Ultrasound-Guided Core Biopsy: An Effective Method of Detecting Axillary Nodal Metastases

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BACKGROUND: Axillary nodal status is an important prognostic predictor in patients with breast cancer. This study evaluated the sensitivity and specificity of ultrasound-guided core biopsy (Ax US-CB) at detecting axillary nodal metastases in patients with primary breast cancer, thereby determining how often sentinel lymph node biopsy could be avoided in node positive patients.

STUDY DESIGN: Records of patients presenting to a breast unit between January 2007 and June 2010 were reviewed retrospectively. Patients who underwent axillary ultrasonography with or without preoperative core biopsy were identified. Sensitivity, specificity, positive predictive value, and negative predictive value for ultrasonography and percutaneous biopsy were evaluated.

RESULTS: Records of 718 patients were reviewed, with 445 fulfilling inclusion criteria. Forty-seven percent (n = 210/445) had nodal metastases, with 110 detected by Ax US-CB (sensitivity 52.4%, specificity 100%, positive predictive value 100%, negative predictive value 70.1%). Axillary ultrasonography without biopsy had sensitivity and specificity of 54.3% and 97%, respectively. Lymphovascular invasion was an independent predictor of nodal metastases (sensitivity 60.8%, specificity 80%). Ultrasound-guided core biopsy detected more than half of all nodal metastases, sparing more than one-quarter of all breast cancer patients an unnecessary sentinel lymph node biopsy.

CONCLUSIONS: Axillary ultrasonography, when combined with core biopsy, is a valuable component of the management of patients with primary breast cancer. Its ability to definitively identify nodal metastases before surgical intervention can greatly facilitate a patient's preoperative integrated treatment plan. In this regard, we believe our study adds considerably to the increasing data, which indicate the benefit of Ax US-CB in the preoperative detection of nodal metastases. (J Am Coll Surg 2012;214:12–17. © 2012 by the American College of Surgeons)

It is now widely accepted that sentinel lymph node biopsy (SLNB) is the most appropriate method of staging the axilla in breast cancer patients with T1-T2 tumors.[1] Adoption of SLNB has led to a marked reduction in the rate of axillary lymph node dissection (ALND), with the associated benefits of decreased morbidity, shorter hospital stay, and significant financial savings. Using axillary ultrasonography (Ax US) to determine nodal status before surgery can allow us to proceed directly to ALND in certain circumstances, thereby avoiding an unnecessary SLNB and a delayed ALND for node positive patients.[2] Using fine-needle aspiration cytology (Ax US-FNAC) or core-biopsy (Ax US-CB) at Ax US further refines this approach. Units have begun to report favorable sensitivity and specificity rates with respect to nodal metastases and, consequently, significant reductions of up to 33% in inappropriate SLNB rates.[3] Which of the 2 techniques (Ax US-FNAC or Ax US-CB) is superior has yet to be established. Recent publications have made strong cases for Ax US-FNAC from an accuracy, complication rate, and cost perspective,[4,5] but introduction of either method has been shown to definitively reduce reoperation rates.[6,7]

The aim of this study was to evaluate the impact of Ax US-CB on breast cancer treatment in a symptomatic breast unit and to clarify the exact role of Ax US and its adjuncts in the management of the axilla in breast cancer patients.

METHODS

We performed a retrospective review of all breast cancers diagnosed in a symptomatic breast unit between January

Disclosure Information: Authors have nothing to disclose. Timothy J Eberlein, Editor-in-Chief, has nothing to disclose.

Received June 25, 2011; Revised August 26, 2011; Accepted September 28, 2011.

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ISSN 1072-7515/12/$36.00
doi:10.1016/j.jamcollsurg.2011.09.024

Abbreviations and Acronyms

ALND	= axillary lymph node dissection
Ax US-CB	= axillary ultrasound-guided core biopsy
AX US-FNAC	= axillary ultrasound-guided fine needle aspiration cytology
EORTC AMAROS	= European Organization for Research and Treatment of Cancer After Mapping of the Axilla: Radiotherapy Or Surgery (AMAROS) trial
LVI	= lymphovascular invasion
SNLB	= sentinel lymph node biopsy

