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BREAST

The Z0011 Trial: Is this the end of axillary ultrasound in the pre-operative assessment of breast cancer patients?

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Abstract
Objectives The Z0011 trial questioned the role of axillary ultrasound (AxUS) in preoperative staging of breast cancer in patients with ≤2 positive sentinel lymph nodes (SLN). The purpose of this study was to correlate the number of abnormal nodes on AxUS with final nodal burden and determine the utility of AxUS with sampling (AxUS+S) in preoperative staging.
Methods Six hundred and seventy-nine patients underwent pre-operative AxUS. Suspicious nodes were sampled. Negative axillae proceeded to SLN biopsy. The number of abnormal nodes identified on ultrasound and final histology as well as sensitivity and specificity for AxUS+S were calculated. Subgroup analysis was performed on Z0011 eligible patients.
Results Two hundred and ninety-six patients had positive axillary nodes on final histology with 169 detected by AxUS+S (sensitivity 86.2 %, specificity 100 %, PPV 100 %, NPV 71.9 %). Patients with nodal metastases identified by AxUS had a mean burden of 7.3 nodes on histology (1 node on AxUS=5.2 nodes on histology, 2 nodes on AxUS=7.5 nodes, >2 nodes=10.1 nodes). Patients diagnosed on SLNB had a mean burden of 2.2 nodes.
Conclusion A single nodal metastasis detected on AxUS+S correlated with a mean of 5.2 nodes on final histology highlighting that AxUS remains essential in guiding appropriate management of the axilla in breast cancer.

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Key Points
- *Axillary ultrasound +/- sampling is an essential technique in preoperative axillary staging.*
- *Axillary ultrasound findings correlate with final histological axillary node disease burden.*
- *Axillary ultrasound can help triage patients who require axillary lymph node dissection.*
- *The role of axillary ultrasound in breast cancer staging continues to evolve.*

Keywords Breast cancer · Axillary staging · Ultrasound · Percutaneous biopsy · Histology

Abbreviations and acronyms

SLNB	Sentinel lymph node biopsy
PPV	Positive predictive value
NPV	Negative predictive value
ALND	axillary lymph node dissection
AxUS	axillary ultrasound
FNAC	Fine needle aspiration cytology
CB	Core biopsy
Ax-US+S	axillary ultrasound+sampling (FNAC or CB)

Introduction

The accurate assessment of axillary lymph node status is essential in the management of breast cancer [1, 2]. Clinical examination is inaccurate in the determination of axillary nodal status [3]. SLNB is the standard practice for staging of the axilla based on prospective, randomized trials, which revealed a reduction in the need for ALND with its associated morbidity [4–6].

Advances in pre-operative imaging with the advent of axillary ultrasound (AxUS) and image-guided needle sampling (fine needle aspiration cytology [FNAC] or core biopsy [CB])

of morphologically abnormal nodes has further changed the algorithm for axillary assessment with over 50 % [7] of node positive patients being triaged directly to ALND avoiding the need for SLNB and possible delayed ALND. This procedure has become routine practice in many breast units [8] and has been included in the most recent NICE guidelines on the management of early and locally advanced breast cancer [9].

A negative nodal status on AxUS with sampling (AxUS+S) does not definitively exclude axillary nodal metastases and these patients must proceed to SLNB to confirm nodal staging [10]. However, the consistently high specificity, positive predictive value (PPV) [7] and convenience of performing AxUS+S during assessment of the primary tumour makes it an excellent pre-operative staging technique.

The results of the Z0011 trial of the American College of Surgeons Oncology Group [11, 12] showed that in a subpopulation of breast cancer patients with ≤2 positive axillary nodal metastases on SLNB, (patients with cT1-2 N0 tumours, undergoing breast conserving surgery with adjuvant whole-breast radiotherapy, appropriate systemic therapy, and without third field axillary radiotherapy) that proceeding to ALND did not impact on overall survival (ALND 91.9 % vs SLNB 92.5 %), disease free survival (ALND 82.2 % vs SLNB 83.8 %) or locoregional recurrence (ALND 0.5 % vs SLNB 0.9 %). The Z0011 study population was noted to have a low axillary nodal burden in comparison to a number of recent studies [13, 14]. The study also had a short follow-up period with a median follow-up of 6.3 years.

