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Neoadjuvant Endocrine Therapy Versus Neoadjuvant Chemotherapy in Node-Positive Invasive Lobular Carcinoma

M. J. Thornton, BA[1], H. V. Williamson, MS[2], K. E. Westbrook, MD[2,3], R. A. Greenup, MD, MPH[1,2], J. K. Plichta, MD, MS[1,2], L. H. Rosenberger, MD, MS[1,2], A. M. Gupta, MD, MA[1], T. Hyslop, PhD[2,4], E. S. Hwang, MD, MPH[1,2], and O. M. Fayanju, MD, MA, MPHS[1,2,5]

[1]Department of Surgery, Duke University Medical Center, Durham, NC; [2]Duke Cancer Institute, Duke University Medical Center, Durham, NC; [3]Department of Medicine, Duke University Medical Center, Durham, NC; [4]Department of Biostatistics and Bioinformatics, Duke University, Durham, NC; [5]Durham VA Medical Center, Durham, NC

ABSTRACT

Background. Neoadjuvant chemotherapy (NACT) is often recommended for patients with node-positive invasive lobular carcinoma (ILC) despite unclear benefit in this largely hormone receptor-positive (HR+) group. We sought to compare overall survival (OS) between patients with node-positive ILC who received neoadjuvant endocrine therapy (NET) and those who received NACT.

Methods. Women with cT1–4c, cN1–3 HR+ ILC in the National Cancer Data Base (2004–2014) who underwent surgery following neoadjuvant therapy were identified. Kaplan–Meier curves and Cox proportional hazards modeling were used to estimate unadjusted and adjusted overall survival (OS), respectively.

Results. Of the 5942 patients in the cohort, 855 received NET and 5087 received NACT. NET recipients were older (70 vs. 54 years) and had more comorbidities (Charlson–Deyo score $\geq$ 1: 21.1% vs. 11.5%), lower cT classification (cT3–4: 44.2% vs. 51.0%), lower rates of mastectomy (72.5% vs. 82.2%), lower rates of pathologic complete response (0% vs. 2.5%), and lower rates of postlumpectomy (73.2% vs. 91.0%) and postmastectomy (60.0% vs. 80.8%) radiation versus NACT recipients (all $p < 0.001$).

NACT recipients had higher unadjusted 10-year OS versus NET recipients (57.9% vs. 36.0%), but after adjustment, there was no significant difference in OS between the two groups ($p = 0.10$).

Conclusions. Patients with node-positive ILC who received NET presented with smaller tumors, older age, and greater burden of comorbidities versus NACT recipients but had similar adjusted OS. While there is evidence from clinical trials supporting efficacy of NET in HR+ breast cancer, our findings suggest the need for further, histology-specific investigation regarding the optimal inclusion and sequence of endocrine therapy and chemotherapy in ILC.

The use of neoadjuvant chemotherapy (NACT) in patients with nonmetastatic, resectable breast cancer was initially investigated in the National Surgical Adjuvant Breast and Bowel Project (NSABP) trials B-18 and B-27 to establish whether preoperative systemic therapy could be a means through which to potentially improve rates of breast-conserving surgery for estrogen receptor-negative (ER–) tumors without compromising disease-free and overall survival.[1] In contemporary breast cancer care, NACT continues to be administered for the purpose of facilitating breast conservation by tumor downstaging, but it is also used to decrease nodal burden in patients with node-positive (LN+) disease and to allow for preoperative, in vivo assessment of tumor response to NACT.

Invasive lobular carcinoma (ILC), which accounts for $\sim$ 10–15% of all breast cancers, has distinct clinical characteristics including a high proportion of low-grade and estrogen receptor-positive (ER+) tumors that influence

both the types of treatment recommended and response to treatment.[2,3] Several studies have demonstrated poor response to NACT among ILC patients, with lower rates of pathologic complete response (pCR) following NACT in ILC patients as compared with patients with invasive ductal carcinoma (IDC).[4–9] Nevertheless, NACT continues to be recommended for many node-positive ILC patients.

Few ILC patients have been included in clinical trials of neoadjuvant endocrine therapy (NET), despite evidence from clinical trials supporting efficacy of NET in ER+ breast cancer.[10,11] The American College of Surgeons Oncology Group (ACOSOG) Z1031 trial demonstrated that NET significantly improved rates of breast conservation in patients with ER+ invasive carcinoma, but < 20% of the trial cohort had lobular histology.[12] A 2011 study by Dixon et al. specifically examined the effectiveness of neoadjuvant letrozole in postmenopausal women with ER+ ILC. NET was found to be successful in reducing tumor size in this patient population, with a mean tumor volume reduction of 66% in 3 months. As with Z1031, over half of the women in this study became candidates for breast-conserving surgery following NET.[2] Nonetheless, NET for HR+ breast cancer continues to be underutilized in the USA, with a previous examination of the National Cancer Data Base (NCDB) demonstrating that only 3% of potentially eligible patients received it.[13] Furthermore, because NET is typically recommended for elderly breast cancer patients who are not considered candidates for chemotherapy or upfront surgery, the potential benefit of NET in younger, healthier patients with locally advanced ILC remains unknown.[14,15] Accordingly, we sought to compare outcomes following NET and NACT in patients with LN + ILC.

