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Differences in sensitivity to neoadjuvant chemotherapy among invasive lobular and ductal carcinoma of the breast and implications on surgery—A systematic review and meta-analysis

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ABSTRACT

Meta-analysis of >87,000 patients demonstrates that patients with invasive lobular carcinoma of the breast are far less likely to achieve pCR of the breast or axilla compared to their ductal counterparts, receive less BCS and more frequently return positive margins.

Background: Neoadjuvant chemotherapy (NACT) facilitates tumour downstaging, increases breast conserving surgery (BCS) and assesses tumour chemosensitivity. Despite clinicopathological differences in Invasive Ductal Carcinoma (IDC) and Invasive Lobular Carcinoma (ILC), decision making surrounding the use NACT does not take account of histological differences.

Aim: To determine the impact NACT on pathological complete response (pCR), breast conserving surgery (BCS), margin status and axillary pCR in ILC and IDC.

Methods: A systematic review was performed in accordance with the PRISMA guidelines. Studies reporting outcomes among ILC and IDCs following NACT were identified. Dichotomous variables were pooled as odds ratios (ORs) with 95% confidence intervals_(CI) using the Mantel-Haenszel method. *P*-values <0.05 were statistically significant.

Results: 40 studies including 87,303 (7596 ILC [8.7%]and 79,708 IDC [91.3%]) patients were available for analysis. Mean age at diagnosis was 54.9 vs. 50.9 years for ILC and IDC, respectively. IDCs were significantly more likely to achieve pCR (22.1% v 7.4%, OR: 3.03 [95% CI 2.5–3.68] $p < 0.00001$), axillary pCR (23.6% vs. 13.4%, OR: 2.01 [95% CI 1.77–2.28] $p < 0.00001$) and receive BCS (45.7% vs. 33.3%, OR 2.14 [95% CI 1.87–2.45] $p < 0.00001$) versus ILCs. ILCs were significantly more likely to have positive margins at the time of surgery (36% vs 13.5%, OR 4.84 [95% CI 2.88–8.15] $p < 0.00001$).

Conclusion: This is the largest study comparing the impact of NACT among ILC and IDC with respect to pCR and BCS. ILC has different outcomes to IDC following NACT and incorporate it into treatment decisions and future clinical guidelines.

Contents

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1. Introduction

Invasive lobular carcinoma (ILC) is the second most common histological subtype of breast cancer, accounting for approximately 5–15% of diagnoses worldwide [1–3]. In spite of representing a minority share among breast cancers, the incidence of ILC is comparable to malignant melanoma or ovarian cancers, indicating that it as a significant contributor to the global cancer burden [4]. ILCs have distinct clinicopathological characteristics; they have the tendency to be large, multifocal, slow growing tumours, which are often mammographically occult. They are almost exclusively hormone sensitive tumours and present in older patients [5]. ILCs infiltrate the affected breast widely, by radiating through the surrounding stroma in a linear pattern of single cells. This growth pattern avoids the anatomical disruption seen in invasive ductal carcinoma (IDC) and an attenuated stromal reaction fails to produce the classic breast 'lump', making clinical and radiological detection challenging to the surgical oncologist [1].

Neoadjuvant chemotherapy (NACT) is now a well-established component of breast cancer treatment involving the administration of cytotoxic chemotherapy in the preoperative setting. Advantages to NACT include tumour downstaging in the setting of locally-advanced stage IIB/III disease, or cases where women hope to achieve BCS, despite not currently being a suitable candidate due to increased tumour to breast ratio [6], and international guidelines now recommend NACT administration in the aforementioned scenarios [7,8]. At present, no guidelines provide physicians with advice in relation to the optimal approach to cytotoxic chemotherapy prescription specifically in lobular histology. Surgery remains the most important single intervention in breast cancer management. In the era of multi-disciplinary management, the selection of the right operation for the right patient can be significantly impacted by the use of NACT.

Despite considerable heterogeneity in the spectrum of breast carcinoma [9], the modern paradigm rarely includes histopathological tumour subtype in therapeutic decision making when considering conventional chemotherapy prescription [10]. Patients with both ILC and IDC histology are equally likely to be indicated to undergo NACT, despite ILC being renowned for de novo chemoresistance, with very few achieving pathological complete response (pCR) [11,12]. Furthermore, data suggest ILC are less likely to successfully downstage to achieve BCS [13,14]. Despite this, NACT remains a fundamental therapeutic option for treating ILC.

While previous studies focus upon the ascertainment of pCR and conversion to BCS as primary analytical endpoints [15], recent large volume data suggests updated pooled analyses should be performed comparing the clinical value of NACT in ILC versus IDC. Accordingly, the aim of the current systematic review and meta-analysis was to determine rates of breast and axillary pCR as well as successful BCS rates following NACT in patients with ILC and IDC and how those outcomes may influence surgical decision making within the context of multi-disciplinary care.

2. Methods

2.1. Search strategy

A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and Meta-Analyses of Observational Studies in Epidemiology (MOOSE) guidelines [16,17]. A comprehensive, electronic search was conducted of the SCOPUS, EMBASE, PUBMED and Web of Science databases, along with the Cochrane Library on the October 8, 2020. Studies were considered for analysis if the following search terms were identified in their titles or abstracts; "Lobular" AND "Ductal" AND "Breast" AND "Neoadjuvant". Secondary referencing was conducted through manually reviewing the reference lists of potentially eligible studies. Studies were not limited according to their year or language of publication. Initial screening was conducted of all titles with subsequent assessment of abstracts. Studies deemed appropriate had their full text reviewed. In studies where the data was potentially derived from the same patient population, the study with the most relevant outcomes was included in the analysis.

