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Clinical benefit from neoadjuvant chemotherapy in oestrogen receptor-positive invasive ductal and lobular carcinomas

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Background: The aim of this study was to compare clinical and pathological outcomes after neoadjuvant chemotherapy between oestrogen receptor (ER)-positive invasive pure lobular carcinoma (ILC) and invasive ductal carcinoma (IDC).

Methods: This analysis included 1895 patients ($n = 177$ ILC; $n = 1718$ IDC), with stage I–III breast cancer, who received neoadjuvant chemotherapy. Clinical and pathological response rates, the frequency of positive surgical margins and rate of breast-conserving surgery were compared.

Results: There was a trend for fewer good clinical responses in ILC compared with IDC. Tumour downstaging was significantly less frequent in ILC. Positive or close surgical resection margins were more frequent in ILC, and breast-conserving surgery was less common ($P < 0.001$). These outcome differences remained significant in multivariate analysis, including tumour size, nodal status, age, grade and type of chemotherapy. Invasive pure lobular carcinoma was also associated with a significantly lower pathological complete response (pCR) rate in univariate analysis, but this was no longer significant after adjusting for tumour size and grade.

Conclusion: Neoadjuvant chemotherapy results in lower rates of clinical benefit, including less downstaging, more positive margins and fewer breast-conserving surgeries in ER-positive ILC compared with ER-positive IDC. Pathological complete responses are rare in both groups, but do not significantly differ after adjusting for other variables.

Pure invasive lobular carcinomas (ILCs) account for 10–15% of all breast cancers and are almost invariably oestrogen receptor (ER)-positive and tend to have low histological grades (grades I and II) (Fisher *et al*, 1975; Wellings *et al*, 1975; World Health Organisation, 1982). Invasive pure lobular carcinoma is characterised by small, round cells with scant cytoplasm that infiltrate the stroma in single files, which makes it more difficult to palpate or detect this type of cancer with mammogram (Katz *et al*, 2007). This histological feature may also lead to higher rates of positive surgical margins after breast-conserving surgery (Porter *et al*, 1999; Molland *et al*, 2004; Waljee *et al*, 2008; Boughey *et al*, 2009). The rates of pathological complete response (pCR) to neoadjuvant chemotherapy are also significantly lower in ILC compared with invasive ductal carcinomas (IDCs) (Cristofanilli *et al*, 2005). Several investigators have suggested that ILC histology is a relative contraindication for preoperative chemotherapy because the expected benefit is modest because of less frequent clinical responses, low pCR rates and more frequent positive surgical

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margins (Katz *et al*, 2007; Boughey *et al*, 2009; Purushotham *et al*, 2010).

Comparing outcomes between ILC and IDC in general has substantial limitations because of the uneven distribution of confounders, including histological grade and ER status between these two distinct histological subtypes. The question whether histology itself, after adjusting for differences in grade and ER, remains a predictor of lower response rates and higher rates of positive margins remain controversial. Previous studies performed multivariate analysis to address this question and most results suggested that histology remains an important independent factor. However, Boughey *et al* (2009) and Wagner *et al* (2009) reported frequent clinical responses in ILCs to preoperative chemotherapy and margin positivity rates after breast-conserving surgery were similar between patients who received neoadjuvant chemotherapy and those who did not. In this study, we compare rates of pathological response, surgical margin status and rates of breast-conserving surgery between ER-positive ILC and IDC that received neoadjuvant chemotherapy. We excluded ER-negative tumours from the analysis to eliminate an important confounder.

PATIENTS AND METHODS

Patient population. Patients were identified for this study from a prospectively maintained clinical database of the University of Texas MD Anderson Cancer Centre. Patients were selected for inclusion if they had ER-positive stage I–III breast cancer diagnosed between 1990 and 2010 and received neoadjuvant chemotherapy. This search initially identified 2592 patients. After reviewing the medical records, the following patients were excluded: male breast cancer ($n=12$), patients with axillary metastasis without an identifiable primary breast tumour ($n=13$), metastatic disease at diagnosis ($n=13$), patients who received preoperative radiation therapy alone ($n=10$) or underwent partial excisional biopsy before neoadjuvant chemotherapy ($n=214$). We also excluded patients with rare or mixed histological subtypes ($n=224$) to focus on the comparison of pure lobular *vs* pure ductal carcinomas. Patients with overexpression of human epidermal growth factor receptor-2 (HER2) were also included. Review of medical records also revealed miscoding of ER and progesterone receptor (PR) results in 21 patients who had hormone receptor-negative breast cancer and in 189 patients who received neoadjuvant endocrine therapy alone. A total of 1895 patients were included in the final analysis (Supplementary Figure 1).