METHODS

Women diagnosed with cT1–4c, LN+ (cN1–3), hormone receptor-positive (HR+) ILC between 2004 and 2015 and who received either NET or NACT and underwent surgery were selected from the NCDB. Patients who received both NET and NACT and those with pertinent unknown or missing information were excluded. Per NCDB reporting guidelines, survival data are unavailable for patients diagnosed during the last reporting year, so patients diagnosed in 2015 were ultimately excluded.

Patient characteristics, including type of surgery received (lumpectomy and mastectomy) and response to neoadjuvant systemic therapy (overall pCR [ypT0N0], breast-only pCR, node-only pCR, upstage, discordant, downstage, and no change; see Supplementary Table 1 for response definitions), were summarized with N (%) for categorical variables and median (interquartile range, IQR)

for continuous variables. Chi-square and t-tests were used to compare study groups on categorical and continuous variables, respectively.

Overall survival (OS) was defined as time from diagnosis to death or last follow-up. Unadjusted OS was estimated using the Kaplan–Meier method. Using the log-rank test, 5- and 10-year unadjusted OS rates were compared among four groups of LN+ ILC patients who received different combinations of endocrine therapy and chemotherapy: (1) NET only, (2) NACT only, (3) NET+ adjuvant chemotherapy (ACT), and (4) NACT+ adjuvant endocrine therapy (AET). Continuation of NET or NACT in the adjuvant setting cannot be discerned in the NCDB, as only the start date of each therapy is available; therefore, patients who received both NACT and ACT or both NET and AET were included in the study but could not be distinguished from those who received all of their chemotherapy or all of their endocrine therapy in the neoadjuvant setting.

To further examine whether there was benefit from receiving *any* neoadjuvant therapy in this patient population, unadjusted OS was also assessed for three groups of patients with nonmetastatic LN+ ILC who underwent surgery but only received adjuvant therapy and were otherwise excluded from the overall study: (5) AET only, (6) ACT only, and (7) ACT+ AET. Trends in rates of NET and NACT receipt over time were calculated out of this larger cohort of patients plus the patients who received both NET and NACT (who were otherwise excluded from all analyses), with $p < 0.05$ defined as significant for the Cochran–Armitage trend test.

Cox proportional hazards modeling was used to estimate the effect of NET versus NACT on OS after adjustment for known covariates, including treatment group, age, race, ethnicity, Charlson–Deyo comorbidity score, pathological T and N classification, grade, breast surgery type, receipt of complementary adjuvant therapy following neoadjuvant therapy (i.e., ACT after NET or AET after NACT), receipt of radiation, income, insurance status, education level, facility type, and facility location. Year of diagnosis, stratified into 2004–2009 and 2010–2014, was also included in the model, with this division being used to account for greater inclusion of biomarker data after 2010, when the NCDB began routinely collecting human epidermal growth factor receptor (HER)2 status information. Receipt of radiation and receipt of complementary adjuvant therapy were allowed to be time-varying in the model to address the time-dependent effects of tumor and treatment characteristics on long-term survival.[16] Interactions were examined and found to be insignificant for both type of neoadjuvant therapy*receipt of complementary adjuvant therapy and type of breast surgery*receipt of radiation, so both interaction terms were excluded from the final model.

A robust sandwich covariance estimator was used for the adjusted model to account for the correlation of patients treated at the same facility. We report hazard ratios (HRs) and 95% confidence intervals (CIs). Two-tailed $p < 0.05$ was considered significant for all analyses.

Patients with missing or unavailable data were excluded from each model, and effective sample sizes are included in all tables and figures. No adjustments were made for multiple comparisons. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). Our institutional review board granted the study exempt status due to use of deidentified data.

RESULTS

Patient, Tumor, and Treatment Characteristics

A cohort of 5942 patients receiving neoadjuvant systemic therapy was identified, including 855 women (14.4%) who received NET and 5087 women (85.6%) who received NACT (Fig. 1). The median age among all patients was 55 (IQR 47–64) years (Table 1). Compared with NACT patients, those who received NET were older (70 vs. 54 years) and had more comorbidities [Charlson–Deyo comorbidity (CDC) score ≥ 1: 21.1% vs. 11.5%), lower cT classification (cT3–4: 44.2% vs. 51.0%), lower rates of mastectomy (72.5% vs. 82.2%), and lower rates of both postlumpectomy (73.2% vs. 91.0%) and postmastectomy (60.0% vs. 80.8%) radiation (all $p < 0.001$). About one-third of patients who received NET received adjuvant chemotherapy ($n = 280$, 32.7%), while a majority of NACT recipients went on to receive adjuvant endocrine therapy ($n = 4380$, 86.1%). Despite similar cN classification at presentation ($p = 0.26$), patients who received NET had higher rates of upstaging in the breast (NET 10.5% vs. NACT 7.0%), nodes (NET 35.6% vs. NACT 29.4%), and overall (NET 31.0% vs. NACT 20.6%, all $p < 0.001$, Supplementary Table 2), however, these findings may be due to breast and nodal understaging at diagnosis rather than true progression during treatment.[17] Overall pCR was observed in only 2.1% of all patients and was not observed in any NET patients (NET 0% vs. NACT 2.5%, $p < 0.001$, Supplementary Table 2).

