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ORIGINAL ARTICLE

Axillary ultrasound-guided core biopsy in breast cancer: identifying higher nodal burden and more aggressive clinicopathological characteristics

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Abstract

Background Patients with sentinel lymph node (SLN) metastases may not require axillary lymph node dissection (ALND) but it remains unclear if patients with a positive ultrasound-guided axillary core biopsy (ACB) would satisfy such criteria.

Aims The aim of this study was to assess if breast cancer patients with a positive pre-operative ACB have more aggressive tumour characteristics/higher axillary nodal burden compared to those with a positive SLN.

Methods Data was extracted from a prospectively maintained breast cancer database between 2012 and 2015. Patients who underwent ALND after either positive ACB or SLN were included and tumour characteristics/nodal burden were compared.

Results One hundred eighty patients underwent ALND, 125/180 after positive ACB and 55/180 after positive SLNB. Patients with positive ACB were more likely to undergo mastectomy (chi-square test; $p = 0.03$) and have higher tumour grades (Mann-Whitney test; $p < 0.01$) compared to the SLNB group. Median positive nodes excised during ALND were 2 (1–22) and 1 (1–11) for ACB and SLNB groups respectively ($p < 0.001$). Fifty-six patients received neoadjuvant chemotherapy (NCT). Of 72/125 patients in the ACB group not receiving NCT, the median number of positive nodes was 4 (range, 1–22). Ten patients within the ACB group satisfied ACOSOG Z011 criteria.

Conclusion Breast cancer patients with a positive ACB are more likely to have aggressive tumour characteristics and higher nodal burden compared to those identified as having axillary nodal disease on SLNB, which may affect surgical decision making.

Keywords Axilla · Biopsy · Breast · Cancer · Ultrasound

Introduction

Optimal management of the axilla remains a critical element in the effective locoregional management of breast cancer [1, 2]. The presence of axillary metastatic disease is a poor prognostic indicator, and over the last decade much attention has focused on improving diagnostic and therapeutic approaches to the axilla in breast cancer. Sentinel lymph node identification and biopsy have become the mainstay of diagnosis and staging of axillary disease and has reduced the proportion of patients requiring axillary lymph node dissection (ALND) [3, 4]. The publication of the American College of Surgeons Oncology Group Z0011 trial indicated that select patients in whom a low burden of sentinel lymph node metastases was present could avoid ALND, sparing them the morbidity associated with this procedure, without compromising oncologic outcomes [5].

The importance of accurate, minimally invasive axillary staging in breast cancer has prompted a significant increase in the use of other diagnostic modalities [6, 7]. Axillary ultrasound is now recommended for all patients diagnosed with breast cancer within Europe, and if suspicious nodes are identified, a targeted biopsy is performed [8, 9]. Ultrasound-guided axillary biopsy is performed either by fine-needle aspiration cytology (FNAC) or by core biopsy and both methods

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have been shown to have specificity rates and positive predictive values approaching 100% respectively [10–12]. Patients commonly proceed directly to ALND at the time of primary surgery if found to have ultrasound-guided biopsy proven metastases and hence avoid unnecessary SLNB.

A number of recent studies have reported that patients found to have axillary metastatic disease proven on ultrasound-guided FNAC have a higher nodal disease burden compared to those with a positive SLNB [13–15]. However, few studies have focussed on subsequent nodal burden in patients who proceed to ALND after a positive ultrasound-guided axillary core biopsy (ACB) and how nodal burden in this cohort compares to those undergoing ALND after a positive SLNB. The aim of this study was to evaluate nodal burden in patients found to have positive ACB and compare this to the burden of axillary metastatic disease in patients with a clinically and radiologically negative axilla but positive SLNB.

Methods

Patient identification

A retrospective review was performed of all patients diagnosed with a primary invasive breast cancer at a symptomatic breast unit (University Hospital Limerick), between January 2012 and July 2015. Patients who underwent ALND following a diagnosis of axillary lymph node metastases by either pre-operative US-guided ACB or SLNB were included for analysis. Patient demographics, clinicopathological characteristics, receptor subtype, surgical procedure performed and neoadjuvant/adjuvant therapies received were recorded for all patients. Patients were excluded from our study if they were found to have evidence of distant metastatic disease, did not undergo ALND or had recurrent disease.