2.2. Inclusion and exclusion criteria

Studies were considered for inclusion if the following inclusion criteria were met [1]: included patients with a diagnosis of invasive lobular or invasive ductal carcinoma [2], patients were administered chemotherapy prior to surgical intervention (neoadjuvant chemotherapy) [3], patient outcome data was reported on any of the following; (a) pCR to NACT in breast, (b) surgical intervention undertaken following completion of chemotherapy, (c) pCR to NACT within the axillary nodes, (d) margin status following the index surgical procedure, (e) the surgical management of the axilla. Studies were excluded from the analysis if any of the following criteria were met [1]: Studies reporting outcomes not within the remit of the current study [2] Data not specified according to histological subtype [3], review articles [4], case reports or studies with less than 10 patients [5], editorials or [6] conference abstracts without a published full text.

2.3. Data extraction and quality assessment

The literature search was conducted independently by the first and second authors (DO'C and MGD) using the predefined search strategy. This predetermined search strategy was designed by the senior author (MJK). Duplicates were removed and manuscripts were retrieved in accordance with the predefined inclusion and

exclusion criteria as detailed above. The following data was extracted from full text manuscripts [1]; First author name [2], year of publication [3], type of study [4], total number of patients and number within each subtype [5], clinicopathological features of enrolled subjects [6] NACT regimen and number of cycles [7], type of surgery performed; index operation and any reoperations required [8], proportion of patients achieving breast pCR and/or axillary pCR. The Newcastle-Ottawa scale was employed to assess study bias and methodology quality [18]. In all cases a consensus was achieved between the first and second author. The senior author (MJK) reviewed any case where a consensus could not be achieved. Studies publishing data thought to be from the same source were assessed for the potential overlap of patient data. Where a risk of overlap was identified, one study was selected for inclusion based on relevance.

2.4. Statistical analysis

Comparisons between the ILC and IDC cohorts were assessed as dichotomous data using the Mantel-Haenszel methods. Results were expressed as odds ratios (OR) and 95% Confidence intervals. I^2 statistics were used to assess heterogeneity between studies and where indicated, a random-effects model was used in this analysis. Categorical variables were assessed by Chi-squared test (χ^2). Statistical significance was considered to be a p value of <0.05 and statistical analysis was performed using Review Manager (RevMan) version 5.4.1.

3. Results

3.1. Literature search

Employing our search strategy across the 5 databases identified 1228 records for potential inclusion. Of these, 324 duplicate records were removed, leaving 904 titles to be screened for relevance. Screening of titles and their associated abstracts resulted in 76 full text articles to be reviewed, of which, 47 and 40 were included in the qualitative and quantitative analysis respectively [19–58]. The process of study selection is summarised in Fig. 1.

3.2. Study characteristics

In total, this analysis included 87,303 patients who received NACT for ILC or IDC. Of these, 7596 received NACT for ILC (8.7%) and 79,708 for IDC (91.3%). The mean age at diagnosis was 51.1 years and the mean age of ILC cases was 4 years older than IDC (54.9 vs. 50.9 years). Included in the meta-analysis were 4 randomised controlled trials, 13 prospective studies and 19 retrospective studies. Included studies were of moderate to good quality with Newcastle-Ottawa scores ranging from 5 to 7. Overall, 31 studies reported pCR rates following NACT (Table 1a) and 4 studies reported rates of axillary pCR (Table 1b). There were 18 studies reporting BCS rates following NACT (Table 2a) and 7 studies included data on the margin status of the surgical specimen (Table 2b).

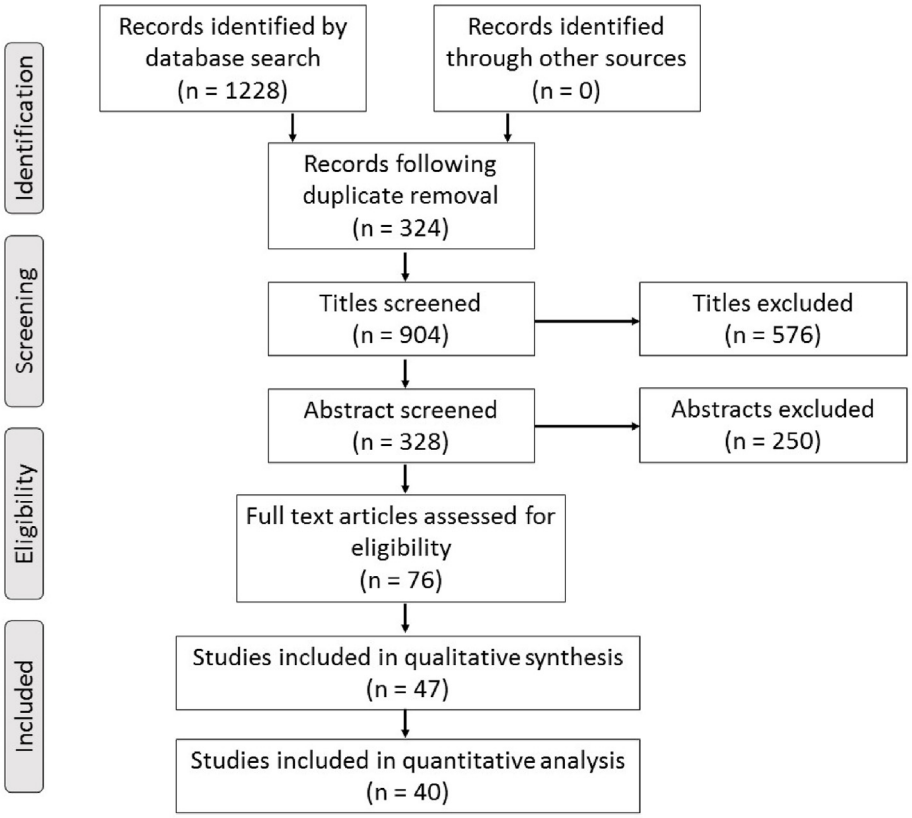

Fig. 1. PRISMA flow diagram illustrating the study selection process.

