Journal Pre-proof

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PII: S1526-8209(22)00219-1
DOI: https://doi.org/10.1016/j.clbc.2022.09.005
Reference: CLBC 1514

To appear in: *Clinical Breast Cancer*

Received date: Jun 4, 2022
Revised date: Sep 6, 2022
Accepted date: Sep 14, 2022

Please cite this article as: Matthew G. Davey , Stephen Keelan , Aoife J. Lowery , Michael J. Kerin , The Impact of Chemotherapy Prescription on Long-Term Survival Outcomes in Early-Stage Invasive Lobular Carcinoma – A Systematic Review and Meta-Analysis, *Clinical Breast Cancer* (2022), doi: https://doi.org/10.1016/j.clbc.2022.09.005

The Impact of Chemotherapy Prescription on Long-Term Survival Outcomes in Early-Stage Invasive Lobular Carcinoma – A Systematic Review and Meta-Analysis

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Abstract word count: 239 words

Main. text word count: 2,413 words

Total word count: 2,652 words

Sources of funding: MGD received funding from the National Breast Cancer Research Institute, Ireland.

Category: Systematic Review article ï This manuscript is not based on a communication to a society or meeting

Keywords: lobular carcinoma; systemic chemotherapy; oncological outcomes; long-term survival

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Abstract

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.

Aims: 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. 10-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 ï 150 months) and mean age was 60 years (range: 22 ï 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 ï 1.23) and OS (OR: 0.92, 95% CI: 0.72 ï 1.18). When using time-to-effect modelling, chemotherapy prescription failed to improve DFS (hazard ratio (HR): 1.01, 95% CI: 0.78 ï 1.31) and OS (HR: 1.07, 95% CI: 0.89 ï 1.27, I^2= 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.

PROSPERO Registration: CRD42022327137

Introduction

Invasive lobular carcinoma (ILC) represents the second most common breast cancer histological subtype and accounts for 5-15% of diagnoses globally [1, 2]. Despite representing a minority share of all breast tumours, ILC contributes a similar share to the global cancer burden as ovarian carcinoma, central nervous system tumours, and malignant melanoma [3]. Notwithstanding, ILCs remain an understudied breast cancer histological subtype [4, 5], particularly as these tumours 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, 6], and these cancers exhibit peculiar metastatic patterns once relapse occurs [7]. Furthermore, ILCs are typically indolent (moderate-to-well differentiated) tumours with the propensity to develop strong estrogen and/or progesterone receptor positivity and human epidermal growth factor receptor-2 negativity (ER+/PgR+/HER2-) [5]. Accordingly, ILCs tend to be endocrine responsive [8], chemoinsensitive cancers [9], with surgery combined with multimodal therapeutics proving curative for the majority [1, 10, 11].

ILC represent a unique histological subtype [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 60-90% [13-15]. Loss of CDH1 expression is a renowned cellular hallmark of ILC, with histopathological measurement of the biomarker recommended within expert statements for breast carcinoma workup [16]. Given these unique histological parameters, it is imperative that the multidisciplinary team consider an array of host, tumour, 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 [9]. Despite these differences, there are currently no expert consensus statements or guidelines which focus on optimising systemic therapy specific to lobular histology [17]. This often leads to breast cancers being treated *en masse* with systemic chemoendocrine therapies with limited consideration for histological subtype [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, randomised 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.

Methods

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 [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.

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: ((carcinoma, lobular[MeSH Terms]) AND (chemotherapies[MeSH Terms])) AND (breast cancer[MeSH Terms]), which were linked with the Boolean operator óANDô. 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.

Inclusion and Exclusion Criteria

Studies meeting the following inclusion criteria were included: (1) Studies assessing the impact of chemotherapy on long-term survival outcomes (i.e.: 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 (e.g.: 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.

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 (e.g.: age at diagnosis, tumour 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 [22].

Definitions

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

Overall survival ï freedom from death due to any cause.

Statistical Analysis

Fisherôs Exact (À) test was used as appropriate to determine the association between chemotherapy prescription and long-term survival [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 *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 (I^2 >50%) existed between studies included in the analysis. Symmetry funnel plots were used to assess publication bias. Statistical heterogeneity was determined using I^2 statistics. All tests of significance were two-tailed with P<0.050 indicating statistical significance. Descriptive statistics were performed using the Statistical Package for Social Sciences (SPSS) version 26 (International Business Machines Corporation, Armonk, New York). Meta-analysis was performed using Review Manager (RevMan), Version 5.4 (Nordic Cochrane Centre, Copenhagen, Denmark).

