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Real-World Survival Outcomes of Adjuvant Chemotherapy Versus Endocrine Therapy Alone in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Invasive Lobular Carcinoma

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What is already known on this topic?

- *Hormone receptor (HR)-positive, HER2-negative invasive lobular carcinoma (ILC) is generally characterized by low proliferative activity and high endocrine responsiveness, but its sensitivity to chemotherapy is considered limited compared with other breast cancer subtypes.*
- *Most evidence supporting adjuvant chemotherapy in early-stage HR-positive breast cancer is derived predominantly from invasive ductal carcinoma, and ILC has been underrepresented in randomized trials and subgroup analyses.*
- *Current treatment guidelines often extrapolate chemotherapy benefit data from ductal carcinoma to ILC, although histology-specific survival data remain scarce.*

What does this study add on this topic?

- *In this real-world cohort of patients with stage I-III HR-positive, HER2-negative ILC, no statistically significant difference in disease-free survival or OS was observed between patients receiving adjuvant chemotherapy plus endocrine therapy and those receiving endocrine therapy alone.*

Abstract

Objective: This study aimed to compare disease-free survival (DFS) and overall survival (OS) between patients with hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative invasive lobular carcinoma (ILC) who received adjuvant chemotherapy plus endocrine therapy and those who received adjuvant endocrine therapy alone in a real-world setting.

Methods: In this single-center retrospective cohort study, patients diagnosed with stage I-III HR-positive, HER2-negative ILC who underwent curative surgery between January 2017 and June 2025 were included. Patients with metastatic disease, prior neoadjuvant therapy, or incomplete follow-up were excluded. Patients were categorized according to receipt of adjuvant chemotherapy. All patients received standard adjuvant endocrine therapy. The primary endpoints were DFS and OS.

Results: A total of 154 patients were included, with a median follow-up of 29.8 months. Patients who received adjuvant chemotherapy had higher-risk clinicopathological features, including more advanced tumor stage and nodal involvement. During follow-up, 6 recurrences (3.9%) were observed. Median DFS was 84.5 months in the endocrine therapy alone group and 95.5 months in the chemotherapy plus endocrine therapy group (log-rank $P = .962$).

Median OS was not reached; the estimated mean OS was 96.4 months. Median OS was 85.6 months in the non-chemotherapy group and 95.8 months, with median OS of 85.6 and 95.8 months, respectively (log-rank $P = .785$). In multivariable analysis, chemotherapy was not an independent predictor of DFS or OS.

Conclusion: In this real-world cohort of HR-positive, HER2-negative ILC, no statistically significant difference in DFS or OS was observed between treatment groups. These findings should be interpreted with caution given the limited number of events and baseline risk imbalance. The potential survival benefit of chemotherapy in this subtype may be limited and should be considered in individualized treatment decisions.

Keywords: Adjuvant chemotherapy, endocrine therapy, invasive lobular carcinoma, overall survival

Introduction

Breast cancer is the most frequently diagnosed malignancy among women worldwide and remains the leading contributor to the global cancer burden. According to the 2022 Global Cancer Observatory estimates, breast cancer accounts for 11.6% of all newly diagnosed cancer cases and 6.9% of cancer-related deaths globally.[1] Among the histological subtypes of breast cancer, invasive lobular carcinoma (ILC) represents the second most common form after invasive ductal carcinoma (IDC), comprising approximately 10%-15% of all cases.[2] Recent epidemiological data indicate that

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- *Notably, patients who received chemotherapy had higher-risk clinicopathological features, including more advanced stage and nodal involvement.*
- *These findings should be interpreted with caution, given the limited number of events and the potential for baseline imbalances between groups.*
- *The absence of survival benefit was consistent across clinically relevant subgroups, including age, menopausal status, body mass index, comorbidity status, and pathological stage.*
- *These findings support a more biology-driven and individualized treatment approach in ILC and suggest that the absolute survival benefit of cytotoxic therapy in this subtype may be modest.*

the incidence of ILC has been increasing at a faster rate compared with other breast cancer subtypes. In 2021, ILC was reported to account for 10.6% of all breast cancer diagnoses, corresponding to an incidence of 14 cases per 100 000 women.[3] Although historically managed using treatment algorithms similar to those applied to IDC, ILC is now recognized as a distinct histopathological subtype with unique biological and clinical characteristics.[4]

At the molecular level, the majority of ILC cases are classified as hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative. This biological profile differs substantially from IDC in terms of clinical and pathological features and is frequently associated with older age at diagnosis, larger tumor size, and a higher prevalence of multifocal or bilateral disease. While the HR-positive, HER2-negative phenotype is generally linked to favorable prognostic features, the diffuse growth pattern of ILC may hinder detection by conventional imaging modalities. Moreover, the propensity for late recurrences—often occurring beyond 10 years—poses additional challenges in long-term disease management.[2,5] Comparative analyses have demonstrated that, despite lower proliferation rates relative to ductal carcinomas, ILC exhibits distinct metastatic patterns and potential mechanisms of therapeutic resistance, suggesting a survival trajectory that may differ from that of IDC beyond traditional prognostic factors such as stage and receptor status.[4,6]

