Ann Surg Oncol (2015) 22:4280–4286
DOI 10.1245/s10434-015-4570-8

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

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

Yasuaki Sagara, MD[1], William T. Barry, PhD[2], Melissa Anne Mallory, MD[1], Ines Vaz-Luis, MD[3], Fatih Aydogan, MD[1], Jane E. Brock, MD, PhD[4], Eric P. Winer, MD[3], Mehra Golshan, MD[1], and Otto Metzger-Filho, MD[3]

[1]Department of Surgery, Brigham and Women's Hospital, Boston, MA; [2]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA; [3]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA; [4]Department of Pathology, Brigham and Women's Hospital, Boston, MA

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 %). During a 72-month median follow-up period, 12 (3.1 %) ipsilateral breast tumor recurrences (IBTR) and 5 (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 [odds ratio (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 1 mm were not.

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.

Invasive lobular carcinoma (ILC) accounts for 10–15 % of breast carcinoma cases nationwide.[1,2] Morphologically, ILC is composed of small, uniform cells that 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 ILCs 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 noncohesive 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 reexcision 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

Otto Metzger-Filho and Mehra Golshan are senior authors. They have contributed equally.

First Received: 30 January 2015;
Published Online: 18 April 2015

Y. Sagara, MD
e-mail: yasuaki@sagara.or.jp

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 compared with 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 investigated how clinicopathologic characteristics of patients influence the surgical procedure performed for diagnoses of ILC and mixed ILC.

PATIENTS AND 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 Database at Dana-Farber Cancer Institute 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 $\geq$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 noncohesive 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 ILC. 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 1–3 mm 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, supraclavicular, 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

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)	
Total	384	352	

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 (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 [odds ratio (OR) 2.7; 95 % confidence interval (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.

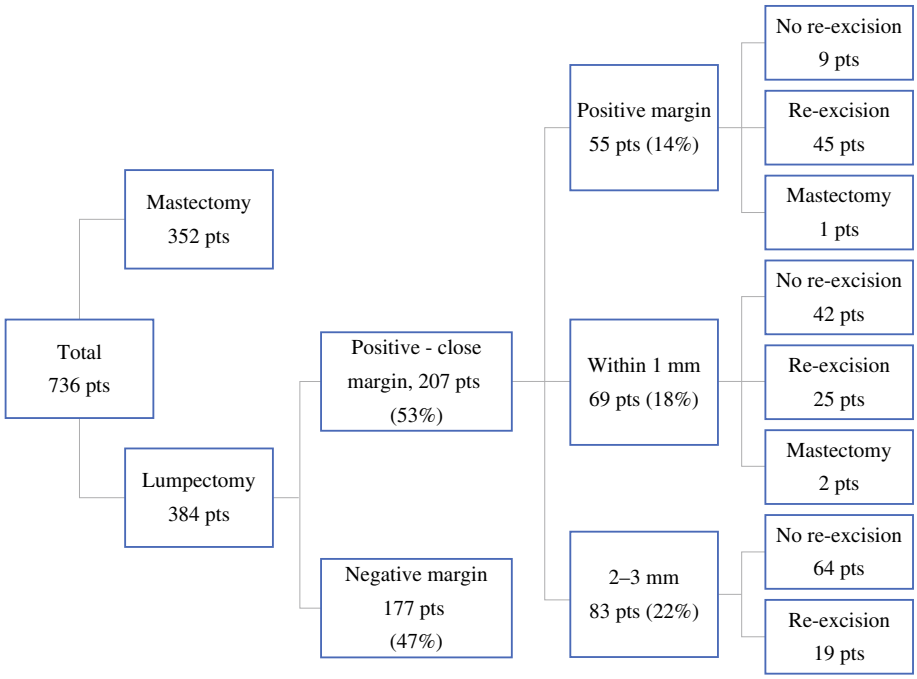

FIG. 1 Margin status of lumpectomy following initial surgery and reexcision

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

BCS breast-conserving surgery, *NS* not significant

Margin Status and Reexcision after BCS

The number of patients with positive surgical margins following initial and subsequent surgical procedures is shown in Fig. 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 reexcision (89/92 or 96.8 %); only three patients (3/92 or 3.2 %) required mastectomy following initial BCS. We will refer to patients who received only BCS or BCS with reexcision 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 before 2002. Preoperative bilateral breast MRI, which was performed before 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 (range 4–161) months, the incidence of LRR following definitive BCS was 4.5 % (17/381) and following mastectomy was 3.4 % (12/355) 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

