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CLINICAL TRIAL

Higher risk tumor features are not associated with higher nodal stage in patients with estrogen receptor-positive, node-positive breast cancer

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Abstract

Introduction Studies support omission of axillary lymph node dissection (ALND) for patients with sentinel node-positive disease, with ALND recommended for patients who present with clinically positive nodes. Here, we evaluate patient and tumor characteristics and pathologic nodal stage of patients with estrogen receptor-positive (ER +) breast cancer who undergo ALND to determine if differences exist based on nodal presentation.

Materials and methods Retrospective chart review from 2010 to 2019 defined three groups of patients with ER + breast cancer who underwent ALND for positive nodes: SLN + (positive node identified at SLN biopsy), cNUS (abnormal preoperative US and biopsy), and cNpalp (palpable adenopathy). Patients who received neoadjuvant chemotherapy or presented with axillary recurrence were excluded.

Results Of 191 patients, 94 were SLN + , 40 were cNUS, and 57 were cNpalp. Patients with SLN + compared with cNpalp were younger (56 vs 64 years, $p < 0.01$), more often pre-menopausal (41% vs 14%, $p < 0.01$), and White (65% vs 39%, $p = 0.01$) with more tumors that were low-grade (36% vs 8%, $p < 0.01$). Rates of PR + ($p = 0.16$), levels of Ki67 expression ($p = 0.07$) and LVI ($p = 0.06$) did not differ significantly among groups. Of patients with SLN + disease, 64% had pN1 disease compared to 38% of cNUS ($p = 0.1$) and 40% of cNpalp ($p = 0.01$). On univariable analysis, tumor size ($p = 0.01$) and histology ($p = 0.04$) were significantly associated with pN1 disease, with size remaining an independent predictor on multivariable analysis ($p = 0.02$).

Conclusion Historically, higher risk features have been attributed to patients with clinically positive nodes precluding omission of ALND, but when restricting evaluation to patients with ER + breast cancer, only tumor size is associated with higher nodal stage.

Keywords Nodal stage · Palpable adenopathy · Clinically node-positive · Breast cancer · Axillary lymph node dissection · Sentinel node biopsy

Introduction

Historically, surgical clearance of the axilla with axillary lymph node dissection (ALND) had been the standard of care for management of the axilla in patients with clinically node-positive breast cancer. More recently, neoadjuvant chemotherapy (NAC) has emerged as an effective strategy for nodal downstaging such that patients who clinically respond are able to undergo sentinel lymph node biopsy (SLNB) rather than ALND for surgical staging [1–3]. Studies have demonstrated that the effectiveness of NAC in achieving nodal pathologic complete response (pCR) varies considerably by subtype with estrogen receptor-negative

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(ER −) and Her2-positive breast cancers having the highest response rates [4–6]. Conversely, patients with estrogen receptor-positive (ER +) and Her2-negative breast cancers have low response rates to both NAC and neoadjuvant endocrine therapy (NET) [7, 8] and are therefore often recommended surgery first, which currently includes ALND for axillary management.

Although studies have demonstrated that patients with sentinel node-positive disease can safely forego ALND without worsened outcome or survival [9, 10], others have suggested that patients with lymph node metastases diagnosed by preoperative ultrasound and biopsy have higher risk features and greater pathologic nodal burden, and should not be considered for omission of ALND [11–14]. Few studies have evaluated patients with palpable adenopathy, but the assumption exists that increasing clinical nodal burden reflects higher risk features and greater pathologic nodal disease. In this present study, we compare preoperative patient and tumor characteristics of patients with ER +, HER2-negative breast cancer who underwent ALND for node-positive disease and assess for variables associated with higher pathologic nodal stage among the different clinical groups.

Methods

This study was approved by the Institutional Review Board of the University of California, Los Angeles.

Study design

This is a retrospective study of patients who underwent ALND for breast cancer between 2010 and 2019 at a single institution. Consecutive patients with ER +, Her2-negative breast cancer were identified from chart review based on Current Procedural Terminology (CPT) codes and International Classification of Diseases, Ninth and Tenth Revision (ICD 9/10) diagnosis codes. ER positivity was defined according to ASCO/CAP guidelines as > 1% ER staining on IHC, and HER2-negativity as 0 or 1 + staining by IHC, or if 2 + by IHC then FISH HER2/CEP17 ratio of < 2 and average HER2 gene copy number < 4 signals/nucleus. Patients were excluded if they were treated with NAC, presented with stage 4 disease, had matted nodes on exam, or underwent ALND for axillary recurrence or contralateral axillary disease.

