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Extranodal Tumor Deposits in the Axillary Fat Indicate the Need for Axillary Dissection Among T1-T2cN0 Patients with Positive Sentinel Nodes

Anita Mamtani, MD¹, Andrea V. Barrio, MD¹, Debra A. Goldman, MS², Hannah Y. Wen, MD³, Alain Vincent, BS¹, Monica Morrow, MD¹

¹Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

²Biostatistics Service, Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

³Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Background: The ACOSOG Z0011 trial demonstrated the safety of omitting axillary dissection (ALND) in T1-T2cN0 patients with <3 positive sentinel nodes (SLN) undergoing breast-conservation therapy. While microscopic extracapsular extension (mECE) >2mm is associated with increased nodal burden, the significance of extranodal tumor deposits (ETDs) in the axillary fat is uncertain.

Methods: Consecutive patients with T1-T2cN0 breast cancer undergoing sentinel node biopsy and ALND for SLN metastases from 1/2010–12/2018 were identified. ETDs were defined as intravascular tumor emboli or metastatic deposits in the axillary fat. Clinicopathologic characteristics and nodal burden were compared by ETD status.

Results: Among 1114 patients, 113 (10%) had ETDs: 81 (72%) were intravascular tumor emboli and 32 (28%) were soft tissue deposits. Patients with ETDs had larger tumors (median 2.2 vs 2.1cm, $p=0.033$) and more often had mECE (83% vs 44%, $p<0.001$). On univariable analysis, presence of ETDs (OR 9.66, 95%CI 6.36–14.68), larger tumors (OR 1.47 95%CI 1.25–1.72), and mECE (OR 10.73, 95%CI 6.86–16.78) were associated with ≥4 additional positive non-sentinel nodes (NSLNs) (all $p<0.001$). On multivariable analysis, ETDs remained associated with ≥4 positive NSLNs (OR 5.67, 95%CI 3.53–9.08, $p<0.001$). ETDs were strongly associated with ≥4 positive NSLNs (OR 11.75, 95%CI 7.00–19.72) among patients with 1–2 positive SLNs ($n=925$).

Conclusions: Among T1-T2cN0 patients with SLN metastases, ETDs are strongly associated with ≥4 positive NSLNs at ALND. Even among those who may otherwise meet criteria for omission of ALND, the presence of ETDs in axillary fat warrants consideration of ALND.

Keywords

extranodal tumor deposits; intravascular tumor emboli; soft tissue deposits; sentinel lymph node biopsy; axillary lymph node dissection

The management of T1-T2cN0 patients with 1 or 2 positive sentinel lymph nodes (SLNs) undergoing upfront breast-conservation therapy (BCT) with sentinel lymph node biopsy (SLNB) alone or with axillary radiation is now routine based on results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 and the After Mapping of the Axilla: Radiotherapy or Surgery? (AMAROS) trials. The ACOSOG Z0011 trial demonstrated the safety of omitting axillary lymph node dissection (ALND) among these patients with no difference seen in locoregional recurrence or overall survival at 10 years of follow-up.¹ Similar low rates of regional recurrence with SLNB and axillary radiation compared with ALND were demonstrated when comparing SLNB and axillary radiation to ALND in the AMAROS trial.²

The clinical application of these studies has raised questions regarding the importance of high-risk features not examined in the ACOSOG Z0011 or AMAROS trials, such as microscopic extracapsular extension (mECE) and extranodal tumor deposits (ETDs) in the axillary fat, in patients with limited SLN metastases. Subsequent studies have shown > 2 mm of mECE to be associated with an increased nodal burden at ALND. Gooch et al found that 33% of T1-T2cN0 patients with 1 or 2 positive SLNs and > 2 mm of mECE had 4 additional positive non-sentinel nodes (NSLNs) at ALND as compared to 9% of those with < 2 mm of ECE and 3% of those without mECE ($p < 0.001$)³, yet nodal recurrences among those with mECE treated with SLNB alone are uncommon.⁴ However, the impact of ETDs in the axillary fat has not been previously evaluated, and the clinical significance of this finding in otherwise Z0011-eligible patients remains unknown. In this study, we sought to examine the incidence of ETD, associated risk factors, and the influence on nodal disease burden among T1-T2cN0 patients with SLN metastases.