The patients received neoadjuvant chemotherapy with anthracycline-based regimen ($n=236$), with a taxane-based regimen ($n=137$) or with a combination of an anthracycline and taxane ($n=1515$); 263 patients also received trastuzumab in combination with neoadjuvant chemotherapy. Postoperatively, 451 patients (24%) received adjuvant chemotherapy and 1522 (81%) received adjuvant hormonal therapy. The Institutional Review Board of the University of Texas MD Anderson Cancer Centre (MDACC) in Houston approved this study.

Assessment of clinical and pathological outcomes. The pretreatment tumour size was determined by physical examination and mammography. If the two methods yielded discordant results, the radiological measurement was used as the tumour's size. Pretreatment lymph node status was evaluated with a combination of clinical and ultrasonographic examination. If ultrasonogram showed suspicious lymph nodes, a diagnostic fine-needle aspiration was performed. Post-treatment, residual cancer size was determined by pathological examination. All outside pathology reports and slides were reviewed by a dedicated breast pathologist at MDACC to confirm diagnosis and to assess the adequacy of ER, PR and HER2 measurements (World Health Organisation, 1982). Oestrogen receptor and PR positivity were defined as nuclear staining $\geqslant 10\%$ and HER2 positivity was defined as $3+$ staining on immunohistochemistry or gene amplification by FISH. Histological grade was assessed following the modified Black's nuclear grading system.

After completion of neoadjuvant chemotherapy, 1827 (96.4%) patients underwent primary breast surgery and 1826 (96.5%) had axillary lymph node staging (level I and II dissection or sentinel lymph node biopsy). If invasive or *in situ* carcinomas were seen within 2 mm of the surgical margin on microscopic examination (i.e. positive or close tumour margins), a second operation was performed to achieve clear margins. Pathological complete response was defined as no evidence of invasive carcinoma in the breast and axillary lymph nodes.

Statistical analysis. The χ^2 test (or Fisher's exact test when the sample size was small) was used to evaluate associations between categorical variables and histological subtype. The Student's *t*-test was used for continuous variables. We also performed stratified analysis by histological grade (grade I/II *vs* III). Univariate logistic regressions were performed, including histological subtype, nuclear grade, nodal status tumour size, multifocality, age, race, menopausal status, HER2 status, Ki-67 score and the type of neoadjuvant chemotherapy as variables to identify predictors of breast-conserving therapy, positive margins and pCR. From this model, an odds ratio (OR) for each variable was determined with a 95% confidence interval (CI). All significant variables from the univariate analysis were included in a subsequent multivariate analysis. Median overall survival and distant disease-free survival were determined using the Kaplan–Meier methods. All analyses were performed using R package with Survival, Design, Hmisc, Rpart and Lexis libraries (http://lib.stat.cmu.edu//R/CRAN/).

RESULTS

Patient characteristics are summarised in Table 1: 177 patients had ILC (9%), and 1718 patients had IDC (91%). Patients with ILC were older, had larger and lower grade (grades I/II) tumours and had fewer HER2-positve cancers compared with IDC. Anthracycline-based or taxane and anthracycline combination regimens were used equally frequently in both histological groups, but trastuzumab use was more common in IDC (Table 1).

Significant downstaging was observed in both histological types ($P<0.0001$) (Supplementary Figure 2A), but it was more common among IDC. Forty-one per cent of ILCs had lower tumour T stage after neoadjuvant chemotherapy compared with baseline, whereas similar downstaging occurred in 64% of IDCs ($P<0.0001$) (Supplementary Figure 2B).

Positive or close surgical resection margins were significantly more frequent in ILC patients (19 *vs* 11%; $P=0.001$) and this remained significant even after multivariate analysis, including tumour size and grade (OR = 1.82; 95% CI, 1.13–2.93; $P=0.01$). At the end, breast-conserving surgery was less frequent in ILC patients than in IDC patients (19 *vs* 34%; $P<0.001$) (Table 2) and histology remained an independent predictor of mastectomy (OR = 1.86; 95% CI, 1.15–2.99; $P=0.01$) even after adjusting for age, tumour grade, initial tumour size, multifocality, nodal status and clinical stage (Table 3).

