reconstructive techniques now should have experience in all breast cancer treatments and their consequences in order to decide the best approach for each individual patient. They can no longer think only about aesthetics. At the same time, breast surgeons have a firm oncologic background, but usually do not have training or experience in plastic and reconstructive techniques, and they have not specifically considered the aesthetic analysis of the breast in most surgical situations. However, it is now time to recognize that these surgeons should not be limited only to oncologic outcomes without consideration and attention to the aesthetic outcome. The "old" approach is a fragmented process and leads to negative consequences in an organ that is aesthetically functional and a critical part of the survivors' quality of life. Most breast cancer patients are currently not undergoing breast reconstruction, even in developed countries. In contrast to this, OPS is a translational way of doing breast surgery, by one surgeon, or by a team. Breast reconstruction, whether partial or total, should be an integral part of breast cancer treatment, not an option or an afterthought [2, 3, 6, 8, 14–18].

Considering that OPS is a group of techniques for breast cancer treatment, concerned with oncologic and aesthetic outcomes, and that we have many differences in Breast Surgery training worldwide, our focus should be on how to obtain individualized skills in different techniques. Countries like Brazil have breast surgery ("Mastology") as a specialty, so naturally the Brazilian Society of Mastology is now including OPS in Residency training programs, and mentors are adapting themselves to this new reality. In UK, OPS is a subspecialty and belongs to Plastic Surgery and General Surgery, but in the USA breast surgery remains firmly as part of a General Surgery background [2, 3, 8, 14, 15]. All of these different approaches have particular challenges for training surgeons.

The time has come for the established breast surgery community to promote a universal mentoring culture for OPS. In previous eras, young surgeons were trained as apprentices by a single senior surgeon as a mentor. In more recent times, multiple mentors have become the dominant surgical model for most surgical specialties which offers the ability to learn various methods and techniques lending the potential for a broader foundation in skills training [13]. In OPS it is quite different. We are mentoring residents, fellows, and specialized surgeons from different ages and levels of experience. When training surgeons with varying levels of competency and knowledge it is critical to include a didactic as well as a hands-on component and to require a minimum amount of educational criteria and certification. Some countries offer facilities for training directly with patients in the operating room, others with cadaver labs. Currently there is no standardized pattern for mentoring such as those that exist for other subspecialties. In some circumstances, a single OP surgeon could be more effective as mentor than a team, while in other situations, a team approach might prove to be best. Inevitably, the training for breast surgeons must contain a well-defined core curriculum that, at a minimum, covers all aspects of the continuum of care and various surgical procedures outlined as Levels I, II, and III (Table 71.1).

Do short courses solve the problem? Of course they cannot. But they are important, because they address the needs of surgeons in practice today and these courses help surgeons learn new techniques, refine other ones, and increase their interest in learning OPS in order to improve their practice. However, while these courses can be very productive, they cannot provide ongoing, hands-on mentoring that helps expedite the integration of new techniques into practice. If possible, this is best done in the apprentice-type of atmosphere with one on one mentoring.

OPS is more than learning in an operating room or in a cadaver lab. It is well-planned surgery, and in order to properly learn the techniques it is necessary to teach preoperative evaluation, during the breast markings and the decision-making process. After the operation, we should deal with specific complications (and how to solve them), which are different from lumpectomy, mastectomy, axillary dissection, or sentinel node biopsy complications. But how to mentor it, and for how long? It depends on the previous surgical background of the mentee, and many other factors as it requires a realignment of the surgeons' thinking and philosophy. OPS training is perhaps more subjective than any other surgical discipline. The learning curve needs to be standardized yet

individualized for each technique and for each surgeon. OPS does not represent a new specialty, but rather it is a refinement in the conservative and radical surgical approaches to breast cancer treatment given the current "state of the arts" from diagnosis through survivorship. Mentors should identify technical limits and establish the borders for their mentees, using a model with levels of competence as presented above. Objective variables of technical skills should be based on competency-based training.

71.5 Conclusions

Above all else, it is necessary to ensure the safe introduction of OPS into surgical practice. Surgeons have two important aims to address in this new reality: to perform appropriate local control of disease and to focus on the long-term quality of life issues important to all breast cancer patients. These quality of life issues are a matter of breast surgery decisions beginning at the moment a breast cancer diagnosis is made. So the curriculum in breast surgery must expand its limits and responsibilities in order to change and improve the ultimate reality of breast cancer patients. There is an exciting future for OPS mentoring. Instruments for performance assessment will be internet based, simulating real cases, with virtual reality and telementoring. Finally, OPS is a completely reshaping and revitalizing breast cancer surgery. But the way that this is accomplished will depend on how mentors will help the present and future generations of surgeons to bridge the gap. Overall, mentoring must be individualized, ethically founded, committed to present and future patients, and to new potential areas for research.

In the end, OPS is not a single technique or approach, but rather, it is a way of thinking differently as a surgeon. It entails looking at breast cancer surgery from multiple different angles—in much the same way that each patient will look at herself in the mirror for years to come after her cancer has been removed. And when she looks at her breast, the goal is to have her feel a sense of relief—seeing herself as whole, healthy, and happy.

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Models for Oncoplastic and Breast Reconstruction Training

72

Gustavo Zucca-Matthes, Mauricio Resende, and Cicero Urban

72.1 Introduction

The high level of responsibility in various vocations draws special attention to the educational programs required for competence. To be an aircraft pilot or naval commander, it is critically necessary to have a great number of hours spent at a simulator. The same condition must be expected from surgeons. The progressive evolution of breast surgery is pushing surgeons up to improve their skills through different training programs.

During medical school, future doctors deal with different models of training. They start with cadaveric dissection and animal labs and finally arrive at clinical training guided by an experienced surgeon. To be a surgeon, it is necessary to spend many hours studying and practicing manual skills. Why not train in some kind of surgical simulator as well? In fact, this type of training already exists and is commonly used for minimally invasive surgeries in laparoscopy and robotic procedures. The main point of these devices is to closely mimic reality, simulate real clinical scenarios, and test and rate performance.

With respect to breast surgery, finding the optimal physical material to simulate a real breast is not easy. Investigators have mentioned the use of foam models trying to simulate human tissues. However, the expected level of realism was not achieved. This made it necessary to find more anatomical models to facilitate surgical training to allow surgeons to develop their skills and practice new techniques without risk to a real patient.

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72.2 Types of Surgical Training

72.2.1 Training Programs

Over time, the apprenticeship method has become the gold standard for surgical training [1–4]. The paradigm of "see one, do one, teach one" clearly reveals the basic tenets of this method. It is a time-honored approach in which a skillful tutor provides practical demonstrations and shares theoretical knowledge with the trainee. Therefore, surgery is learned by example and repetition. This model of training demands a very large number and variety of cases to train a new surgeon. By the end of the 1800s, William Osler and William Halsted were responsible for pioneering and popularizing this method. They also established a more formal and structured system involving a team of trainees and mentors. In fact, the organization of residency training currently employed in the majority of medical schools derives mostly from their work. Surgical rotations and close relationships between masters and novices help the trainee gain competence, optimizing and amplifying the learning curve. Finally, on completion of the residency program, residents must demonstrate their proficiency through board examinations to be fully certified.