In early-stage HR-positive, HER2-negative breast cancer, adjuvant endocrine therapy constitutes the cornerstone of systemic treatment. However, the decision to add chemotherapy in order to minimize recurrence risk remains a matter of ongoing debate and represents a critical point in clinical practice.[7,8] Current guideline recommendations, particularly for intermediate risk tumors such as T2N1M0 disease, do not always provide definitive guidance, and uncertainty persists regarding the absolute survival benefit conferred by chemotherapy.[9] One of the underlying reasons for this clinical dilemma is the historically low pathological response rates of the HR-positive, HER2-negative phenotype to chemotherapy, raising concerns about whether the potential benefits of cytotoxic therapy outweigh its associated toxicities.[10] Indeed, even in large prospective trials including node-positive patients, the addition of chemotherapy to endocrine therapy in postmenopausal women did not demonstrate a significant improvement in invasive disease-free survival (DFS), suggesting a limited contribution of cytotoxic treatment in this population.[11] Similarly, in specific populations such as older patients, the role of chemotherapy remains controversial, and no significant improvement in overall survival (OS) has been observed even among those with high genomic risk scores.[12]

Most randomized trials and large scale clinical studies have predominantly included populations composed mainly of patients with IDC, and ILC has rarely been analyzed as a distinct subgroup or stratification factor. Consequently, conclusions regarding the benefit of adjuvant chemotherapy in lobular carcinoma have largely been extrapolated from data derived from ductal carcinoma.[4,5] Even in practice-changing trials such as RxPONDER, which demonstrated that chemotherapy may be omitted in selected patients with node-positive disease, individuals with ILC constituted only a limited proportion of the study population.[11]Furthermore, the absence of histology-specific efficacy analyses and the dominance of ductal carcinoma cases in shaping OS curves have contributed to ongoing uncertainty regarding the clinical validity of genomic test results in ILC and their reliability in guiding chemotherapy decisions in this subgroup.

Given the paucity of histology-specific data and the limited evidence provided by current treatment guidelines for the ILC subtype, the present study aimed to evaluate the real-world impact of adjuvant chemotherapy on survival outcomes in patients with HR-positive, HER2-negative ILC. In this retrospective cohort study, patients who received adjuvant chemotherapy were compared with those treated with endocrine therapy alone in order to assess the contribution of cytotoxic therapy to OS and DFS in a real-world clinical setting, where treatment decisions are influenced by baseline risk factors. By focusing on this clinically and biologically distinct population, this study aimed to provide real-world evidence that may inform treatment decision-making in patients with HR-positive, HER2-negative ILC.

Methods

Study Design and Patient Selection

This was a single-center, observational retrospective cohort study including patients diagnosed with HR-positive, HER2-negative ILC. Patients who were followed at the institution between January 2017 and June 2025 and had histopathologically confirmed ILC were eligible for inclusion.

The inclusion criteria were as follows: female patients aged ≥18 years; treatment with curative-intent surgery (mastectomy or breast-conserving surgery); immunohistochemically confirmed HR-positive and HER2-negative tumor status; stage I-III disease at diagnosis; and availability of complete adjuvant treatment and follow-up data.

Patients with de novo metastatic disease (stage IV) at diagnosis, those who received neoadjuvant systemic therapy, and those with insufficient follow-up data were excluded.

Data Collection and Pathological Assessment

Demographic and clinical characteristics, including age at diagnosis, menopausal status, body mass index (BMI), presence of comorbidities, Eastern Cooperative Oncology Group (ECOG) performance status, and family history, were retrospectively obtained from medical records and the institutional electronic database.

Pathological variables included tumor size, lymph node involvement, histological grade (Nottingham grading system), lymphovascular invasion, perineural invasion, and Ki-67 proliferation index (%). Hormone receptor status was assessed using immunohistochemistry (IHC); tumors showing ≥1% nuclear staining for estrogen receptor (ER) and/or progesterone receptor (PR) were considered positive. The HER2 status was evaluated by IHC and, when indicated, by silver in situ hybridization (SISH). Tumors with IHC scores of 0 or 1+ were classified as HER2-negative. Cases with an IHC score of 2+ underwent SISH analysis; those without gene amplification were classified as HER2-negative, whereas those with amplification were considered HER2-positive. Tumors with an IHC score of 3+ were classified as HER2-positive. Tumor staging was performed according to the American Joint Committee on Cancer TNM classification system in use at the time of diagnosis.

Treatment Protocols, Follow-up, and Endpoints

All patients received standard adjuvant endocrine therapy (tamoxifen or an aromatase inhibitor, with the addition of a luteinizing hormone-releasing hormone (LHRH) analog in premenopausal patients when indicated). Patients were categorized into 2 groups according to receipt of adjuvant chemotherapy:

(1) those who received chemotherapy in addition to endocrine therapy and
(2) those who received endocrine therapy alone.

The decision to administer adjuvant chemotherapy was individualized and determined by a multidisciplinary breast tumor board based on clinical risk factors, tumor biological characteristics, and comorbidity status. Therefore, treatment allocation was not randomized and was influenced by baseline clinicopathological risk factors, introducing the potential for confounding by indication.

The primary endpoints of the study were OS and DFS. The overall survival was defined as the time from the date of diagnosis to death from any cause. The disease-free survival was defined as the time from the date of curative surgery to the first occurrence of local recurrence, regional recurrence, distant metastasis, or death from any cause. Patients without an event were censored at the date of last follow-up.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics software version 28.0 (IBM SPSS Corp.; Armonk, NY, USA). The distribution of variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. In descriptive analyses, categorical variables were presented as frequencies and percentages, while continuous variables were expressed as mean ± standard deviation or median (minimum–maximum), according to distribution characteristics.

Comparisons of categorical variables between groups were conducted using the chi-square test or Fisher's exact test, as appropriate. Survival analyses were performed using the Kaplan–Meier method, and differences between groups were evaluated using the log-rank test. To determine the independent effect of adjuvant chemotherapy on survival and to identify prognostic factors, univariable and multivariable Cox proportional hazards regression analyses were performed. A 2-sided *P*value <.05 was considered statistically significant.