Table 1a
Studies included in the assessment of pCR.

Author/Year	Type of study	No. pts. (ILC vs IDC)	Inclusion criteria (TNM and subtype)	Neoadjuvant regime	No. of cycles	pCR definition	Newcastle – Ottawa Scale
Alamgeer et al., 2014	Randomised Controlled Trial	11 vs. 108	T1-3, N0-3, M0 Mixed	FEC and Docetaxel	4 and 4	No invasive in breast or axilla	7
Boidot et al., 2009	Prospective Cohort	1 vs. 28	T1-3, N0-3, M0 Mixed	FEC, Docetaxel and Epirubicin	6 and 6	No invasive in breast or axilla	6
Bollet et al., 2008	Retrospective Cohort	68 vs. 672	T2-3, N0-1, M0 Mixed	Anthracycline	1–6	N/a	6
Chan et al., 2011	Prospective Cohort	6 vs. 42	T3/4, T1-4 N1–3, M0 Mixed	TAC	6	No invasive in breast or axilla	5
Cocquyt et al., 2003	Prospective Cohort	26 vs. 101	>3 cm Mixed	CMF and CAF	3	No invasive in breast	7
Cristofanilli et al., 2005	Retrospective Cohort	122 vs. 912	T1-3, N0-2, M0 Mixed	CVAP, CAF and taxane	4–8	No invasive in breast or axilla	6
Dave et al., 2017	Prospective Cohort	20 vs. 223	T1-3, N0-2 Mixed	Epirubicin, cyclophosphamide and docetaxel/paclitaxel	6	No invasive in breast	7
De Los Santos et al., 2013	Retrospective Cohort	61 vs. 637	T1-3, N0-3 Mixed	AC-T, Carboplatin, Bevacizumab, Trastuzumab	Varied	No invasive or in situ in breast	7
Delpech et al., 2013	Retrospective Cohort	177 vs. 1718	T1-4, N0-1, M0 ER+, HER2 ±	Anthracycline, Taxane, Trastuzumab	Varied	No invasive in breast or axilla	6
Fisher et al., 2012	Retrospective Cohort	7 vs. 120	T1-4, N0-3 TNBC	Adriamycin, Taxane	Varied	No invasive in breast	6
Fitzal et al., 2011	Retrospective Cohort	67 vs. 258	T1-4, N0-1, M0 Mixed	CMF, ED, EDC, pegfilgastrim	Varied	No invasive in breast or axilla	7
Gahlaut et al., 2016	Prospective Cohort	12 vs. 180	T1-4, N0-1, M0 Mixed	Anthracycline, Taxane, Trastuzumab	6	No invasive in breast	6
Gentile et al., 2017	Prospective Cohort	22 vs. 276	T4, T1-4 and N1-3, M0 Mixed	AC-T, Trastuzumab and Pertuzumab	Varied	No invasive in breast or axilla	7
Goldstein et al., 2007	Retrospective Cohort	3 vs. 65	T1-3 and N0-3 Mixed	Anthracycline, 5-FU, Taxane, Trastuzumab	Varied	No invasive in breast	6
Keskin et al., 2011	Retrospective Cohort	24 vs. 294	T1-4,N0-3, M0 Mixed	Anthracycline	Varied	No invasive or in situ breast or axilla	6
Lips et al., 2011	Prospective Cohort	46 vs. 157	T1-4, N0-3 Mixed	AC and CD	6	No invasive in breast or axilla	7
Lips et al., 2012	Prospective Cohort	75 vs. 601	T1-4, N0-3, M0 Mixed	AC, ACT and Trastuzumab	6	No invasive in breast or axilla	6
Mathieu et al., 2004	Prospective Cohort	38 vs. 419	T2-4, N0-2, M0 Mixed	AVCMF, CAF and FEC	3 or 4	No invasive in breast	7
Nagao et al., 2011	Retrospective Cohort	29 vs. 500	T2-4, N0-2 Mixed	FEC, AC, AT, wPTX and Trastuzumab	4 and 12	No invasive in breast	7
Petruola et al., 2017	Retrospective Cohort	91 vs. 310	T1-4, N0-3 ER/PR + HER2-	NA	NA	No invasive or in suite in breast or axilla	6
Pu et al., 2005	Prospective Cohort	3 vs. 41	T1-4, N0-3, M0 Mixed	Doxorubicin and Docetaxel	4	No invasive in breast	6
Reitsamer et al., 2005	Randomised Controlled Trial	7 vs. 38	T1-4, N0-3, M0 Mixed	Epidoxorubicin and Docetaxel	3 or 6	No invasive in breast	7
Riba et al., 2018	Retrospective Cohort	2417 vs. 47,697	T1-4, N0-3, M0 Mixed	Varied	Varied	No invasive in breast	7
Sinn et al., 1994	Randomised Controlled Trial	11 vs. 35	NA	Epirubicin and Cyclophosphamide	NA	No invasive or in situ in breast	6
Straver et al., 2010	Retrospective Cohort	37 vs. 197	T1-3, N0-1, M0 Mixed	AC, CD, PTC, AD	6 and 3	No invasive in breast or axilla	7
Sullivan et al., 2009	Retrospective Cohort	9 vs. 40	T1-4, N0-3 Mixed	CD, AC, ADC, ACP	Varied	No invasive in the breast or axilla	6
Tubiana-Hulin et al., 2006	Retrospective Cohort	118 vs. 742	T2-4, N0-2, M0 Mixed	Anthracycline based Varied	Varied	No invasive in breast or axilla	6
Untch et al., 2011	Prospective Cohort	13 vs. 189	T1-4, N0-3, M0 HER2+	Epirubicin/Cyclophosphamide and Paclitaxel/Trastuzumab	3 and 3	No invasive in breast or axilla	6
Vugts et al., 2017	Retrospective Cohort	39 vs. 279	T1-4, N0-3, M0 Mixed	TAC, AC-T ± Trastuzumab	NA	No invasive or in situ in the breast	6
Wenzel et al., 2007	Prospective Cohort	37 vs. 124	T0-3, N0-3, M0 Mixed	Epidoxorubicin and Docetaxel	NA	No invasive in breast	7

