The Efficacy of Axillary Ultrasound in the Detection of Nodal Metastasis in Breast Cancer

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OBJECTIVE. Recent reports indicate a lack of survival benefit for axillary lymph node dissection (ALND) versus sentinel lymph node biopsy in early breast cancer. To study this issue further, we assessed the accuracy and effectiveness of ultrasound examination in detecting axillary nodal involvement in breast cancer patients with the aim of refining our current clinical pathways.

MATERIALS AND METHODS. Ultrasound data were collected from breast cancer cases over 3 years. Images were reviewed by experienced radiologists and the following characteristics were assessed: size, morphology, hyperechoic hilum, and cortical thickness of the ipsilateral axillary nodes. The findings were correlated with histologic outcomes after ALND.

RESULTS. Two hundred twenty-four cases were included in the analysis, 113 (50.4%) of which had evidence of metastatic nodal involvement at final histology. Of these 113 cases, ultrasound findings for 59 (52.2%) were positive. The overall positive predictive value of ultrasound for detecting metastatic nodal involvement measured 0.81. The negative predictive value was 0.60. The sensitivity was 53.7%; specificity, 85.1%; and accuracy, 67.9%. The ultrasound morphologic lymph node features with the greatest correlation with malignancy were the absence of a hyperechoic hilum ($p = 0.003$) and increased cortical thickness ($p = 0.03$). Patients with a metastatic nodal burden density of at least 20% were more likely to have abnormal findings on axillary ultrasound examination ($p = 0.009$).

CONCLUSION. Axillary ultrasound has a low negative predictive value and negative ultrasound results do not exclude axillary node metastases with sufficient sensitivity to justify its routine clinical use. Clinical pathways need to consider an evidence-based approach, focusing on the criteria by which we select breast cancer patients for ALND.

Keywords: axilla, breast cancer detection, lymph node dissection, metastases, surgery, ultrasound

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Ultrasound examination of the axilla has become common practice in the presurgical assessment of breast cancer patients for staging purposes when assessing regional lymph node status remains a relevant prognostic factor in breast cancer, second in prognostic value only to the presence of distant metastases [1]. The current clinical pathway at our center involves axillary ultrasound examination combined with fine-needle aspiration (FNA) cytology to identify malignant lymph nodes preoperatively. If the FNA cytologic result shows no evidence of metastatic nodal involvement, then the patient undergoes a sentinel lymph node biopsy (SLNB); if the cytologic result is positive for malignant involvement, then axillary lymph node dissection (ALND) is recommended. However, the accuracy of ultrasound at identifying involved lymph nodes particularly in patients with early-stage breast cancer is variable [2, 3]. Thus, many centers rely on ALND as the reference standard for staging disease. In recent years, SLNB has become the accepted management for breast cancer patients whose sentinel lymph nodes are free of metastatic involvement [4], whereas ALND remains the standard of care for patients with evidence of metastatic nodal disease [5–7].

SLNB is associated with less morbidity than ALND [8–10]. Whether or not further nodal dissection—can be therapeutic to improve overall survival—is unclear. A recent study including the American College of Surgeons Oncology Group Z0011 Trial indicated that among patients with limited SLND involvement of only one or two positive sentinel nodes receiving tangential external beam radiotherapy, ALND neither confers any additional overall survival benefit nor reduces the risk of local recurrence over SLNB alone [8]. These data call into question the current clinical breast cancer pathways and highlight the need to reevaluate the evidence for current clinical practice.

With this premise in mind, identifying the appropriate selection criteria for SLNB becomes increasingly important. Our aim was to define the sonographic criteria for assessing involved axillary nodes, and to evaluate the accuracy of axillary ultrasound in the staging workup of individuals with breast malignancy.

Materials and Methods

Patient Population

This study was carried out at Charing Cross Hospital, Imperial College Healthcare NHS trust, London. Data on 224 consecutive breast cancer patients who underwent presurgical axillary ultrasound within 3 weeks before surgery from January 2007 until January 2010 were collected and reviewed.

