

The 21-Gene Recurrence Score in Clinically High Risk Lobular and Ductal Breast Cancer: A National Cancer Database Study

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Abstract

Purpose: To evaluate whether patients with ILC are more likely to have discordant clinical and genomic risk than those with IDC when using the 21-gene recurrence score (RS), and to assess overall survival outcomes of patients with 1-3 positive nodes and $RS \leq 25$ with and without chemotherapy, stratified by histology.

Methods: We performed a cohort study using the National Cancer Database and included patients with hormone receptor positive, HER2 negative, stage I-III invasive breast cancer who underwent 21-gene RS testing. Our primary outcome was rate of discordant clinical and genomic risk status by histologic subtype. Propensity score matching was used to compare 60-month overall survival in individuals with 1-3 positive nodes and $RS \leq 25$ who did and did not receive chemotherapy.

Results: 186,867 patients were included in our analysis, including 37,685 (20.2%) patients with ILC. There was a significantly higher rate of discordant clinical and genomic risk in patients with ILC compared to IDC. Among patients with 1-3 positive nodes and $RS \leq 25$, there was no significant difference in survival between those who did and did not receive chemotherapy in the IDC or ILC cohorts. Unadjusted exploratory analyses of patients under age 50 with 1-3 positive nodes and $RS \leq 25$ showed improved overall survival in IDC patients who received chemotherapy, but not among those with ILC.

Conclusion: Our findings highlight the importance of lobular-specific tools for stratifying clinical and genomic risk, as well as the need for histologic subtype-specific analyses in randomized trials.

Introduction

Despite major advances in the treatment of breast cancer, personalizing therapy to reduce recurrence risk while minimizing harm remains a challenge. Recommendations for treatment such as adjuvant chemotherapy rely upon multiple factors, including patient characteristics and overall health status, tumor features, and often molecular assays such as the 70-gene signature or the 21-gene Recurrence Score (RS) [1–3]. When patient and tumor factors suggest a high risk of recurrence, patients are deemed to have high “clinical” risk, and chemotherapy may be considered. Similarly, when molecular assays suggest a high risk of recurrence, tumors are considered to have high “genomic” risk, and patients with these high-risk tumors are predicted to benefit from chemotherapy.

However, when clinical and genomic risk are discordant, decisions about the efficacy of chemotherapy become more difficult. In the recently published RxPONDER trial, chemotherapy did not improve invasive disease-free survival in clinically high-risk post-menopausal patients with low genomic risk (based on $RS \leq 25$), although benefit was seen in those who were pre-menopausal [4]. These findings illustrate some of the challenges of treatment selection for those with discordant clinical and genomic risk.

We previously showed that such discordant risk status disproportionately affects patients with invasive lobular carcinoma (ILC) compared to invasive ductal carcinoma (IDC) when genomic risk is evaluated

with 70-gene signature testing [5]. As the second most common histologic subtype of breast cancer, ILC is thought to have a more indolent course but often presents at higher stages with considerable cumulative risk of late recurrence [6–11]. We therefore sought to investigate rates of discordant clinical and genomic risk by histologic subtype in patients who underwent RS testing in the National Cancer Database.

Specifically, we evaluated the following questions: (1) whether patients with ILC are more likely to have discordant clinical and genomic risk than those with IDC using the 21-gene RS; (2) whether use of chemotherapy differs by histologic subtype stratified by clinical and genomic risk category; and (3) whether patients with 1-3 positive nodes and $RS \leq 25$ have different overall survival outcomes with or without adjuvant chemotherapy stratified by histologic subtype.

Methods

Data Source and Study Cohort

Our study cohort consisted of patients in the National Cancer Database (NCDB). The NCDB is a national comprehensive clinical surveillance resource and represents over 70% of all newly diagnosed cancer cases in the United States [12, 13]. Participants User Files from 2010-2016 were used in our analysis. Due to the de-identified nature of the public-access user files, the study did not require institutional review board approval.

We limited our analysis to patients with invasive HR positive and human epidermal growth factor-receptor 2 (HER2) negative tumors with an available 21-gene RS result. We excluded patients with stage IV disease, those who received neoadjuvant therapy, individuals who did not undergo surgery for breast cancer, and those who were missing critical clinical information including histologic subtype, tumor grade, number of positive lymph nodes on pathology, tumor size, and timing of chemotherapy or endocrine therapy.

