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ORIGINAL ARTICLE – BREAST ONCOLOGY

The Extent of Extracapsular Extension May Influence the Need for Axillary Lymph Node Dissection in Patients with T1–T2 Breast Cancer

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ABSTRACT

Background. Whether extracapsular extension (ECE) of tumor in the sentinel lymph node (SLN) is an indication for axillary lymph node dissection (ALND) in patients managed by American College of Surgeons Oncology Group Z0011 criteria is controversial. Here we examine the correlation between ECE in the SLN and disease burden in the axilla.

Methods. Patients meeting Z0011 clinicopathologic criteria (pT1–2, cN0 with <3 positive SLNs) were selected from a prospectively maintained database (2006–2013). Chart review documented the presence and extent of ECE. Neoadjuvant chemotherapy patients were excluded. Comparisons were made by presence and extent (≤2 vs. >2 mm) of ECE.

Results. Of 11,730 patients, 778 were pT1–2, cN0 with <3 positive SLNs without ECE, and 331 (2.8 %) had ECE. Of these, 180 had ≤2 mm and 151 had >2 mm of ECE. Patients with ECE were older (57 vs. 54 years; $p = 0.001$) and had larger (2.0 vs. 1.7 cm; $p < 0.0001$), multifocal ($p = 0.006$), hormone receptor–positive tumors ($p = 0.0164$) with lymphovascular invasion ($p < 0.0001$). Presence and extent of ECE were associated with greater axillary disease burden; 20 and 3 % of patients with and without ECE, respectively, had ≥4 additional positive nodes at completion ALND ($p < 0.0001$), and 33 % of patients with >2 mm ECE had ≥4 additional positive nodes at completion ALND, compared with 9 % in the <2 mm group ($p < 0.0001$). On multivariate analysis, >2 mm of ECE was the strongest predictor of ≥4 positive nodes at completion ALND (odds ratio 14.2).

Conclusions. Presence and extent of ECE were significantly correlated with nodal tumor burden at completion ALND, thus suggesting that >2 mm of ECE may be an indication for ALND or radiotherapy when applying Z0011 criteria to patients with metastases in <3 SLNs. ECE reporting should be standardized to facilitate future studies.

Axillary nodal involvement has long been recognized as a key prognostic factor in invasive breast cancer, and sentinel lymph node biopsy (SLNB) is the accepted standard of care for axillary staging.[1–3] Recently, approaches to axillary management have undergone major changes, and there is great interest in identifying patients who do not require completion axillary lymph node dissection (ALND) despite the presence of positive sentinel nodes. Two randomized clinical trials have addressed this question. The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial demonstrated no differences in locoregional recurrence or survival for women with T1–2, clinically N0 tumors undergoing breast-conserving surgery with whole-breast irradiation when metastases in 1 or 2 sentinel lymph nodes (SLNs) were managed with SLNB alone versus SLNB and ALND.[4,5] The After Mapping of the Axilla: Radiotherapy or Surgery? (AMAROS) trial showed no advantage for ALND compared with SLNB plus radiation to the axillary and medial supraclavicular

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fields (ART) in patients with <3 positive sentinel nodes.[6] Thus, selection criteria for management with SLNB alone, or SLNB plus ART, are a major clinical controversy.

Extracapsular extension (ECE) is the growth or spread of tumor cells outside of the lymph node capsule. ECE is recognized as an indicator of poor prognosis.[7] Retrospective analyses have shown that ECE is correlated with negative prognostic factors, including lymphovascular invasion (LVI) and macrometastases in the SLN.[8,9] ECE has also been demonstrated to predict the presence of non-SLN involvement.[1,10,11]

Whether the presence of ECE in the SLN is an indication for ALND or ART in patients otherwise eligible to be managed with SLNB alone according to ACOSOG Z0011 criteria is uncertain. Patients with gross ECE were excluded from ACOSOG Z0011, and the presence of microscopic ECE was not evaluated in that study. We sought to determine the correlation between the presence and extent of ECE in the SLN and disease burden in the axilla in clinically node-negative women with T1 and T2 breast carcinomas and to identify factors associated with the presence of ECE in the SLN.