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 [24-32] (**Figure 1**).

Study Characteristics

Of the 9 included studies, 44.4% provided data from the United States [26, 28, 29, 31] and European [25, 27, 30, 32] 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 ï 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 [24, 25, 27, 28, 30-32] and the mean follow-up was 74 months (range: 0 ï 150 months). Three studies reported patient age [24, 30, 31] and the mean age of included patients was 60 years (range: 22 ï 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*=0.001, À). 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 ï 1.23, I^2= 83%) (**Figure 2.A**). Similarly, DFS was similar for those who received chemotherapy versus those who did not receive chemotherapy when using time-to-effect modelling (HR: 1.01, 95% CI: 0.78 ï 1.31, I^2= 73%) (**Figure 2.B**).

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 receive chemotherapy (76.3% - 4,421/5,792 vs. 75.9% 6,459/8,510, *P*=0.563, À). 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 ï 1.18, I^2= 89%) (**Figure 3.A**). 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 ï 1.27, I^2= 67%) (**Figure 3.B**).

Discussion

The most important finding in this meta-analysis is the data illustrating that there is no survival advantage associated with prescribing systemic chemotherapies in the setting of localised ILC. These results are of the utmost importance within the current breast cancer management paradigm, as there is currently a paucity of expert consensus statements or guidelines providing recommendations for optimising systemic chemotherapy use in ILC. Several translational and clinical research studies have illustrated the chemoinsensitive nature of ópureô ILC [1, 9, 33]. Although improved oncological outcomes are typically observed in patients who respond favourably to chemotherapy [34, 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 ï 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 ï 1.23) and OS (OR: 0.92, 95% CI: 0.72 ï 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 ï 1.31), OS - HR: 1.07 (95% CI: 0.89 ï

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 [37-39]. 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 [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 [38]. Furthermore, this analysis illustrated no survival advantage associated with chemotherapy use in ILC (HR: 0.99, 95% CI: 0.70 ï 1.39) when adjusted for age, race, ethnicity, rurality, median income and educational level of area of residence, RS, tumour 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 [41]. As evidenced by the recent TAILORx and RxPONDER trials [18, 19], reliance upon traditionally actionable clinicopathological parameters (such as tumour 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 [18]. 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 randomised 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 [42, 43] 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 inequity surrounding the management of this common, understudied cancer subtype. Until this partiality is recognised and subsequent re-evaluation 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 tumour size, degree of nodal burden, and tumour 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 two included studies [26, 31] [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 (e.g.: pleomorphic variants), with all patients classified under the umbrella term óILCô. Finally, current expert consensus statements and guidelines do not recommend histological subtype to guiding therapeutic decision-making in ER+/HER2- disease and emphasise the importance of multigene expression assays for adjuvant chemoendocrine prescription in early-stage ER+/HER2- [44, 45]. Adherence to such guidelines is of critical importance, irrespective of histological tumour 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 chemoinsensitive 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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Table 1. Details of the 9 included studies in this analysis.

Author	Year	Study	Country	Number	Number Chemo	Number Control	Mean age in years (Range)	Follow-up in months (Range)	NOS
Chen	2018	China	RC	6467	1246	5221	60 (22-90)	63 (0-143)	5
de Nonneville	2019	France	RC	2308	823	1485	-	58	5
Hu	2020	USA	RC	3570	1785	1785	-	-	6
Iorfida	2012	Italy	RC	981	345	636	-	89 (0-150)	5
Jenkins	2022	USA	RC	2561	459	2102	-	40	5
Marmor	2017	USA	RC	4095	1347	2748	-	-	7
Metzger-Filho	2019	Portugal	RC	337	170	167	55(48-64)	95	6
Truin	2012	NL	RC	3685	1515	2170	-	67	7
Watanuki	2020	USA	RC	4214	2107	2107	60	129	7

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

Table 2. Clinicopathological data of the 9 included studies in this analysis.

