The Impact of Chemotherapy Sequence on Survival in Node-Positive Invasive Lobular Carcinoma

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Abstract

Background and Objectives: We sought to evaluate the impact of chemotherapy sequence on survival by comparing node-positive ILC patients who received neoadjuvant (NACT) and adjuvant (ACT) chemotherapy.

Methods: cT1–4c, cN1–3 ILC patients in the National Cancer Data Base (2004–2013) who underwent surgery and chemotherapy were divided into NACT and ACT cohorts. Kaplan-Meier curves and Cox proportional hazards modeling were used to estimate unadjusted and adjusted overall survival (OS), respectively.

Results: 5,551 (35.6%) of 15,573 ILC patients treated with chemotherapy received NACT. NACT patients had similar rates of pT3/4 disease (26.6% vs 26.2%), nodal involvement (median 3 vs 4), and number of lymph nodes examined (median 13 vs 14) but higher rates of mastectomy (81.8% vs 74.5%, p<0.001) vs ACT patients. 3.4% of NACT patients experienced pathologic complete response (pCR). Unadjusted 10-year OS was worse for NACT vs ACT patients (65.1%

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vs 54.4%, log-rank p<0.001). After adjustment for known covariates, NACT continued to be associated with worse OS (HR 1.38, 95% CI 1.25–1.52).

Conclusions: In node-positive ILC, NACT yielded low rates of pCR, was not associated with lower rates of mastectomy or less extensive axillary surgery, and was associated with worse survival vs ACT, suggesting limited benefit for these patients.

Keywords

chemotherapy; invasive lobular breast cancer; locally advanced breast cancer; neoadjuvant

INTRODUCTION

Invasive lobular carcinoma (ILC) is the second most common histological subtype of breast cancer and affects approximately 10–15% of patients with invasive disease. Several studies have demonstrated significant differences in tumor biology and response to treatment between patients with ILC and the most common subtype, invasive ductal carcinoma (IDC), but staging and treatment recommendations do not differentiate between these two types of breast histology.[1,2]

Patients with ILC have higher rates of lymph node metastasis than patients with IDC and tend to present with larger tumor size.[3,4] As a result, neoadjuvant chemotherapy (NACT) is not infrequently recommended for patients with ILC. But ILC is also nearly always hormone receptor (HR)-positive, and previous studies have demonstrated that patients with low-grade, HR-positive (HR+) ILC have a poor response to neoadjuvant chemotherapy, experiencing lower rates of pathologic complete response (pCR) than patients with IDC.[5–7] Concomitantly, NACT has historically been less successful in enabling breast conservation or omission of more extensive axillary surgery among ILC patients, who have higher rates of mastectomy and completion axillary lymph node dissection (ALND) than those with IDC. [8–11] Nevertheless, similar criteria – including nodal involvement – are used to determine whether NACT should be administered in both histologic subtypes.[12]

Data from several clinical trials and population-based studies report an association between pCR and improved survival, though some studies have also demonstrated that the lower pCR rates seen in ILC patients do not necessarily correlate with worse outcomes.[13–17] With conflicting evidence of clinical benefit and a greater likelihood of advanced stage at presentation, the delay to surgery that results from NACT administration in ILC patients may translate into a delay in administering locoregional (e.g., surgery, radiation) and systemic (e.g., endocrine) treatments that are potentially more beneficial for patients with ILC. Accordingly, we sought to determine the impact of chemotherapy sequence on survival among node-positive (cN+) ILC patients receiving chemotherapy. We hypothesized that in this subset of patients, a delay in receiving locoregional and endocrine therapy in order to administer NACT may result in worse survival.

MATERIALS AND METHODS

Patients diagnosed with clinical tumor stage (cT) 1–4c, clinical node stage (cN) 1–3, ILC between 2004 and 2014 were identified in the National Cancer Data Base (NCDB). Patients with metastatic disease; those who did not undergo chemotherapy, lumpectomy, or mastectomy; those who received neoadjuvant endocrine; and those with unknown or missing survival or treatment data were excluded. As required by NCDB guidelines, patients diagnosed in 2014 were excluded from survival analyses due to insufficient length of follow-up. Patients were classified as having received either NACT (which, in the NCDB, also includes some patients who received both neoadjuvant *and* adjuvant chemotherapy) or only adjuvant chemotherapy (ACT) based on whether their chemotherapy start date was before or after surgery, respectively.