Clinical Measures and Outcomes

Our primary outcome was the rate of discordant clinical and genomic risk status by histologic subtype. We assigned clinical risk using a modified Adjuvant! Online calculator as described in the MINDACT trial; we also categorized patients by number of positive lymph nodes on surgical pathology (0, 1-3, or >3 nodes) [3, 4, 14–16]. The modified Adjuvant! Online risk score includes tumor size, tumor grade, and number of positive lymph nodes identified at surgery; those with a 92% or greater probability of breast-cancer specific survival at 10 years without chemotherapy were deemed to have low clinical risk [17, 18]. We assigned genomic risk using the 21-gene RS result, with $RS > 25$ considered as high genomic risk and $RS \leq 25$ as low genomic risk, consistent with RxPONDER.

Histologic subtype was determined by defined codes in the NCDB. The ILC cohort included codes for ILC or mixed ILC/IDC (histology codes 8520 and 8524 if behavior was invasive). The IDC cohort comprised codes for IDC or invasive mammary carcinoma not otherwise specified (histology codes 8500, 8501,

8502, 8503, and 8523 if behavior was invasive). Menopausal status was approximated using age under 50 years (pre-menopausal) and over 50 years (post-menopausal) and included as a predictor in our model. Additionally, the Charlson-Deyo Co-Morbidity Index was used as a marker of severity of co-morbid conditions. The Charlson-Deyo Co-Morbidity Index is a weighted score from 0-3 derived from multiple comorbid conditions, including myocardial infarction, diabetes, and renal disease, with higher score reflecting more comorbid disease [19–21].

Statistical Analysis

Patient characteristics were described and differences between histologic subtype were evaluated using chi-square tests for categorical variables and t-tests for continuous variables. Additionally, the frequency of patients in each of the four clinical and genomic risk categories (clinical high/genomic low, clinical low/genomic low, clinical high/genomic high, clinical low/genomic high) was described by histologic subtype, with chi-square testing used to compare the clinical high/genomic low risk cohort compared to other risk categories combined and across all four risk categories. We also performed subgroup analyses evaluating concordance of genomic and clinical risk by categorical nodal status, histology, and age. Receipt of chemotherapy stratified by histology, nodal status, RS, and age was also assessed. All analyses were pre-specified.

Finally, propensity score matching was used to compare 60-month overall survival in individuals who did and did not receive chemotherapy among patients with 1-3 positive nodes and $RS \leq 25$, stratified by histology. A greedy, fixed 1:1 matching method was used, and patients were matched by age at diagnosis in years, pathologic stage of disease (stage 2/3 vs. stage 1), and facility type. The upper limit of the absolute values of weighted matched standardized mean differences was set at 0.2. While we planned a pre-specified propensity score matched analysis evaluating the relationship between chemotherapy and overall survival in the subgroup of women aged under 50 years, with 1-3 positive nodes, and $RS \leq 25$, there were too few patients to allow for matching. We therefore performed exploratory analyses evaluating overall survival with and without chemotherapy using the log-rank test in this subgroup of women, stratified by histology; we also used the Cox proportional hazards model to evaluate overall survival both unadjusted and adjusted for Charlson-Deyo Co-Morbidity Index.

Hypothesis tests were two-sided, and the significance threshold was set to 0.05. Statistical analyses were performed using Stata 16 and SAS version 9.4.

Results

A total of 2,696,734 patients with breast cancer were included in the original NCDB database. After excluding patients based on the criteria previously described, there were 186,867 patients with stage I-III, HR positive, HER2 negative disease without neoadjuvant therapy who underwent breast surgery and received 21-gene RS testing that were included in our analysis (Figure 1). Of these, 149,182 (79.8%) patients had IDC, and 37,685 (20.2%) patients had ILC.

ILC versus IDC Cohorts

Patients in the ILC cohort were slightly older than those in the IDC cohort (mean age 60.5 years versus 58.9, $p < 0.001$). Additionally, they were more likely to present with higher stage disease and underwent mastectomy at higher rates (Table 1). The ILC tumors were significantly less likely to be grade 3, and overall chemotherapy was used less often in the ILC cohort compared to those with IDC. There was also a statistically significant difference in Charlson-Deyo score between the ILC and IDC cohorts, with ILC patients as more likely to have a Charlson-Deyo score of 0 compared to those with IDC (85.0% vs. 84.5%, $p = 0.015$).