Invasive lobular histology was also associated with significantly lower pCR rates (3.5 *vs* 14%; $P<0.001$) (Table 2). In univariate analysis, multifocal tumour, higher tumour size, node-positive status and lower nuclear grade were also significantly associated with lower pCR rates. In multivariate analysis, including the above variables, histology was no longer significant (Table 4). Similarly, in an analysis stratified by grade, pCR rates were no longer

Table 1. Patient demographic and treatment clinical characteristics

	ILC ($n=177$)		IDC ($n=1718$)		
Demographic or clinical characteristics	**No. of patients**	**%**	**No. of patients**	**%**	**χ^2 *P*-value**
Age (years)					
Median	54		50		<0.001
Range	35–62		21–83		
Race					
Asian	6	3	96	6	0.51
Black	19	11	223	13	
White	150	85	1375	80	
Other	2	1	24	1	
Menopausal status					
Yes	114	64	899	52	0.003
Concurrent bilateral breast cancer					
Yes	16	9	74	4	0.008
Tumour size (cm)					
Median	4.5		3.4		<0.001
Range	0.4–12		0.4–20		
Multifocal tumour					
Yes	42	24	326	19	0.1
T stage					
T1–2	99	56	1187	69	<0.001
T3–4	78	44	529	31	
N stage					
N1 or sup	102	58	1089	63	0.15
AJCC stage					
I/II	111	63	1076	63	0.94
III/IV	66	37	641	37	
HER2 status					
Negative	84	47	793	46	0.006
Positive	13	7	288	17	
Nuclear grade					
I–II	145	82	722	42	<0.001
III	24	14	980	57	
Ki-67 score[a]					
<20	48	27	224	13	<0.001
⩾20	28	16	518	30	
Neoadjuvant chemotherapy regimen[b]					
Anthracycline and taxane based	137	77	1378	80	0.4
Anthracycline-based only	27	15	209	12	0.5
Taxane-based only	13	7	124	7	1
Trastuzumab	9	5	254	15	<0.001
Neoadjuvant hormonotherapy in combination with chemotherapy	3	2	54	3	0.4
Adjuvant chemotherapy	32	18	419	24	0.07
Adjuvant hormonotherapy	146	82	1382	80	0.6
Adjuvant radiotherapy	146	82	1311	76	0.08

Abbreviations: A = adriamycin; AJCC = American Joint Committee on Cancer; C = cyclophosphamide; E = epirubicin; F = 5-fluorouracil; H = herceptin; HER2 = human epidermal growth factor receptor 2; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; T = taxane.

[a]Ki-67 score were available in 76 patients in ILC group and in 742 IDC group.

[b]The most common regimen consisted of T, F, A or E and C (T/FAC or FEC), $n=1106$; FAC or FEC, $n=230$; FAC or FEC ± H and TH (TH/FAC or FEC ± H), $n=218$; ET or AT, $n=74$; T alone, $n=91$.

significantly different between ILC and IDC (Supplementary Table 1).

Disease-free survival and overall survival were evaluated with a median follow-up time of 44 months (range, 1–221 months). In all, 290 patients had developed a recurrence (222 distant recurrences only, 19 local recurrences only, 49 distant and local recurrences), and 262 had died. Histological type was not associated with significant difference in overall survival (hazard ratio = 1.01; 95% CI, 0.7–1.47; $P = 0.9$), disease-free survival (hazard ratio = 0.92; 95% CI, 0.66–1.28; $P = 0.13$) (Figure 1) or local recurrence-free survival (hazard ratio = 0.8; 95% CI, 0.36–1.90; $P = 0.65$) (Supplementary Figure 3).

Table 2. Surgical and pathological outcomes

	ILC ($n = 177$)		IDC ($n = 1718$)		
	No. of patients	%	No. of patients	%	χ^2 *P*-value
Final surgical outcome					
Conservative	33	19	576	34	<0.001
Mastectomy	139	79	1078	63	
No surgery	5	3	64	4	
Pathological response					
No pCR	165	93	1404	82	<0.001
pCR	6	3	246	14	

Abbreviations: IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; pCR = pathological complete response.

DISCUSSION

We examined if patients with pure ILC benefit differently from neoadjuvant chemotherapy than patients with IDC. Approximately, 30–40% of IDCs are ER-negative and these cancers have different chemotherapy sensitivity and clinical behaviour compared with ER-positive IDCs (Arpino *et al*, 2004; Rouzier *et al*, 2005). Previous studies tried to adjust for the variable distribution of ER status by performing multivariate analysis. However, multivariate analysis has limitations particularly when confounders are only partially independent (Katz, 2003). In this study, we excluded ER-negative IDCs from the current analysis to address directly whether histology confers significant differences in sensitivity to neoadjuvant chemotherapy. Chemotherapy sensitivity was measured by pathological tumour response rates and the rate of breast-conserving surgery.

