Abstract

Invasive lobular carcinoma are typically endocrine responsive breast cancers which respond poorly to chemotherapy. This meta-analysis which included over 28,000 patients from 9 studies illustrated the non-inferiority of treating early stage lobular carcinoma with chemotherapy. These findings should be incorporated into multidisciplinary team discussions when deciding upon the value of chemotherapy for prospective patients.

Introduction: Invasive lobular carcinoma (ILCs) are typically endocrine responsive breast cancers which respond poorly to chemotherapy. The long-term survival advantage of prescribing chemotherapy in such cases remains unclear. To perform a systematic review and meta-analysis assessing, the impact of prescribing chemotherapy in such patients on long-term disease-free (DFS) and overall (OS) survival outcomes. Methods: A systematic review and meta-analysis was performed in accordance with the PRISMA guidelines. Ten-year DFS and OS were pooled as odds ratios (ORs) with 95% confidence intervals (CI) using the Mantel-Haenszel method. Time-to-effect modelling was performed using the generic inverse variance method. Results: Overall, 9 studies including 28,218 patients were included. The mean follow-up was 74 months (range: 0-150 months) and mean age was 60 years (range: 22-90 years). Of these, 34.7% received chemotherapy (9,797/28,218) and 66.3% did not receive chemotherapy (18,421/28,218). Chemotherapy prescription failed to improve 10-year DFS (OR: 0.89, 95% CI: 0.65-1.23) and OS (OR: 0.92, 95% CI: 0.72-1.18). When using time-to-effect modelling, chemotherapy prescription failed to improve DFS (hazard ratio (HR): 1.01, 95% CI: 0.78-1.31) and OS (HR: 1.07, 95% CI: 0.89-1.27, \( P = 0.67\)). Conclusion: This meta-analysis illustrates no long-term survival advantage associated with chemotherapy prescription in the setting of early-stage ILC. In the absence of well-designed, prospective clinical trials evaluating the impact of chemotherapy on long-term outcomes in ILC, these results should be considered by the multidisciplinary team when deciding on the value of systemic chemotherapy prescription in ILC.

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Keywords: Systemic chemotherapy, Oncological outcomes

Introduction

Invasive lobular carcinoma (ILC) represents the second most common breast cancer histological subtype and accounts for 5% to 15% of diagnoses globally.\(^1\)\(^2\) Despite representing a minority share of all breast tumors, ILC contributes a similar share to the global cancer burden as ovarian carcinoma, central nervous system tumors, and malignant melanoma.\(^3\) Notwithstanding, ILCs remain an understudied breast cancer histological subtype,\(^4\)\(^5\) particularly as these tumors possess unique biological characteristics and illustrate a different natural history to the more common IDC subtype. ILCs have the tendency to develop in older patients, who typically have more advanced disease,\(^1\)\(^4\)\(^6\) and these cancers exhibit peculiar metastatic patterns once relapse occurs.\(^7\) Furthermore, ILCs are typically indolent (moderate-to-well differentiated) tumors with the propensity to develop strong estrogen and/or progesterone receptor positivity and human epidermal growth factor receptor-2 negativity (ER+/PgR+/HER2-).\(^8\) Accordingly, ILCs tend to be endocrine responsive,\(^9\) chemoinensitive cancers,\(^1\) with surgery
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combined with multimodal therapeutics proving curative for the majority.\textsuperscript{1,10,11}

ILC represent a unique histological subtype.\textsuperscript{12} These cancers are characterized by small, non-cohesive epithelial cells which are dispersed individually in a single-file linear pattern in a fibrous stroma of the breast parenchyma, with loss of expression of E-cadherin (CDH1) cell adhesion molecule occurring in 60% to 90%.\textsuperscript{13-15} Loss of CDH1 expression is a well-established cellular hallmark of ILC, with histopathological measurement of the biomarker recommended within expert statements for breast carcinoma workup.\textsuperscript{16} Given these unique histological parameters, it is imperative that the multidisciplinary team consider an array of host, tumor, and therapeutic factors when treating patients with ILC disease, for example the propensity for strong responsiveness to endocrine agents combined with reported modest sensitivity to systemic chemotherapy, when compared to patients with other histological subtypes.\textsuperscript{9} Despite these differences, there are currently no expert consensus statements or guidelines which focus on optimizing systemic therapy specific to lobular histology.\textsuperscript{17} This often leads to breast cancers being treated en masse with systemic chemotherapeutic regimens with limited consideration for histological subtype.\textsuperscript{18,19} Thus, the perceived benefit of prescribing systemic chemotherapy in the setting of early-stage ILC may be brought into question or may not be completely understood.