2007 and June 2010. All patients with tumor recurrences, in situ disease only, and those who underwent radiologic investigation or surgical resection in another institution were excluded from the study. In our institution, all patients with newly diagnosed breast cancer undergo ultrasonography of their axilla before their surgical resection with core biopsy if suspicious nodes are identified. Therefore, all patients who were not excluded based on the criteria described above underwent ultrasound assessment of their axilla and were included within the study. Ultrasound assessment of the axilla was performed by an experienced radiologist, with particular care taken when scanning the lower axilla because this is a common site of the sentinel node.[8,9] Nodes were assessed based on their shape and the morphology of their cortex. Nodes were considered abnormal in shape if their longitudinal-to-transverse axis ratio was less than 2. Abnormal morphology included absence of a fatty hilum as well as concentric or, in particular, eccentric thickening of the cortex to more than 2.5 mm. Abnormal nodes were biopsied using an 18- or 20-gauge core biopsy needle under ultrasonographic guidance. If more than 1 abnormal node was visualized, then the most suspicious appearing node was biopsied. There were no complications after core biopsy during the study period.

All biopsies were discussed at a weekly multidisciplinary team meeting. Patients with positive nodal biopsies were scheduled for ALND at the time of their primary tumor resection. Patients with negative biopsies or patients whose axillary ultrasound scan revealed no suspicious lymph nodes underwent an SLNB. A 2-day protocol was used for all SLNBs, similar to that described by Mansel and colleagues,[1] except that ^{99m}TC-nanocolloid was injected in a periareolar distribution rather than peritumorally.

Lymph nodes were deemed positive for malignancy if they contained either macrometastases (parenchymal focus $\geq$ 2 mm) or micrometastases (parenchymal focus $<$ 2 mm or subcapsular deposit between 0.2 and 2 mm in diameter). Isolated tumor cells (tumor deposits $\leq$ 2 mm in subcapsular sinus) on histology were classified as negative because

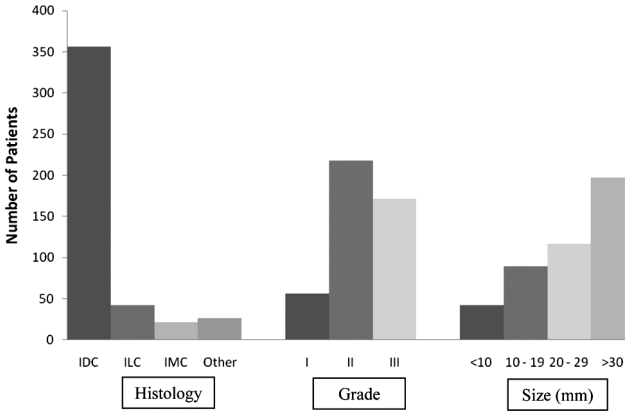

Figure 1. Baseline tumor characteristics (IDC, invasive ductal carcinoma, ILC, invasive lobular carcinoma, IMC, invasive mixed carcinoma).

they are associated with limited prognostic significance.[10] Patients with a positive sentinel lymph node proceeded to delayed ALND. Statistical analysis was performed using StatsDirect, with $p < 0.05$ considered significant. Primary outcomes variables were sensitivity and specificity of axillary ultrasonography and ultrasound-guided core biopsy at detecting axillary nodal metastases.

RESULTS

Between January 2007 and June 2010, 718 consecutive patients who presented to the breast unit of our institution were diagnosed with breast cancer. Of these, 445 patients were included in the study, with the remainder excluded based on the exclusion criteria previously described. Detailed tumor characteristics are shown in Figure 1 and Table 1. Twenty-three patients received neoadjuvant chemotherapy, with nodal metastases confirmed by ultrasound-guided core biopsy in all except 1; nodal metastases were confirmed in this patient by SLNB before neoadjuvant treatment.

A total of 121 (27.2%) of the 445 patients who underwent Ax US had suspicious nodes identified and underwent core biopsy. After Ax US-CB, 110 (91%) of these 121 patients had metastases identified and they proceeded to ALND at the primary operation. All 11 patients with abnormal Ax US but negative biopsies, as well as the 324 patients with normal Ax US, underwent SLNB for axillary staging.

