Consequences of Axillary Ultrasound in Patients with T2 or Greater Invasive Breast Cancers

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ABSTRACT

Background. Axillary ultrasound (AUS) with needle biopsy is used to detect metastasis in patients with invasive breast cancers. Our hypothesis is that preoperative AUS significantly reduces sentinel node biopsy (SLNB) use in patients with invasive breast tumors >2 cm upon clinical examination.

Methods. A single-institution database of patients with breast cancer and AUS was reviewed. Patients with incomplete records, clinical tumor <2 cm, or postoperative AUS were excluded. A control cohort of non-AUS patients with clinical T2 (cT2) or greater disease was identified. Clinicopathologic data were collected. Simple Kappa coefficient and chi-square statistical analyses were performed.

Results. AUS was performed in 153 patients vs. 370 controls. Of AUS patients, 112 (73.2%) had cT2 disease vs. 272 (73.5%) controls. Median AUS patient age was 53.7 (range, 22.8–85.8) years vs. 53.8 (range, 26.7–91.6) years; median pathologic tumor was 3.8 (range, 1.0–20.0) cm in AUS patients vs. 2.5 (range, 0.1–11.0) cm. Among AUS patients, 78% had needle biopsy; 85 of 120 (70.8%) were positive. Sixty-eight patients had SLNB: 33 after negative AUS and 35 after negative needle biopsy. Twenty-three SLNB (37.3%) were positive; 15 of 33 after negative AUS and 8 of 35 after a negative needle biopsy. Axillary dissection was performed in 102 of 153 vs. 225 of 370

controls. Sensitivity and specificity of AUS was 86.2% and 40.5%. Sensitivity of AUS plus needle biopsy was 89.3% with 100% specificity. Neoadjuvant chemotherapy was given to 49.7% of AUS patients. AUS reduced costs by more than \$4,000 per patient.

Conclusions. AUS reduces SLNB use and affects treatment in patients with cT2 or greater breast cancer. Routine AUS should be considered in this population.

INTRODUCTION

Axillary imaging with ultrasound is a rapidly developing practice for preoperative assessment in patients with invasive breast cancer. The technique of axillary ultrasound for breast cancer evaluation was first described in the European literature approximately 25 years ago and has been adopted as a diagnostic modality for detection of axillary metastasis, particularly in conjunction with needle biopsy of abnormal-appearing lymph nodes.^{1,2} Specificity of axillary ultrasound in identifying metastatic lymph nodes ranges between 70% and 95%, with sensitivity ranging from 50–70%.^{3–7} The specificity is significantly improved with the addition of needle biopsy of abnormal lymph nodes, increasing to 100% in some studies.^{8,9} Preoperative diagnosis of axillary metastasis is an excellent tool for staging and operative planning, especially with regards to patient selection for neoadjuvant chemotherapy.

Careful evaluation of the lower axilla is crucial to identify abnormal lymph nodes. Several well-established characteristics aid in the determination of abnormal nodes. These characteristics are based on the morphology of the node rather than its absolute size. Suspicious morphologic characteristics include cortical thickening with concomitant narrowing of the hilum, focal eccentric cortical thickening (bulge in cortical contour), and absence of a central fatty hilum.^{10,11} The nodal shape also aids in differentiating

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First Received: 3 March 2010;

Published Online: 3 September 2011

This article was originally published in *Annals of Surgical Oncology*, volume 18, pp. 72–77, DOI 10.1245/s10434-010-1171-4.

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Normal Node:
Small, hypoechoic hilum,
even cortex

Metastatic Nodes:
Eccentric cortical thickening
Irregular hilar contours
("rat bites")
Hilar displacement
Complete obliteration of hilum
Loss of nodal integrity/irregular
nodal contours

FIG. 1 Findings on axillary ultrasound

malignant from benign nodes. Nodal shape is evaluated by determining the ratio of the long to short axis. Malignant nodes tend to be more round, possessing a long-to-short axis ratio <2 .¹¹ Nodes with spiculated margins suggest extranodal tumor extension. Analysis of the nodal color-flow Doppler characteristics may enhance the diagnostic sensitivity of ultrasound. Malignant nodes often lack a hilar blood flow pattern. This is characterized by hypervascularity and

visualization of multiple feeding vessels for a single lymph node.¹² Lymph nodes with one or more of the above-noted characteristics are more likely to be malignant. Features of abnormal lymph nodes are illustrated in Fig. 1.