Patients were categorized into three clinical groups: clinically negative axilla but positive sentinel lymph nodes identified on SLNB (SLN +), non-palpable but positive lymph nodes on preoperative ultrasound and biopsy (cNUS), and palpable lymphadenopathy on preoperative exam (cNpalp). We considered cNUS and cNpalp patients to have clinically node-positive (cN +) disease. Although not all patients with cNpalp underwent preoperative nodal biopsy, patients who did not have pathologically positive nodes at surgery were omitted from the analysis to ensure exclusion of patients with clinically false-positive disease.

Patient demographic and tumor characteristics, type of breast and axillary surgery, and adjuvant therapies received were collected from medical records. The presence of positive nodes was assessed from documentation of preoperative clinical exam, imaging, and pathology results. Clinical tumor size was defined by imaging or exam before surgery based on standard American Joint Commission on Cancer (AJCC) staging criteria. To provide predictive guidance of nodal status prior to surgery, tumor histology, nuclear grade, prognostic markers [estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2/neu (HER2neu) status], Ki67 levels, and presence of lymphovascular invasion (LVI) were captured from the preoperative core needle biopsy results of the primary breast cancer.

The total number of positive lymph nodes was determined from the final surgical pathology specimen. Lymph node burden was dichotomized as pN1 (1–3 positive nodes) and > pN1 (≥ 4 positive nodes) disease.

Statistical analysis

Descriptive statistics on patient, tumor, and nodal characteristics were compiled by clinical group or nodal stage and assessed using analysis of variance for continuous variables and Fisher's exact test for categorical variables. Post hoc pairwise comparisons were performed using Tukey's test or Fisher's exact test with Benjamini–Hochberg correction for multiple testing. Logistic regression analysis was carried out to evaluate the association between lymph node burden and patient/tumor characteristics. The R software environment version 4.0.2 was used for all statistical analyses. Two-sided $p < 0.05$ was considered significant.

Results

Patient and tumor characteristics by nodal presentation

Table 1 describes the preoperative demographic and tumor characteristics of patients with ER + breast cancer who underwent ALND compared across the three nodal groups. Of 191 patients total, 94 (49.2%) were SLN +, 40 (20.9%) were cNUS, and the remaining 57 (29.8%) were cNpalp. The overall mean age was 59.1 years, with most patients being female (98.9%) and post-menopausal (69.1%), and tumors predominantly of ductal histology (70.8%).

The three patient groups showed significant differences in demographic variables but demonstrated fewer

Table 1 Patient demographic and tumor characteristics stratified by clinical nodal group

Characteristic	Overall[a] ($n=191$)	Clinical nodal group[a]			p value
		SLN + ($n=94$)	cNUS ($n=40$)	cNpalp ($n=57$)	
Age (yrs), mean ± SD	59.1 ± 12.6	56.4 ± 12.5	58.3 ± 10.8	64.3 ± 12.7	**< 0.01**
Sex at birth					1
Male	2 (1.1)	1 (1.1)	0 (0.0)	1 (1.8)	
Female	188 (98.9)	92 (98.9)	40 (100.0)	56 (98.2)	
Race/ethnicity					**0.01**
White	99 (52.1)	60 (64.5)	17 (42.5)	22 (38.6)	
Hispanic	17 (8.9)	7 (7.5)	0 (0.0)	10 (17.5)	
Black	5 (2.6)	1 (1.1)	2 (5.0)	2 (3.5)	
Asian	20 (10.5)	8 (8.6)	5 (12.5)	7 (12.3)	
Other	49 (25.8)	17 (18.3)	16 (40.0)	16 (28.1)	
Menopausal status					**< 0.01**
Pre	58 (30.9)	38 (41.3)	12 (30.0)	8 (14.3)	
Post	130 (69.1)	54 (58.7)	28 (70.0)	48 (85.7)	
Positive nodes					**< 0.01**
1–3 (pN1)	98 (51.3)	60 (63.8)	15 (37.5)	23 (40.4)	
4 + (pN2 +)	93 (48.7)	34 (36.2)	25 (62.5)	34 (59.6)	
Histology					0.97
Ductal	131 (70.8)	66 (71.0)	26 (68.4)	39 (72.2)	
Lobular	47 (25.4)	24 (25.8)	10 (26.3)	13 (24.1)	
Other	7 (3.8)	3 (3.2)	26 (68.4)	39 (72.2)	
PR stain					0.16
0	12 (6.4)	3 (3.2)	3 (7.5)	8 (14.0)	
1 +	176 (93.6)	90 (96.8)	37 (92.5)	49 (86.0)	
Tumor grade					**< 0.01**
1	44 (25.1)	32 (36.0)	8 (22.9)	4 (7.8)	
2	99 (56.6)	44 (49.4)	21 (60.0)	34 (66.7)	
3	32 (18.3)	13 (14.6)	6 (17.1)	13 (25.5)	
Ki67					0.07
< 15%	68 (43.0)	39 (52.0)	16 (45.7)	13 (27.1)	
15–35%	62 (39.2)	24 (32.0)	12 (34.3)	26 (54.2)	
> 35%	28 (17.7)	12 (16.0)	7 (20.0)	9 (18.8)	
Tumor size					0.38
T1 (≤ 20 mm)	62 (33.5)	36 (38.7)	12 (30.8)	14 (26.4)	
T2 (21–50 mm)	87 (47.0)	37 (39.8)	21 (53.8)	29 (54.7)	
T3 (> 50 mm)	36 (19.5)	20 (21.5)	6 (15.4)	10 (18.9)	
LVI					0.06
Present	29 (16.9)	9 (10.3)	8 (22.2)	12 (24.5)	
Absent	143 (83.1)	78 (89.7)	28 (77.8)	37 (75.5)	