Table 1
Clinicopathologic characteristics of study cohort.

| | ILC (N = 37,685) | IDC (N = 149,182) | P-Value |
|-------------------------------------|-----------------------------------|------------------------------------|----------------|
| Age at diagnosis (years), mean (SD) | 60.5 (10.0) | 58.9 (10.6) | < 0.001 |
| Pathologic stage, n (%) | 21,384 (56.7) | 104,748 (70.2) | < 0.001 |
| I | 15,302 (40.6) | 43,194 (29.0) | |
| II | 999 (2.7) | 1,240 (0.8) | |
| III | | | |
| Nodal involvement | 30,401 (80.7) | 123,470 (82.8) | <0.001 |
| Node negative | 6,869 (18.2) | 24,919 (16.7) | |
| 1-3 positive | 415 (1.1) | 793 (0.5) | |
| >3 positive | | | |
| Tumor grade, n (%) | 9,451 (25.1) | 43,276 (29.0) | < 0.001 |
| 1 | 25,403 (67.4) | 78,871 (52.9) | |
| 2 | 2,831 (7.5) | 27,035 (18.1) | |
| 3 | | | |
| Clinical risk, n (%) | 21,464 (57.0) | 96,060 (64.4) | < 0.001 |
| Low | 16,221 (43.0) | 53,122 (35.6) | |
| High | | | |
| Genomic risk, n (%) | 34,534 (91.6) | 125,030 (83.8) | < 0.001 |
| 21-gene RS ≤ 25 | 3,151 (8.4) | 24,152 (16.2) | |
| 21-gene RS > 25 | | | |
| Surgical therapy, n (%) | 21,373 (56.7) | 102,467 (68.7) | < 0.001 |
| Lumpectomy | 16,312 (43.3) | 46,715 (31.3) | |
| Mastectomy | | | |
| Adjuvant therapy, n (%) | 6,383 (17.3) | 33,534 (22.9) | < 0.001 |
| Chemotherapy | 35,161 (94.6) | 137,003 (93.4) | < 0.001 |
| Endocrine Therapy | | | |

| | ILC (N = 37,685) | IDC (N = 149,182) | P-Value |
|----------------------------|---------------------|----------------------|---------|
| Charlson-Deyo Score, n (%) | 32,039 (85.0) | 126,007 (84.5) | 0.015 |
| 0 | 4,629 (12.3) | 18,834 (12.6) | |
| 1 | 799 (2.1) | 3,312 (2.2) | |
| 2 | 218 (0.6) | 1,029 (0.7) | |
| ≥3 | | | |

Legend: ILC = invasive lobular carcinoma; IDC = invasive ductal carcinoma; RS = recurrence score

Clinical and Genomic Risk Discordance

We found a significantly higher rate of discordant clinical and genomic risk in patients with ILC compared to IDC. Patients with ILC were more likely to have high clinical risk by modified Adjuvant! Online than those with IDC (43% versus 35.6%, $p < 0.001$, Table 1). Consistent with this finding, those with ILC were less likely to be node negative than those with IDC (80.7% versus 82.8%, $p < 0.001$). While clinical risk was higher in ILC patients, genomic risk by RS was much lower, with an incidence of RS > 25 in ILC patients of 8.4% compared to 16.2% in IDC patients ($p < 0.001$). Together, this resulted in significantly higher rates of discordant clinical and genomic risk, with 37.8% of the ILC group being clinical high/genomic low compared to 24.9% of the IDC group ($p < 0.001$, Table 2).

Table 2
Distribution of clinical and genomic risk categories by histology. Genomic risk was categorized as either 21-gene RS \leq 25 or 21-gene RS > 25.

| | ILC (n = 37,685) | IDC (n = 149,182) | P-Value ¹ | P-Value ² |
|------------------------------------|---------------------|----------------------|----------------------|----------------------|
| Clinical high/21-gene RS \leq 25 | 14,253 (37.8) | 37,126 (24.9) | < 0.001 | <0.001 |
| Other | 23,432 (62.1) | 112,056 (75.1) | | |
| Clinical low/21-gene RS \leq 25 | 19,601 (52.0) | 85,078 (57.0) | | |
| Clinical high/21-gene RS > 25 | 1,968 (5.2) | 15,996 (10.7) | | |
| Clinical low/21-gene RS > 25 | 1,863 (4.9) | 10,982 (7.4) | | |

Legend: ILC = invasive lobular carcinoma, IDC = invasive ductal carcinoma. ¹P-value from chi square comparing clinical high / genomic low compared to other risk categories combined. ²P-value from chi square comparing across all four risk categories.