In total, 210 (47%) of the 445 patients had axillary nodal metastases confirmed on final histopathologic assessment: 200 (95%) had nodal macrometastases and 10 (5%) had micrometastases only in their ALND. Isolated tumor cells alone were identified in 23 (5%) of the 445 specimens. Five patients who underwent neoadjuvant chemotherapy

Table 1. Lymph Node Positivity in Relation to Tumor Histology

Histology	All patients	Lymph node positive	
		n	%
Ductal carcinoma	356	171	48
Lobular carcinoma	42	22	52
Mixed carcinoma	21	9	43
Medullary carcinoma	8	3	37.5
Tubular carcinoma	7	0	0
Mucinous carcinoma	4	1	25
Other	7	4	57

had a complete axillary pathologic response with a negative ALND; however, all had pretreatment, biopsy-confirmed macrometastases, so were considered positive for nodal metastases. Ax US-CB identified 110 of the 210 node positive patients preoperatively, with the remaining 100 node positive patients identified by SLNB. The remaining 235 patients were correctly classified as node negative using Ax US-CB, and there were no false positive results. Patients with nodal metastases identified by Ax US-CB had a median of 7 positive lymph nodes (range 1 to 67 nodes); those with positive SLNB had a median of 1 positive lymph node (range 1 to 29 nodes).

Ax US had a sensitivity of 54.3% (114 of 210 patients), specificity of 97% (228 of 235 patients), a positive predictive value of 94.2% (114 of 121 patients), a negative predictive value of 70.4% (228 of 324 patients), and an accuracy of 77% (342 of 445 patients) for identifying nodal status. Ninety-one percent (110 of 121) of patients with suspicious lymph nodes identified by ultrasonography had nodal metastases confirmed by Ax US-CB and underwent primary ALND at the time of their initial surgery. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of Ax US-CB in patients with suspicious nodes on Ax US were 96.5% (110 of 114), 100% (7 of 7), 100% (110 of 110), 63.6% (7 of 11), and 96.7% (117 of 121), respectively.

Overall, Ax US-CB had a sensitivity of 52.4% (110 of 210), specificity of 100% (235 of 235), a positive predictive value of 100% (110 of 110), a negative predictive value of 70.1% (235 of 335 patients), and an accuracy of 77.5% (345 of 445 patients) for identifying nodal metastases.

Ax US-CB resulted in 110 (52.4%) of 210 node positive patients avoiding unnecessary SLNB biopsy. Overall, 110 (24.7%) of 445 patients were spared the need to undergo an axillary staging procedure. Ax US-CB did not identify any patient with nodal micrometastases (n = 10) or isolated tumor cells (n = 23). There were no complications after Ax US-CB.

The sensitivity of Ax US-CB at detecting nodal metastases correlated with tumor grade (Table 2). Ax US-CB was significantly more likely to detect nodal metastases in grade 3 cancers compared with grade 1 cancers ($p = 0.0146$), with the sensitivity increasing from 35% in grade 1 to 61% in grade 3 malignancies. Nodal metastases from both invasive ductal and invasive lobular malignancies were detected by Ax US-CB with a sensitivity of 53% (90 of 171) and 45% (10 of 22), respectively.

Lymphovascular invasion (LVI) was present in 182 resection specimens, absent in 235, and not documented in the remaining 28 specimens. Lymph node metastases were present in 126 patients with LVI present (69.2%); 71 LVI negative patients (30.2%) were found to have nodal metastases. The sensitivity, specificity, positive predictive value, and negative predictive value of LVI for predicting lymph node metastases were 64% (126 of 197), 74.5% (164 of 220), 69.2% (126 of 182), and 69.8% (164 of 235), respectively, with LVI significantly associated with nodal disease ($p < 0.0001$, odds ratio 5.2; 95% CI 3.34 to 8.1).

DISCUSSION

Axillary nodal metastases are a significant prognostic indicator in breast cancer as well as determining the need for adjuvant chemotherapy and radiotherapy. Axillary lymph node clearance is the most accurate way of determining the burden of axillary disease and facilitates the excision of macroscopic deposits of tumor. The associated morbidity of axillary dissection[11,12] has resulted in the development of SLNB to reduce the rate of negative axillary clearances. However, patients with a positive SLNB then require a further delayed ALND to fully stage the axilla, especially if intraoperative frozen sectioning is not available or is negative. This has prompted the widespread use of ultrasonography with or without biopsy to preoperatively identify patients who have axillary nodal metastases and who can proceed directly to ALND without the need to undergo SLNB. Accuracy of Ax US and Ax US-FNAC has been widely published,[4,5,13-16] with their sensitivity varying considerably,[13] possibly due to operator experience. However, routine use of Ax US-FNAC or Ax US-CB has not been

