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Neoadjuvant Chemotherapy in Invasive Lobular Carcinoma May Not Improve Rates of Breast Conservation

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ABSTRACT

Background. Patients with invasive lobular carcinoma (ILC) experience a lower pathological complete response rate to neoadjuvant chemotherapy than patients with invasive ductal carcinoma. This study was intended to evaluate the impact of neoadjuvant chemotherapy in ILC on breast-conserving surgery (BCS) rates.

Methods. Two-hundred eighty-four consecutive patients with pure ILC treated between May 1998 and September 2006 were reviewed. Surgical procedures and long-term outcomes were compared between patients receiving neoadjuvant chemotherapy and those receiving surgery first.

Results. Neoadjuvant chemotherapy was administered to 84 patients; 200 patients underwent surgery first. The mean tumor size in the neoadjuvant group (4.9 cm) was significantly larger than in patients who underwent surgery first (2.5 cm, $p < 0.0001$). In the neoadjuvant group, clinical complete response was seen in 10% and partial response in 59%. Overall BCS rates were 17% in the neoadjuvant group compared with 43% in the surgery-first group ($p < 0.0001$). When controlled for initial tumor size, there was no difference (all $p > 0.05$) between the groups in terms of (1) the proportion of patients who underwent an initial attempt at BCS, (2) rate of failure of BCS or (3) the proportion of patients undergoing BCS as their final procedure. With a mean follow-up of 47 months, local recurrence (LR) rates were similar between the two groups (1.2% versus 0.5%, $p = 0.5$).

Conclusion. The use of neoadjuvant chemotherapy does not increase the rates of breast conservation in patients with pure ILC.

Invasive lobular carcinoma (ILC) is the second most common form of invasive breast cancer, accounting for 4–15% of all breast cancers.^{1–3} While ILC and invasive ductal carcinoma (IDC) are often treated similarly, there is growing appreciation that there are differences in response to treatment and long-term outcomes based on histology.

Neoadjuvant chemotherapy is increasingly used in patients with breast cancer. Initially utilized for inflammatory and locally advanced breast cancer, it is now often used to decrease the size of the primary breast tumor in order to achieve breast conservation. National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 was the initial pivotal study that showed a change in breast conservation rate from 60% in patients undergoing surgery first compared with 68% in patients receiving neoadjuvant chemotherapy.⁴ This study included patients with both invasive ductal and invasive lobular histology.

Whether patients with ILC can achieve successful downsizing that would allow for BCS is an important question since response to neoadjuvant chemotherapy is often less impressive in ILC when compared with IDC. ILC has been shown to be an independent predictor for ineligibility for BCS.⁵ Pathological complete response rates have been reported in multiple studies to be lower in patients with ILC (0–3%) compared with IDC (9–20%).^{6–8} These studies also showed breast-conservation rates to be lower in patients with ILC (16–51%) compared with IDC (29–79%).^{6–8} All these studies compare patients with ILC to patients with IDC. Thus, although patients with ILC tend to have lower rates of BCS, it is not clear whether the use

of neoadjuvant chemotherapy improves on the baseline BCS rates for ILC patients. Therefore, we retrospectively reviewed our population of patients with ILC in order to assess the impact of neoadjuvant chemotherapy on BCS rates in patients with ILC compared with ILC patients who did not receive neoadjuvant chemotherapy.

METHODS

Patient Population

All patients diagnosed with pure ILC at our institution between May 1998 and September 2006 were identified from the surgical pathology database. Patients with mixed lobular and ductal tumors were excluded from this study. Patients with DCIS as the preoperative diagnosis were excluded. Patient records were reviewed for clinical and pathological factors, surgical procedures, and long-term outcomes. Tumor size at presentation was the largest recorded dimension as measured by physical examination, ultrasound or mammography. Comparisons were performed between patients receiving neoadjuvant chemotherapy with those undergoing surgery as their first treatment. Follow-up status was assessed as the time from diagnosis of breast cancer to the status at the time of last contact. Approval for the study was obtained from the M. D. Anderson Cancer Center Institutional Review Board.