The purpose of this study was to evaluate the role of pre-operative AxUS+/-S in the setting of an unselected breast cancer population undergoing SLNB or ALND with histology as a reference standard. Correlation between the number of morphologically abnormal nodes identified on AxUS and the final number of positive axillary nodes on histology was performed. The study aimed to evaluate whether AxUS can identify those patients with positive axillary nodes and predict final axillary nodal burden; thereby identifying patients who based on current evidence should proceed to ALND. We performed a subgroup analysis of patients fulfilling the Z0011 inclusion criteria to evaluate the role of AxUS+/-S in this population and to assess if any of these patients would have avoided ALND if they had undergone SLNB rather than AxUS for initial axillary assessment.

Materials and methods

A retrospective review of all breast cancer cases diagnosed at a symptomatic breast unit between January 2009 and December 2012 was performed. Data was obtained from a prospectively maintained database. Exclusion criteria included patients who did not undergo AxUS, surgical axillary staging with SLNB or ALND, patients operated on in another institute and those receiving neoadjuvant therapy.

Ultrasound assessment of the breast and ipsilateral axilla was performed by a consultant breast radiologist. Our institute's protocol to define morphologically abnormal nodes includes cortical thickness >3 mm, prominent eccentric lobulation, and a replaced/eccentric hilum. As the Z0011 eligibility criteria requires ≤2 positive SLN, our cohort was stratified into groups with 1, 2, or >2 abnormal nodes identified on ultrasound.

Abnormal nodes were sampled predominantly using FNAC (88 %) but CB (12 %) was also performed depending on the radiologist's preference. Results for both techniques were combined (AxUS+sampling; AxUS+S) for evaluation given the predominant use of FNAC. Three FNA samples were obtained using a 21-gauge needle and aspirates were rinsed into CytoLyte (Cytyc Corp., Boxborough, MA) solution for analysis by a cytopathologist. The CB was performed with a 14G needle and the sample placed in formalin for analysis by a breast histopathologist. If >1 abnormal node was visualized, then the lowest most morphologically abnormal node was sampled as this corresponds to the most common site of the sentinel node [15, 16].

Confirmation of a positive axillary nodal status at sampling resulted in concurrent ALND with primary breast surgery. SLNB with intra-operative frozen section analysis at the time of primary surgery was reserved for patients with a negative AxUS+/-S and immediate ALND was performed if the node was positive. Final nodal status was confirmed by analysis of fixed formalin paraffin-embedded nodal tissue. Delayed ALND was performed if positive nodal status was confirmed on final histology in cases with initial negative intra-operative histology. Each case was discussed at a breast cancer specific multidisciplinary meeting consisting of consultant radiologists, pathologists, surgeons, and medical/ radiation oncologists.

Patient demographics, clinico-pathological features, and AxUS+/-S findings were recorded. Sensitivity, specificity, PPV, NPV, and utility for AxUS alone and AxUS+S were calculated. Fisher's exact test was used for categorical data. In patients with confirmed nodal involvement by AxUS+S, Spearman's Rank-Order Correlation (r_s) was used to assess for correlation between the number of abnormal nodes identified on AxUS and final axillary nodal histology. A subgroup analysis was performed on all patients fulfilling the Z0011 eligibility criteria. Statistical analysis was performed using GraphPad Prism software (version 6.05 GraphPad, California, USA) with a p-value <0.05 considered significant.