Although the current apprenticeship system of training has a proven track record of success, restrictions in resident work hours, financial pressures, patient safety issues, heated debates about early specialization, duration of training, and the search for a better quality of life have led some renowned surgeons to propose more efficient alternatives to this teaching method. Furthermore, technological advances, such as computer-based simulators, have allowed young surgeons to gain surgical experience in a protected environment with no risk to the patient and to quickly improve their skills.

The breast is an important symbol of femininity, and so today, we see an increased number of cosmetic surgeries. In addition, breast cancer has spread around the world, and each country has their own set of customs for the specialties involved in breast reconstruction. However, all of them have

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_72

in common the realization that breast cancer surgery is changing and must adapt in order to provide current, safe, and refined treatment for women.

Over the last few decades, surgical techniques have advanced to the point where breast-conserving surgery (BCS) has become the standard of care for treatment of early-stage breast carcinomas. By the early 1990s, some authors suggested the integration of plastic surgery techniques with BCS in the treatment of breast cancer. Conceptually, this approach, referred to as "oncoplastic surgery," aims at providing safe oncologic treatment through careful preoperative planning with the incorporation of plastic surgery techniques in order to obtain good oncologic control with favorable immediate cosmetic results. Moreover, oncoplastic surgery very often offers improved overall aesthetic outcomes and seeks to optimize contralateral breast symmetry.

In 2003, Rainsbury wrote about future training and skills for breast surgeons in the new millennium [5]. He commented that breast surgery was becoming more specialized as a result of fellowship training, greater patient demand for specialists, increasing trainee expectations, and new skills learned by existing breast surgeons. As a result, modern training programs need to recognize these requirements by supporting interprofessional cross-training initiatives and encouraging professional development.

In the United Kingdom, the oncoplastic concept has made the breast subspeciality a more popular and attractive career option to a new generation of surgical trainees. The general surgery programs do not offer adequate numbers of breast cancer cases for residents to adequately train, so residents go on to breast surgery or surgical oncology fellowships. Oncoplastic fellowships must train specialists who have an active role in the comprehensive management of breast cancer patients, capable of providing the most appropriate cancer surgery with the best cosmetic results. Robertson et al. proved that trained breast surgeons specialists perform implant-based immediate breast reconstructions with a satisfactory outcome when evaluated by subjective and objective analyses.

This leads to the evolution of breast surgery with improvement in surgical techniques looking for better results, especially regarding breast reconstruction and aesthetic procedures. It is important to mention that for good immediate results, breast reconstruction with implants requires a skillfully performed mastectomy.

The goal is to provide education for surgeons with large practices in breast surgery, but without oncoplastic or reconstructive surgery experience. Also of importance is the structure of postgraduate training courses and the level of activity of the breast reconstruction training unit. Breast cancer centers with high volume should be certified as training programs [6].

With increased subspecialization as exemplified by the growing number of physicians solely devoted to breast surgery, surgeons are required to develop more sophistication in a relatively shorter period of time. However, the apprenticeship-based method relies on an extended period of time to provide the trainee with sufficient experience (Fig. 72.1) [7–18].

72.2.2 Simulators

The development and use of newly created simulators in residency or continuing medical educational programs has promoted a shift in surgical education [13–17]. Through an unlimited number of repeated exercises and in a calm, stress-free environment, surgeons can theoretically gain extensive experience in a brief duration of time. The creation of an optimal simulator model as an adjunct to breast and plastic surgery education can improve the training process for both specialties and allow for more rapid attainment of competency. Different kinds of simulators or teaching techniques have been employed and have revealed good results in different aspects of training. The use of foam models allows for a three-dimensional structure compared to the standard two-dimensional reconstructed breast surface used when teaching local flap techniques. It illustrates, for example, how the flap is harvested and how the nipple is fashioned in nipple-areola complex reconstruction. The use of tissue-like phantoms is widely used to calibrate and compare imaging systems and to train surgeons to operate under image guidance. There are also breast examination models being used to teach breast exams, to improve a doctor's skill of palpation, and to increase the effectiveness of this examination to allow the physician to become less anxious with this interaction and more comfortable with this skill.

Training models have also been developed with adjustable breast masses; with varying densities and sizes and physical relationships with underlying rib and muscle structures in a silicone breast, it makes the phantom very realistic.

72.2.3 Cadaver Lab

Cadaveric dissection is broadly used for specialty laboratory training. Recently it has been used for breast aesthetic and reconstruction training. However, this practice is hampered by the costs involved in the preparation of cadavers and