Diagnostic process

All patients in our institution found to have radiological evidence of breast cancer on conventional imaging performed as part of triple assessment (R5) subsequently underwent targeted ipsilateral axillary ultrasound, performed by dedicated breast radiologists. When suspicious findings were observed on axillary imaging, ultrasound-guided core biopsy (ACB) of the suspicious node was performed. Characteristics of suspicious nodes included hilar replacement or gross hilar abnormalities, cortical thickening ≥ 2.5 mm or eccentric cortical thickening. If more than one abnormal node was identified, then the most abnormal appearing node was biopsied. A core biopsy was performed using a standard 18-gauge or 20-gauge core biopsy needle gun. Core biopsies were assessed for the presence or absence of metastatic disease and did not report on the presence of micrometastatic disease or isolated tumour cells. The presence of micrometastatic disease or isolated tumour cells on final histology was not included in our analysis. Patients found to have metastatic disease subsequently underwent routine staging investigations which in our institution include CT TAP imaging and radionucleotide bone scan. If the axillary ultrasound was normal or if the ACB was negative for metastatic disease, then patients proceeded to undergo SLNB for axillary evaluation as part of their therapeutic breast cancer surgery.

Quantification of nodal disease

Patients with a positive ACB without evidence of distant metastatic disease underwent ALND. Patients with evidence of macrometastatic disease after SLNB proceeded to ALND if they did not satisfy ACOSOG Z011 criteria. All cases were discussed and a final treatment decision was made at a weekly multidisciplinary meeting. Decisions regarding use of neoadjuvant chemotherapy (NCT) were made based on National Cancer Control Programme guidelines and after discussion at the multidisciplinary meeting. Any patient with a positive ultrasound-guided ACB who received NCT underwent ALND after NCT. Within our institution, ALND is standardised to involve excision of anatomical axillary levels 1 and 2. For each patient, the total number of nodes excised during ALND and the number of positive nodes were recorded. For patients who had undergone previous SLNB, the total number of nodes removed was calculated by adding the number removed during SLNB and ALND. Nodal burden within this group was similarly recorded. Standard histopathological assessment of excised nodes was then performed by dedicated breast pathologists.

Cohort analysis

Differences between the two groups were assessed using the chi-square test, Fisher's exact test and the Mann-Whitney U test where appropriate. A p value of < 0.05 was deemed to be statistically significant.

Results

Over a 43-month period (Jan 2012–July 2015), a total of 180 patients diagnosed with primary breast cancer underwent ALND. One hundred twenty-five of 180 (69.4%) patients underwent ACB that confirmed metastatic disease in the ipsilateral axilla and proceeded to ALND. Similarly, over the same time period, 55/180 (30.6%) patients proceeded to ALND after a positive SLNB, as detailed in Table 1. The median age in those with a positive ACB and a positive SLNB was 58 (range, 27–88) and 60 (range, 37–81)

Table 1 Patient demographics/tumour characteristics

Total patients undergoing axillary lymph node dissection (ALND)	$n = 180$		
Total patients proceeding to ALND after positive ACB	$n = 125$		
	ACB-positive group	SLNB-positive group	p value
Total patients	125	55	
Median age	58 (range, 27–88)	60 (range, 37–81)	
Surgery type			
Mastectomy	86 (68.8%)	29 (52.7%)	0.03
Wide local excision	39 (31.2%)	26 (47.3%)	
Tumour subtype			
Invasive ductal carcinoma	105 (84%)	40 (73%)	> 0.05
Invasive lobular carcinoma	19 (15%)	14 (25%)	
Other	1 (1%)	1 (2%)	
Tumour grade			
Median	III	II	< 0.01
Grade I	0	1 (2%)	
Grade II	60 (48%)	43 (78%)	
Grade III	65 (52%)	11 (20%)	
Tumour characteristics			
Lymphovascular invasion	21%	4%	< 0.001
Extra-nodal extension	13%	7%	0.22
Receptor status (%)			
Oestrogen receptor positive	64%	84%	0.008
HER2 positive	26%	16%	0.07
Level of Ki67 expression	30%	15%	< 0.001
Number of patients receiving neoadjuvant chemotherapy	53 (42.4%)	3 (5.45%)	< 0.001

respectively (Mann-Whitney U test; $p = 0.97$). Across both groups, 99.5% of patients were female. Fifty-three of 125 (42.4%) patients in the ACB group received neoadjuvant therapy (NCT) before ALND compared to 3/55 (5.45%) in the SLNB group (chi-square test; $p < 0.001$). All three patients in the SLNB group who received NCT underwent SLNB before treatment began.