METHODS

After institutional review board approval, retrospective review of prospective databases was undertaken to identify patients with clinical stage T1–2, node-negative breast cancer who underwent SLNB at Memorial Sloan Kettering Cancer Center (MSKCC) from January 2006 to March 2013. Patients receiving neoadjuvant therapy, those with pathologically negative or immunohistochemistry-only positive SLNs, and those with ≥3 positive SLNs were excluded, leaving a cohort of patients with early-stage breast cancer and 1 or 2 positive SLNs by routine hematoxylin and eosin staining. Although most patients were treated before the adoption of ACOSOG Z0011 criteria at MSKCC (August 2010), they were retrospectively considered eligible for this approach according to clinical and pathologic staging criteria regardless of the type of breast surgery performed.

Before the adoption of ACOSOG Z0011 criteria, patients with 1 or 2 positive SLNs typically underwent ALND. In the post-Z0011 era, patients having breast-conserving surgery were managed according to the Z0011 protocol, with ALND performed for gross ECE and/or ≥3 positive SLNs. There was no defined policy for completion ALND based on microscopic ECE. Standard clinical and pathologic data, including the presence and extent of ECE in the SLN, defined as absent, ≤2 mm, or >2 mm of ECE, were abstracted from the medical record. Cases where this information was missing were reviewed by the study pathologist (A.C.). Comparisons were made between patients with and without ECE and by the extent of ECE by using Fisher's, Wilcoxon rank-sum, and Kruskal–Wallis tests. All statistical analysis was done in SAS 9.2 (SAS

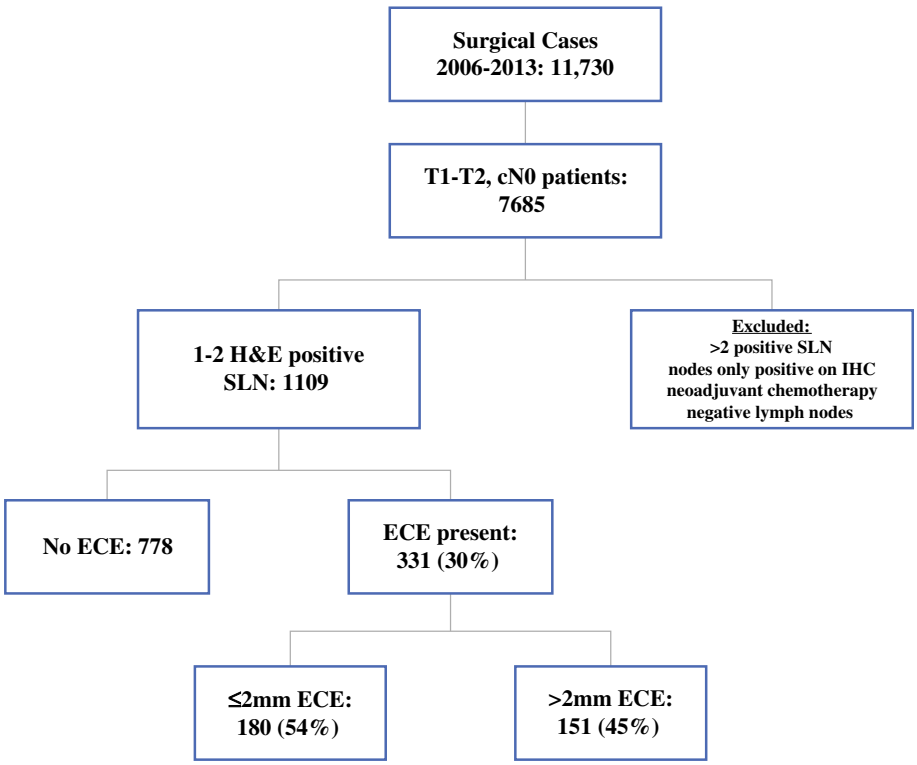

FIG. 1 Patient selection

Institute, Cary, NC), and p-values <0.05 were considered significant. Univariate and multivariate logistic regression models were used to assess associations between selected factors and the involvement of ≥4 nodes in patients with completion ALND.

