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Efficacy of chemotherapy in patients with HR+/HER2–Invasive lobular breast cancer

Marita Yaghi [a,1,*], Nadeem Bilani [b,2], Barbara Dominguez [a], Maroun Bou Zerdan [c,3], Hong Li [d], Diana Saravia [a,4], Elizabeth Stone [a], Zeina Nahleh [a,5,*]

[a] Department of Hematology-Oncology, Maroone Cancer Center, Cleveland Clinic Florida, Weston, FL, US
[b] Department of Medicine, Icahn School of Medicine at Mount Sinai Morningside-West, New York, NY, US
[c] Department of Internal Medicine, SUNY Upstate Medical University, Syracuse, NY, US
[d] Department of Quantitative Health Sciences, Cleveland Clinic Foundation, Cleveland Clinic, OH, US

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ABSTRACT

Introduction: : Invasive Lobular Breast Cancer (ILC) harbors unique clinicopathologic features. Data on optimal treatment modalities focusing on ILC remain scarce. We aim to investigate the benefit of chemotherapy in early-stage hormone receptor-positive (HR+) and human epidermal growth factor receptor-2 negative (HER2-) ILC.

Methods: : Female patients with early HR+/HER2- ILC (stages I-III) who underwent surgery were selected from the National Cancer Database (2010–2016) and grouped into four treatment cohorts: surgery only(S), chemotherapy alone (CT), endocrine therapy alone (ET), and combined chemotherapy followed by endocrine therapy (CET). Descriptive and bi-variate statistics summarized baseline characteristics and compared them across cohorts. A secondary analysis accounting for OncotypeDX (ODX) information was performed, stratifying for low (<26) and high (≥26) ODX. Kaplan–Meier (KM) and Cox proportional hazard models evaluated the relationship between treatment modality and overall survival (OS), stratifying for ODX scoring.

Results: : $N = 15{,}271$ patients were included. The CET cohort (29.8%) was more likely to be younger and have no co-morbidities, advanced tumor stage or high ODX score (≥26). No significant difference in OS comparing ET to CET (HR:1.08, 95%CI:0.93–1.26, $p = 0.31$) was observed, adjusting for confounders. $N = 5{,}561$ patients had ODX results available. No significant difference in 5-year OS was observed comparing the ET to CET cohorts, both in patients an ODX score <26 (HR:1.10; 95%CI:0.69–1.76, $p = 0.69$) and ODX score ≥26 (HR:1.18; 95% CI:0.51–2.75, $p = 0.69$).

Conclusion: : Chemotherapy demonstrated no added survival benefit in HR+/HER2- ILC, even in tumors with ODX ≥26. Prospective trials identifying potential subgroups of patients with ILC who could benefit from chemotherapy are needed.

Abbreviations: CET, Chemotherapy followed by Endocrine Therapy; CT, Chemotherapy alone; ET, Endocrine Therapy alone; HER2, Human Epidermal growth factor Receptor 2; HR, Hormone Receptor; IDC, Invasive Ductal Carcinoma; ILC, Inavsive Lobular Carcinoma; NCDB, National Cancer Database; ODX, Oncotype DX; S, Surgery alone.

* Corresponding author at: Department of Hematology-Oncology, Maroone Cancer Center, Cleveland Clinic Florida, 2950 Cleveland Clinic Blvd., Weston, FL, US
* Zeina Nahleh, MD 2950 Cleveland Clinic Blvd.Department of Hematology-OncologyMaroone Cancer CenterCleveland Clinic FloridaWeston, FL 33331Email: nahlehz@ccf.org
E-mail addresses: mey05@mail.aub.edu (M. Yaghi), nahlez@ccf.org (Z. Nahleh).
[1] Marita Yaghi: @DrMaritaY
[2] Nadeem Bilani: @BilaniMD
[3] Maroun Bou Zerdan: @MarounBouZerdan
[4] Diana Saravia: @DianaSaravia
[5] Zeina Nahleh: @drznahleh

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Introduction

Lobular breast cancer is the second most common histologic subtype of breast cancer after ductal carcinoma (IDC), accounting for 5–15% of all invasive breast cancers [1]. However, invasive lobular carcinoma (ILC) exhibits unique clinical and pathologic features. These include the hallmark loss of E-cadherin expression, resulting in dysregulated cell-to-cell adhesion and proliferation of neoplastic cells in single-file strands. This process is also a significant contributing factor to ILC's predisposition to metastasize to distant sites [2].

