Published in final edited form as:

Ann Surg Oncol. 2015 December ; 22(13): 4280–4286. doi:10.1245/s10434-015-4570-8.

Surgical Options and Locoregional Recurrence in Patients Diagnosed with Invasive Lobular Carcinoma of the Breast

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Abstract

Purpose—Recent consensus guidelines on margins for breast conserving surgery (BCS) recommend the use of “no ink on tumor” as the standard for an adequate margin. The recommendations extend to invasive lobular carcinoma (ILC), but the data on this subset are limited. We reviewed our modern dataset on margin status with outcomes of ILC.

Methods—We performed a retrospective cohort study on 736 patients with a diagnosis of Stage I-III ILC treated at our cancer center between May 1997 and December 2007. Clinicopathologic data were extracted from the Clinical Research Information Systems Database. Margin status was defined using the latest ASCO/ASTRO/SSO consensus guideline criteria.

Results—The initial surgery performed was mastectomy in 352 patients (48%) and BCS in 384 patients (52%). In multivariate analysis, tumor size and multifocality were significantly associated with high rates of mastectomy and positive surgical margins at initial BCS. After initial BCS, additional surgery was performed in 92 patients (24%). Over a 72 month median follow-up period, 12 (3.1%) ipsilateral breast tumor recurrences (IBTR) and five (1.3%) other locoregional recurrences (LRR) were observed. Patients with margins with ink on tumor who did not receive further surgery were found to have significantly increased LRR (OR, 5.5; $p=0.02$) and IBTR (OR, 8.5; $p=0.006$), whereas patients with close margins (1–3 mm) and margins within 1mm were not.

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Competing Interest: The authors have no conflicts of interest concerning this study.

The original publication of this manuscript first appeared in the *Annals of Surgical Oncology* (Sagara Y, Barry WT, Mallory MA, Vaz-Luis I, Aydogan F, Brock JE, Winer EP, Golshan M, Metzger-Filho O. Surgical Options and Locoregional Recurrence in Patients Diagnosed with Invasive Lobular Carcinoma of the Breast. *Ann Surg Oncol.* 2015 Dec;22(13):4280-6. PubMed PMID: 25893416.)

The final publication is available at <http://link.springer.com/article/10.1245%2Fs10434-015-4570-8>. Doi: 10.1245/s10434-015-4570-8.

Conclusions—Our study supports the validity of using ‘no ink on tumor’ as the standard for a negative margin for pure and mixed ILC treated with multimodality therapy.

Keywords

Invasive lobular carcinoma; Ipsilateral breast cancer recurrence; Local recurrence; Surgical margin

Introduction

Invasive lobular carcinoma (ILC) accounts for 10–15% of breast carcinoma cases nationwide [1, 2]. Morphologically, ILC is composed of small, uniform cells which either invade the surrounding breast parenchyma in a linear, single-file arrangement or form concentrically around benign ducts in a target-like fashion [2]. Variations of ILC (e.g., pleomorphic) have been described, representing subtypes that lack the characteristic diffuse, linear growth pattern of classic ILC [3, 4]. Mixed invasive lobular carcinomas also exist, which are commonly defined as tumors which contain both ILC and invasive ductal carcinoma [1, 5–7].

The clinical presentation of ILC can vary from an ill-defined palpable mass to a mass with diffuse nodularity [6, 8, 9], and diagnosis for ILC can be challenging. Screening and diagnostic modalities including mammography and ultrasound have a lower sensitivity in detecting ILC than IDC [6, 9–12], and the non-cohesive and infiltrative nature of ILC creates difficulties for estimating tumor size not only on clinical exam but also with imaging and by gross pathology evaluation. ILC tumors similarly present therapeutic challenges, reflected by the high frequency of positive surgical margins (17.5–63%) and high re-excision rates (42–88%) following breast-conserving surgery (BCS) for ILC tumors [13–17].

Six large randomized prospective studies have consistently demonstrated that BCS with radiation and mastectomy have equivalent survival outcomes, establishing BCS as a less invasive treatment option for both ILC and IDC, however retrospective studies have found that ILC is associated with higher rates of mastectomy following BCS when compared to IDC [13, 18–24]. The extent to which the higher rates of mastectomy for ILC are related to positive surgical margins remains unknown.

