

Accuracy of Axillary Ultrasound in the Detection of Nodal Metastasis in Breast Cancer: Experience on 620 cases

Abstract

Purpose: Axillary lymph node status is one of the most important prognostic factors in early-stage breast cancer. Sentinel lymph node biopsy is used to determine the status of axillary nodes. There is a subset of patients in whom preoperative identification of nodal metastases could lead directly to axillary dissection. Preoperative axillary ultrasonography is a generally available noninvasive technique for assessing nodal status.

Materials and Methods: Based on retrospective data, we analyzed the sensitivity, specificity, positive and negative predictive values, and accuracy of preoperative ultrasonography performed at our institution on patients who underwent surgery for breast cancer from January 2009 to December 2010 (24 months). A total of 620 axillary ultrasonographic examinations were included, and results were compared with pathological exam.

Results: Ultrasonography revealed unremarkable findings in 500/620 (80%) axillae. There were 368 true negatives, 91 true positives, 29 false positives and 132 false negatives. Sensitivity was 40.8% and specificity 92.7%. Preoperative ultrasonography had a positive predictive value of 75.8%, and a negative predictive value of 73.6%, with an accuracy of 74.0%.

Conclusion: This sample from our institution represents one of the largest reported in the literature and shows that preoperative axillary ultrasound is a method with high specificity but relatively low sensitivity for detecting the presence of axillary metastasis.

Keywords: Axillary ultrasound; Breast cancer; Sentinel lymph node; Axillary dissection; AUS; ALND; SLNB

Case Report

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Synopsis

Preoperative identification of nodal metastases could lead directly to axillary dissection in a subset of patients. This large series from our institution shows that this technique has high specificity but relatively low sensitivity for detecting the presence of axillary metastasis.

Introduction

Axillary node status is one of the most important prognostic factors for breast cancer [1]. Staging based on tumor size and node status constitutes a reliable predictor of survival. Sentinel lymph node biopsy (SLNB) represents a standard for staging the axilla in early-stage breast cancer [2]. This method helps to determine the current surgical approach of the axilla in many scenarios and the number of involved nodes plays an important role in decisions for postoperative radiotherapy and systemic treatment.

For many years axillary lymph node dissection was the gold standard to determine lymph node status, but it is associated with increase morbidity and not necessarily a benefit in terms of rate of distant metastasis [3-4].

SLNB is associated with markedly fewer complications compared to complete axillary lymph node dissection (ALND) [4-

5]. However, further preoperative assessment of the axilla by other methods may provide additional information to aid improving the performance of SLNB or in some instances to avoid it, sparing operating time and costs. Axillary ultrasound (AUS) represents a proven technique for preoperative assessment of axillary node status and is a cost-effective and noninvasive method [6-12].

Despite recent evidence that questions the role of axillary dissection in selected cases with positive SLNB [13]; information deriving from preoperative AUS is still useful in a subset of patients.

We present our experience with preoperative AUS for breast cancer and determine the accuracy of the procedure at our institution.

Materials and Methods

This study was based on retrospective data from patients who underwent surgery for breast cancer from January 2009 to December 2010 at Humanitas Cancer Center in Milan, Italy. Data was retrospectively collected in a database designed for the study. SLNB was performed in all cases and if positive for micro or macrometastasis, ALND was performed.

Patient Population

The total number of breast cancer cases operated during the study period was 1420, from which 766 had undergone a preoperative AUS within 100 days before surgery. Thirty patients were excluded due to lack of lymph node description on ultrasound report. Furthermore, 116 cases for which final histopathologic information on axillary status was not available (pNx) were also excluded. The remaining 620 cases with complete AUS and final histopathology reports were the subjects of this study.

Ultrasonography

US was performed using high-frequency linear array transducer (14 MHz/5 MHz, Hitachi Logos HiVision Gold and Philips iU22) by five physicians with more than 5 years of experience and about 2000 cases/year by operator. Preoperative ultrasonographic examination and findings were documented on a written report for the 620 cases.

Examinations were completed using a standardized protocol performed in supine position with both hands placed behind the head, thereby externally rotating and abducting the arms. In this position, axillary structures can be well assessed. Transverse and sagittal planes were imaged.

Morphological characteristics of axillary lymph nodes were evaluated and classified as unsuspecting (negative), indeterminate or suspicious for metastasis.