Despite ILC's unique features, national guidelines have not distinguished workup and treatment of breast cancer by histologic subtype [3]. More recently, however, a novel and more personalized approach to the treatment of ILC is being considered, given that lobular and ductal carcinomas also respond to treatment in distinct ways. ILC is less chemo-sensitive than IDC, leading to lower rates of complete pathological response (pCR) and, consequently, more prominent use of mastectomy versus breast-conserving therapy when chemotherapy is used in the neoadjuvant setting [4]. In the adjuvant setting of early-stage, hormone-receptor positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) breast cancer, treatment is generally guided by the precision medicine practice of risk stratification of patients using multigene panels [5]. The 21-gene recurrence score (RS) – Oncotype DX (ODX) – assay is one of the commonly used panels that prognosticates the risk of disease recurrence and has a predictive value that can guide clinical practice. As validated in the TAILORx and RxPONDER trials – for node-negative and node-positive disease, respectively – treatment regimens, including chemotherapy with endocrine therapy, over endocrine therapy alone, improve long-term survival outcomes in patients with higher recurrence scores [6–8]. However, these landmark trials did not model sub-analyses by histologic subtype, and it remains unclear whether ODX or other genomic assays perform as well in lobular disease.

Overall, there is still a paucity of large-scale studies focusing on ILC as a separate disease entity [9]. In this study, we aim to use a large national registry to clarify the benefit of chemotherapy in early-stage ILC by comparing the survival outcome of endocrine therapy alone versus chemotherapy followed by endocrine therapy in HR+/HER2- ILC.

Methods

Patients

Our study is a retrospective analysis of patients with invasive lobular breast cancer, stages I-III and estrogen-receptor positive (ER+) and/or progesterone-receptor positive (PR+) *aka* HR+ and human epidermal growth factor receptor-2 negative (HER2-) subtype, who underwent surgery and were treated in the United States between 2010 and 2016. Data was gathered from the National Cancer Database (NCDB), a national registry supported by the Commission on Cancer (CoC) and the American College of Surgeons (ACS). The NCDB gathers real-world information from over 1500 medical institutions and includes over 70% of all cancer patients in the United States [10,11], allowing accurate representation of disease, treatment, and outcome on a national level. After review, a year-stratified simple random sampling method, 10% of all patients meeting inclusion criteria were included in the study.

Clinical and pathologic evaluation

The clinicopathological data collected included: patient age, race, insurance status, year of diagnosis and last follow-up, tumor site, T stage, N stage, overall stage, grade, ILC histology, radiation therapy, 21-gene recurrence score – Oncotype DX (ODX) – results, 70-gene signature test – MammaPrint (MP) – genomic testing, and treatment modalities, including surgery, chemotherapy, endocrine therapy, and radiation therapy. The tumor subtypes were categorized as classical ILC (ILC only tumors) and mixed histologic subtypes (mixed IDC and ILC). The tumor stage in NCDB was assessed in accordance with the 7th edition of the AJCC staging. Histologic grade was defined according to the International Classification of Diseases for Oncology version 3 (ICD-O-3). Response to therapy was determined by information on overall survival (OS), defined from the date of diagnosis to the date of death from any cause or last follow-up.

Statistical analysis

Patients were grouped into four treatment cohorts: surgery only (S), chemotherapy alone (CT), endocrine therapy alone (ET), and combined chemotherapy followed by endocrine therapy (CET). Patients' characteristics were summarized using descriptive statistics. Comparisons of these characteristics among different treatment cohorts were made using the Chi-squared test for categorical variables. The Cochrane-Armitage test was applied to explore the trends of each treatment administration in our population from 2010 to 2016. In addition, proportions of ODX testing by stage over time was also described using same method.