METHODS

Following Institutional Review Board approval, all women with T1-T2cN0 invasive breast cancer treated with SLNB and ALND for SLN metastases at Memorial Sloan Kettering Cancer Center between January 2010 and December 2018 were identified. Patients with recurrent or bilateral tumors, and those who received neoadjuvant therapy, were excluded. ETDs were defined as discrete foci of carcinoma in the axillary fat which were not contiguous with the lymph node itself, categorized as either intravascular tumor emboli in the axillary fat (Fig. 1A), or discrete metastatic soft tissue deposits in the axillary fat (Fig. 1B). Patients with both types of ETDs were categorized as patients with soft tissue deposits. These findings were uniformly reported in a standardized synoptic format throughout the study period. Patients were considered to have ETDs if cancerous cells were identified in the SLN specimen and/or the ALND specimen. Standard clinical and pathologic data were collected, including patient age, tumor size, grade, and nodal and extranodal pathologic findings.

Clinicopathologic characteristics and nodal disease burden were compared between those with and without ETDs using Fisher's exact test and the Wilcoxon rank sum test, where appropriate. Univariable and multivariable logistic regression were used to examine the association between ETDs and nodal burden. In multivariable models, all covariates were included regardless of significance in univariable results. We also examined the interaction between ECE with ETDs, and the number of positive SLNs with ETDs in the association with nodal burden. Analyses were performed both in the overall population of T1-T2cN0 patients with positive SLNs, and among the subset with 1 or 2 positive SLNs only. This subset analysis was performed based on the results of the interaction analysis and to assess our findings in the Z0011-eligible sample. Two-sided p-values less than 0.05 were considered statistically significant, and no corrections were made for multiple testing. All analyses were performed using SAS 9.4 TS1M6 (SAS Institute, Cary, NC).

RESULTS

From January 2010 to December 2018, 1114 consecutive patients with T1–2cN0 invasive cancers treated with SLNB and ALND for SLN metastases, were identified. Of these, 895 (80.3%) underwent mastectomy, while 219 (19.7%) underwent lumpectomy. Indications for ALND among lumpectomy patients included presence of ≥ 3 positive SLNs (36.5%), treatment during the early period after publication of ACOSOG Z0011 results (44.3%), or based upon clinical judgment (19.2%).

Overall, 113 (10.1%) patients had ETDs, of whom 81 (71.7%) were intravascular tumor emboli and 32 (28.3%) were soft tissue deposits. Clinicopathologic characteristics of those with and without ETDs are summarized in Table 1. Patients with ETDs had larger tumors (median 2.2 cm vs 2.1 cm, $p = 0.033$) and more often had mECE (83.2% vs 44.0%, $p < 0.001$). Lymphovascular invasion was more frequently observed among those with ETDs (77.7% vs 68.8%), although this did not reach statistical significance ($p = 0.06$). Patients with ETDs more frequently had ≥ 3 positive SLNs identified than those without ETDs (36.3% vs 14.8%, $p < 0.001$). Positive NSLNs were identified at ALND in 48.5% of patients and was significantly more common among patients with ETDs as compared to those without ETDs (85.8% vs 44.3%, $p < 0.001$). The proportion of ≥ 4 additional positive NSLNs at ALND was also significantly higher among those with ETDs than those without ETDs (58.4% vs 12.7%, $p < 0.001$), respectively (Table 2).