Similar to previous reports, we observed low pCR rates in both histological subtypes, IDC (14%) and ILC (3.5%) (Cocquyt *et al*, 2003; Mathieu *et al*, 2004; Cristofanilli *et al*, 2005; Tubiana-Hulin *et al*, 2006; Katz *et al*, 2007; Sullivan and Apple, 2009; Huober *et al*, 2010; Straver *et al*, 2010). However, pCR rates were not significantly different by histological type after adjusting for differences in tumour grade. This is different from earlier reports that suggested significantly lower pCR rates in ILC. Our results show that low- and intermediate-grade ILC and IDC both have similar, very low pCR rates. This result supports the idea that response to neoadjuvant chemotherapy in terms of pCR is more related to intrinsic tumour characteristics, reflected to some extent in grade than histology itself (Lips *et al*, 2012). Pathological complete response is a powerful early surrogate of good survival in ER-negative and HER2-positive cancers, but its prognostic value is less important in ER-positive cancers because many patients with

Table 3. Predictors of mastectomy after neoadjuvant chemotherapy

	Univariate analysis			Multivariate analysis		
Factor	**OR[a]**	**95% CI**	***P*-value**	**OR[a]**	**95% CI**	***P*-value**
Age (years)	0.99	0.98–1.00	0.02	0.99	0.98–1.00	0.02
Multifocal tumour			<0.001			
No	1.00	—	—	1.00	—	—
Yes	4.6	3.28–6.46		3.85	2.70–5.48	<0.001
Tumour size (cm)	1.42	1.33–1.51	<0.001	1.30	1.21–1.40	<0.001
N stage						
N0	1.00	—	—	1.00	—	—
N1 or sup	2.03	1.66–2.48	<0.001	1.39	1.09–1.77	0.007
AJCC stage						
I/II	1.00	—	—	1.00	—	—
III/IV	3.51	2.78–4.41	<0.001	1.89	1.41–2.54	<0.001
Nuclear grade						
I	1.00	—	—	1.00	—	—
II	0.81	0.47–1.37	0.43	1.43	0.75–2.69	0.27
III	0.51	0.35–1.00	0.05	0.85	0.44–1.62	0.61
Histological subtype						
IDC	1.00	—	—	1.00	—	—
ILC	2.25	1.52–3.33	<0.001	1.86	1.15–2.99	0.01

Abbreviations: AJCC = American Joint Committee on Cancer; CI = confidence interval; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; OR = odds ratio.
[a]OR = 1 is the reference; OR < 1, factor associated with lower mastectomy rate; OR > 1, factor associated with higher mastectomy rate.

Table 4. Predictors of pathological complete response

	Univariate analysis			Multivariate analysis		
Factor	**OR[a]**	**95% CI**	***P*-value**	**OR[a]**	**95% CI**	***P*-value**
Age (years)	0.99	0.98–1	0.2	1	0.99–1.01	0.8
Multifocal tumour[a]						
No	1.00	—	—	1.00	—	—
Yes	0.69	0.48–1	0.05	0.75	0.5–1.12	0.15
Nuclear grade						
I	1.00	—	—	1.00	—	—
II	4.91	0.67–36.14	0.1	2.91	0.38–22.56	0.31
III	20.33	2.81–147.17	0.002	11.26	1.47–86.39	0.01
Baseline T stage						
T1–T2	1.00	—	—	1.00	—	—
T3–T4	0.69	0.51–0.93	0.01	0.65	0.46–0.92	0.01
Baseline N stage						
N0	1.00	—	—	1.00	—	—
N1 or sup	0.73	0.56–0.96	0.02	0.66	0.49–0.9	0.008
Histological subtype						
IDC	1.00	—	—	1.00	—	—
ILC	0.21	0.09–0.47	<0.001	0.5	0.19–1.3	0.1
Neoadjuvant chemotherapy regimen						
Taxane based[b]	2.67	1.56–4.59	<0.001	2.14	1.2–3.84	0.01
Traztuzumab[c]	6	4.44–8.12	<0.001	5.03	3.64–6.95	<0.001

Abbreviations: CI = confidence interval; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; OR = odds ratio; pCR = pathological complete response.
[a]OR = 1 is the reference; OR < 1, factor associated with lower pCR rate; OR > 1, factor associated with higher pCR rate.
[b]Taxane-based regimen was compared with no taxane-based regimen.
[c]Trastuzumab regimen was compared with no trastuzumab regimen.