In the era of modern systemic therapies, there has been wide variability in the definition of what constitutes a negative surgical margin [25]. With the purpose of standardizing current margin definitions, the American Society of Clinical Oncology (ASCO)/American Society for Radiation Oncology (ASTRO)/Society of Surgical Oncology (SSO) established consensus guidelines in 2014. They recommended that a ‘negative margin’ be defined as a margin with ‘no ink on tumor’ (i.e., no cancer cells adjacent to any inked edge/surface of the specimen) [26]. The consensus extended its primary recommendation for ‘no ink on tumor’ to patients diagnosed with ILC. Existing research evaluating the impact of surgical margin status for ILC tumors has considered different definitions for negative margin, but has not yet evaluated the impact that the ‘no-ink on tumor’ definition has on outcomes.

We sought to investigate the impact the current definition of margin assessment (i.e. no ink on tumor) has on locoregional recurrence (LRR) for patients diagnosed with ILC and mixed ILC tumors treated at our comprehensive cancer center. In addition, we aimed to investigate how clinicopathologic characteristics of patients influence the surgical procedure performed for diagnoses of ILC and mixed ILC.

Patients & Methods

Study Design and Data Source

This study was undertaken as a single institutional retrospective cohort study at Dana-Farber/Brigham and Women's Cancer Center (DF/BWCC) after Institutional Review Board approval was obtained. Using the Clinical Research Information Systems (CRIS) Database at Dana-Farber Cancer Institute (DFCI) in conjunction with computerized order-entry system records, we identified 736 eligible patients who were diagnosed with Stage I -III ILC (311 pure ILC; 425 mixed ILC) between May 1997 and December 2007. Patients were included if they were aged ≥ 18 years, had a histologically confirmed ILC or mixed ILC tumor and had been followed for at least 5 years at DF/BWCC. They were excluded if they had inflammatory breast cancer, pathological T4 disease or preoperative therapy.

The following variables were collected: histological subtype (i.e., pure ILC or mixed ILC), type of surgery (i.e. BCS or mastectomy), whether or not axillary dissection was performed, nodal status, multifocality, margin assessment, patient age, hormone receptor status, histologic grade, adjuvant therapy (hormone therapy, chemotherapy, targeted therapy, and radiotherapy), site(s) of disease recurrence, time from diagnosis to recurrence, and final pathology report. HER2 status was evaluated by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). HER2 status was considered positive when IHC was 3+ or FISH was positive. HER2 status was considered negative when IHC was 0 or 1+, or when IHC was 2+ with a negative FISH. The definitions of both pure ILC and mixed ILC were based on morphology and not on IHC or molecular studies. Pure ILC was defined as invasive carcinoma composed of non-cohesive cells individually dispersed or arranged in a single-file linear pattern in a fibrous stroma. Mixed ILC was defined as invasive carcinoma with features of both invasive ductal carcinoma (cohesive nests of tumor cells) and invasive lobular carcinoma. Ductal carcinoma in situ (DCIS) associated with ILC was not considered as part of mixed ILC for this study.

Main Outcome Measure

The negative margin definition utilized for the purpose of this study follows recent ASCO/ASTRO/SSA consensus guidelines [26]. A positive margin was defined by the presence of cancer cells on the ink of the surgical specimen; a very close margin was defined by cancer cells present not on ink but within <1 mm of the margin; a close margin was defined by cancer cells present not on ink but within 1 to 3mm of the surgical margin. Both invasive carcinoma and DCIS contributed to the classification of margin status for this study. LRR was defined as ipsilateral breast, chest wall, skin, axillary, supra-clavicular or parasternal nodal recurrence of invasive disease confirmed either histologically or cytologically. Ipsilateral breast tumor recurrence (IBTR) was defined as an ipsilateral breast cancer

recurrence (DCIS or invasive carcinoma) after BCS. LRR events were inclusive of IBTR events. Margins associated with the final procedure performed were used when examining the relationship between margin status and recurrence rates. Contralateral breast cancer was not included as a LRR event. The time from the date of breast cancer diagnosis to the date of confirmation of IBTR or LRR was calculated as the disease-free survival period.

Statistical Analysis

The relationship between clinicopathologic features, type of surgery performed and margin status at initial BCS was examined using a chi-square test and Fisher's exact test. For the multivariable analysis, logistic regression models were used. Additionally, a multivariable Cox proportional hazards model was used to report adjusted odds ratios for performing mastectomy by adjusting the following variables: patient age (continuous), pathological tumor size classification (T1-T3), the presence of lymphovascular invasion (LVI) (present, absent), multifocality (unifocal, multifocal and multicentric), subtype of ILC (pure, mixed) and HER2 status (positive, negative). In addition, the model was used to report adjusted odds ratios for a positive surgical margin by adjusting the following variables: patient age (continuous), year of surgery (1997-2002, 2003-2007), pathological tumor size classification (T1-T3), multifocality (unifocal, multifocal and multicentric), subtype of ILC (pure, mixed) and preoperative MRI (performed, not performed).