Ultrasound Analysis

Axillary examinations were performed using a 14-mHz linear-array transducer on an ultrasound scanner (Antares, Siemens Healthcare). All studies were performed by one of four breast radiologists, each with more than 10 years' clinical experience as part of routine clinical practice and standard of care. According to the local hospital guidelines, axillary lymph nodes were reported at the time of examination as abnormal on the basis of size criteria and morphology (short-axis diameter > 10 mm, cortical thickening, and lobulation or loss of the normal hyperechoic hilum) [11].

Retrospective Analysis of Ultrasound Images

For the purpose of this study, randomized data and images of these 224 patients were retrospectively reviewed by two experienced breast radiologists who were blinded to the final outcome and nodal involvement. There were few conflicts between the reports from the two radiologists. When conflicts arose, the cases were reviewed again and a consensus was achieved without the need for an arbitrating radiologist.

Ultrasound morphologic criteria used in this study for identification of axillary lymph adenopathy nodes included a height-length ratio of greater than 0.5; cortical thickening at the thickest portion of the lymph node greater than 3 mm; the presence or effacement of the normal central hyperechoic hilum; and documentation of abnormal vascularity.

The vascularity of a lymph node is defined as normal on Doppler imaging if the predominant blood flow is detected within the hilum of the node. Vascularity is defined as abnormal if multiple peripheral neoangiogenic vessels are detected. This latter feature is well documented in axillary lymphadenopathy [11]. These data were compared with histologic outcomes with the aim of validating these measurements as useful standard criteria for assessing nodal involvement in breast cancer.

Histology

All breast cancer and lymph node specimens were reviewed by a dedicated breast pathologist. The histologic details including the size, and type of primary breast cancer, number of lymph nodes removed, and number of lymph nodes with evidence of metastatic involvement were collected from the final pathologic reports.

Cytology

FNA cytologic analysis was carried out of selected cases. Ultrasound-guided FNA was performed with a 23-gauge needle attached to a 20-mL disposable plastic syringe and an aspirator. Aspirated material was smeared and fixed in 70% ethanol for Papanicolaou staining.

Statistical Analysis

The final pathologic results from SLNB and ALND were correlated with the axillary ultrasound reports. Data about specific ultrasound features were collected. Statistics were based on a description of variable results and on the assessment of sensitivity, specificity, and predictive values. Comparisons between variables were performed using the chi-square test to assess the relationship between these features and the results of the ultrasound examination findings. The paired Student t test was used to compare the relationship between continuous data and mean values. Receiver operating characteristic (ROC) curve analysis was used to evaluate the sensitivity and specificity of axillary ultrasound as a diagnostic test. Statistical significance was established at a p value of ≤ 0.05.

Results

Patient Data

The clinical characteristics of the primary breast cancers included in this study have been described in a recent study examining receptor staining in primary tumors [12]. The median age of patients in this study was 60.4 years (range, 23–92 years).

TABLE 1: Patient and Disease Characteristics

Characteristic	Value
Patient age (y)	
Median	60.4
Range	23–92
Pathologic stage, no. (%) of cases	
T1	77 (34.3)
T2	93 (41.5)
T3	15 (6.8)
Unrecorded size	25 (11.2)
Biopsy and fine-needle aspiration of node	14 (6.2)
Tumor type, no. (%) of patients	
Invasive ductal	193 (86.2)
Invasive lobular	16 (7.1)
Other	15 (6.7)
Modified Bloom-Richardson grading score, no. (%) of patients	
G1	32 (14.3)
G2	131 (58.5)
G3	61 (27.2)
No. of lymph node metastases per patient, no. (%) of patients	
0	109 (48.7)
1	43 (19.2)
2	20 (8.9)
3	8 (3.6)
≥ 4	30 (13.4)
Cytologic result, no. (%) of patients	
Positive	12 (5.4)
Negative	2 (0.8)