Sonographically abnormal lymph nodes should undergo ultrasound-guided needle biopsy via fine needle aspiration or core needle biopsy to confirm the presence of metastases. Patients with biopsy-proven nodal disease can be spared the time and expense of sentinel lymph node biopsy and proceed directly to axillary lymph node dissection at the time of lumpectomy or mastectomy.

There are some clear controversies in axillary staging with regards to neoadjuvant chemotherapy. The practice of performing a sentinel node biopsy before neoadjuvant chemotherapy is a primary focus of debate; the utility of a separate operative procedure before commencing systemic therapy is subject to much scrutiny, because prognosis and postmastectomy radiation recommendations rely heavily on the presence of axillary disease before neoadjuvant chemotherapy.^{13–15} The accuracy of sentinel node biopsy performed after neoadjuvant chemotherapy has been demonstrated in multiple studies; however, preoperative axillary staging with ultrasound and fine needle aspiration or core needle biopsy is being widely used.^{3–6,16–24} A majority of patients who undergo neoadjuvant chemotherapy at our institution undergo definitive axillary staging via axillary ultrasound with needle biopsy or sentinel node biopsy before commencing induction chemotherapy. The algorithm for preoperative axillary assessment at Moffitt is outlined in Fig. 2.

FIG. 2 Algorithm for axillary assessment

With the current focus on health care expenditures, the cost–benefit ratio of diagnostic procedures is perpetually under scrutiny. Clearly, avoidance of a surgical procedure not only avoids the risks of surgery but may reduce the cost of care, as demonstrated in multiple studies.^{5,19,20} Patients in whom axillary disease is detected by ultrasound and needle biopsy forego the sentinel node biopsy procedure and undergo axillary lymph node dissection at the time of their definitive breast operation. However, routine performance of axillary ultrasound on all patients with a T2 or greater tumor may diminish the cost-efficacy.

The purpose of this study was to determine not only the utility of axillary >2 cm on clinical examination, but also the logistical effects of adding axillary ultrasound and needle biopsy to the routine preoperative evaluation of these patients at a high-volume, tertiary cancer center.

MATERIALS AND METHODS

After obtaining institutional review board approval, a single-institution database of patients with invasive breast cancer who received axillary ultrasound between 2004 and 2009 was reviewed. An additional cohort of patients without axillary ultrasound having clinical T2 (cT2) or greater disease and sentinel node biopsy from 2002–2009 was identified as a control from the institutional NCCN database (Moffitt Cancer Center is a contributing institution to the NCCN breast database). All patients in both groups were surgically treated for biopsy-proven invasive breast carcinoma at Moffitt Cancer Center with a minimum tumor size of 2.0 cm on clinical assessment, via breast examination, excisional biopsy, or initial breast imaging (mammography, sonography, or breast magnetic resonance imaging). Mammographic microcalcifications without evidence of a mass on imaging or physical examination were not considered for inclusion. Patients with palpable axillary adenopathy were not excluded from this study. Patients with multicentric disease with at least one focus >2 cm were included. All axillary ultrasounds and ultrasound-guided needle biopsies at Moffitt Cancer Center are and were performed by radiologists specializing in breast imaging, or fellowship-trained breast surgical oncologists.

All of the patients had a comprehensive review of their breast imaging and pathology slides by the physicians participating in the Moffitt Breast Cancer Multidisciplinary Tumor Board (fellowship-trained breast radiologists and breast-specific pathologists, surgeons, medical oncologists, and radiation oncologists) and had their medical records entered into the Moffitt electronic medical record system. Patients who received abnormal axillary ultrasound and needle biopsies at outside institutions were eligible provided that original ultrasound and pathology reports were

scanned into the electronic medical record at Moffitt Cancer Center. Negative ultrasounds from outside institutions were not considered for this study. Patients with incomplete records, clinical tumor size <2 cm, or axillary ultrasound after axillary surgery (i.e., excisional biopsy for diagnosis) also were excluded. Additionally, patients deemed inoperable due to extenuating health problems or metastatic disease were excluded.