SLN + clinically negative, sentinel lymph node-positive disease; *cNUS* clinically positive, non-palpable, US + nodal disease; *cNpalp* clinically positive, palpable nodal disease; *PR* progesterone receptor; *LVI* lymphovascular invasion

Bold values indicate $p < 0.05$

[a]Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and may not total 100

differences in tumor characteristics. The differences were investigated with multiple pairwise group comparisons (Fig. 1). For race/ethnicity, more patients identified as White in the SLN + group compared with the cNUS (64.5% vs. 42.5%, $p = 0.03$) and cNpalp (64.5% vs. 38.6%, $p < 0.01$) groups, with no difference noted between cNUS versus cNpalp ($p = 0.83$) patients. SLN + patients were younger (− 7.9 years, 95% CI [-12.7, − 3.0], $p < 0.01$) and

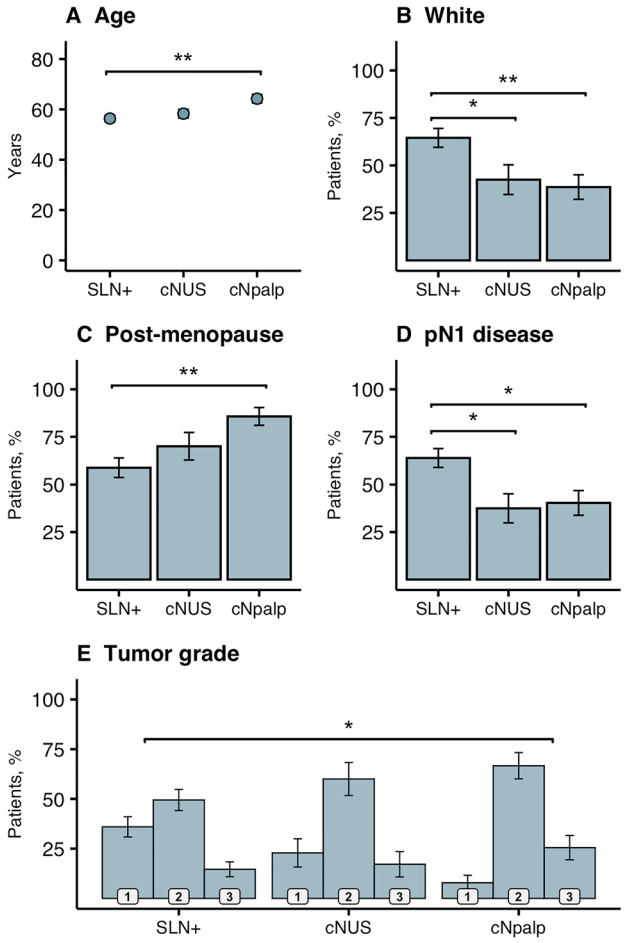

Fig. 1 Pairwise comparisons of the nodal groups SLN+, cNUS, and cNpalp for age (**A**), White race (**B**), post-menopausal status (**C**), pN1 disease (**D**), tumor grade (**E**). Error bars indicate ± 1 standard error. Statistically significant group differences are shown. * $p < 0.05$. ** $p < 0.01$

more often pre-menopausal (41.3% vs. 14.3%, $p < 0.01$) compared to cNpalp but not cNUS patients ($ps > 0.24$). Rates of pN1 disease were different between SLN+ versus cNUS (63.8% vs. 37.5%, $p = 0.01$) and SLN+ versus cNpalp (63.8% vs. 40.4%, $p = 0.01$) but not between cNUS versus cNpalp ($p = 0.84$) patients.