The majority ($n = 925$, 83.0%) of patients in this study had 1 or 2 positive SLNs identified, of whom 72 (7.8%) had ETDs. Patients with ETDs in this subgroup had larger tumors (median 2.3 cm vs 2.1 cm, $p = 0.015$), and more often had mECE (80.6% vs 39.2%, $p < 0.001$) and lymphovascular invasion (79.2% vs 68.2%, $p = 0.06$), although this did not reach statistical significance (Table 3). Positive NSLNs were identified at ALND in 43.5% of patients, and this was significantly more common among those with ETDs than those without ETDs (84.7% vs 40.0%, $p < 0.001$). The proportion of ≥ 4 additional positive NSLNs at ALND was also significantly higher among those with ETDs compared to those without (55.6% vs 9.6%, $p < 0.001$), respectively (Table 2).

Associations with nodal involvement were examined using logistic regression models both in the overall sample of T1–2cN0 patients with any positive SLNs (Table 4) and among the subgroup with 1 or 2 positive SLNs only (Table 5). In the overall sample, on univariable analysis, the presence of ETDs (odds ratio [OR] 9.66, 95% CI 6.36–14.68), older age (OR 1.03, 95% CI 1.01–1.04), larger tumor size (OR 1.47, 95% CI 1.25–1.72), mECE (OR 10.73, 95% CI 6.86–16.78), and a greater number of positive SLNs (3 vs 1–2, OR 3.96, 95% CI 2.79–5.62) were associated with ≥4 additional positive NSLNs at ALND (all $p < 0.001$). On multivariable analysis, the presence of ETDs remained significantly associated with ≥4 positive NSLNs (OR 5.67, 95% CI 3.53–9.08, $p < 0.001$) (Table 4). There was no significant interaction between the presence of mECE and ETDs ($p = 0.78$). When the two types of ETDs were examined separately in a multivariable model, intravascular tumor emboli and soft tissue deposits were found to have similar associations with the presence of ≥4 positive NSLNs (OR 5.61, 95% CI 3.27–9.60; and OR 5.83, 95% CI 2.52–13.52, respectively) ($p < 0.001$).

We repeated the above analysis in the 925 patients with 1 or 2 positive SLNs only and found similar results. On univariable analysis, older age (OR 1.03, 95% CI 1.01–1.04), larger tumor size (OR 1.60, 95% CI 1.31–1.95), mECE (OR 9.02, 95% CI 5.47–14.9), and presence of ETDs (OR 11.75, 95% CI 7.00–19.72) were associated with ≥4 positive NSLNs (all $p < 0.001$). On multivariable analysis, presence of ETDs remained strongly predictive of ≥4 positive NSLNs (OR 7.15, 95% CI 4.04–12.67, $p < 0.001$) (Table 5).

DISCUSSION

This study provides evidence in a large consecutive cohort of T1–T2cN0 patients with SLN metastases treated over an 8-year period that ETDs in the axillary fat, found in 10% of study patients, were strongly predictive of a heavy nodal burden of ≥4 additional positive NSLNs, and this association between ETDs and a heavier NSLN nodal burden was also present among Z0011-eligible patients with 1–2 positive SLNs. To our knowledge, this is the first study examining the occurrence and impact of this entity in breast cancer. The not-insignificant incidence of this finding even among early-stage breast cancer patients, and the associated heavy nodal burden, warrants recognition and standardized reporting of this high-risk pathologic feature. Given the shift toward surgical de-escalation in the axilla, it is important to identify features associated with a high residual tumor burden in the axilla, particularly among patients with limited SLN metastases who are eligible for omission of ALND.

A number of clinicopathologic risk factors have been associated with a higher likelihood of additional NSLN metastases among patients with positive SLNs, including tumor size, lymphovascular invasion, mECE, and the metastases size and number of positive SLNs.^{5–11} In a study of 402 patients with invasive breast cancer and 1–3 positive SLNs who underwent completion ALND, these factors were independently predictive of the presence of ≥4 additional positive NSLNs.⁸ Our study is the first to evaluate and identify ETDs in the axillary fat as being another risk factor predictive of NSLN positivity. Presence of ETDs was associated with both larger tumor size and mECE, reinforcing that ETDs are a marker of high-risk tumor biology commonly found in association with other high-risk features.