Clinicopathologic data, including pathologic tumor size, clinical examination findings, breast imaging results, axillary ultrasound dates and findings, type of axillary biopsy (fine needle aspiration vs. core biopsy), dates and results of axillary and sentinel node biopsies, performance of axillary node dissection, axillary node dissection data, clinical stage, and final pathologic stage, were all recorded. At our institution, as well as for this study, isolated tumor clusters are noted but not considered node-positive, in concordance with the sixth edition of the American Joint Committee on Cancer (AJCC) breast cancer stage classification, published in 2006.

With the assistance of the Moffitt Biostatistics core, Cohen's Kappa coefficient was used to test the agreement among measurements of the tumor size. Pearson's chi-square test was performed to assess the association between treatment and outcome. The log-rank test was implemented to assess the effect of axillary ultrasound on surgical timing. A basic cost analysis was performed using standard institutional charges to insurance. Surgeons' fees and reimbursement numbers were not included in the cost analysis calculations due to the inability to obtain consistent figures.

RESULTS

A total of 212 patients received axillary ultrasound at diagnosis; those with incomplete records (25 cases), clinical tumors <2 cm (31 cases), or axillary ultrasound performed after excisional axillary biopsy (3 cases) were eliminated. All of the patients were women. At diagnosis, 153 patients had axillary ultrasound ("treatment" group) compared with 370 controls (those without axillary ultrasound and clinical tumors >2 cm). Clinical tumor size was based on physical examination or breast imaging by mammography, sonography, or MRI. In the treatment group, 57 patients had ≥ 2 cm mass on physical examination, and 26 patients had a $\geq$ T2 mass on mammography: 25 patients by ultrasound, 42 patients by MRI, and 2 by excisional breast biopsy.

Median age of the axillary ultrasound treatment group was 53.7 (range, 22.8–85.8) years compared with 53.8 (range, 26.7–91.6) years in the control group; median pathologic breast tumor size was 2.2 (range, 1.0–20.0) cm

in the treatment group versus 2.5 (range, 0.1–11.0) cm for the control group after surgery. Among the patients who underwent neoadjuvant chemotherapy, the median tumor size was 1.5 cm in the axillary ultrasound group compared with 2.2 cm in the control group. One hundred twelve (73.2%) of axillary ultrasound patients had clinical T2 disease compared with 272 (73.5%) of controls ($P = 1$). There were 31 patients in the treatment group (20.1%) with clinical T3 tumors and 8 patients with T4 disease (5.2%) compared with 52 (14.1%) and 18 (4.9%) in the control group, respectively. Two patients in the axillary ultrasound and 28 patients in the control group had diffuse inflammatory disease and were not assigned tumor sizes, although they were classified as T4d.

Seventy-six axillary ultrasound patients (49.7%) had neoadjuvant chemotherapy compared with 78 (21.1%) control patients—a statistically significant difference ($P < 0.0001$). Twenty (20/153, 13.1%) of the axillary ultrasound patients who underwent breast conservation did so after neoadjuvant chemotherapy. Of the study population (treatment group), 112 patients had mastectomy and 41 (26.8%) had breast-conserving surgery. Twenty-five axillary ultrasound patients had immediate breast reconstruction; 4 were post-neoadjuvant chemotherapy. In the control group, 181 had mastectomy and 189 (51.1%) had breast-conserving surgery ($P < 0.0001$).

One hundred twenty (77.9%) axillary ultrasound patients had a needle biopsy based on an abnormal axillary ultrasound result; of these 120 women, 85 (70.8%) had pathologic evidence of malignancy, avoiding sentinel node biopsy ($P < 0.0001$). Only 4 patients of the 120 had axillary core biopsies performed, and all 4 were positive; the remaining patients were evaluated with fine needle aspiration. After axillary ultrasound, 69 patients had sentinel node biopsy: 33 patients after a normal axillary ultrasound (thus no biopsy) and 35 patients after an abnormal axillary ultrasound but a negative needle biopsy. One patient had a positive needle biopsy and refused axillary node dissection but demanded sentinel node biopsy at the time of definitive surgery; therefore, she had both positive needle biopsy and positive sentinel node biopsy.