Ethical Approval

This study was approved by the Clinical Research Ethics Committee of İstanbul University İstanbul Faculty of Medicine(Approval No.: 3903778; Date: February 9, 2026). The study was conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective design of the study, the requirement for informed consent was waived by the ethics committee.

Results

Patient Characteristics

A total of 154 patients with HR-positive, HER2-negative ILC were included in the study. The median follow-up duration was 29.8 months. The median age at diagnosis was 53.5 years (range, 28-85), and 59.1% (n = 91) of patients were aged ≥50 years. Premenopausal patients accounted for 45.5% (n = 70) of the cohort, and the majority had an ECOG performance status of 0-1.

At least 1 comorbid condition was present in 52.6% (n = 81) of patients. A BMI ≥30 kg/m^2 was observed in 20.8% (n = 32). A first-degree family history of breast cancer was reported in 23.4% (n = 36). Breast Cancer Susceptibility Genes 1 and 2 (BRCA1/2) mutations were identified in 1.9% (n = 3) of patients; however, BRCA status was unknown in the majority of the cohort.

Baseline demographic and clinical characteristics were generally comparable between treatment groups; however, a significant difference was observed in BRCA status distribution (*P* = .047) (Table 1).

Tumor and Pathological Characteristics

Most patients were clinically staged as T1-T2 (94.8%) and N0 (87.7%). Grade II tumors were the most common histological grade (51.3%). Pathological stage I-II disease predominated (84.4%).

When analyzed according to treatment groups, patients who received adjuvant chemotherapy had significantly higher pathological tumor stage (pT), nodal stage (pN), and overall pathological stage compared with those treated with endocrine therapy alone (all *P* < .001). In addition, axillary biopsy positivity was more frequent in the chemotherapy group (*P* = .007).

The classical lobular subtype was the most frequent histological variant, accounting for 86.4% of cases. Lymphovascular invasion was present in 31.2% (n = 48), and positive surgical margins were observed in 12.3% (n = 19). Loss of E-cadherin expression, a characteristic feature of ILC, was detected in 90.3% (n = 139) of tumors. These pathological features were similarly distributed between the treatment groups (Table 2).

Treatment Characteristics

Breast-conserving surgery and mastectomy were performed at comparable rates (48.1% and 51.9%, respectively). Regarding axillary management, 89% of patients underwent limited axillary surgery, while 9.7% underwent axillary lymph node dissection or axillary clearance.

Adjuvant chemotherapy was administered to 41.6% of patients, whereas 58.4% received endocrine therapy alone. Consistent with baseline clinicopathological differences, adjuvant chemotherapy was more frequently administered to patients with higher-risk disease features. Adjuvant radiotherapy was delivered to 72.1% of the cohort. Aromatase inhibitors were the most frequently prescribed endocrine agents (53.9%). Radiotherapy use and type of

Table 1. Baseline Demographic and Clinical Characteristics of Patients with HR-Positive, HER2-Negative Invasive Lobular Carcinoma

Variable	All Patients (n = 154) 154 (100)	Endocrine Therapy Only (n = 90) 90 (58.4)	Chemotherapy + Endocrine Therapy (n = 64) 64 (41.6)	*P*
Age at diagnosis, median (min-max)	53.5 (28-85)	55.0 (28-85)	52.0 (34-73)	.136†
Age group, n (%)				
<50 years	63 (40.9)	35 (38.9)	28 (43.8)	.661‡
≥50 years	91 (59.1)	55 (61.1)	36 (56.2)	
Height (cm), median (min–max)	160.0 (140-176)	160.0 (140-170)	160.0 (149-176)	.152†
Weight (kg), median (min–max)	70.0 (42-145)	73.0 (42-145)	69.0 (49-100)	.245†
BMI (kg/m^2), median (min–max)	27.3 (19-39)	28.1 (19-39)	26.6 (19-39)	.085†
BMI category, n (%)				
<30	76 (49.4)	33 (36.7)	43 (67.2)	.313‡
≥30	32 (20.8)	18 (20.0)	14 (21.9)	
Unknown	46 (29.9)	39 (43.3)	7 (10.9)	
Comorbidity, n (%)				
(–)	73 (47.4)	42 (46.7)	31 (48.4)	.958‡
(+)	81 (52.6)	48 (53.3)	33 (51.6)	
ECOG PS, n (%)				
0	140 (90.9)	78 (86.7)	62 (96.9)	.090‡
I	13 (8.4)	11 (12.2)	2 (3.1)	
II	1 (0.6)	1 (1.1)	0 (0.0)	
Family history, n (%)				
(–)	69 (44.8)	44 (48.9)	25 (39.1)	.141‡
Breast cancer	36 (23.4)	23 (25.6)	13 (20.3)	
Prostate cancer	1 (0.6)	1 (1.1)	0 (0.0)	
Ovarian cancer	2 (1.3)	0 (0.0)	2 (3.1)	
Other cancers	46 (29.9)	22 (24.4)	24 (37.5)	
BRCA status, n (%)				
BRCA (–)	20 (13.0)	8 (8.9)	12 (18.8)	.047‡
BRCA 1+	2 (1.3)	0 (0.0)	2 (3.1)	
BRCA 2+	1 (0.6)	0 (0.0)	1 (1.6)	
Unknown	131 (85.1)	82 (91.1)	49 (76.6)	
Menopausal status, n (%)				
Premenopausal	70 (45.5)	40 (44.4)	30 (46.9)	.893‡
Postmenopausal	84 (54.5)	50 (55.6)	34 (53.1)	

