Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

Association for Academic Surgery

Predictors of false negative axillary ultrasound in breast cancer

Iheoma Y. Nwaogu, MD,[a] *Yan Yan, PhD,*[b] *Catherine M. Appleton, MD,*[c] *Amy E. Cyr, MD,*[a,d] *and Julie A. Margenthaler, MD, FACS*[a,d,*]

[a] *Department of Surgery, Washington University School of Medicine, St. Louis, Missouri*
[b] *Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St. Louis, Missouri*
[c] *Department of Radiology, Washington University School of Medicine, St. Louis, Missouri*
[d] *The Alvin J. Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine, St. Louis, Missouri*

ARTICLE INFO

Article history:
Received 2 January 2015
Received in revised form
8 March 2015
Accepted 19 March 2015
Available online 25 March 2015

Keywords:
Breast cancer
Axilla
Staging
Ultrasound

ABSTRACT

Background: We sought to identify clinicopathologic factors related to false negative axillary ultrasound (AUS) results.

Methods: Patients with a clinically node-negative stage I–II breast cancer who also had a normal AUS were identified from our prospectively maintained database. All AUS studies were interpreted by dedicated breast radiologists as "normal" according to the absence of specific characteristics shown to be commonly associated with metastatic involvement. True- and false-negative AUS studies were compared statistically based on clinical, radiographic, and histologic parameters.

Results: Of the 118 patients with a normal AUS, 25 (21%) were ultimately found to be node-positive on pathologic assessment after axillary surgery. On bivariate analysis, primary tumor size and lymphovascular invasion (LVI) were found to be significantly different between true- and false-negative AUS. The average tumor size was smaller in the true-negative group compared with that in the false-negative group (16 *versus* 21 mm [$P < 0.01$]). The presence of LVI was more likely in the false-negative group (44%) compared with that in the true-negative group (8%, $P < 0.0001$). No significant difference was noted between groups with regard to patient age, race, body mass index, tumor grade, histologic type, hormone receptor status, and time between AUS and axillary surgery. On multivariate analysis, only the presence of LVI achieved statistical significance ($P = 0.0007$).

Conclusions: AUS is a valuable tool that accurately predicted absence of axillary disease in 79% of patients with clinically node-negative breast cancer. AUS findings may be less accurate in the setting of LVI, and a negative AUS in patients with LVI should be interpreted cautiously.

* *Corresponding author*. 660 S. Euclid Ave, Campus Box 8109, St. Louis, MO 63110. Tel.: +1 314 362 7534; fax: +1 314 222 6260.
E-mail address: margenthalerj@wudosis.wustl.edu (J.A. Margenthaler).

0022-4804/$ – see front matter
http://dx.doi.org/10.1016/j.jss.2015.03.057

1. Introduction

Axillary lymph node status is an important prognostic determinant in the outcome for patients with invasive breast cancer; hence, it is crucial to accurately stage the axilla to make appropriate treatment recommendations [1]. It is well recognized that clinical examination is insufficient to predict axillary lymph node metastases so axillary surgery is widely used for a more accurate appraisal of the axillary lymph nodes [2]. Axillary surgery—sentinel lymph node biopsy or axillary lymph node dissection—is not without its risks so there has been great interest in improving noninvasive ways of staging the axilla [3,4].

Axillary ultrasound (AUS) is an economical and minimally invasive tool that has been increasingly used to identify patients with potential axillary lymph node metastases in an attempt to identify subclinical node-positive disease. One of the limitations of AUS is the potential to miss axillary lymph node metastases when present (i.e., false-negative results). As a result, a negative AUS still does not obviate the need for surgical staging of the axilla. In this study, we examined cases with a negative AUS with the aim of identifying clinical, imaging, or pathologic factors potentially related to false-negative AUS results.