Results

Between January 2009 and December 2012, 887 patients were diagnosed with breast cancer in our institute. Of these, 679

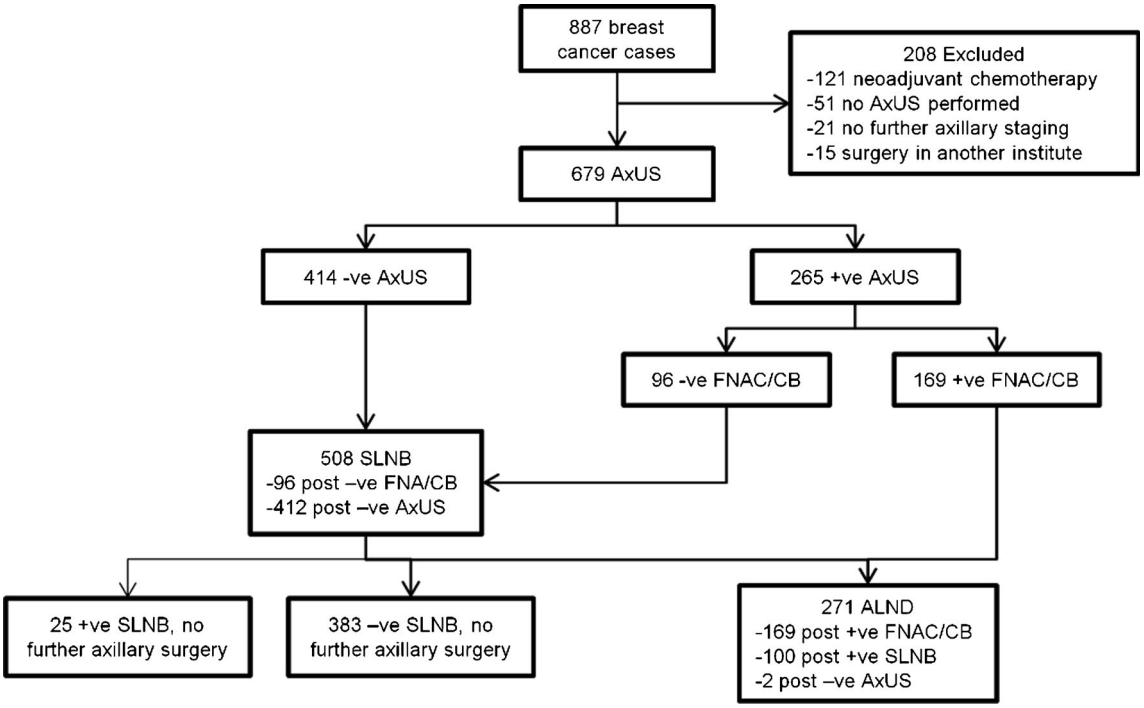

Fig. 1 Flow diagram of study patients

patients were included in the study with 208 excluded based on the criteria outlined in Fig. 1 (73/121 patients who underwent neoadjuvant chemotherapy had positive axillary lymph nodes on AxUS+S). Tumour and clinico-pathological characteristics are shown in Table 1.

Abnormal nodes were identified in 265 of the 679 patients on AxUS. All 265 patients proceeded to FNAC or CB. Two hundred and thirty-three patients (88 %) underwent FNAC and 32 patients underwent CB (12 %). Nodal metastases were identified in 169 patients. The remaining 96 patients had a negative FNAC or CB and all underwent SLNB. Four hundred and fourteen patients had a normal AxUS and 412 of these proceeded to SLNB. Two of the 414 patients proceeded to ALND based on patient preference following discussion at a multidisciplinary meeting.

In total, 296 patients had axillary nodal metastases on final histology (44 % of patients) with 169 of these identified preoperatively by AxUS+S. The remaining 127 cases were identified by SLNB. A total of 25 patients with positive nodes at SLNB did not proceed to ALND. Twenty-two of these patients had one positive SLN with three patients having two positive SLN. Twenty of these 25 patients fulfilled the Z0011 inclusion criteria. These patients were excluded when assessing for correlation between AxUS nodal burden and final nodal histology. Three hundred and eighty-three patients had negative nodal staging on final histology, and all were correctly identified on AxUS+/-S with no false positive results.