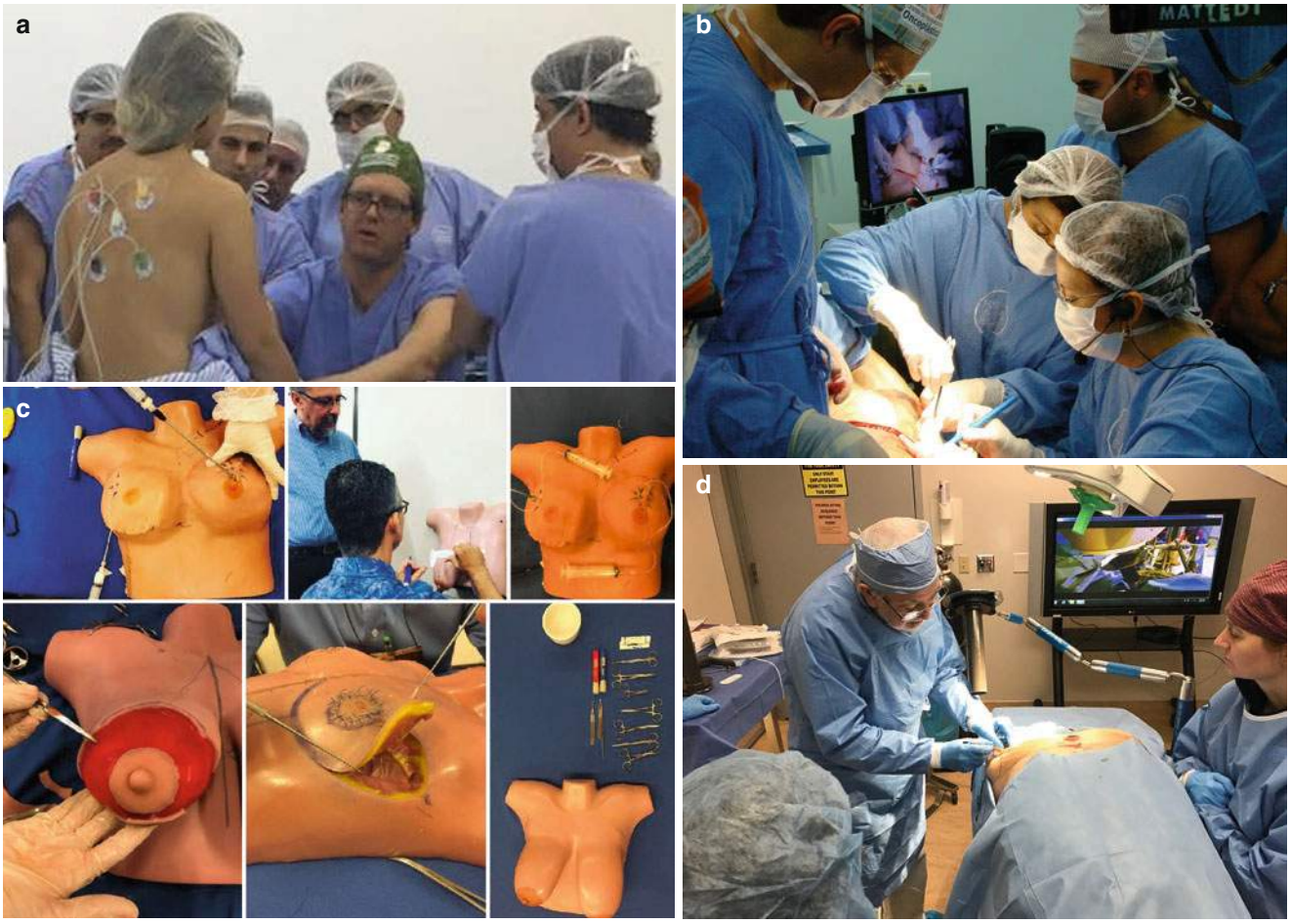

Fig. 72.1 (**a**) Guided preoperative drawings. (**b**) Training in the surgical theater. (**c**) Cadaveric surgical mentoring by an expert. (**d**) Mastotrainer simulator for training in oncoplastic breast surgery

laboratory, not to mention the many ethical issues that make this practice difficult in some countries.

72.2.4 Mastotrainer

The Neoderma model called Mastotrainer was created with a focus on breast aesthetics and reconstruction [6].

For this model, it was necessary to create differing planes of dissection, e.g., subcutaneous tissues, breast, muscles, and ribs. The "Mastotrainer" relies on this lifelike recreation of the organ and falls into a new class of simulators: "R.E.S.T. (Realistic Endo Surgical Trainer) simulators." This technology was introduced in 42 countries and includes such specialties as neurosurgery, urology, gynecology, and general surgery among others. It makes use of a type of moldable rubber that, together with a group of polymers, allows for more than 60 types of consistencies ranging from mucoid secretions to cartilage. It allows for different colorations, which helps in creating a vast variety of different anatomical tissue planes as well as lesions. The combination of these components stimulates the formation of cysts, solid tumors, and masses of different consistency, including ones with calcifications and the formation of cleavage planes. The Neoderma is used in a customized manner that corresponds with the variable pathologies that can be chosen before the training process. These simulators are placed on a fiberglass base that allows for the manipulation and practice on the body part of interest. The used anatomical part is discarded after the practice surgery, and the fiberglass base is now ready for another surgical unit and training run. Manufacturers offer Neoderma technology which mimics closely the color, consistency, feel, elasticity, and resilience of human tissues. More advanced technologies allow for bleeding inside body cavities. There are tissues that can be cut by an electric or ultrasonic scalpel and laser as well.

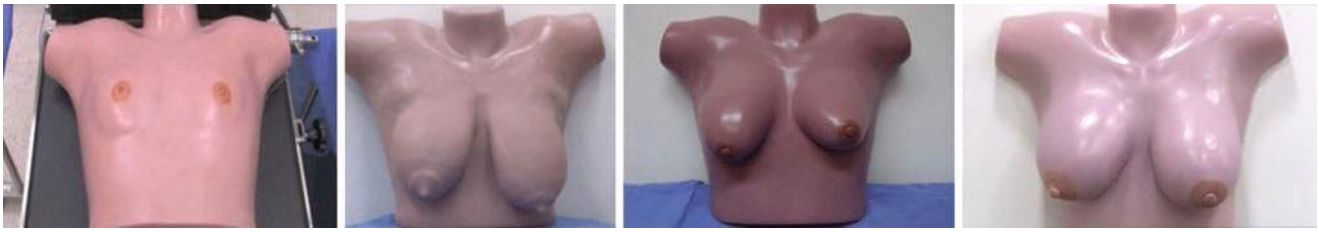

Fig. 72.2 Mastotrainer different generations

When practicing suturing, it can provide the appropriate resistance to the specific tissues being worked on in addition to the type of sutures being used and maneuvers being performed. These advanced teaching techniques decrease the learning curve for new professionals when learning to perform procedures for the first time.

The "Mastotrainer" was introduced as a new concept of simulators for use in surgical training. The Mastotrainer has proved very useful in training various surgical techniques, with the first version of the simulator being focused on breast augmentation and reconstruction following mastectomy. The second version of Mastotrainer, simulating larger and ptotic breasts, provides hands-on training for preoperative markings and various mammaplasty techniques, including breast-conserving surgery, reconstructive lumpectomy, and oncoplastic procedures. Third version, medium size breast, allows mastopexy, vertical mammoplasty in additional to other techniques. More recently the fourth version is a large breast model improved. All of the Mastotrainer models are valuable for training oncologic, aesthetic, and/or reconstructive breast surgeries (Fig. 72.2).

This training model allows beginning surgeons to gain experience with fundamental surgical skills and principles such as making incisions, suturing, and identifying surgical planes which will diminish the risk of future preventable mistakes that can occur in the practice of surgery. There are an enormous list of factors that contribute to error prevention such as adequate experience, familiarity with the surgical field, and immediate recognition and successful solution of prior critical problems. All errors are discussed after the exercises are completed, and this is crucial to the surgeon's learning experience and ability to prevent real future morbidity for their patients.

Multiple virtual challenging clinical scenarios can be simulated by this program, and the surgeon's performance under stress situations can be evaluated. These tutorials focus on improving surgeon performance using both basic and more advanced modules.

72.3 Discussion

In aviation, pilot experience is recognized to be invaluable, and this is gained in simulation programs and tutoring before they fly a plane. They are therefore required to undergo yearly training with new technology in different crisis simulators. Why not surgeons too?

Medical mistakes are, and will always be, inevitable in the practice of medicine. The goal here would be to give the novice surgeon experience with difficult operative challenges on a simulator before he is forced with a similar situation in a live patient.

The continuing evolution of surgical education in breast disease is a complex process that has been affected by several variables. During the last decade, many factors, such as an increasing demand for subspecialty care by patients and referring physicians, have forced some changes to the current method of training. In fact, breast and plastic surgeons have been pushed to develop their surgical skills in a relatively shorter period of time. Surgical training in breast reconstruction has some specific requirements. A unique set of instruments is required, as is a practice model that closely resembles the different tissue types with which a breast surgeon will be faced.

