

# Diagnostic Performance of Axillary Ultrasound in Breast Cancer

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## Abstract

The status of axillary lymph nodes is one of the most important prognostic factors among patients with invasive breast cancer. Our objective was to determine the performance of axillary ultrasound imaging in our institution for the detection of metastatic axillary lymph nodes at the time of presentation of invasive breast cancer. A total of 530 patients with breast tumors less than or equal to 5 cm with clinically negative axillary lymph nodes were assessed by imaging specialists. Any lymph node with diffuse cortical thickening greater than 3.5 mm, cortical lobulation and/or displacement of hilar contour, total hilar replacement, and/or peripheral lymph node vascularity was considered suspicious for malignancy. When suspicious axillary lymph nodes were found, an ultrasound-guided axillary biopsy, a selective sentinel lymph node biopsy and/or axillary lymphadenectomy were performed. We achieved a sensitivity of 67.11% and a specificity of 97.88%. Axillary ultrasound scanning is sensitive and specific in detecting metastatic lymph nodes in patients with clinically negative axillary breast cancer.

**Keywords:** Axillary ultrasound scanning; Breast cancer

## Introduction

Lymph node status is one of the most important prognostic factors in patients with invasive breast cancer [1]. Selective Sentinel Lymph Node Biopsy (SLNB) has become the standard procedure in the staging of axillary lymph nodes in patients with breast cancer worldwide [2]. Until 2011, axillary lymphadenectomy had been the standard treatment in breast cancer patients with metastases on SLNB [3,4]. However, axillary lymphadenectomy was associated with a high morbidity rate [5,6].

SLNB after neoadjuvant chemotherapy in clinically axillary negative patients is recommended by current guidelines [7-9]. However, studies show that neoadjuvant chemotherapy may eradicate axillary nodal disease at the time of presentation [10-13]. These findings also led to the questioning of current recommendations that all suspicious lymph nodes on axillary ultrasound scanning in patients who will be subjected to neoadjuvant chemotherapy should be biopsied [14].

The extent of disease at presentation and the tumor biologic subtype should also be considered in the selection of the axillary approach [15]. In this setting, current guidelines from the National Comprehensive Cancer Network (NCCN) have incorporated SLNB after neoadjuvant chemotherapy as an accepted part of management and state that SLNB can be performed on selected patients with breast cancer who have clinically positive axilla that converted to negative after neoadjuvant chemotherapy, and that SLNB false negative rate

can be improved by removing more than two lymph nodes, using dual mapping or marking biopsied lymph nodes to document their removal [7].

Preoperative axillary lymph node ultrasound assessment is systematically performed at some centers in all patients with newly diagnosed breast cancer with reported specificities of up to 100% [15,16]. The identification of metastatic lymph node involvement prior to surgery is of great importance for accurate staging. These findings associated with the extent of disease at presentation and the biological subtype of the tumor should also be considered when selecting the axillary approach [14,17].

## Objectives

The objective of this study was to determine the performance of axillary ultrasound imaging in our institution for the detection of metastatic axillary nodes at the time of presentation in patients diagnosed with invasive breast cancer.

## Methods

It is a prospective study to evaluate the performance of axillary ultrasound scanning in the detection of metastatic axillary nodes at the time of presentation in patients with breast cancer less than or equal to 5 cm (cT1-2) with clinically negative axillary lymph nodes. A total of 530 patients with diagnosis of invasive breast cancer at presentation were assessed by imaging specialists at our institution

(ELAS) from January 2016 to September 2019. Any lymph node that met the following features of the Classification of Bedi was considered suspicious: a) diffuse cortical thickening >3.5 mm, b) cortical lobulation or displacement of hilar contour, c) total hilar replacement, and d) peripheral lymph node vascularity. Patients with distant metastases, other previous malignancy, pregnancy or lactation, neoadjuvant therapy or clinically suspicious axillary lymph nodes were excluded.

Suspicious lymph nodes on axillary ultrasound scanning were biopsied, either by ultrasound-guided Fine Needle Aspiration Biopsy (FNAB) and/or Core Needle Biopsy (CNB) of axillary lymph nodes with the above mentioned ultrasonographic features. SLNB with the dual technique was used in non-suspicious axillary lymph nodes on ultrasound imaging. Afterwards, when an axillary lymph node was found to be positive, the standard axillary dissection of level I and II lymph nodes was performed. The sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of axillary ultrasound scanning in the detection of metastatic axillary lymph nodes at presentation were estimated. Simple statistical tests were applied with a 95% confidence level. Fisher's exact test was calculated with a statistically significant  $p < 0.05$  value.