Suspicious ultrasound finding for axillary metastasis included [14-19]:

- A. loss of fat hilum
- B. cortical thickening >3 mm
- C. irregular shape
- D. markedly hypoechoic cortex
- E. round shape
- F. increased peripheral blood flow

Lymph nodes were classified as benign if the cortex was even and measured <3 mm, indeterminate if the cortex was even but measured ≥ 3 mm or measured <3 mm but was focally thickened, and suspicious if the cortex was focally thickened and measured ≥ 3 mm or the fatty hilum was absent [20].

Lymph nodes were classified as indeterminate when only one or two of the criteria above were met, but it was considered that further evaluation was required. The size of the axillary lymph nodes has limited utility for determining the likelihood of metastatic disease and was therefore not used as a criterion [21].

Histopathologic Examination of the Sentinel Lymph Node and Estimation of the Size of Metastases

SLNs were serially and completely sectioned and examined intraoperatively on frozen sections or on formalin-fixed and paraffin-embedded sections. Briefly, each lymph node was carefully isolated from the surrounding fatty tissue leaving intact the nodal capsule. The node was then bisected along its major axis and both moieties were processed. Nodes less than 5 mm in thickness were processed uncut. Fifteen pairs of adjacent 5 μ m

sections were cut at 100- μ m intervals from both lymph node halves, until the node was completely sectioned. One section of each pair was routinely stained with hematoxylin and eosin (H&E), the other section was stained for cytokeratins using the MNF116 monoclonal antibody (Dako, Glostrup, Denmark), as previously reported [22], whenever deemed necessary to assess the nature of atypical cells suspicious for malignancy seen in the corresponding H&E preparations. The original histologic slides of all positive SLNs were reviewed and the actual size of the metastases was assessed as described by others [22]. The largest axis of the metastatic nests in the plane of the tissue sections was measured histologically with an ocular micrometer, and the thickness was calculated according to the number of involved contiguous sections and to the sectioning interval between them. To avoid underestimation of the thickness of the metastases, the cutting intervals immediately preceding the first and following the last involved sections were also included. The recorded largest size corresponded to the maximum diameter in the plane of the section or to the thickness of the metastatic foci, whichever was larger. If multiple but distinct (i.e., separated by uninvolved tissue sections) metastases were identified in the same SLN, the size of the largest was recorded.

According to the size of the SLN metastases, 3 categories were devised: Isolated tumor cells (ITCs) as malignant cells in regional lymph node(s) no greater than 0.2 mm, micrometastases, greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm (>0.2-2 mm), and macrometastases (> 2 mm).

Statistical Analysis

A database including ultrasonographic characteristics of the lymph nodes, definitive histologic diagnosis after SNLB and/or axillary dissection and staging among other variables was created. Lymph nodes classified as indeterminate were considered together with suspicious nodes. Data were described as number and percentage, or mean and standard deviation, where appropriate.

We calculated sensitivity, specificity, predictive values and accuracy of AUS based on final pathology reports. Patients without definitive histologic confirmation of axillary findings were excluded from the analysis. Values were recalculated after excluding in situ and pT1 lesions and only including \geq pT2 tumors. All calculations were made with Stata11 (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP).

Results

From January 2009 to December 2010, 620 breast cancer cases operated at our institution had available complete reports on preoperative AUS and final histopathology results. Patient and tumor characteristics are shown on Table 1.

Mean patient age was 55.5 \pm 12.1 years. Mean tumor size was 18.6 \pm 12.4 mm with a range from 1 to 100 mm Table 2.

Invasive ductal carcinomas was observed in 75% (465/620) of patients, invasive lobular carcinoma in 13% (81/620), followed by other invasive types like mucinous and tubular carcinomas observed in 3,3% (21/620) and ductal carcinoma in situ in 8,5% (53/620) of cases.

Ultrasonography revealed unremarkable findings in 500/620 (80.6%) cases. The number of true negatives was 368 and of false negatives 132. From 120/620 positive axillary ultrasonographic examinations for the presence of metastasis, true positives were 91 and false positives 29. The calculated sensitivity was 40.8% and specificity 92.7%. Preoperative ultrasonography had a positive predictive value of 75.8%, a negative predictive value of

73.6%, and an accuracy of 74.0%.