Despite the ability of cadaveric models to provide excellent lifelike simulation of multiple varied reconstructive procedures, the access, ethical issues, safety, and cost-effectiveness of this strategy have impaired the widespread use of such models.

Another nonsurgical issue but perhaps equally important role for training centers is to teach the surgeons the value of really listening to their patients. Very often aesthetic results are poor from the viewpoint of the surgeon, but the patient is contented, mainly because she was treated for cancer and still has an acceptable breast shape. Of course, aesthetic results are important; however, for a breast specialist, the results cannot be evaluated in isolation but must take into account the goals, motivations, desires, and psyche of the woman that is being treated. As a surgeon gains experience with oncoplastic methods, the approach is much like a Swiss

army knife replete with different surgical options, some more or less appropriate for the clinical scenario and the expectations of the patient. In the twenty-first century, treatment of breast cancer has become more and more individualized, on both the molecular level and on the level of the whole human being, respecting the wishes and expectations of the patient in front of you. In addition, patients have become more demanding, with the increased expectations of their treating physicians pushing us to continuously refine our surgical techniques. The communication between breast surgeons and plastic surgeons is certainly important for this improvement in the standard of care regardless of the specific roles of each surgeon.

Critically important to teaching oncoplastic surgery is the use of a variety of methods including demonstrations of the relevant anatomy for breast reconstruction, small group tutorials, implant workshops, and experience with anatomical dissection. Students should perform cadaver-based procedures reinforced by teaching videos and live operative demonstrations. The training centers should provide comprehensive oncological and reconstructive training with structured educational supervision, assessment, and feedback.

72.4 Conclusions

A well-organized educational program in oncoplastic breast surgery can elevate the current standard of care. We strongly believe that surgical simulators will provide a critical experience in the training of future oncoplastic surgeons to ensure the safe transition to surgery on live patients.

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Bioethics and Medicolegal Aspects in Breast Cancer Reconstruction

73

Cicero Urban, Iris Rabinovich, James Hurley II, Mario Rietjens, and Karina Furlan Anselmi

73.1 Introduction

The integration of bioethics in reconstructive breast cancer surgery is essential, because few diseases represent such a complexity from the scientific, psychological, therapeutic, ethical, and social point of view as breast cancer. Surgeons who are dedicated to this delicate field of work face daily situations that demand great sensibility and deep bioethical and medicolegal analysis.

Bioethics is one of the most dynamic emerging fields of philosophy applied to professional praxis and research in biotechnology and in medical practice. Although bioethics was born in the USA in 1970, in Brazil and in Latin America, it appeared only in the mid-1980s and is considered now as late bioethics within the global scenario. Yet, it has been taking an increasing importance among the main specialized medical societies and medical associations. That is so because of its relationship with both individual and professional dilemmas that affect health professionals, legislators, and citizens. Therefore, this chapter will approach the most relevant bioethical issues and medicolegal aspects concerning breast cancer treatment, with a special focus on breast reconstruction.

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73.2 Current Concept

The concept that has come the closest to the ideal that bioethics proposes was elaborated by Reich in 1995 in his *Encyclopedia of Bioethics*: "A systematic study of the moral dimensions – including moral visions, decisions, conduct, and policies – of the life sciences and health care, employing a variety of ethical methodologies in an interdisciplinary setting" [1].

Bioethics must be considered a tool for medical decision-making, although being interdisciplinary is its most important characteristic. This is what makes it different from classical medical ethics, which is traditionally marked by an almost exclusive emphasis on the doctor-patient relationship. This deontological approach has proven to not be enough to encompass the emerging situations that have been aroused in the past decades [2]. Thus the domains of medical ethics and of today's deontology interact with bioethics for the resolution of conflicts in research, public health, and internal medicine.

73.3 Bioethics and Research in Breast Cancer

Breast cancer is one of the most currently researched diseases involving human subjects. The ethical regulations that govern such pieces of research were developed from events that raised great concern among the academic community due to history such as the research performed by the Nazi physicians and by the American postwar physicians, especially those in the study of Tuskegee, in the state of Alabama [1, 3].

One of the main bioethical elements found in the regulations for research involving human beings is the expectation that the knowledge and advances produced will ideally lead to the well-being of all humanity. Therefore, a moral principle in research with humans is respect for human dignity. Two components must be highlighted here. The first one is

C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8_73

the choice of subjects for research, aiming to provide the subjects themselves and other groups with benefits, and also for the advance of science. The second one is the use of morally acceptable means to reach the same ends. The key point in moral objections of research is using another human being as a means to legitimate ends. It is unacceptable to treat people as a means or an object. Such an attitude harms the dignity that is innate to human beings, as it also downgrades the medical professionals, researchers, and humanity as a whole [3–5].

Risks in research must be interpreted from the bioethical principle of no harm, that is, the duty of forecasting or avoiding harm to the subjects involved in research. They must not be involved in unnecessary risks. Research with humans must be beneficial to society as a whole, but also to the subjects themselves. That means that all patients with breast cancer involved in research need to be benefited as well [3–5]. Professor Umberto Veronesi states that "*si cura meglio dove si fà ricerca*," which means we can treat patients better where we can perform research. It is necessary that this principle be respected and advocated by members of the institutional review board and also by the sponsors involved and by the researchers themselves.

The ethical approach to this research needs to center on the patient with cancer. Sometimes the expectations, interests, and hopes of the patient in research are not proportional to their real benefits. In order for their free and clear consent to be established in its full potential, the transmission of information must be technically adequate, individualized, and with clear language. Therefore, a positive and collaborative relationship between researcher and research subject is established. Considering the patients with breast cancer, it is important to highlight the vulnerability existing among patients diagnosed with a serious, chronic, and potentially mutilating disease. These patients demand special attention as to free and clear consent in order to respect their autonomy.

Research in breast surgery that involves patients either directly or indirectly (for instance, those researches that use health records or test results) must follow the principles specified in international recommendations like the Helsinki Declaration, the norms for good clinical practice, and the Human Rights Declaration. Research protocols must go through the approval of an Institutional Review Board, in agreement of each country's standards. Research involving areas such as genetics and human reproduction and research with new drugs with industry cooperation need special attention in order to protect patients and prevent them from being the subject of exploitation in research that involves significant conflict of interest, especially in developing countries and vulnerable populations [5]. Particularly, in breast reconstruction research, patients should be respected in regard to their privacy, with special care with photos.

73.4 Breast Cancer and Public Health Care

The remarkable American bioethicist Daniel Callahan has had severe criticism to the ways of western medicine. He argues that one of western medicine's main problems is setting unlimited horizons for its range of work. This lack of limits and the uncontrolled expansion (even disregarding the health-disease relationship) end up resulting in an increase of medical care costs that not always corresponds to an improvement in most people's health. Therefore, the use of sophisticated resources, with high costs and benefits that are not always proportional to such costs, has turned modern medicine into an impossible project to be accomplished [6].