## Results

A total of 530 patients were evaluated for preoperative axillary staging with ultrasound scanning. Out of the 530 patients, 71 underwent preoperative cytology by ultrasound-guided FNAB (68 patients) and/or CNB (3 patients) of axillary lymph nodes. Of these biopsied patients, 35 (49%) had positive cytology/histology. In those cases with evidence of metastatic disease identified on fine needle biopsy, standard axillary dissection was performed. By contrast, 21 (60%) of the 35 patients with positive cytology/histology had more than one lymph node involved. In all remaining cases (495), 36 patients with negative cytology/histology for malignancy and 459 patients with normal or non-suspicious axillary lymph nodes on preoperative ultrasound scanning underwent the gold standard selective SLNB. With evidence of metastatic disease identified by intraoperative selective SLNB, axillary lymph nodes were dissected.

True Positive (TP) were the cases with suspicious ultrasound findings of axillary lymph node disease that were histologically positive (Table 1,  $n=102$ ).

True Negative (TN) were the cases without suspicious ultrasound findings of axillary lymph node disease that were histologically negative for malignancy (Table 1,  $n=370$ ).

False Negative (FN) were the cases without suspicious ultrasound findings of axillary lymph node disease that were histologically positive for malignancy (Table 1,  $n=50$ ).

**Table 1:** Axillary ultrasound scanning.

| Diagnostic test | Reference standard |          |       |
|-----------------|--------------------|----------|-------|
|                 | Positive           | Negative | Total |
| Positive        | 102                | 8        | 110   |
| Negative        | 50                 | 370      | 420   |
| Total           | 152                | 378      | 530   |

Diagnostic test: Axillary ultrasound scanning.

Reference standard: Selective sentinel lymph node and or biopsy axillary dissection.

False Positive (FP) were the cases with suspicious ultrasound findings of axillary lymph node disease that were histologically negative (Table 1,  $n=8$ ).

The following results were obtained: Sensitivity 67.11% (CI 59.31-74.90), Specificity 97.88% (CI 96.30-99.47), Validity index 89.06% (CI 86.30-91.81), PPV 92.73% (CI 87.42-98.03), NPV 88.10% (CI 84.88-91.31), Prevalence 28.68% (CI 24.73-32.62). Of the 50 false negative cases, half were micrometastases and the other half were macrometastases. Sensitivity or the true positive rate (TPR) [ $102 \div (102+50)$ ], specificity or the True Negative Rate (TNR) [ $370 \div (370+8)$ ], PPV and NPV are shown on table 2.

## Discussion

Axillary lymph nodes are the most common sites of metastasis in breast cancer. The prevalence of axillary involvement varies between 30 and 70% [18-21]. In patients with tumors less than or equal to 20 mm in size, axillary involvement is about 25%, and it is up to 15% in patients with tumors of 10 mm or less [22].

Axillary lymph node status is essential to determine the stage of the disease at the time of diagnosis [23,24]. And it continues being one of the most important prognostic factors for patients with breast cancer [1,23]. Selective SLNB has become a standard procedure for axillary staging in breast cancer patients worldwide [2].

Preoperative axillary lymph node ultrasound assessment is systematically performed at some centers in all patients with newly diagnosed breast cancer with reported specificities of up to 100% [15,16]. Identification of metastatic lymph node involvement prior to surgery is of paramount importance for accurate staging [14,17].

Axillary ultrasound scanning and ultrasound-guided biopsy of suspicious lymph nodes are quick and simple procedures, associated with low morbidity [18,21,25,26].

The extent of axillary lymph node disease at presentation and the tumor biologic subtype should also be considered in the selection of the axillary approach [15].

In this setting, given the extension of axillary disease at the time of presentation of breast cancer, doing an ultrasound imaging and/or ultrasound-guided FNAB or CNB of suspicious axillary lymph nodes could avoid an unnecessary SLNB, considering the possibilities of selecting neoadjuvant chemotherapy or a standard axillary lymphadenectomy [7,14,17].

A number of morphological features of lymph nodes have been described as predictors of abnormality in the literature [27-29].

**Table 2:** Results.

|                           | Value (%) | CI (95%)    |
|---------------------------|-----------|-------------|
| Sensitivity               | 67.11     | 59.31-74.90 |
| Specificity               | 97.88     | 96.30-99.47 |
| Positive predictive value | 92.73     | 87.42-98.03 |
| Negative predictive value | 88.1      | 84.88-91.31 |
| Prevalence                | 28.68     | 24.73-32.62 |

Sensitivity or the True Positive Rate (TPR) [ $102 \div (102+50)$ ]; Specificity or the True Negative Rate (TNR) [ $370 \div (370+8)$ ]; Validity index 89.06% (CI 86.30-91.81).