RESULTS

Between January 2006 and March 2013, 11,730 patients underwent surgical treatment for breast cancer; 1109 (9.5 %) had clinical T1–2, N0 breast cancer and 1 or 2 positive nodes. Of these, 331 (29.8 %) had ECE in the SLN; 180 (54.4 %) had ≤2 mm of ECE, and 151 (45.6 %) had >2 mm of ECE (Fig. 1).

TABLE 1 Characteristics of patients with and without ECE

Factor	No ECE ($n = 778$)	All ECE ($n = 331$)	p-value
Median age, years (range)	54 (20–96)	57 (24–92)	0.0012
Median tumor size (range)	1.7 cm (0.09–5.0 cm)	2.0 cm (0.3–5.0 cm)	<0.0001
Nuclear grade			
1	85 (10.9 %)	50 (15.1 %)	
2	333 (42.8 %)	142 (42.9 %)	
3	276 (35.5 %)	111 (33.5 %)	
Missing[a]	84 (10.8 %)	28 (8.5 %)	0.1844
Subtype			
$HR^+/HER2^-$	597 (76.7 %)	279 (84.3 %)	
$HR^+/HER2^+$	70 (9.0 %)	25 (7.6 %)	
$HR^-/HER2^+$	35 (4.5 %)	7 (2.1 %)	
$HR^-/HER2^-$	73 (9.4 %)	18 (5.4 %)	
Missing[a]	3 (0.4 %)	2 (0.6 %)	0.0164
Multifocality	231 (29.7 %)	126 (38.1 %)	
Missing[a]	0 (0 %)	1 (0.3 %)	0.0062
LVI	396 (50.9 %)	210 (63.4 %)	<0.0001
Differentiation			
Poor	412 (52.9 %)	173 (52.3 %)	
Moderate	234 (30.1 %)	103 (31.3 %)	
Well	36 (4.6 %)	6 (1.8 %)	
Missing[a]	96 (12.3 %)	49 (14.8 %)	0.0806
Median number SLNs removed (range)	3 (1–19)	3 (1–14)	<0.0001
Number positive SLNs removed			
1	626 (80.5 %)	215 (65 %)	
2	152 (19.5 %)	116 (35 %)	<0.0001
Completion ALND	513 (65.9 %)	249 (75.2 %)	0.0023
Positive nodes at cALND[b]	112 (21.8 %)	135 (54.2 %)	<0.0001
Additional positive nodes at cALND[b]			
0	401 (78.2 %)	114 (45.8 %)	
1–3	99 (19.3 %)	84 (33.7 %)	
≥4	13 (2.5 %)	51 (20.5 %)	<0.0001

ECE extracapsular extension, *HR* hormone receptor, *LVI* lymphovascular invasion, *ALND* axillary lymph node dissection, *cALND* completion axillary lymph node dissection

[a] Missing excluded for calculation of p-values

[b] Among patients with cALND

The characteristics of patients with and without ECE in the SLN are compared in Table 1. Patients with ECE were older (median 57 vs. 54 years; $p = 0.0012$) and had larger (2.0 vs. 1.7 cm; $p \leq 0.0001$) tumors which were more often hormone receptor positive (91.8 vs. 85.7 %; $p = 0.0164$). Multifocality/multicentricity and LVI were also significantly associated with ECE. There were no significant differences in nuclear grade or histologic differentiation between groups. The median number of SLNs removed in both groups was 3, and most patients had one positive SLN; however, patients with ECE were more likely to have 2 positive sentinel lymph nodes (35 vs. 19.5 %; $p < 0.0001$). Completion ALND was performed in 249 (75.2 %) patients with ECE and in 513 (65.9 %) patients without ECE. Additional positive nodes were found in 54.2 % of patients with ECE compared with 21.8 % of patients without ECE; patients with ECE were also more likely to have ≥4 positive nodes: 20.5 versus 2.5 % ($p < 0.001$), respectively (Table 1).