At the time of writing, there are no prospective, randomized clinical trials evaluating the impact of chemotherapy prescription on long-term survival outcomes in patients who are being treated with curative intent for early-stage ILC. Accordingly, the aim of the current study was to perform a systematic review and meta-analysis assessing the impact of prescribing chemotherapy in such patients on long-term survival outcomes.

\section*{Methods}

\subsection*{Materials and Methods}

A systematic review was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist and meta-analysis and systematic reviews of observational studies (MOOSE) guidelines.\textsuperscript{20,21} This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42022327137). Local institutional ethical approval was not required for this study.

\subsection*{Search Strategy}

An electronic search was performed of the PubMed, Embase, and Cochrane databases on the 3rd March 2022 for relevant studies suitable for inclusion in this study. The search was performed of all fields under the following headings: ((cancer[MeSH Terms]) AND (chemotherapies[MeSH Terms])) AND (breast cancer[MeSH Terms]), which were linked with the Boolean operator ‘AND’. Included studies were limited to those published in the English language and to studies with full-text articles available. Included studies were not restricted based on the year of publication. Initially, all titles were screened, and studies deemed appropriate had their abstracts and full texts reviewed.

\section*{Inclusion and Exclusion Criteria}

Studies meeting the following inclusion criteria were included: (1) Studies assessing the impact of chemotherapy on long-term survival outcomes (ie: hazard ratios (HR), 10-year disease-free (DFS) and/or overall (OS) survival) for patients diagnosed with early-stage ILC; (2) eligible studies had to provide full-text manuscripts. Studies meeting any of the following exclusion criteria were excluded from this study: (1) Studies not evaluating the impact of chemotherapy on long-term survival outcomes for patients diagnosed with early-stage ILC; (2) studies reporting outcomes solely in relation to ILC subgroups (eg: pleomorphic ILC); (3) conference abstracts; (4) review articles; (5) studies including less than 100 patients in their series; (6) case reports, or (7) editorial articles.

\section*{Data Extraction and Quality Assessment}

Two independent reviewers performed the literature search using a predesigned search strategy. Duplicate studies were manually removed. Each reviewer then reviewed the titles, abstracts and/or full texts of the retrieved manuscripts to ensure all inclusion criteria were met, before extracting the following data: (1) first author name; (2) year of publication; (3) study design; (4) country of origin; (5) number of patients diagnosed with ILC included; (6) number of patients undergoing chemotherapy; (7) number of patients not undergoing chemotherapy; (8) basic clinicopathological data (eg: age at diagnosis, tumor staging; follow-up, etc.); and (11) long-term DFS and OS outcomes from each study. Methodological and risk of bias assessment of the included studies was undertaken using the Newcastle Ottawa Risk of Bias Assessment tool for observational studies.\textsuperscript{22}

\section*{Definitions}

Disease-free survival – freedom from invasive disease recurrence or death.

Overall survival – freedom from death due to any cause.

\section*{Statistical Analysis}

Fisher’s Exact (\textit{p}) test was used as appropriate to determine the association between chemotherapy prescription and long-term survival.\textsuperscript{23} Thereafter, survival outcomes were expressed as dichotomous or binary outcomes, reported as odds ratios (OR) and 95% confidence intervals (95% CI) following estimation using the Mantel-Haenszel method. Data specific to patient outcomes and chemotherapy prescription (expressed as HR, 95% confidence intervals (95% CI) and \textit{p}-values) were directly extracted from tables and study text. HR and associated standard errors were calculated from Kaplan-Meier curves where relevant. Time-to-effect modelling was then performed using the generic inverse variance method. Either fixed or random-effects modelling were applied on the basis of whether significant heterogeneity (\textit{I}^2 > 50\%) existed between studies included in the analysis. Symmetry funnel plots were used to assess publication bias. Statistical heterogeneity was determined using \textit{I}^2 statistics. All tests of significance were 2-tailed with \textit{p} < .050 indicating statistical significance. Descriptive statistics were performed using the Statistical Package for Social Sciences (SPSS) version 26 (International Business Machines Corporation, Armonk, NY). Meta-analysis was performed using Review Manager.
Results

Literature Search

The systematic search strategy identified a total of 853 studies, of which 7 duplicate studies were manually removed. The remaining 846 studies had their titles screened for relevance before 30 abstracts and 17 full texts were reviewed for edibility. In total, 9 studies fulfilled the inclusion criteria and were included in this systematic review (Figure 1).