Patient characteristics were summarized with N (%) and median (interquartile range) values for categorical and continuous variables, respectively. Chi-square and t-tests compared study groups' categorical and continous variables as appropriate. Among patients who received NACT, response to treatment was categorized as: (1) overall pCR (ypT0N0, i.e., the absence of any residual invasive or noninvasive carcinoma in the breast or lymph nodes on pathologic review); (2) breast-only pCR (ypT0, cN=ypN); (3) node-only pCR (cT=ypT, ypN0); (4) no stage change (cTN = ypTN); (5) upstage (ypT>cT and ypN>cN, i.e., a change from lower cT and cN stage to higher ypT and ypN stage); or (6) discordant (i.e., breast was upstaged while axilla was downstaged or vice versa)/partial (i.e, breast or nodal downstaging without achieving pCR) response.

Overall survival (OS) was defined as the time from diagnosis to death or last follow-up. Unadjusted OS was estimated using the Kaplan-Meier method, and differences in unadjusted OS between ACT and NACT patients were tested using the log-rank test. The Cox proportional hazards model estimated the effect of chemotherapy timing on OS after adjustment for known covariates. After testing the proportional hazards assumption for the included variables, the model was modified to stratify by age at diagnosis, year of diagnosis (grouped into 2004–2009 and 2010–2013 to reflect the fact that the NCDB only began to collect HER2 receptor information in 2010), and HR status. HR+ patients were estrogen (ER) and/or progesterone receptor (PR)-positive, while HR-negative (HR-) patients were ER and PR-negative. To address the time-dependent effects of tumor and treatment characteristics on long-term survival,[18] radiation (analyzed separately for patients undergoing lumpectomy and mastectomy) and endocrine therapy were allowed to be time-varying in the model. Stage-specific sensitivity analyses were performed to only include patients with stage II or III cancer as defined in the 7th edition of the American Joint Commission on Cancer (AJCC) Staging Manual. To account for the correlation of patients treated at the same facility, a robust sandwich covariance estimator was used for the adjusted model. We report hazard ratios (HRs) and 95% confidence intervals (CIs). Two-tailed $p < 0.05$ was considered significant for all analyses.

Only patients with available data were utilized in 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), with

which figures were also created. Due to use of de-identified data, our institutional review board granted the study exempt status.

RESULTS

Patient, Tumor, and Treatment Characteristics

Of 20,295 operative patients with cT1–4c, cN+ ILC, 15,573 (76.7%) received chemotherapy and were included in our study cohort (Figure 1). 35.6% (N=5,551) underwent NACT. Median age among all patients was 56 (IQR 48–64). A higher proportion of patients with cT1/2 disease received ACT (77.5% vs NACT 48.4%, p<0.001) and a higher proportion of patients with cT3/4 disease received NACT (51.6% vs ACT 22.5%, p<0.001). Among HR+ patients, a majority received adjuvant endocrine therapy, and treatment rates between groups were not significantly different (NACT 74.3% vs ACT 79.7%, p=0.91). A majority of both NACT and ACT patients underwent mastectomy, but a higher proportion of NACT patients (81.8%) underwent mastectomy as compared to ACT patients (74.5%, p<0.001). Among patients who underwent mastectomy, most received post-mastectomy radiation (PMRT), but rates of PMRT were higher among NACT patients (76.9% vs ACT 67.0%, p<0.001). Among lumpectomy patients, rates of post-lumpectomy radiation were also high but did not differ between groups (NACT 89.0% vs ACT 87.8%, p=0.33). Likewise, the median number of lymph nodes examined (NACT 13 vs ACT 14) and that were positive (NACT 3 vs ACT 4) were similar (Table 1). NACT resulted in an overall pCR rate of 3.4%, and a higher rate of pCR in the lymph nodes (3.3%) vs the breast (0.9%).

Unadjusted Survival Analyses

Unadjusted OS was higher for patients who received ACT compared to those who received NACT at 10 years (65.1% vs 54.4%, p<0.001). When stratified by HR status, patients with HR- ILC, who made up 9% (n=1404) of the entire cohort, had worse OS than patients with HR+ ILC, regardless of chemotherapy sequence; NACT patients had worse OS than adjuvant patients within both the HR+ and HR- cohorts. Among patients <50, those who received NACT had worse OS compared to those who received ACT at 10 years (61.5% vs 75.6%, log-rank p<0.001). Similarly among patients   50, NACT patients had worse OS compared to ACT patients at 10 years (49.6% vs 61.2%, p<0.001).

We compared patients with known endocrine therapy status (n=15,038) to node-positive ILC patients who only received endocrine therapy (n=3,025, Figure 2).We compared 5- and 10-year survival among 5 groups: (1) NACT alone, (2) ACT alone, (3) Endocrine therapy alone, (4) NACT + Adjuvant endocrine therapy, and (5) ACT + Adjuvant endocrine therapy. We found that patients treated with NACT alone had worse 10-year survival compared to all other groups including those who only received endocrine therapy (38.6% vs 45.4%, log-rank p<0.001). However, patients who received chemotherapy of any kind in combination with adjuvant endocrine therapy had the best overall survival compared to patients treated with only endocrine therapy or only chemotherapy. Among patients who received a combination of chemotherapy and adjuvant endocrine therapy, NACT + endocrine patients had worse survival compared to ACT + endocrine patients (58.4% vs 67.3%, log-rank p<0.001).