While no other studies have yet examined extent of nodal burden among patients with ETDs in the axillary fat, mECE is a similar biologic entity that has been studied to a greater degree. Defined as the contiguous spread of tumor cells outside of the lymph node capsule, mECE is recognized to be a poor prognostic indicator^{12,13} that is associated with other risk factors, such as tumor size³, lymphovascular invasion^{3,14}, and NSLN positivity.^{3,15} Multiple retrospective studies have found mECE to be an independent predictor of NSLN positivity, and this has since been incorporated into various tools for prediction of NSLN involvement.^{6,10,16} In a study of 1109 patients with T1-T2cN0 breast cancers with 1 or 2 positive SLNs, Gooch et al found both the presence and extent of mECE to be correlated with nodal burden at ALND, with > 2 mm of mECE being independently predictive of 4 additional positive NSLNs (OR 14.2, 95% CI 7.1–28.4, $p < 0.001$).³ This result was supported by Vane et al, who also found mECE to be associated with involvement of 4 additional positive NSLNs (OR 2.8 95% CI 1.9–4.3, $p < 0.001$) in a Dutch cohort of 2111 patients with T1-T2cN0 cancers with 1 or 2 positive SLNs.¹⁷ The similar strong association of ETDs in the axillary fat with extensive NSLN positivity in our study, and without a significant interaction with mECE in statistical models, underscores the aggressive biology associated with ETDs and their distinct association with heavy nodal disease burden.

The efficacy of management of the SLN positive axilla without ALND is based upon limited nodal disease remaining after SLNB that is adequately controlled by radiotherapy and modern systemic therapies. In the ACOSOG Z0011 trial, 27% of patients who underwent ALND had any additional nodal metastases; however, only 14% had 4 additional positive NSLNs.¹⁸ Similarly, in the AMAROS trial, while 33% of patients who underwent ALND had additional nodal metastases, only 8% had 4 additional positive NSLNs.² In our study, we identified a markedly heavier nodal burden among those with ETDs in the axillary fat, with 86% of these patients harboring any additional nodal metastases, and 58% having had 4 additional positive NSLNs. Notably, 17% of patients in our study had > 3 positive SLNs, falling outside of Z0011 criteria and likely accounting, in part, for the heavier NSLN tumor burden observed. However, even among patients in our study with 1–2 positive SLNs only, 56% had 4 additional positive NSLNs. Whether ALND can be safely omitted in patients with limited SLN metastases and ETDs in the axillary fat—given the more extensive NSLN disease burden—remains unclear, and it is arguable that this extent of underlying nodal disease may not be adequately controlled by radiation and systemic therapy alone. Further studies are required to directly compare locoregional recurrence outcomes with varying combinations of treatment.

This approach has been specifically examined in those with mECE. In a study of 811 patients with T1-T2cN0 breast cancer and SLN metastases who were prospectively managed accordingly to Z0011 criteria, Barrio et al reported a low 5-year rate of any nodal recurrence of 2.3% among patients with mECE treated with SLNB alone, suggesting that while mECE is associated with an increased nodal burden, this finding by itself should not be regarded as a routine indication for ALND. However, these favorable outcomes may be secondary to the more frequent use of nodal irradiation in this group.⁴ Our current study is not designed to evaluate rates of locoregional recurrence among patients with ETDs in the axillary fat who are treated with SLNB alone. During the study period, there were only 30 such patients who were not included in this analysis, and the majority (87%) received comprehensive nodal

irradiation. However, our study provides evidence for a definite association between ETDs and extensive nodal disease, even among the otherwise Z0011-eligible T1-T2cN0 patients with 1 or 2 positive SLNs, and supports consideration of further axillary treatment in this population given the substantial NSLN tumor burden which exceeds that noted with mECE.