Patient age, nuclear grade, or hormone receptor status did not differ according to the extent of ECE (Table 2). Patients with ≤2 mm of ECE had smaller tumors (median, 1.8 vs. 2.2 cm; $p = 0.0004$) and were more likely to have only one positive SLN (73.9 vs. 54.3 %; $p < 0.0001$; Table 2). Completion ALND was performed in 128 (71.1 %) patients with ≤2 mm of ECE and in 121 (80.1 %) patients with >2 mm of ECE. Additional positive nodes were found in 42.9 % of patients with ≤2 mm of ECE compared with 66.1 % of patients with >2 mm of ECE ($p < 0.0001$); patients with >2 mm of ECE were also more likely to have ≥4 positive nodes (33.1 vs. 8.6 %, $p < 0.0001$, respectively; Table 2).Table 3 examines the relationship among the number of positive SLNs, the extent of ECE, and additional nodal disease burden. Among patients with only one positive SLN, 38.5 % of patients with ≤2 mm of ECE had additional positive nodes, as compared with 57.2 % of patients with >2 mm of ECE ($p = 0.0021$). Similarly, among patients with two positive SLNs, 54 % of patients with ≤2 mm of ECE had additional positive nodes, compared with 76 % of patients with >2 mm of ECE ($p = 0.0070$). In contrast, within groups of patients with the same extent of ECE, the number of positive SLNs was not significantly associated with more extensive nodal burden. A total of 28.6 % of patients with one positive SLN and >2 mm of ECE and 38 % of patients with two positive SLNs and >2 mm ECE had ≥4 additional positive nodes.

Univariate and multivariate analyses of clinicopathologic factors associated with involvement of ≥4 nodes at completion ALND are displayed in Table 4. Tumor size

TABLE 2 Characteristics and axillary disease burden of patients with no ECE, ≤2 mm of ECE, or >2 mm of ECE

Factor	No ECE ($n = 778$)	≤2 mm ($n = 180$)	>2 mm ($n = 151$)	p-value (≤2 vs. >2 mm)	p-value (≤2 vs. >2 mm vs. no ECE)
Patient characteristics					
Median age, years (range)	54 (20–96)	57.0 (24–87)	57.0 (31–92)	0.8777	0.0049
Median tumor size (range)	1.7 cm (0.09–5.0 cm)	1.8 cm (0.4–4.5 cm)	2.2 cm (0.3–5 cm)	0.0004	<0.0001
Nuclear grade					
1	85 (10.9 %)	23 (12.8 %)	27 (17.9 %)		
2	333 (42.8 %)	82 (45.6 %)	60 (39.7 %)		
3	276 (35.5 %)	63 (35.0 %)	48 (31.8 %)		
Missing[a]	84 (10.8 %)	12 (6.7 %)	16 (10.6 %)	0.3394	0.2237
Subtype					
$HR^+/HER2^-$	597 (76.7 %)	150 (83.3 %)	129 (85.4 %)		
$HR^+/HER2^+$	70 (9.0 %)	15 (8.3 %)	10 (6.6 %)		
$HR^-/HER2^+$	35 (4.5 %)	5 (2.8 %)	2 (1.3 %)		
$HR^-/HER2^-$	73 (9.4 %)	9 (5.0 %)	9 (6.0 %)		
Missing[a]	3 (0.4 %)	1 (0.6 %)	1 (0.6 %)	0.7422	0.0132 for HR^+ versus HR^-
Patient axillary disease burden					
Median number SLNs removed (range)	3 (1–19)	3 (1–14)	2 (1–11)	0.0095	<0.0001
Number positive SLNs removed					
1	626 (80.4 %)	133 (73.9 %)	82 (54.3 %)		
2	152 (19.6 %)	47 (26.1 %)	69 (45.7 %)	<0.0001	<0.0001
Completion ALND	513 (65.9 %)	128 (71.1 %)	121 (80.1 %)	0.0732	0.0015
Positive nodes at cALND[b]	112 (21.8 %)	55 (42.9 %)	80 (66.1 %)	<0.0001	<0.0001
Number additional positive nodes at cALND[a]					
0	401 (78.2 %)	73 (57.0 %)	41 (33.9 %)		
1–3	99 (19.3 %)	44 (34.4 %)	40 (33.1 %)		
≥4	13 (2.5 %)	11 (8.6 %)	40 (33.1 %)	<0.0001	<0.0001