A majority of the 15,573 patients in the cohort had stage II (71.3%, N=11,100) disease. In stage-specific sensitivity analyses, 34.8% (N=3,865) of stage II patients received NACT, and 37.7% (N=1,686) of stage III patients received NACT. Similar to the overall cohort, NACT was associated with worse survival compared to ACT in both stage II and stage III patients.

Adjusted Survival Analysis

After adjustment for known covariates, patients who underwent NACT had worse OS than patients receiving ACT (HR 1.38, 95% CI 1.25–1.52, p<0.001, Table 2). Other factors associated with worse survival were black vs white race (HR 1.25, 95% CI 1.09–1.43); government vs private insurance (HR 1.55, 95% CI 1.42–1.69); and higher grade, cT stage, and cN stage (all p<0.001). Improved survival was associated with age <50 (HR 0.73, 95% CI 0.66–0.81), adjuvant endocrine therapy (HR 0.75, 95% CI 0.67–0.84), and post-lumpectomy radiation (HR 0.66, 95% CI 0.51–0.86, all p<0.01). In stage-specific sensitivity analyses, NACT continued to be associated with worse adjusted survival compared to ACT in stage II and III patients (Supplemental Tables 1–2).

DISCUSSION

In our analysis of node-positive ILC patients, receipt of NACT was associated with worse OS compared to ACT even among those with stage III disease. NSABP B-18 demonstrated comparable rates of overall and disease-free survival in patients receiving adjuvant and neoadjuvant chemotherapy as well as higher rates of breast conservation in NACT patients, in whom pCR rates of >20% were reported.[19] However, our data support findings from additional studies that demonstrated low rates of overall and anatomically limited pCR in ILC,[6,12,19] and, concomitantly, that patients with ILC may not derive the same clinical benefit from NACT as patients with IDC.

An important initial consideration is whether chemotherapy confers *any* additional benefit over endocrine therapy alone for ILC, the majority of which is low-grade and HR+. Truin et al published a study of patients selected from the Netherlands cancer registry evaluating adjuvant endocrine therapy only vs endocrine therapy and chemotherapy in a cohort of 19,609 postmenopausal patients, 3,865 of whom had a diagnosis of lobular cancer. They concluded that adjuvant chemotherapy did not confer an additional benefit in patients with lobular cancer.[20] In addition, a more recent study by Marmor et al addressed the impact of adjuvant chemotherapy in the survival of patients with invasive lobular vs invasive ductal cancer within a California data registry.[21] In this study, likewise, adjuvant chemotherapy did not improve outcomes in 4,638 patients with ER+ stage I/II invasive lobular cancer. Our study evaluated 15,573 patients with cN+ ILC who received chemotherapy, which is frequently recommended for cN+ patients regardless of histology. Indeed, this tendency was confirmed in our manuscript, which demonstrated that on a national level, a majority of node-positive lobular patients (76.7%) received chemotherapy. Among the groups of patients for whom endocrine therapy status was known, ACT patients who did not receive endocrine therapy outperformed NACT patients who did not receive endocrine therapy, and similarly, ACT patients who did receive endocrine therapy had improved survival as compared to NACT patients who also received endocrine therapy. Notably, the only group of patients to

perform worse than those who only received endocrine therapy were those who only received NACT. Nevertheless, we can conclude that in cN+ ILC, there is a survival benefit conferred with the combination of chemotherapy and endocrine therapy and that sequence of chemotherapy does in fact matter, with worse outcomes seen among those who received NACT and adjuvant endocrine therapy as compared to those who received ACT and adjuvant endocrine therapy.

We sought to determine whether higher presenting stage among NACT patients contributed to the survival difference noted between NACT and ACT patients. Tsung et al. demonstrated that the 77 patients who received NACT had higher clinical stage at presentation and higher rate of mastectomy (84%) compared to ACT patients.[22] In our study, 51.6% of NACT patients had clinical T3 or T4 disease, and despite achieving pathological T3 and T4 disease rates that were similar to those among ACT patients (NACT 26.6% vs ACT 26.2%), a greater proportion of NACT patients (81.8%) underwent mastectomy compared with patients who underwent surgery first (74.5%). Of the ILC patients in our cohort who underwent NACT, only 3.4% experienced pCR, with less than 1% experiencing pCR in the breast. The low rates of pCR among ILC patients in our study have been observed by other authors, including a pooled analysis of 6 clinical trials by Cristofanilli et al. in which 122 patients with ILC had lower rates of pCR as compared with IDC patients (3% v 15%).[6] In a study examining the benefits of MRI in post-NACT surgical planning, patients with ILC had higher rates of mastectomy vs lumpectomy even after NACT.[23] Our data is in keeping with previous studies that suggest that across a large population of ILC patients, clinicians may not observe sufficient clinical benefit in the form of tumor downstaging preoperatively to warrant routine use in patients with high clinical T stage even if on final pathology they are found to have some evidence of response.