One of the examples that can be mentioned regards the USA, a country that spends over 2 trillion dollars on health, which corresponds almost to the amount spent by all the other countries together [7, 8]; there are over 46 million Americans out of the health system. Suffice it to say that one of the key points of Barack Obama's presidential past campaign was health reform in the USA. This is something that will become even more difficult to be completed in a period of a global economic crisis.

Breast cancer, as a health problem all over the world, may bring important consequences if erroneous decisions in health policies are made. In Brazil, breast cancer is the main cause of death from cancer among females. The use of only 2–3% of the gross internal product (GIP) on health (in the USA more than 15% is used) results in an ethical dilemma of considerable proportions within the public health system, which is known by all Brazilian health professionals. The public health system in Brazil is a Universalist one, and it is similar to most of European models (guaranteed by article 196 of the Brazilian Federal Constitution of 1988—"… health is the right of all people and the duty of the State…"). However, as it happens in many European countries, the State cannot keep its costs unlimited, so it risks becoming bankrupt. That is why in the specific case of breast cancer, mammographic screening and timely access to updated treatments are inadequate given the distribution of existing resources. So the Universalist model does not manage to reach everybody equally. The unequal conditions in diagnosing and treating breast cancer in the Brazilian environment have not been properly studied yet. The damages in terms of life expectancy and years lost on work are noticeable and may increase in the forthcoming years.

The aim of health policies on cancer in developed countries is focused on prevention and early diagnosis. The mammographic screening test and the routine clinical exam may reduce mortality caused by breast cancer by 25–30% among women over 50 years of age. Such measures aim to find tumors of smaller size, which implies treatments will have more effective results and at lower costs. An example of how this can work is ductal carcinoma in situ (DCIS), which is the

sort of breast tumor with the highest incidence in developed countries. Over 90% of the cases are not palpable, and their diagnosis is only possible through mammography. There is no need for chemotherapy or sentinel node biopsy as well as axillary dissection. The rate of cure is approximately 100%, and for most of patients with breast preservation techniques.

Considering that the potential of years wasted with breast cancer is second only to cardiovascular diseases, its economic and social importance is evident. The reduction in the mortality of breast cancer, first noticed in the USA and then followed by Sweden and England and now reaching most of the countries in the European Union, is a result of investments in detection and access of most of the population to better diagnostic and therapeutic modalities. It is clear that the early diagnosis not only benefits women in terms of survival and less mutilating surgeries but also reduces treatment costs and keeps an important portion of society with breast cancer economically active.

On the other hand, in developing countries in reproductive age groups, breast cancer is considered a substantial problem with similar importance to major global priorities such as maternal mortality [8, 9]. Advanced tumors demand therapeutic resources at higher costs. Results in terms of disease-free survival, however, are less satisfactory than at the early breast cancer stages. Local recurrences and distant metastasis require the use of chemotherapy schemes, hormone therapy, radiotherapy, and monoclonal antibodies of growing complexity in relation with those applied to more precocious tumors. Besides that, they diminish the labor capacity of these patients and require longer rehabilitation periods. A patient with metastatic breast cancer currently under the recommended treatment will cost the state and health insurance companies more than the transplant of organs and a few mammography and ultrasonography devices.

In developing countries, an increase in both the incidence of cases and in the mortality caused by this disease is expected [8, 9]. Therefore, it is imperative that the population has access to early diagnosis and proper treatment at the right time. These are some of the challenges in breast cancer that public health systems all over the world have to face. In this situation, bioethics may work as an element of facilitation in the formation of governmental decisions, following the example of other countries such as the USA and Italy, which have national committees of bioethics involved in public health matters.

73.5 Genetics and Breast Cancer

Although a positive family history is reported between 15% and 20% among women with breast cancer, congenital breast cancer occurs only in 5–6% of all cases [10], and mutations in genes BRCA1 or BRCA2 are found in most of these cases [11]. Although mutations of the BRCA 1 and BRCA2 genes are most frequent, there are gene mutations associated with hereditary syndromes that may increase familial risk for breast cancer such as P53, PTEN, CDH1, STK11, MLH1, MSH2, MSH6, and PMS2 [12]. Today genetic tests to identify such mutations are commercially available. The frequency of these mutations is rare; however, they occur in approximately 0.1% of the population in general [12]. The prevalence of mutations BRCA is higher among Ashkenazi Jewish women, reaching 2% [13]. These genes are considered tumor suppression genes, and they work on repairing DNA. When there is a mutation, this function is not performed properly, which allows for the formation of a tumor. Transmission is dominant autosomal, but the penetration is incomplete; therefore, genetic mutation points to a higher susceptibility of developing a breast cancer, but that does not occur in all cases. It is estimated that a person holding mutation in gene BRCA1 or BRCA2 has a risk of developing breast cancer around 50–87% throughout life, and a risk of developing ovary cancer between 15% and 44% [14, 15].

Genetic consultaion and a genetic test should be proposed when (a) the patient has a personal or family history that points to a genetic condition susceptible to cancer (the criteria established by the *National Comprehensive Cancer Network* are as follows: family history of a patient in the family with ovarian cancer, a history of breast cancer before age 50, a history of triple-negative breast cancer diagnosed before 60 years of age, two primary breast cancers in the same individual, breast cancer at any age with a first-degree relative with a history of breast cancer before age 50 or ovarian cancer at any age or two high-grade relatives with breast cancer and or pancreatic cancer at any age, individual with no personal history of cancer but with a family history of two primary cancers in the same individual, male breast cancer, and family history of three or more family tumors such as pancreas, prostate, sarcoma, adrenal, lung, leukemia, colon, stomach, endometrial, and thyroid) [16]; (b) the genetic test may be adequately interpreted; (c) test results contribute to the diagnosis or influence the clinical or surgical treatment of the patients or of their families with risk of congenital cancer. It is recommended that the genetic test be only performed together with genetic advice pre- and posttest, which must include a discussion over possible risks and benefits of early detection of cancer and the modalities of prevention [17].

It is critical to interpret results adequately. There are three types of results: (a) positive result (the mutation with deleterious effects in BRCA1 or BRCA2 was found, and it put the person at risk by increasing the development of a breast cancer and ovarian cancer), (b) negative result (there is a mutation known by the family, but the person tested is not a holder of such mutation), and (c) inconclusive or

undetermined (no mutation is identified in the person tested, and there is no case of mutation known in the family, or a mutation was found in the test but its meaning is unknown).

The choice for undergoing the diagnostic test must be exclusively made by the patients. They must be aware of their choice to either accept or refuse the genetic test. In the pretest advice session, all of the important and necessary information must be given to the patient. This must cover the advantages and limitations of the test, the possible types of results, and the measures to minimize risk that can be taken. Informed consent is, therefore, a mandatory prerequisite for any type of genetic test. The principle of autonomy is the base of informed consent, and it is essential for preserving the individual's freedom and his right to make choices [18].

When an inherited breast cancer syndrome is suspected in a family, the first person that has to be tested is the relative affected with the disease. Once the test identifies the mutation, a genetic test to this specific mutation can be done in the other family members. Each relative has 50% chance of being a mutation carrier [19].