68.8% (86/125) of patients in the ACB group undergoing ALND had a mastectomy as their primary breast procedure compared to the 52.7% (29/55) in the SLNB group (chi-square test; $p = 0.03$), as detailed in Table 1. Although not statistically significant (Mann-Whitney U test; $p = 0.16$), initial tumour size radiologically was larger in the ACB group (median = 28 mm; range, 2–100 mm) compared to the SLNB group (median = 25 mm; range, 3–80 mm). Invasive ductal carcinoma was the most common pathological subtype in both groups: 84% in the ACB group and 71% in the SLNB group (chi-square test; $p = 0.04$). However, more aggressive pathological characteristics such as tumour grade (median grade, 3 vs 2; Mann-Whitney U test; $p < 0.01$) and the presence of lymphovascular invasion (21% vs 4%; chi-square test; $p < 0.001$) were evident in the ACB group compared to the SLNB group. Oestrogen receptor negativity was more common in the ACB group (36% vs 16%; chi-square test; $p = 0.008$) as was progesterone receptor negativity (46% vs 31%; chi-square test; $p = 0.06$) although this was not statistically significant. HER2 receptor positivity was observed more frequently in the ACB group although this was not statistically significant (26% vs 16%; chi-square test; $p = 0.17$). Consequently, the percentage of patients in the ACB group with luminal A [16] tumours was lower than that in the SLNB group (45.6% vs 61%; chi-square test; $p < 0.05$). The percentage of patients with triple negative tumours was higher in the ACB group versus the SLNB group; 27/125 patients (21.6%) had triple negative tumours in the ACB group compared to 6/55 (11%) in the SLNB group (chi-square test; $p < 0.01$). Higher levels of Ki67 expression were also observed in the ACB group compared to the SLNB group (30% vs 15%; Student's t test; $p < 0.001$).

The median number of nodes excised at ALND in the ACB group was higher than that in the SLNB group (13 (4–26) vs 11 (4–21), Mann-Whitney U test; $p = 0.01$). The median number of total positive nodes excised in the ACB group was also higher at 2 (1–22) compared to 1 (1–11) in the SLNB group

(Mann-Whitney test; $p < 0.001$). The median number of positive nodes in the ACB group that had not received NCT was 4 (1–22) compared to 1 (1–11) for those who had (Mann-Whitney test; $p < 0.001$). The largest metastasis with regard to nodal burden after ALND in the core biopsy and SLNB groups was 22/25 and 11/21 respectively (Table 2). Seven patients who had not received NCT were found to have no positive nodes on ALND, indicating a positive predictive value for ultrasound-guided core biopsy of 91% (65/72) when those who received NCT were excluded (ACB false positive rate = 9%; 7/72). Extra-nodal extension was also more common in the ACB group when compared to the SLNB group (13% vs 7%) but this difference was not statistically significant (chi-square test; $p = 0.22$). Sixty percent (75/125) of patients in the ACB group had ≤ 2 positive nodes compared to 76% (42/55) in the SLNB group (chi-square test; $p = 0.03$). Of the 75 patients in the ACB group that had ≤ 2 positive nodes retrieved during ALND, 45 (60%) had received NCT. Of patients found to be oestrogen receptor positive and Her2 receptor negative, 11 from the core biopsy group received NCT compared to 0 in the SLNB group.

On assessment of patient and treatment factors to determine eligibility for application of ACOSOG Z011 criteria to those who had a positive ACB, 53 had received NCT. Of the remaining 72 patients, 56 had undergone mastectomy. Of those who had had breast-conserving surgery two had evidence of extra-nodal extension. Of the remaining 14 patients, four had three or more positive nodes retrieved during ALND. Therefore, only ten patients (8%) out of 125 with a positive ACB would have satisfied criteria for inclusion in the ACOSOG Z011 trial.