Of the patients who underwent sentinel node biopsy for diagnosis, 23 of 68 (33.8%) had a positive sentinel node biopsy, 15 of 33 had a negative axillary ultrasound, and 8 of 35 had a negative needle biopsy. These results are summarized in Fig. 3. No significant difference was found in the proportion of axillary node dissections between the two groups based on both Fisher's exact test and Pearson's chi-square test. In the 153 women who had an axillary ultrasound, 102 (66.7%) had completion axillary node dissection compared with 225 of 370 (60.8%) controls ($P = 0.234$). Nine additional patients with known axillary metastases refused axillary node dissection; one patient

FIG. 3 Results of axillary ultrasound and needle biopsy

was found to have distant metastasis and declined additional surgery. The remaining seven node-positive patients were lost to follow-up. The sensitivity and specificity of axillary ultrasound was 86.2% and 40.5%, respectively. The sensitivity of axillary ultrasound combined with needle biopsy was 89.3% with 100% specificity.

Incorporating additional tests and procedures to the preoperative evaluation of patients with breast cancer introduces the potential of further delaying treatment. To address this issue, a subset analysis of patients who did not undergo neoadjuvant chemotherapy was performed to assess whether addition of axillary ultrasound and possible needle biopsy impeded progress to definitive surgery. Eighty-two axillary ultrasound patients treated from 2004 to 2009 proceeded to surgery as their initial treatment. A contemporaneous control group of 192 patients treated initially with extirpative surgery from 2004–2009 also were identified from the larger NCCN control cohort for comparison. The mean time from diagnosis to primary surgery of the axillary ultrasound patients was 59 days compared with 62 days for the controls. No significant difference in the time from diagnosis to surgery was detected between the control and treatment groups ($P = 0.9260$).

A simple cost analysis was performed using average institutional charges to insurance for the calculations; physicians' fees and reimbursement for procedures were not included in this analysis; this is summarized in Fig. 4. Average cost to insurance of a sentinel node biopsy with lymphoscintigraphy, including perioperative costs, is

Charges to insurance (physician fees not included):

- Sentinel Lymph Node Biopsy: \$12,099
- Breast/axillary US: \$440
- Ultrasound-guided FNA: \$2412
- 85 Sentinel Lymph Node Biopsies = \$1,028,415.00
- 153 AUS + 120 FNA = \$67,320 + \$289,440 = \$356,760
- Total cost reduction = \$671,655
- \$671,655/153 patients = \$4,389/patient

FIG. 4 Cost efficacy of axillary ultrasound

\$12,099. Sentinel node biopsies in conjunction with definitive breast surgery are assessed intraoperatively with touch-prep analysis; the cost used for this study includes intraoperative and permanent pathologic analysis of the nodal specimens. A breast/axillary US with interpretation costs \$440. At our institution, image-guided aspirations are generally performed with a cytology technician for immediate assessment of specimen adequacy. Ultrasound-guided FNA, including immediate review for adequacy and cytology, costs \$2,412. Using our results to assess the cost difference, we found 85 patients who avoided sentinel node biopsy due to a suspicious ultrasound and a positive needle biopsy. The cost of insurance for 85 sentinel node biopsy procedures is \$1,028,415. The performance of routine axillary ultrasound ($n = 153$) and FNA ($n = 120$) equals \$356,760 in our study. The cost analysis, therefore, demonstrates a reduction of \$671,655 in charges to insurance for this cohort of patients; approximately \$4,389 per patient.

DISCUSSION

Axillary ultrasound and axillary needle biopsy of abnormal-appearing lymph nodes is a growing practice for patients with newly diagnosed breast cancer, both in the United States and abroad. Ultrasound is a noninvasive, readily available, and inexpensive imaging modality, and the criteria for sonographic lymph nodes evaluation are widely accepted. With a sensitivity of 86.2% for abnormal nodes on axillary ultrasound, this retrospective study confirms the conclusions of other investigators that axillary ultrasound is a useful modality for assessing nodal disease. Our findings also concur with the sensitivity and specificity of percutaneous sampling of abnormal nodes from other institutions. Although all of the axillary core biopsies were positive, because the vast majority of patients in this study had fine-needle aspiration (96.7%), we cannot comment on the utility of fine needle versus core needle in this setting.

