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ORIGINAL ARTICLE – BREAST ONCOLOGY

Lobular Histology Does Not Predict the Need for Axillary Dissection Among ACOSOG Z0011-Eligible Breast Cancers

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ABSTRACT

Background. The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial demonstrated that axillary lymph node dissection (ALND) may be omitted for women with two or fewer positive sentinel nodes (SLNs) undergoing breast-conservation therapy (BCT). Lobular histology comprises a minority of patients, and applicability to these discohesive cancers has been questioned.

Methods. From August 2010 to March 2017, patients undergoing BCT for cT1-2N0 cancer with positive SLNs were prospectively managed with ALND for three or more positive SLNs or gross extracapsular extension (ECE). In this study, clinicopathologic characteristics and nodal burden were compared between pure/mixed invasive lobular cancer (ILC) and invasive ductal cancer (IDC) patients.

Results. Among 813 consecutive patients, 104 (12.8%) had ILC and 709 (87.2%) had IDC. ILC was more often multifocal and low grade, and less frequently had lymphovascular invasion (all $p < 0.001$). ILC more often had SLN macrometastases (81.7% ILC vs. 69.4% IDC; $p = 0.01$) and more than 2 mm of ECE (30.8% ILC vs. 19.5% IDC; $p = 0.03$), but the proportions of cases with three or more positive SLNs were similar in the two groups (14.4% ILC vs. 9.9% IDC; $p = 0.2$). The ALND procedure was performed for 20 ILC patients (19.2%) compared with 97 IDC patients (13.7%) ($p = 0.2$). Additional positive nodes were found in 80% of the ILC patients versus 56.7% of the IDC patients ($p = 0.09$). The ALND and nodal burden rates were similar in the estrogen receptor-positive (ER+) subset analysis. In the multivariable analysis, lobular histology ($p = 0.03$) and larger tumors ($p = 0.03$) were associated with additional positive nodes. During a median follow-up period of 42 months, there were no isolated axillary recurrences.

Conclusions. Despite a higher proportion of SLN macrometastases and association with more positive nodes at ALND, lobular histology does not predict the need for ALND. ALND is not indicated on the basis of histology among patients otherwise meeting Z0011 criteria.

The past decade has seen significant progress in the management of the axilla in breast cancer. Sentinel lymph node biopsy (SLNB) has become the standard method for axillary staging of clinically node-negative (cN0) disease,[1,2] allowing for oncologically appropriate treatment while minimizing unnecessary morbidity.

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial randomized women with T1–T2 cN0 tumors undergoing breast-conserving surgery followed by whole-breast irradiation (BCT) for fewer than three positive sentinel lymph nodes (SLNs) to either SLNB alone or SLNB and axillary lymph node dissection (ALND). Recently updated 10-year results demonstrate no difference in locoregional recurrence or overall survival, providing evidence for the safe omission of ALND in this population.[3] Similar results were seen in the AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery?)

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randomized trial, which demonstrated noninferiority of SLNB with axillary irradiation compared with ALND for T1–T2 cN0 patients with fewer than three positive SLNs.[4]

The widespread adoption of the ACOSOG Z0011 trial results has allowed ALND to be safely omitted for many women who meet the specified criteria.[5] However, the applicability of the ACOSOG Z0011 trial results to patients with lobular histology has been questioned due to its innately discohesive tumor biology[6], and widely varying data on patterns of nodal positivity.[7–14] Furthermore, patients with lobular histology comprised only 7% of the ACOSOG Z0011 trial population.[3] Studies of patients treated in the post-Z0011 era have shown that lobular histology independently predicts the use of ALND, even among those meeting the eligibility criteria for safe omission of the procedure.[15,16]

In this study of consecutive T1–T2 cN0 patients with positive SLNs undergoing BCT and with prospectively defined criteria for ALND, we sought to examine the need for ALND and residual nodal disease burden at ALND among those with lobular histology compared with their more common ductal counterparts.