Response to NACT in the nodal basins is also a potentially important intermediate outcome among ILC patients given high rates of node-positivity at diagnosis. In our study, only 3.3% of patients had nodal pCR. Interestingly, while 76.8% of the neoadjuvant patients in our study had cN1 disease, 74.4% of NACT patients were ypN1-N3 post-chemotherapy, indicating high rates of post-NACT residual disease and even upstage. These rates could also represent inadequate staging at diagnosis, in keeping with ILC's tendency to be underestimated by conventional imaging.[23] Overall and positive lymph node yields were similar (NACT 13 and 3 vs ACT 14 and 4), suggesting that NACT rarely obviated ALND or downstaged the axilla. Other authors have also demonstrated high rates of persistent nodal involvement in ILC patients that ultimately made ALND unavoidable. [11,24] In our study, 48.4% of patients who received NACT had T1 or T2 disease suggesting that in these cases, presentation with node-positive disease may have driven the decision to pursue NACT. With high rates of persistent nodal involvement, our data suggest that use of NACT to downstage the axilla in ILC patients may also be of limited utility.

Patients who underwent NACT had worse unadjusted survival compared to patients receiving ACT (77.8% vs 84.7%), and this finding persisted in the adjusted analysis, where NACT conferred a 38% increased risk of death. We recognize that NACT is typically administered for patients with higher stage disease, which may – as a reflection of as-yet undetected systemic disease – intrinsically contribute to worse OS. However, in stage-

specific sensitivity analyses, worse survival outcomes persisted in patients who received NACT vs ACT regardless of stage.

In our subset analysis comparing HR- and HR+ ILC patients, HR- patients had worse OS compared to HR+ patients. Similarly, in a retrospective study using tumor registry data to evaluate disease-specific survival between stage-matched ILC and IDC patients, ILC was associated with worse survival outcomes in HR- patients.[15] We also found that even among HR- patients, who had worse survival than HR+ patients, receipt of NACT yielded worse survival than ACT. These findings suggest that ILC has a distinct tumor biology that is potentially resistant to chemotherapy regardless of HR status, a conclusion further supported by studies demonstrating that ILC is typically low grade with a low to intermediate mitotic index, thus limiting the response to NACT.[6]

After adjusting for multiple covariates, adjuvant endocrine therapy was associated with improved survival among ILC patients in our study. Given this finding, there may be potential for improved survival outcomes with the use of aromatase inhibitors in the neoadjuvant setting. ACOSOG Z1031 demonstrated improved surgical outcomes in postmenopausal women with ER-rich, stage II/III breast cancer treated with neoadjuvant aromatase inhibitors.[25] A tailored approach to treatment with neoadjuvant endocrine therapy may improve survival outcomes in ILC patients presenting with locally advanced disease.

In the NSABP B-18 and B-27 trials, there were no differences in disease-free or overall survival between NACT and ACT patients, with NACT resulting in pCR rates of 26.1%, a 175% increase in breast conservation, and a 37% increase in the incidence of pathologically negative nodes. However, these findings did not account for differences in histology.[19] With very low rates of pCR, mastectomy rates and lymph nodes yields comparable to ACT as well as worse OS than ACT, NACT appears to offer no additional benefit to node-positive ILC patients and may even be detrimental.

Limitations

There were several limitations to our study. The NCDB does not report breast cancer-specific survival or recurrence rates so the only long-term outcome examined was survival. We could not account for patients with disease progression prompting earlier surgical intervention or for patients who did not complete recommended treatment. Among those patients who received NACT, selection bias may have contributed to decisions regarding initial treatment with chemotherapy though our survival analysis adjusted for several known pre-treatment variables including presenting stage. Furthermore, it is impossible to discern which patients might have chosen mastectomy after NACT even if lumpectomy were feasible. Our study specifically selected patients with cN+ disease, thus our results may not be applicable to node-negative patients with ILC who receive NACT for other indications (e.g., inflammatory carcinoma). Finally, in its NACT designation, the NCDB does not distinguish between patients who received only NACT or both NACT and ACT, a group who may have more extensive, chemoresistant disease and whose inclusion may have contributed to the worse survival observed in the NACT group.