FEC: 5-FU, Epirubicin and Cyclophosphamide, AC-T: Doxorubicin, Cyclophosphamide and Taxane, TAC: Docetaxel, Doxorubicin and Cyclophosphamide, CMF: Cyclophosphamide, Methotrexate and 5-FU, CAF: Cyclophosphamide, Doxorubicin and 5-FU, CVAP: Cyclophosphamide, Vincristine, Doxorubicin and Prednisalone, ED: Epirubicin, Docetaxel, EDC: Epirubicin, Docetaxel and Capecitabine, EC-D: Epirubicin, Docetaxel and Cyclophosphamide, AC: Doxorubicin and Cyclophosphamide, AVCMF: Doxorubicin, Vincristine, Cyclophosphamide, Methotrexate and 5-FU, AT: Doxorubicin and Paclitaxel, wPTX: Paclitaxel, PTC: Paclitaxel, Traztusumab and Carboplatin, AD: Doxorubicin and Docetaxel, ACP: Doxorubicin, Cyclophosphamide and Paclitaxel, CD: Cyclophosphamide and Doxorubicin, ADC: Doxorubicin, Docetaxel and Cyclophosphamide.

Table 1b
Studies included in the assessment of axillary pCR.

Author/Year	Type of Study	N. pts. (ILC vs. IDC)	Inclusion criteria (TNM and subtype)	Definition of axillary pCR	No. Axillary pCR	Newcastle − Ottawa Scale
Tubiana-Hulin et al., 2006	Retrospective Cohort	118 vs. 742	T2-4, N0-2, M0 Mixed	No invasive in axillary nodes	304	6
Petruola et al., 2017	Retrospective Cohort	91 vs. 310	T1-4, N0-3 ER/PR + HER2-	No invasive or in situ in axillary nodes	44	6
Vugts et al., 2017	Retrospective Cohort	39 vs. 279	T1-4, N0-3, M0 Mixed	No micro/macro-metastases in nodes	59	6
Zeidman et al., 2020	Retrospective Cohort	3718 vs. 21,397	T1-4, N0-3, M0 ER/PR + HER-	No invasive in axillary nodes	3537	7

Table 2a
Studies included in assessment BCS vs. Non BCS.

Author/Year	Type of study	No. pts. (ILC vs IDC)	Inclusion criteria (TNM and subtype)	% Receiving BCS	% Not Receiving BCS	Newcastle − Ottawa Scale
Bollet et al., 2008	Retrospective Cohort	68 vs. 672	T2-3, N0-1, M0 Mixed	57%	43%	6
Boughey et al., 2009	Retrospective Cohort	84 (ILC only)	T1-4, N0-3, M0	30%	70%	6
Cho et al., 2013	Retrospective Cohort	6 vs. 407	T1-3, N0-3, M0 Mixed	28%	72%	7
Cocquyt et al., 2003	Prospective Cohort	26 vs. 101	>3 cm Mixed	47%	53%	7
Cristofanilli et al., 2005	Retrospective Cohort	122 vs. 912	T1-3, N0-2, M0 Mixed	31%	69%	6
Delpech et al., 2013	Retrospective Cohort	177 vs. 1718	T1-4, N0-1, M0 ER+, HER2 ±	33%	67%	6
Fitzal et al., 2011	Retrospective Cohort	67 vs. 258	T1-4, N0-1, M0 Mixed	66%	33%	7
Grover et al., 2017	Retrospective Cohort	130 vs. 4251	T1-3, N1-3, M0 Mixed	42%	58%	7
Gusic et al., 2018	Retrospective Cohort	17 vs. 133	T1-4, N0-3, M0 Mixed	68%	32%	6
Lips et al., 2012	Prospective Cohort	75 vs. 601	T1-4, N0-3, M0 Mixed	45%	55%	6
Loibl et al., 2006	RCT	105 vs. 444	T2-3, N0-2, M0 Mixed	75%	25%	6
Mathieu et al., 2004	Prospective Cohort	38 vs. 419	T2-4, N0-2, M0 Mixed	43%	57%	7
Nagao et al., 2011	Retrospective Cohort	29 vs. 500	T2-4, N0-2 Mixed	50%	50%	7
Petruola et al., 2017	Retrospective Cohort	91 vs. 310	T1-4, N0-3 ER/PR + HER2-	41%	59%	6
Rouzier et al., 2004	Retrospective Cohort	67 vs. 527	T2-3, N0-2, M0 Mixed	48%	52%	6
Straver et al., 2010	Retrospective Cohort	37 vs. 197	T1-3, N0-1, M0 Mixed	50%	50%	7
Tubiana-Hulin et al., 2006	Retrospective Cohort	118 vs. 742	T2-4, N0-2, M0 Mixed	51%	49%	6
Wenzel et al., 2007	Prospective Cohort	37 vs. 124	T0-3, N0-3, M0 Mixed	73%	27%	7