Discussion

This study demonstrates that breast cancer patients with a positive ultrasound-guided ACB have more aggressive clinicopathological characteristics, often require more extensive breast surgery (mastectomy) and have a more extensive nodal disease burden than those who proceed to ALND after a positive SLN. This supports the hypothesis that the majority of patients with a positive ultrasound-guided ACB should still proceed directly to ALND. Previous studies have examined differences in clinicopathological characteristics between patients with a positive ultrasound-guided axillary fine-needle aspiration cytology or core biopsy and SLN [17–20], with similar results observed. To our knowledge, this is the first study that compares nodal burden in patients with a positive axillary core biopsy (ACB) and those with a positive SLN.

The use of axillary ultrasound as a means of assessing the axilla in breast cancer patients has increased significantly in the last decade. Both core biopsy and fine-needle aspiration cytology represent inexpensive, easily accessible and reliable methods of sampling abnormal looking axillary lymph nodes [21]. As such, many European centres now perform a routine axillary ultrasound in newly diagnosed breast cancer patients, and in cases where suspicious nodes are identified, a biopsy is performed for histological diagnosis [8, 9]. Previous studies have advocated the use of axillary ultrasound-guided biopsy because, if positive, patients can avoid unnecessary SLNB and proceed to ALND as their primary axillary procedure [11, 20]. The findings of our study support that approach as patients in the ACB cohort who did not receive neoadjuvant chemotherapy had a median of four positive nodes compared to one in the SLN group, vindicating the use of ALND as a component of their primary therapeutic surgery. The publication of the ACOSOG Z0011 study in 2011 attempted to identify those with a positive SLN who could avoid ALND [5, 22]. The study found that patients who satisfied specific criteria and had ≤ 2 positive sentinel lymph nodes could avoid completion of ALND and receive standard adjuvant therapy without any effect on overall and disease-free survival. It is clear that a minority (< 10%) of our study cohort would have satisfied such criteria or been eligible for this approach. Nearly half of our cohort had received NCT whilst others had undergone mastectomy or had evidence of extra-nodal extension, all exclusion factors for the Z011 study. Our results are similar to studies examining the burden of disease in those with a

Table 2 Nodal burden

Total patients	$n = 180$		
	ACB-positive group	SLNB-positive group	p value (Mann-Whitney test)
Patients proceeding to ALND	125	55	
Total number of nodes excised during ALND (median)	13	11	0.01
Total number of positive nodes excised (median)	2	1	< 0.001
Total number of positive nodes excised in patients not receiving neoadjuvant chemotherapy (median)	4	1	< 0.001
% of patients with ≤ 2 positive nodes found on ALND	60%	76%	
% of patients with extra-nodal extension	13%	7%	0.22 (chi-square)

positive FNAC when compared with a positive SLNB [23]. This data supports the practice that patients with an abnormal axillary ultrasound that yields a positive biopsy still require ALND without unnecessary SLNB.

Our institutional diagnostic pathway involves axillary ultrasound for all newly diagnosed breast cancer patients. Axillary ultrasound was not performed routinely within the ACOSOG Z011 protocol and so patients who had a normal axillary exam proceeded immediately to SLNB. Although patients within our SLNB group were found to have a median one positive node, they are likely to have fewer positive nodes compared to the group within the ACOSOG Z011 study as they had already had a negative axillary ultrasound before proceeding to SLNB, lowering the likelihood of metastatic disease.

A number of recent studies have examined the need for ALND in patients who are clinically node negative [24–26]. Two studies by Pilewskie et al. demonstrated that patients who have only one abnormal lymph node on pre-operative axillary ultrasound may be treated as per ACOSOG Z011 protocols and could potentially avoid ALND. In one of these studies, patients who had T1-2/N0 disease with a positive axillary ultrasound-guided biopsy were examined [25]. The presence of more than one abnormal lymph node on ultrasound was shown to have a statistically significant association with three or more positive nodes on final histology. However, a significant proportion of patients (47%) with a positive pre-operative biopsy were found to have only ≤ 2 positive nodes after ALND and therefore may have been treated as per Z011 protocols. Although our study did not examine the number of abnormal nodes on axillary ultrasound, 30/72 patients who did not receive NCT had ≤ 2 positive nodes after ALND. However, only 10/72 would have satisfied Z011 criteria when other factors such as surgery type (mastectomy) and the presence of extra-nodal extension were accounted for. Whilst the studies by Pilewskie et al. and Harris et al. demonstrate a role for a minimal approach to the axilla in patients with early-stage low-volume disease on pre-operative ultrasound, our study shows that in the absence of NCT, the majority of patients should still proceed to ALND.