TABLE 2: Results and Sensitivity of Axillary Ultrasound by Size of Primary Tumor and Characteristics of Lymph Nodes on Ultrasound Examination

Tumor Stage	Normal Ultrasound Findings		Abnormal Ultrasound Findings		Total ($n = 224$)	Sensitivity (%)
	No Nodal Involvement (TN)	Positive Nodal Involvement (FN)	No Nodal Involvement (FP)	Positive Nodal Involvement (TP)		
T1	42	16	5	14	77	46
T2	34	31	5	23	93	42
T3	1	4	2	8	15	67
Unrecorded T size	5	6	2	12	25	
Biopsy and fine-needle aspiration of node	4	0	1	9	14	

Note—TN = true-negative, FN = false-negative, FP = false-positive, TP = true-positive.

The histologic reports showed that 193 cases were infiltrating ductal carcinoma (IDC); 16 cases were infiltrating lobular carcinoma (ILC); and the remaining 15 cases involved rarer subtypes including invasive cribriform carcinoma (three cases), invasive micropapillary carcinoma (eight cases), invasive tubular carcinoma (three cases), and mucinous carcinoma (one case).

Seventy-seven cases were T1 tumors that were 2 cm or less in greatest diameter; 93 cases, T2 tumors that were more than 2 cm but not more than 5 cm in greatest diameter; and 15 cases, T3 tumors more than 5 cm in greatest diameter (Table 1).

Histologic Results

Final postoperative ALND histologic results showed that 111 (49.6.%) cases had no evidence of metastatic nodal involvement and 113 (50.4%) cases had metastatic nodal involvement. Of the 113 cases with metastatic nodal involvement, 19.2% had only one lymph node involved; 8.9%, two lymph nodes involved; 3.6%, three lymph nodes involved; and 13.4%, four or more lymph nodes involved (Table 1).

Cytologic Results

In 14 cases, preoperative ultrasound-guided FNA cytologic assessments were not followed up with ALND. The decision to follow up with ALND was based on the risks associated with the medical comorbidities and ages of these patients.

Ultrasound Data

Of the 224 cases analyzed, 81 (36.2%) ultrasound examinations were reported as detecting an abnormal lymph node and 143 (63.8%) cases were reported as not detecting any abnormality in the axilla on ultrasound (Table 2).

Histologic data after axillary node dissection were analyzed and compared against the results of the axillary ultrasound reports. This comparison yielded a positive predictive value (PPV) of 81.5%, a negative predictive value (NPV) of 60.1%. and accuracy of 67.9% with a sensitivity of 53.7% and specificity of 85.1% (Table 3).

Retrospective Ultrasound Image Analysis

Ultrasound features including height-length ratio (abnormal > 0.5) and cortical thickness of the thickest portion of the lymph node (abnormal > 3 mm) were assessed. In addition, the presence or effacement of the normal central hyperechoic hilum and the presence of abnormal vascularity within the lymph node were noted.

Height-length ratio—Negative lymph nodes by ultrasound criteria appeared to have smaller height-length ratios, with 65.1% (28/43 cases) having a height-length ratio of 0.5 or less and the remaining 34.9% (15/43 cases) showing a height-length ratio of greater than 0.5 [12]. None of the lymph nodes had a height-length ratio of greater than 1.0.

When results were analyzed according to the histologic findings, the mean height-length ratio of the group of nodes with positive histologic results was 0.529 (SD, 0.167) versus 0.506 (SD, 0.174) in the group of nodes with negative histologic results (standard error [SE] = 0.032; Student t test, 0.752; 95% CI, –0.04 to 0.09; $p = 0.454$). These results suggest that there is no significant difference between the cases with a height-length ratio of 0.5 or less and a height-length ratio of greater than 0.5 in relation to metastatic nodal involvement (chi-square, 0.17; $p = 0.68$).