CONCLUSIONS

Among node-positive ILC patients in our study, receipt of NACT rarely conferred pCR, was associated with worse survival compared with receipt of ACT, and did not decrease rates of mastectomy or extensive axillary surgery. Our findings suggest that the NACT-associated delay to locoregional and endocrine treatment in these patients may result in worse long-term outcomes. Patients with locally advanced ILC would benefit from prospective clinical trials to inform the development of evidence-based, histology-specific guidelines as to the optimal use and sequence of both chemotherapy and endocrine therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

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Synopsis:

In node-positive invasive lobular breast cancer, NACT was not associated with lower rates of mastectomy or less extensive axillary surgery. NACT was associated with worse survival compared with adjuvant chemotherapy, suggesting NACT may be of limited benefit in node-positive ILC.
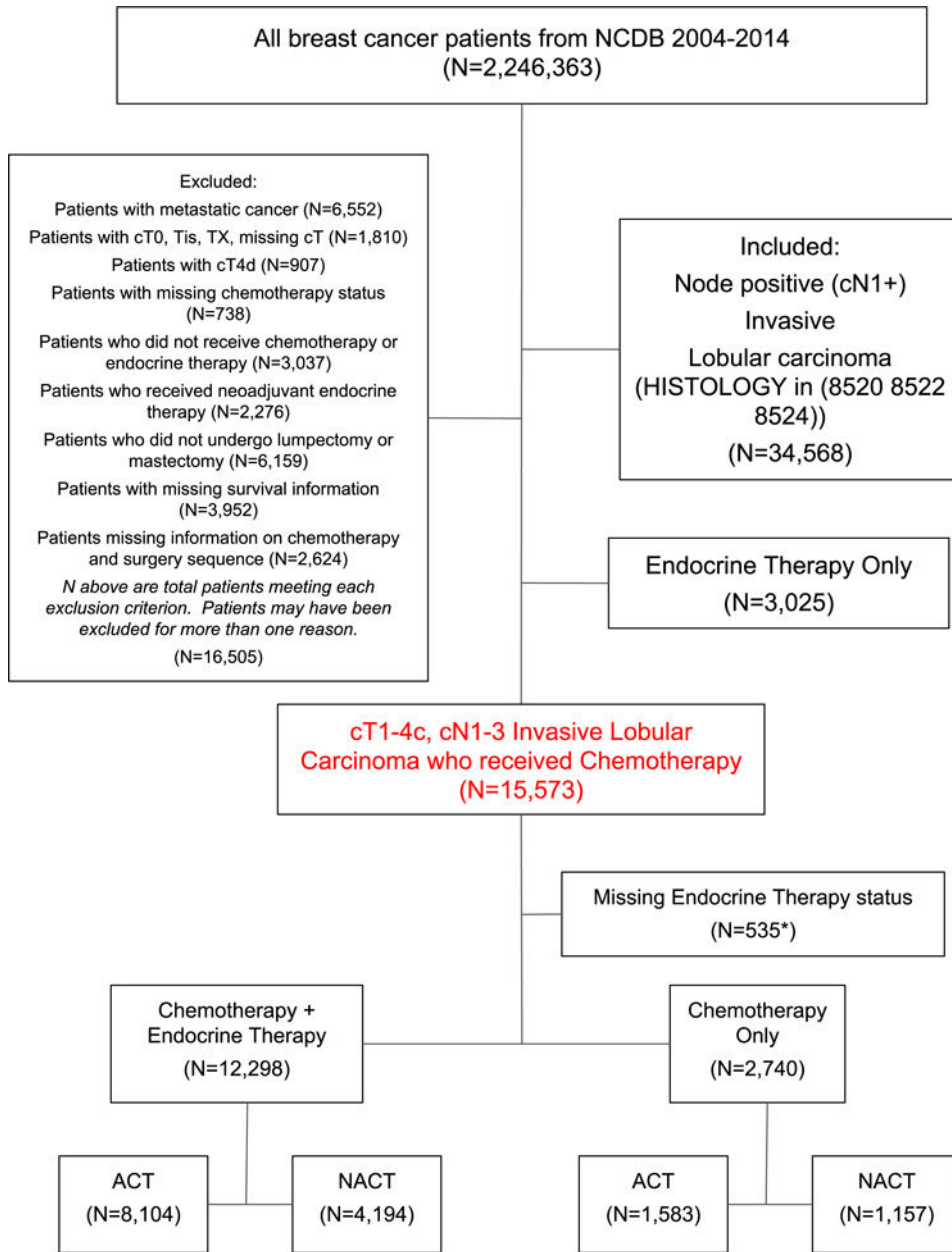
Fig. 1.
Study Cohort–Patients with cT1–4c, cN1–3 Invasive Lobular Carcinoma, National Cancer Data Base, 2004–2013 (N=15,573)
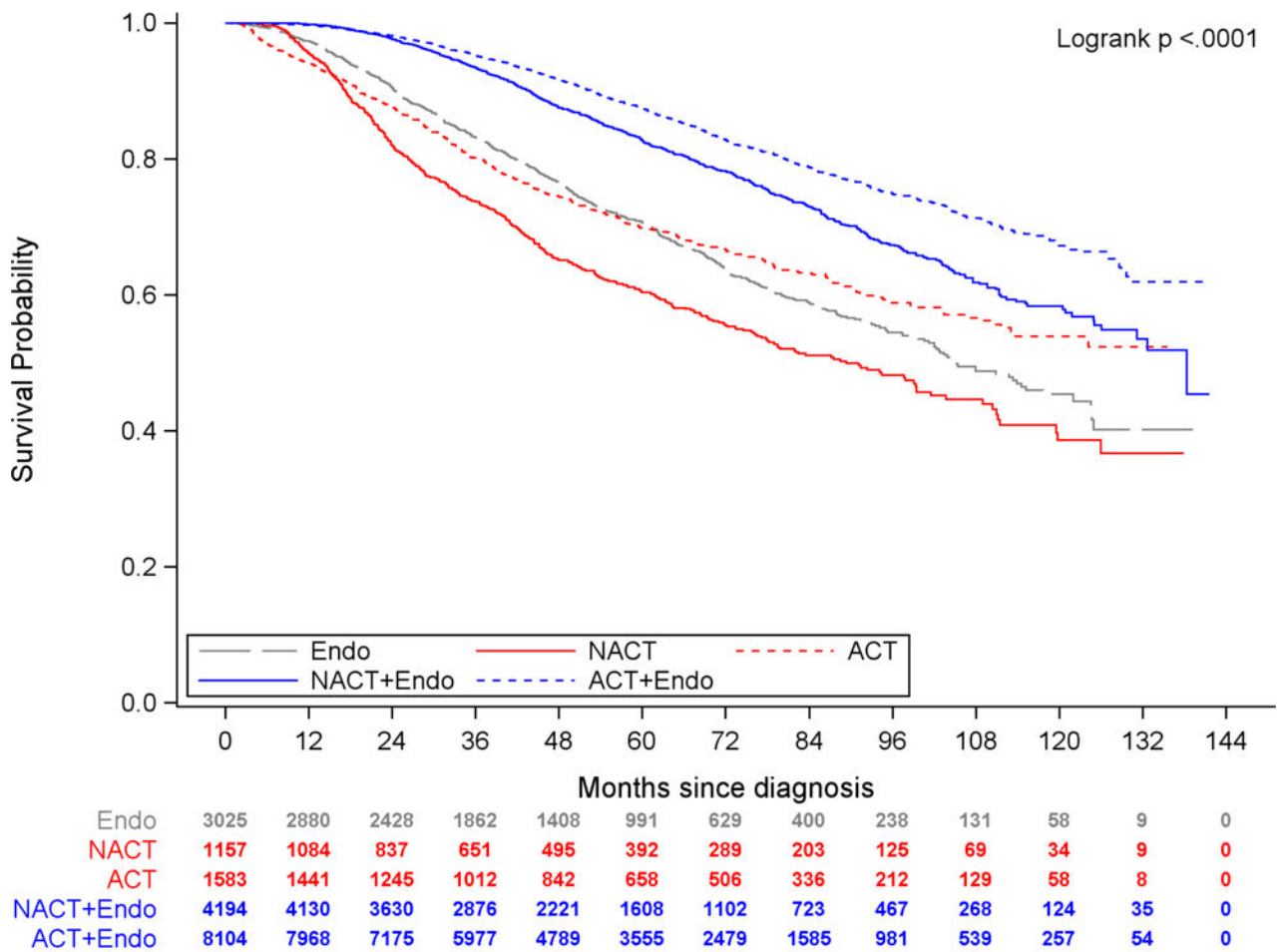
	Total	Deaths	Censored	5-Year Survival Rate (95% CI)	10-Year Survival Rate (95% CI)
Endo	3025	862 (28%)	2163 (72%)	0.706 (0.687 - 0.725)	0.454 (0.412 - 0.495)
NACT	1157	453 (39%)	704 (61%)	0.604 (0.571 - 0.635)	0.386 (0.329 - 0.443)
ACT	1583	485 (31%)	1098 (69%)	0.698 (0.672 - 0.723)	0.540 (0.497 - 0.580)
NACT+Endo	4194	744 (18%)	3450 (82%)	0.828 (0.813 - 0.841)	0.584 (0.549 - 0.616)
ACT+Endo	8104	1131 (14%)	6973 (86%)	0.874 (0.865 - 0.882)	0.673 (0.647 - 0.696)
Total	18063	3675 (20%)	14388 (80%)		

ACT, adjuvant chemotherapy. Endo, endocrine therapy. NACT, neoadjuvant chemotherapy.