Table 2b
Studies included in assessment of margin status.

Author/Year	Type of study	No. pts. (ILC vs IDC)	Inclusion criteria (TNM and subtype)	Definition of clear surgical margin	No. Involved Surgical Margins	No. Clear Surgical Margin	Newcastle − Ottawa Scale
Loibl et al., 2006	RCT	105 vs. 444	T2-3, N0-2, M0 Mixed	No invasive or in situ at surgical margin	99	450	6
Fitzal et al., 2011	Retrospective Cohort	67 vs. 258	T1-4, N0-1, M0 Mixed	Tumor margin of >1 mm	17	197	7
Tubiana-Hulin et al., 2006	Retrospective Cohort	118 vs. 742	T2-4, N0-2, M0 Mixed	Not provided by authors	49	391	6
Straver et al., 2010	Retrospective Cohort	37 vs. 197	T1-3, N0-1, M0 Mixed	Tumor margin of >2 mm	9	120	7
Mathieu et al., 2004	Prospective Cohort	38 vs. 419	T2-4, N0-2, M0 Mixed	No invasive at surgical margin	49	165	7
Boughey et al., 2009	Retrospective Cohort	84 (ILC only)	T1-4, N0-3, M0	Not provided by authors	11	13	6
Volders et al., 2016	Retrospective Cohort	71 vs. 532	Mixed	No invasive at surgical margin	152	474	6

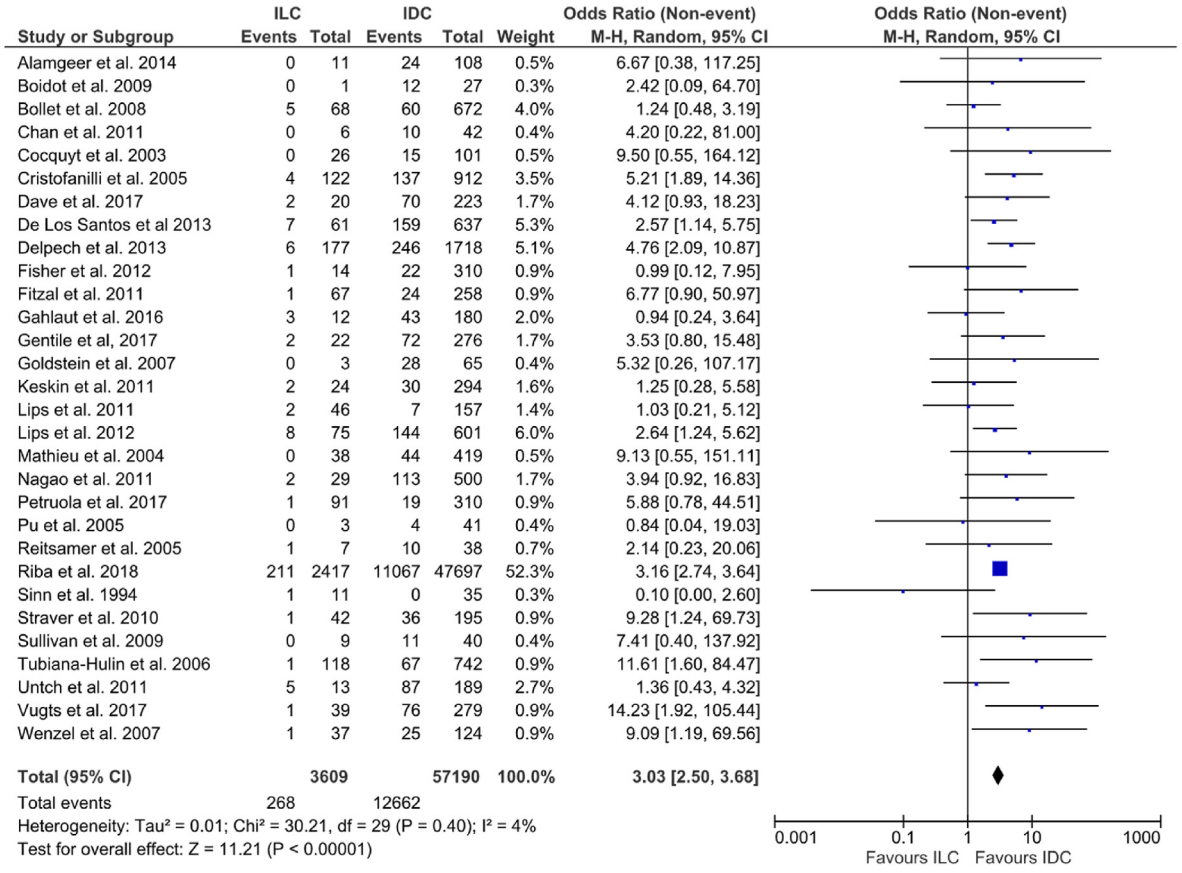

Fig. 2. Forrest plot of odds ratio (OR) and 95% Confidence Interval (CI) for pathological complete response (pCR) in invasive lobular carcinoma (ILC) vs. invasive ductal carcinoma (IDC) breast cancer patients following neoadjuvant chemotherapy (NACT).

