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Breast conservation therapy versus mastectomy in the surgical management of invasive lobular carcinoma measuring 4 cm or greater

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Abstract

Background: The safety of breast conservation therapy (BCT) has not been demonstrated in large ILC tumors, potentially contributing to the higher mastectomy rates seen in ILC.

Methods: We queried a prospectively maintained database to identify patients with ILC measuring ≥4 cm and evaluated difference in recurrence free survival (RFS) between those treated with BCT versus mastectomy using a multivariate model.

Results: Of 180 patients, 30 (16.7%) underwent BCT and 150 (83.3%) underwent mastectomy. Patients undergoing mastectomy were younger (56.6 vs. 64.3 years, p=0.003) and had larger tumors (7.2 vs. 5.4 cm, p<0.001). While tumor size, nodal stage, receptor subtype, and margin status were significantly associated with RFS, there was no difference in RFS at 5 (p=0.88) or 10 (p=0.65) years for individuals undergoing BCT versus mastectomy.

Conclusions: For patients with ILC ≥4 cm, BCT provides similar tumor control as mastectomy, provided that negative margins are achieved.

Keywords

invasive lobular carcinoma; large tumors; recurrence-free survival; breast conservation surgery; mastectomy

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INTRODUCTION

Prospective randomized clinical trials have established the safety of breast conservation therapy (BCT) with lumpectomy followed by radiation for early-stage breast cancers.[1-5] Most of these pivotal trials included patients with tumors up to 4-5 cm in size, thereby excluding patients with stage T3 primary cancers. However, as oncoplastic techniques have improved, the ability to offer BCT to patients with large tumors has increased. Retrospective analyses of BCT in large tumors suggest no difference in overall and disease-specific survival when compared to patients undergoing mastectomy.[6-8] However, this has not been studied in invasive lobular carcinoma (ILC), the second most common type of breast cancer.

ILC affects between 10-15% of breast cancer patients worldwide.[9,10] It is considered a unique subtype of breast cancer due to its diffuse growth pattern caused by the lack of adhesion protein E-cadherin, later disease recurrence, higher false-negative rate on imaging, high rates of incomplete surgical excision, and higher burden of nodal disease compared to invasive ductal carcinoma (IDC).[9,11-14] Moreover, significantly more patients with ILC are diagnosed with stage T3 disease compared to patients with the more common IDC.[15] These issues have led some to argue that mastectomy is the best treatment for ILC, with the safety of BCT for these diffuse, larger tumors being unknown.[6-8]

Given the absence of such data, we sought to investigate outcomes in a cohort of ILC patients with large tumors treated with BCT instead of mastectomy. In particular, we evaluated whether undergoing BCT versus mastectomy impacts recurrence-free survival (RFS) or locoregional recurrence for patients with ILC measuring ≥ 4 cm in size.

MATERIALS AND METHODS

We conducted a cross-sectional analysis in a cohort of women treated for ILC at the University of California, San Francisco between 1994 and 2019. The study was approved by our Institutional Review Board. We queried a prospectively maintained surgical database and identified patients with unilateral or bilateral ILC. Tumor size was measured according to the American Joint Commission on Cancer guidelines (pathologic tumor size or ypT longest diameter for neoadjuvantly treated patients).[16] We excluded patients who had small tumors (< 4 cm), de novo stage 4 disease, fewer than six months of follow-up, or missing data about radiation therapy or tumor size. BCT was defined as lumpectomy with or without local tissue rearrangement or oncoplastic reduction mammoplasty. Local tissue rearrangement and shave margins were used at the discretion of the operating surgeon and patient. All patients undergoing BCT received adjuvant radiotherapy. Our primary outcomes were 5- and 10-year RFS estimates, defined as the absence of locoregional or distant recurrence at date of last follow-up. Our secondary endpoint was time to locoregional recurrence and final positive margin rate.

Data were analyzed in Stata 14.2 (StataCorp LLC, College Station, TX, USA), using the chi-squared test for categorical variables, analysis of variance for continuous variables, and Kaplan-Meier survival estimates. A multivariate logistic regression model was used that included a time-varying regression coefficient to account for non-proportional hazards. Size

of tumor was treated as a continuous variable in one-centimeter increments. The sample size was predetermined based on the total number of cases with available data in the study period. Based on this sample size, power was 66% to detect a 40% increase in hazard ratio for RFS in the BCT group compared to the mastectomy group, using a one-sided alpha of 0.1, and 77% to detect a 50% increase. For positive margin rates, the power was 79% to detect a 20% increase in positive margin rates in the BCT group compared to the mastectomy group, using a one-sided alpha of 0.05. Results are reported as hazard ratios (HR) with 95% confidence intervals (CI).