Patient Treatment and Staging

Chemotherapy was delivered, when indicated, in the neoadjuvant or adjuvant setting at the discretion of the medical oncologist. At the time of surgery, patients underwent segmental mastectomy or mastectomy for resection of the primary tumor and sentinel lymph node surgery or axillary lymph node dissection as deemed appropriate by the surgical oncologist. The choice of segmental mastectomy or mastectomy was dependent on the advice of the surgical oncologist and the patient's preference. In patients undergoing more than one operation, the number of operations and the initial breast procedure and final breast procedure were recorded to evaluate attempts at breast conservation as well as breast conservation as the final surgical outcome. Pathological staging was based on the final pathology report after completion of all surgical therapy. Lymph nodes with the largest metastasis measuring > 0.2 mm were classified as positive nodes. Clinical response was based on a comparison of the largest clinical tumor size (by physical examination, ultrasound or mammogram) and the largest clinical tumor size after completion of neoadjuvant chemotherapy using response evaluation criteria in solid tumors (RECIST).⁹ Complete response was defined as no detectable

residual disease, partial response as a greater than 30% reduction in size, stable disease as less than 30% reduction in size, and progressive disease as greater than 20% increase in size. Complete pathological response was defined as no residual invasive carcinoma in the breast.

Statistical Analysis

Statistical analysis of continuous variables was performed using Student's *t*-test, and differences in the distribution of characteristics between groups were determined with Fisher's exact test, chi-squared test, and Mantel-Henszel exact test as appropriate. Values of *p* less than or equal to 0.05 were considered to be statistically significant.

RESULTS

Two hundred and eighty-four women with a diagnosis of pure ILC treated at the M. D. Anderson Cancer Center were identified. Patient and tumor characteristics are listed in Table 1. The mean age of the patients at presentation was 57.7 years (range 35–86 years), and the majority of patients (46%) presented with clinical T1 tumors.

Two hundred patients (70%) underwent surgery as their first line of treatment and 84 patients (30%) received chemotherapy prior to surgical resection. Patients receiving neoadjuvant chemotherapy were younger than patients undergoing surgery first (mean age 54.3 years compared with 59.1 years, respectively, $p = 0.001$). The proportion of patients presenting with a palpable tumor was significantly higher in the neoadjuvant group (92%) compared with the surgery-first group (53%, $p < 0.0001$). Similarly the rate of palpable axillary nodes at presentation was higher (45% versus 11%, $p < 0.0001$) and the rate of documented axillary lymph node metastases by fine-needle aspiration was also higher (48% versus 7%, $p < 0.0001$) in the neoadjuvant group.

The clinical stage at presentation of the two patient groups is shown in Table 1, with the patients receiving neoadjuvant chemotherapy having more advanced disease in terms of clinical T stage, N stage, and overall stage at presentation compared with those patients who underwent surgery first ($p < 0.0001$).

Data on the clinical response to neoadjuvant chemotherapy by RECIST criteria was available for 61 patients, of whom 6 patients (10%) had complete clinical response, 36 patients (59%) had partial response, 19 patients (31%) had stable disease, and no patients had disease progression. Clinical response could not be assessed in 23 patients (27%) due to unavailability of clinical tumor size either at presentation or after chemotherapy. One patient showed evidence of complete pathologic response (1.2%).

TABLE 1 Patient and tumor characteristics for all patients with invasive lobular carcinoma

	All patients, <i>n</i> = 284	Neoadjuvant chemotherapy, <i>n</i> = 84	Surgery first, <i>n</i> = 200	<i>p</i> -Value
Average tumor size at presentation (cm)	3.3 (0.2–12.0)	4.9 (1.0–12.0)	2.5 (0.2–10.0)	<0.0001
Age (years)	57.7 (35–86)	54.3 (35–86)	59.1 (36–84)	0.001
	All patients, <i>n</i> = 284 (%)	Neoadjuvant chemotherapy, <i>n</i> = 84 (%)	Surgery first, <i>n</i> = 200(%)	<i>p</i> -Value
Palpable tumor at presentation	183 (64.4)	77 (91.7)	106 (53)	<0.0001
Palpable axillary nodes at presentation	60 (21.1)	38 (45.2)	22 (11)	<0.0001
Method of diagnosis				
FNA or core-needle biopsy	228 (80.3)	73 (87)	155 (77.5)	0.05
Excision	56 (19.7)	11 (13)	45 (22.5)	
Positive axillary LN on US-guided FNA at presentation	54 (19.0)	40 (47.6)	14 (7)	<0.0001
Clinical T stage				
T1	130 (45.8)	8 (9.5)	122 (61)	<0.0001
T2	106 (37.3)	44 (52.4)	62 (31)	
T3	38 (13.4)	24 (28.6)	14 (7)	
T4	9 (3.2)	8 (9.5)	1 (0.5)	
Unknown	1 (0.3)	0 (0)	1 (0.5)	
Clinical N stage				
N0	219 (77.1)	37 (44)	182 (91)	<0.0001
N1	54 (19.0)	37 (44)	17 (8.5)	
N2	1 (0.4)	1 (1.1)	0 (0)	
N3	10 (3.5)	9 (10.8)	1 (0.5)	
Clinical stage				
I	121 (42.6)	3 (3.5)	118 (59)	<0.0001
IIA	85 (29.9)	29 (34.5)	56 (28)	
IIB	45 (15.8)	24 (28.6)	21 (10.5)	
IIIA	14 (4.9)	12 (14.2)	2 (1)	
IIIB	8 (2.8)	7 (8.3)	1 (0.5)	
IIIC	10 (3.5)	9 (10.7)	1 (0.5)	
IV	1 (0.3)	0	1 (0.5)	