The Kaplan–Meier method and Cox proportional hazard model were used to evaluate the relationship between treatment cohort modality and the patients' OS. A set of covariates including age, pathological stage, Charlson/Deyo co-morbidity score, tumor histology, radiation therapy, insurance status and ODX that are known to be associated with OS were selected to control any confounding effects between ET and CET. A secondary analysis focusing on patients with ODX was then performed, stratifying for with low ODX (<26) and high ODX (≥ 26).

Among patients with ODX data, a propensity score (PS) matching was performed to identify ET and CET pairs with similar demographics and clinical characteristics. PS was estimated from a logistic regression model with integrated the aforementioned demographic and clinical characteristics; a 1:1 Greedy PS matching with exact matching on AJCC stage and without replacement on their PS was used. Kaplan-Meier survival curves in the ET and CET cohorts in both the unmatched and propensity score-matched samples are graphically displayed. It was followed by multivariate adjusted overall survival curves in the CET and ET cohorts for patients with ODX score, stratifying for low (ODX <26) and high (ODX$\geq$ 26) risks of recurrence. All data analysis was conducted using SAS version 9.4 (SAS Software).

Ethical approval was obtained from the Cleveland Clinic Institutional Review Board (IRB) before conducting this study, under the exempt category. All patient data were strictly de-identified and provided, with approval, from the American College of Surgeons as part of the National Cancer Database.

Results

Patient and tumor characteristics

We identified 252,171 female with HR+/HER2- ILC (stages I-III) from the NCDB breast cancer Participant User Files (PUF). 242,041 (96.0%) patients underwent surgery for ILC resection and were selected. Among patients who had surgery, 197,834 (81.7%) had data available on tumor ER/PR/Her2 status, treatment receipt and follow up.177,887 of them were classified as having HR+/HER2- (89.9%) and were selected. A diagnosis-year stratified random selection were then performed to select 10% of HR+/Her2- patients ($N = 17{,}653$).

A total of $N = 15{,}271$ patients who received ET or CET were included in the analysis; their characteristics are summarized in Table 1. 51.2% of tumors were stage I, and 61.7% were moderately differentiated. Focusing on ILC histological subtype, 54.7% of tumors were pure "classical" ILC, and 45.3% harbored mixed ILC histology. 3.6% of patients received MP genomic testing. We focused then on the $N = 5561$ (36.4%) of patients who had information available for ODX. Among the latter, 485 (8.7%) patients had an ODX score ≥ 26 and were classified as

Table 1
Cross-tabulation of baseline characteristics in the ET and CET cohorts and proportion of patients in the CET cohort in every subgroup.

Factor	ET (N = 10,720)	CET (N = 4551)	p-value	Proportion in CET cohort
Age				
< 65	4883(45.5)	3334 (73.2)	**<0.001**	81.5%
≥ 65	5837(54.5)	1217 (26.8)		35.8%
Race *N (%)*				
White	8949(84.4)	3605 (80.1)	***<0.001***	28.7%
Black	853(8.0)	466(10.3)		35.3%
Other	804(7.6)	432(9.6)		35.0%
Insurance Type *N (%)*				
Non-private	5829(54.9)	1593 (35.4)	***<0.001***	21.5%
Private	4794(45.1)	2909 (64.6)		37.8%
Charlson/Deyo Score *N (%)*				
0	8845(82.5)	3857 (84.8)	***<0.001***	30.4%
≥ 1	1875(17.5)	694(15.2)		27.0%
Tumor Stage *N (%)*				
Stage I	6993(65.2)	831(18.3)	***<0.001***	10.6%
Stage II	3323(31.0)	2088 (45.9)		38.6%
Stage III	404(3.8)	1632 (35.9)		80.2%
Lobular Mixed Histology *N (%)*				
Classical Histology	5808 (54.2)	2545 (55.9)	***0.048***	30.5%
Mixed Histology	4912(45.8)	2006 (44.1)		29.0%
Radiation Therapy *N (%)*				
No	4305 (42.5)	1118 (24.3)	***<0.001***	19.5%
Yes	6145(57.5)	3433 (75.7)		35.8%
ODX *N (%)*				
< 26	4338 (96.4)	674 (67.6)	***<0.001***	13.3%
≥ 26	162(3.6)	323(32.4)		66.6%
Not done	6157(57.4)	3553 (78.1)		36.6%

having a high risk of cancer recurrence.