As only 72 (8.4%) of the 855 patients who received NET were under 50 years, we compared NET recipients < 50 years with NACT recipients < 50 years (Supplementary Table 3). As compared with women < 50 years who received NACT ($n = 1892$), NET recipients < 50 years had more T3 and less T4 disease both at presentation (cT3: NET 47.2% vs. NACT 43.0%; cT4: NET 1.4% vs. NACT 8.9%, $p = 0.002$) and following systemic therapy (ypT3: NET 27.8% vs. NACT 13.2%;

ypT4: NET 0% vs. NACT 2.4%, $p < 0.001$). Young patients with NET also had higher rates of mastectomy (94.4% vs. 85%, $p = 0.03$) and lower rates of postmastectomy radiation (PMRT, 64.7% vs. 81.2%, $p < 0.001$) compared with young patients undergoing NACT. Notably, there was no significant difference in comorbidities between young NET and NACT recipients ($p = 0.08$).

Among NET patients (Supplementary Table 4), patients under 50 years ($n = 72$) had more c/ypT3 disease ($p < 0.01$) and higher rates of both mastectomy (94.4% vs. 70.5%) and adjuvant chemotherapy (56.9% vs. 30.5%, both $p < 0.001$) compared with NET recipients ≥ 50 years ($n = 783$), but there was no difference in rates of PMRT ($p = 0.40$).

Notably, among all nonmetastatic LN+ ILC patients who underwent surgery and received all combinations of neoadjuvant and adjuvant endocrine therapy and chemotherapy including both NET and NACT ($n = 18,931$), annual rates of both NET and NACT increased over time (Supplementary Table 5, both $p < 0.001$).

Unadjusted Overall Survival Analyses

Ten-year unadjusted OS favored patients who received NACT compared with those who received NET (NACT: 57.9%, 95% CI 55.2–60.5% vs. NET: 36%, 95% CI 27.4–44.6%, $p < 0.001$, Supplementary Fig. 1). Among NET patients, those who received ACT had improved survival versus those who did not, and likewise, among NACT patients, those who received AET had improved survival as compared with those who did not take AET (NET + ACT: 53.4%, 95% CI 38.4–66.2%; NACT + AET: 59.9%, 95% CI 56.8–62.8%, $p < 0.001$; Supplementary Fig. 2). When we examined nonmetastatic LN+ ILC patients who underwent surgery and received all combinations of neoadjuvant and adjuvant endocrine therapy and chemotherapy except both NACT and NET ($n = 18,154$), we found that patients treated with NET alone ($n = 575$) had worse OS compared with all other groups, with a 10-year survival rate of 26.5% (95% CI 16.1–38.1%) while patients treated with ACT + AET ($n = 7856$) had the best survival (68.4%, 95% CI 66.4–70.4%, $p < 0.001$, Fig. 2).

Adjusted Overall Survival Analyses

After adjustment for covariates, there was no significant difference in OS between patients who received NET and those who received NACT (HR 0.84, 95% CI 0.68–1.03, $p = 0.10$, Table 2). Factors associated with worse OS included having government versus private insurance (HR 1.39, 95% CI 1.20–1.61) and having higher grade, pT
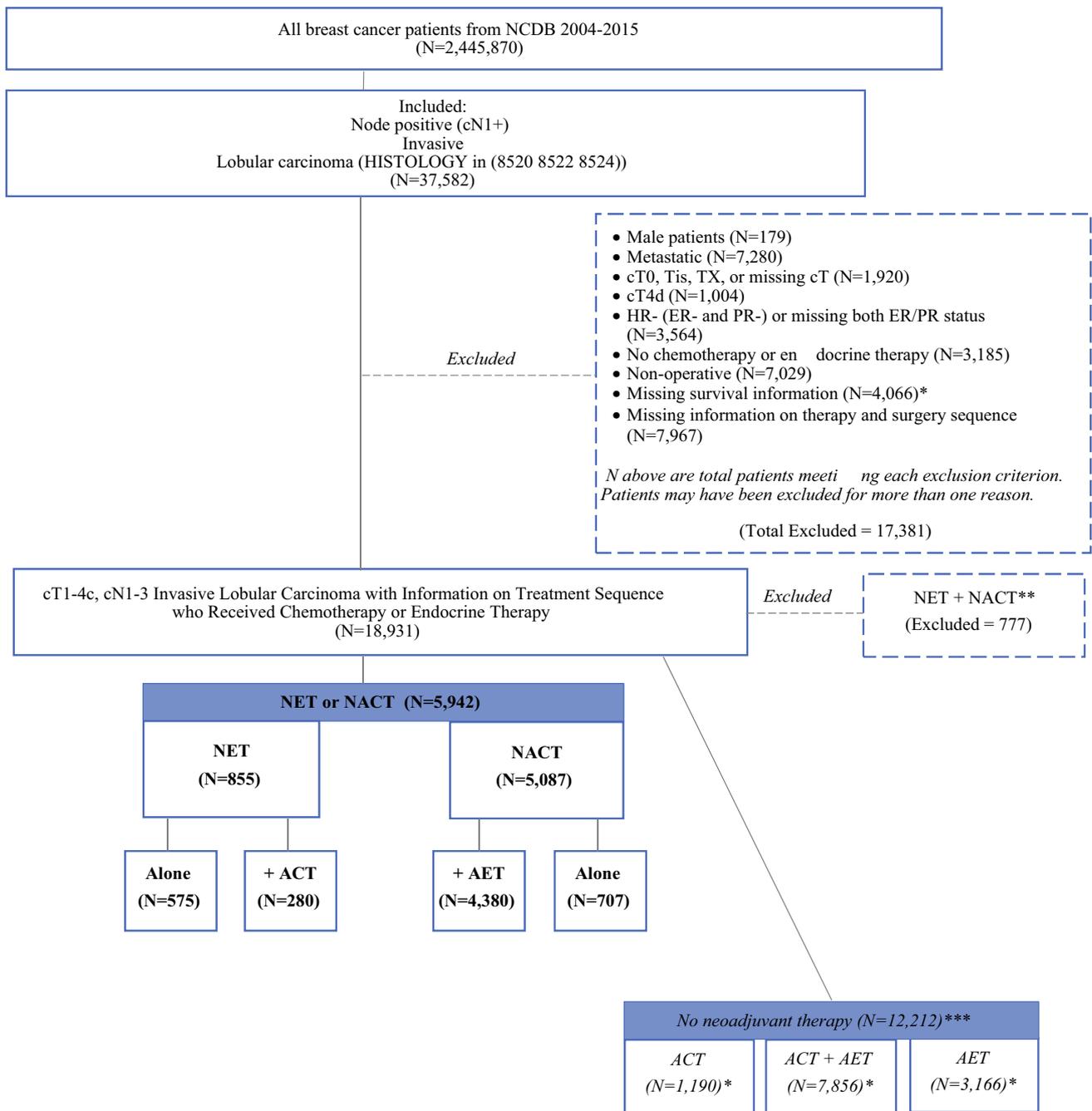
FIG. 1 Patient flow diagram, women with cT1–4c, cN1–3, HR+ invasive lobular carcinoma, National Cancer Data Base, 2004–2014. *ACT* adjuvant chemotherapy, *AET* adjuvant endocrine therapy, *NACT* neoadjuvant chemotherapy, *NET* neoadjuvant endocrine therapy. Boldface indicates inclusion in final study cohort