† Mann–Whitney *U*-test (continuous variables).
‡ Chi-square test (categorical variables).
Bold *P* values: <.05 (statistically significant).
BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Tumor and Pathological Characteristics

Variable	All Patients (n = 154) 154 (100)	Endocrine Therapy Only (n = 90) 90 (58.4)	Chemotherapy + Endocrine Therapy (n = 64) 64 (41.6)	*P*
Clinical stage T, n (%)				
0	1 (0.6)	1 (1.1)	0 (0.0)	.525‡
I	73 (47.4)	47 (52.2)	26 (40.6)	
II	73 (47.4)	38 (42.2)	35 (54.7)	
III	3 (1.9)	2 (2.2)	1 (1.6)	
IV	4 (2.6)	2 (2.2)	2 (3.1)	
Clinical stage N, n (%)				
0	135 (87.7)	83 (92.2)	52 (81.2)	.093‡
I	18 (11.7)	7 (7.8)	11 (17.2)	
II	1 (0.6)	0 (0.0)	1 (1.6)	
Histological grade (MBR), n (%)				
I	13 (8.4)	9 (10.0)	4 (6.2)	.086‡
II	79 (51.3)	50 (55.6)	29 (45.3)	
III	8 (5.2)	2 (2.2)	6 (9.4)	
Not available	54 (35.1)	29 (32.2)	25 (39.1)	
Axillary biopsy, n (%)				
Negative	75 (48.7)	51 (56.7)	24 (37.5)	.007‡
Positive	13 (8.4)	3 (3.3)	10 (15.6)	
Not performed	66 (42.9)	36 (40.0)	30 (46.9)	
Surgery, n (%)				
Breast-conserving surgery	74 (48.1)	48 (53.3)	26 (40.6)	.164‡
Mastectomy	80 (51.9)	42 (46.7)	38 (59.4)	
Pathological stage T, n (%)				
pT0	1 (0.6)	1 (1.1)	0 (0.0)	<.001‡
pT1	53 (34.4)	44 (48.9)	9 (14.1)	
pT2	81 (52.6)	38 (42.2)	43 (67.2)	
pT3	17 (11.0)	6 (6.7)	11 (17.2)	
pT4	2 (1.3)	1 (1.1)	1 (1.6)	
Pathological stage N, n (%)				
pN0	93 (60.4)	69 (76.7)	24 (37.5)	<.001‡
pN1	45 (29.2)	17 (18.9)	28 (43.8)	
pN2	13 (8.4)	3 (3.3)	10 (15.6)	
pN3	3 (1.9)	1 (1.1)	2 (3.1)	

(*Continued*)

Table 2. Tumor and Pathological Characteristics

Variable	All Patients (n = 154) 154 (100)	Endocrine Therapy Only (n = 90) 90 (58.4)	Chemotherapy + Endocrine Therapy (n = 64) 64 (41.6)	*P*
Pathological stage, n (%)				
I A	43 (27.9)	38 (42.2)	5 (7.8)	<.001‡
II A	54 (35.1)	35 (38.9)	19 (29.7)	
II B	33 (21.4)	9 (10.0)	24 (37.5)	
III A	14 (9.1)	3 (3.3)	11 (17.2)	
III B	7 (4.5)	3 (3.3)	4 (6.2)	
III C	2 (1.3)	1 (1.1)	1 (1.6)	
Not available	1 (0.6)	1 (1.1)	0 (0.0)	
Histological subtype, n (%)				
Classic	130 (84.4)	81 (90.0)	49 (76.6)	.081‡
Pleomorphic	5 (3.2)	0 (0.0)	5 (7.8)	
Solid	4 (2.6)	2 (2.2)	2 (3.1)	
Alveolar	7 (4.5)	4 (4.4)	3 (4.7)	
Tubulolobular	1 (0.6)	0 (0.0)	1 (1.6)	
Other	4 (2.6)	3 (3.3)	1 (1.6)	
Lymphovascular invasion, n (%)				
(+)	48 (31.2)	21 (23.3)	27 (42.2)	
Surgical margin, n (%)				
Negative	135 (87.7)	80 (88.9)	55 (85.9)	.764‡
Positive	19 (12.3)	10 (11.1)	9 (14.1)	
Loss of E-cadherin, n (%)				
(–)	15 (9.7)	8 (8.9)	7 (10.9)	1.000‡
(+)	49 (31.8)	26 (28.9)	23 (35.9)	
Multicentricity, n (%)				
(–)	121 (78.6)	69 (76.7)	52 (81.2)	.628‡
(+)	33 (21.4)	21 (23.3)	12 (18.8)	
ER (%), median (min–max)	92.5 (20-100)	90.0 (20-100)	95.0 (40-100)	.468†
PR (%), median (min–max)	80.0 (0-100)	80.0 (0-100)	80.0 (0-100)	.499†
Ki-67, n (%)				
<20%	101 (65.6)	63 (70.0)	38 (59.4)	.154‡
≥20%	40 (26.0)	19 (21.1)	21 (32.8)	

† Mann–Whitney *U*-test (continuous variables).
‡ Chi-square test (categorical variables).
Bold *P* values: <.05 (statistically significant).
ER, estrogen receptor; MBR, modified Bloom–Richardson; PR, progesterone receptor.

endocrine therapy were comparable between treatment groups. The overall recurrence rate during follow-up was 3.9%, with a similar distribution between treatment groups. (Table 3).