In our study, any axillary lymph node that met the following ultrasonographic features was considered suspicious: a) diffuse cortical thickening >3.5 mm, b) cortical lobulation or displacement of hilar contour, c) total hilar replacement, and d) peripheral lymph node vascularity. A sensitivity of 67.11% and a specificity of 97.88% were obtained; these figures do not vary from the results published in the literature, where a sensitivity of 42 to 56% and a specificity of 70 to 90% are described [30-33].

This study was started at a time when we were not performing systematic ultrasound-guided axillary biopsies of lymph nodes considered suspicious. Of the 71 biopsies performed, more than 95% were fine needle biopsies (68 patients), of which 49% (35 patients) were positive cytology results. This is probably due to the low sensitivity of fine needle biopsy [34]. The remaining 36 patients (51%) with negative cytology results were pathological in the selective SLNB.

The aim of our study was to evaluate the sensitivity of ultrasound scanning for the detection of axillary lymph node metastases, based on lymph node histology obtained from reference standards. Our study was based on abnormalities in a single lymph node. A Mayo Clinic study suggested documenting the number of suspicious lymph nodes on scanning prior to biopsy [35]. They observed that patients who had multiple suspicious lymph nodes on scanning and a positive lymph node on biopsy, predicted for 3 or more lymph node involvement and extranodal extension at the time of SLNB, requiring axillary lymphadenectomy. They concluded that in this subset of patients, ultrasound imaging and ultrasound guided FNAB or CNB of suspicious lymph nodes of the axilla were a good indication for proceeding to axillary lymphadenectomy directly. In our study, 21 of 35 patients with positive FNAB were found to have more than one lymph node involved (60%). These findings were also confirmed by Boland MR, et al. [36]. However, Cools-Lartigue J, et al. [37] observed no increased lymph node involvement or extranodal extension in their group of patients with pathological nodes in the ultrasound-guided biopsy [37]. We obtained a PPV of 92.73% and a NPV of 88.10%. Of the 50 false negative cases, 50% were micrometastases (lymph node involvement  $\leq 2$  mm) and the other 50% were macrometastases (lymph node involvement  $>2$  mm). The IBCSG 23-01 trial found additional axillary lymph nodes involved in 13% of patients in the micrometastasis group who underwent axillary lymphadenectomy, and taking into account the prevention of arm morbidity, together with a low axillary recurrence rate, it supports the omission of axillary lymphadenectomy in this group of patients [38].

The Sentinel Node vs. Observation after Axillary Ultra-sound (SOUND) trial at the European Institute of Oncology was designed to investigate whether ultrasound staging of the axilla could replace selective SLNB to improve patients' quality of life. Patients with breast cancer and clinically negative lymph nodes by axillary ultrasound scanning or axillary biopsy (cT1N0) were randomized to SLNB  $\pm$  axillary lymphadenectomy or observation without axillary staging [39]. We will have to wait for the publication of the results to endorse the omission of SLNB for patients with breast cancer and clinically negative lymph nodes by axillary ultrasound scanning or axillary biopsy.

Our study had a number of limitations. Not all patients with lymph nodes with suspicious features on ultrasound imaging were subjected to an ultrasound-guided biopsy. On the other hand, it is a single-center study with a likely bias related to external validity.

Among the strengths, it is a prospective study with a consecutive series of patients treated in the same institution that centralizes the screening process and surgery of patients diagnosed with breast cancer.

This means that ultrasound scans were performed by experienced radiologists who are specialized in breast imaging.

Axillary ultrasound scanning of patients with breast cancer allows the detection of pathological lymph nodes in a high percentage of cases. The procedure is well tolerated by patients and it is an easy, fast and reproducible technique that allows the detection of metastasis in this area. This technique allows physicians to modify the axillary approach, avoid unnecessary procedures and/or morbidity [14,15,17].

## Conclusions

The performance of axillary ultrasound imaging in detecting metastatic axillary nodes at the time of presentation of patients with invasive breast cancer is sensitive and specific. The number of involved lymph nodes was higher in patients in whom axillary metastases were detected by ultrasound-guided biopsy. Axillary ultrasound scanning at presentation of breast cancer may be a useful tool to identify patients with axillary tumor burden. This finding allows for a better adaptation of the axillary approach in breast cancer.

## Conflict of Interest

The authors have no conflicts of interest to declare.

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