Systemic therapy administration and survival response

The majority of patients in the overall sample received either ET (60.7%) or CET (25.8%). Only 2.1% of patients received CT only, while 11.4% did not receive any systemic treatment after surgery. Analyzing treatment trends over time shows that ET administration alone shows a significant increase (from 54.0% to 66.9%) from 2010 to 2015, followed by a slight decrease to 63.7% in 2016 ($p<0.001$) and a steady, significant decrease in both CT administration (from 2.5% to 1.5%, $p = 0.004$) and no administration of systemic treatment after surgery (from 13.7% to 10.4%, $p<0.001$) from 2010 to 2016. A similar significant decrease in CET administration (from 29.7% to 21.4%) can be seen between 2010 and 2015, followed by an increase to 24.4% in 2016 ($p<0.001$ () (Supplementary Fig 1).

Kaplan-Meier analysis of 5-year OS in the overall patient population reveals significant improvement in OS with the administration of ET (90.7%) or CET (90.4%), as compared to CT alone (79.4%) or surgery only (79.7%) ($p<0.001$) (Table 2).

Survival analysis for CET and ET cohorts

$N = 10{,}720$ received ET and $N = 4551$ CET (Table 1). Patient and tumor characteristics were distinct between the ET and CET cohorts. Patients receiving CET were more likely to be younger than 65 years old (81.5% vs. 35.8%), with private insurance (37.8% vs. 21.5%), and have no co-comorbidities as per the Charlson/Deyo score (30.4% vs. 27.0%) as compared to their older, non-privately insured counterparts with a comorbidity score ≥1. Focusing on tumor characteristics, patients with a tumor stage of II or III (respectively 38.6% and 80.2%) or with had a high ODX score (66.6%) ($p<0.001$) were more likely to be treated with CET than those with Stage I tumors (10.6%) or low ODX score (13.3%). Additionally, patients who received radiation therapy were more likely to receive CET than those who did not (35.8% vs. 19.5%; $p<0.001$). Comparing ILC histological subtypes in both cohorts, more patients with classical ILC histology received CET than patients with mixed ILC tumor histology (30.5% vs. 29.0%, $p = 0.048$).

After adjusting for clinical and pathologic characteristics predicting survival using a Cox multivariable regression, no significant difference in survival was seen between ET or CET administration (HR: 1.08, 95% CI: 0.93–1.26, $p = 0.31$) (Table 2). Kaplan-Meier 5-year OS survival curves showed similar survival in both the ET and CET cohorts: 94.7% vs. 94.3% ($p = 0.31$), after accounting for the various patient and tumor characteristics that influence survival (Fig. 1A).

Survival analysis for CET and ET cohort with 21-gene recurrence score (Oncotype DX)

A total of $N = 5561$ patients had ODX results available. Stage stratification of ODX testing and results shows that 40.7% of patients with stage I disease and 40.5% of patients with Stage II disease underwent ODX testing. Only 9.0% of patients with Stage III disease received ODX testing. Looking at the proportion of patients with a low risk of recurrence (ODX <26), Stage I tumors represented 57.6%, followed by Stage II tumors at 39.3% and Stage III tumors at 3.1%. In those with a high risk of recurrence (ODX ≥26), the proportion Stage I tumors was 54.2%, Stage II tumors 40.6% and Stage III tumors 5.2% (eTable 3). Analyzing the proportion of patients who received ODX testing per stage over time showed a significant increase overall, from 26.4% in 2010 to 42.5% in 2016 ($p<0.001$). Looking at stage-specific proportions, patients with stage I and Stage II received more ODX testing than those with Stage III disease. Testing in stage I was initially the highest between 2010 and 2012, while those with Stage II tested the most for ODX between 2012 and 2016. Despite a steady increase over time, the proportion of patients with Stage III who received ODX testing was generally low (5.9% in 2012 and 13.1% in 2016) (eFigure 2).