Regarding tumor characteristics, low-grade tumors were more prevalent among SLN+ patients than cNpalp patients ($p < 0.01$), but the cNUS group did not differ significantly from the SLN+ or the cNpalp group ($ps > 0.21$). No significant differences were noted among the nodal groups regarding histologic subtype ($p = 0.97$), PR-positivity ($p = 0.16$), Ki67 level, ($p = 0.07$), tumor size ($p = 0.38$), or presence of LVI ($p = 0.06$).

Predictors of pN1 disease in the study cohort

Univariable analysis demonstrated that patients with T3 tumors had 70% lower odds [OR 0.30, 95% CI (0.12, 0.71), $p = 0.01$] of having pN1 disease than patients with T1 tumors, and patients with lobular histology had 51% lower odds [OR 0.49, 95% CI (0.25, 0.98), $p = 0.04$] (Table 2). Age, sex, race/ethnicity, menopausal status, tumor grade, Ki67 level, and presence of LVI were unrelated to pathologic nodal stage (all $ps > 0.14$). A multivariable logistic regression of pN1 disease in the entire study cohort using histology and tumor size as predictors found that patients with T3 tumors had 68% lower odds [OR 0.32, 95% CI (0.13, 0.82), $p = 0.02$] of having pN1 disease than patients with T1 tumors, but the effect of histology was not significant ($p = 0.29$) (Table 3).

Surgical treatment, adjuvant therapies, and outcomes

Overall, 72.8% (139/191) of patients underwent mastectomy in this study cohort of node-positive disease with no difference in numbers of mastectomies performed between the SLN+ (68/94) and cN+ (71/97) groups ($p = 1$). Receipt of adjuvant radiation therapy ($p = 0.91$) and systemic chemotherapy ($p = 1$) did not differ between patients who presented with SLN+ or cN+ disease. However, significantly more patients with SLN+ disease (95.6%) received endocrine therapy compared to patients with cN+ disease (82.6%) ($p = 0.01$).

Of patients with pN1 disease (98/191), 70.4% (69/98) were treated with mastectomy. Of those, 68.2% received post-mastectomy and regional nodal irradiation, including the supraclavicular and internal mammary nodes. Over half of patients with pN1 disease (58.5%) received both chemotherapy and endocrine therapy, which did not differ based on nodal presentation ($p = 0.62$). Of note, the study period of our retrospective analysis pre-dated the publication of RxPONDER data.

Discussion

Historic randomized study data have failed to demonstrate a survival benefit for axillary lymph node dissection for patients with clinically positive nodes [15–17], yet ALND has remained the standard of care for these patients. Recent practice-changing clinical trials assessing de-escalation of axillary surgery have excluded patients with clinically positive nodes [9, 10] resulting in a significant dearth of contemporary data to guide surgical management of the axilla in this patient cohort. More recently, nodal downstaging with NAC has become an acceptable strategy to avoid ALND for

Table 2 Patient demographic and tumor characteristics and univariable logistic regression analysis of pN1 disease