TABLE 3 Relationship between clinicopathologic factors and LRR/IBTR after definitive BCS

Clinical factor	LRR ($n = 17$)[a]			IBTR ($n = 12$)		
	Odds ratio	95 % CI	p value	Odds ratio	95 % CI	p value
Age at diagnosis (>40 vs <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 1 mm, close vs positive)	5.5	1.3–24.0	0.02	8.5	1.8–38.7	0.006

LRR locoregional recurrence, *IBTR* ipsilateral breast tumor recurrence, *BCS* breast-conserving surgery

[a] 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 ($n = 17$)[a]				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 1 mm ($n = 43$)	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

LRR locoregional recurrence, *IBTR* ipsilateral breast tumor recurrence, *BSC* breast-conserving surgery

[a] LRR for locations other than the ipsilateral breast, $n = 5$

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, whereas age younger than 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 vs 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 to investigate 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.

During the past 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 reexcision rates nationwide, and rates of reexcision (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 reexcision rate following BCS. The highest reexcision rates were observed for margins <1 mm (41 %) and close margins (23 %). The high reexcision 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, reexcision rates would have decreased to 16 %. This potentially could have led to

a concomitant reduction in the economic and psychological burden faced by our patients, because fewer would have required reexcision 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 cutoff 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 IBRT events. As a result of these limited events, we could only perform univariate analysis to investigate 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, because it examined a larger number of ILC cases than prior studies and was derived entirely from one institution. Additionally, all of the pathology slides, including those for referral cases, were reviewed centrally 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 (1–3 mm) and margins of <1 mm. 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.

ACKNOWLEDGMENT 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. The authors gratefully acknowledge the support and generosity of Linda Cutone and Hakuaikai Medical Cooperation.

DISCLOSURE The authors have no conflicts of interest concerning this study.

REFERENCES

1. Li CI, Anderson BO, Daling JR, Moe RE. Trends in incidence rates of invasive lobular and ductal breast carcinoma. *JAMA*. 2003;289:1421–4.
2. Yoder BJ, Wilkinson EJ, Massoll NA. Molecular and morphologic distinctions between infiltrating ductal and lobular carcinoma of the breast. *Breast J*. 2007;13:172–9.
3. Buchanan CL, Flynn LW, Murray MP, et al. Is pleomorphic lobular carcinoma really a distinct clinical entity? *J Surg Oncol*. 2008;98:314–7.
4. Jacobs M, Fan F, Tawfik O. Clinicopathologic and biomarker analysis of invasive pleomorphic lobular carcinoma as compared with invasive classic lobular carcinoma: an experience in our institution and review of the literature. *Ann Diagn Pathol*. 2012;16:185–9.
5. Iorfida M, Maiorano E, Orvieto E, et al. Invasive lobular breast cancer: subtypes and outcome. *Breast Cancer Res Treat*. 2012;133:713–23.
6. Yeatman T, Cantor A, Smith T. Tumor biology of infiltrating lobular carcinoma: implications for management. *Ann Surg*. 1995;222:549–61.
7. Pestalozzi BC, Zahrieh D, Mallon E, et al. Distinct clinical and prognostic features of infiltrating lobular carcinoma of the breast: combined results of 15 International Breast Cancer Study Group clinical trials. *J Clin Oncol*. 2008;26:3006–14.
8. Tan SM, Behranwala KA, Trott PA, et al. A retrospective study comparing the individual modalities of triple assessment in the preoperative diagnosis of invasive lobular breast carcinoma. *Eur J Surg Oncol*. 2002;28:203–8.
9. Arpino G, Bardou VJ, Clark GM, Elledge RM. Infiltrating lobular carcinoma of the breast: tumor characteristics and clinical outcome. *Breast Cancer Res*. 2004;6:R149–56.
10. Berg WA, Gutierrez L, NessAiver MS, et al. Diagnostic accuracy of mammography, clinical examination, US, and MR imaging in preoperative assessment of breast cancer. *Radiology*. 2004;233:830–49.
11. Krecke KN, Gisvold JJ. Invasive lobular carcinoma of the breast: mammographic findings and extent of disease at diagnosis in 184 patients. *AJR Am J Roentgenol*. 1993;161:957–60.
12. Arps DP, Healy P, Zhao L, et al. Invasive ductal carcinoma with lobular features: a comparison study to invasive ductal and invasive lobular carcinomas of the breast. *Breast Cancer Res Treat*. 2013;138:719–26.
13. Wilke LG, Czechura T, Wang C, et al. Repeat surgery after breast conservation for the treatment of stage 0 to II breast carcinoma: a report from the national cancer database, 2004-2010. *JAMA Surg*. 2014;149:1296–305.
14. Arps DP, Jorns JM, Zhao L, et al. Reexcision rates of invasive ductal carcinoma with lobular features compared with invasive ductal carcinomas and invasive lobular carcinomas of the breast. *Ann Surg Oncol*. 2014;21:4152–8.
15. Wanis ML, Wong JA, Rodriguez S, et al. Rate of re-excision after breast-conserving surgery for invasive lobular carcinoma. *Am Surg*. 2013;79:1119–22.