On survival analysis, similar results were observed in the group of patients with recorded ODX information ($N = 5561$) compared to the overall patient population. CET administration showed similar survival compared to ET administration (HR: 1.10, 95% CI: 0.74–1.63, $p = 0.65$) after accounting for other predictors of survival (Table 2).

As significant differences exist between the ET and CET cohorts for patient and tumor characteristics, a propensity score match was conducted to correct these differences. 788 pairs ($N = 1576$) were generated with exact stage match: 327 (41.5%) pairs with Stage I, 401 (50.9%) pairs with Stage II and 60 (7.6%) pairs with Stage III. Within each stratum of the propensity score, age, Charlson/Deyo score, ILC subtype histology, private insurance status, radiation therapy administration, and ODX score ≥26 status had similar means or prevalences with reductions in standardized differences to less than 5%. Kaplan-Meier 5-year OS showed similar survival results between the ET and CET cohorts in the matched patient sample: 95.6% vs. 96.4% ($p = 0.85$) (Fig. 1B).

Stratifying for ODX score, there was no significant difference in 5-year OS observed between the ET and CET cohorts in the patient sample with an ODX score < 26 (HR:1.10; 95%CI: 0.69–1.76, $p = 0.69$)

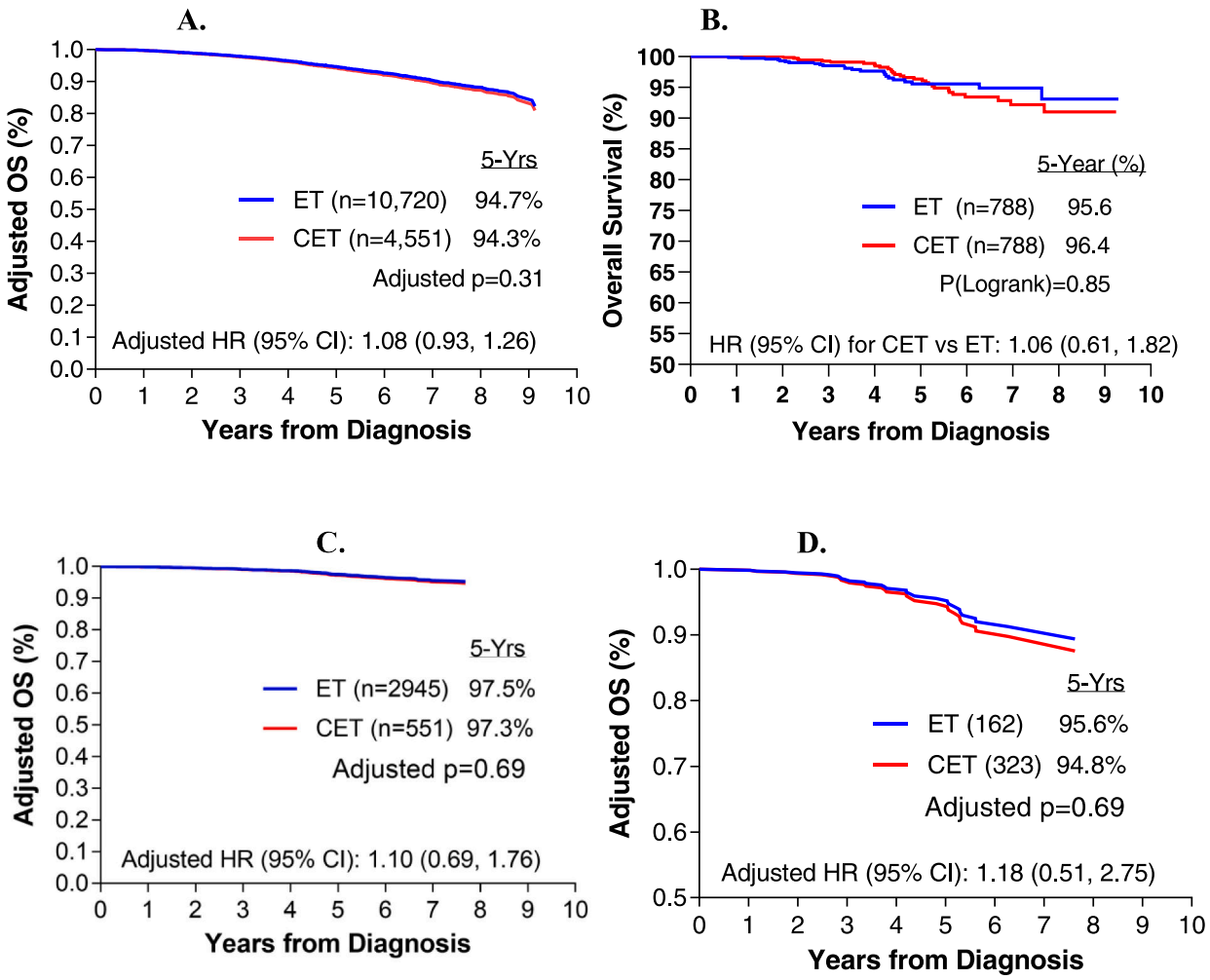

Fig. 1. Kaplan-Meier 5-Years Overall Survival in the ET and CET cohorts in
A. The overall patient population ($N = 15{,}271$), adjusted for clinico-pathological characteristics
B. The propensity score matched patient sample (788 pairs) with Oncotype DX information
C. The patient sample with Oncotype DX score < 26 ($N = 5076$)
D. The patient sample with Oncotype DX score ≥ 26 ($N = 485$).