LN Lymph node,
FNA Fine-needle aspiration,
US Ultrasound

When comparing the neoadjuvant group versus the surgery-first group, the number of patients who had BCS attempted at the initial operation was significantly lower in the neoadjuvant chemotherapy group (30.5% compared with 50.3%, $p = 0.004$) (Table 2). Of those patients who had BCS attempted, the proportion of patients who failed an attempt at BCS was significantly higher in the neoadjuvant chemotherapy group (44% versus 14.3%, $p = 0.004$) (Table 2). Similarly, the overall number of patients who achieved BCS as their final outcome was significantly lower in the neoadjuvant chemotherapy group (17.1% versus 43.1%, $p < 0.001$) (Table 3).

However, when the data was stratified by clinical tumor size at presentation, the proportion of patients with attempted BCS, those with a failed attempt at BCS, and

those undergoing BCS as their final procedure were not significantly different between the groups (Tables 2 and 3). The rates of initial attempt at BCS decreased in both groups as tumor size at presentation increased. The frequency of attempted BCS for tumors < 2 cm, 2.1–4 cm, 4.1–6 cm, and > 6 cm at presentation were 50%, 33%, 40%, and 13% in the neoadjuvant group compared with 62%, 40%, 21%, and 25% in the surgery-first group (p for each tumor size category > 0.05). The proportion of patients who had failed attempts at BCS in the two groups stratified by tumor size was also not significantly different (Table 2). Therefore, overall, the final rate of successful BCS between the groups, when taking into account the clinical size of the tumor at presentation, was not different. Specifically, the final rate of BCS across the neoadjuvant and surgery-first

TABLE 2 Rates of attempted breast-conservation surgery by treatment group

Size at presentation (cm)	Initial attempt at BCS			Failed attempt at BCS (expressed as proportion of patients with attempted BCS)		
	Neoadjuvant chemotherapy	Surgery first	<i>p</i> -Value	Neoadjuvant chemotherapy	Surgery first	<i>p</i> -Value
0–2.0	3/6 (50%)	66/106 (62.3%)	0.68	1/3 (33.3%)	7/66 (10.6%)	0.31
2.1–4.0	11/33 (33.3%)	19/48 (39.6%)	0.64	4/11 (36.4%)	3/19 (15.8%)	0.37
4.1–6.0	8/20 (40%)	4/19 (21.1%)	0.30	4/8 (50%)	2/4 (50%)	1.00
>6.0	3/23 (13%)	2/8 (25%)	0.58	2/3 (66.6%)	1/2 (50%)	1.00
All patients	25/82 (30.5%)	91/181 (50.3%)	0.003	11/25 (44%)	13/91 (14.3%)	0.004

TABLE 3 Proportion of patients who had breast-conserving surgery as their final surgical procedure

Size at presentation (cm)	Final outcome BCS (expressed as proportion of patients with attempted BCS)			Final outcome BCS (expressed as proportion of all patients)		
	Neoadjuvant chemotherapy	Surgery first	<i>p</i> -Value	Neoadjuvant chemotherapy	Surgery first	<i>p</i> -Value
0–2.0	2/3 (66.6%)	59/66 (89.4%)	0.31	2/3 (33.3%)	59/106 (55.7%)	1.00
2.1–4.0	7/11 (63.6%)	16/19 (84.2%)	0.37	7/33 (21.2%)	16/48 (33.3%)	0.32
4.1–6.0	4/8 (50%)	2/4 (50%)	1.00	4/20 (20%)	2/19 (10.5%)	0.66
>6.0	1/3 (33.3%)	1/2 (50%)	1.00	1/23 (4.3%)	1/8 (12.5%)	0.46
All patients	14/25 (56%)	78/91 (85.7%)	0.004	14/82 (17.1%)	78/181 (43.1%)	<0.001

cohorts were 33%, 21%, 20%, and 4%, and 56%, 33%, 11%, and 13%, respectively, for tumors < 2 cm, 2.1–4 cm, 4.1–6 cm, and over 6 cm (Table 3).