Study Characteristics

Of the 9 included studies, 44.4% provided data from the United States and European translational research facilities respectively (both 4/9). All included studies were of retrospective design (100.0%, 9/9). Publication dates of included studies ranged from 2012 to 2022. Basic study data from the included 9 studies are outlined in Table 1. Risk of bias performed using the Newcastle-Ottawa Scale are outlined in detail in the supplementary material (S1).

Clinicopathological Characteristics

Overall, 28,218 patients were included in the 9 included studies. Of these, 34.7% received chemotherapy (9,797/28,218) and 66.3% did not receive chemotherapy (18,421/28,218). Seven studies reported follow-up data and the mean follow-up was 74 months (range: 0-150 months). Three studies reported patient age and the mean age of included patients was 60 years (range: 22-90 years) (Table 2).

Impact of Chemotherapy on Disease-free Survival

At 10-years follow-up, a higher proportion of patients who had received chemotherapy remained free of disease recurrence or death (83.4%-2,444/2,930 vs. 80.3%, 2,883/3,592 P = .001, †). At meta-analysis, 10-year DFS was similar for those who received chemotherapy versus those who did not receive chemotherapy (OR: 0.89, 95% CI: 0.65-1.3, P = 83%) (Figure 2A). Similarly, DFS was similar for
The Impact of Chemotherapy Prescription on Long-Term Survival Outcomes in Early-Stage Invasive Lobular Carcinoma – A Systematic Review and Meta-Analysis

### Table 1: Details of the 9 Included Studies in This Analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study</th>
<th>Country</th>
<th>Number</th>
<th>Number Chemo</th>
<th>Mean age in Years (Range)</th>
<th>Follow-up in Months (Range)</th>
<th>NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen</td>
<td>2018</td>
<td>China</td>
<td>RC</td>
<td>6467</td>
<td>1246</td>
<td>5221</td>
<td>60 (22-90)</td>
<td>5</td>
</tr>
<tr>
<td>de Nonville</td>
<td>2019</td>
<td>France</td>
<td>RC</td>
<td>2308</td>
<td>823</td>
<td>1485</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Hu</td>
<td>2020</td>
<td>USA</td>
<td>RC</td>
<td>3570</td>
<td>1785</td>
<td>1785</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>Iorfida</td>
<td>2012</td>
<td>Italy</td>
<td>RC</td>
<td>981</td>
<td>345</td>
<td>636</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>Jenkins</td>
<td>2022</td>
<td>USA</td>
<td>RC</td>
<td>2561</td>
<td>459</td>
<td>2102</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>Marmor</td>
<td>2017</td>
<td>USA</td>
<td>RC</td>
<td>4095</td>
<td>1347</td>
<td>2748</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>Metzger-Filho</td>
<td>2019</td>
<td>Portugal</td>
<td>RC</td>
<td>337</td>
<td>170</td>
<td>167</td>
<td>55 (48-64)</td>
<td>6</td>
</tr>
<tr>
<td>Truin</td>
<td>2012</td>
<td>NL</td>
<td>RC</td>
<td>3685</td>
<td>1515</td>
<td>2170</td>
<td>67</td>
<td>7</td>
</tr>
<tr>
<td>Watanuki</td>
<td>2020</td>
<td>USA</td>
<td>RC</td>
<td>4214</td>
<td>2107</td>
<td>2107</td>
<td>129</td>
<td>7</td>
</tr>
</tbody>
</table>

Chemo = chemotherapy, NL = Netherlands, RC = retrospective cohort, USA = United States of America, NOS = Newcastle Ottawa Scale