ECE extracapsular extension, *HR* hormone receptor, *SLN* sentinel lymph node, *ALND* axillary lymph node dissection, *cALND* completion axillary lymph node dissection

[a] Missing excluded for calculation of p-values

[b] Among patients with cALND

[odds ratio (OR) 1.7], multifocality (OR 1.9), LVI (OR 2.1), and presence of ECE (OR 9.9) were all significantly associated with ≥4 positive nodes at ALND. When ECE was stratified by none versus ≤2 mm versus >2 mm, the greater extent of ECE was associated with an OR of 19 for >4 positive nodes, and ≤2 mm of ECE was associated with an OR of 3.6. On multivariate analysis, >2 mm of ECE remains significantly associated (OR 14.2) with ≥4 positive nodes at completion ALND, after taking into account other clinicopathologic variables. Having two positive SLNs was significantly associated with ≥4 additional positive nodes at ALND (OR 2.5; $p = 0.0005$) on univariate analysis but was not a significant predictor of having >4 additional axillary nodes at completion ALND on multivariate analysis ($p = 0.1906$).

DISCUSSION

ECE is a common clinical finding, as illustrated in our study, in which ECE was identified in the SLN in 30 % of clinically node-negative patients with early-stage breast cancer. This is consistent with other contemporary studies reporting ECE in 19–26 % of SLNs.[1,12] In a multicenter European study of 675 patients with involvement of 1–3 SLNs, the reported incidence of ECE varied significantly among centers, ranging from 21 to 57 %, although other patient characteristics were similar.[13] Previous studies have uniformly demonstrated that ECE was a predictor of a higher likelihood of non-SLN metastases.[1,9,10,12,13] Until recently, this finding was of little practical import because ALND was the standard management approach for patients

TABLE 3 The relationship among the number of positive SLNs, extent of ECE, and additional nodal burden among patients with cALND

	No ECE ($n = 513$)		≤2 mm ($n = 128$)		>2 mm ($n = 121$)		Overall	
No. of additional positive ALNs	1 positive SLN ($n = 396$)	2 positive SLNs ($n = 117$)	1 positive SLN ($n = 91$)	2 positive SLNs ($n = 37$)	1 positive SLN ($n = 63$)	2 positive SLNs ($n = 58$)	1 positive SLN ($n = 550$)	2 positive SLNs ($n = 212$)
0	311 (78.5 %)	90 (76.9 %)	56 (61.5 %)	17 (45.9)	27 (42.8 %)	14 (24.1 %)	394 (71.6 %)	121 (57.1 %)
1–3	76 (19.2 %)	23 (19.7 %)	28 (30.8 %)	16 (43.2 %)	18 (28.6 %)	22 (37.9 %)	122 (22.2 %)	61 (28.8 %)
>4	9 (2.3 %)	4 (3.4 %)	7 (7.7 %)	4 (10.8 %)	18 (28.6 %)	22 (37.9 %)	34 (6.2 %)	30 (14.2 %)
p-value	0.7140		0.2390		0.0936		<0.0001	

SLN sentinel lymph node, *ECE* extracapsular extension, *cALND* completion axillary lymph node dissection, *ALN* axillary lymph node

TABLE 4 Univariate and multivariate analyses of factors associated with involvement of 4 or more lymph nodes at completion ALND