RESULTS

A total of 180 patients with ILC met the eligibility criteria for this study (Figure 1). The clinicopathologic characteristic of the cohort are summarized in Table 1. Most tumors were grade 2 (n=122, 68.5%) and of the subtype that was estrogen-receptor positive (ER+), progesterone receptor-positive (PR+), and human epidermal growth factor receptor 2-negative (HER2−) (n=120, 71.9%). Of 180 patients, 30 underwent BCT, and 150 underwent mastectomy with or without radiation therapy (48.7% and 51.3%, respectively). Among the 30 patients who had BCT, 12 (40.0%) had oncoplastic reduction mammoplasty, 3 (10.0%) had local tissue rearrangement, and 21 (70.0%) had shave margins excised. Positive margins occurred at initial resection in 17 (56.7%). Of those, 15 (88.2%) had re-excision, which cleared the margin in 13 (86.7%), leaving a total of 4 patients with persistently positive margins in the BCT group. We found no association between tumor size, nodal stage, or receptor subtype and margin status.

Of the 150 patients undergoing mastectomy, 29 (19.3%) had an initial attempt at BCT followed by subsequent mastectomy. There were 20 patients with persistently positive margins after mastectomy (13.3%). Those undergoing mastectomy were significantly younger (mean age 56.6 years vs. 64.3 years, p=0.003) and had larger tumors (mean size 7.2 cm vs. 5.4 cm, p<0.001) compared to those undergoing BCT. The two groups did not differ significantly with respect to era of diagnosis, tumor grade, tumor receptor subtype, N-stage, receipt of neoadjuvant therapy, presence of lymphovascular invasion, rate of positive margins, or surgical complication rate (Table 1). The mean follow-up time was 5.3 years ranging from 0.53-21.8 years.

Unadjusted analysis showed no significant difference in RFS estimates at 5 and 10 years among the groups who underwent BCT, mastectomy alone, or mastectomy with radiation (Figure 2, Table 2). Specifically, the RFS at 5 and 10 years was 80.6% and 80.6% for those who underwent BCT, 86.2% and 71.8% for those who underwent mastectomy alone, and 78.5% and 66.8% for those who underwent mastectomy with radiation (p=0.45 and p=0.15, respectively). Without taking follow-up time into account, there were a total of 30 local or regional recurrence events in the mastectomy cohort (20.0%) and 3 recurrence events in the BCT cohort (10.0%).

Our multivariate model that adjusted for age, size of tumor, tumor receptor subtype, grade, N-stage, lymphovascular invasion, and positive margin status showed no benefit of mastectomy without radiation (HR=1.14, 95% CI 0.21-6.32, p=0.88) or mastectomy with

radiation (HR=0.66, 95% CI 0.10-4.14, p=0.66) compared to BCT on RFS (Table 3). Larger tumor size was significantly associated with shorter RFS, independent of type of surgical treatment (HR=1.29, 95% CI 1.10-1.51, p=0.002). Other factors that were predictive of RFS in the multivariate model included positive margin status (HR=4.16, 95% CI 1.38-12.58, p=0.012), increasing N-stage (N-Stage 1: HR=5.50, 95% CI 1.18-25.50, p=0.030; N-Stage 2: HR=6.12, 95% CI 1.11-33.79, p=0.038; N-Stage 3: HR=17.95, 95% CI 3.25-99.10, p=0.001), and tumor receptor subtype (HER2 positive: HR=41.96, 95% CI 6.37-2876.40, p<0.001; triple negative disease: HR=43.87, 95% CI 6.62-290.92, p<0.001, Table 3). We also performed a multivariate analysis to evaluate the relationship between type of operation and locoregional recurrence as a secondary endpoint. After adjusting for age, tumor size, N-stage, lymphovascular invasion, and positive margins, we found no association between type of operation and time to locoregional recurrence.