(Fig. 1C). Interestingly, similar results were seen in the patient sample with an ODX score ≥ 26: the ET cohort showed a 5-year OS of 95.6% as compared to 94.8% in the CET cohort (HR: 1.18; 95% CI: 0.51–2.75, $p = 0.69$) (Fig. 1D).

Discussion

This study using real-world data provided by a large national registry suggested a lack of survival benefit for using chemotherapy followed by ET compared to ET alone in patients with ILC and corroborated findings from previously reported analyses [12–14]. Of interest, the lack of added chemotherapy benefit over endocrine therapy was also noted among patients with ILC and a high risk of recurrence defined by ODX with RS$\geq$ 26. This data highlights several points, including the need for prospective trials in breast cancer to identify subgroups of patients with ILC, if any, who could benefit from chemotherapy in ILC, and the consideration of designing future trials with the capacity to perform stratified analyses by histologic subtype, which has not been historically the case in clinical trials [7,8,15–19]. Some data suggest that chemotherapy may still benefit the treatment of micrometastatic disease in ILC and possibly improve long-term outcomes [19,20]. In addition, a recent meta-analysis of 38,387 patients did not show any additional benefit of chemotherapy overall but showed some benefit in high-risk patients after subgroup analysis [21]. Another study corroborated this benefit, which suggested a different classification system for low vs. high risk-ILC based on tumor size and lymph node invasion [22]. Therefore, it would be necessary to consider lobular carcinoma and its several histologic variants, including solid, tubulo-lobular, alveolar, and pleomorphic [23], and their distinct clinical behavior, as a pathologically distinct disease entity when designing future trials and as a separate category from ductal carcinoma.