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Tumor Staging</th>
<th>Nodal Status</th>
<th>Subtypes</th>
<th>Chemotherapy</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen</td>
<td>2018</td>
<td>T1-T2</td>
<td>N0 or N1</td>
<td>ER+/HER2-</td>
<td>aCT + aIF</td>
<td>aIF</td>
</tr>
<tr>
<td>de Nonville</td>
<td>2019</td>
<td>T1-T2</td>
<td>N0 or N1</td>
<td>ER+/HER2-</td>
<td>aCT + aIF</td>
<td>aIF</td>
</tr>
<tr>
<td>Hu</td>
<td>2020</td>
<td>T1</td>
<td>N0 or N1</td>
<td>ER+/HER2-</td>
<td>aCT + aIF</td>
<td>aIF</td>
</tr>
<tr>
<td>Iorfida</td>
<td>2012</td>
<td>T1-3</td>
<td>N1-3</td>
<td>All subtypes</td>
<td>aCT</td>
<td>aIF or none</td>
</tr>
<tr>
<td>Jenkins</td>
<td>2022</td>
<td>T1-3</td>
<td>N or N+</td>
<td>ER+</td>
<td>aCT</td>
<td>None</td>
</tr>
<tr>
<td>Marmor</td>
<td>2017</td>
<td>Stage I-II</td>
<td>N0 or N1</td>
<td>ER+/HER2-</td>
<td>aCT + aIF</td>
<td>aIF</td>
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<tr>
<td>Metzger-Filho</td>
<td>2019</td>
<td>T1-3</td>
<td>N or N+</td>
<td>ER+</td>
<td>aCT</td>
<td>-</td>
</tr>
<tr>
<td>Truin</td>
<td>2012</td>
<td>T1-T4</td>
<td>N0 or N1</td>
<td>ER+</td>
<td>aCT + aIF</td>
<td>aIF</td>
</tr>
<tr>
<td>Watanuki</td>
<td>2020</td>
<td>T1-T4</td>
<td>N0-N3</td>
<td>All subtypes</td>
<td>NAC or aCT</td>
<td>NET or aHT</td>
</tr>
</tbody>
</table>

T = tumor stage, N = nodal status, ER+ = estrogen receptor positive, HER2- = human epidermal growth factor receptor-2 negative, aCT = adjuvant chemotherapy, aIF = adjuvant hormonal therapy, NAC = neoadjuvant chemotherapy, NET = neoadjuvant endocrine therapy

Impact of Chemotherapy on Overall Survival

At 10-years follow-up, a similar proportion of patients who had received chemotherapy were still alive compared to those who did not receive chemotherapy (76.3%-4.421/5,792 vs. 75.9%, 6,459/8,510, P = .563, t). At meta-analysis, 10-year OS was similar for those who received chemotherapy versus those who did not receive chemotherapy (OR: 0.92, 95% CI: 0.72-1.18, 6 = 89%) (Figure 3A). Similarly, OS was similar for those who received chemotherapy versus those who did not receive chemotherapy when using time-to-effect modelling (HR: 1.07, 95% CI: 0.89 - 1.27, 6 = 67%) (Figure 3B).

Discussion

The most important finding in this meta-analysis is the data illustrating that there is no survival advantage associated with prescribing systemic chemotherapy in the setting of localized ILC. These results are of utmost importance within the current breast cancer management paradigm, as there is currently a paucity of expert consensus statements or guidelines providing recommendations for optimizing systemic chemotherapy use in ILC. Several translational and clinical research studies have illustrated the chemoinnervating nature of ‘pure’ ILC, 1, 9, 33 Although improved oncological outcomes are typically observed in patients who respond favorably to chemotherapy, 14, 35 these results are non-representative of ILC disease: Cortazar et al., illustrated that ILC demonstrates poor sensitivity to neoadjuvant chemotherapies (NAC) and no impact on OS outcomes overall [pCR rate in ILC: 7.8%, HR: 0.93 (95% CI: 0.50-1.70)]. 36 While achieving a pCR to NAC is perceived to carry prognostic significance in certain breast cancer molecular subtypes, 34, 35 the ILC histological subtype fails to corroborate such results, based on the work of the Collaborative Trials on Neoadjuvant Breast Cancer (CTNeoBC). 36 Therefore, perhaps it is somewhat unsurprising that prescribing chemotherapy failed to improve the long-term survival observed in the current analysis of over 28,000 patients treated for ILC. Thus, these results indicate a more judicious approach to systemic therapy prescription in ILC is warranted in future.