Disease-Free Survival

In the overall population, the estimated median DFS was 95.6 months. The median DFS was 84.5 months in patients who did

Table 3. Adjuvant Treatment Characteristics and Early Clinical Outcomes

Variable	All Patients (n = 154) 154 (100)	Endocrine Therapy Only (n = 90) 90 (58.4)	Chemotherapy + Endocrine Therapy (n = 64) 64 (41.6)	*P*
Response to first-line adjuvant treatment, n (%)				
Complete response	148 (96.1)	89 (98.9)	59 (92.2)	0.185‡
Lost to follow-up	4 (2.6)	1 (1.1)	3 (4.7)	
Ongoing treatment	1 (0.6)	0 (0.0)	1 (1.6)	
Radiotherapy, n (%)				
No	42 (27.3)	25 (27.8)	17 (26.6)	0.684‡
Adjuvant	111 (72.1)	64 (71.1)	47 (73.4)	
Palliative	1 (0.6)	1 (1.1)	0 (0.0)	
Type of adjuvant endocrine therapy, n (%)				
None	5 (3.2)	2 (2.2)	3 (4.7)	0.175‡
Tamoxifen (TMX)	30 (19.5)	19 (21.1)	11 (17.2)	
Aromatase inhibitor (AI)	83 (53.9)	49 (54.4)	34 (53.1)	
LHRH analog + AI	11 (7.1)	3 (3.3)	8 (12.5)	
LHRH analog + TMX	25 (16.2)	17 (18.9)	8 (12.5)	
Progression/Recurrence, n (%)				
(–)	148 (96.1)	87 (96.7)	61 (95.3)	0.693§
(+)	6 (3.9)	3 (3.3)	3 (4.7)	
First metastasis, n (%)				
(–)	151 (98.1)	89 (98.9)	62 (96.9)	0.571§
(+)	3 (1.9)	1 (1.1)	2 (3.1)	

‡ Chi-square test (categorical variables).
§ Fisher's exact test (when expected cell count <5).
Bold *P* values: <.05 (statistically significant).
AI, aromatase inhibitor; LHRH, luteinizing hormone-releasing hormone; TMX, tamoxifen.

not receive adjuvant chemotherapy and 95.5 months in those who received chemotherapy.

Despite numerically longer DFS observed in the chemotherapy group, no statistically significant difference was identified between the groups (log-rank $P = .962$) (Table 4, Figure 1).

It is noteworthy that patients receiving chemotherapy had higher-risk clinicopathological features, including more advanced stage and nodal involvement.

Subgroup analyses stratified by age (<50 vs. ≥50 years), BMI (<30 vs ≥30 kg/m^2), presence of comorbidities, menopausal status, multicentricity, and pathological stage did not demonstrate a significant association between chemotherapy and DFS (all $P > .05$) (Table 5).

Overall Survival

In the overall cohort, median OS was not reached, and the estimated mean OS was 96.4 months. The median OS was 85.6 months in the non-chemotherapy group and 95.8 months in the chemotherapy group.

Although numerically higher OS was observed in the chemotherapy group, this difference did not reach statistical significance (log-rank $P = .785$) (Table 6, Figure 2).

As in DFS analyses, the chemotherapy group included patients with higher-risk disease characteristics.

Similarly, subgroup analyses did not demonstrate a statistically significant association between chemotherapy and OS (Table 5).

Discussion

In this single-center retrospective cohort study, the contribution of adjuvant chemotherapy to survival outcomes was evaluated in patients with HR-positive, HER2-negative ILC using real-world data. The findings demonstrate that although numerically longer survival outcomes were observed in patients receiving adjuvant chemotherapy, no statistically significant advantage was demonstrated within the observed follow-up period. Importantly, patients who received adjuvant chemotherapy had higher-risk clinicopathological features, including more advanced tumor stage and greater nodal involvement. Despite this unfavorable baseline

Table 4. Disease-Free Survival According to Receipt of Adjuvant Chemotherapy

		Disease-Free Survival Time (Months)	95% GA			*P*
Chemotherapy in first-line treatment	(–)	84.5	80.0	–	88.9	.962
	(+)	95.5	89.2	–	101.8	
Total		95.6	91.2	–	100.0	

Kaplan–Meier (Log Rank).

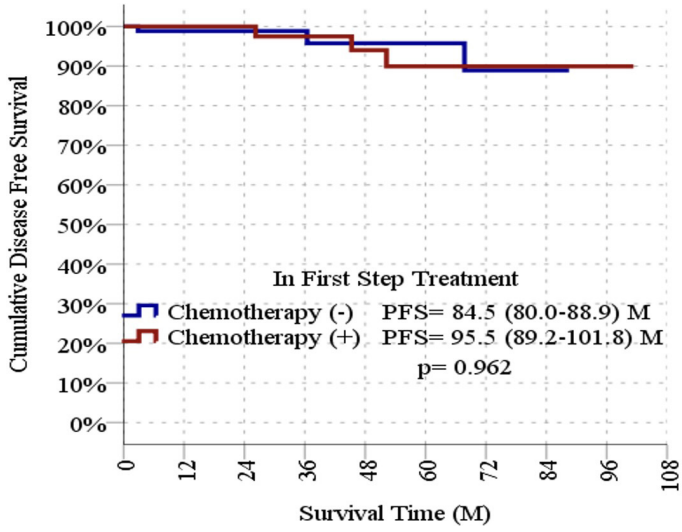

Figure 1. Kaplan–Meier curve for disease-free survival according to adjuvant chemotherapy status.

profile, no statistically significant difference in survival outcomes was observed between treatment groups, raising the possibility that adjuvant chemotherapy may have mitigated the negative prognostic impact of higher-risk disease. However, given the retrospective design and potential for residual confounding, this interpretation should be approached with caution. This pattern was consistently observed across clinically relevant subgroups, including age, menopausal status, BMI, comorbidity status, and pathological stage. These findings suggest that the absolute benefit of cytotoxic therapy in lobular carcinomas characterized by an HR-positive, HER2-negative phenotype may be limited. They also raise important questions regarding the widespread application of treatment algorithms largely derived from ductal carcinoma data to ILC. Given the distinct biological features of ILC, including