Within the group of patients with 1-3 positive nodes, patients with ILC were significantly more likely to have a RS \leq 25 compared to those with IDC (92.5% versus 85.8% respectively, $p < 0.001$, Table 3). This difference was more pronounced in those with > 3 positive nodes, with the vast majority of ILC patients in this group (90.1%) having a RS \leq 25 compared to 78.3% in the IDC group ($p < 0.001$, Table 3). Interestingly, among patients under the age of 50, ILC patients remained significantly more likely to have RS \leq 25 than those with IDC across all nodal involvement categories. In patients under age 50 with 1-3 positive nodes, low RS occurred in 94.8% of ILC group versus 85.1% of IDC group; among the small number of patients with > 3 positive nodes, low RS occurred in 94.7% of ILC group versus 70.6% of IDC group (both $p < 0.001$, Table 3).

Table 3

Breakdown of nodal status by histology and 21-gene recurrence score in all patients (top) and for those with age less than 50 years (bottom).

| All Patients | ILC Overall (n) | IDC Overall (n) | ILC 21-Gene RS \leq 25 (n [%]) | IDC 21-Gene RS \leq 25 (n [%]) | P-Value ¹ |
|---------------------------|-----------------|-----------------|----------------------------------|----------------------------------|----------------------|
| Node Negative | 30,401 | 123,470 | 27,804 (91.5%) | 103,039 (83.5%) | < 0.001 |
| 1-3 Positive Nodes | 6,869 | 24,919 | 6,356 (92.5%) | 21,370 (85.8%) | < 0.001 |
| > 3 Positive Nodes | 415 | 793 | 374 (90.1%) | 621 (78.3%) | < 0.001 |
| Patients Age < 50 Years | ILC Overall (n) | IDC Overall (n) | ILC 21-Gene RS \leq 25 (n [%]) | IDC 21-Gene RS \leq 25 (n [%]) | P-Value ¹ |
| Node Negative | 4,911 | 26,038 | 4,644 (94.6%) | 22,016 (84.6%) | < 0.001 |
| 1-3 Positive Nodes | 1,120 | 4,996 | 1,062 (94.8%) | 4,251 (85.1%) | < 0.001 |
| > 3 Positive Nodes | 57 | 163 | 54 (94.7%) | 115 (70.6%) | < 0.001 |

Legend: ILC = invasive lobular carcinoma, IDC = invasive ductal carcinoma, RS = recurrence score. ¹P-value from chi square comparing ILC 21-gene RS \leq 25 and 21-gene IDC RS \leq 25 across nodal categories.

Chemotherapy Use

We then evaluated the receipt of chemotherapy by histology, nodal status, RS category, and age. Among patients with RS \leq 25, there was no difference in receipt of chemotherapy by histology across the node negative, 1-3 positive nodes, and > 3 positive nodal groups (Figure 2). However, among patients with RS > 25 , those with ILC were significantly less likely to receive chemotherapy than those with IDC among patients with negative nodes or 1-3 positive nodes (both $p < 0.001$). In those with high clinical risk and RS

> 25, chemotherapy was used significantly more often in patients under 50 years old compared to those age 50 years or older, in both ILC and IDC groups. However, among clinically high risk patients with RS > 25 and age over 50 years, those with ILC were still less likely to receive chemotherapy than those with IDC (63.3% versus 74.8%, $p < 0.001$). In ILC patients with high clinical risk and RS > 25, 88.7% of patients were age 50 years or older, and 63.3% received chemotherapy compared to 80.5% of those under age 50 years ($p < 0.001$). Among IDC patients with high clinical risk and RS > 25, 78.2% of patients were age 50 years or older, and 74.8% received chemotherapy compared to 88.2% of those under age 50 years ($p < 0.001$).

Overall Survival Outcomes

Finally, we performed a propensity score matched analysis to compare overall survival in individuals who received chemotherapy compared to those who did not receive chemotherapy by histology among those with 1-3 positive nodes and $RS \leq 25$, including patients of all ages. The absolute values of the weighted matched standardized mean differences were less than the recommended upper limit of 0.2, and all weighted matched variance ratios were between 0.5 and 2. Among patients with IDC, there was no statistically significant difference in survival between those who did and did not receive chemotherapy (stratified log-rank test $p = 0.278$, Figure 3a). Similarly, for patients with ILC, survival between those who did receive chemotherapy and those who did not receive chemotherapy was not significantly different from one another (stratified log-rank test $p = 0.532$, Figure 3b). There were too few patients under the age of 50 years to perform a propensity score matched analysis, so exploratory results from unmatched survival analyses are reported. For women under age 50, with 1-3 positive nodes, and $RS \leq 25$, unadjusted analysis showed that chemotherapy was associated with a significant improvement in overall survival for those with IDC (hazard ratio [HR] 0.44, 95% confidence interval [CI] 0.22-0.86, $p = 0.016$) but not for those with ILC (HR 0.54, 95% CI 0.14-2.18, $p = 0.39$). The association between chemotherapy and improved overall survival in those with IDC persisted when adjusted for Charlson-Deyo Index (HR 0.44, 95% CI 0.22-0.85, $p = 0.016$). There was no statistical interaction between chemotherapy and histology on overall survival.