(n = 5942). *Includes patients diagnosed in 2015. **Only included in calculation of NACT and NET rates over time (N = 18,931). ***Only included in calculation of NACT and NET rates over time (N = 18,931) as well as unadjusted overall survival analyses (N = 18,154)

classification, and pN classification (all $p < 0.001$). Higher CDC scores were also associated with worse OS (vs. CDC = 0, CDC = 1: HR 1.16, 95% CI 0.93–1.43; CDC $\geq$ 2: HR 1.71, 95% CI 1.19–2.44; $p = 0.009$), suggesting that the inferior survival outcomes observed after NET in our unadjusted analysis may reflect a greater burden of

comorbidities among NET recipients. Improved survival was associated with age < 50 years (HR 0.76, 95% CI 0.65–0.88) and with receipt of both adjuvant radiation (HR 0.77, 95% CI 0.65–0.02) and complementary adjuvant systemic therapy (HR 0.60, 95% CI 0.50–0.72, all $p < 0.01$).

TABLE 1 Women with cT1–4c, cN1–3, HR+ invasive lobular carcinoma who received neoadjuvant endocrine therapy or chemotherapy, National Cancer Data Base, 2004–2014 (N = 5942)

	All patients (N = 5942) n (%)[a]	Neoadjuvant endocrine therapy (N = 855) n (%)[a]	Neoadjuvant chemotherapy (N = 5087) n (%)[a]	p value[f]
Age (years)				< 0.001
≥ 50	3978 (66.9%)	783 (91.6%)	3195 (62.8%)	
< 50	1964 (33.1%)	72 (8.4%)	1892 (37.2%)	
Median (IQR)	55.0 (47.0–64.0)	70.0 (59.0–78.0)	54.0 (46.0–62.0)	< 0.001
Race				0.79
White	5018 (84.4%)	729 (85.3%)	4289 (84.3%)	
Black	682 (11.5%)	97 (11.3%)	585 (11.5%)	
Other	188 (3.2%)	24 (2.8%)	164 (3.2%)	
Ethnicity				0.007
Hispanic	364 (6.1%)	35 (4.1%)	329 (6.5%)	
Non-Hispanic	5324 (89.6%)	783 (91.6%)	4541 (89.3%)	
Charlson–Deyo comorbidity score				< 0.001
0	5175 (87.1%)	674 (78.8%)	4501 (88.5%)	
1	638 (10.7%)	137 (16.0%)	501 (9.8%)	
≥ 2	129 (2.2%)	44 (5.1%)	85 (1.7%)	
Clinical T classification				< 0.001
1	715 (12.0%)	139 (16.3%)	576 (11.3%)	
2	2254 (37.9%)	338 (39.5%)	1916 (37.7%)	
3	2344 (39.4%)	261 (30.5%)	2083 (40.9%)	
4	629 (10.6%)	117 (13.7%)	512 (10.1%)	
Pathological T classification				< 0.001
0	184 (3.1%)	1 (0.1%)	183 (3.6%)	
1	1311 (22.1%)	137 (16.0%)	1174 (23.1%)	
2	1802 (30.3%)	337 (39.4%)	1465 (28.8%)	
3	1320 (22.2%)	220 (25.7%)	1100 (21.6%)	
4	210 (3.5%)	55 (6.4%)	155 (3.0%)	
X	947 (15.9%)	87 (10.2%)	860 (16.9%)	
Clinical N classification				0.26
1	4626 (77.9%)	683 (79.9%)	3943 (77.5%)	
2	919 (15.5%)	117 (13.7%)	802 (15.8%)	
3	397 (6.7%)	55 (6.4%)	342 (6.7%)	
Pathological N classification				< 0.001
0	753 (12.7%)	69 (8.1%)	684 (13.4%)	
1	1771 (29.8%)	266 (31.1%)	1505 (29.6%)	
2	1416 (23.8%)	208 (24.3%)	1208 (23.7%)	
3	1027 (17.3%)	193 (22.6%)	834 (16.4%)	
X	858 (14.4%)	99 (11.6%)	759 (14.9%)	
Grade				< 0.001
1	924 (15.6%)	211 (24.7%)	713 (14.0%)	
2	3209 (54.0%)	467 (54.6%)	2742 (53.9%)	
3	999 (16.8%)	77 (9.0%)	922 (18.1%)	
Surgery type				< 0.001
Lumpectomy	1143 (19.2%)	235 (27.5%)	908 (17.8%)	
Mastectomy	4799 (80.8%)	620 (72.5%)	4179 (82.2%)	