Characteristic	Overall[a] ($n=191$)	Number of positive nodes[a]		Logistic regression of pN1		
		1–3 (pN1) ($n=98$)	4 + (> pN1) ($n=57$)	OR	95% CI	p value
Age (years), mean ± SD	59.1 ± 12.6	58.1 ± 12.1	60.2 ± 13.2	0.99	[0.96, 1.01]	0.24
Sex at birth						
Male	2 (1.1)	1 (1.0)	1 (1.1)	–	–	–
Female	188 (98.9)	97 (99.0)	91 (98.9)	1.07	[0.07, 17.3]	0.96
Race/ethnicity						
White	99 (52.1)	53 (54.6)	46 (49.5)	–	–	–
Hispanic	17 (8.9)	6 (6.2)	11 (11.8)	0.47	[0.16, 1.38]	0.17
Black	5 (2.6)	3 (3.1)	2 (2.2)	1.30	[0.21, 8.13]	0.78
Asian	20 (10.5)	14 (14.4)	6 (6.5)	2.03	[0.72, 5.70]	0.18
Other	49 (25.8)	21 (21.6)	28 (30.1)	0.65	[0.33, 1.30]	0.22
Menopausal status						
Pre	58 (30.9)	32 (33.3)	26 (28.3)	–	–	–
Post	130 (69.1)	64 (66.7)	66 (71.7)	0.79	[0.42, 1.47]	0.45
Histology						
Ductal	131 (70.8)	73 (77.7)	58 (63.7)	–	–	–
Lobular	47 (25.4)	18 (19.1)	29 (31.9)	0.49	[0.25, 0.98]	**0.04**
Other	7 (3.8)	3 (3.2)	4 (4.4)	0.60	[0.13, 2.77]	0.51
Tumor grade						
1	44 (25.1)	24 (26.7)	20 (23.5)	–	–	–
2	99 (56.6)	49 (54.4)	50 (58.8)	0.82	[0.40, 1.66]	0.58
3	32 (18.3)	17 (18.9)	15 (17.6)	0.94	[0.38, 2.35]	0.90
Ki67						
< 15%	68 (43.0)	36 (43.4)	32 (42.7)	–	–	–
15–35%	62 (39.2)	34 (41.0)	28 (37.3)	1.08	[0.54, 2.15]	0.83
> 35%	28 (17.7)	13 (15.7)	15 (20.0)	0.77	[0.32, 1.86]	0.56
Tumor size						
T1 (0–20 mm)	62 (33.5)	37 (38.9)	25 (27.8)	–	–	–
T2 (21–50 mm)	87 (47.0)	47 (49.5)	40 (44.4)	0.79	[0.41, 1.54]	0.49
T3 (> 50 mm)	36 (19.5)	11 (11.6)	25 (27.8)	0.30	[0.12, 0.71]	**0.01**
LVI						
Present	29 (16.9)	11 (12.6)	18 (21.2)	–	–	–
Absent	143 (83.1)	76 (87.4)	67 (78.8)	1.86	[0.82, 4.21]	0.14

LVI lymphovascular invasion

Bold values indicate $p < 0.05$

[a]Unless otherwise indicated, data are expressed as number (percentage) of patients. Percentages have been rounded and may not total 100

patients with clinically positive nodes who respond to treatment [1–3], but nodal response rates vary considerably by tumor subtype. For patients with ER-positive disease, nodal pCR rates rarely exceed 20% [4–6] although rates as high as 35% were noted for the subgroup with high-grade tumors and PR-negative disease [18]. Nonetheless, since residual disease is not prognostic of outcome for this cancer subtype [5, 19, 20], many patients are recommended for surgery first, and often ALND.

The concern for de-escalation of axillary surgery for patients with clinically positive nodes not treated with NAC appears to stem from data that demonstrate that these patients have less favorable tumor characteristics than patients with SLN + disease. Studies have suggested that certain high-risk features predict for higher nodal stage, which have led authors to conclude that patients with clinically positive nodes should not be considered for omission of ALND [12–14]. However, a disproportionately high number of patients in these studies had ER-negative (23.9–29.7%) and Her2-positive (18.7–31.2%) disease. In the study by Verheuvel et al. [12], patients with cNUS disease had higher risk features and worsened overall (hazard ratio [HR] 2.67, 95% CI [1.48, 4.84]) and disease-free survival [HR = 2.71, 95% CI (1.49, 4.92)] than patients with SLN + disease.

Table 3 Multivariable logistic regression analysis of pN1 disease, $N = 181$

Predictor	OR	95% CI	*p* value
Histology			
Ductal	–	–	–
Lobular	0.67	[0.32, 1.41]	0.29
Other	0.70	[0.14, 3.39]	0.66
Tumor size			
T1 (0–20 mm)	–	–	–
T2 (21–50 mm)	0.79	[0.40, 1.55]	0.49
T3 (> 50 mm)	0.32	[0.13, 0.82]	**0.02**

Patients with T3 tumors had 68% lower odds [OR 0.32, 95% CI (0.13, 0.82)] of having pN1 disease than patients with T1 tumors

However, the cNUS group compared to the SLN + group had a significantly higher proportion of patients with triple-negative breast cancer (TNBC) (15.8% vs 9.2%, $p = 0.04$). Recognizing that TNBC patients have higher rates of distant relapse, the disparity in histologic subtypes between the two nodal groups likely contributed to the survival differences noted. Modern-day treatment paradigms would typically include NAC for patients with node-positive ER-, Her2-positive, or TNBC, which make these study results less applicable for guiding surgical management of the ER-positive, Her2-negative breast cancer patients who proceed straight to surgery.