If the genetic test is positive for a mutation, one of the most effective methods that can be considered to reduce the breast cancer risk is prophylactic surgery. The prophylactic surgery includes prophylactic bilateral mastectomy and/or prophylactic bilateral salpingoophorectomy. If the patient doesn't want to undergo a prophylactic surgery, chemoprevention (tamoxifen) and surveillance (clinical breast examination, self breast examination, mammography, and magnetic resonance imaging) could also be discussed [19].

Although there are no randomized prospective trials that evaluated the efficacy of prophylactic bilateral mastectomy, and not many studies approached this issue, the literature shows that bilateral prophylactic mastectomy reduces the risk of breast cancer by approximately 90% in BRCA 1/2 mutation carriers and high-risk breast cancer patients [20–24]. Even though the accomplishment of a prospective randomized trial would be the best way to evaluate the efficacy of the prophylactic surgery, it probably would be not possible because not many patients would accept to be randomized to do a prophylactic surgery or nothing.

In terms of surgery, there are four kinds of prophylactic mastectomy: total mastectomy, skin-sparing total mastectomy, nipple-sparing mastectomy, and areola-sparing mastectomy. The lack of prospective randomized studies comparing these different techniques makes more difficult to establish which one is the ideal approach. The total mastectomy initially appears to be the safest procedure, because it removes the breast tissue, skin, and nipple-areola complex; on the other hand, the aesthetic outcome is poor. The skin-sparing mastectomy emerged as an alternative to total mastectomy, with better aesthetic outcome because it preserves the skin and, when it is associated with a reconstruction procedure, can reach a better outcome. Recently, the subcutaneous mastectomy (nipple-sparing mastectomy) has appeared as a surgical variation that consists in preservation of the skin and the nipple-areola complex ensuring an even better aesthetic result, with a more natural appearance of the breast. This technique however brings a serious concern, because a greater amount of tissue is preserved along with the nipple-areola complex and this could be associated with a higher incidence of cancer. Although this fear came from pathologic studies that shown the presence of cancer cells in the nipple ducts, there are insufficient data to support this argument, and some studies has already demonstrated good results with this technique [19, 25]. At last, the areola-sparing mastectomy consists in the preservation of the skin and the areola and the removal of the breast and the nipple. There are insufficient data with this kind of surgery in terms of aesthetic-functional outcomes and/or long-term oncologic results.

Privacy and confidentiality: respect to the privacy of patient's genetic information demands that the result of the test be not revealed to anyone without the consent of the individual tested. When family mutations are identified, individuals should be strongly encouraged to share results with other family members who are also at risk, especially when risk reduction measures can be taken [17]. However, some people may not feel like revealing genetic information to other members of the family. The doctor may face an ethical dilemma if the patient refuses to reveal genetic information to relatives that are at risk. In such situations, the subject of reliability is in conflict with the ethical principle of avoiding damage to others [18]. Most authors do not support the revealing of family genetic information without the patient's consent, unless the possibility of serious damage exists and is very high [26, 27].

Another important aspect to be considered is genetic discrimination. This refers to less favorable or adverse treatment that an individual without traces or symptoms of the disease gets, based on their genetic or genotypic characteristics [26]. The affected individual may experience discrimination from insurance companies and job agencies. The fear of discrimination is one of the most commonly identified reasons among women who are not willing to take a BRCA genetic test [28–30]. Considering that, preserving the individual's confidentiality of genetic information is very important.

Finally, the psychosocial influences that the result of the genetic test will bring to the life of the patient must be considered. Knowing that a genetic mutation is present and the consequences of the personal risk of breast cancer may affect a person in various ways. Women with positive test results might experience a wide variety of emotions such as anxiety, depression, fear, and anger. Women who have already had breast cancer may feel disturbed when learning that they have the risk of developing other types of cancer. Also, individuals

might have a feeling of guilt, despite the existence of a possible mutation. Bearers of mutation BRCA may experience "transmission sense of guilt" for they can transfer an increased genetic risk of cancer to their children, while non-bearers may experience the "survivor's sense of guilt" for being among the members of the family who did not inherit the mutation. Therefore, a proper psychological preparation of the patient before performing the genetic test is important.

73.6 Clinical Bioethics

> *Clinical case study*: A 37-year-old, white, homemaker, Catholic, diagnosed with breast cancer, T2N0, ER/PR positive, and HER-2 negative. She is in her 7th week of pregnancy and wants to have an immediate breast reconstruction. The breast surgeon was asked to give an opinion of the case.

Regardful medical virtues such as integrity, compassion, and altruism are determinant for the exercise of medicine [24]. Albert Jonsen, professor emeritus of medical ethics at the University of Washington, created a practical method to aid in the resolution of complex clinical cases, like the one presented above. It is based on four fundamental points: medical indications, patients' preferences, quality of life, and contextual aspects [2]. A favorable point of this method is that it allows for a shared bioethical sense that is easy to understand.

73.6.1 Medical Indications

It is the relationship between pathophysiology and therapeutic/diagnostic interventions that are indicated to solve the case properly. It refers to the application of medical and scientific knowledge. Whenever possible (and when such conditions are available), they must be based on clear scientific evidence. In breast oncology, around 60–80% of all decisions can use data from evidence-based medicine (MBE), in contrast with general medicine, in which a little more than 15% of the clinical decisions are based on consistent scientific evidence, and around 40% are based solely on professional expertise, since they do not provide published clinical studies that could respond to all existing questions. Important points to be considered and those with bioethical implications:

- What is the patient's health problem?
- Is it a severe or a chronic problem? A critical one? An emergency? Is it reversible?
- What are the targets of the treatment?
- What are the probabilities of success?
- What are the perspectives of failure of the treatment?
- To sum up, how can the patient benefit from the treatment in question?

73.6.2 Patients' Preferences

In all medical treatments, patients' preferences, based on their own values and perceptions as to the benefits and risks, are ethically relevant. The following points must be clarified before decision-making:

- Did the patient express their preferences concerning the treatment?
- Was the patient correctly informed about the risks, benefits, and their consent?
- Is the patient mentally capable and legally competent?
- If incapable, who is the legally responsible individual?
- To sum up, is the patient's autonomy being respected?

73.6.3 Quality of Life

Besides preserving the life of the patient, another major target of medical intervention is to reestablish, keep, and improve the quality of life. What is the expectation with and without the treatment for the patient to go back to a normal life? The questions that must be clarified:

- What problems may impede the evaluation of the patient's quality of life?
- What physical, mental, and social limitations will the patient present with after treatment?
- Is present or future condition of the patient be considered undesirable?
- What are the plans to offer the patient some comfort or palliation?

73.6.4 Contextual Aspects

The care of patients is influenced either positively or negatively by the family and by a variety of contexts such as personal, emotional, psychological, religious, financial, educational, legal, institutional, scientific, and social. The questions that must be clarified:

- Are there family problems that may influence therapeutic decisions?
- Are there any financial problems?
- Are there any medical or nursing problems?
- Are there any religious or cultural problems involved?
- What about the allocation of resources?
- Is there any reason for breaking confidentiality?
- And how about legal matters?
- Is there any research/teaching involved?
- Is there any conflict of interest?