DISCUSSION

The safety of BCT for women with small tumors has been well established in the scientific literature. Several randomized controlled trials have shown that for patients with stage I or II breast cancers ≤ 4 cm in size, there is no difference in disease free survival or overall survival between BCT and mastectomy cohorts.[1-5] For tumors greater than 4 cm in size, however, data are more limited.[6-8] This is a particularly important question for patients with large ILC tumors, as the unique growth pattern seen in ILC makes complete surgical excision more difficult, and positive margin rates are often higher for patients with ILC compared to those with IDC.[17] Additionally, imaging tests have higher false-negatives rates for patients with ILC, raising the possibility that BCT would leave behind undetected tumor cells at higher rates.[14] Because the safety of BCT in patients with large ILC tumors remains understudied, we sought to evaluate the impact of BCT versus mastectomy on RFS and found that the extent of operation does not drive recurrence in these large ILC tumors.

Our study, albeit small, represents the largest reported series of ILC patients with large tumors undergoing BCT to date. Nearly all studies examining the safety of BCT in ILC exclude patients with tumors greater than 4 cm in size. In fact, only one study has included ILC tumors greater than 5 cm in size, but their population was small with only 15 cases.[18] The absence of safety data for BCT in this setting may be driving the higher rates of mastectomy seen in these patients; as such, identifying ILC patients with large tumors treated with BCT who have recurrence outcomes is exceedingly challenging[6-8]. However, we and others have demonstrated the ability of oncoplastic surgery to facilitate successful BCT in large ILC tumors, thereby offering women less invasive treatment.[18-22] Before these techniques are applied, however, more safety data is needed to evaluate the efficacy and long-term outcomes, and the data provided herein contribute to our understanding of optimal surgical management for ILC.

Although we found that extent of operation does not impact recurrence in patients with large ILC tumors, certain tumor characteristics did influence the study outcomes. Larger tumor size and more advanced nodal stage were associated with reduced recurrence-free survival. Moreover, the rate of positive margins did not differ between the BCT and mastectomy cohorts, indicating that even mastectomy may fail to provide clear margins in large ILC.

Taken together, these findings highlight the need for improved neoadjuvant approaches that can reduce the size of the tumor before an operation, regardless of surgical approach, and enhanced imaging techniques to identify tumors at earlier stages of disease.

In our study, patients who underwent mastectomy were significantly younger and had even larger tumors than those undergoing BCT. This is consistent with literature showing higher mastectomy rates in younger breast cancer patients.[23] However, concerns about tumor recurrence owing to the lack of safety data for BCT in ILC tumors may have influenced surgical recommendations and choices. Our findings contribute to the safety data and may dispel some of these concerns regarding recurrence risk.

There are many important strengths to our study, including a well-managed institutional ILC database that contains over 700 patients with 180 cases of large tumors, a mean follow-up time of 5.3 years, and recurrence data that are unavailable in larger datasets. However, there are important limitations to our study. The retrospective study design limits the ability to determine why certain treatments were chosen for patients. Moreover, procedures that were performed were subject to patient and provider bias and surgeon-dependent factors that are unaccounted for in our analysis. We were unable to evaluate breast size relative to tumor size, but we do note that 40% of the BCT cohort underwent oncoplastic reduction mammoplasty as their surgical procedure, suggesting that larger breast size may have facilitated these resections. Additionally, there were few patients in our analysis who had HER2 positive or triple negative disease, although this does reflect the distribution of receptor subtypes commonly seen in ILC.

CONCLUSION

In summary, our study is one of the first to evaluate the use of BCT rather than mastectomy in patients with ILC tumors that are ≥ 4 cm in size, which appears to be safe provided that negative margins are obtained. Our findings can be used to help patients and providers make informed choices about surgical options for ILC, which currently has a higher rate of mastectomy than that of IDC. Increased representation of ILC patients in clinical trials is needed to improve outcomes and tailor care to patients with this unique tumor type.

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Highlights

- Lumpectomy and mastectomy outcomes are similar in lobular breast cancers ≥4 cm
- Positive margins in large lobular cancers are associated with recurrence
- Breast conservation is safe in large lobular cancers if margins are negative