	Univariate analysis		Multivariate analysis	
	OR (95 % CI)	p-value	OR (95 % CI)	*p*-value
Age	1.0 (0.99–1.0)	0.0779	1.0 (1.0–1.0)	0.1104
T size	1.7 (1.3–2.2)	<0.0001	1.4 (1.1–1.9)	0.0166
Multifocality[a]	1.9 (1.1–3.1)	0.0170	1.8 (1.0–3.3)	0.0437
LVI	2.1 (1.2–3.7)	0.0106	1.1 (0.6–2.2)	0.7178
ECE		<0.0001		<.0001
None	Ref		Ref	
≤2 mm	3.6 (1.6–8.3)		3.1 (1.3–7.2)	
>2 mm	19.0 (9.7–37.1)		14.2 (7.1–28.4)	
No. positive SLNs		0.0005		0.1906
1	Ref		Ref	
2	2.5 (1.5–4.2)		1.5 (0.8–2.7)	

ECE extracapsular extension, *ALND* axillary lymph node dissection, *OR* odds ratio, *CI* confidence interval, *LVI* lymphovascular invasion, *SLN* sentinel lymph node

[a] One patient missing

with macrometastases in the SLN. With the publication of the ACOSOG Z0011 trial indicating that clinically node-negative patients with T1 and T2 tumors found to have metastases in 1–2 SLNs and undergoing breast-conserving surgery with whole-breast irradiation and systemic therapy can be managed without ALND, ECE as a predictor of nodal disease burden takes on new significance.[4]

The success of the ACOSOG Z0011 approach is predicated on a limited burden of disease remaining in the axilla after the SLNs are removed, which is likely to be controlled with systemic therapy and radiotherapy. Only 27 % of patients randomized to ALND in ACOSOG Z0011 had additional nodal disease.[4] In our study, although limited to women who met ACOSOG Z0011 eligibility criteria, ECE was associated with non-SLN disease in 54.2 % of cases, compared with 21.8 % in patients without ECE ($p < 0.0001$). Additionally, ≥4 additional involved nodes were present in 20.5 % of patients with ECE, compared with 2.5 % of those without ECE ($p < 0.0001$).

Other studies support the presence of ECE as a predictor of a larger numbers of nodes with metastases. Rivers et al.[14] examined features associated with ≥4 non-SLN metastases in 285 patients with positive SLNs. Tumor size, LVI, ECE, size of SLN metastases, and ratio of number of positive to resected SLNs were all significantly associated with disease in ≥ 4 non-SLNs. In our study, ECE was associated with larger tumor size, multifocality, LVI, and a greater number of positive SLNs.[1,8,11,15,16] We also noted an association between ECE and older patient age and hormone receptor–positive, HER2-negative tumors, characteristics not generally associated with poor prognosis. After adjustment for known prognostic variables, including age, tumor size, and multifocality, ECE remains a predictor of more extensive axillary nodal involvement, as demonstrated in the multivariate analysis in which >2 mm of ECE was the strongest predictor (OR 14.2) of ≥4 additional nodes at completion ALND. Data from Meretoja et al.[13] support this finding; using 675 patients with macrometastases in 1–3 SLNs, they developed a model to identify patients with involvement of ≥4 non-SLNs and validated the model in an additional 760 patients. In this model, ECE was also a strong predictor ($p < 0.0001$) of involvement of ≥4 additional nodes. In another study of 74 patients with tumor-containing SLNs, the mean number of involved non-SLNs was 2.5 for patients with no ECE compared with 7.6 in patients with ECE ($p = 0.0061$). On multivariate analysis, only the presence of ECE was a significant predictor of non-SLN involvement.[12] Mittendorf et al. also found ECE to be a significant predictor of non-SLN involvement in a multivariate model constructed with 509 patients.[17]