On the basis of ROC analysis, lymph nodes with a height-length ratio of greater than 0.35 by ultrasound criteria had a sensitivity of 90.1% but a low specificity of 33.3%. This height-length ratio corresponded to a PPV of 0.71 and an NPV of 0.65 (area under the curve [AUC], 0.64; SE, 0.05; 95% CI, 0.547–0.733; $p = 0.0093$) (Fig. 1).

Figure 2A illustrates an enlarged lymph node with metastases with a height-length ratio of 0.81, and Figure 2B shows a normal lymph node with a normal height-length ratio.

Cortical thickness—Cortical thickness was measured on the maximum transverse section in most cases; on occasion, the transverse section images were unavailable, so cortical thickness was measured on the longitudinal section [13]. Unfortunately, the potential bias associated with the use of the longitudinal section is an unavoidable limitation of a retrospective study. If a node showed asymmetric thickening, the widest diameter was taken. Although this asymmetry makes the node appear suspicious for cancer, there was no significant difference in whether a node was malignant or not.

The relationship between nodal features and metastatic nodal disease appears to show a significant correlation between an increased cortical thickness in lymph nodes with metastatic disease present. The mean cortical thickness of nodes with positive histologic results was 6.43 mm (SD, 5.88) versus 3.68 mm (SD, 4.42) in the nodes with negative findings (SE, 0.99; Student t test, 2.78; 95% CI, 0.79–4.72; $p = 0.006$). There were 33.8% histologically positive lymph node cases versus 16.5% histologically negative cases with a cortical thickness of greater than 3

TABLE 3: Predictive Value of Axillary Ultrasound Based on Histologic and Cytologic Results

Nodal Metastasis	No. (%) of Cases ($n = 224$)	
	Positive Findings on Axillary Ultrasound	Negative Findings on Axillary Ultrasound
Present	66 (29.5)	57 (25.4)
Absent	15 (6.7)	86 (38.4)

Note—Positive predictive value = 81.5%, negative predictive value = 60.1%, accuracy = 67.9%, sensitivity = 53.7%, specificity = 85.1%.

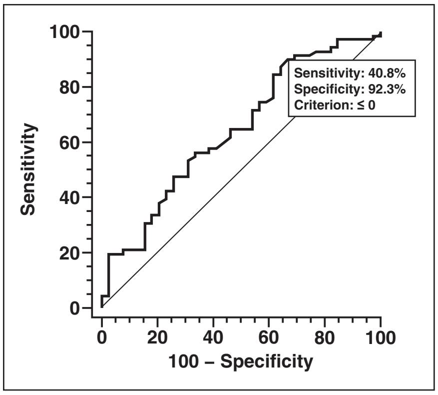


Fig. 1—Receiver operating characteristic curve analysis of height-length ratio of axillary nodes by ultrasound assessment. Diagonal line = ROC classifier.

mm. In comparison, cases with cortical thickness of less than or equal to 3 mm appear to be less likely to have metastatic involvement: 27.7% of cases were free of nodal disease but 22% of cases still showed malignancy (chi-square, 5.456; $p = 0.02$ between the groups)

When cortical thickness was assessed by ROC curve analysis, it was shown that a criterion of greater than 3.8 mm corresponded to a sensitivity of 56.34% and a specificity of 92.31%. The PPV was 0.93 and the NPV, 0.53 (AUC, 0.79; SE, 0.04; 95% CI, 0.702–0.862; $p < 0.0001$) (Fig. 3).

Figure 4A illustrates a node that shows borderline cortical thickness of 3 mm in contrast to Figure 4B, a node that has a significantly thickened cortex.