Next, we examined whether patients who achieved complete or partial clinical response were more likely to undergo BCS. Although the proportion of patients attempting BCS and undergoing successful BCS was highest in the patients with complete clinical response, this was not significantly different than those who had achieved only a partial response to chemotherapy (66% versus 28%, $p = 0.16$ and 75% versus 60%, $p = 1.0$). When comparing

across all three groups (complete response, partial response, and stable disease) again no significant differences were seen in the proportion of patients having either attempted or successfully undergoing BCS (Table 4).

Lastly, given the greater proportion of patients in the neoadjuvant chemotherapy group who presented with palpable disease, we limited analysis to those patients with palpable tumors. We found that the mastectomy rate remained higher in patients who received neoadjuvant chemotherapy (84%) compared with those who underwent surgery first (62%) ($p = 0.001$) (Table 5).

TABLE 4 Breast-conserving surgery rates in the neoadjuvant cohort based on extent of clinical response by RECIST criteria ($n = 61$)

	Complete response ($n = 6$)	Partial response ($n = 36$)	Stable disease ($n = 19$)	<i>p</i> -Value
Size at presentation (cm, average and range)	5.4 (2.3–8)	4.9 (1.5–12.0)	4.9 (2.1–8.8)	0.898
Attempted BCS	4 (66%)	10 (28%)	5 (26%)	0.163
Successful BCS	3	6	1	
Successful BCS (% of attempted)	3/4 = 75%	6/10 = 60%	1/5 = 20%	0.234

TABLE 5 Comparison of final surgical procedure in patients presenting with palpable tumor by treatment

Treatment	Mastectomy, <i>N</i> (%)	BCS, <i>N</i> (%)	<i>p</i> -Value
Neoadjuvant chemotherapy ($n = 77$)	65 (84%)	12 (16%)	0.001
Surgery first ($n = 106$)	66 (62%)	40 (38%)	

Follow-up was available for a mean of 56 months in the neoadjuvant chemotherapy group and 41 months in the surgery-first group. One patient in each group had recurrence. Overall local recurrence rates were not significantly different between the two groups (1.2% versus 0.5%, $p = 0.5$). One patient who received neoadjuvant chemotherapy underwent a failed attempt at BCS, followed by mastectomy. Subsequently she underwent resection of a chest wall recurrence. One patient who underwent surgery first completed BCS and at the time of in-breast recurrence underwent mastectomy. Both of these patients are alive without evidence of disease at the time of last follow-up. None of the 14 patients who underwent BCS after completion of neoadjuvant chemotherapy have developed a local recurrence at a mean follow-up of 47 months.

DISCUSSION

As the use of neoadjuvant chemotherapy increases, it is important to evaluate which patient subgroups benefit most from neoadjuvant chemotherapy, as well as to identify those patients who may not benefit from this approach. Previous studies have shown lower pathologic complete response rates in patients with ILC when compared with IDC.⁶⁻⁸ However, in order to downsize tumors and allow for an attempt at BCS, a pathologic complete response (pCR) is not necessary and tumors that show a partial response may decrease in size enough to allow for a breast-conserving approach. Thus we were interested in assessing whether the lesser degree of response achieved in ILC patients is nonetheless sufficient to allow sizable numbers of women to undergo a breast-conserving procedure. We found that overall neoadjuvant chemotherapy did not improve breast-conservation rates in patients with ILC in this study.