Table 5. Subgroup Analyses of Disease-Free and Overall Survival According to Adjuvant Chemotherapy

	Univariate Survival					Univariate Disease-Free Survival				
	HR	95% GA			*P*	HR	95% GA			*P*
Chemotherapy	1.283	0.213	–	7.730	.786	0.962	0.193	–	4.801	.962
Age at diagnosis										
<50						0.609	0.038	–	9.799	.726
≥50	1.995	0.332	–	11.98	.450	1.359	0.191	–	9.682	.760
BMI										
<30	0.595	0.084	–	4.238	.604	0.282	0.026	–	3.119	.302
≥30	29.71	0.000	–	>100	.742	1.348	0.114	–	15.92	.813
Comorbidity										
(–)	47.91	0.000	–	>100	.645	0.641	0.040	–	10.25	.753
(+)	1.151	0.161	–	8.213	.889	1.227	0.172	–	8.746	.839
Menopausal status										
Premenopause						0.387	0.035	–	4.289	.439
Postmenopause	1.492	0.249	–	8.951	.661	2.163	0.194	–	24.07	.530
Multicentricity										
(–)	1.323	0.220	–	7.945	.759	1.458	0.242	–	8.773	.680
(+)						0.023	0.000	–	>100	.661
Pathological stage										
I						0.030	0.000	–	>100	.713
II	0.443	0.028	–	7.088	.565	0.011	0.000	–	11 89	.447
III	0.569	0.049	–	6.634	.652	29.086	0.000	–	>100	.584

BMI, body mass index; HR, hormone receptor.

Table 6. Overall Survival According to Receipt of Adjuvant Chemotherapy

		Survival Time (Months)	95% GA			*P*
Chemotherapy in first-line treatment	(–)	85.6	81.6	–	89.6	.785
	(+)	95.8	90.0	–	101.7	
Total		96.4	92.2	–	100.5	

Kaplan–Meier (Log Rank).

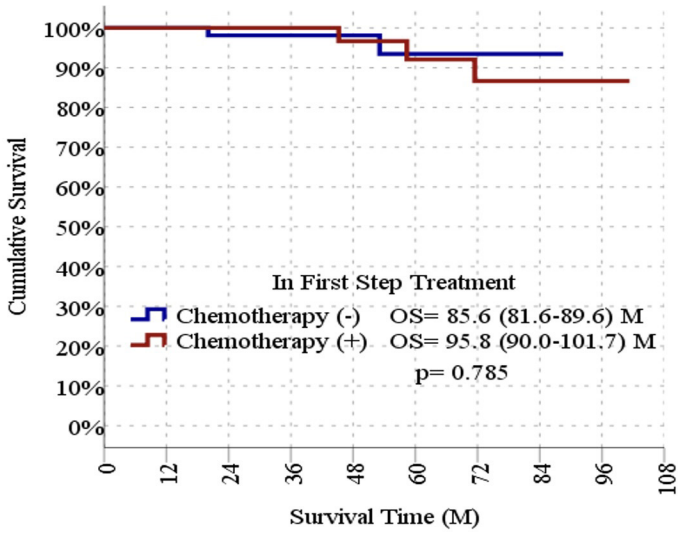

Figure 2. Kaplan–Meier curve for overall survival according to adjuvant chemotherapy status.

generally lower proliferation indices and a well-recognized tendency for late recurrence, the absence of a demonstrable survival benefit from chemotherapy across different risk strata supports a more biology-driven and individualized treatment strategy. The observed imbalance in baseline risk profiles between treatment groups, reflecting real-world clinical decision-making, should be considered when interpreting these findings. In this context, treatment decisions may need to extend beyond conventional clinicopathological risk factors and incorporate a deeper consideration of tumor-specific biological characteristics. In this context, treatment decisions may need to extend beyond conventional clinicopathological risk factors and incorporate a deeper consideration of tumor-specific biological characteristics.

The findings are consistent with those of recent large retrospective analyses focusing specifically on ILC. In a contemporary cohort study by Öztekin et al,[13] which evaluated the impact of (neo)adjuvant chemotherapy in patients with ILC receiving endocrine therapy, no significant survival benefit associated with chemotherapy was observed. These results further support the notion that the absolute contribution of cytotoxic therapy in HR-positive, HER2-negative lobular carcinoma may be limited, particularly in biologically low-risk populations. However, similar to the study, differences in baseline risk profiles between treatment groups should be considered when interpreting these findings.

Hormone receptor-positive and HER2-negative breast cancer is biologically characterized by a lower proliferative rate and marked endocrine sensitivity, features that are generally associated with limited responsiveness to chemotherapy. This pattern appears to be even more pronounced in tumors with lobular histology and low histological grade. In the ASTER-70s trial, even among older patients with genomically high-risk HR-positive, HER2-negative disease, the addition of adjuvant chemotherapy did not result in a significant survival benefit, while being associated with increased toxicity and adverse effects on quality of life.[12] The authors suggested that these findings are consistent with intrinsic chemoresistance in HR-positive tumors and emphasized that the benefit of chemotherapy should not be generalized without careful consideration of age, tumor biology, and recurrence dynamics.[14] Similarly, in a retrospective study based on Surveillance, Epidemiology, and End Results (SEER) database analyses, patients with HR-positive, HER2-negative T2N1M0 disease demonstrated low rates of pathological complete response (pCR) following neoadjuvant chemotherapy. Moreover, patients who did not achieve pCR had significantly worse survival outcomes compared with those treated with adjuvant chemotherapy, underscoring the clinical implications of limited chemosensitivity in this subgroup.[9] In addition, a review evaluating the evolution of adjuvant treatment strategies in HR-positive, HER2-negative early-stage breast cancer within a Chinese population reported that the benefit of chemotherapy appears to be largely confined to highly proliferative and genomically aggressive subgroups, whereas endocrine therapy remains the principal treatment modality in low-risk or lobular-like tumors.[15] Taken together, these data suggest that chemosensitivity in HR-positive, HER2-negative ILC is generally limited; however, the potential benefit of chemotherapy in higher-risk subgroups remains uncertain and warrants careful interpretation.