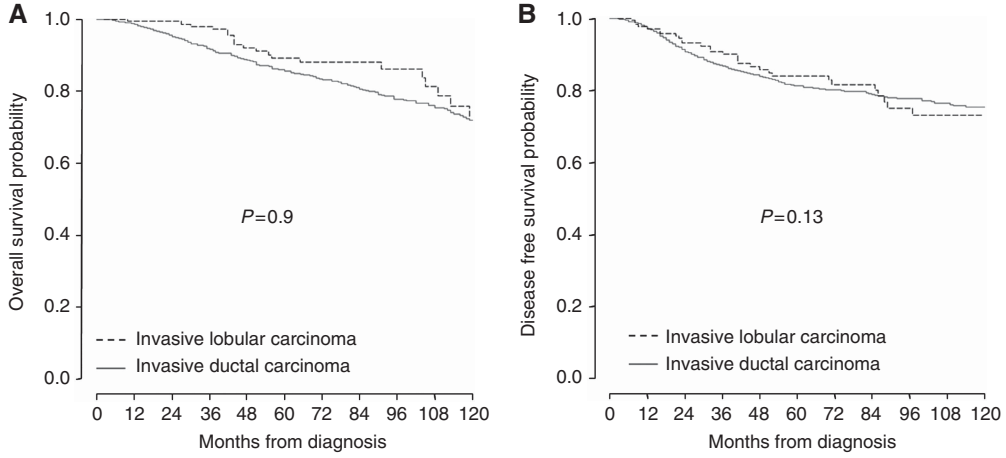

Figure 1. (**A**) Overall survival probability and (**B**) disease-free survival probability by histological subtype.

extensive residual cancer continue to do well probably because of the benefit from adjuvant endocrine therapy (von Minckwitz *et al*, 2012). Our findings confirm that survivals were similar for both ER-positive IDC and ILC. We recognise that a median follow-up of 44 months is short for ER-positive breast cancers, which is a limitation of the current analysis. However, it is unlikely that late recurrence rates would differ significantly by histology among ER-positive cancers.

An important clinical benefit from neoadjuvant chemotherapy is clinical tumour response that leads to downstaging and smaller surgical resection volume (Fisher *et al*, 1998; Boughey *et al*, 2006). Tumour resection margins were more commonly positive or close

(⩽2 mm) in ILC (19 *vs* 11%) and the rate of breast-conserving surgery was also lower (19 *vs* 34%). These differences in clinical benefit remained significant after adjusting for other clinical variables, including grade and tumour size. These observations are consistent with the majority of the literature that reports low rates of breast conservation therapy for patients with ILC following neoadjuvant chemotherapy (Soucy *et al*, 2008; Boughey *et al*, 2009). These results collectively indicate that clinical benefit from neoadjuvant chemotherapy in operable ER-positive ILC is less compared with ER-positive IDCs due to the inherently lower chemotherapy sensitivity of these cancers and their unique anatomical features, which make determination of cancer margins more difficult intraoperatively.

Our study is the largest report of outcomes of ILC subtype after neoadjuvant chemotherapy, but there were some limitations. As a retrospective survey there was heterogeneity in our population, especially regarding chemotherapy regimens. Moreover, important variables, such as proliferation (i.e. Ki-67 staining), were not available. However, nuclear grade may be considered as a crude surrogate for proliferation activity.

However, a simple conclusion that ILC does not respond to neoadjuvant chemotherapy would represent an oversimplification. Forty-one per cent of ILCs had lower tumour T stage compared with baseline after neoadjuvant chemotherapy. What further complicates clinical decision-making for patients with ILC is that clinical response rates over 50% have also been reported with the use of 3–6 months of neoadjuvant endocrine therapy alone (Eiermann *et al*, 2001; Cataliotti *et al*, 2006; Semiglazov *et al*, 2007; Mlineritsch *et al*, 2008; Mustacchi *et al*, 2009; Ellis *et al*, 2011). In addition, the majority of patients with ILC have a low or intermediate recurrence score (Oncotype DX, Redwood, CA, USA), which is associated with no or very modest benefit from adjuvant chemotherapy in terms of improved survival (Kelly *et al*, 2010; Mook *et al*, 2010; Allison *et al*, 2012). Taking all this information together, it is reasonable to conclude that most patients with ILC are unlikely to derive substantial short-term clinical benefit (substantial tumour reduction with clear margins or pathological CR) from neoadjuvant chemotherapy. However, ILC may derive similar long-term survival benefit from neoadjuvant chemotherapy as ER-positive IDCs, but this benefit is likely to be modest.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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