A Cox proportional hazards model was used to examine the relationship between clinicopathologic factors and IBTR and LRR. The limited numbers of IBTR and LRR events did not allow us to adjust for other prognostic factors through multivariate analysis. Results were analyzed with SPSS software (Version 22.0, IBM Corp., Armonk, NY) and differences were considered statistically significant when two-tailed p-values were <0.05.

Results

Patient Characteristics and Initial Surgery

Clinicopathologic characteristics matched to initial surgery are shown in Table 1. Mastectomy was performed as an initial surgery in 352 patients (48%); BCS was performed as an initial surgery in 384 patients (52%). In multivariate analysis, pathologic tumor size (OR, 2.7; 95%CI, 1.8–3.9; $p<0.0001$), multifocality (OR, 3.5; 95%CI, 2.4–5.0; $p<0.001$), histological subtype (OR, 1.5; 95%CI, 1.02–2.1; $p=0.04$) and HER2 positivity (OR, 2.4; 95%CI, 1.1–5.0; $p=0.02$) were found to be significant factors associated with the decision to perform a mastectomy.

Margin Status and Re-excision after BCS

The number of patients with positive surgical margins following initial and subsequent surgical procedures is shown in Figure 1. Of the 384 patients initially treated with BCS, additional surgery was performed in 24% ($n=92$). The final procedure in the majority of patients was re-excision (89/92 or 96.8%); only 3 patients (3/92 or 3.2%) required mastectomy following initial BCS. We will refer to patients who received only BCS or BCS with re-excision as cases of 'definitive BCS' for the purposes of this paper. Residual invasive cancer and/or DCIS situ was found in 29% ($n=27$) of the surgical specimens from

patients who had additional surgery. Clinicopathologic characteristics associated with margin positivity are displayed in Table 2. These include tumor size >2 cm, multifocal disease and surgical procedures performed prior to 2002. Pre-operative bilateral breast MRI, which was performed prior to BCS for 77 patients (20%), was not found to reduce the rate of positive margins after adjusting for other clinical factors.

Locoregional and Ipsilateral Breast Tumor Recurrence

After a median follow-up period of 72 months (4–161 months), the incidence of LRR following definitive BCS was 4.5% (17/381) and was 3.4% (12/355) following mastectomy performed either as an initial operation or after BCS (hazard ratio, 1.2; 95%CI, 0.59–2.6; $p=0.58$). The incidence of IBTR was 3.1% (12/381) after definitive BCS. A total of 29.4% of the observed LRR ($n=5$) represented disease recurrence outside of the breast. The relationship between clinicopathologic factors and LRR and IBTR among patients who underwent definitive BCS is shown in Table 3. Pathologic tumor size >2 cm ($p=0.02$), positive lymph node metastasis ($p=0.04$), histologic grade III status ($p=0.02$) and positive margin status ($p=0.02$) were associated with LRR, while age under 40 years at diagnosis ($p=0.02$) and positive margin status ($p=0.006$) were associated with IBTR. IBTR was significantly increased for patients with positive margins, but it was not increased for patients with close margins (Table 4).

Discussion

The results from this retrospective study suggest that the ‘no ink on tumor’ definition for a negative surgical margin should be routinely used for patients diagnosed with ILC or mixed ILC tumors. A descriptive analysis of clinicopathologic characteristics associated with the surgical procedure performed for ILC (mastectomy versus BCS) suggests that multifocality is an important factor associated with the choice for mastectomy for patients diagnosed with ILC. To the best of our knowledge this study is the largest series investigating the impact that the current definition for negative margin assessment (i.e. no ink on tumor) has on LRR for patients diagnosed with ILC and mixed ILC tumors.

Over the last decade, multidisciplinary care has dramatically improved the prognosis of patients with breast cancer [27] and breast cancer surgery has witnessed a shift towards less invasive treatment options, with BCS and sentinel node biopsy becoming part of standard surgical breast cancer management. Nevertheless, wide variability has been observed with respect to re-excision rates nationwide, and rates of re-excision (42–88%) and mastectomy (57%) are high especially among patients with ILC [13–15, 24, 28, 29]. In our study, we observed a 24% overall re-excision rate following BCS. The highest re-excision rates were observed for margins <1 mm (41%) and close margins (23%). The high re-excision rate we observed for patients with close margins could be related to the lack of consensus previously existing for margin assessment in ILC, as the definition of clear margins at our institution remained at 3 mm for the duration of the study period. If our institution had relied upon the new definition of positive margins currently recommended by the ASCO/ASTRO/SSA consensus guidelines, re-excision rates would have decreased to 16%. This could have

potentially led to a concomitant reduction in the economic and psychological burden faced by our patients, as fewer would have required re-excision operations.