16. Mai KT, Yazdi HM, Isotalo PA. Resection margin status in lumpectomy specimens of infiltrating lobular carcinoma. *Breast Cancer Res Treat*. 2000;60:29–33.
17. Moore MM, Borossa G, Imbrie JZ, et al. Association of infiltrating lobular carcinoma with positive surgical margins after breast-conservation therapy. *Ann Surg*. 2000;231:877–82.
18. Blichert-Toft M, Rose C, Andersen JA, et al. Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. Danish Breast Cancer Cooperative Group. *J Natl Cancer Inst Monogr*. 1992;(11):19–25.
19. Arriagada R, Le MG, Rochard F, Contesso G. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institut Gustave-Roussy Breast Cancer Group. *J Clin Oncol*. 1996;14:1558–64.
20. Poggi MM, Danforth DN, Sciuto LC, et al. (2003) Eighteen-year results in the treatment of early breast carcinoma with mastectomy versus breast conservation therapy: The National Cancer Institute randomized trial. *Cancer*. 98:697–702.
21. Van Dongen JA, Voogd AC, Fentiman IS, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. J Natl Cancer Inst. 2000;92: 1143–50.
22. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med*. 2002;347:1227–32.
23. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, Jeong JH. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med.* 2002;347:1233–41.
24. Truin W, Roumen RM, Siesling S, et al. Patients with invasive lobular breast cancer are less likely to undergo breast-conserving surgery: a population based study in the Netherlands. *Ann Surg Oncol*. 2015;22:1471–8.
25. McCahill LE, Single RM, Aiello Bowles EJ, et al. Variability in reexcision following breast conservation surgery. JAMA. 2012;307:467–75.
26. Buchholz TA, Somerfield MR, Griggs JJ, et al. Margins for breast-conserving surgery with whole-breast irradiation in stage I and II invasive breast cancer: American Society of Clinical Oncology endorsement of the Society of Surgical Oncology/ American Society for Radiation Oncology consensus guideline. *J Clin Oncol*. 2014;32:1502–6.
27. Sledge GW, Mamounas EP, Hortobagyi GN, et al. Past, present, and future challenges in breast cancer treatment. *J Clin Oncol.* 2014;32:1979–86.
28. Mai KT, Yazdi HM, Isotalo P. Resection margin status in lumpectomy specimens of infiltrating lobular carcinoma. *Breast Cancer Res Treat*. 2000;60:29–33.
29. Moore MM, Borossa G, Imbrie JZ, et al. Association of infiltrating lobular carcinoma with positive surgical margins after breast-conservation therapy. *Ann Surg*. 2000;231:877–82.
30. Van den Broek N, van der Sangen MJC, van de Poll-Franse L V, et al. Margin status and the risk of local recurrence after breast-conserving treatment of lobular breast cancer. *Breast Cancer Res Treat*. 2007;105:63–8.
31. Galimberti V, Maisonneuve P, Rotmensz N, et al. Influence of margin status on outcomes in lobular carcinoma: experience of the European Institute of Oncology. *Ann Surg.* 2011;253:580–4.