Hyperechoic hilum—The loss of the hyperechoic hilum with histologically confirmed nodal involvement was seen in 22.6% of cases compared with 37.4% of true-negative cases with neither metastatic spread nor absence of a hyperechoic hilum (chi-square, 10.0; $p = 0.007$). ROC curve analysis showed a sensitivity of 40.8% and a specificity of 92.3% for the absence of hyperechoic hilum with nodal involvement, with a PPV of 0.90 and NPV of 0.46 (AUC, 0.67; SE, 0.03; 95% CI, 0.569–0.753; $p < 0.0001$) (Fig. 5).

Vascularity—Central vascularity was seen in 7.8% of cases with histologically confirmed nodal involvement and in 5.2% of cases without nodal involvement. Peripheral vascularity was noted in 47.9% of cases with nodal involvement compared with 39.1% of cases without nodal involvement (chi-square, 1.706; $p = 0.426$).

Tumor Burden

When node-positive cases were categorized according to the number and ratio of involved nodes to uninvolved nodes, with the total number of nodes removed as the denominator and the number of metastatic nodes as the numerator, this analysis showed that false-negatives are significantly higher when tumor burden is low. When nodal density is greater than or equal to 0.2, an abnormal lymph node is more likely to be detected on axillary ultrasound examination (chi-square, 8.75; $p = 0.003$; Tables 4 and 5).

Discussion

The current West London clinical guidelines recommend that the preoperative workup for all patients scheduled to undergo surgery includes a breast ultrasound examination followed by an axillary ultrasound examination. The sensitivity and specificity data presented here are supported by a meta-analysis undertaken by Alvarez et al. [13]. Based on lymph node size as the criterion for positivity, they reported sensitivities between 48.8% and 87.1% and specificities between 55.6% and 97.3%. If lymph node morphology was used as the basis for positive detection, then sensitivity ranged from 26.4% to 75.9% and specificity ranged from 88.4% to 98.1% [12, 13]. The results of our study and other smaller reports suggest that axillary ultrasound is at best moderately sensitive and fairly specific in diagnosing axillary nodal metastases, but few studies have correlated ultrasound findings with the overall stage of disease, ALND findings, or tumor burden and few have addressed the fact that negative ultrasound results rarely exclude axillary node metastases.

The combination of percutaneous biopsy of axillary nodes with axillary ultrasound can improve the accuracy of this procedure. A 40–50% identification rate for node-positive patients by percutaneous biopsy of axillary nodes has been reported [14–16]. This figure is still too low to be of significant value in clinical practice.

Micrometastases may comprise 20–40% of tumor deposits when only a solitary sentinel lymph node is found to be involved [17]. To address this issue, we assessed the correlation between involved nodal density with the results of axillary ultrasound and found that patients with 20% or greater metastatic nodal burden, when assessing the ratio of