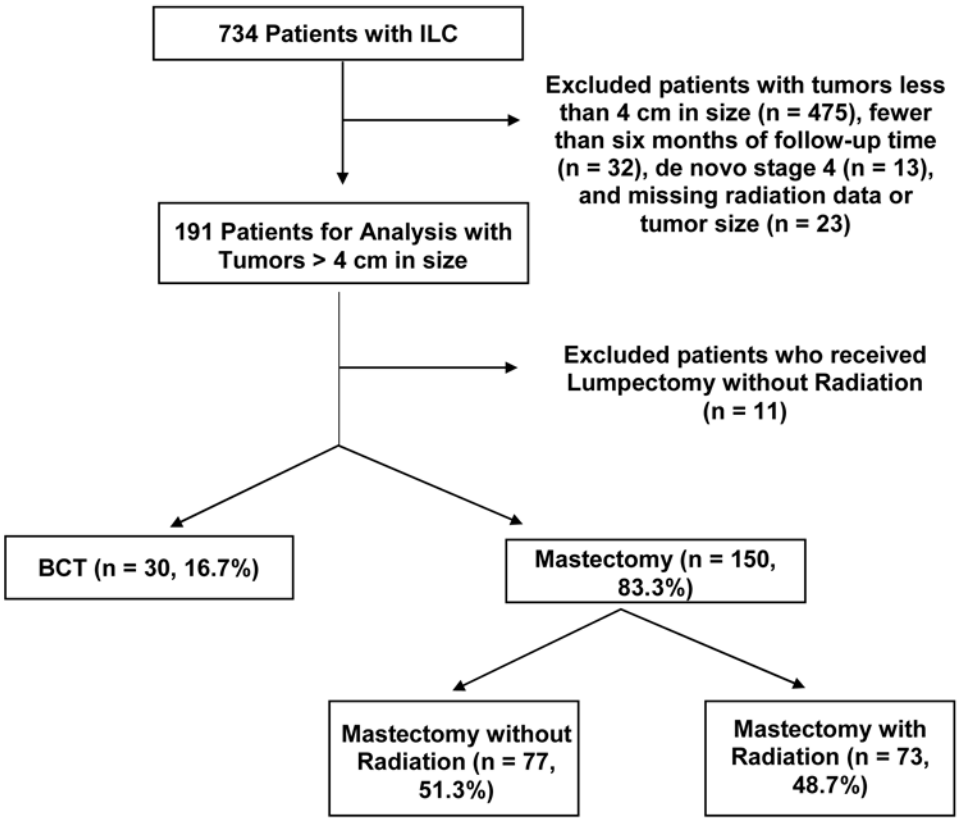

Figure 1:
Flow Chart Depicting Study Design for Analysis of ILC Patients; ILC = invasive lobular carcinoma.

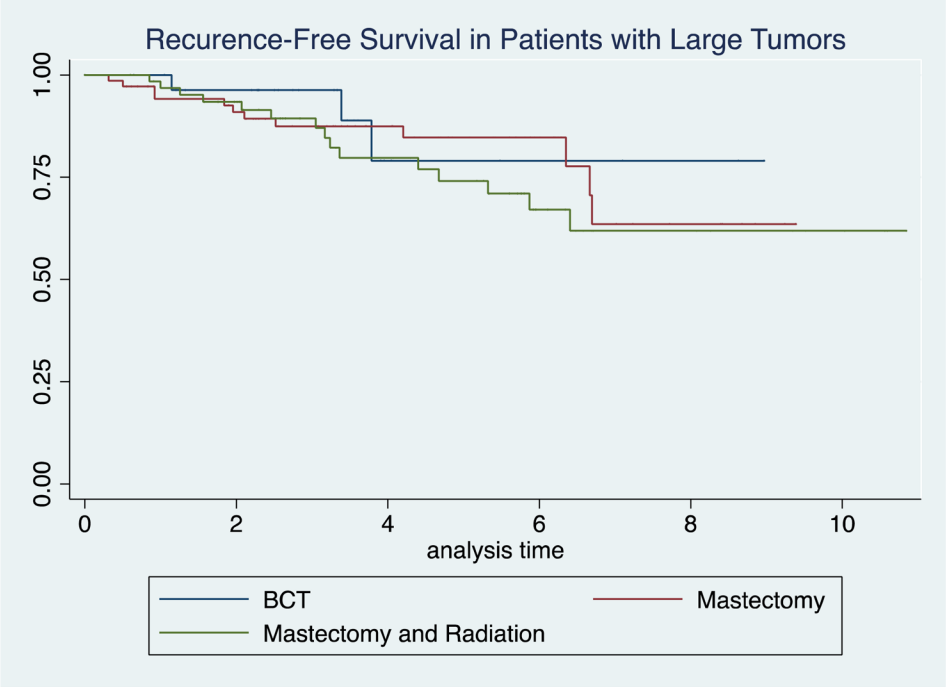

Figure 2:

Kaplan Meier survival curve depicting recurrence-free survival in ILC patients with large tumors (≥4 cm) who received either BCT (blue), mastectomy alone (red), or mastectomy and radiation therapy (green). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1:

Clinicopathologic Characteristics of ILC Patients with Large Tumors (≥4 cm) who received either BCT or Mastectomy