The 169 patients with nodal metastases identified by AxUS+S had a median nodal burden of 5 and mean nodal burden of 7.3 nodes on final histology (Range 1-41, SEM= 0.61, 95 % CI=6.1-8.5) with correlation noted between

Table 1 Patient and tumour characteristics

Characteristic	
Age (years)	
Mean	57.8 yrs
Median	56 yrs
Range	19–89 yrs
T stage (% of total)	
T1	50 %
T2	44 %
T3	5 %
T4	1 %
Tumour histology (% of total)	
Ductal	77 %
Lobular	12 %
Others	11 %
Breast surgery (% of total)	
Breast conserving surgery (BCT)	60.4 %
BCT prior to mastectomy	0.2 %
Mastectomy	38.4 %
Not specified	1 %
Number of SLN per procedure	
Mean	2.3
Median	2
Range	1–10

AxUS+S and final histology node numbers (r_s=0.38, 95 % CI=0.23-0.52, p-value<0.0001). The mean final metastatic nodal burden based on the number of abnormal nodes on AxUS is summarized in Table 2. Patients with one abnormal node on AxUS had a median nodal burden of 3 and mean of 5.2 on final histology (Range 1-21, SEM 0.59, 95 % CI 4.0-6.4). Patients with two abnormal nodes on AxUS had a median nodal burden of 5 and mean of 7.5 (Range 1-28, SEM 2.5, 95 % CI 1.9-13.1). Those with >2 abnormal nodes on AxUS had a median nodal burden of 7 and mean of 10.1 (Range 1-41, SEM 1.1, 95 % CI 7.8-12.5). The mean nodal burden of patients diagnosed with metastatic axillary nodes on SLNB with negative AxUS+/-S was 2.2 (SEM 0.25, 95 % CI 1.7-2.7) with a median of 1 node.

AxUS alone had a sensitivity of 64 %, specificity of 76.9 %, PPV of 63.8 % and NPV of 77.1 %. AxUS+S had a sensitivity of 86.2 %, specificity of 100 %, PPV of 100 % and NPV of 71.9 %. Of all node positive patients, 57.1 % were detected by AxUS+S directly triaging 24.9 % of all patients to ALND.

A subgroup analysis was performed on 322 patients fulfilling Z0011 inclusion criteria excluding the requirement of ≤2 involved sentinel lymph nodes given our protocol of performing routine AxUS+/-S on all patients. Patients with a negative AxUS who proceeded to SLNB and patients with a positive AxUS+S proceeding to ALND who otherwise fulfil Z0011 eligibility criteria were included. Ninety-four of these patients had a positive AxUS, 62 of whom had a negative biopsy and proceeded to SLNB. The remaining 32 patients had a positive AxUS+S and proceeded to ALND. Twenty of these 32 patients had ≥3 positive nodes on final histology. The remaining 12 patients had ≤2 nodes on final histology. The 32 patients with nodal metastases identified by AxUS+S had a median nodal burden of 4 and mean nodal burden of 6.6 on final histology (Range 1-28, SEM=1.3, 95 % CI=3.8-9.3) with correlation noted between AxUS-S and final histology node numbers (r_s=0.68, 95 % CI=0.42-0.84, p-value< 0.0001).

In this subgroup, the mean final metastatic nodal burden based on the number of abnormal nodes identified on AxUS is summarized in Table 3. Patients with one abnormal node identified on AxUS had a median nodal burden of 2 and mean of 2.6 on final histology (Range 1-10, SEM 0.6, 95 % CI 1.4-3.9). Patients with two abnormal nodes had a median nodal burden of 5 and mean of 9.5 (Range 2-28, SEM 6.2, 95 % CI -10.2-29.2) and those with >2 abnormal nodes had a median nodal burden of 9 and mean of 9.6 (Range 3-20, SEM 1.9, 95 % CI 5.3-13.9). A total of 290 patients in this subgroup proceeded to SLNB (228 with negative AxUS, 62 with negative AxUS+S). These patients had a mean nodal burden of 0.3 (SEM .05, 95 % CI 0.21-0.41) and a median nodal burden of 0 on final histology. Twenty-nine patients had a final nodal burden of >2 positive nodes on final histology and 20 (69 %) of these patients were detected using AxUS-S.

Discussion

Accurate staging of the axilla is important in determining treatment in breast cancer and is a significant prognostic indicator [1, 2]. ALND is the reference standard for determining nodal status [17, 18] as well as resecting macroscopic disease, but this comes at the cost of significant morbidity [19, 20], which is of particular relevance given the considerable rate of negative ALND if other axillary staging techniques are not used.

