Editorial

Is Australia lagging behind in the use of neoadjuvant chemotherapy for breast cancer?

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Comment on: Patiniott PD, Wong GY, Lam YH, *et al.* Neoadjuvant chemotherapy rates for breast cancer in Australia—"are we there yet?". Ann Breast Surg 2019;3:9.

Received: 13 June 2019; Accepted: 24 June 2019; Published: 02 August 2019.

doi: 10.21037/abs.2019.07.01

View this article at: http://dx.doi.org/10.21037/abs.2019.07.01

Neoadjuvant chemotherapy (NAC) is an important treatment option for patients with breast cancer. This paper utilises data from the Breast Surgeons of Australia and New Zealand Quality Audit (BQA). This is a large bi-national audit which collects approximately 80% of all breast cancer cases in Australia and New Zealand. Although data from the BQA is encouraging with NAC use more than doubling from 2011 to 2016 (3.08% to 6.65%) in many centres it remains an underutilized option. A NAC usage target of 20% of patients presenting with breast cancer would be likely to improve outcomes in Australia. Australia appears to be lagging behind the USA, Canada and The Netherlands. Quoted in the paper, US National Data Base reported 24% use of NAC in 2011. A population-based review in Canada showed 8.53% utilisation 2012–2014. And the Dutch National Breast Cancer Audit showed 14% utilisation in 2015.

Why have we been slower to adopt this treatment option?

Numerous benefits of NAC are highlighted by Patiniott *et al.* These and others are listed below.

Locally advanced breast cancer is more operable translating to higher rates of breast conserving surgery (BCS).

BCS was increased from 60% to 68% with NAC in NSABP B-18 (1). N2 and N3, lymphovascular invasion, >2 cm residual disease and multifocality can predict a higher locoregional recurrence rate in those patients converted to BCS by NAC. NAC can also be useful in facilitating extreme OPBCS (Oncoplastic Breast Conserving Surgery). DCIS extent is not altered by NAC. Converting a patient to BCS after successful NAC is safe (2).

NAC use has a low risk of infective complications post-surgery (3). NAC use in immediate implant reconstruction does not lead to higher rates of implant loss (4).

NAC allows for pathological assessment of tumour response. A pathological complete response (pCR) helps determine prognosis and in some cases may alter the treatment pathway such as the need for axillary clearance rather than a SN biopsy (5) and the need for post mastectomy radiotherapy. The impact of this is the subject of numerous current investigations. For example patient selection for post mastectomy radiotherapy after a pCR (NSABP B_51/RTOG 1304 and RAPCHEM).

A poor response to NAC is expected in only 3% of patients, however in these cases there may still be an advantage in being able to switch to alternate treatment regimens.

Chemotherapy is the only modality that can sterilize distant metastases. Beginning treatment with locoregional therapies (surgery and radiotherapy) delays whole body treatment.

NAC can be useful as a temporising measure. It allows time for genetic testing which may alter surgical decision

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making. Early use of chemotherapy can allow lifestyle factors such as smoking, obesity and glycaemic control to be optimised in preparation for breast reconstruction to become viable. Delaying surgery can allow time for a patient's grief reaction to pass. They may reach more informed rational conclusions as to their surgical options which are increasingly numerous and complex.

NAC can be a helpful option in breast cancer presenting in pregnancy.

Margins do not need to be treated any differently in BCS where NAC has been given (6). Margins are less likely to be involved in mastectomies for locally advanced cancer.

Where surgical complications, cavity re-excision and staged axillary dissection, may have led to delayed commencement of adjuvant chemotherapy, pre- operative systemic therapy avoids this risk.

Neoadjuvant radiotherapy is increasing in use and may help to facilitate an immediate autologous flap reconstruction. This has been termed "reverse sequencing" and involves giving NAC then radiotherapy then mastectomy and immediate autologous breast reconstruction (7).

Patiniott *et al.* do not address some of the difficulties that may be encountered by a multidisciplinary team deciding on whether or not to organise NAC.

There is potential loss of prognostic information as the true extent of lymph node involvement and exact tumour size must be estimated from the imaging and clinical examination at the time of diagnosis rather than from the postoperative pathological assessment. At the same time however prognostic information is gained from the response to treatment.