The majority of classical adjuvant chemotherapy trials have been conducted either without stratification by histological subtype or predominantly in populations composed of the dominant histological subtype, IDC. Consequently, the existing evidence regarding the benefit of chemotherapy in early-stage HR-positive, HER2-negative breast cancer, as well as the treatment guidelines derived from these data, largely reflect ductal carcinoma biology. This has resulted in the underrepresentation of critical biological and clinical differences specific to ILC, despite it being the second most common histological subtype of breast cancer.[3,11] As a result, histology-specific differences relevant to ILC remain underrepresented in the literature, despite it being the second most common histological subtype of breast cancer. Large real-world analyses evaluating the integration of genomic testing into clinical decision-making for early-stage HR-positive disease have reported high rates of chemotherapy omission, particularly in tumors with biologically low proliferative features, and this approach has increasingly aligned with international guideline recommendations.[16] In parallel, the RxPONDER trial demonstrated that the benefit of adjuvant chemotherapy in node-positive HR-positive/HER2-negative disease is strongly influenced by menopausal status, with no significant improvement in invasive DFS or distant recurrence observed among postmenopausal patients.[11]Conversely, analyses based on real-world data from the National Cancer Database (NCDB) have reported a survival advantage associated with chemotherapy within specific Oncotype DX score ranges. However, these studies also lacked detailed histology-specific analyses, and their findings predominantly reflect IDC biology, thereby limiting the generalizability of these results to lobular histology.[17] Taken together, the current body of evidence regarding chemosensitivity in HR-positive breast cancer is largely IDC driven. Given the distinct biological characteristics of ILC, the assumption that chemotherapy confers a comparable benefit in this subtype warrants careful consideration.

Invasive lobular carcinoma is recognized as a distinct subtype characterized by loss of E-cadherin expression, a diffuse growth pattern, low proliferative activity, and frequent luminal A–like biological features, all of which have been associated with limited sensitivity to systemic chemotherapy.[2,6,18] In the prospective ACOSOG Z1071 analysis evaluating pathological pCR rates after neoadjuvant chemotherapy, the pCR rate among HR-positive, HER2-negative tumors was approximately 11%, which was significantly lower than that observed in triple-negative and HER2-positive subtypes. Furthermore, lobular histology was more frequently associated with residual disease. The same study also reported a higher residual nodal burden in lobular tumors following chemotherapy, suggesting that the impact of neoadjuvant chemotherapy on surgical downstaging may be more limited in this subtype.[13] Recent reviews addressing adjuvant treatment strategies in early-stage HR-positive, HER2-negative breast cancer have similarly indicated that the absolute survival benefit of chemotherapy appears limited in tumors with low proliferative and lobular features, whereas endocrine therapy remains the principal component of long-term disease control in this setting.[2,14] In light of these data, treatment approaches in ILC may be more appropriately guided by its high endocrine responsiveness and propensity for late recurrence rather than by expectations of cytotoxic response, with endocrine therapy playing a central and defining role in the management of this subtype.[7]

Several limitations and strengths of this study should be considered. First, the retrospective and single-center design introduces an inherent risk of selection bias, particularly given that decisions regarding adjuvant chemotherapy were individualized based on clinical risk factors, tumor characteristics, and comorbidities. In addition, the reliance on medical records for data collection carries the potential for measurement error and incomplete data. In particular, the observed imbalance in tumor stage and nodal involvement between treatment groups indicates the presence of confounding by indication, which may have influenced the comparative survival analyses. The relatively short follow-up duration and low number of events may have limited the ability to capture long-term outcomes and detect small but clinically meaningful differences, especially considering the well-recognized tendency for late recurrence in lobular carcinoma. This limitation is particularly relevant for ILC, which is characterized by a risk of late recurrence often occurring beyond 5-10 years after diagnosis; therefore, the current findings primarily reflect early survival outcomes and may not fully capture the long-term impact of adjuvant chemotherapy in this subtype.

Furthermore, the limited number of events and sample size may have reduced the statistical power of the study to detect a potentially meaningful difference between groups, increasing the risk of a type II error. Furthermore, genomic risk stratification tools (e.g., Oncotype DX) and detailed information regarding chemotherapy regimens and treatment adherence were not uniformly available for all patients, which may have restricted a more granular evaluation of potential subgroup-specific effects of chemotherapy. Despite these limitations, this study also has notable strengths. By focusing on a homogeneous biological subtype (HR-positive, HER2-negative ILC) within a real-world cohort, the effects of adjuvant chemotherapy versus endocrine therapy alone on DFS and OS were systematically compared in a population that remains underrepresented in the literature. Clearly defined inclusion and exclusion criteria, comprehensive documentation of surgical and adjuvant treatment variables, and the use of standard survival analysis methods enhance the clinical relevance of the findings and their potential contribution to treatment decision-making.