Values were recalculated after excluding in situ and pT1 lesions and only including \geq pT2 tumors (N =182). The sensitivity of AUS increased to 55.6%, specificity decreased to 87.7%, positive predictive value 87.0%, negative predictive value 57.1% and the accuracy to 68.5% Tables 3 & 4.

Table 1: Patient and tumor characteristics of 620 breast cancer cases operated at our institution with available reports on preoperative axillary ultrasound and final histopathology.

Characteristic	N = 620	(%)
Age (mean, SD)	55.5 ± 12.1	
Mean tumor size (mm)	18.6 ± 12.4	
Tumor size		
pTx	4	0.7
pT0	3	0.5
pTis	53	8.5
pT1	378	61.0
pT2	158	25.5
pT3	18	2.8
pT4	6	1.0
Nodal status		
pN0	396	63.8
pN1	152	24.5
pN2	40	6.5
pN3	32	5.2
Histotype		
IDC	465	75.0
ILC	81	13.1
Other (invasive)	21	3.3
DCIS	53	8.5
Grade		
I	82	13.3
II	322	51.9
III	152	24.5
Unknown	64	10.3
Estrogen receptors		
Negative (<1%)	81	13.1
Positive (\geq 1%)	507	81.7
Unknown	32	5.2
Progesterone receptors		
Negative (<1%)	119	19.2
Positive (\geq 1%)	471	76.0
Unknown	30	4.8
HER2 status		
Positive	90	14.5
Negative	479	77.3
Unknown	51	8.2

Table 2: US results correlated with final pathology tumor size and axillary status.

Pathologic Characteristic	AUS result		
	Unsuspectious (negative)	Indeterminate	Suspicious
N	501	35	84
Tumor size			
pTx	4 (0.8%)	0	0
pT0	3 (0.6%)	0	0
pTis	51 (10.2%)	1 (2.9%)	1 (1.2%)
pT1	330 (65.8%)	19 (54.3%)	29 (34.5%)
pT2	101 (20.2%)	13 (37.1%)	44 (52.4%)
pT3	9 (1.8%)	2 (5.7%)	7 (8.3%)
pT4	3 (0.6%)	0	3 (3.6%)
Nodal status			
pN0	368 (73.4%)	17 (48.5%)	11 (13.1%)
pN1	105 (21.0%)	14 (40.0%)	33 (39.3%)
pN2	22 (4.4%)	3 (8.6%)	15 (17.8%)
pN3	6 (1.2%)	1 (2.9%)	25 (29.8%)

Table 3: AUS results and final pathology status.

Pathology status AUS result	Positive nodes	Negative nodes	Total
Positive	91 (TP)	29 (FP)	120
Negative	132 (FN)	368 (TN)	500
Total	223	397	620

Table 4: Sensitivity, Specificity, predictive values and accuracy of AUS across reports.

Study	YEAR	Number of patients	Sensitivity	Specificity	PPV	NPV	Accuracy
Bruneton et al. [8]	1986	60	72.7%	97.3%	na	na	na
Bonnema et al. [28]	1997	148	87%	56%	na	na	na
Rajesh et al. [29]	2002	84	74%	89%	87%	84%	83%
Damera et al. [30]	2003	187	55%	82%	na	na	na
Van Rijk et al. [32]	2006	726	35%	82%	na	na	na
Nori et al. [11]	2007	132	45.2%	86.80%	61.30%	77.20%	73.5%
Koehler et al. [37]	2010	429	53.6%	75.5%	77.3%	51.3%	69.0%
Present study	2011	620	40.8%	92.7%	75.8%	73.6%	74.0%

Discussion

Our study shows that the sensitivity of AUS in our institution for all breast tumor sizes and during a two-year period goes along with the lower range reported in the literature (40%) [23], whereas the specificity is high (92.7%).

There is an increasing body of literature addressing the challenge of axillary ultrasound assessment in primary breast cancer. The reported sensitivity and specificity of ultrasonography for detecting metastases in axillary lymph nodes ranges from

35% to 87% and from 55% to 97%, respectively (Table 4) [24-27].

There are many reasons for this marked heterogeneity. Some studies, like our own, utilized axillary ultrasound alone to predict nodal metastasis without the routine addition of fine needle aspiration or biopsy [24,26-32]. The involved node identification rate, where stated, was very variable; in some studies as low as 35% [27] and in others it was much higher at 53.6% [22] and even up to 87% [24]. In many studies the node identification rate is not specifically mentioned; only that absence of an abnormal

node was taken as an indication of an axilla free from metastatic disease.