Author	Year	Tumour Staging	Nodal Status	Subtypes	Chemotherapy	Control
Chen	2018	T1-T2	N0 or N1	ER+/HER2-	aCT + aHT	aHT
de Nonneville	2019	T1-T2	N0 or N1	ER+/HER2-	aCT + aHT	aHT
Hu	2020	T1	N0 or N1	ER+/HER2-	aCT + aHT	aHT
Iorfida	2012	T1-3	N1-3	All subtypes	aCT	aHT or none
Jenkins	2022	T1-3	N- or N+	ER+	aCT	None
Marmor	2017	Stage I-II	N0 or N1	ER+/HER2-	aCT + aHT	aHT
Metzger-Filho	2019	T1-3	N- or N+	ER+	aCT	-
Truin	2012	T1-T4	N0 or N1	ER+	aCT + aHT	aHT
Watanuki	2020	T1-T4	N0-N3	All subtypes	NAC or aCT	NET or aHT

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

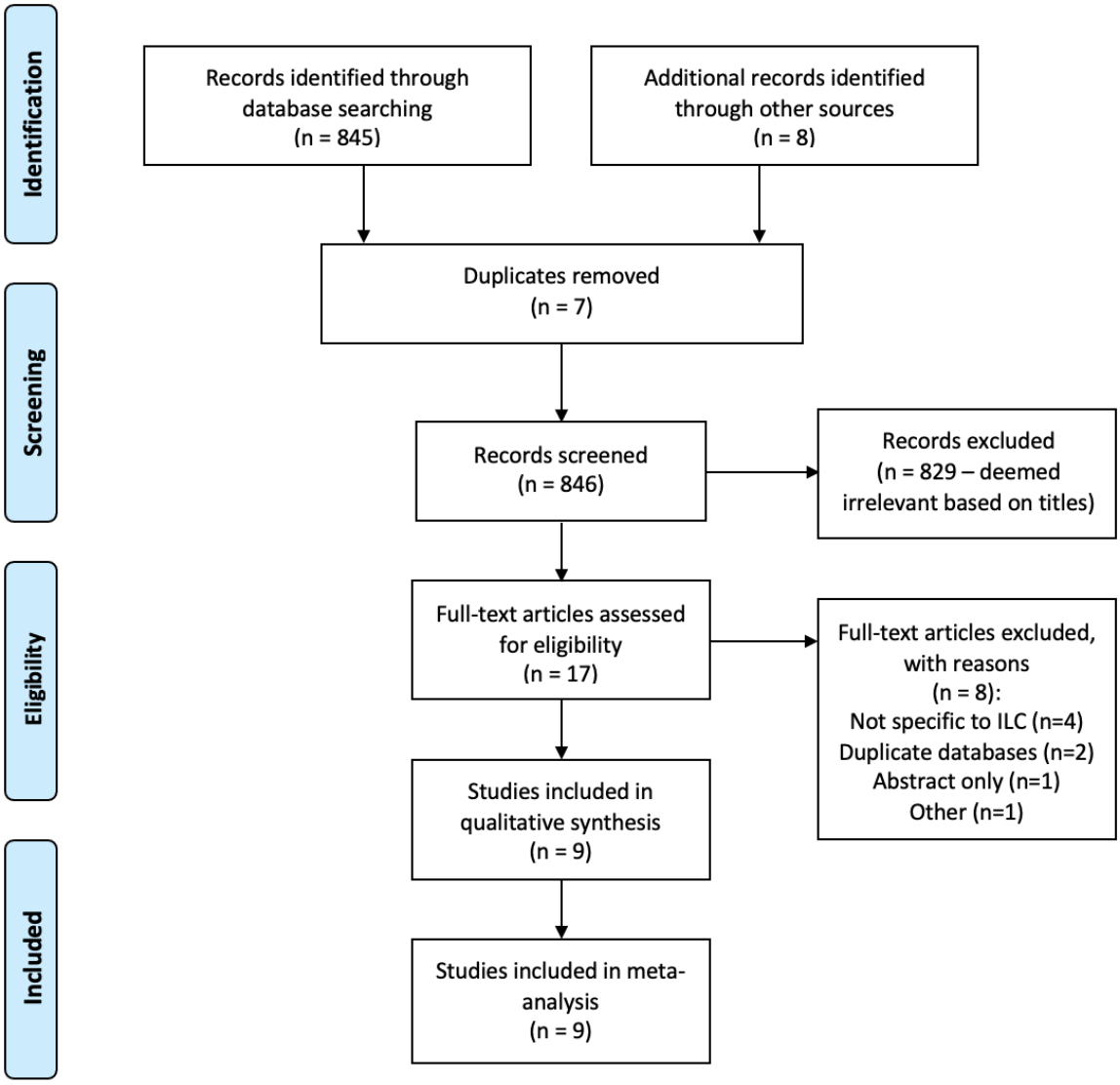

Figure 1. PRISMA flowchart illustrating the systematic search process.