Discussion

In this study of 186,867 patients with HR positive, HER2-negative invasive breast cancer who underwent 21-gene RS testing in the National Cancer Database, we found that patients with ILC have higher rates of discordant clinical and genomic risk than those with IDC. This finding is consistent with our prior work, which showed higher rates of discordant clinical and genomic risk in ILC patients using the 70-gene signature [5]. Additionally, we found that ILC patients with 1-3 positive nodes were significantly more likely to have $RS \leq 25$ compared to those with IDC, in both those under age 50 years and those age 50 years or older.

Among those with $RS \leq 25$, there was no difference in receipt of chemotherapy by histology regardless of nodal involvement. However, among those with $RS > 25$, those with ILC were significantly less likely to

receive chemotherapy than those with IDC among patients with negative nodes or 1-3 positive nodes. While these findings are consistent with our prior study, which showed lower rates of chemotherapy use in patients with high clinical risk ILC and high genomic risk as defined by 70-gene signature testing, they are nonetheless surprising given the general acceptance of chemotherapy in the setting of $RS > 25$ and did not appear to be driven by older age in the ILC group [5, 14]. These findings may reflect hesitation on the part of clinicians and patients to utilize chemotherapy in ILC, where multiple studies have shown less benefit in the neoadjuvant and adjuvant settings [22, 23]. Together, this illustrates the treatment dilemma that clinicians and patients face: while patients with ILC are more likely to have high clinical risk, which portends increased risk of recurrence without chemotherapy, genomic assays and reported series suggest decreased chemotherapy benefit [24].

We did not demonstrate any effect of chemotherapy on overall survival among patients with 1-3 positive nodes and $RS \leq 25$ in our propensity score matched analyses, regardless of histologic subtype. Interestingly, we did find an association between chemotherapy and overall survival in unmatched analysis of IDC patients under age 50 with 1-3 positive nodes and $RS \leq 25$, but not among those under age 50 with ILC. Given the retrospective nature of this analysis, differences in patient selection for receiving chemotherapy likely contribute to chemotherapy related outcomes. While we attempted to account for potential confounders in treatment selection by using propensity score matching by age at diagnosis, pathologic stage, and facility type, it is unlikely that we were able to fully adjust for potential bias between the chemotherapy and non-chemotherapy groups.

This bias is greater in our exploratory unmatched analysis in patients under age 50, which showed a significant improvement in overall survival among IDC patients who received chemotherapy compared to those who did not but no difference in those with ILC. There are several potential explanations for the findings of our exploratory analyses. One possibility is that among those under age 50 with 1-3 positive nodes and $RS \leq 25$, the overall survival difference observed in the IDC group resulted from patient selection bias and not chemotherapy effect. Another explanation is that we were unable to detect an overall survival benefit in the ILC patients under age 50, with 1-3 positive nodes, and $RS \leq 25$ because of small numbers in this subgroup. Lastly, it is possible that chemotherapy improves overall survival in IDC patients but not ILC patients under the age of 50 with 1-3 positive nodes and $RS \leq 25$; for this reason, reporting of long-term and overall survival outcomes by histologic subtype from trials such as RxPONDER is needed.

While the RxPONDER trial showed a significant improvement in invasive disease-free survival in patients under age 50 who had 1-3 positive nodes and $RS \leq 25$ who received chemotherapy, we cannot directly compare our results since the National Cancer Database lacks recurrence endpoints. It is important to note that for patients with HR positive HER2 negative tumors, and ILC especially, recurrence events and consequently impact on overall survival can happen at later timepoints, highlighting the need for longer term follow-up [25, 26]. Additionally, we lacked data on type of endocrine therapy which likely impacts outcomes.