3.3. Breast pathological complete response

Overall, pCR following NACT was 21% across all cases (12,930/60,799). Rates of pCR for ILC ranged from 0 to 38.5% and 0–46% for IDC among included studies. The pooled pCR rate was 7.4% for ILC and 22.1% for IDC. Patients with IDC were more likely to achieve breast pCR (OR: 3.03, 95% CI: 2.5–3.68, $p < 0.00001$, $I^2 = 4\%$) (Fig. 2).

3.4. Axillary pathological complete response

Four studies including 17,657 patients provided data in relation to axillary pCR following NACT:. Overall, axillary pCR was 22.3% among all patients (3944/17,657). Rates of axillary pCR ranged from 5.3% to 25.4% for ILC and 16.3%–43.6% for IDC. Patients with IDC were more likely to achieve breast pCR (13.4% vs. 23.6% [OR: 2.01, 95% CI: 1.77–2.28, $p < 0.00001$, $I^2 = 27\%$] (Fig. 3).

3.5. Breast conserving surgery

Overall, BCS was performed in 44.5% (5917/13,295) of cases. BCS in ILC varied from 0%–61.1% and from 28.2% to 79% in IDC. Patients with IDC were more likely to undergo BCS [33.3% vs. 45.7% (OR: 2.14, 95% CI: 1.87–2.45, $p < 0.00001$), $I^2 = 41\%$] (Fig. 4.) Seven studies including 643 ILCs and 4420 IDCs reported on tumour staging and size; 52.0% of ILCs and 35.3% of IDCs were T3-4 ($p < 0.00001$, χ^2).

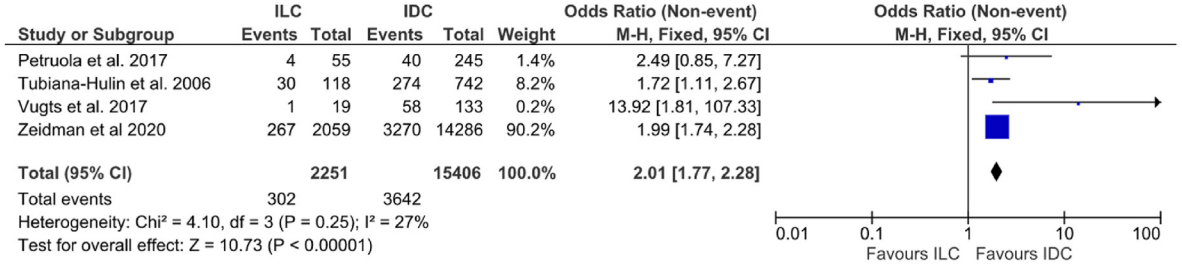

Fig. 3. Forrest plot of odds ratio (OR) and 95% Confidence Interval (CI) for the rates of axillary pathological complete response (pCR) in invasive lobular carcinoma (ILC) vs. invasive ductal carcinoma (IDC).

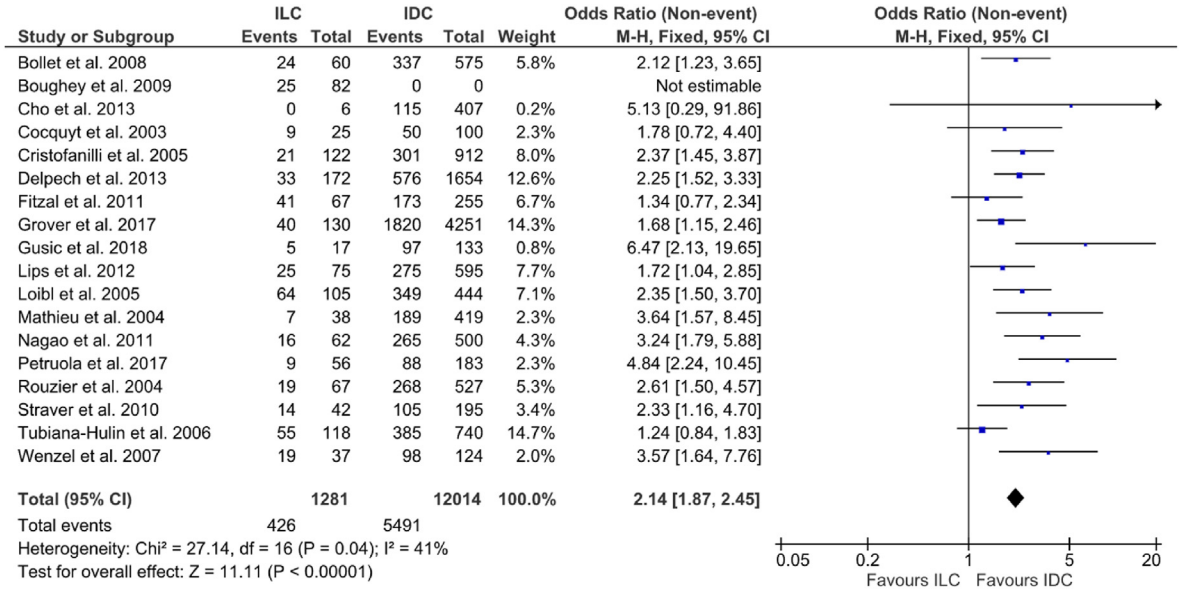

Fig. 4. Forrest plot of odds ratio (OR) and 95% Confidence Interval (CI) for the rates of breast conserving surgery (BCS) in invasive lobular carcinoma (ILC) vs. invasive ductal carcinoma (IDC).