To our knowledge, this study is the first to examine the clinical significance of ETDs in the axillary fat among T1-T2cN0 patients with positive SLNs. Limitations of our study include its retrospective nature with the possibility of selection bias, and inability to directly compare locoregional recurrence outcomes between varying combinations of axillary surgery and radiotherapy. However, we have examined a large, consecutive cohort of patients with standardized pathologic reporting of ETDs throughout an 8-year study period and have identified a strong independent association with ≥ 4 additional positive NSLNs at ALND, observed in nearly 60% of patients with ETDs in the axillary fat. These results emphasize that this entity may indicate a heavy residual nodal disease burden, and consideration of further axillary treatment is warranted, even among patients who may otherwise meet criteria for omission of ALND.

Conclusions

In this consecutive population of T1-T2cN0 patients treated with both SLNB and ALND for the presence of SLN metastasis, ETDs in the axillary fat were observed in 10% of cases. This finding was strongly and independently predictive of ≥ 4 additional positive NSLNs at ALND. Even among patients otherwise meeting criteria for omission of ALND, the presence of ETDs warrants consideration of completion ALND.

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Synopsis:

Among T1-T2cN0 patients with SLN metastases, the presence of extranodal tumor deposits in the axillary fat is strongly associated with 4 positive NSLNs. Even in patients meeting ACOSOG Z0011 criteria for omission of ALND, this finding may warrant completion ALND.

Fig. 1.
Types of extranodal tumor deposits: (A) intravascular tumor emboli in the axillary fat, and
(B) metastatic soft tissue deposits in the axillary fat.

TABLE 1

Clinicopathologic characteristics, overall and stratified by presence of ETDs in the axillary fat among T1-T2cN0 patients with any positive SLNs

Characteristic	T1-T2cN0 with any positive SLNs n = 1114	ETDs in axillary fat n = 113	No ETDs n = 1001	p
Age, median (range), years	51 (19–92)	51 (24–92)	51 (19–91)	0.46
Tumor size, median (range), cm	2.1 (0.1–5.0)	2.2 (0.2–4.6)	2.1 (0.1–5.0)	0.033
Nuclear grade				
Low	15 (1.3%)	1 (0.9%)	14 (1.4%)	0.78
Intermediate	557 (50.0%)	56 (49.6%)	501 (50.0%)	
High	456 (40.9%)	52 (46.0%)	404 (40.4%)	
Unknown	86 (7.7%)	4 (3.5%)	82 (8.2%)	
Receptor status				
HR+/HER2–	933 (83.8%)	91 (80.5%)	842 (84.1%)	0.20
HER2+	115 (10.3%)	17 (15.0%)	98 (9.8%)	
HR–/HER2–	66 (5.9%)	5 (4.4%)	61 (6.1%)	
Lymphovascular invasion *	761 (68.3%)	87 (77.7%)	674 (68.8%)	0.06
Histology				
Ductal	870 (78.1%)	93 (82.3%)	777 (77.6%)	0.49
Lobular/mixed	237 (21.3%)	20 (17.7%)	217 (21.7%)	
Other	7 (0.6%)	0 (0%)	7 (0.7%)	
Microscopic ECE present	534 (47.9%)	94 (83.2%)	440 (44.0%)	< 0.001
Size of ECE				
None	580 (52.1%)	19 (16.8%)	561 (56.0%)	< 0.001
2 mm	207 (18.6%)	24 (21.2%)	183 (18.3%)	
> 2 mm	313 (28.1%)	70 (61.9%)	243 (24.3%)	
Present but extent unknown **	14 (1.3%)	0 (0%)	14 (1.4%)	
# of SLNs positive				
1	657 (59.0%)	37 (32.7%)	620 (61.9%)	< 0.001
2	268 (24.1%)	35 (31.0%)	233 (23.3%)	
3	189 (17.0%)	41 (36.3%)	148 (14.8%)	

* Lymphovascular invasion unknown in n = 22 patients

** Patients with unknown extent of ECE (n = 14) were not included in calculation

ETDs extranodal tumor deposits, SLNs sentinel lymph nodes, HR+ hormone receptor positive, ECE extracapsular extension

TABLE 2

Nodal disease burden, overall and stratified by presence of ETDs in the axillary fat, among T1-T2cN0 patients with any positive SLNs, and T1-T2cN0 patients with 1 or 2 positive SLNs only