This study has many strengths, including the use of a relatively large numbers of ILC patients, and is now the second study to demonstrate that patients with ILC have high rates of discordance between clinical and genomic risk based on widely used molecular assays. While many studies show that ILC tumors have lower response rates to chemotherapy in the neoadjuvant setting, and less benefit from chemotherapy in the adjuvant setting, there may still be a subset of chemotherapy sensitive ILC cases. Recent work has identified genomic signatures that identify subtypes within ILC, suggesting heterogeneity within this tumor type [27, 28]. The high incidence of high clinical risk among patients with ILC highlights the need for both more effective therapies, and potentially ILC specific prediction tools. More broadly, improving outcomes for these patients with ILC will require not only equitable enrollment of ILC patients into breast cancer clinical trials, but also histologic subtype specific reporting of trial results.

Declarations

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Competing Interests

Dr. A. Jo Chien receives research funding from Merck, Puma, Amgen, and Seattle Genetics. Dr. Hope S. Rugo receives research support for clinical trials through the University of California from Pfizer, Merck, Novartis, Lilly, Roche, Odonate, Daiichi, Seattle Genetics, MacroGenics, Sermonix, Astra Zeneca, OBI, Gilead, and Ayala. She has also received honoraria from Puma, Samsung, and Napo. Dr. Michelle Melisko receives research funding from Astra Zeneca, Novartis, KCRN Research, and Puma and consulting fees from Biotheranostics. Dr. Baehner is the Chief Medical Officer of Precision Oncology at Exact Sciences. The remaining authors declare no competing interests.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Mary Kathryn Abel, Amy M. Shui, and Dr. Rita A. Mukhtar. The first draft of the manuscript was written by Mary Kathryn Abel and Dr. Rita A. Mukhtar, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The data that support the findings of this study are available from the National Cancer Database (NCDB), 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 NCDB.

Ethics Approval

Our study was deemed exempt by University of California, San Francisco institutional review board.