Table 2. Influence of Tumor Grade on Sensitivity of Axillary Ultrasonography with Core Biopsy

Tumor grade (Bloom-Richardson)*	Patients with nodal metastases, n	Positive axillary ultrasound-core biopsy (sensitivity)	
		n	%
1 (n = 56)	17	6	35
2 (n = 218)	98	46	47
3 (n = 171)	95	58	61

*Chi-square for $\text{trend}_{(df = 1)} = 5.966758$, $p = 0.0146$.

widely adopted and, to date, their use has been recommended by only 1 clinical cancer guideline.[17]

In this study, ultrasound evaluation of the axilla in patients with primary operable breast cancer presenting to a symptomatic unit had a sensitivity and specificity rate of 54% and 97%, respectively, which are comparable to rates from other studies.[14,18,19] Core biopsy of suspicious nodes had a sensitivity rate of 96.5%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 63.6%. This is superior to previously published data on Ax US-FNAC, which has a sensitivity ranging from 50% to 80%.[4,13-16,20] Indeed, a recent meta-analysis of 31 studies found a pooled sensitivity rate of 79.6% (95% CI 74.1 to 84.2), specificity of 98.3% (95% CI 97.2 to 99.0), and a positive predictive value of 97.1% (95% CI 95.2 to 98.3).[21] The overall sensitivity of Ax US-CB of 52.4% is comparable to that in similar studies assessing ultrasound-guided core biopsies (sensitivity 42% to 53.4%)[18,22,23] and again superior to Ax US-FNAC.[5,16,18]

Although increasing tumor size and grade are well described as correlating with the risk of nodal metastases, we also found a significant association between LVI and nodal involvement, with a sensitivity rate greater than that of axillary ultrasonography alone (64% vs 54%). The combination of these 3 parameters (available after triple assessment) therefore provides more accurate predictive information of lymph node involvement than Ax US alone. In light of this we suggest that Ax US without the adjunct of lymph node sampling has no role in the management of the axilla in breast cancer patients. These results assume greater significance when applied to breast units that have yet to adopt Ax US with sampling of suspicious nodes, given that a recent analysis of axillary management in the United Kingdom has revealed that almost 7% of UK breast units do not yet use Ax US in any capacity.[24]

The American College of Surgeons Oncology Group (ACSOG) recently published the results of its Z0011 trial in which it evaluated the impact of ALND on survival and locoregional recurrence rates in patients with early-stage breast cancer and positive SLNB. It found that in patients with clinical T1 or T2N0M0 breast cancer and 2 or less positive sentinel nodes, there was no difference in locoregional recurrence, overall survival (ALND 91.9% vs SLNB only 92.5%), or disease-free survival (ALND 82.2% vs SLND only 83.8%; $p = 0.13$) at 5 years between patients who underwent ALND and those who did not, despite positive SLNB.[25,26] This raises a very interesting and important consideration in the treatment of early-stage breast cancer. If ALND can be avoided in a clearly defined cohort of patients with no significant detrimental impact on survival or recurrence rates, this will allow a significant number of patients to avoid the potential morbidities associated with ALND. The Z0011 trial randomized patients based on the number of positive sentinel lymph nodes, with those having 3 or more positive lymph nodes or with clinically advanced cancers excluded from the study. This limits the overall population of patients to whom this benefit applies, but it does highlight a subgroup of patients who will benefit from reduced axillary surgery. The ongoing European Organization for Research and Treatment of Cancer (EORTC) After Mapping of the Axilla: Radiotherapy Or Surgery (AMAROS) trial, comparing ALND with radiotherapy only in patients with positive SLNB, will further clarify the need for surgical resection in patients with axillary nodal disease.[27] If this also finds no survival or recurrence benefit in patients undergoing ALND, then current clinical practice of ALND is potentially obsolete. The use of Ax US-CB could take the results of these 2 trials one step further. If nodal metastases could be identified without requiring surgical intervention in the form of SLNB, thereby determining the need for adjuvant axillary radiotherapy by Ax US-CB alone, patients could receive the appropriate treatment without having to undergo any form of axillary surgery. Although this practice is still only speculation, it has the potential to radically change the current surgical approach to axillary nodal metastases, in essence, reducing the need for such surgery only to patients who have normal-appearing nodes on ultrasonography.