In addition, potential implications of these findings, if confirmed in prospective trials, are their consideration for treatment guidelines updates. Current National Comprehensive Cancer Network (NCCN) guidelines recommend ODX testing for all HR+/HER2- breast cancers regardless of histologic subtype [5]. Previous studies have demonstrated a survival benefit with the use of chemotherapy in addition to endocrine therapy in patients with a recurrence score ≥ 26 but not in those with an ODX score < 26. The use of multigene profiles, including ODX, has impacted the decision-making process of breast cancer management in clinical practice. These biomarkers can lead to a change in treatment in more than 30% of the patients tested, leading to chemotherapy administration to treat tumors classified as low risk using only conventional clinical and pathologic criteria and no chemotherapy administration in the reverse scenario [24,25]. Other genomic assays may be better suited for identifying ILC tumors with a high risk of recurrence if

Table 2
Kaplan-Meier 5-year OS and Cox Multivariable Survival Analysis in A) overall patient population B) patients with Oncotype DX information.

			Overall Patient Population *N = 15,271*		Patients with ODX Information *N = 5561*	
	Kaplan-Meier		Cox Multivariate		Cox Multivariate	
	5-Year OS% (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Treatment cohort						
ET	90.8 (90.2,91.5)	0.072	–	–	–	–
CET	91.3 (90.3,92.3)		1.08 (0.93,1.26)	0.31	1.10 (0.74,1.63)	0.65
Age category						
< 55	96.1 (95.3,96.8)	***<0.001***	–	–	–	–
55–64	94.6 (93.7,95.5)		1.44 (1.17,1.77)	***<0.001***	1.78 (1.08,2.91)	***0.023***
65–74	91.5 (90.5,92.5)		1.92 (1.54,2.39)	***<0.001***	2.49 (1.45,4.27)	***<0.001***
>=75	75.0 (72.9,77.2)		5.70 (4.54,7.16)	***<0.001***	6.54 (3.59,11.93)	***<0.001***
Radiation therapy						
Yes	92.2 (91.5,92.9)	***<0.001***	–	–	–	–
No	89.0 (88.0,90.0)		1.44 (1.28,1.62)	***<0.001***	1.324 (0.993,1.765)	0.056
Tumor stage						
Stage I	93.5 (92.8,94.2)	***<0.001***	–	–	–	–
Stage II	91.3 (90.3,92.2)		1.30 (1.14,1.48)	***<0.001***	1.44 (1.07,1.95)	***0.017***
Stage III	81.1 (79.0,83.1)		3.38 (2.88,3.97)	***<0.001***	3.17 (1.84,5.46)	***<0.001***
Charlson/Deyo score						
0	85.2 (83.3,87.1)	<***0.001***	–	–	–	–
1	81.2 (75.9,86.5)		1.38 (1.21,1.58)	***<0.001***	2.21 (1.60,3.07)	***<0.001***
2	64.4 (52.0,76.8)		1.86 (1.43,2.41)	***<0.001***	1.31 (0.53,3.22)	0.55
≥3	85.2 (83.3,87.1)		3.21 (2.21,4.65)	***<0.001***	3.55 (1.12,11.25)	0.031
Tumor histology						
Classical type	90.2 (89.4,91.0)	***0.001***	–	–	–	–
Mixed histology	91.9 (91.2,92.7)		0.98 (0.88,1.10)	0.77	1.07 (0.80,1.42)	0.66
Private Insurance						
Yes	95.3 (94.7,95.9)	***<0.001***	–	–		
No	86.3 (85.3,87.3)		1.49 (1.27,1.75)	***<0.001***	1.60 (1.08,2.37)	***0.020***
Oncotype Dx Score						
0–10	95.1 (93.7,96.5)	<0.001	–	–	–	–
11–25	96.4 (95.5,97.2)		–	–	0.78 (0.57,1.07)	0.13
26–100	92.8 (89.8,95.9)		–	–	1.33 (0.82,2.16)	0.24

treated with ET alone, which may benefit from additional chemotherapy. For instance, one study showed that the 70-gene signature test – MammaPrint (MP) – correctly classified ILC as low-risk or high risk, with similar success rates as in classifying the recurrence risk for IDC [26]. However, in our database, MP genomic testing was not widely used, and we could not corroborate this finding. This may be better evaluated in the future, given that a wider variety of genomic signature assays are being used.