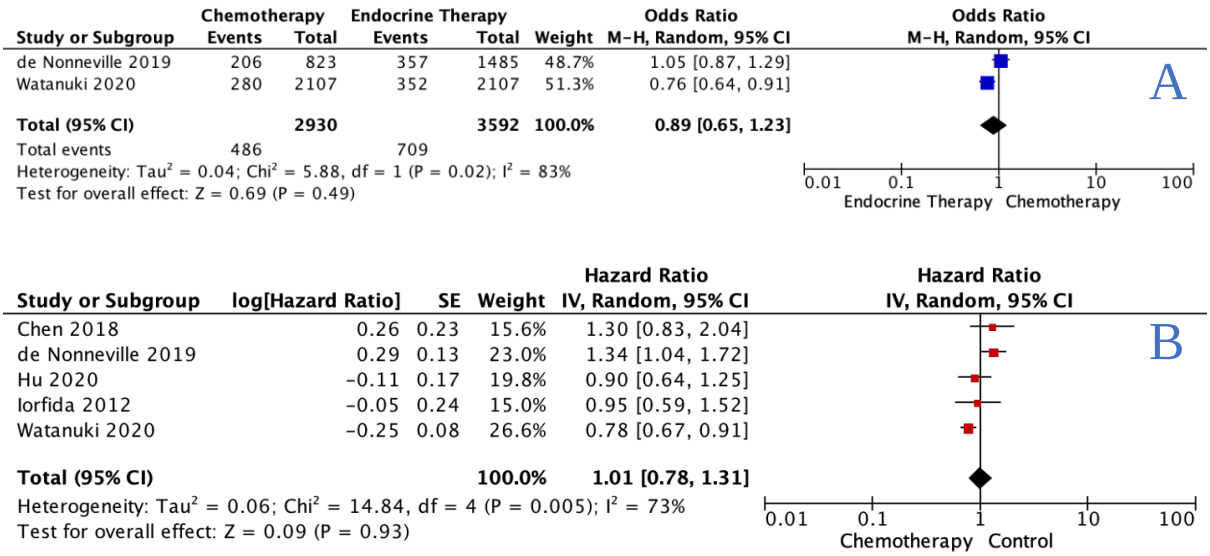

Figure 2. Forest plots illustrating the impact of chemotherapy prescription on disease-free survival at (A) 10-years post treatment and (B) using time-to-effect modelling in patients previously treated with curative intent for early-stage invasive lobular carcinoma.

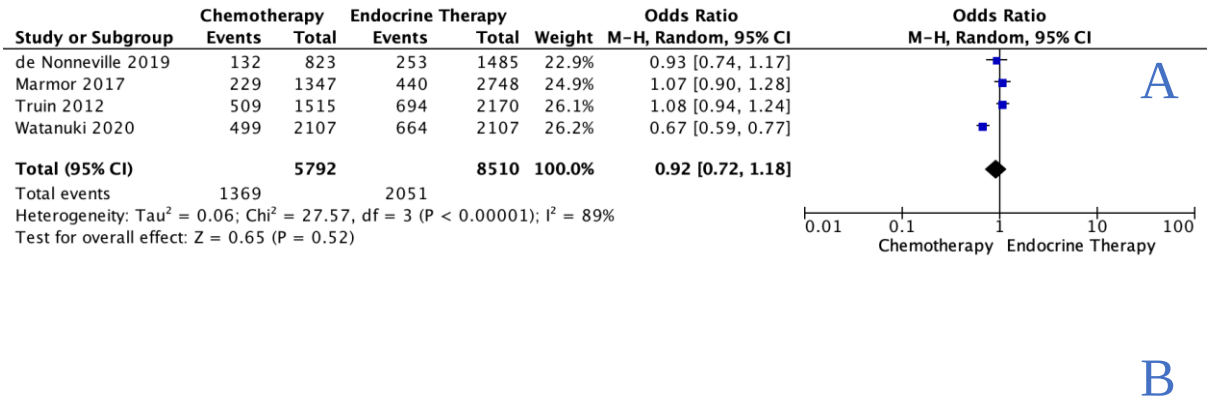

Figure 3. Forest plots illustrating the impact of chemotherapy prescription on overall survival at (A) 10-years post treatment and (B) using time-to-effect modelling in patients previously treated with curative intent for early-stage invasive lobular carcinoma.