3.6. Positive surgical margins following excision

Eight studies provided information on 2301 patients regarding the success of the index operation following NACT, either by reporting the margin status directly or the proportion of cases requiring re-operation for incomplete excision. Of the included studies, there was an overall margin positivity rate of 17% (391/2301). Among the individual studies margin positivity ranged from 9.8% to 75% in ILC vs. 4%–19.8% in IDCs. Patients with ILC were more likely to have positive margins [36% vs.13.5% (OR: 4.84, 95% CI 2.88–8.15, $p < 0.00001$) $I^2 = 61\%$] (Fig. 5). No further analysis was made on the distinction between the type of index operation (BCS vs. mastectomy) or reoperation (Re-excision of involved margins vs. completion mastectomy).

3.7. Molecular subtype

Expression of ER, PR and HER2 receptor is of paramount importance when considering the response of IDC and ILC to NACT. Among the included studies 6 studies provided detail of hormone and HER2 receptor status among their included patients [25,29,31,39,42,47]. Receptor status was not reported consistently across all 6 studies and outcomes of were not stratified according to ILC and IDC molecular subtypes. As such, a pooled analysis was not possible from the available data. Among individual studies, IDC had a greater proportion of HER2 enriched and triple negative breast cancer, while ILC had a greater proportion of hormone sensitive tumours (Supplementary Table 1.)

4. Discussion

This is the largest study of its kind, including a number of large, recent studies not yet incorporated into a meta-analysis such as this [19,28,32,33,35,44,47,54,55,57,58]. The additional studies have enabled the authors to refine inclusion criteria, disregarding conference abstracts in favour of peer reviewed articles only, a discretion not afforded previous authors [15]. This analysis updates pCR and BCS rates while adding additional outcomes (i.e.: margin status and axillary pCR), in our appraisal of the oncological and surgical outcomes following NACT prescription in cases of ILC versus IDC.

In this analysis, overall pCR rates were more likely in IDC patients in receipt of NACT than their ILC counterparts (OR: 3.03, 95% CI: 2.50–3.68). pCR following NACT is a renowned biomarker of

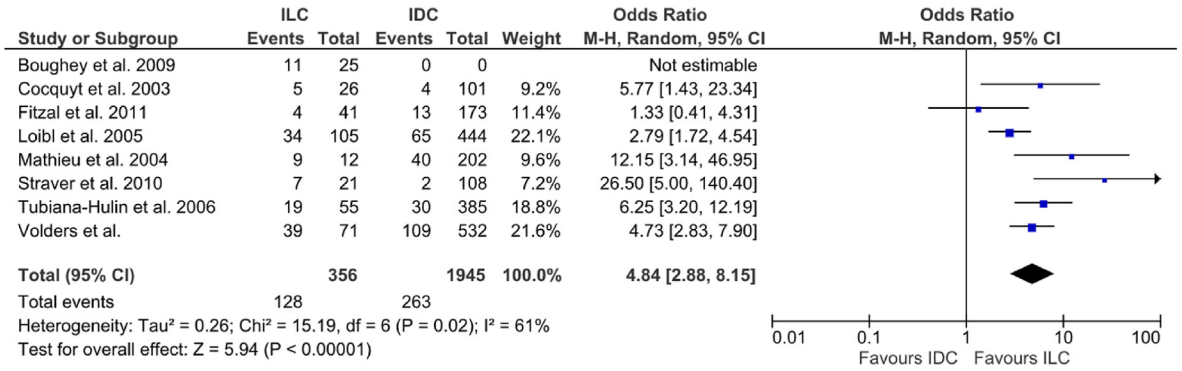

Fig. 5. Forrest plot of odds ratio (OR) and 95% Confidence Interval (CI) for the rates of positive margins post resection in invasive lobular carcinoma (ILC) vs. invasive ductal carcinoma (IDC).

prognosis [45,47,59,60], with those achieving pCR having an increased recurrence free survival of 20% versus those with residual disease [47]. Although the objective of the current analysis was not to quantify pCR as a surrogate of enhanced survival, comparisons in pCR within histological subtype and survival poses questions of interest to the oncologist, particularly when data from the current analysis illustrates a 3-fold discrepancy in expected pCR rates (7.4% for ILC vs. 22.1% for IDC). This data suggests achieving pCR to be an unlikely outcome in ILC following NACT. Given the strong hormone receptor expression in ILC, these patients may be better served with neoadjuvant endocrine therapy in an attempt to achieve tumour downstaging [61], while sparing the toxicities associated with NACT [62].