METHODS

Starting in August 2010, consecutive patients with T1–T2 cN0 invasive breast cancer undergoing BCT who were found to have SLN metastases on routine hematoxylin and eosin (H&E) staining were managed with ALND if metastases were present in three or more SLNs or if they were noted to have gross extracapsular (ECE), defined as matted nodes or macroscopically evident extranodal disease at the time of SLNB. For the remaining patients, ALND was omitted.

Microscopic ECE, the presence of abnormal nodes in preoperative imaging studies, and biopsy-proven metastases in nonpalpable nodes were not considered a priori indications for ALND. Intraoperative frozen section was not used, and completion ALND was performed as a separate procedure when required. Patients were prospectively followed in a registered institutional database. Those who received neoadjuvant chemotherapy, underwent mastectomy after attempted BCT, or had SLN metastases detected only by immunohistochemistry (IHC) were excluded.

After institutional review board approval, patients treated between August 2010 and March 2017 were identified. Those with pure invasive lobular carcinoma or mixed ductal/lobular features were categorized as ILC. Patients with invasive ductal carcinoma (IDC) were used for comparison, and patients with non-ductal/non-lobular histology ($n = 7$) were excluded from this analysis.

Standard clinicopathologic characteristics, details of axillary operation(s), and nodal burden were compared between the ILC and IDC patients. The rates for administration of adjuvant systemic therapies, and for the occurrence of locoregional recurrence (LRR) and distant disease (DD) were assessed. The primary outcomes of interest were rates of ALND, nodal burden, and rates of nodal recurrence.

Comparisons were made between groups using Fisher's exact test or the Chi square test for categorical variables, and the Wilcoxon rank-sum test for continuous variables. Uni- and multivariable analyses were performed using logistic regression models, with a priori determination of factors included for analysis. A p value less than 0.05 was considered statistically significant. All statistical analyses were conducted using R software version 3.5.0 (R Core Development Team, Vienna, Austria).

RESULTS

From August 2010 to March 2017, 813 consecutive patients with cT1-T2N0 tumors and positive SLNs undergoing BCT were identified. Of these patients, 104 (12.8%) had ILC and 709 (87.2%) had IDC. The clinicopathologic characteristics of both groups are summarized in Table 1. Preoperative nodal imaging was not routine, and was performed before referral or by physician discretion, with a similar minority of patients in both groups having abnormal lymph nodes visualized (22.1% ILC vs. 25.5% IDC; $p = 0.5$).

Preoperative nodal biopsy was performed for a small number of patients, and its use did not vary with histology (3.8% ILC vs. 6.3% IDC; $p = 0.4$). The vast majority of the ILC patients (96%) were estrogen receptor-positive (ER+). Compared with the IDC patients, the patients with ILC more often had low (2.6% IDC vs. 19% ILC) or intermediate (56% IDC vs. 62% ILC) nuclear grade ($p < 0.001$) and multifocality (25.0% ILC vs. 12.1% IDC; $p < 0.001$), and less frequently had lymphovascular invasion (25.0% ILC vs. 62.9% IDC; $p < 0.001$).

A median of three SLNs were excised in both groups ($p = 0.8$), with a median of one positive SLN in both groups. The patients with ILC were more likely to harbor macrometastases in the SLNs (81.7% ILC vs. 69.4% IDC; $p = 0.01$) and to have more than 2 mm of ECE (30.8% ILC vs. 19.5% IDC) versus 2 mm or less of ECE or no ECE ($p = 0.03$), and this pattern persisted in the subset analysis of the ER+ patients (Table 2). However, the proportion of patients with one or two positive SLNs meeting the criteria for SLNB alone was similar in the two groups, both overall (85.6% ILC vs. 90.1% IDC; $p = 0.2$) and in the ER+ subset analysis (85.0% ILC vs. 89.8% IDC; $p = 0.2$).