We also examined the effect of the extent of ECE in the SLN, arbitrarily defined as ≤2 or >2 mm, on axillary disease burden. Patients with >2 mm of ECE were significantly more likely than those with lesser amounts of ECE to have additional positive nodes (66.1 vs. 42.9 %; $p < 0.0001$), and one third of this group had ≥4 involved

nodes, compared with only 2.5 % of patients with no ECE and 8.6 % with ≤2 mm of ECE. The extent of ECE was a significant predictor of residual disease in patients with 1 or 2 sentinel nodes containing tumor, indicating that it is not just a surrogate for involvement of a larger number of sentinel nodes. Few other studies have examined the importance of the extent of ECE. Palamba et al.[18] compared patients with no ECE ($n = 83$) with those with ≤1 mm of ECE ($n = 77$) and those with >1 mm of ECE ($n = 65$). As in our study, the proportion of patients with ≥4 involved nodes differed significantly among groups: 14.5, 37.6, and 84.6 % ($p < 0.001$), respectively. Although these results suggest that the extent of ECE might be useful in further stratifying the risk of extensive involvement of non-SLNs, the lack of a standardized method of measuring ECE makes the reproducibility of these findings among different pathologists uncertain.

Strengths of our study include a large, well-defined patient population and a standard method of reporting the presence of ECE which has been in place at our institution since 2006. Limitations include the lack of a centralized pathology review and possible unrecognized heterogeneity in the patient population because only patients seen after 2010 were actually treated according to the Z0011 approach. Although patients included between 2006 and 2010 appeared to meet study eligibility criteria, it is possible that some of these patients had a more extensive disease burden than evident in the medical record.

Whereas our study and the published literature clearly demonstrate that the finding of ECE in SLNs is associated with a higher risk of additional nodal disease in the axilla, the immediate clinical implications of this finding are uncertain. Many patients with ECE undergo ALND because of the finding of metastases in ≥3 SLNs or the identification of grossly abnormal nodes during surgery. In the remainder, axillary recurrence risk is unknown because the ACOSOG Z0011 study did not include microscopic ECE as a stratification factor. In addition, a recent report examining the radiation fields among a subset of patients in the Z0011 trial suggests that approximately 19 % of patients in both the ALND arm and the SLN-only arm received direct nodal irradiation, the significance of which remains unknown.[19] In a prospective study conducted at MSKCC of managing patients meeting Z0011 eligibility criteria without ALND, of the initial 287 patients, 111 had ECE.[20] ALND was performed in 29 for involvement of ≥3 sentinel nodes and in 16 because of surgeon preference based on the presence of ECE.[21] In the remaining 66 patients, no nodal recurrences had occurred after a median follow-up of 21 months. Although this is reassuring, the follow-up is clearly too short to draw firm conclusions. Conversely, it may be premature to conclude that all patients with ECE require ALND. There is a lack of consensus in the literature on the impact of ECE on regional failure rates in patients treated with ALND, and the nodal tumor burden which can be successfully managed without surgery in the setting of multimodality therapy is unknown, but it is clear that the risk of nodal recurrence is substantially lower than the incidence of disease left behind in the nodes.[7,22–24]

An increasing body of evidence indicates that as improvements in systemic therapy prolong disease-free and overall survival, a similar improvement in locoregional control is observed.[25] While we await additional data, recognition of the significance of ECE as a predictor of a heavy nodal tumor burden is useful in making decisions about the need for completion ALND or ART in patients who otherwise meet eligibility criteria for avoidance of ALND but have multiple unfavorable tumor characteristics, such as larger T2 tumors and LVI in the breast. Information from the AMAROS trial on the impact of ECE on patient outcomes, if available, will also help to clarify this issue. Determining the appropriate management of the patient with ECE in the SLN would be greatly facilitated by the adoption of a standard pathologic technique for measuring the extent of ECE to allow comparison among studies.

CONCLUSIONS

In this large series of consecutively treated patients meeting Z0011 criteria, the presence and extent of ECE were significantly correlated with nodal tumor burden at ALND. Factors that portend a more aggressive tumor phenotype, including LVI and larger, multifocal tumors, were associated with the presence of ECE. These data, in conjunction with existing literature and emerging data from recent studies, suggest that >2 mm of ECE may be an indication for ALND or regional node irradiation when Z0011 criteria are applied to patients with metastases in <3 SLNs.

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