Some important points emerge from this type of methodology. One of the most important of them is that no bioethical analysis of clinical problems should be performed without a deep scientific knowledge and clinical experience of the matter. A lack of knowledge invalidates any conclusion a posteriori. The second one is that a bioethical background is fundamental to the specialist decision.

By applying Albert Jonsen's method to help the breast surgeon find an answer to the clinical dilemma, one can find (a) *medical indications*—it refers to a 37-year-old patient with a breast neoplasia in the 7th week of pregnancy who is asking to maintain the pregnancy (in some countries it is not allowed to perform unless the patient is at risk to die) and wants a breast reconstruction. The patient is not a good candidate for neoadjuvant chemotherapy due to the risk of malformation. Since the patient is not in an urgent situation, there is no need to make an immediate decision—the decision can be discussed with the bioethical committee, patient, and family. Breast reconstruction in this case can be done with less aggressive techniques like expander/implants, without compromising the pregnancy or oncologic treatment. (b) Patient's preferences—the patient requested a breast reconstruction and to maintain the pregnancy. She is legally competent. (c) *Quality of life*—the quality of life without reconstruction is expected to be worse. The patient has a chance to return to a normal life, and the absence of the breast will cause damage to her quality of life in the near future. (d) *Contextual aspects*—there are legal-medical implications for abortion in Brazil, and the patient would not terminate the pregnancy influenced by her Catholic origins [31]. Breast reconstruction in this case, once it is well documented in the medical records and properly authorized by the patient, is ethically acceptable in such case.

Albert Jonsen's method improves the knowledge about conflicts, protects patients' autonomy, and integrates medical decisions. On the other hand, although it examines these situations and organizes them systematically, it does not solve them in all cases. The conflicts may occur within each of these points mentioned. Decision-making is sometimes so complex that it is necessary to resort to technical support from a consultancy professional with bioethical competence in the resolution of problems or, preferentially, of a bioethical committee.

73.7 Medicolegal Aspects in Breast Cancer Reconstruction

According to the American Society of Plastic Surgeons in 2010, 93,083 breast reconstruction procedures were performed. Seventy-four percent of these used either saline (20%) or silicon (54%) implants. Another 19.5% were accomplished using various flaps including TRAM, latisimus dorsi, DIEP, and others. Twenty-two percent of the implants were ultimately removed. According to Mark Gorney from The Doctors' Company [32, 33], 31% of claims against plastic surgeons involve elective breast operations. Of these, 55% are related to scarring or tissue loss/necrosis, and 45% are related to augmentation or reconstruction of the breast done with expanders and subsequent implants [33]. As oncoplastic surgery done by breast surgeons is a relatively new concept in the USA, further evaluation in this area is not available but will be carefully examined in the near future. This section will outline several areas that both plastic and oncoplastic breast surgeons need to address to limit their liability. These include patient selection and expectation, communication, informed consent, documentation, and event management.

73.7.1 Patient Selection and Expectations

It is important to realize that patients that present for purely aesthetic breast procedures are very different in their expectations from those that need reconstruction as part of their breast cancer treatment. The former will want a result that is better than their baseline in terms of aesthetics and symmetry. These patients will not present ordinarily with a breast cancer diagnosis and may be unrealistic in their expectations. The ability of the surgeon to perform to these expectations is fundamental. The cancer patient will undergo a destructive procedure to cure their cancer, and the final result is not usually expected to be as good as the original breast. Reconstructive surgeons should be well suited to this task with appropriate training. Though expectations are somewhat lower, a near normal breast with symmetry should be accomplished. This, of course, is made harder by the removal of breast tissue, chemotherapy, and radiation therapy. These patients may also return some time after their initial care for further aesthetic-functional adjustments and surgery. The surgeon should be able to handle this as well. Surgeons should learn to identify these patients when they present to serve them in the most appropriate manner.

When dealing with a patient's expectations, a careful history is very important to ascertain the patient's motives and desires. This requires good patient contact, empathy, attention, and questioning. It may also be useful to talk with significant others such as spouse or family members to further determine the results desired.

Not only are patient factors important in planning surgery, but the surgeon's comfort level with the patient, experience, and training are also variables to consider before operating. The patient must have reasonable expectations regarding what is possible, and the surgeon must be comfortable that he can deliver the desired result. If not, then not operating or referring the patient to someone more qualified is certainly a good outcome.

73.7.2 Communication

Honest and timely communication is of utmost importance in any doctor-patient encounter. Being on time in the office or giving the patient a cell phone number or email address is powerful communication. Eye contact, body language, and vocabulary choice also come together to send a message to the patient and her family, either good or bad. The ability to communicate and establish a relationship will significantly add to the credibility of the surgeon. The acronym HEAL [34] has been very useful in establishing and continuing relationships with patients and families especially in times of poor outcomes. H is for hear. Hear what your patients and families are trying to say. E is emotions. Address the patient's and family's emotions. A is for ask and answer. Ask patients and their families to tell you what they already know and answer what they want to know. Finally, L is loyalty. Foster already existing loyalty and rebuild that portion that may have been lost. Most medical malpractice cases are caused by no or misunderstood information and the patient's or family's need to learn the facts of the care given [34, 35]. The surgeon must learn to be a good communicator and, thus, educator of his patients. This education informs the patient of the disease process, prognosis, treatments, and alternatives and explains possible negative outcomes. This begins with the first handshake and never ends.

73.7.3 Informed Consent

The process of informed consent is the foundation of the doctor/patient relationship. Through this interaction, the patient comes to understand her diagnosis, options for management, potential outcomes and risks of each option, and what can be expected as an ultimate result. From this information, the patient can choose a course of action by including her own preferences and desires. Informed consent is not a simple form the patient signs but a process that begins with the first consultation and continues with each encounter. It involves the previously mentioned areas of patient selection, communication, and management of expectations. It is the surgeon's best friend in malpractice litigation. It is one of the first areas of examination by plaintiff's attorneys and, if absent or weak, is almost always included in complaints.

In documenting informed consent, a preprinted form (Fig. 73.1) is usually required, but in addition hospital or office notes should reflect the thought process the surgeon and patient have taken in support of the final written consent. These notes should include the patient's thoughts, expectations, and specific refusal of offered options. A specific summary statement should be included in the notes (e.g., I have talked with the patient at length regarding her diagnosis, proposed procedure, potential risks, possible benefits, and alternative modes of therapy. Risks discussed included but were not limited to _____. She understands the procedure, accepts the risks, and wishes us to proceed. We will do so in the near future.) Risks should be listed but this is not meant to be all inclusive. Table 73.1 lists the most common potential risks of oncoplastic surgery. A good informed consent process will not only protect the surgeon but enhance the relationship with the patient.

