The role of axillary ultrasound in the detection of metastases from primary breast cancers

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Abstract

BACKGROUND: The value of diagnostic axillary ultrasound (AUS) in the preoperative evaluation of lymph nodes for breast cancer patients has yet to be completely clarified.

METHODS: Results of AUS were reviewed for all patients with invasive cancers who were clinically node negative (cN0) and had subsequent axillary lymphadenectomy. Patients with positive ultrasound-guided node core biopsies bypassed sentinel lymph node biopsy (SLNB) and had axillary lymph node dissection, whereas those with sonographically normal nodes or benign/non-diagnostic biopsy results had SLNB.

RESULTS: Of 128 cN0 patients with invasive cancer, 23 (18%) had abnormal axillary AUS. Of 18 core biopsies, 12 (67%) were malignant. SLNB was positive in 19 of 110 (17%) patients. ALND was performed in 32 (25%) patients. For determining axillary metastases, AUS sensitivity was 16 of 31 (52%), specificity was 90 of 97 (93%), the positive predictive value was 16 of 23 (69%), and the negative predictive value was 90 of 105 (86%).

CONCLUSIONS: AUS examination was a valuable method for evaluating the axilla in newly diagnosed cN0 breast cancer patients.

Oncologists are entering an era when the status of the axillary lymph nodes in breast cancer patients is becoming less important in treatment decisions. Patients with Estrogen Receptor (ER)-negative cancers frequently receive a recommendation for chemotherapy based on biomarker status, and those with ER-positive cancers commonly receive treatment recommendations based on gene profiling of the primary tumor. However, the status of the axillary lymph nodes will remain as a prognostic indicator of recurrence and survival.

When sentinel lymph node biopsy (SLNB) became a routinely accepted surgical procedure in the mid-1990s, early investigators determined their false-negative and nonmapping rates by performing SLNB followed by routine axillary lymph node dissection (ALND). False-negative rates ranged from 0% to 8%, and nonmapping rates were approximately 5%. Patients with extensive nodal involvement had a significantly greater chance of mapping failure. Among node-negative patients, those who were older were more likely to have mapping failure than those who were younger.

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial enrolled women from 1999 to 2004 with T1-T2 invasive cancers who were clinically node negative (cN0). Those with 1 to 2 sentinel node metastases identified by SLNB were randomized to completion ALND.

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or SLNB alone. SLNB alone compared with ALND did not result in inferior survival rates. With a median follow-up of 6.3 years, the axillary nodal recurrence rate was 9% in the SLNB-alone group and 5% in the ALND group \( (P = .11) \). These favorable results were predicated on the use of adjuvant whole breast radiation and an accurate SLNB technique. However, surgical educators have now trained a large number of surgeons who will never be able to validate the accuracy of their SLNB technique using completion ALND. This potential systematic problem with quality control raises the question of whether preoperative axillary ultrasound (AUS) can enhance axillary staging. Because the value of AUS has yet to be completely clarified, preliminary experience with this technique was examined in the setting of a comprehensive cancer center.

### Methods

Patients with a mammographic or palpable abnormality of the breast had simultaneous breast and AUS. Patients diagnosed with an invasive cancer at an outside institution had AUS as part of surgical planning. The examinations were performed by dedicated breast radiologists using a 12-MHz linear array transducer (HDI 5000; Philips Ultrasound, Andover, MA). Data on AUS were prospectively collected as part of an imaging protocol that was approved by the institutional review board. Results were analyzed for all patients with invasive cancers who were cN0 and had definitive surgical procedures between June 2006 and May 2008. Patients who had neoadjuvant therapy were excluded from the study. Criteria for abnormal lymph nodes were the loss of reniform shape, focal or diffuse cortical thickening, or eccentric/replaced fatty hilum. Ultrasound-guided biopsies were performed using a 16-G spring-loaded core biopsy device (16-G MD TECH SuperCore, Angiotech Pharmaceuticals, Vancouver, BC, Canada). Patients with positive axillary node core biopsies (including N1mic) bypassed SLNB and had ALND, whereas those with sonographically normal nodes or benign/nondiagnostic biopsy results had SLNB at the time of definitive surgery followed by ALND for sentinel node positivity.