TABLE 1 Clinicopathologic characteristics of ILC and IDC patients

Characteristic	ILC (n = 104) n (%)	IDC (n = 709) n (%)	P value
Age at surgery: years, median (IQR)	58 (34–92)	58 (30–86)	0.8
Pathologic tumor size: cm, median (IQR)	1.75 (0.40–5.20)	1.70 (0.10–5.70)	0.3
Palpable tumor	40 (38.5)	299 (42.2)	0.5
Abnormal nodes on imaging	23 (22.1)	181 (25.5)	0.5
Preoperative node biopsy done	4 (3.8)	45 (6.3)	0.4
Receptor status			0.3
ER+/HER2–	95 (91.3)	589 (83.1)	
ER+/HER2+	5 (4.8)	58 (8.2)	
ER–/HER+	1 (1.0)	21 (3.0)	
ER–/HER2–	3 (2.9)	41 (5.8)	
Nuclear grade[a]			< 0.001
1	19 (18.8)	18 (2.6)	
2	63 (62.4)	390 (55.6)	
3	19 (18.8)	294 (41.9)	
Multifocal	26 (25.0)	86 (12.1)	< 0.001
Lymphovascular invasion	26 (25.0)	446 (62.9)	< 0.001

ILC pure invasive lobular or mixed ductal/lobular carcinoma; *IDC* pure invasive ductal carcinoma; *IQR* interquartile range; *ER* estrogen receptor; *HER2* human epidermal growth factor receptor 2

[a]Unknown for 10 patients (3 ILC, 7 IDC)

Completion ALND was performed for 20 ILC patients (19.2%) and 97 IDC patients (13.7%) (p = 0.2). The indications for ALND were similar in the two groups, with the majority of ALNDs performed for three or more positive SLNs (75.0% ILC vs. 60.8% IDC) versus clinical judgment or ECE (p = 0.6) (Table 2). Additional positive nodes were found in 80% of the ER+ ILC patients compared with 58.9% of the ER+ IDC patients (p = 0.13), with a median of two additional positive nodes retrieved in the ER+ ILC patients compared with one node in the ER+ IDC patients (p = 0.08). Completion ALND was not performed for 11 patients despite the presence of three or more positive SLNs due to significant clinical comorbidities believed to preclude re-operation (n = 4), patient refusal despite recommendation (n = 2), or the surgeon's clinical judgment (n = 5).

On multivariable analysis, lobular histology (odds ratio [OR] 3.37, 95% confidence interval [CI] 0.29–6.45, p = 0.03) and increasing pathologic tumor size (OR 1.25, 95% CI 0.11–2.38, p = 0.03) were independently associated with additional positive lymph nodes at ALND, after adjusting for both ER status and HER2 status.

Adjuvant radiotherapy was received as planned by 759 (93%) of the patients, 92 (90.2%) with ILC and 667 (94.1%) with IDC (p = 0.2). The status of radiotherapy receipt was unknown for two patients. Systemic chemotherapy was administered to 70 (68%) of the ILC patients compared with 531 (75.4%) of the IDC patients (p = 0.13), and all the HER2 positive (HER2+) patients received targeted anti-HER2 therapy. Endocrine therapy was administered to 93 (93.9%) of the hormone receptor-positive ILC patients and 616 (96%) of the hormone receptor-positive IDC patients (p = 0.4).

During a median follow-up period of 3.5 years (range 0.1–7.9), neither group had an isolated axillary recurrence. Overall, 49 patients experienced a recurrence of disease (15 isolated LRRs, 8 synchronous locoregional/distant recurrences, and 26 distant recurrences). Nine IDC patients experienced in-breast recurrence only, with none observed in the ILC group. Two patients in each group had synchronous breast and axillary recurrence, and two IDC patients had a non-axillary nodal recurrence. Combined locoregional/distant recurrence was observed in 1 ILC patient and 7 IDC patients, and distant disease alone in 5 ILC and 21 IDC patients.