Consent to Participate

Not applicable

Consent to Publish

Not applicable

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Figures

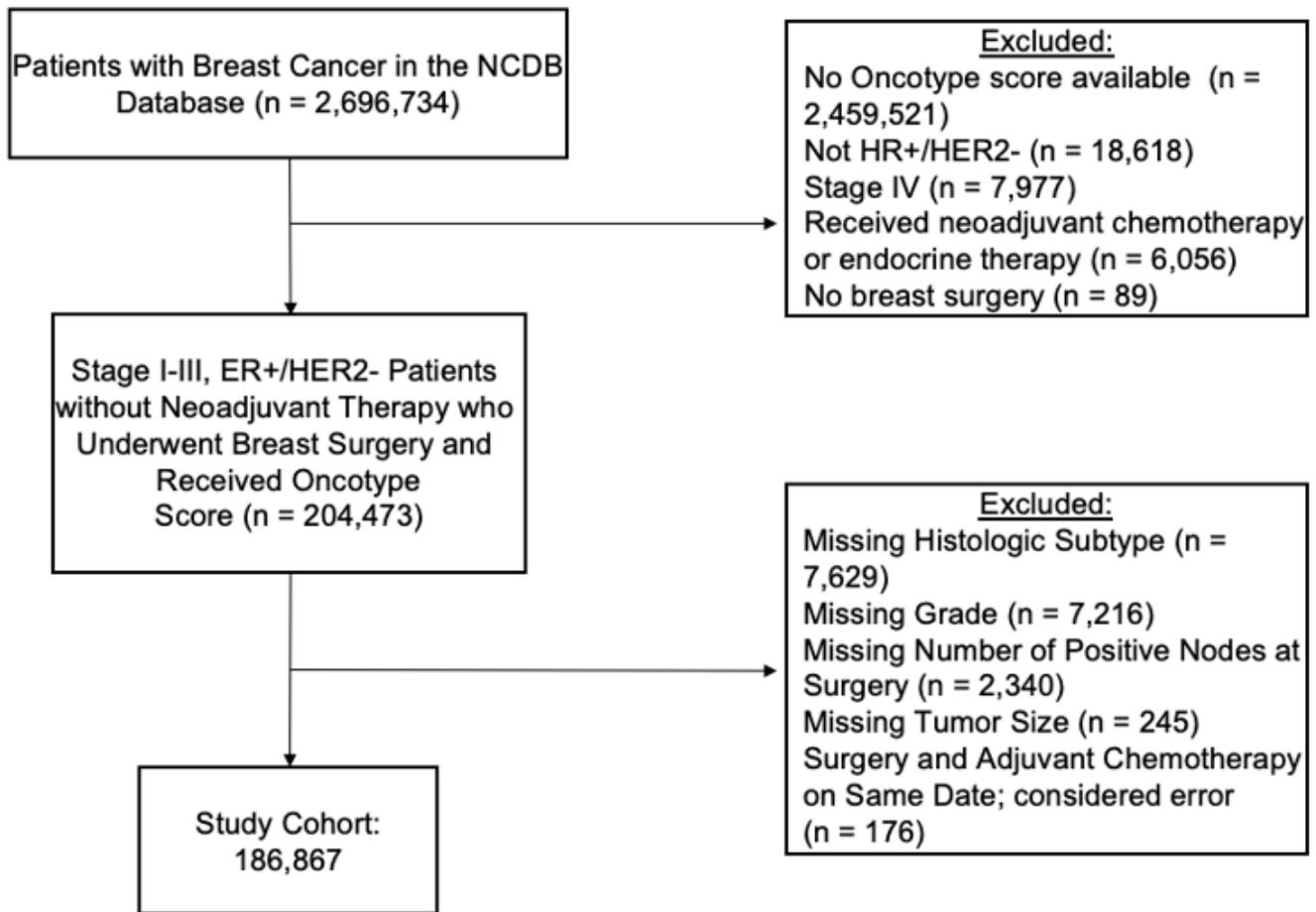


Figure 1

CONSORT Diagram for Study Population

Legend: CONSORT diagram for study. NCDB = National Cancer Database; HR = hormone receptor; HER2 = human epidermal growth factor-receptor 2