AxUS+S and SLNB help reduce the rate of negative ALND. AxUS+S allows for immediate ALND at the time of primary breast surgery in a significant number of node positive patients [14]. Such an approach allows for earlier referral for adjuvant therapies [14], cost savings if a delayed ALND is avoided [21], and avoids the potentially increased morbidity of a 2-stage axillary procedure.

The results of the Z0011 trial called into question the role of ALND in a sub-population of breast cancer patients with ≤2 positive SLNs. In patients fulfilling the trial's inclusion criteria, proceeding to ALND did not lead to a difference in overall and disease free survival or locoregional recurrence [11, 12]. This would suggest that AxUS no longer has a role in these patients, as it cannot determine the number of sentinel

Table 2 Number of abnormal nodes identified on AxUS compared with final nodal burden on histology

Number of abnormal nodes identified on AxUS	Median number of metastatic nodes on final histology	Mean number of metastatic nodes on final histology	Range of metastatic nodes on final histology	95 % CI for mean number of metastatic nodes
1 node	3	5.2	1–21	4–6.4
2 nodes	5	7.5	1-28	1.9–13.1
>2 nodes	7	10.1	1-41	7.8–12.5
All patients	5	7.3	1-41	6.1–8.5

Table 3 Z0011 eligible patients: Number of abnormal nodes identified on AxUS compared with final nodal burden on histology

Number of abnormal nodes identified on AxUS	Median number of metastatic nodes on final histology	Mean number of metastatic nodes on final histology	Range of metastatic nodes on final histology	95 % CI for mean number of metastatic nodes
1 node	2	2.6	1–10	1.4–3.9
2 nodes	5	9.5	2–28	-10.2–29.2
>2 nodes	9	9.6	3–20	5.3–13.9
All patients	4	6.6	1–28	3.8–9.3

nodes involved. The downside of performing SLNB on all of these patients includes the extra cost [22, 23], the possibility of delayed ALND [14], and a delay in adjuvant treatment.

Recent consensus data has highlighted the importance of not extrapolating the results of the Z0011 trial beyond the patient population fulfilling the trial's eligibility requirements [24] in whom the protocol has been validated. Of particular importance is the requirement to receive whole breast tangential field radiation therapy, typically with significant axillary coverage, as well as appropriate systemic therapy, if indicated. Both of these may play important roles in treating axillary nodal metastases.

In the Z0011 trial, the median metastatic axillary nodal burden in patients undergoing ALND was 1 with a median of 17 nodes resected [12]. This is considerably lower than our cohort of 169 AxUS+S positive patients who had a median axillary nodal burden of 5. A recent study looking at the role of AxUS+CB in detecting axillary nodal metastases similarly had a greater nodal burden than the Z0011 cohort with a median of seven metastatic nodes [13]. This may be partly explained by the Z0011 trial eligibility requirements, which stated that during SLNB if a surgeon felt there was extensive axillary disease on palpation, then these patients should be excluded [11].

Our study showed that in patients with positive AxUS+S, there is a correlation between an increasing number of abnormal nodes on AxUS (1, 2 or >2 nodes) and the mean number of metastatic nodes on final histology (r_s=0.38, 95 % CI=0.23-0.52, p-value<0.0001). Patients with a positive AxUS+S had a mean nodal burden of 7.3 nodes suggesting that the majority of these patients would not fulfil the Z0011 inclusion criteria based on nodal status, and ineligibility is more likely with an increasing burden of abnormal nodes on AxUS.

However, patients with a negative AxUS+/-S proceeding to positive SLNB followed by ALND had a mean nodal burden of 2.2 and median of 1 node. Furthermore the mean nodal burden of all patients with negative AxUS+/-S (n=510) regardless of SLN status was 0.5 (SEM 0.07, 95 % CI 0.35-0.65) with a median of 0 nodes. This suggests that a negative axillary work-up predicts a low axillary nodal burden and can help identify those patients who may be suitable for the Z0011 protocol based on nodal criterion [11, 12].