DISCUSSION

In this large population of cT1-T2N0 patients who underwent BCT with positive SLNs, we found that ILC patients were no more likely to require ALND. Uncertainty regarding the applicability of Z0011 results to ILC arises

TABLE 2 Pathologic nodal characteristics at SLNB and ALND

SLNB	All patients (n = 813)			ER+ patients (n = 747)		
	All ILC (n = 104) n (%)	All IDC (n = 709) n (%)	P value	ER+ ILC (n = 100) n (%)	ER+ IDC (n = 647) n (%)	P value
No. of SLNs excised: median (IQR)	3 (1–9)	3 (0–18)	0.8	3 (1–9)	3 (0–18)	0.7
No. of positive SLNs			0.2			0.2
1 or 2	89 (85.6)	639 (90.1)		85 (85.0)	581 (89.8)	
≥ 3	15 (14.4)	70 (9.9)		15 (15.0)	66 (10.2)	
Extracapsular extension (ECE)[a]			0.027			0.03
None	54 (51.9)	437 (62.7)		50 (50.0)	388 (61.0)	
≤ 2 mm	18 (17.3)	124 (17.8)		18 (18.0)	118 (18.6)	
> 2 mm	32 (30.8)	136 (19.5)		32 (32.0)	130 (20.4)	
Size of nodal metastasis			0.013			0.007
Micrometastasis	19 (18.3)	217 (30.6)		17 (17.0)	199 (30.8)	
Macrometastasis	85 (81.7)	492 (69.4)		83 (83.0)	448 (69.2)	

ALND	All ILC (n = 20) n (%)	All IDC (n = 97) n (%)	P value	ER+ ILC (n = 20) n (%)	ER+ IDC (n = 90) n (%)	P value
Indication			0.6			0.7
≥ 3 Positive SLNs	15 (75.0)	59 (60.8)[b]		15 (75.0)	56 (62.2)	
Gross ECE	4 (20.0)	31 (32.0)		4 (20.0)	28 (31.1)	
Clinical judgment	1 (5.0)	7 (7.2)		1 (5.0)	6 (6.7)	
Additional positive nodes at ALND	16 (80.0)	55 (56.7)	0.091	16 (80.0)	53 (58.9)	0.13
No. of additional positive nodes: median (IQR)	2 (0–53)	1 (0–25)	0.06	2 (0–53)	1 (0–25)	0.08
No. of additional nodes excised: median (IQR)	15 (6–53)	15 (0–36)	0.6	15 (6–53)	15 (0–36)	0.6

SLNB sentinel lymph node biopsy; *ALND* axillary lymph node dissection; *ILC* pure invasive lobular or mixed ductal/lobular carcinoma; *IDC* pure invasive ductal carcinoma; *ER+* estrogen receptor-positive; *SLN* sentinel lymph node; *IQR* interquartile range; *ECE* extracapsular extension

[a]Unknown for 12 patients with IDC

[b]ALND deferred for 11 patients with ≥ 3 positive SLNs due to significant comorbidities (n = 4), patient refusal (n = 2), or clinical judgment (n = 5)

from these patients having comprised a small minority (7%, $n = 60$) of the trial population,[3] and their innately discohesive biology.[6]

In a single-institution study examining a sample of Z0011-eligible patients treated in the early post-Z0011 era, ALND was more frequently performed in patients with lobular histology ($p = 0.01$).[15] Similar findings were reported in a more recent population-based series including 8191 cT1-T2N0 patients with positive SLNs treated between 2011 and 2015, with lobular histology being independently associated with performance of ALND (OR 1.2, 95% CI 1.0–1.4, $p = 0.02$).[16]