Up to about fifteen years ago, preoperative staging was based only on palpation and physical examination; physical examination has low sensitivity (34–76%) [7,33] and cannot distinguish between metastatic and reactive lymph nodes [5]. Ultrasonography is now the most useful non-invasive diagnostic technique for the evaluation of axillary lymph nodes. It is widely available, and inexpensive. It causes little if any patient discomfort and provides access to all the lymph node chains. It can assess the morphological characteristics of both palpable and no palpable lymph nodes.

In an early work that included 60 patients in 1986, Bruneton et al. [8] compared the significance of preoperative axillary ultrasonography with palpation. The authors stated that ultrasonography had a sensitivity of 72.7% and a specificity of 97.3%, whereas palpation had a sensitivity of only 45.4% and a specificity of 97.3%, i.e. a value identical to that of ultrasonography.

In 1997, Bonnema et al. [24] published a study including 148 patients. The inclusion criteria were histologically proven breast cancer and the absence of suspicious axillary lymph nodes on palpation. In this study, the sensitivity of axillary ultrasonography was 87% and its specificity was 56%.

Ultrasonography shows changes in the size and shape of lymph nodes that can reflect the presence of underlying metastases. Some authors calculate the ratio between the longitudinal and transversal diameters of the lymph node [33]. Nevertheless, the size of benign and malignant lymph nodes can be similar. Others assess the presence of Doppler flow in the hilum [15]. However, most authors agree that the morphology and cortical thickness are the most valuable parameters for determining metastatic involvement [6,16,33].

Figures published by Rajesh et al. [25] were also slightly higher than in our study, with a sensitivity of 74%, a specificity of 89%, and a positive predictive value of 87%. The examined population was quite similar to our patients regarding mean age and tumor size.

A study published by Damera et al. [26] in 2003 including 187 patients showed a sensitivity of 55% and a specificity of 82%, which is similar to our report.

In 2005, Podkrajsek et al. [34] published a study including 165 patients. Lymph nodes appearing suspicious or malignant underwent fine-needle biopsy and were cytologically examined. Ultrasound by itself had a sensitivity of 58%, its specificity was 89%.

A study by Van Rijk et al. [27] with 726 patients and the study by Nori et al. [11] with 132 cases both showed a rather low sensitivity of 35% and 45.2%, respectively, with a relatively high specificity of 82% and 86.8%; a positive predictive value of 61.3% and a negative predictive value of 77.2% with an accuracy of 73.5%.

On Table 4, the three largest reports (ours included), tend to show lower sensitivity (35–53%) for detecting lymph node metastasis compared to smaller and older series. This could be likely explained by relatively higher disease stages in older series

and differences in patient selection.

After excluding in situ carcinomas and small lesions (pT1), the sensitivity of AUS was 55.6% and PPV increased. It could be assumed this would increase its cost-effectiveness, which represents an important aspect for ultrasound, as it is a time-consuming task for the operator and efforts should be made to optimize its indications.

Despite that specificity of AUS is fairly high as demonstrated in the literature [8,11,25–27,33,34] and in our study, and although there are several studies dedicated to better characterize suspicious lymph nodes [6,8,10–14,18,33,35], it seems that there is no clear or absolute reliable correlation between sonographic appearance and pathological anatomy of metastatic lymph nodes. Operator experience and methodology during ultrasound examination play an essential role when searching for suspicious axillary lymph nodes [35]. Based on these factors, AUS should be considered a separate procedure from breast ultrasound, so that experience can be evaluated individually.

Given that our study population was mostly represented by early-stage disease (approximately 70% of cases with pTis or pT1), the expected rate of axillary node involvement is quite low, as evidenced by the high proportion of cases with unremarkable findings on AUS (80%). This indicates that efforts should focus in improving patient selection for this exam. Moreover, after the advent of recent evidence that questions the benefit of ALND in patients with early-stage breast cancer who have one to two positive SLNs and who undergo breast conservation with whole breast radiotherapy [13], the rationale for preoperative AUS in breast cancer needs to be reformulated.

Patients with larger tumors in whom sparing ALND is not planned in advance would likely be adequate candidates for this exam. Means to assess regional nodes with less invasive methods could still provide useful information in these cases, sparing operating time and costs [36,37].

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