Previous studies comparing patients with ILC versus IDC after neoadjuvant chemotherapy have shown significant differences in BCS rates based on tumor histology. Tubiana-Hulin et al. reported an overall 30% BCS rate in ILC, which was significantly lower compared with the 48% BCS rate in IDC ($p = 0.006$).⁶ However despite a significantly larger tumor size at presentation in the ILC cohort, the BCS rates were not controlled for tumor size at presentation. Similarly, Cocquyt noted differences in response rates and BCS rates between ILC and IDC cohorts, but did not determine BCS rates as a function of presenting tumor size.⁸ In a series with a small ILC cohort, Mathieu et al. and Newman et al. have reported that ILC is an independent predictor of ineligibility for BCS after neoadjuvant chemotherapy compared with IDC.^{5,10} Although all these studies show that ILC patients are less likely to achieve BCS after neoadjuvant chemotherapy, they do not address

whether the use of neoadjuvant chemotherapy improves on the baseline BCS rates for ILC patients. By comparing ILC patients receiving neoadjuvant chemotherapy with those who had surgery as their first treatment, and by controlling for tumor size, our data demonstrates that neoadjuvant chemotherapy did not increase the likelihood of BCS for ILC patients in this study.

Clinical response to neoadjuvant chemotherapy was seen in 69% in our study, similar to those reported in patients with IDC.^{4,8,10} A pCR was seen in only one patient (1%), which is also consistent with other ILC series in the literature.^{6-8,10,11} Of interest, when we assessed the success rate of BCS based on extent of clinical response, we saw no differences. This surprising finding likely stems from the difficulty in accurate imaging of ILC patients. It is often challenging to assess tumor size reliably in ILC patients due to ill-defined tumor mass and thickening, which can be difficult to measure on ultrasound and mammogram. Therefore clinical tumor stage may have been underestimated in our study, which would result in underestimating the response to chemotherapy. This remains a challenge in the clinical care of patients with ILC and may improve with use of magnetic resonance imaging (MRI) or molecular breast imaging studies.¹² Additionally, our failure to see improvement in BCS rates among the clinical responders may reflect the many factors that enter into surgical decision making, including patient preference, which could not be controlled for in this study.

It has been suggested that the lower response rate to neoadjuvant chemotherapy in ILC patients would place them at increased risk of local recurrence following BCS.⁸ In our series, however, with nearly 5 years of follow-up in the neoadjuvant cohort, LR rates after BCS remain exceedingly small and well within the 5-year LR rates reported for all cohorts undergoing BCS.¹³⁻¹⁵ Thus, it appears that the use of neoadjuvant chemotherapy is not an independent risk factor for the development of LR in ILC patients who undergo BCS following systemic therapy. In this regard careful evaluation of margin status is likely to be critical. We have recently reported that ILC patients who undergo neoadjuvant chemotherapy require excision margins of at least 1 mm to ensure low residual tumor burden and thus low LR events.¹⁶

The primary goals of neoadjuvant chemotherapy are to permit breast conservation and to achieve pCR as a surrogate of improved long-term outcome.^{4,17,18} All studies to date demonstrate that pCR rates in ILC are minimal and this report now shows that BCS rates did not appear to be substantially improved with the use of neoadjuvant chemotherapy in this population. Taken together, these findings indicate that current standard cytotoxic chemotherapy regimens in the neoadjuvant setting do not markedly improve the surgical options for ILC patients

with invasive lobular carcinoma of the breast. ILC tend to be low-grade tumors, which are associated with a minor response to chemotherapy compared with higher-grade tumors. ILC are frequently estrogen receptor (ER) and progesterone receptor (PR) positive, and usually Her2 negative. Hormone-receptor-positive tumors are known to be more responsive to endocrine therapy and less responsive to chemotherapy. It is known that large tumors, low grade, and ER positivity are associated with minor response to neoadjuvant chemotherapy. Since the hormonal and biologic profile of ILC suggest that it may be more responsive to hormonal therapy, neoadjuvant endocrine therapy in hormone-receptor-positive ILC may be a better strategy to downsize tumors and increase breast-conservation rates.

A number of important limitations need to also be noted. First, this remains a retrospective study and thus there were significant differences, and thus potential biases, between the neoadjuvant chemotherapy and surgery-first groups. Second, given the limitations of sample size, we cannot entirely exclude the possibility of a small improvement in BCS rates due to neoadjuvant chemotherapy. Lastly, this study was limited to "pure ILC" to avoid inclusion of tumors which were mixed ductal and lobular and therefore may have a greater response to neoadjuvant chemotherapy. This was based on final pathologic assessment. At time of core biopsy it may not always be possible to differentiate pure ILC from mixed mammary carcinoma and this may limit extrapolation of these data.

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