TABLE 1 continued

	All patients (N = 5942) n (%)[a]	Neoadjuvant endocrine therapy (N = 855) n (%)[a]	Neoadjuvant chemotherapy (N = 5087) n (%)[a]	p value[f]
Median no. of nodes examined (IQR)	13.0 (8.0–18.0)	13.0 (7.0–18.0)	13.0 (8.0–18.0)	0.07
Median no. of positive nodes (IQR)	3.0 (1.0–8.0)	4.0 (1.0–9.0)	3.0 (1.0–8.0)	< 0.001
Treated with radiation postlumpectomy[b]				< 0.001
No	145 (12.7%)	63 (26.8%)	82 (9.0%)	
Yes	998 (87.3%)	172 (73.2%)	826 (91.0%)	
Treated with radiation postmastectomy[c]				< 0.001
No	1051 (21.9%)	248 (40.0%)	803 (19.2%)	
Yes	3748 (78.1%)	372 (60.0%)	3376 (80.8%)	
Treated with adjuvant endocrine therapy[d]				–
No	536 (9.0%)	–	536 (10.5%)	
Yes	4380 (73.7%)	–	4380 (86.1%)	
Treated with adjuvant chemotherapy[e]				–
No	563 (9.5%)	563 (65.8%)	–	
Yes	280 (4.7%)	280 (32.7%)	–	
Year of diagnosis				< 0.001
2004	247 (4.2%)	21 (2.5%)	226 (4.4%)	
2005	265 (4.5%)	21 (2.5%)	244 (4.8%)	
2006	328 (5.5%)	40 (4.7%)	288 (5.7%)	
2007	392 (6.6%)	50 (5.8%)	342 (6.7%)	
2008	460 (7.7%)	57 (6.7%)	403 (7.9%)	
2009	521 (8.8%)	88 (10.3%)	433 (8.5%)	
2010	685 (11.5%)	103 (12.0%)	582 (11.4%)	
2011	654 (11.0%)	121 (14.2%)	533 (10.5%)	
2012	725 (12.2%)	116 (13.6%)	609 (12.0%)	
2013	762 (12.8%)	112 (13.1%)	650 (12.8%)	
2014	903 (15.2%)	126 (14.7%)	777 (15.3%)	
Income level (US $)				0.001
< 35,000	1429 (24.0%)	241 (28.2%)	1188 (23.4%)	
≥ 35,000	4287 (72.1%)	574 (67.1%)	3713 (73.0%)	
Insurance status				< 0.001
Private	3682 (62.0%)	256 (29.9%)	3426 (67.3%)	
Government	1966 (33.1%)	564 (66.0%)	1402 (27.6%)	
Not insured	181 (3.0%)	15 (1.8%)	166 (3.3%)	
Education level				0.73
> 80% high school graduation rate	3789 (63.8%)	536 (62.7%)	3253 (63.9%)	
≤ 80% high school graduation rate	1927 (32.4%)	279 (32.6%)	1648 (32.4%)	
Facility type				0.72
Academic	2333 (39.3%)	334 (39.1%)	1999 (39.3%)	
Integrated network	747 (12.6%)	116 (13.6%)	631 (12.4%)	
Comprehensive	2450 (41.2%)	351 (41.1%)	2099 (41.3%)	
Community	412 (6.9%)	54 (6.3%)	358 (7.0%)	
Facility location				0.18
Midwest	1540 (25.9%)	215 (25.1%)	1325 (26.0%)	
Northeast	1293 (21.8%)	199 (23.3%)	1094 (21.5%)	
South	2224 (37.4%)	299 (35.0%)	1925 (37.8%)	

TABLE 1 continued

	All patients (N = 5942) n (%)[a]	Neoadjuvant endocrine therapy (N = 855) n (%)[a]	Neoadjuvant chemotherapy (N = 5087) n (%)[a]	p value[f]
West	885 (14.9%)	142 (16.6%)	743 (14.6%)	