Previous studies have examined the relationship between surgical margin status and prognosis in ILC. Broek et al. found no statistically significant difference in local recurrence rates between ILC patients with positive margins and negative margins, however the definition of positive margins utilized was not reported in this study [30]. Galimberti et al. used a margin cut-off of 10 mm, and similarly observed no statistical differences in IBTR and LRR between cases with margins >10 mm and margins <10 mm [31]. In our study, under conditions where surgery achieved negative or close margins (<1 mm or 1–3 mm), the rates of LRR and IBTR for patients diagnosed with ILC and treated with BCS remained low after a median follow-up time of 6 years. Contrarily, significantly higher IBTRs were observed among patients with positive margins (i.e. ink on tumor) than negative margins. Therefore, we suggest that the ASCO/ASTRO/SSO consensus guideline's recommendation that negative margins be defined as 'no ink on tumor' can be applied to ILC for optimal surgical management of breast cancer patients.

It is important to acknowledge that limitations of this study include the retrospective design of the analysis and the small number of LRR and IBTR events. As a result of these limited events, we could only perform univariate analysis in investigating the relationship between the clinicopathologic factors and IBTR and LRR. Additional research is warranted to validate our findings using larger datasets. Although the actual margin width may no longer be important, attention should be paid to findings suggestive of additional tumor burden in the breast, including results from preoperative mammography and ultrasound, and findings of multifocal ILC.

Our study is unique in that it examined a larger number of ILC cases than prior studies and it was derived entirely from one institution. Additionally, all of the pathology slides including those for referral cases were centrally reviewed at DF/BWCC.

In conclusion, LRR rates for ILC patients were found to be low following breast-conserving therapy for patients with close surgical margins (1-3mm) and margins of <1 mm, and these rates did not differ significantly from those seen in patients with negative margins. Our study supports the validity of using 'no ink on tumor' as the standard definition for a negative margin for patients who are diagnosed with pure or mixed ILC treated with multimodality therapy.

Acknowledgments

This work was supported by the Susan G. Komen Foundation for the Cure grant (PDF14302599) and by the NIH grant R25CA089017. Dr. Sonal Jhaveri at Dana-Farber's Postdoc and Graduate Student Affairs Office (PGSAO) edited an earlier version of the manuscript. I gratefully acknowledge the support and generosity of Linda Cutone and Hakuai Medical Cooperation.

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Fig. 1. Margin status of lumpectomy following initial surgery and re-excision

Table 1
Patient Clinicopathologic Characteristics

Clinical factors		Initial surgery		p-value
		BCS, n, (%)	Mastectomy, n, (%)	
Age	– 39	27 (7.0)	30 (8.5)	0.82
	40 – 59	231 (60.2)	215 (61.1)	
	60 – 79	115 (29.9)	98 (27.8)	
	80 –	11 (2.9)	9 (2.6)	
Pathologic Tumor size	T1	303 (78.9)	180 (51.1)	< 0.001
	T2	76 (19.8)	129 (36.7)	
	T3	5 (1.3)	43 (12.2)	
Number of Positive lymph nodes	0	251 (65.3)	157 (44.6)	< 0.001
	1 – 3	92 (24.0)	123 (34.9)	
	4 –	21 (5.5)	59 (16.8)	
	Unknown	20 (5.2)	13 (3.7)	
LVI	Positive	81 (21.1)	115 (32.7)	< 0.001
	Negative	303 (78.9)	237 (67.3)	
Multifocality	Unifocal	305 (79.4)	174 (49.4)	< 0.001
	Multifocal	67 (17.4)	104 (29.6)	
	Multicentric	12 (3.1)	74 (21.0)	
Subtype of ILC	Pure ILC	143 (37.2)	168 (47.7)	0.005
	Mixed ILC	241 (62.8)	184 (52.3)	
ER	Negative	13 (3.4)	14 (4.0)	0.70
	Positive	370 (96.3)	337 (95.7)	
	Unknown	1 (0.3)	1 (0.3)	
PgR	Negative	37 (9.6)	45 (12.8)	0.20
	Positive	337 (87.8)	301 (85.5)	
	Unknown	10 (2.6)	6 (1.7)	
HER2	Negative	330 (85.9)	291 (82.7)	0.01
	Positive	13 (3.4)	28 (8.0)	
	Unknown	41 (10.7)	33 (9.3)	
Histological Grade	1	97 (25.3)	75 (21.3)	0.34
	2	235 (61.2)	220 (62.5)	
	3	48 (12.5)	53 (15.1)	
	Unknown	4 (1.0)	4 (1.1)	
Adjuvant Systemic Therapy	Performed	370 (96.4)	334 (94.9)	0.32
	Not-Performed	1 (0.3)	0 (0)	
	Unknown	13 (3.4)	18 (5.1)	
Radiation Therapy	Performed	367 (95.6)	147 (41.8)	< 0.001
	Not-Performed	17 (4.4)	205 (58.2)	