2. Materials and methods

This study was initiated after institutional review board approval was obtained, with a waiver of consent given the retrospective nature of the study. The surgical, pathology, and radiology databases at Washington University/Barnes Jewish Hospital were queried from January 1, 2005 and December 31, 2006 to identify all patients with a diagnosis of clinically node-negative stage I–II invasive breast cancer who also had a normal AUS and underwent surgical treatment of their cancer at our institution. Patients who were male, did not have a preoperative AUS, underwent neoadjuvant therapy, had known metastatic disease, or had breast metastases from a primary cancer of a different site were excluded from the study. Additionally, patients who had evidence of and/or suspicion for metastatic disease in the axilla, either by clinical examination or AUS, were excluded from the study.

All AUS studies were performed by dedicated breast radiologists at our institution and interpreted as "normal" according to the absence of specific characteristics previously shown to be more commonly associated with metastatic involvement, namely nodal enlargement, compression, displacement, or complete replacement of the hilum, node matting, perinodal edema, unclear node margins, or focal cortical thickening [5–7].

The study patients were divided into true- and false-negative AUS groups based on the study outcome. Clinical, radiographic, and histologic parameters—including patient age, race, body mass index (BMI), primary tumor size, grade, histologic type, presence of lymphovascular invasion (LVI), receptor status, and time between AUS and axillary surgical staging—were compared between the two groups, using chi-squared analysis or Fisher exact test for categorical variables. A two-sample *t*-test or Wilcoxon rank-sum test (Mann–Whitney *U* test) was used to compare the continuous variables, respectively. Variables with a *P* value of <0.2 on univariate analysis were entered into a backward stepwise multiple logistic regression to ensure the inclusion of important variables into the multivariate regression model. Variables with resulting *P* values of >0.1 were then eliminated from the regression model. Using this method, the significant risk factors for a false-negative ultrasound were identified, and the magnitude of effect was quantified by odds ratios with 95% confidence intervals. All tests were two-sided. *P* values of <0.05 were considered significant. All analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, NC).

3. Results

Of the 312 patients reviewed, 118 met inclusion criteria. A majority of patients were ultimately found to have node-negative disease on final pathologic assessment (true-negative AUS, $n = 93$, 79%), whereas 25 patients (21%) were node-positive after axillary surgery (false-negative AUS). Of the 25 patients with false-negative AUS, 12 patients (48%) had micrometastases, 9 patients (36%) had metastases ranging from 2–10 mm, 1 patient had metastases >10 mm, and 3 patients did not have the size of the metastases noted. Of note, only 3 of the 25 patients with false-negative AUS had 3 or more total positive axillary lymph nodes on the final pathologic assessment.

Also noted was the fact that the average tumor size in the true-negative AUS group was 16 mm, compared with a size of 21 mm in the false-negative AUS group. Although the average length of time from preoperative AUS to axillary surgery did not differ significantly between the two groups (with 28 d for the true-negative AUS group compared with 31 d for the false-negative group), a trend was noted where more patients in the true-negative AUS group underwent axillary surgery within 30 d—72% *versus* 48% of the false-negative AUS group (Table 1).

On bivariate analyses, primary tumor size, LVI, and Her2-neu receptor status were found to be significantly different between true- and false-negative AUS. The average tumor size was smaller in the true-negative group compared with that in the false-negative group (16 *versus* 21 mm, respectively [$P < 0.01$]). The presence of LVI was more likely in the false-negative group (11/25 [44%]) compared with that in the true-negative group (7/93 [8%]; $P < 0.0001$). Her2neu receptor status was more likely amplified in the false-negative group (8/25 [32%]) compared with that in the true-negative group (13/93 [14%]; $P = 0.037$). No significant difference was noted between groups with regard to patient age, race, BMI, tumor grade, histologic type, estrogen or progesterone receptor status, and time between AUS and axillary surgery. On multivariable analysis, only the presence of LVI achieved statistical significance ($P = 0.0007$, Table 2).

4. Discussion

AUS is a relatively inexpensive imaging modality in the initial staging of breast cancer. It provides a minimally invasive method for preoperatively determining the extent of lymph