HR+ hormone receptor positive, *IQR* interquartile range

[a]Percentages are out of total population counts unless otherwise indicated and may not add up to 100 due to rounding or missing values

[b]Percentages represent rates of radiation receipt among patients receiving lumpectomy

[c]Percentages represent rates of radiation receipt among patients receiving mastectomy

[d]Adjuvant endocrine therapy rates are only summarized for patients who did not receive neoadjuvant endocrine therapy

[e]Adjuvant chemotherapy rates are only summarized for patients who did not receive neoadjuvant chemotherapy

[f]p values for categorical variables are from Chi square tests. p values from continuous variables are from pooled t-tests

DISCUSSION

After adjusting for patient and treatment characteristics, we found that OS did not differ between patients with LN+ ILC who received NET and those who received NACT. While many clinical trials, including Z1031, show benefit for NET in ER+ invasive carcinoma, ILC remains underrepresented in these studies. To date, there has been no direct comparison of NET and NACT among patients with LN+ ILC. Most of these patients are potentially eligible for chemotherapy, and most will receive adjuvant endocrine therapy, which has been shown to be beneficial in ILC.[18–22] Accordingly, it is important to examine which of these two forms of systemic therapy should be prioritized in the treatment sequence of patients who could potentially benefit from receiving both.

Several studies, including ours, suggest that NET is disproportionately administered to older, sicker patients. Notably, a majority of the patients in our study who received NET were ≥ 50 years old at diagnosis (91.6%). Accordingly, it is unclear what, if any, role NET might play in the care of younger, healthier patients. Furthermore, we must question the benefit of current practice, in which NACT is administered to approximately one-third of node-positive ILC patients (Supplementary Table 5), the vast majority of whom are strongly HR+, and traditionally experience less robust responses to NACT than patients with HER2+ and triple-negative tumors.[7]
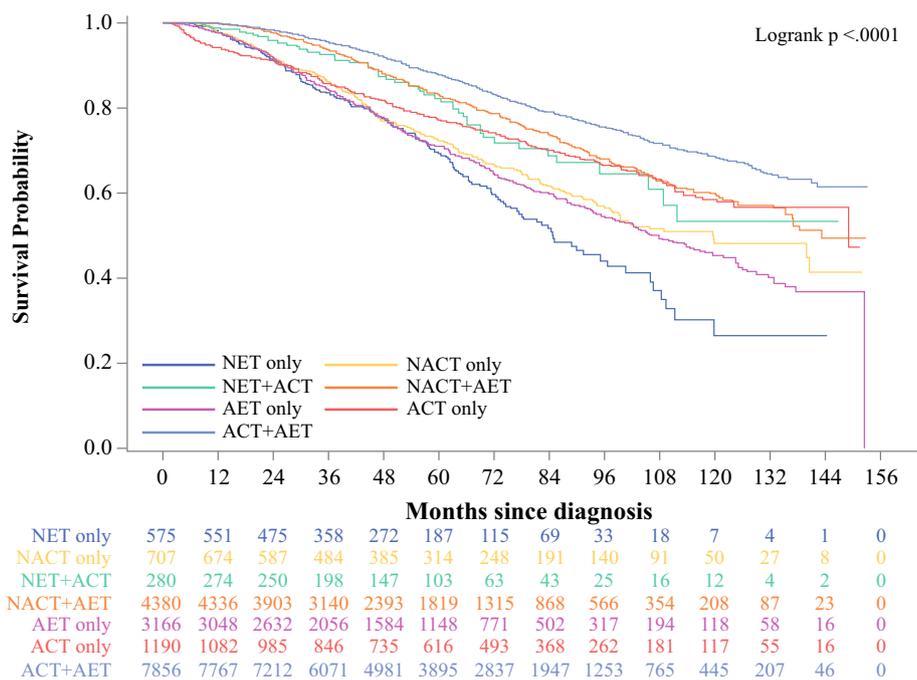
The administration of neoadjuvant therapy in patients with resectable, nonmetastatic breast cancer has historically been reserved for facilitating breast conservation, downstaging the axilla, and providing information about the effectiveness of chemotherapy on particular breast cancer subtypes. Accordingly, success has been gauged by extent of tumor and nodal downstaging—as evidenced by rates of pCR—or improved opportunity to perform breast-conserving surgery. Given low rates of pCR in both our NET and NACT cohorts, it is important to consider which ILC patients are likely to benefit most from neoadjuvant therapy of *any* kind. Previous work from our group comparing the impact of neoadjuvant versus adjuvant chemotherapy on long-term outcomes in LN+ ILC demonstrated no difference in receipt of mastectomy between these two groups.[23] In our current study, the overall pCR rate of 2.1% in all ILC patients receiving neoadjuvant therapy supports data from previous studies demonstrating that pCR is not commonly achieved after neoadjuvant therapy in ILC patients.[4–6] Thus, although some previous studies have demonstrated higher rates of lumpectomy following NACT and NET in HR+ patients, neither forms of neoadjuvant treatment appear to have had this effect in the patients with lobular histology in our study.