Clinical factors	Initial surgery		p-value
	BCS, n, (%)	Mastectomy, n, (%)	
Total	384	352	

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Table 2
Relationship Between Clinical Factors and Positive Margin Status Associated with Initial BCS

Clinical factor	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
Age at Diagnosis (Continuous)	1.01	0.99-1.04	0.64	NS		
Year of Surgery (1997-2002 vs. 2003-2007)	0.46	0.24-0.86	0.02	0.43	0.22-0.84	0.01
Pathological Tumor Size (T1 vs. T2, T3)	2.3	1.4-4.0	0.002	2.3	1.2-4.3	0.01
Multifocality (Unifocal vs. Multifocal, Multicentric)	2.3	1.4-3.7	0.001	3.0	1.6-5.7	0.001
Subtype of ILC (Mixed ILC vs. Pure ILC)	2.1	1.2-3.7	0.01	1.6	0.89-3.0	0.12
Preoperative MRI (No vs. Yes)	1.1	0.56-2.3	0.74	1.2	0.56-2.6	0.65

Abbreviations: BCS, breast conserving surgery; NS, not significant

Table 3
Relationship Between Clinicopathologic Factors and LRR /IBTR After Definitive BCS

Clinical factor	LRR (n= 17)*			IBTR (n=12)		
	Odds Ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
Age at diagnosis (Over 40. vs. Under 40)	3.1	0.89-10.8	0.08	4.7	1.2-17.4	0.02
Year of surgery (1997-2002 vs. 2003-2007)	1.2	0.38-4.0	0.72	0.54	0.11-2.7	0.45
Pathologic tumor size (T1 vs. T2, T3)	3.0	1.2-8.0	0.02	2.2	0.66-7.2	0.20
Lymph node metastasis (Negative vs. Positive)	2.7	1.0-7.0	0.04	1.7	0.55-5.4	0.35
Histological grade (I, II vs. III)	3.5	1.2-10.0	0.02	2.9	0.78-10.9	0.11
Multifocality (Unifocal vs. Multifocal, Multicentric)	0.95	0.27-3.3	0.94	0.91	0.20-4.2	0.91
Subtype of ILC (Mixed ILC vs. Pure ILC)	0.86	0.33-2.3	0.76	0.81	0.25-2.7	0.74
Final margin status (Negative, Within 1mm, Close vs. Positive)	5.5	1.3-24.0	0.02	8.5	1.8-38.7	0.006

Abbreviations: LRR, locoregional recurrence; IBTR, ipsilateral breast tumor recurrence; BCS, breast conserving surgery

* LRR for locations other than the ipsilateral breast, n=5

Table 4**LRR and IBTR After BCS According to Final Margin Status**

Final Margin	LRR (n=17)*				IBTR (n=12)			
	Number of events (%)	Hazard Ratio	95% CI	p-value	Number of events (%)	Hazard Ratio	95% CI	p-value
Negative (n=265)	9 (3.4)		Reference		8 (3.0)		Reference	
Close (n=62)	3 (4.8)	1.6	0.4-5.7	0.51	1 (1.6)	0.57	0.07-4.6	0.60
Within 1mm (n=43)	3 (7.0)	2.0	0.5-7.3	0.31	1 (2.3)	0.73	0.09-5.8	0.77
Positive (n=11)	2 (18.2)	6.6	1.4-30.7	0.02	2 (18.2)	7.5	1.6-35.3	0.01

Abbreviations: LRR, locoregional recurrence; IBTR, ipsilateral breast tumor recurrence; BSC, breast conserving surgery

* LRR for locations other than the ipsilateral breast, n=5