Characteristic	T1-T2cN0 with any positive SLNs				T1-T2cN0 with 1 or 2 positive SLNs			
	All T1-T2cN0 with any positive SLNs n = 1114	ETDs in axillary fat n = 113	No ETDs n = 1001	p	T1-T2cN0 with 1 or 2 positive SLNs n = 925	ETDs in axillary fat n = 72	No ETDs n = 853	p
Number of SLNs positive								
1	657 (59.0%)	37 (32.7%)	620 (61.9%)	< 0.001	657 (71.0%)	37 (51.4%)	620 (72.7%)	< 0.001
2	268 (24.1%)	35 (31.0%)	233 (23.3%)		268 (29.0%)	35 (48.6%)	233 (27.3%)	
3	189 (17.0%)	41 (36.3%)	148 (14.8%)		-	-	-	
Additional positive nodes found at ALND	540 (48.5%)	97 (85.8%)	443 (44.3%)	< 0.001 *	402 (43.5%)	61 (84.7%)	341 (40.0%)	< 0.001
Number of additional positive NSLNs at ALND								
0	574 (51.5%)	16 (14.2%)	558 (55.7%)	< 0.001 **	523 (56.5%)	11 (15.3%)	512 (60.0%)	< 0.001
1-3	347 (31.1%)	31 (27.4%)	316 (31.6%)		280 (30.3%)	21 (29.2%)	259 (30.4%)	
4	193 (17.3%)	66 (58.4%)	127 (12.7%)		122 (13.2%)	40 (55.6%)	82 (9.6%)	

* P-value derived from univariable logistic regression with any additional positive lymph nodes at ALND as outcome

** P-value derived from univariable logistic regression comparing 4 vs < 4 additional positive lymph nodes at ALND

ETDs extranodal tumor deposits, SLNs sentinel lymph nodes, NSLNs non-sentinel lymph nodes, ALND axillary lymph node dissection

TABLE 3

Clinicopathologic characteristics, overall and stratified by presence of ETDs in the axillary fat among T1-T2cN0 patients with 1 or 2 positive SLNs only

Characteristic	T1-T2cN0 with 1 or 2 positive SLNs n = 925	ETDs in axillary fat n = 72	No ETDs n = 853	p
Age, median (range), years	51 (19–92)	51 (24–92)	51 (19–91)	0.46
Tumor size, median (range), cm	2.1 (0.1–5.0)	2.3 (0.6–4.6)	2.1 (0.1–5.0)	0.015
Nuclear grade				
Low	12 (1.3%)	1 (1.4%)	11 (1.3%)	0.68
Intermediate	459 (49.6%)	35 (48.6%)	424 (49.7%)	
High	385 (41.6%)	34 (47.2%)	351 (41.1%)	
Unknown	69 (7.5%)	2 (2.8%)	67 (7.9%)	
Receptor status				
HR+/HER2–	769 (83.1%)	57 (79.2%)	712 (83.5%)	0.49
HER2+	103 (11.1%)	11 (15.3%)	92 (10.8%)	
HR–/HER2–	53 (5.7%)	4 (5.6%)	49 (5.7%)	
Lymphovascular invasion *	625 (67.6%)	57 (79.2%)	568 (68.2%)	0.06
Histology				
Ductal	740 (80.0%)	64 (88.9%)	676 (79.2%)	0.19
Lobular/mixed	178 (19.2%)	8 (11.1%)	170 (19.9%)	
Other	7 (0.8%)	0 (0%)	7 (0.8%)	
Microscopic ECE present	392 (42.4%)	58 (80.6%)	334 (39.2%)	<0.001
Size of ECE				
None	533 (57.6%)	14 (19.4%)	519 (60.8%)	<0.001
2 mm	173 (18.7%)	16 (22.2%)	157 (18.4%)	
> 2 mm	207 (22.4%)	42 (58.3%)	165 (19.3%)	
Present but extent unknown **	12 (1.3%)	0 (0%)	12 (1.4%)	