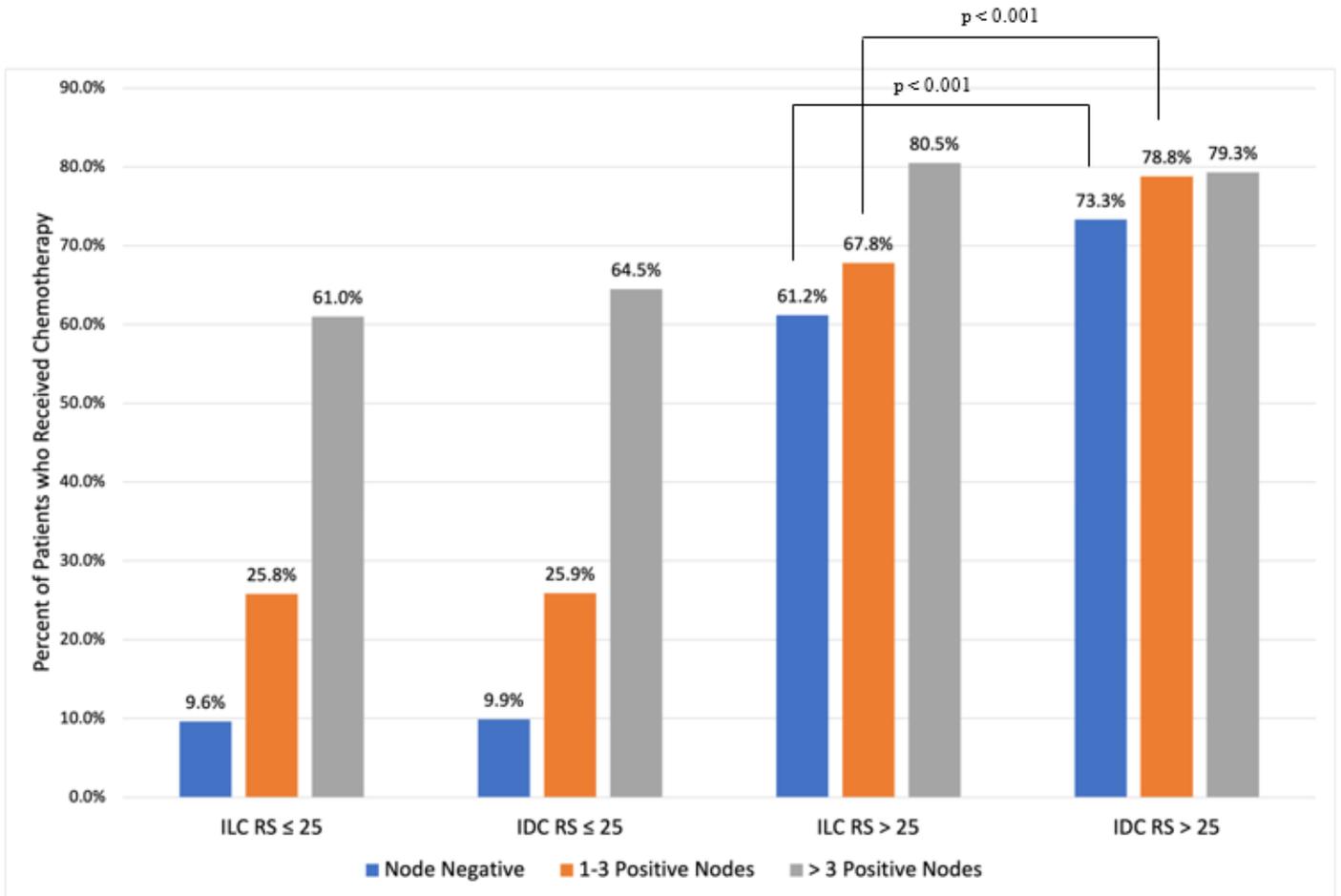


Figure 2

Proportion of patients who received chemotherapy by histology, nodal status, and recurrence score.

Legend: ILC = invasive lobular carcinoma; IDC = invasive ductal carcinoma; RS = recurrence score. Chi-square test comparing patients with ILC/RS > 25/node negative vs. IDC/RS > 25/node negative and ILC/RS > 25/1-3 positive nodes vs. IDC/RS > 25/1-3 positive nodes both yielded $p < 0.001$. All other comparisons were not statistically significant.

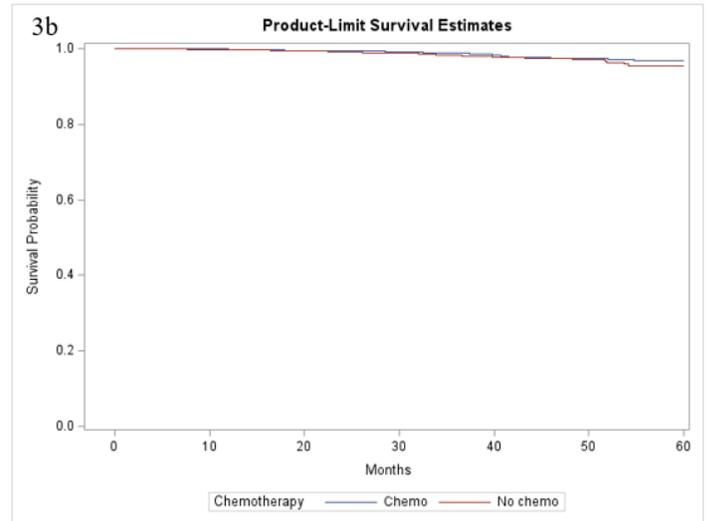
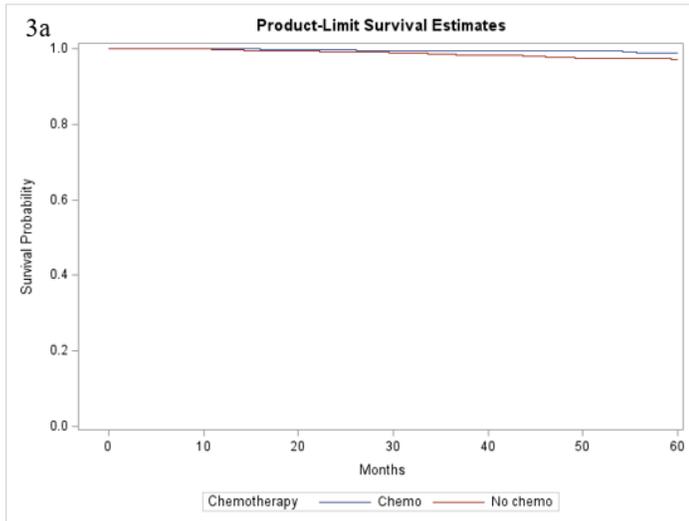


Figure 3

Propensity score matched analysis using greedy fixed matching method comparing overall survival in individuals who received chemotherapy compared to those who did not among patients with 1-3 positive nodes and RS ≤ 25 by histology. For patients with IDC, survival between those who did received chemotherapy and those who did not was not significantly different from one another (stratified log-rank test $p = 0.278$, Figure 3a). Similarly, for patients with ILC, survival between those who did received chemotherapy and those who did not was not significantly different from one another (stratified log-rank test $p = 0.532$, Figure 3b).

Legend: ILC = invasive lobular carcinoma; IDC = invasive ductal carcinoma; RS = recurrence score. Survival estimates of in individuals who received chemotherapy (blue solid line) compared to those who did not (red dotted line) among patients with 1-3 positive nodes and RS ≤ 25 by histology.