Fig. 2.
Unadjusted Overall Survival by Treatment Sequence, cT1–4c, cN1–3 Invasive Lobular Carcinoma Patients, National Cancer Data Base, 2004–2013 (N=18,063)

Table 1.

Patient Characteristics, Patients with cT1–4c, cN1–3 Invasive Lobular Carcinoma, National Cancer Data Base, 2004–2013 (N=15,573)

	All patients (N=15,573) n (%)[a]	NACT (N=5551) n (%)[a]	ACT (N=10,022) n (%)[a]	P-Value[e]
Age (years)				<0.001
50	10,862 (69.7%)	3450 (62.2%)	7412 (74.0%)	
<50	4711 (30.3%)	2101 (37.8%)	2610 (26.0%)	
Median (IQR)	56.0 (48.0–64.0)	53.0 (46.0–61.0)	58.0 (49.0–66.0)	<0.001
Gender				0.98
Female	15,497 (99.5%)	5524 (99.5%)	9973 (99.5%)	
Male	76 (0.5%)	27 (0.5%)	49 (0.5%)	
Race				0.03
White	13,159 (84.5%)	4655 (83.9%)	8504 (84.9%)	
Black	1714 (11.0%)	655 (11.8%)	1059 (10.6%)	
Other	533 (3.4%)	176 (3.2%)	357 (3.6%)	
Ethnicity				0.009
Hispanic	942 (6.0%)	374 (6.7%)	568 (5.7%)	
Non-Hispanic	13,773 (88.4%)	4885 (88.0%)	8888 (88.7%)	
Charlson/Deyo comorbidity score				<0.001
0	13,485 (86.6%)	4937 (88.9%)	8548 (85.3%)	
1	1767 (11.3%)	538 (9.7%)	1229 (12.3%)	
2	321 (2.1%)	76 (1.4%)	245 (2.4%)	
Grade				0.01
1	2184 (14.0%)	721 (13.0%)	1463 (14.6%)	
2	8243 (52.9%)	2771 (49.9%)	5472 (54.6%)	
3	3325 (21.4%)	1207 (21.7%)	2118 (21.1%)	
ER status				<0.001
ER+	14,079 (90.4%)	4790 (86.3%)	9289 (92.7%)	
ER-	1233 (7.9%)	664 (12.0%)	569 (5.7%)	
PR status				<0.001
PR+	12,085 (77.6%)	4060 (73.1%)	8025 (80.1%)	
PR-	3146 (20.2%)	1370 (24.7%)	1776 (17.7%)	
HER2 status[b]				<0.001
HER2+	845 (10.9%)	432 (14.9%)	413 (8.5%)	
HER2-	6620 (85.3%)	2354 (81.5%)	4266 (87.7%)	
Tumor size				<0.001
<1 cm	676 (4.3%)	189 (3.4%)	487 (4.9%)	
>1 to 2 cm	2753 (17.7%)	618 (11.1%)	2135 (21.3%)	