The use of axillary ultrasound at our institution has evolved rapidly during the past 6 years. Initially, it was applied selectively for patients with suspicious nodes on mammogram or physical examination. However, it has been used routinely in the evaluation of patients with T2 or greater breast tumors since 2007, regardless of clinical axillary examination. This evolution in practice clearly introduces selection bias in this retrospective cohort, as earlier patients evaluated with axillary ultrasound may have had a suggestion of axillary fullness or adenopathy, thereby skewing the earlier axillary ultrasound population toward positive axillae, and the latter toward smaller in-breast disease. In addition to the increasing use of breast MRI for tumor assessment, the change in practice over

time introduces the greatest source of unmeasurable bias in this population. Despite these biases, our study demonstrates a marked reduction in the number of node-positive patients who undergo sentinel node biopsy and no difference in the proportion of patients who undergo axillary node dissection ($P = 0.169$), further supporting the routine use of axillary ultrasound in patients with a ≥ 2 cm breast mass on clinical assessment.

The addition of yet another imaging study to the battery of tests performed on patients with breast cancer is a legitimate cause for concern. Axillary ultrasound alone can be accomplished quickly due to the ease and availability of ultrasonography and may be performed in conjunction with other imaging studies. Given the technical difficulty of freehand needle aspiration of axillary lymph nodes, image guidance for needle biopsy is likely beneficial even in patients with grossly palpable adenopathy. The performance of a needle biopsy, however, often requires additional resources and insurance authorization, which may not be readily available, resulting in another visit for the actual biopsy procedure. Despite the potential for an additional visit, our subset analysis of patients proceeding to primary surgery demonstrated no difference between the axillary ultrasound group and the controls at our institution.

The impact of preoperative axillary staging is most important for its effect on breast cancer management with regards to surgery, chemotherapy, and radiation. Clearly, it affects the number of sentinel node biopsies being performed, and in our population, axillary ultrasound was significantly associated with neoadjuvant chemotherapy use; 49.7% of patients who underwent axillary ultrasound had neoadjuvant chemotherapy compared with 21.1% of the control group. The effects of selection bias and the evolution of neoadjuvant chemotherapy, particularly in the earlier axillary ultrasound patients, clearly have a role in this finding.

Our basic cost analysis suggests that universal performance of axillary ultrasound in patients with clinical T2 or greater disease likely reduces the overall cost of care. Using our data and average cost-to-insurance figures, we demonstrated a reduction of more than \$4,000 per patient, despite the negative and false-negative rates. The routine addition of axillary ultrasound, therefore, not only improves care for patients relative to surgical planning and oncologic decision making, it also promotes the efficient use of health care resources. Health care providers offering effective care should be recognized for their expertise.

We did find a significantly higher proportion of axillary ultrasound patients (73.2%) undergoing mastectomy compared with the control group (48.9%). Because a greater proportion of the axillary ultrasound patients actually had neoadjuvant chemotherapy than the control group, this

finding appears counterintuitive. More than selection bias, this alludes to the recent progression away from breast conservation—a trend seen markedly at our own institution.²⁵ The decision for mastectomy is affected by a variety of factors, including patient preference, recent media attention, breast reconstruction, neoadjuvant chemotherapy, the effect of breast MRI, and patient age. This finding, therefore, is more likely a reflection of the parallel growth of both axillary ultrasound and mastectomy in a single institution, rather than a cause-and-effect relationship.

It is important to note that, because ultrasound is an operator-dependent examination, specificity of axillary ultrasound in detecting metastatic disease may be relatively higher at a high-volume breast cancer center than in facilities offering a wider variety of services. This retrospective study demonstrates several advantages to performing axillary ultrasound on all patients with invasive breast cancer who have a mass ≥ 2 cm. With this data, we continue to utilize axillary ultrasound routinely at our institution and hope to see similar results from other centers as axillary ultrasound expands to the broader community. Further investigation in the form of multi-institutional data and a prospective trial are warranted.

ACKNOWLEDGMENT This study was supported in part by the Don and Erika Wallace Breast Cancer Foundation Fund.

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