Characteristic	Overall Population (n = 180)	BCT (n = 30)	Mastectomy (n = 150)	P-Value
Age, years [mean (SD)]	57.9 (13.0)	64.3 (12.4)	56.6 (12.7)	0.003
Tumor Size [mean (range)]	6.9 cm (4-15.3)	5.4 cm (4-12)	7.2 cm (4-15.3)	< 0.001
Tumor Grade[1]				0.980
1	43 (24.1)	7 (23.3)	36 (24.3)	
2	122 (68.5)	21 (70.0)	101 (68.2)	
3	13 (7.3)	2 (6.7)	11 (7.4)	
Receptor Subtype[2]				0.491
ER+/PR+/HER2−	120 (71.9)	19 (73.0)	101 (72.1)	
ER+/PR−/HER2−	38 (22.8)	8 (29.6)	30 (21.4)	
HER2+	4 (2.9)	0 (0)	4 (2.4)	
Triple negative	5 (3.6)	0 (0)	5 (3.0)	
N Stage				0.910
0	80 (45.2)	15 (50.0)	65 (43.3)	
1	57 (31.7)	9 (30.0)	48 (32.0)	
2	20 (11.1)	3 (10.0)	17 (11.3)	
3	23 (12.8)	3 (10.0)	20 (13.3)	
Neoadjuvant Therapy[3]	79 (53.0)	9 (30.0)	70 (47.0)	0.087
Lymphovascular Invasion[4]	23 (13.1)	6 (20.0)	17 (11.6)	0.339
Positive Margins	24 (13.3)	4 (13.3)	20 (13.3)	1.00
Post-operative Seroma[5]	10 (7.0)	1 (4.0)	9 (7.8)	0.51
Surgical Site Infection[5]	13 (9.2)	3 (12)	10 (8.6)	0.60
Post-operative Hematoma[5]	2 (1.4)	0 (0)	2 (1.7)	0.51

There were also no differences in post-operative complications between the BCT and mastectomy cohorts (20.0% vs. 18.1%, p=0.82), including seroma formation (4.0% vs. 1.7%, p=0.51), infection (12.0% vs. 8.6%, p=0.60), hematoma formation (0.0% vs. 1.7%, p=0.51), or skin necrosis (0.0% vs. 4.3%, p=0.29).

Data are expressed as n (%) unless otherwise specified

Total N = 182 unless otherwise specified

[1] data available in 178

[2] ER = estrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor receptor 2; data available in 167

[3] data available in 179

[4] data available in 176

[5] data available in 141

Table 2:

Unadjusted Recurrence-Free Survival (RFS) Estimates in ILC Patients with Large Tumors (≥ 4 cm) who Received either BCT, Mastectomy, or Mastectomy and Radiation Therapy

Patient Subgroup	RFS	Percent	95% CI
BCT (n = 30)	5 Year	80.6%	48.3-93.8%
	10 Year	80.6%	48.3-93.8%
Mastectomy (n = 77)	5 Year	86.2%	74.8-92.7%
	10 Year	71.8%	51.6-84.8%
Mastectomy and Radiation (n = 73)	5 Year	78.5%	64.9-87.4%
	10 Year	66.8%	50.4-78.8%

Table 3:

Results of Multivariate Logistic Regression Analysis that Included a Time-Varying Regression Coefficient to Account for Nonproportional Hazards

	Hazard Ratio	95% CI[1]	P-Value
Treatment Type			
BCT	Ref		
Mastectomy without Radiation	1.14	0.21-6.32	0.88
Mastectomy with Radiation	0.66	0.10-4.14	0.65
Positive Margins	4.16	1.38-12.58	0.012
Age at Diagnosis	1.02	0.97-1.07	0.44
Size of Tumor	1.29	1.10-1.51	0.002
N-Stage			
0	Ref		
1	5.50	1.18-25.50	0.030
2	6.12	1.11-33.79	0.038
3	17.95	3.25-99.10	0.001
Histological Subtype[2]			
ER+/PR+/HER2−	Ref		
ER+/PR−/HER2−	2.18	0.70-6.74	0.18
HER2+	41.96	6.37-276.40	< 0.001
Triple negative	43.87	6.62-290.92	< 0.001
Grade			
1	Ref		
2	0.63	0.23-1.68	0.35
3	1.18	0.19-7.38	0.86
Lymphovascular Invasion	1.32	0.45-3.84	0.61

[1] CI = confidence interval

[2] ER = estrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor receptor 2