Many recent studies have focussed on the differences between FNAC and core biopsy as a means for assessing abnormally appearing nodes [10, 11]. The reported sensitivity and specificity of these tests have ranged from 54 to 72% and from 77 to 100% respectively. It is arguable that core biopsy may be marginally superior with regard to specificity but at an increased cost [27]. This demonstrates that in specialist centres with dedicated breast radiologists, few patients will have a false positive result that leads to unnecessary intervention and over-treatment. In our study, few patients were found to have no further axillary disease after ALND if they had not received NCT and so proceeding to clear the axilla after a positive ACB is warranted in this cohort of patients. This indicates a positive predictive value within our institution of 91% which is in keeping with previously published values [11, 12]. A study by Solon et al. also demonstrates that the specificity of ACB increases between ultrasound alone and the use of a core biopsy [11]. The addition of core biopsy results in specificity rising close to 100% and so we would advocate the use of either biopsy technique in addition to ultrasound when assessing the axilla.

Many of the reports on this topic to date did not include patients who had received NCT and so our study also highlights the impact of axillary response in those who do receive chemotherapy before definitive surgery. Forty-two of the patients in the ACB cohort had no further positive nodes after ALND, 35(84%) of these patients received NCT. NCT can be very successful in patients with node-positive disease, especially in patients with Her2-overexpressing tumours or triple negative tumours for whom complete pathologic response rates of 43% and 47%% have been reported respectively [28]. However, avoiding ALND after NCT in patients with a positive axillary core biopsy remains controversial. It is likely however that as the management of breast cancer patients becomes more individualised and as adjuvant therapies continue to improve, the requirement for ALND in patients with node-positive disease pre NCT will decrease [29, 30]. The SENTINA, ACOSOG Z1071 and Canadian SN FNAC studies have demonstrated the feasibility of SLNB post NCT, with false negative rates of 8–14% for patients who presented with node-positive disease [31–33]. The use of NCT to downstage the axilla, with post-NCT SLNB as a means of re-assessing axillary nodal status, is likely to become a clinically relevant approach for patients with Her2-positive and triple-negative disease. Thus, ALND may be reserved for patients with residual nodal disease, sparing those who exhibit an axillary pCR.

Our study has a number of limitations. The data examined is from a single tertiary referral centre in Ireland and so may not be applicable to institutions, where axillary ultrasound is only performed in the context of a suspicious clinical exam. Our cohort only includes patients who presented through a symptomatic breast clinic and therefore does not account for patients diagnosed through a screening programme. However, it is likely that our results are more applicable to a symptomatic cohort who present more commonly with axillary metastases. It is also clear from our study that many patients did not satisfy Z11 criteria on account of receiving NCT. Whilst the indications for NCT have not been included, it is possible that some patients with a positive ACB proceeded to receive NCT based on their axillary nodal positivity and may not have done so if axillary ultrasound and biopsy had not been performed as part of diagnostic work-up, and therefore may have satisfied Z11 criteria. Certain patients with a positive ACB may benefit from repeat staging of the axilla after NCT to assess response and potentially avoid ALND but this requires further investigation. However, it is clear that patients with a positive ACB

have more aggressive clinicopathological characteristics and are unlikely to satisfy such criteria.

Conclusion

This study demonstrates that newly diagnosed breast cancer patients with a positive axillary ultrasound-guided core biopsy have more extensive nodal disease as well as more aggressive clinicopathological characteristics compared to those with a positive sentinel lymph node biopsy. At present, axillary lymph node dissection remains the preferred surgical approach for these patients. However, with the increasing use of NCT, as well as advances in individualised biologic information such as receptor status and subtype, certain patients who are likely to exhibit high rates of pathological response within this cohort may be suitable for avoidance of ALND if the axillary nodes are accurately staged post neoadjuvant NCT.

Compliance with ethical standards

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

Informed consent Informed consent was obtained from all individual participants included in the study.

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