* Lymphovascular invasion unknown in n = 20 patients

** Patients with unknown extent of ECE (n = 12) were not included in calculation

ETDs extranodal tumor deposits, SLNs sentinel lymph nodes, HR+ hormone receptor positive, ECE extracapsular extension

TABLE 4

Univariable and multivariable regression analysis of risk factors for 4 positive NSLNs at ALND among T1-T2cN0 patients with any positive SLNs

	Univariable analysis			Multivariable analysis		
	OR	95% CI	p	OR	95% CI	p
Presence of ETDs						
No	REF		< 0.001	REF		< 0.001
Yes	9.66	6.36–14.68		5.67	3.53–9.08	
Age, years (continuous)	1.03	1.01–1.04	< 0.001	1.02	1.0–1.03	0.038
Tumor size, cm (continuous)	1.47	1.25–1.72	< 0.001	1.32	1.07–1.64	0.009
Nuclear grade						
Low	REF		0.15	REF		0.09
Intermediate	0.37	0.12–1.09		0.26	0.07–0.98	
High	0.43	0.14–1.30		0.32	0.08–1.26	
Lymphovascular invasion						
No	REF		0.37	REF		0.69
Yes	1.17	0.83–1.66		1.1	0.69–1.76	
Receptor status						
ER+/HER2–	REF		0.64	REF		0.45
HER2+	1.13	0.69–1.85		1.45	0.77–2.72	
ER–/HER2–	0.75	0.36–1.55		0.85	0.34–2.12	
Presence of mECE						
No	REF		< 0.001	REF		< 0.001
Yes	10.7	6.86–16.8		7.63	4.57–12.75	
Number of positive SLNs						
1 or 2	REF		< 0.001	REF		< 0.001
3	3.96	2.79–5.62		2.21	1.41–3.48	
Breast Surgery						
Lumpectomy	REF		0.002	REF		0.80
Mastectomy	0.56	0.39–0.80		1.06	0.66–1.70	

NSLNs non-sentinel lymph nodes, ALND axillary lymph node dissection, SLNs sentinel lymph nodes, OR odds ratio, CI confidence interval, ETDs extranodal tumor deposits, ER estrogen receptor, mECE microscopic extracapsular extension

TABLE 5

Univariable and multivariable regression analysis of risk factors for 4 positive NSLNs at ALND among T1-T2cN0 patients with 1 or 2 positive SLNs only

	Univariable analysis			Multivariable analysis		
	OR	95% CI	p	OR	95% CI	p
Presence of ETDs						
No	REF		< 0.001	REF		< 0.001
Yes	11.75	7.0–19.72		7.15	4.04–12.67	
Age, years (continuous)	1.03	1.01–1.04	< 0.001	1.01	0.99–1.03	0.19
Tumor size, cm (continuous)	1.6	1.31–1.95	< 0.001	1.36	1.05–1.76	0.021
Nuclear grade						
Low	REF		0.26	REF		0.17
Intermediate	0.39	0.1–1.49		0.27	0.06–1.35	
High	0.49	0.13–1.87		0.37	0.07–1.85	
Lymphovascular invasion						
No	REF		0.07	REF		0.39
Yes	1.51	0.97–2.36		1.29	0.72–2.30	
Receptor status						
ER+/HER2–	REF		0.44	REF		0.41
HER2+	1.32	0.75–2.32		1.55	0.77–3.14	
ER–/HER2–	0.7	0.27–1.79		0.81	0.24–2.73	
Presence of mECE						
No	REF		< 0.001	REF		< 0.001
Yes	9.02	5.47–14.88		7.08	3.99–12.54	
Breast Surgery						
Lumpectomy	REF		0.21			0.92
Mastectomy	0.73	0.44–1.19		1.03	0.56–1.91	

NSLNs non-sentinel lymph nodes, ALND axillary lymph node dissection, SLNs sentinel lymph nodes, OR odds ratio, CI confidence interval, ETDS extranodal tumor deposits, ER estrogen receptor, mECE microscopic extracapsular extension