In conclusion, given the known tendency of ILC for late recurrence, longer follow-up is required to draw definitive conclusions regarding the long-term survival impact of chemotherapy in this population. This real-world retrospective cohort study did not demonstrate a statistically significant survival benefit associated with adjuvant chemotherapy in patients with HR-positive, HER2-negative ILC during the observed follow-up period. These findings should be interpreted with caution, as the study may have been underpowered to detect small but clinically meaningful differences. In addition, the imbalance in baseline risk profiles between treatment groups should be considered when interpreting these findings. The findings suggest that survival outcomes in this biological subtype may be largely influenced by endocrine responsiveness, and that the absolute contribution of cytotoxic therapy may be modest. Given the distinct proliferative characteristics and late recurrence pattern of lobular histology, treatment decisions should be guided not by direct extrapolation from ductal carcinoma data, but rather by tumor biology, individual clinical risk profile, and the anticipated absolute benefit for each patient. Prospective studies specifically designed for histological subtypes with adequate sample size and long-term follow-up are warranted.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

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References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229-263. [CrossRef]
2. Christgen M, Steinemann D, Kühnle E, et al. Lobular breast cancer: clinical, molecular and morphological characteristics. *Pathol Res Pract*. 2016;212(7):583-597. [CrossRef]
3. Giaquinto AN, Freedman RA, Newman LA, et al. Lobular breast cancer statistics, 2025. *Cancer*. 2025;131(20):e70061. [CrossRef]
4. Van Baelen K, Sawyer E, Van Cauwenberge J, et al. Clinical challenges and proposed solutions for patients with invasive lobular breast cancer. *Ann Oncol*. Elsevier Limited; Amsterdam. 2025;36(11):1285-1298. [CrossRef]

5. Mouabbi JA, Hassan A, Lim B, et al. Invasive lobular carcinoma: an understudied emergent subtype of breast cancer. *Breast Cancer Res Treat*. Springer; Berlin. 2022;193(2):253-264. [CrossRef]
6. Danzinger S, Hielscher N, Izsó M, et al. Invasive lobular carcinoma: clinicopathological features and subtypes. *J Int Med Res*. 2021;49(6):3000605211017039. [CrossRef]
7. Karihtala P. How to choose optimal adjuvant therapies for high-risk hormone receptor-positive, HER2-negative breast cancer after chemotherapy? *Acta Oncol*. 2025;64:815-829. [CrossRef]
8. Nardin S, Ruelle T, Giannubilo I, et al. Adjuvant treatment in hormone receptor-positive early breast cancer: new approaches of endocrine therapy. *Tumori*. SAGE Publications Ltd; Thousand Oaks. 2024;110(3):162-167. [CrossRef]
9. Shang Y, Wang X, Liu Y, et al. Comparing survival outcomes between neoadjuvant and adjuvant chemotherapy within T2N1M0 stage hormone receptor-positive, HER2-negative breast cancer: a retrospective cohort study based on SEER database. *Breast Cancer*. 2024;31(4):684-694. [CrossRef]
10. Guzik G, Kurian M, Patell K, et al. A review of current literature and real-world outcomes with neoadjuvant chemotherapy in hormone receptor positive, HER2 negative breast cancer. *Clin Breast Cancer*. 2025;25(5):e666-e677. [CrossRef]
11. Kalinsky K, Barlow WE, Gralow JR, et al. 21-gene assay to inform chemotherapy benefit in node-positive breast cancer. *N Engl J Med*. 2021;385(25):2336-2347. [CrossRef]
12. Brain E, Mir O, Bourbouloux E, et al. Adjuvant chemotherapy and hormonotherapy versus adjuvant hormonotherapy alone for women aged 70 years and older with high-risk breast cancer based on the genomic grade index (ASTER 70s): a randomised phase 3 trial. *Lancet*. 2025;406(10502):489-500. [CrossRef]
13. Öztekin S, Hooning MJ, van Deurzen CHM, et al. The effect of (neo)adjuvant chemotherapy on long-term survival outcomes in patients with invasive lobular breast cancer treated with endocrine therapy: a retrospective cohort study. *Cancer*. 2024;130(6):927-935. [CrossRef]
14. Boughey JC, McCall LM, Ballman KV, et al. Tumor biology correlates with rates of breast conserving surgery and pathologic complete response after neoadjuvant chemotherapy for breast cancer findings from the ACOSOG Z1071 (alliance) prospective multicenter clinical trial. In: *Ann Surg*. Lippincott Williams and Wilkins; Philadelphia. 2014;260(4):608-14; discussion 614. [CrossRef]
15. Fan Y, Ji D, Jiang M, et al. Adjuvant treatment strategy evolution and risk stratification for hormone receptor-positive, human epidermal growth factor receptor-2 negative early breast cancer in China. *Oncologist*. 2024;29(9):e1104-e1112. [CrossRef]
16. Hequet D, Hajjaji N, Charafe-Jauffret E, et al. Compliance to genomic test recommendations to guide adjuvant chemotherapy decision-making in the case of hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer, in real-life settings. *Cancer Med*. 2023;12(16):16889-16895. [CrossRef]
17. Stabellini N, Cao L, Towe CW, et al. Adjuvant chemotherapy is associated with an overall survival benefit regardless of age in ER+/HER2- breast cancer pts with 1-3 positive nodes and oncotype DX recurrence score 20 to 25: an NCDB analysis. *Front Oncol*. 2023;13:1115208. [CrossRef]
18. Gamallo C, Palacios J, Suarez A, et al. Short communication correlation of E-cadherin expression with differentiation grade and histological type in breast carcinoma. *Am J Pathol*. 1993;142: 987–993.