### Results

Of 128 patients diagnosed with invasive cancer, 23 (18%) had an abnormal AUS at the time of the initial diagnosis. Biopsies were performed in 18 of the 23, of which 12 (67%) were malignant and 6 (33%) were benign. Of the remaining 5, 3 went directly to ALND, and 2 had SLNB without core biopsies. Ultrasounds were negative in 105 (82%) patients.

SLNB was performed in 110 patients: 103 with a negative AUS; 4 patients with an abnormal AUS but negative axillary biopsies, 2 patients with an abnormal AUS but no core biopsies, and 1 patient with a positive AUS biopsy. SLNB was negative in 91 (83%) patients and positive in 19 (17%). The node-positive status was N1a in 14 patients and N1mic in 5. ALND was performed in 32 (25%) of 128 patients comprised of 11 patients with AUS-guided positive biopsies, 12 with positive sentinel nodes, 2 with AUS-guided negative biopsies, 2 with a negative AUS, 3 with an unbiopsied abnormal AUS, and 2 with a false-negative SLNB. Of 32 patients having ALND, an abnormal AUS eliminated the need for SLNB in 17 (53%). The AUS and SLNB findings according to tumor size are portrayed in Table 1. For determining the presence of axillary metastases with AUS, the sensitivity was 16 of 31 (52%), specificity was 90 of 97 (93%), the positive predictive value was 16 of 23 (69%), and the negative predictive value was 90 of 105 (86%).

### Comments

For patients with breast cancer, the objective of an axillary clinical examination and diagnostic modalities is to accurately stage the axilla. The current study confirmed previously published results, affirming the ability of AUS to identify axillary lymph node metastases from breast cancer.\(^5\)–\(^8\) Some previous authors have included patients with clinically positive axillary nodes. For example, Mills et al\(^9\) reported on 653 patients with invasive breast cancer. For identifying axillary metastases with AUS, the positive predictive value was 100%, and the negative predictive value was 79%. There were 53 (35%) of 150 pathologically node-positive patients who had a clinically abnormal axilla at the time of presentation. However, the real value of AUS is in the detection of clinically occult axillary metastases in the setting in which clinical examination is associated with high false-positive and false-negative rates. As would be expected in the current study of cN0 patients, the positive predictive value (69%) was lower and the negative predictive value (86%) was higher than the series of Mills et al, in which 35% of patients had an abnormal axillary clinical examination. It should be emphasized that all AUS and core biopsies in the current study were performed by dedicated breast radiologists. The fact that the results of AUS are operator dependent may have implications for the widespread application of this technique.

In the context of the findings in the ACOSOG Z0011 trial, there are 2 important questions for surgeons regarding

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\*Numbers in parentheses are horizontal percentages.

AUS = axillary ultrasound; AX EPL + = positive axillary exploration.
the use of AUS in cN0 patients. For patients who are cN0 and then have a suspicious node identified by AUS and are core biopsy positive, should they be staged as cN0 or as cN1? Second, should they be disqualified from SLNB and from inclusion in the Z0011 criteria, leading directly to ALND?

According to the rules of classification used by the American Joint Committee on Cancer for breast cancer staging, “imaging findings are considered elements of staging...Such imaging findings would include the presence or absence of regional or distant metastases.”

Literal interpretation of the rules would define a cN0 patient with a suspicious node on AUS and a subsequent positive core biopsy as cN1. Yet, in the Z0011 trial, the axilla was evaluated solely by clinical examination (no imaging performed), and only cN0 patients were enrolled. Should such a patient, now staged as cN1, be consigned to bypass SLNB and go directly to ALND?

One way to sort out this conundrum would be to wire or radioactive seed localize a histologically positive node that had been subjected to AUS-guided core biopsy in preparation for SLNB. At the time of operation, if this were a sentinel node and there were fewer than 3 positive sentinel nodes and axillary exploration did not reveal any further adenopathy, then according to the Z0011 criteria ALND would not be necessary. On the other hand, if this were a nonsentinel node at the time of operation, it would represent a false-negative SLNB, and ALND should be considered.