Supporting our results demonstrating correlation between AxUS nodal burden and nodal burden on final histology, Hiroyuki et al. [25] found that a normal AxUS predicted the likelihood of pN0-1 disease, suggesting that SLNB would likely be sufficient for further axillary staging in these patients. Furthermore, when ≥2 abnormal nodes were noted on AxUS, this predicted pN2 disease or worse with a PPV of 82 %.

The sensitivity, specificity, PPV and NPV of AxUS+S in our study compare favorably with a recent meta-analysis by Houssami et al. [7]. The utility of preoperative AxUS in our cohort is comparable with the results of this meta-analysis with AxUS+S directly triaging 24.9 % of patients to ALND and detecting 57.1 % of node positive patients in our cohort versus 19.8 % and 55.2 %, respectively. In this meta-analysis the percentage of patients triaged to ALND following AxUS+S was noted to be dependent on the underlying metastatic nodal disease prevalence with a median prevalence of 47.2 % in the studies included [7]. The high prevalence of axillary nodal disease in our cohort of 44 % is accounted for by the fact that the study group represents predominantly a symptomatic population rather than a screening population.

The results of FNAC and CB were combined in our study (AxUS+S) due to the predominant use of FNAC (88 %). This is primarily due to the preference of the radiologists and pathologists in our institute. The above meta-analysis did not identify a statistically significant difference in the sensitivity and specificity of these two techniques [7]. Radiologists, therefore, should continue to use the technique that they deem most appropriate according to their skill set and local cytopathology availability.

Within the subgroup fulfilling Z0011 trial inclusion criteria, 32 of the 322 patients had a positive AxUS+S and all proceeded to ALND. Twenty of the 32 patients had >2 metastatic nodes on final histology and were appropriately triaged to ALND. Twelve of these 32 patients, or 0.4 % of this 322 patient subgroup, had final axillary nodal involvement of ≤2 nodes and based on the results of the Z0011 trial were over treated with ALND not conferring a benefit. Eleven of these 12 patients had only one abnormal node identified on AxUS-S with the remaining patient having two abnormal nodes. In all but one patient with ≥2 abnormal nodes identified on AxUS-S, the final nodal burden was ≥4 with a median of nine positive nodes and a mean of 10.8 (SEM 2.2, 95 % CI 5.9-15.6) with correlation noted between AxUS-S and final nodal histology (r_s=0.68, p-value<0.0001). Those patients with a negative AxUS+/-S had a mean nodal burden of 0.3 and a median of 0 nodes on final histology.

Thus, similarly in this subgroup, a negative AxUS+/-S can help predict eligibility for the Z0011 trial protocol whilst a positive AxUS+S can identify those patients with nodal disease likely requiring ALND based on current evidence. Given that all but one patient with ≥2 abnormal nodes on AxUS+S had ≥4 nodes on final histology, the use of a cut-off of ≥2 abnormal nodes on AxUS with positive sampling for direct triage to ALND should be considered. Our study suggests that, patients fulfilling Z0011 eligibility criteria with only one abnormal node on ultrasound should no longer undergo sampling and should instead proceed to SLNB. In contrast, the population with one abnormal node on ultrasound who did not meet Z0011 eligibility requirements had a higher nodal burden on final histology, and; therefore, these patients should continue to undergo sampling as per current practice.

The management of locoregional disease in breast cancer is an evolving area and a multidisciplinary approach to treatment

is essential in each patient utilizing current best evidence based practice. AxUS+S continues to play an important role in decision-making algorithms. Our study suggests that AxUS+S can predict metastatic axillary nodal burden. A positive AxUS+S can help identify patients with a higher nodal burden who are more likely to require ALND based on current evidence [24]. In patients who fulfil the criteria for Z0011 eligibility, a negative AxUS+/-S can help identify those patients with ≤2 positive SLN who may be suitable for treatment utilizing the Z0011 protocol. In this group of eligible patients, we propose that patients with one abnormal lymph node on ultrasound do not undergo ultrasound guided sampling and instead proceed to SLNB to avoid the potential for over treating the axilla. An appropriately powered prospective study is needed to demonstrate further the clinical validity and reliability of such an approach.

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