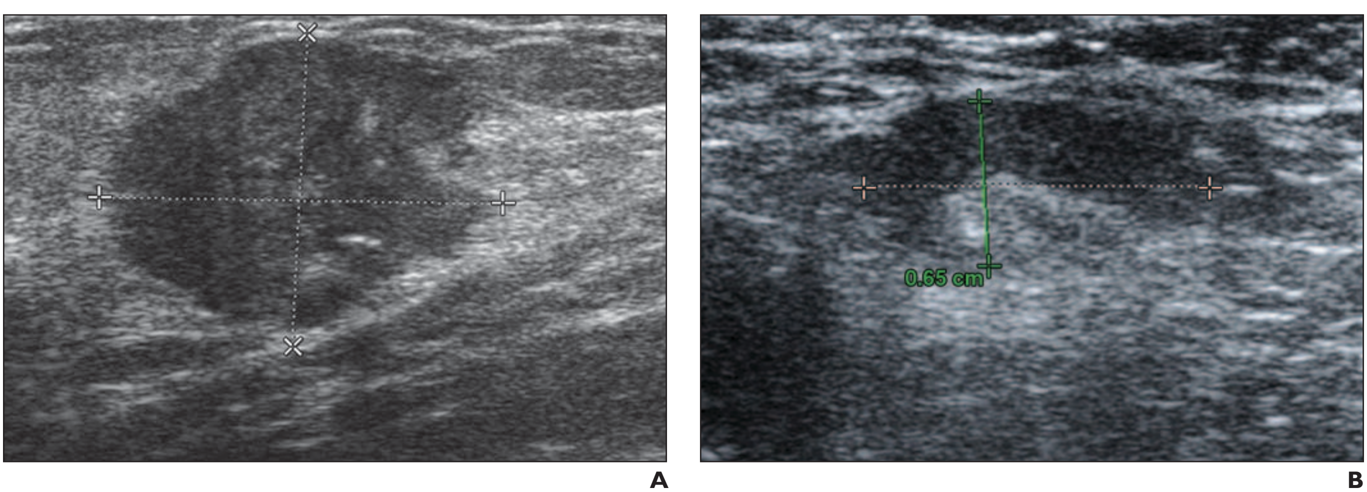


Fig. 2—69-year-old woman with infiltrating ductal carcinoma.
A, Ultrasound image illustrates enlarged lymph node with metastases with height-length ratio of 0.81 (height = 17.4 mm, length = 21.5 mm).
B, Ultrasound image shows normal lymph node with normal height-length ratio (height = 0.65 cm, length = 14.3 mm) and no histologic evidence of nodal metastases after axillary lymph node dissection.

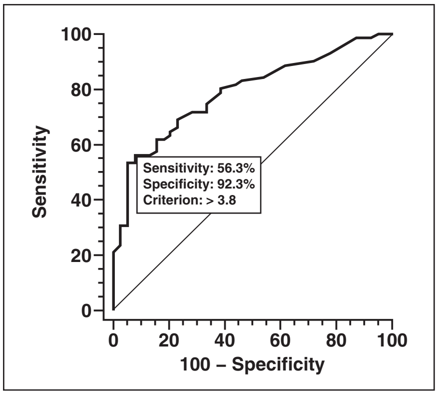


Fig. 3—Receiver operating characteristic curve analysis of axillary nodal cortical thickness measurements by ultrasound assessment. Diagonal line = ROC classifier.

involved nodes to uninvolved nodes removed at dissection, were more likely to have axillary ultrasound findings reported as abnormal. Our study also confirms that axillary ultrasound is most useful in the preoperative assessment of patients with primary breast tumors that are stage T3 or higher, although sensitivity is still only 67%. Further studies are needed to assess whether ultrasound has a role in a select group such as patients with large primary tumors and whether a cutoff can be determined.

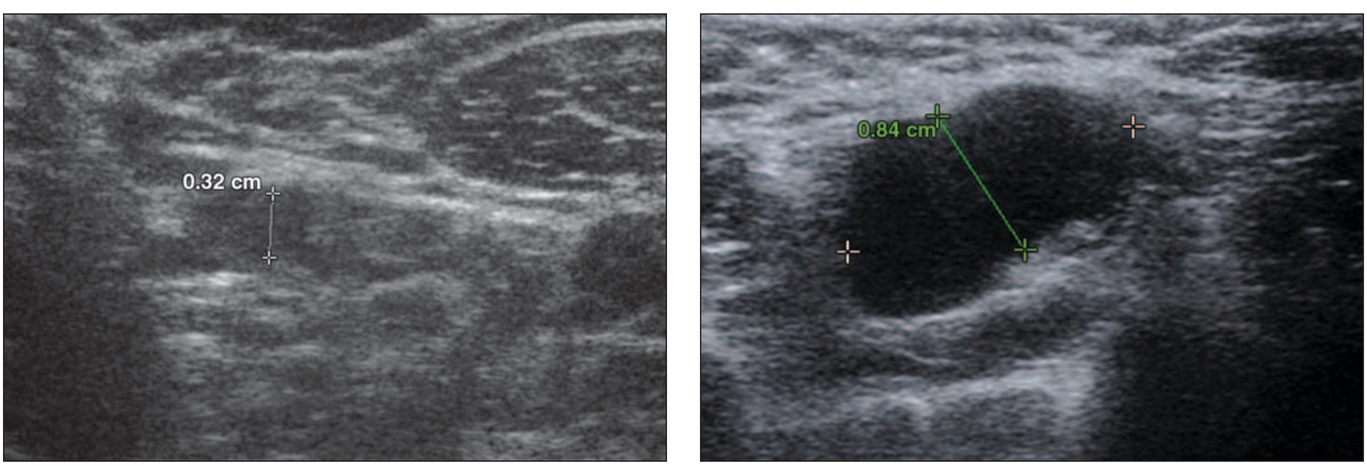
Our analysis of nodal features assessed during ultrasound confirms that a loss of hyperechoic hilum or an increased cortical thickness of greater than 3.8 mm in lymph nodes is indicative of the presence of metastatic disease. The ratio of the height to the length of the identified lymph node of greater than 0.35 has a 90.1% sensitivity, but a low specificity of 33.3%, for detecting nodal involvement and does not appear to be a useful measure of nodal involvement, with an NPV of 0.65. Vascular distribution within the lymph node may indicate a degree of abnormality within the lymph node at ultrasound but does not appear to correlate with metastatic involvement at final histology after dissection.