Nevertheless, despite evidence that tumor downstaging is typically less dramatic in patients with ILC as compared to patients with IDC, rates in excess of 50% have been reported.[24,25] Furthermore, it is important that we not simply assume that high rates of mastectomy necessarily represent failed attempts to downstage the breast and facilitate BCT; there are many reasons why women choose to undergo mastectomy, even with tumors that are small to begin with or with tumors that shrink significantly with neoadjuvant treatment, including concerns for cosmesis, peace of mind, and a desire to potentially avoid adjuvant radiation.[26–28] These reasons are not routinely captured in large databases such as the NCDB, and their potential contribution to overall mastectomy rates in our patient cohort should not be discounted.

Collectively, our findings raise the possibility that the best sequence of treatment for many patients with ILC may involve receipt of all systemic therapy after surgery, but neoadjuvant therapy could still be an important option for particular groups of patients including those who are strongly HR+ and low-grade but unresectable at

FIG. 2 Unadjusted overall survival, women with cT1-4c, cN1-3, HR+ invasive lobular carcinoma who received endocrine therapy or chemotherapy, National Cancer Data Base, 2004–2014 (N = 18,154). *ACT* adjuvant chemotherapy, *AET* adjuvant endocrine therapy, *NACT* neoadjuvant chemotherapy, *NET* neoadjuvant endocrine therapy

Logrank p <.0001

	0	12	24	36	48	60	72	84	96	108	120	132	144	156
NET only	575	551	475	358	272	187	115	69	33	18	7	4	1	0
NACT only	707	674	587	484	385	314	248	191	140	91	50	27	8	0
NET+ACT	280	274	250	198	147	103	63	43	25	16	12	4	2	0
NACT+AET	4380	4336	3903	3140	2393	1819	1315	868	566	354	208	87	23	0
AET only	3166	3048	2632	2056	1584	1148	771	502	317	194	118	58	16	0
ACT only	1190	1082	985	846	735	616	493	368	262	181	117	55	16	0
ACT+AET	7856	7767	7212	6071	4981	3895	2837	1947	1253	765	445	207	46	0

presentation due to local invasion and those who are unable to proceed with surgery immediately due, for example, to having a second synchronous tumor or anticoagulation that cannot be interrupted. For patients unwilling or unable to receive NACT but who seek to improve candidacy for BCT, pretreatment counseling regarding NET must include information as to the likelihood of success given available data; these patients must also be counseled that NET may require upwards of 3–4 months for a significant treatment effect to be observed.[25] Furthermore, neoadjuvant therapy can play an important role in the "window trial" space as treatment strategies for CDK4/6 inhibitors and other new therapies are developed and continue to evolve.

While our findings also suggest that neoadjuvant therapy may not obviate the need for additional systemic therapy in the adjuvant setting, definitive clinical recommendations cannot be made until results from the ALTERNATE trial assessing need for chemotherapy following response to NET are available.[29] The results of this trial will be especially welcome given our finding that rates of both NET and NACT administration have increased over time (Supplementary Table 5), even as our unadjusted survival analyses showed that patients who received all of their chemotherapy and endocrine therapy in the adjuvant setting had the highest OS (Fig. 2). While it is important to prioritize adjusted analyses, there was also evidence in a recently published paper from our group that receipt of

adjuvant chemotherapy was associated with improved survival in ILC patients as compared with neoadjuvant chemotherapy.[23]

Molecular genomic testing, such as Oncotype DX and MammaPrint, may be useful in determining which patients may safely avoid chemotherapy altogether; however, further investigation into the predictive and prognostic value of these tests for node-positive invasive lobular cancer is needed to determine how they should be interpreted and incorporated into systemic treatment decisions.[30,31] A 2016 study specifically analyzing the prognostic value of MammaPrint in ILC patients demonstrated an association between having a high-risk MammaPrint score and having worse survival after a diagnosis of early-stage ILC.[32] Although MammaPrint has also been prospectively validated in node-positive patients, Oncotype DX will not be validated in node-positive patients until results from the RxPonder trial are available.[33] Several studies have reported a significant difference between ductal and lobular patients in distribution of Oncotype DX recurrence scores (RS), suggesting that the clinical applicability of the test for ILC patients may be different from that in IDC. Felts et al. found that almost all ILC patients in their cohort fell within the low/intermediate RS categories (97.8%).[31] Similarly, in their study of node-negative patients, Kelly et al. reported no ILC patients with a high Oncotype RS: 67.5% of patients were classified as low risk, and 32.5%

TABLE 2 Adjusted overall survival, women with cT1–4c, cN1–3, HR+ invasive lobular carcinoma who received neoadjuvant endocrine therapy or chemotherapy, National Cancer Data Base, 2004–2014 (N = 4478)