Prior to this study, the long-term impact of prescribing systemic chemotherapy to improve oncological and survival outcomes in early-stage ILC had not previously been evaluated. Therefore, this meta-analysis provides novel data highlighting the limited premise for using such therapies to improve DFS (OR: 0.89, 95% CI: 0.65-1.23) and OS (OR: 0.92, 95% CI: 0.72-1.18) at 10-years outcomes following treatment and over the full trajectory of the included studies [DFS - HR: 1.01 (95% CI: 0.78-1.31), OS - HR: 1.07 (95% CI: 0.89-1.27)]. These are interesting findings which speak to the
tendency of ILCs to develop larger, more indolent cancers which are ER+/PgR+, with lower 21-gene expression assay recurrence scores (RS) and metastatic potential, which derive limited benefit from chemotherapy.\textsuperscript{17,39} The modern breast cancer treatment paradigm for early-stage ER+/HER2- disease relies heavily upon multigene expression assays (such as RS) to guide therapeutic decision making surrounding chemoendocrine therapies,\textsuperscript{18,19,40} which of course may influence ILC management prospectively: Makower et al. previously demonstrated that just 7.2% of patients with ILC had high-risk RS (RS 26-100) versus 16.9% of those with ductal histology in their analysis using patients from the National Cancer Database.\textsuperscript{38} Furthermore, this analysis illustrated no survival advantage associated with chemotherapy use in ILC (HR: 0.99, 95% CI: 0.70-1.39) when adjusted for age, race, ethnicity, rurality, median income and educational level of area of residence, RS, tumor size, grade, nodal involvement, and Charlson-Deyo comorbidity index. Interestingly, patients in the aforementioned study with RS 11-25 being treated for ILC disease were more likely to receive adjuvant chemotherapy than other histological subtypes, which is best explained by the overestimated benefit of such therapies in the setting of larger ILC...
cancers by the medial oncology community. As evidenced by the recent TAILORx and RxPONDER trials, reliance upon traditionally actionable clinicopathological parameters (such as tumor size and nodal status) to guide chemoendocrine prescription in ER+ disease is now becoming almost obsolete. Furthermore, trials such as RxPONDER were not powered to estimate the survival advantage of chemoendocrine therapies based on subgroups, such as histological subtypes. The evidence reported in the current analysis illustrates that the case of lobular histology provides an obvious exception to this concept, with limited premise to prescribe chemotherapy for cases of ILC, unless directed by multigene expression assays.

There are currently no prospective randomized clinical trials attempting to ascertain the value of chemotherapy use on long-term oncological and survival outcomes in ILC. The poor response previously observed in ILC to NAC in prospective clinical trials precludes efforts to design such studies which may inform the long-term impact of cytotoxic chemotherapy on survival outcomes for those with ILC, and further exacerbates the research inadequacy surrounding the management of this common, studied cancer subtype. Until this partiality is recognized and subsequent reevaluation is performed, reliance upon studies such as the current meta-analysis to provide insights into the optimal managerial strategy for ILC will remain.

The current study suffers from several limitations. Firstly, all the included studies are retrospective in design, rendering this data subject to potential selection, confounding and ascertainment biases. For example, the potential for confounding factors such as tumor size, degree of nodal burden, and tumor biology to influence therapeutic decision-making regarding systemic therapies must be considered when interpreting the results of this analysis. Secondly, to build on this previous limitation, just 2 included studies [representing 27.6% of the entire patient group (7,782/28,218)] performed propensity matching to accurately inform the impact of systemic chemotherapy on outcome. The remaining seven studies failed match ILC cases based on clinicopathological information, limiting the robustness of these results. Thirdly, this analysis failed to illustrate the survival outcomes according to ILC subgroups (eg: pleomorphic variants), with all patients classified under the umbrella term “ILC.” Finally, current expert consensus statements and guidelines do not recommend histological subtype to guiding therapeutic decision-making in ER+/HER2- disease and emphasize the importance of multigene expression assays for adjuvant chemoendocrine prescription in early-stage ER+/HER2-. Adherence to such guidelines is of critical importance, irrespective of histological tumor subtype.

This systematic review and meta-analysis illustrates no long-term oncological or survival advantage associated with chemotherapy prescription in the setting of early-stage ILC breast cancer. Survival outcomes 10-years following treatment were similar for those receiving chemotherapy and their counterparts, highlighting the chemoinensitive nature of ILC. In the absence of well-designed, prospective clinical trials evaluating the impact of chemotherapy on long-term outcomes in ILC, these results should be considered by the multidisciplinary team when deciding on the value of systemic chemotherapy prescription in these cases.

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Declaration of Competing Interest
None of the authors have any conflicts of interest to disclose.

Supplementary materials
Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clbc.2022.09.005

References