There is evidence that cortical thickness and loss of hyperechoic hilum are important indicators of malignancy; for example, some studies advocate FNA of lymph nodes with a cortical thickness of greater than 3 mm [2, 3]. However, our results show that the NPV for cortical thickness of greater than 3.8 mm is low (0.53) and that the sensitivity (56%) is inadequate to reliably exclude metastatic nodal involvement, thereby limiting its clinical utility.

Studies showing improved results with FNA of suspicious nodes rarely address the fact that the node being characterized may not actually be the malignant involved node and therefore a negative FNA would be falsely reassuring. In addition, the extra cost and morbidity of the FNA procedure also need to be considered when advocating this practice because a proportion of the results can be nondiagnostic. Furthermore, negative FNA findings based on ultrasound may still lead to an SLNB procedure, whereas a positive finding often leads to more surgical axillary investigation rather than less.

More recently, the use of ultrasound elastography and microbubbles in detecting tumor activity has been investigated. This technique involves peritumoral rather than IV injections. The contrast medium is taken up by the lymphatics in a matter of minutes and the sentinel node can be detected. Typically malignant-involved nodes will show areas of defect or will appear void of microbubbles, thus denoting tumor involvement [18]. The accuracy of assessing axillary lymph nodes using other technologies such as elastography or pulse wave imaging (in which pulse waves are sent directly from the probe and calculations are made on the shear waves that a lesion causes), may be more reproducible. However, these studies are still investigational [19, 20].

In the context of early breast cancer treatment pathways, reports are starting to indicate a potential paradigm shift in axillary management. A recent report from the American College of Surgeons Oncology Group Z0011 Trial [8] showed that there was no difference in either locoregional recurrence or overall survival benefit for early breast cancer patients with positive nodal involvement detected on SLND who were randomized to undergo either ALND or SLND and observation only [8]. Similarly, the B04 Study, which randomized breast cancer patients with negative clinical findings for nodal involvement into three treatment arms—radical mastectomy, total mastectomy and nodal irradiation, or total mastectomy and delayed ALND if nodal recurrence occurred—showed no significant difference in any of the groups at 25-year follow-up [1]. Martelli et al. [21] reported an incidence of less than 4.2% axillary disease after



A B

Fig. 4—Cortical thickness.
A, Ultrasound image shows node with borderline cortical thickness of 3 mm in 42-year-old woman with invasive ductal carcinoma (height = 0.32 cm).
B, Ultrasound image shows node has significantly thickened cortex in 72-year-old woman with invasive micropapillary carcinoma (height = 0.84 cm).