Partial response to systemic therapy may mean that chemo-resistant tumour lineages have more time to spread before locoregional treatment is commenced. However DFS and OS are unaltered by NAC. Clinicians may be delayed in recognising patients with cancers that respond poorly to NAC and worse still, those in whom tumours progress (3% of patients). This may occur due to patient and clinician optimism, a desire to adhere to treatment protocols and in some cases a lack of access to specialised breast radiology resulting in inaccurate tumour sizing during treatment. Ironically too great a reliance on radiology to assess response can be misleading since tumour volume may shrink while the overall size remains the same. Clinical examination is therefore the best tool for assessing response.

While NAC may facilitate better surgery in some instances, the physiological response to chemotherapy (anaemia, hypoalbuminaemia, and weight gain) may reduce a patient's peri-operative fitness. Timing of surgery should take these factors into account along with measures to prevent significant weight gain. Delaying surgery 4 weeks after the last dose of chemotherapy is usually long enough.

It is the role of the surgeon to manage these complex issues in the MDT setting with the treatment plan mapped out. Does the pre-treatment "footprint" need to be removed? Has the tumour shrunk like a deflating balloon or become like swiss cheese? Accurate breast staging pre and post NAC with modalities such as MRI and possibly Contrast Enhanced Mammography can help to answer these questions.

Sentinel node biopsy has been shown to have a higher false negative rate in the setting of NAC (8% in NSABP B-18, 11% in B-27). This is likely due to scarring in an involved sentinel node preventing accurate identification of it as the sentinel node. Clip marking abnormal LNs, using both radioactive tracer and patient blue v dye and removing 3 or more LNs has been shown to improve the false negative rate to acceptable levels (5). If there is genuine concern on the MDT as to loss of prognostic information or the possibility of a false negative sentinel node after NAC the option of a sentinel node biopsy prior to the NAC should be considered.

An MDT that aims to increase the rate of immediate breast reconstruction should develop a policy of considering chemotherapy neoadjuvantly in every case where the patient desires breast reconstruction. This paper should spark discussion in every MDT throughout Australia and New Zealand on the policies of their unit regarding who they offer NAC to with a view to their unit increasing the use of NAC.

The methods section of the paper highlights that data has been obtained from the BQA. This includes data from New Zealand. The paper only addresses rates of NAC uptake in Australia. I would be interested to know whether similar trends were found in New Zealand. Table 3 in Patiniott's study comments on the pathologically determined tumour size including 52.2% of patients with a tumour size of 0 mm (those with pCR) who had NAC. Pre-treatment clinical and radiological sizing data would perhaps be more meaningful data. The BQA data fields does not stipulate pre-treatment tumour size. The BQA should consider altering this data field.

Unsurprisingly the data shows that neo adjuvant chemotherapy is predominately used in the setting of high-grade triple negative or HER2 positive cancers, young patients and those with a larger tumour size. By these inclusions it is therefore being offered to the patients

most likely to obtain a pCR. Surprisingly to me the data shows that 66.59% of those patients receiving NAC completed their chemotherapy after their surgery. This is not explained by Patiniott *et al.*, we can surmise this may reflect continuing Herceptin or perhaps it is a glitch in the data collection. Sandwiching the surgery in-between chemotherapy doses is not recommended in guidelines. In their discussion the author has highlighted that 20% of cases are either triple negative or HER2+ve and these patients are the ideal subset for consideration for NAC. However, there are other subsets where NAC should still be considered. A reasonable policy would be to consider NAC for all breast cancers larger than 2.5 cm, all triple negative breast cancers larger than 5 mm, all Her-2 positive breast cancers larger than 5 mm, core needle or FNA positive axillary lymph nodes, any T3 or T4 breast cancers, all inflammatory breast cancers. A reasonable target for a unit to try and achieve would be 20% of cases being offered NAC.

I support the author's conclusion that NAC is currently underutilized in Australia. Its use appears to be growing and I believe MDT's should review their policies as to who they offer NAC to. We need better education and understanding of the pros and cons of NAC amongst breast surgeons and medical oncologists in order to achieve higher rates of NAC usage. There should be tangible benefits to breast cancer patients should this occur.

Acknowledgments

None.

Footnote

Conflicts of interest: The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/abs.2019.07.01
Cite this article as: Littlejohn DR. Is Australia lagging behind in the use of Neoadjuvant chemotherapy for breast cancer? Ann Breast Surg 2019;3:15.