73.7.4 Documentation

Documentation is the cornerstone of any malpractice defense. Good documentation may convince a plaintiff's attorney not to pursue a case. In addition, it certainly is valuable when reviewing a patient's care and outcomes as well as making treatment plans. Documentation includes many aspects of the medical record. The hospital chart should be complete in a timely manner including the history, physical, consents, operative notes, and discharge summary. The office records should include all interactions and contacts with the patient such as telephone calls, literature given to the patient, notes of office visits, consents, correspondence, and photographs (preop and postop). The office notes should include history, physical, diagnostic results, diagnosis, treatment plans, referrals, alternatives, risks, and the patient's desires and expectations. Of course, no record should be altered after being signed off as this greatly weakens the credibility of the medical record. Late entries are allowable if identified as such. The records should also be legible.

73.7.5 Event Management

Despite the surgeon's best efforts, poor outcomes do occur (Table 73.1). Patients and their families are often very disappointed in these results. They have trusted the surgeon to meet their expectations, and when that does not occur, trust is shaken, and the surgeon is likely to be second guessed. It is at this point that the relationship with the patient may be lost. The surgeon must continue to communicate. A full and honest explanation to the patient and family is required. Sincere and empathic apologies may also help to ease the disappointment. In this regard, many lawsuits are filed simply because of lack of explanation [36]. These patients and families may not have been personally approached by their surgeon or feel that there may be something "covered up." Many plaintiffs file complaints to find the truth.

In addition, some progressive malpractice insurers wish to be notified of adverse events when they happen to help guide the surgeon in recovering the patient's trust.

CONSENT FOR SURGERY

1. I,…….. according to my own will, hereby authorize doctor CICERO URBAN and all the other members of his team of professionals related to my medical assistance to perform the surgery herein described…….. …… …… ……, as well as the medical treatments and follow-up care derived from it.
2. I certify that this surgery I now consent has been fully explained to me by doctor CICERO URBAN and his team both in person and through printed information material, therefore I understand that:

   A permanent **SCAR** will form as a result of the surgery, but all the necessary measures will be taken in order to minimize its effects and visibility.

   There might be a **SWELL** in the operated site, which may remain for weeks and even, though rarely, for a few months.

   SPOTS or **DEPIGMENTATION OR DISCOLOURATION AREAS** may also appear in the operated site for some time. In very rare cases they can remain permanently.

   Occasionally, **LIQUIDS** (blood or secretion or fluids) may accumulate in the operated site, so there is the need for draining, aspiration or surgical repair. This is more frequent after axillary dissection.

   There may be **LOSS OF SENSITIVITY AND/OR MOBILITY** in the operated site for an indefinite period of time, which varies from patient to patient. It occurs more frequently after axillary dissection.

   There may be **LOSS OF BIOLOGICAL VITALITY** in the operated site, caused by blood vascularisation reduction, which may result in alterations of the skin and, in more rare cases, necrosis, which demands repair through another operation or even operations.

   There may be **POSTOPERATIVE PAIN**, in either higher or lower levels of intensity, for an indefinite period of time, which varies from patient to patient.

   Every surgery may demand better **FINISHING** or small complementary surgeries performed to achieve better results.

   Considering that I have been informed of all the above:

3. **I assume** that throughout the surgical procedure there may be unexpected situations that had not previously been identified and, as a result, **ADDITIONAL PROCEDURES OR**

Fig. 73.1 Informed consent model for oncoplastic and reconstructive surgery from Our Lady of Grace Hospital Breast Unit, Curitiba, Brazil

DIFFERENT ONES from those that had been arranged may be needed. Bearing that in mind, I allow the team to perform procedures that match such new situations.

4. **I assume** that Doctor XXXXXXXXX and his team will solely use all the necessary technical and scientific means at their disposal to achieve the results that are so desired, nevertheless such results are not guaranteed. Medicine is not an exact science, and consequently **GUARANTEES OF GOOD RESULTS CANNOT BE OFFERED.**

5. **I assume** that **TOBACCO SMOKING**, the use of **DRUGS** and **ALCOHOL**, though they are not able to prevent the surgery from being performed, are risk factors that can produce surgical-medical complications.

6. **I allow** the recording (photos, sound and/or filming) of the surgical procedures to be made because I understand that such registering is a legal-medical demand and a source of study and scientific information.

7. **I accept** that considering breast implants, the possibility of hardening may occur, as well as shape alterations, local pain and loss of sensitivity, and implant rupture, which derive from the use of silicon (or other kind of implants), and reactions of my body to it. This effect might imply that new surgeries be performed.

8. **I am aware** that I may experience limitations to perform everyday activities for an indefinite period of time.

I have had the opportunity to **CLARIFY ALL OF MY DOUBTS** concerning the surgery that I am voluntarily about to undergo, reason why **I ALLOW Doctor _____ and his team** to perform all the necessary procedures.

Location:

Date: _____

Doctor's signature: _____

ID:_____

Witnesses:

1._____

ID:_____

2._____

ID:_____

Fig. 73.1 (continued)

Table 73.1 Potential complications in oncoplastic surgery

Death
Myocardial infarction
Stroke
Deep venous thrombosis
Pneumonia
Infection
Bleeding
Prolonged drainage
Partial or total necrosis of skin or flaps
Seroma
Hematoma
Multiple surgeries/reoperation
Loss of implant or expander
Non-symmetry of breasts
Expectations not met
Recurrence of cancer
Prolonged care/wound care
Necrosis of nipple/areolar complex
Loss of sensation of nipple/areolar complex
Chronic pain
Keloids/scars
Discoloration
Need for drainage/aspiration
Lymphedema
Pain, swelling, numbness, disability, dysfunction of arms
Nerve or blood vessel damage
Hernia
Pneumothorax
Fat necrosis
Implant contracture, immediate or delayed
Rejection of implant at any time
Rupture of expander or implant

This interaction is important as the surgeon and his ego are most vulnerable at this time. The initial impulse is to avoid the situation and that is precisely the wrong approach [37–39]. Advice from an event manager can prove to be quite helpful in avoiding litigation. Many feel that this transparency is full of potential problems, but, in fact, this approach can actually decrease the frequency of lawsuits, increase credibility, and maintain the physician-patient relationship.

73.8 Conclusions and Perspectives

Bioethics has been walking together with the development of biotechnology and with its dilemmas, which go far beyond the technical-scientific debate. Within reconstructive breast cancer surgery specifically, there is the need for introducing bioethics and medicolegal aspects in the educational programs for specialists. It is true that technological development has improved the possibilities of the diagnosis and therapy of breast cancer, but the individual experience of those who deal with this malady daily is not the only object of scientific calculation. In addition to scientific competence, the physicians must have the humility to recognize their role and their limits: taking care above curing. This is the most important virtue to be cultivated by the breast surgeon with the aid of bioethics, reducing claims and improving breast cancer patient's survival and quality of life.

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C. Urban et al. (eds.), *Oncoplastic and Reconstructive Breast Surgery*, https://doi.org/10.1007/978-3-319-62927-8