Our data of exclusively ER-positive patients with nodal disease demonstrate fewer differences in tumor characteristics based on nodal presentation. Patients with cNpalp have higher-grade tumors than SLN + patients, but rates of LVI, PR-positivity, and levels of Ki67 expression do not differ significantly among the nodal groups. Importantly, higher risk features are not indicators of higher nodal stage in patients with ER + disease regardless of nodal presentation, and approximately 40% of patients who present with clinically positive nodes have minimal nodal disease at surgery. Only tumor size remains an independent predictor of pN1 disease.

Few studies to date have evaluated nodal burden in patients with palpable adenopathy and ER + disease, which represents an understudied patient cohort for de-escalation of axillary surgery. Angarita et al. [21] performed a subgroup analysis and demonstrated that 45% of patients with ER + disease and palpable nodes had pN1 disease. Crown et al. [22] similarly demonstrated that 57% of patients with palpable adenopathy had ≤ 3 positive nodes in a cohort in which more than 97% had ER-positive disease. Both studies demonstrated that tumor size and lobular histology predicted for higher nodal stage, not high-risk features such as LVI, high tumor grade, or palpable adenopathy.

Certainly, among the cohort of patients with ER + breast cancer, tumor heterogeneity exists, which may reflect increased risk for systemic disease in patients with high-risk features, but this should not necessarily obligate patients to more extensive lymphatic axillary surgery. Data from the TAILORx [23] trial demonstrate that among patients with ER + disease, high-risk tumor biology predicts chemotherapy benefit even in the absence of nodal metastases. Initial results from the RxPONDER trial [24] suggest that this tumor heterogeneity persists even among patients with node-positive disease, suggesting that nodal status is not a reliable surrogate for high-risk disease among patients with ER + breast cancers. Our retrospective analysis that includes patients with node-positive disease regardless of nodal presentation suggests that patients with cNpalp disease have more grade 3 tumors than patients with SLN + disease, but grade is not predictive of pN1 disease. Only tumor size, which did not vary among the nodal groups, was independently associated with higher nodal stage. With the risk of disabling lymphedema, functional morbidity, and lack of oncologic benefit associated with this procedure, ALND should be continually re-assessed for all patients. Certainly, there is opportunity to consider de-escalation of axillary surgery in patients with estrogen receptor-positive disease who present with clinically positive nodes and proceed to surgery first for whom effective multimodality therapies exist.

We acknowledge the limitations of our study, including its retrospective design and small sample size. Many patients with clinically positive lymph nodes during this study period were treated with NAC at our institution, which decreased the number of patients available for inclusion in our study cohort. Furthermore, while some studies found a significant association between presence of LVI and nodal burden [25], we did not see this same effect, which may be a result of using the core needle biopsy rather than the surgical specimen to assess LVI. We purposefully chose this approach to determine whether any features identified preoperatively could predict nodal disease and therefore affect the decision for nodal surgery. The absence of a direct association in our dataset could be due to the inherent risk of a false-negative result on a core biopsy, or the small sample size. However, others have also demonstrated an absence of correlation with LVI and nodal burden [11, 21, 22, 26].

In addition, many of the SLN + patients in our database who underwent ALND were considered ineligible for Z0011 based on type of surgery (76.6% underwent mastectomy) rather than number of nodes involved or extranodal extension, which may result in more favorable tumor features attributed to the SLN + group. Similarly, some of the SLN + patients included in our study may have been eligible for treatment with axillary radiation rather than ALND based on AMAROS data.

Conclusions

In this era of effective multimodality therapy, the pressing challenge is to identify the cohort of patients with clinically positive nodes who can avoid the morbidity of ALND. For ER + patients who proceed to surgery first, over one-third have low-volume nodal disease, and only large tumor size appears to predict for higher nodal stage; higher risk features are not associated with > pN1 disease. For the significant minority of patients with ER-positive, node-positive disease with minimal nodal burden, studies evaluating the safety of de-escalating axillary surgery are necessary.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This study was reviewed and approved by the UCLA Institutional Review Board and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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