In patients with axillary involvement, axillary pCR has been demonstrated in previous analyses to be a more accurate prognostic biomarker than breast pCR [39,56,60,63–65]. For patients with node positive disease, our analysis illustrates patients with IDC are twice as likely to achieve axillary pCR than their ILC counterparts which may facilitate less invasive axillary surgery consequently. Nevertheless, there is significant evidence that patients with ILC and nodal involvement are more likely to achieve axillary pCR than overall pCR (ILC rate of axillary pCR – 22.3%, ILC overall pCR rate – 7.4%) This may indicate that the attainment of pCR in the axilla alone is more achievable due to a relatively lower burden of disease in this location [66], but may also indicate an important molecular distinction between the primary tumour and the axillary metastasis.

When considering pCR of the breast or axilla, breast cancer histological subtype should not be taken in isolation. ILC have the overwhelming tendency to express strong estrogen receptor positivity and assume the luminal A breast cancer (LABC) molecular subtype (90–95% of ILC cases). In contrast, only 50% of ductal cancers manifest the LABC phenotype [67–70]. LABC is considered classically to be chemoresistant disease [71–73], indicating cancer molecular subtyping must be assessed for included patients. Six studies provided details of estrogen receptor (ER), progesterone receptor (PgR) and human epidermal growth factor receptor-2 (HER2) status among both cohorts: IDC were associated with triple negative and HER2 enriched molecular subtypes, while luminal disease was associated with ILC [25,29,31,40,42,47]. This data implicates molecular subtyping as a confounding factor in analyses comparing the respective responses of ILC and IDC, which must be considered before attributing oncological and surgical outcomes, such as pCR and BCS rates, to histological subtyping alone. Therefore, when determining the 'true' impact of histological subtype on pCR, future translational research must focus on matching ILC and IDC cases based on ER, PgR and HER2 status, mitigating molecular subtyping as a confounder. Furthermore, clinicopathological data which contribute to NACT response, such as tumour grade [74] and Ki-67 proliferation indices [75,76] must be considered in order to truly appraise the variability in outcomes between ILC and IDC.

The current analysis of post-NACT BCS comparing ILC and IDC is the largest performed in medico-oncological literature, and includes data on an additional 4495 patients not available to previous authors [15]. Findings in this study are consistent with the previous analysis, with BCS rates following NACT twice as likely in patients with IDC versus those with ILC. However we must acknowledge further confounding data; results from 7 included studies provided data in relation to tumour staging, with 52.0% of ILCs being T3/4 versus 36.0% of IDCs [21,29,31,40,44,52,56]. In reiteration of our recommendations in relation to pCR and immunohistochemical data, more selective matching of clinicopathological features of ILC and IDC cases is warranted in future to yield more meaningful results. While ILC disease tend to be large cancers requiring mastectomy [66] reliance upon NACT to facilitate BCS serves as a poorer strategy of tumour downstaging compared to in IDC disease. The relative failure of the NACT to achieve BCS in ILC is demonstrated in our findings illustrating that margin positivity rates were significantly higher in ILC post NACT than in IDC. This finding is confounded by the higher prevalence of large tumour size as outlined above. In considering the clinical significance of these findings however, it should be noted that with the use of radiotherapy, the decision to treat a patient with BCS or mastectomy result in similar breast cancer specific survival as outlined by Fodor et al. [77].

Traditionally, NACT was indicated in the setting of locally-advanced stage IIB/III disease, or in patients where a tumour size reduction would improve surgical resectability [6]. In the molecular era, clinical indications for NACT have expanded, such that neoadjuvant strategies are considered in early-stage and operable disease [78,79]. There has been a reported increase in NACT prescription in early breast cancer between 2008 and 2017 (20% vs. 57.7%) [80] and the increased use occurs across all molecular subtypes [81]. While these expansion of indications for NACT may imply progressive practice in the setting of breast carcinoma, clinicians should proceed with caution within the context of ILC disease – the current analysis suggests these patients are not as well served with NACT as global perceptions may believe. The same is also true of the prescription of adjuvant chemotherapy for ILC patients, which has been expertly outlined in a recent meta-analysis by Trapani et al. where a large proportion of patients being treated for ILC experienced poorer outcomes after chemotherapy administration when compared to other histopathological breast cancer subtypes [82]. The authors highlight that ILC should be considered distinct clinical entity to other breast epithelial cancers, such as IDC, possessing several unique oncological and surgical implications when included indistinctly in conventional breast cancer management. The solution for the ILC cohort, which have a strong tendency towards hormone positivity, may be a more widespread use of Neoadjuvant Endocrine Therapy (NET); in their review, Sella et al. reported that NET prescription is underutilised despite its capabilities of achieving tumour downstaging in select cases, indicating that NET may have a more conventional use in prospective HR + breast cancer management [83,84]. Similarly, Davey et al. illustrated the efficacy of NET following low-risk substratification using the 21-gene recurrence score expression assay in the setting of locally advanced estrogen receptor positive breast cancers in their recent meta-analysis [84]. Similar to the results of the current study, these previous authors highlight the value of NET as a modern management strategy of HR + breast cancers, particularly in the setting of double hormone positive (ER+/PR+) lobular disease as has been previously outlined in cases of low-risk disease [85].

In conclusion, as current thresholds for prescribing cytotoxic chemotherapy become lowered even further, histological breast cancer subtype must become incorporated into the paradigm for breast cancer therapeutic decision making, and given similar consideration to other parameters such as molecular subtype, tumour staging and nodal status. The current analysis suggests ILC histology are less likely to derive oncological or surgical benefit from NACT prescription when compared to their counterparts with ductal morphology. In the era of precision medicine, multidisciplinary therapeutic decision making should incorporate these findings into clinical practice to further personalise oncological breast cancer patient care.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.11.017.

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