In the current study, 14% of the Z0011-eligible ILC patients had three or more positive SLNs, thereby meeting the criteria for ALND. This rate was similar to the rate for the IDC patients. Widely varying data exist on patterns of nodal positivity in ILC. A number of retrospective studies have found lobular histology to be associated with the presence of nodal micrometastases and isolated tumor cells,[11–13] which are thought to show the discohesive nature of ILC. The largest of these studies included 89,971 patients with T1–T2 cancers, of whom 10,146 had ILC and 79,825 had IDC. Although the ILC patients were more likely to have isolated tumor cells (OR 1.8; 95% CI 1.6–2.0), they were found less likely to harbor both micrometastases (OR 0.91; 95% CI 0.83–0.99) and macrometastases (OR 0.95; 95% CI 0.90–0.99).[11] Conversely, Vandorpe et al.[17] reported a lower likelihood of any nodal involvement with ILC histology than with non-ILC histology (20.5% vs. 28.3%; OR 0.66; 95% CI

0.41–1.0) in a population of 1506 cN0 patients treated with SLNB between 2000 and 2009. Our results suggest a more frequent presence of macrometastases but an overall similar distribution of sentinel nodal involvement in ILC and IDC, with the majority of patients in both groups having only one or two positive sentinel nodes.

Multiple nomograms have been developed to predict the likelihood of non-SLN metastases. Van Zee et al.[10] studied 702 consecutive SLN positive patients treated from 1996 to 2002 who underwent completion ALND and found in their multivariate analysis that lobular histology was not associated with non-SLN metastases ($p = 0.8$), although these patients were grouped with those who had low-grade IDC. Conversely, Mittendorf et al.[9] found lobular histology to be independently associated with non-SLN metastases (OR 1.3; 95% CI 0.59–2.96; $p = 0.03$) in a study of 509 patients with positive SLNs who underwent ALND. In this study, neither the frequency of additional non-SLN metastases found at ALND nor the number of involved nodes at ALND differed significantly between the ILC and IDC patients, even in a subset analysis of ER+ patients alone.

Receptor status is recognized to have an impact on patterns of nodal positivity. Multiple studies have shown that patients with triple-negative tumors are significantly less likely than patients with other subtypes to have metastases in four or more axillary nodes, whereas those with HER2+ tumors are significantly more likely to have four or more positive nodes, even after adjustment for age, tumor size, grade, and lymphovascular invasion.[18–20]

Given the impact of subtype on the likelihood of a heavy nodal burden, our ER+ subset analyses and multivariable model with adjustment for both receptor subtype and tumor size strengthen the finding that although lobular histology was associated with additional positive nodes at ALND, the likelihood of requirement of ALND was no different. A similar result was reported by Caudle et al.[7] in a retrospective study of T1–T2 patients with a positive node biopsy, in which lobular histology was associated with the presence of three or more additional positive nodes at completion ALND after adjustment for tumor size and subtype. However, in a retrospective review of 309 SLN-positive patients who had completion ALND, lobular histology was found to have no bearing on the likelihood of four or more positive nodes in the multivariate analysis.[8] This contemporary population of patients treated prospectively supports the applicability of the Z0011 approach to patients meeting the trial eligibility criteria regardless of histology.

The limitations of this study included its retrospective nature and the presence of fewer ILC patients than IDC patients. However, we examined a large, contemporary population of patients treated prospectively in the Z0011 era during a 7-year period. During a 3.5-year follow-up period, no isolated axillary failures occurred, and because the majority of recurrences in the axilla occur within 5 years after diagnosis,[21] the rates are unlikely to increase significantly with a longer follow-up period. Although lobular carcinomas are recognized to have a distinct biology and behavior, these results support the safe application of Z0011 to eligible patients based on similar rates of ALND, nodal burden, and the absence of any isolated axillary recurrences at the time of this writing.

CONCLUSIONS

In this consecutive population of cT1-T2N0 patients undergoing BCT with positive sentinel nodes who were prospectively treated with ALND for three or more positive SLNs or gross ECE, we found that the patients with lobular histology were no more likely to require ALND than those with ductal histology, both overall and in the subset analysis of ER+ patients alone. Although lobular histology was associated with positive nodes at ALND after adjustment for size and subtype, the nodal burden itself was not significantly different. Despite the unique biology of lobular carcinoma, these results support the omission of ALND for invasive lobular cancers that otherwise meet Z0011 clinical eligibility criteria.

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