	HR (95% CI)	p value	Overall p value
Treatment group			0.10
Neoadjuvant chemotherapy	REF		
Neoadjuvant endocrine therapy	0.84 (0.68–1.03)	0.10	
Adjuvant therapy[a]			< 0.001
No	REF		
Yes	0.60 (0.50–0.72)	< 0.001	
Age (years)			< 0.001
≥ 50	REF		
< 50	0.76 (0.65–0.88)	< 0.001	
Race			0.05
White	REF		
Black	1.17 (0.95–1.45)	0.14	
Other	0.61 (0.37–1.03)	0.06	
Ethnicity			0.01
Hispanic	REF		
Non-Hispanic	1.67 (1.12–2.48)	0.01	
Charlson–Deyo comorbidity score			0.009
0	REF		
1	1.16 (0.93–1.43)	0.18	
≥ 2	1.71 (1.19–2.44)	0.003	
Pathological T classification			< 0.001
1	REF		
0	1.78 (1.11–2.86)	0.02	
2	1.33 (1.07–1.65)	0.010	
3	1.54 (1.24–1.92)	< 0.001	
4	2.01 (1.47–2.75)	< 0.001	
X	1.30 (0.82–2.04)	0.26	
Pathological N classification			< 0.001
0	0.87 (0.65–1.15)	0.33	
1	REF		
2	1.51 (1.25–1.83)	< 0.001	
3	2.75 (2.28–3.32)	< 0.001	
X	0.60 (0.38–0.95)	0.03	
Grade			< 0.001
1	REF		
2	1.30 (1.08–1.57)	0.006	
3	1.69 (1.35–2.10)	< 0.001	
Surgery type			0.001
Lumpectomy	REF		
Mastectomy	1.37 (1.13–1.67)	0.001	
Treated with radiation[b]			0.003
No	REF		
Yes	0.77 (0.65–0.92)	0.003	
Income level (US $)			0.87
< 35,000	REF		
≥ 35,000	0.99 (0.82–1.18)	0.87	
Insurance status			< 0.001
Private	REF		
Government	1.39 (1.20–1.61)	< 0.001	
Not insured	1.45 (0.99–2.12)	0.05	

TABLE 2 continued

	HR (95% CI)	p value	Overall p value
Education level			0.06
≤ 80% high school graduation rate	REF		
> 80% high school graduation rate	0.85 (0.72–1.01)	0.06	
Facility type			0.01
Academic	REF		
Integrated network	1.36 (1.08–1.71)	0.009	
Comprehensive	1.26 (1.07–1.48)	0.005	
Community	1.06 (0.81–1.39)	0.66	
Facility location			0.14
South	REF		
Midwest	1.12 (0.93–1.34)	0.24	
Northeast	0.97 (0.80–1.19)	0.79	
West	0.85 (0.67–1.07)	0.16	

Hazard ratios, confidence intervals, and p values are from a Cox proportional hazards model, stratified by year of diagnosis (grouped as 2004–2009 and 2010–2014). A robust sandwich covariance estimator was used to account for correlation of patients treated at the same facility

HR hazard ratio, *CI* confidence interval

[a]Receipt of complementary adjuvant systemic therapy that was not received in neoadjuvant setting (i.e., ACT for patients receiving NET, AET for patients receiving NACT)

[b]Interaction with type of breast surgery received was tested and not significant

were classified as intermediate risk.[34] But as our study on ILC suggests, chemotherapy may still have significant benefit in locally advanced ILC patients, even if some would have been predicted to derive little or no benefit from chemotherapy using current methods and thresholds for genomic testing.

Limitations

There are several limitations to this study. The NCDB does not report breast cancer-specific survival or recurrence rates, thus OS was the only long-term outcome studied. Future studies may consider capturing survival outcomes past the 10-year mark, as there is evidence that recurrence may be a late event in ILC patients.[35,36] Although we were unable to determine cause-specific mortality, we were partially able to account for burden of nonmalignant disease using the Charlson–Deyo comorbidity score. Our study specifically examined patients with clinically node-positive disease, thus our results may not be applicable to node-negative patients with ILC. Because ILC is often understaged at presentation, we recognize that findings of tumor and axillary upstaging may not truly reflect progression during neoadjuvant therapy but rather underappreciation of extent of disease at presentation.[17] Similarly, we recognize that downstaging cannot be equated with successfully enabling BCT, given that a patient's tumor may shrink significantly enough to allow for BCT without experiencing a change in T classification. The NCDB determines neoadjuvant and adjuvant status based on the start date of therapy as compared with the date of surgery, so we were unable to distinguish patients who received all of their chemotherapy or endocrine therapy in the neoadjuvant setting from patients who received the same treatment in *both* the neoadjuvant and adjuvant setting (i.e., NACT + ACT or NET + AET, respectively). Finally, we could not account for patients who did not complete recommended treatments, and information on duration of adjuvant chemotherapy or endocrine therapy is also unavailable in the NCDB.

CONCLUSIONS

After adjustment for known covariates, there was no significant difference in overall survival between node-positive ILC patients receiving NET and those receiving NACT. In this patient population, overall survival was improved in patients who received a combination of both endocrine therapy and chemotherapy, but given low rates of in-breast and nodal downstaging following both NET and NACT as well as evidence of improved survival among patients who received all systemic therapy in the adjuvant setting, it may be preferable to defer all systemic therapy to the postoperative setting if patients can safely proceed to upfront surgery. But in patients who are unable to undergo surgery first, NET may represent a safe, less morbid, but, as yet, minimally explored alternative to NACT. While further investigation is warranted, our findings call into question the overall benefit of neoadjuvant systemic therapy for node-positive ILC and point toward

the need for large, prospective cohort studies with balanced populations to investigate the optimal inclusion and sequence of endocrine therapy and chemotherapy in the management of locally advanced ILC.

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