Our findings likely reflect differences in tumor biology associated with lobular versus ductal carcinomas. ILC tumors exhibit lower proliferation rates, as highlighted through mitotic index analysis with Ki-67 immunohistochemistry [4], a characteristic that makes them more chemo-resistant. Others have also hypothesized that, among ER-positive tumors, differential responses to ET may be explained by the extent of receptor expression, but data on this is mixed. While it is known that a more significant proportion of lobular breast cancer cases are ER+ compared to cases of ductal carcinoma, a recent retrospective study found no difference in the quantity of hormone receptor expression levels comparing ILC and IDC [27]. Finally, this differential response pattern may pertain to differences in estrogen signaling cascade further downstream of initial receptor binding. FOXA1, for example, is a key transcription modulator of ER activity and shows mutations in approximately 7% of all ILC cases [2]. These differences may explain the differential response to estrogen-receptor targeted therapies such as Tamoxifen compared to aromatase inhibitors observed in ILC but not IDC as seen in the BIG 1–98 trial [28,29]. More molecular research is thus warranted to understand the differences in the response of breast cancer histologic subtypes to various forms of systemic therapy.

It remains essential to consider the limitations of our study in the context of a retrospective study design and a small sample size. In addition, the nature of the database adds another limitation to our results due to the unavailability of some relevant data, such as disease-free survival and progression-free survival. Furthermore, results on the lack of benefit of chemotherapy in patients with high ODX scores need to be interpreted with caution, as the overall number of patients in this category is small. This could be related to our random year-stratified 10% selection of the HR+/Her2- ILC patient population. The low percentage of patients with Stage I (31.7%) and Stage II disease (31.5%) who underwent ODX testing could be due to many reasons, namely the inclusion of patients from years prior to 2015 and the prospective validation of the ODX assay in node-negative BC as part of the TailorX trial [15]. Nonetheless, these results warrant further investigation concerning the benefit of ODX testing and the therapeutic implications of testing outcomes. Our results are still most relevant for tumors classified as Stage I and Stage II, as most patients with Stage III disease did not have ODX information available. With the results of the RxPONDER trial, more data that includes the use of ODX in the NCDB may become available in the future for node-positive patients with 1–3 positive nodes [30], and our results did show an increase in ODX testing over time. Careful attention should be placed in the future on the benefits of chemotherapy in node-positive ILC with high ODX to make sure patients with ILC receive similar benefit to their counterparts with IDC. While this study is not sufficient to negate the clinical value of genomic assays in ILC subtypes of breast cancer, it highlights the need to tailor and validate them across various subtypes of the disease to guide optimal treatment decisions and tailor the de-escalation of chemotherapy whenever possible.

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Data presentation

Our findings were presented as a part of the spotlight poster discussion presentation on lobular breast cancer at the San Antonio Breast

Cancer (SABC) Breast Cancer Symposium in San Antonio, TX in December 2021.

Availability of data and material

The data that support the findings of this study are available from the American College of Surgeons/American Cancer Society, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the American College of Surgeons/American Cancer Society.

Code availability

Not applicable.

Additional declarations for articles in life science journals that report the results of studies involving humans and/or animals

Not applicable.

Ethics approval

Ethical approval was obtained from the Cleveland Clinic Institutional Review Board (IRB) before conducting this study. All patient data were strictly de-identified and provided, with approval, from the American College of Surgeons as part of the National Cancer Database.

Consent to participate

Ethical approval was obtained from the Cleveland Clinic Institutional Review Board (IRB) prior to conducting this study. All patient data were strictly de-identified and provided, with approval, from the American College of Surgeons as part of the National Cancer Database.

Consent for publication

No individual person's data were included; all data is reported in an aggregated manner.

Authors' contributions

M.Y., N.B. and B.D. are major contributors in study design, conduction of statistics and data interpretation, and manuscript writing. Z. N. participated in study design, interpretation of the data, and writing the manuscript. H.L. participated in the conduction of statistics. M.B.Z., D.S. and E.S. participated in writing and editing. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no conflict of interest. The authors declare that they have no competing interests.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2022.100666.

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