While we await the outcomes of the EORTC AMAROS trial, there are other modalities currently used to immediately identify metastases within SLNB, allowing for ALND without the need for subsequent surgical resection. These include intraoperative frozen sectioning of the lymph node. Prospective trials show the sensitivity of frozen sections to be approximately 60%,[28,29] however, this does not necessarily spare the patient further surgery, with more than half of patients undergoing breast conserving surgery found to require re-excision of margins.[28] This, as well as the low overall yield of positive frozen section specimens and false negative rates of up to 45%, has resulted in a decline in the use of frozen sectioning, with some institutions not routinely performing it at all.[28,29] Indeed, if the EORTC AMAROS trial demonstrates no significant difference between ALND and radiotherapy only, the need for frozen sectioning might be removed almost entirely.

The absolute superiority of Ax US-CB over Ax US-FNAC has yet to be established because there has been no prospective trial comparing these diagnostic techniques. False positive cytology[15,30] and inadequate sampling[14,15,22] are pitfalls of FNAC, yet Ax US-CB is associated with greater cost.[17] In the 1 retrospective and comparative study published to date, numbers were small, with Ax US-CB

sensitivity of 82% (n = 25) superior to that of Ax US-FNAC (75%; n = 22).[17] We report the highest sensitivity rate for Ax US-CB (96.5%) recorded in the literature. We do not perform Ax US-FNAC within our institution, so we are unable to perform a direct comparison between the 2 techniques. In this study, there were no false positive biopsies and all samples contained adequate tissue amounts for histopathologic assessment. We did not explore the financial implications of our choice of tissue sampling; however, it is logical to assume that any modest expense incurred with the preferential use of Ax US-CB over Ax US-FNAC is addressed by fewer SLNBs performed as a result of the high sensitivity demonstrated.

The use of Ax US-FNAC or Ax US-CB in the routine preoperative staging of patients with breast cancer has not been definitively evaluated through a randomized prospective clinical trial; however, pooled data from multiple studies suggest that it is beneficial as both a triage and utility test, especially in patients with tumors > 20 mm.[21] Our specificity rate of 100% confirms that Ax US-CB is indeed a useful triage test, with no patient undergoing an unnecessary ALND as a result of a false positive biopsy. With a number clinical trials showing a benefit in neoadjuvant therapy in locally advanced disease as well, the ability to accurately confirm the presence of nodal metastases, with a negligible likelihood of a false positive result, will enable clinicians to identify patients suitable for treatment. Ax US-CB is generally well tolerated, with no complications observed in any of our patients, ensuring it is a safe and effective method of staging the axilla. In our study, Ax US-CB spared more than half of all patients with nodal metastases (n = 110/210) and almost one-quarter (n = 110/445) of all patients with breast cancer an unnecessary SLNB, confirming its ability to streamline surgical intervention in primary breast cancers.

Ultrasonographic evaluation of the axilla, with the addition of a core biopsy if any abnormality is detected, is a valuable component of the multidisciplinary approach to the treatment of patients with breast cancer. Although the treatment of elderly patients has evolved over the last number of years, with rates of breast conserving surgery increasing, there still remains a small cohort of patients who are not suitable for surgical intervention due to medical comorbidities or who refuse surgery. Their treatment is therefore based on receptor status, which is determined from the primary breast cancer biopsy. Early identification of these patients is required at multidisciplinary team discussions to avoid unnecessary biopsies, including Ax US-CB, because their outcomes will not change the overall treatment strategy and could result in an avoidable complication.

CONCLUSIONS

Axillary ultrasonography, when combined with core biopsy, is a valuable component of the management of patients with primary breast cancer. Its ability to definitively identify nodal metastases before surgical intervention can greatly facilitate a patient's preoperative integrated treatment plan. In this regard, we believe our study adds considerably to the increasing data, which indicate the benefit of Ax US-CB in the preoperative detection of nodal metastases.

Author Contributions

Study conception and design: Solon, Power, Al-Azawi, Duke, Hill
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Drafting of manuscript: Solon, Power, Al-Azawi, Duke, Hill
Critical revision: Solon, Power, Al-Azawi, Duke, Hill

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