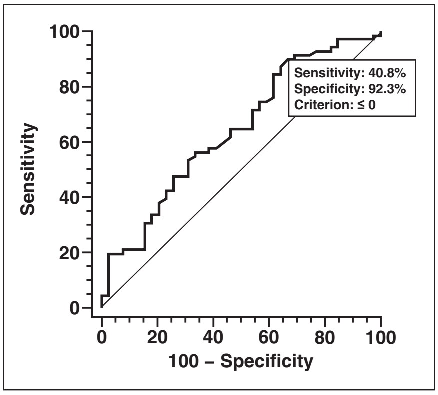


Fig. 5—Receiver operating characteristic curve analysis for effacement of hyperechoic hilum in metastatic axillary nodes when assessed by axillary ultrasound. Diagonal line = ROC classifiers.

15 years of follow-up of elderly patients, over the age of 70 years at the time of diagnosis, who did not have clinically detectable nodal disease and were managed with breast-conserving surgery and endocrine therapy without ALND or radiotherapy [1, 21].

Studies including the Z0011 Trial and AMAROS (After Mapping of the Axilla: Radiotherapy Or Surgery) Study are showing that high rates of locoregional control and improved long-term outcomes can be achieved with multimodality therapy [8, 22]. The AMAROS Trial has even reported that axillary radiotherapy could replace completion ALND in patients with low-volume nodal disease [22]. These latest developments bring into question the value of performing ALND and, hence, of also performing presurgical axillary ultrasound assessments of all breast cancer patients.

We acknowledge that this study has a number of limitations including its retrospective nature and the limited availability of FNA data. However, many of the "normal" nodes that would not have undergone FNA were shown to have disease involvement on final histology. In many cases, the abnormal node may not have been detected on ultrasound either.

Conclusion

If axillary ultrasound is to continue to be part of standard practice, then additional criteria need to be identified that can select patients more accurately for diagnostic intervention. Axillary ultrasound has a low NPV and negative ultrasound results cannot definitively exclude axillary node metastases. The sensitivity for detecting malignancy is only average and therefore the use of axillary ultrasound alone has not proved to be sufficiently accurate to justify its routine use in all preoperative breast cancer patients. The results of this study suggest that axillary ultrasound is more likely to detect an abnormal node if there is a metastatic nodal tumor burden of at least 20% and morphologic features of increased cortical thickness and loss of hyperechoic hilum. Axillary ultrasound may be more useful in the preoperative assessment of large primary tumors that are stage T3 or higher; however, more studies are needed to assess this issue further. Undoubtedly a multidisciplinary effort is needed to reduce unnecessary axillary dissections and design a less invasive approach to accurately stage disease in patients with nodal metastases.

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TABLE 4: Relationship Between Metastatic Nodal Burden and Axillary Ultrasound Detection

No. of Nodes Involved at ALND	Normal Ultrasound Findings: No Nodal Involvement (TN)	Normal Ultrasound Findings: Positive Nodal Involvement (FN)	Abnormal Ultrasound Findings: No Nodal Involvement (FP)	Abnormal Ultrasound Findings: Positive Nodal Involvement (TP)	Total (*n* = 224)
0	89	0	20	0	109
1	0	29	0	14	43
2	0	12	0	8	20
3	0	4	0	4	8
4	0	1	0	3	4
> 4	0	7	0	19	26
Fine-needle aspiration only					14

Note—ALND = axillary lymph node dissection, TN = true-negative, FN = false-negative, FP = false-positive, TP = true-positive.

TABLE 5: Relationship Between Tumor Burden[a] and Axillary Ultrasound Examination Detection

Tumor Burden	Normal Ultrasound Findings	Abnormal Ultrasound Findings	Total (*n* = 224)
< 0.2	42	116	158
> 0.2	26	26	52
Fine-needle aspiration only	4	10	14

Note—Chi-square = 8.75, $p = 0.003$.
[a]Ratio of involved metastatic nodes / uninvolved nodes.

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