	All patients (N=15,573) n (%)[a]	NACT (N=5551) n (%)[a]	ACT (N=10,022) n (%)[a]	P-Value[e]
>2 to 4 cm	5597 (35.9%)	1622 (29.2%)	3975 (39.7%)	
>4 cm	6191 (39.8%)	2876 (51.8%)	3315 (33.1%)	
Median (IQR)	3.5 (2.2–5.5)	4.5 (2.6–6.6)	3.0 (2.0–5.0)	<0.001
Clinical T stage				<0.001
1	3541 (22.7%)	614 (11.1%)	2927 (29.2%)	
2	6911 (44.4%)	2073 (37.3%)	4838 (48.3%)	
3	4313 (27.7%)	2246 (40.5%)	2067 (20.6%)	
4	808 (5.2%)	618 (11.1%)	190 (1.9%)	
Pathological T stage				<0.001
0	281 (1.8%)	269 (4.8%)	12 (0.1%)	
1	3756 (24.1%)	1321 (23.8%)	2435 (24.3%)	
2	6353 (40.8%)	1698 (30.6%)	4655 (46.4%)	
3	3657 (23.5%)	1260 (22.7%)	2397 (23.9%)	
4	442 (2.8%)	216 (3.9%)	226 (2.3%)	
X	823 (5.3%)	609 (11.0%)	214 (2.1%)	
Clinical N stage				<0.001
1	11,585 (74.4%)	4265 (76.8%)	7320 (73.0%)	
2	2641 (17.0%)	880 (15.9%)	1761 (17.6%)	
3	1347 (8.6%)	406 (7.3%)	941 (9.4%)	
Pathological N stage				<0.001
0	1102 (7.1%)	874 (15.7%)	228 (2.3%)	
1	6182 (39.7%)	1801 (32.4%)	4381 (43.7%)	
2	4140 (26.6%)	1364 (24.6%)	2776 (27.7%)	
3	3244 (20.8%)	964 (17.4%)	2280 (22.7%)	
X	724 (4.6%)	445 (8.0%)	279 (2.8%)	
Median no. of positive nodes (IQR)	4.0 (1.0–9.0)	3.0 (1.0–8.0)	4.0 (2.0–9.0)	<0.001
Median no. of nodes examined (IQR)	14.0 (9.0–19.0)	13.0 (8.0–18.0)	14.0 (9.0–20.0)	<0.001
Treated with endocrine therapy				
Out of all patients	12,298 (79.0%)	4194 (75.6%)	8104 (80.9%)	<0.001
Out of ER+ or PR+ patients	12114 (77.8%)	4127 (74.3%)	7987 (79.7%)	0.91
Surgery type				<0.001
Lumpectomy	3561 (22.9%)	1008 (18.2%)	2553 (25.5%)	
Mastectomy	12012 (77.1%)	4543 (81.8%)	7469 (74.5%)	
Radiation				
Post-lumpectomy[c]	3139 (88.1%)	897 (89.0%)	2242 (87.8%)	0.33
Post-mastectomy[d]	8496 (70.7%)	3492 (76.9%)	5004 (67.0%)	<0.001

[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 for HER2 status are out of patients diagnosed on or after 2010 (Overall N=7757, NACT N=2890, ACT N=4867).

*c*Percentages represent rates of radiation receipt among patients receiving lumpectomy.

*d*Percentages represent rates of radiation receipt among patients receiving mastectomy.

*e*P-values for categorical variables are from chi-square tests. P-values from continuous variables are from pooled t-tests.

ACT: adjuvant chemotherapy. ER: estrogen receptor. HER2: human epidermal growth factor receptor 2. IQR: interquartile range. LN: lymph node. NACT: neoadjuvant chemotherapy. PR: progesterone receptor.

Table 2.

Adjusted Overall Survival, cT1–4c, cN1–3 Invasive Lobular Carcinoma Patients, National Cancer Data Base, 2004–2013 (N=12,312)

	HR (95% CI)	P-Value	Overall P-Value
Treatment group			<0.001
ACT	REF		
NACT	1.38 (1.25 – 1.52)	<0.001	
Age (years)			<0.001
50	REF		
<50	0.73 (0.66 – 0.81)	<0.001	
Race			<0.001
White	REF		
Black	1.25 (1.09 – 1.43)	<0.001	
Other	0.68 (0.51 – 0.93)	0.01	
Ethnicity			<0.001
Hispanic	REF		
Non-Hispanic	1.43 (1.16 – 1.78)	<0.001	
Charlson/Deyo comorbidity score			<0.001
0	REF		
1	1.26 (1.13 – 1.42)	<0.001	
2	1.41 (1.10 – 1.81)	0.006	
Clinical T stage			<0.001
1	REF		
2	1.29 (1.137 – 1.47)	<0.001	
3	1.55 (1.35 – 1.77)	<0.001	
4	2.26 (1.88 – 2.71)	<0.001	
Clinical N stage			<0.001
1	REF		
2	1.24 (1.11 – 1.38)	<0.001	
3	1.95 (1.72 – 2.21)	<0.001	
Grade			<0.001
1	REF		
2	1.24 (1.09 – 1.42)	0.002	
3	1.69 (1.46 – 1.96)	<0.001	
Treated with radiation post-lumpectomy			0.002
No	REF		
Yes	0.66 (0.51 – 0.86)	0.002	
Treated with endocrine therapy			<0.001
No	REF		
Yes	0.75 (0.67 – 0.84)	<0.001	

Hazard ratios (HRs), confidence intervals (CIs), and p-values are from a Cox proportional hazards model, stratified by year of diagnosis (grouped as 2004–2009 and 2010–2013) and hormone receptor status (positive/negative). A robust sandwich covariance estimator was used to account for correlation of patients treated at the same facility. Other covariates for which HRs are not shown include Surgery type, Treatment with radiation post-mastectomy, Income level, Education level, and Facility Type (all non-significant) as well as Facility location (p<0.001).

ACT: adjuvant chemotherapy. NACT: neoadjuvant chemotherapy.