Why bother to complicate AUS with the staging process defined in the Z0011 trial, which was associated with a 5-year axillary node recurrence rate of <1%? As previously alluded to, surgeons who trained after the late 1990s, when the initial validation phases of SLNB were completed, will never be able to validate the accuracy of their own SLNB techniques. Without being able to perform completion ALND after SLNB, there is a systematic lack of quality assurance for the SLNB technique built into surgical training programs. However, instead of defining false-negative SLNB rates by performing completion ALND, each surgeon could determine his/her false-negative rate by determining how often histologically positive nodes identified by AUS are nonsentinel. In addition, for patients having a mastectomy (who do not qualify for the Z0011 inclusion criteria), a positive AUS-guided core biopsy would eliminate the need for SLNB and lead directly to ALND.

In conclusion, AUS was a valuable method for evaluating the axilla in newly diagnosed cN0 breast cancer patients. In this study, which was performed in the era before the publication of ACOSOG Z0011, abnormal AUS eliminated the need for SLNB in 17 (53%) of 32 patients having an ALND. Because patients in this study who had AUS-guided positive nodes were submitted to ALND without SLNB, the frequency with which AUS identified an abnormal nonsentinel node was not determined. This should be the topic of further clinical study.

References


Discussion

Lynne M. Jalovec, M.D. (Peoria, IL): Dr Sener, you said you would consider the patient with a positive ultrasound core needle biopsy lymph node to be a false-negative sentinel node if you took them to surgery. We all know that a fully replaced sentinel node will not necessarily track with the blue dye or the radioisotope, so are you absolutely excluding those patients from avoiding a completion axillary dissection and would you consider them for Z11 trial as far as how you manage them with completion axillary dissection? My other questions had to do with several studies evaluating sensitivity and specificity, just as you showed in your discussion of ultrasound core needle biopsies in patients with larger tumors or with poor tumor characteristics, like patients with triple-negative cancers or those with lymphovascular invasion, that the sensitivity and specificity are clearly improved. Have you thought about eliminating doing ultrasound core needle biopsies or ultrasound examinations of those patients with very small T1 lesions? Lastly, the literature suggests doing the ultrasound core biopsies allows consideration of neoadjuvant chemotherapy in more N1 cases. Have you noticed if your incidence of neoadjuvant chemotherapy was increased since you started doing this?

Stephen F. Sener, M.D. (Los Angeles, CA): So as far as the false-negative sentinel node biopsy goes, we have not
quite sorted out exactly where that fits in the armamentarium yet. I think that one of the key features that I try to train our fellows to do is to explore the axilla after we have performed the sentinel node biopsy. I think you are more likely to find other nonsentinel nodes positive in that setting. I agree with you that a completely replaced lymph node has a higher probability of being a false-negative sentinel node, but that, to me, indicates that there is a higher risk of other nonsentinel nodes being positive in that axilla. So you have to be cautious about what rules you make in that kind of setting. We have not excluded T1 lesions because I think the risk of node positivity is equal to the size of the tumor in millimeters, so for a 1-cm cancer you have a 10% risk of axillary node metastasis. I am not ready to exclude that from consideration yet. We are an I-SPY investigator unit, so we do a lot of neoadjuvant therapy, but lymph node status rarely, if ever, causes us to think neoadjuvant. I think an ER-negative tumor or a human epidermal growth factor receptor (HER-2)–positive tumor is much more likely to put us into the neoadjuvant setting. ER triple-negative patients have a 50% chance of getting a pathologic complete response from neoadjuvant therapy, so we are using biomarkers much more than node status to determine therapy.

Scott Wilhelm, M.D. (Cleveland, OH): You said that you feel that a lot of surgeons are not able to do an adequate sentinel lymph node and then completion axillary dissection in terms of finding what one needs to find. Were you doing these ultrasounds yourself or is this your radiology colleagues? From the endocrine perspective, surgeons were good at doing their own thyroid and parathyroid ultrasounds, but I think nodal ultrasounds are more difficult, even for radiologists. Do you think that this is going to be able to be something that can be widespread unless you have either a dedicated, ultrasound-experienced surgeon and/or dedicated radiologist?

Dr Sener: So, Scott, I think you have identified one of the issues with this article, and that is that we had 3 dedicated radiologists who are really world-class imagers. They are very interested in this. They are well published. So whether this translates outside of our institution is clearly dependent on the person performing the ultrasound. I do not do them because I have got a radiologist literally 10 feet from me who is an expert, and we do not train our fellows to do this. However, we do train them to perform ultrasound on the primary tumor and use ultrasound daily in the operating room, so it is sort of local ground rules.