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Diagnostic Accuracy and Impact on Management of Ultrasonography-Guided Fine-Needle Aspiration to Detect Axillary Metastasis in Breast Cancer Patients: A Prospective Study

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Keywords

Fine-needle aspiration biopsy · Lymph node status · Staging · Treatment strategies · Ultrasound

Summary

Background: The axillary nodal status is essential to determine the stage of disease at diagnosis. Our aim was to prospectively assess the diagnostic accuracy of ultrasonography-guided fine-needle aspiration (US-FNA) for the detection of metastasis in axillary lymph nodes in patients with breast cancer (BC) and its impact on the therapeutic decision. **Materials and Methods:** Ultrasonography (US) was performed in 407 axillae of 396 patients who subsequently underwent surgery. US-FNA was conducted when lymph nodes were detected by US. Axillary dissection (AD) was performed when US-FNA was positive for metastasis. Patients with negative US-FNA and breast tumors of 30 mm in size were candidates for selective sentinel lymph node biopsy (SLNB). The anatomopathological results of AD or SLNB were used as reference tests. **Results:** Lymph nodes were detected by US in 207 (50.8%) axillae. Of these, US-FNA was performed on 180 (86.9%). 94 axillae (52.2%) were positive for carcinoma and 79 women received AD. US-FNA had 77.5% sensitivity, 100% specificity, 100% positive predictive value, 69.3% negative predictive value, and 85.1% diagnostic accuracy. US-FNA avoided SLNB in 18.1% of patients who underwent AD. **Conclusions:** Axillary US-FNA is an accurate technique in the staging of patients with BC. It allows reducing the number of SLNB and, when positive, offers a fast and useful tool.

Introduction

Axillary lymph nodes are the most common sites of metastases in breast cancer (BC). The prevalence of axillary involvement varies between 30 and 70% [1–4]. In patients with tumors of 20 mm in size or less, axillary involvement is around 25%, and up to 15% in patients with tumors of 10 mm or less [5].

The axillary nodal status is essential to determine the stage of disease at diagnosis [6, 7]. This information is compiled from the histological assessment of axillary lymph nodes obtained by axillary dissection (AD) or selective sentinel lymph node biopsy (SLNB) [8]. SLNB is a complex and invasive technique [1]. It involves the administration of a radiotracer, the distribution of which can be slow, poor, or absent. It is also associated with a longer surgical time and requires the coordination of different specialists and pathologists to make fast decisions based on the pathology of the

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lymph node biopsies. Besides, some series show a risk of systemic allergic reaction to the radiotracer used in sentinel node mapping [9].

Ultrasonography-guided fine-needle aspiration (US-FNA) of the axillary lymph nodes is a fast non-surgical staging procedure associated with low morbidity [1, 4, 10, 11]. A positive diagnosis can avoid SLNB and enables to consider approaches such as AD or primary chemotherapy. Several studies report a sensitivity of US-FNA in the preoperative staging of BC of up to 80%, with 100% specificity [1, 2, 10, 12]. US-FNA improves the negative predictive value (NPV) of SLNB and reduces the time to diagnosis [2–4, 11, 13]. Nevertheless, published studies are either retrospective series [10] or prospective series that include few patients [1–4].

In the last years, a more conservative approach has been adopted in the surgical treatment of BC (e.g. conservative and no AD in axillary micrometastases). Likewise, patients with positive axillary lymph nodes who will undergo AD should be selected preoperatively in order to omit SLNB [12].

The aim of our study was to prospectively evaluate the diagnostic accuracy of US-FNA for the detection of metastasis in axillary lymph nodes in patients with BC, based on the histology of lymph nodes obtained by SLNB or AD as a reference test.

Patients and Methods

Design

Prospective intervention study.

Patients

All patients who consecutively presented at the radiology department of Althaia Xarxa Assistencial Universitària de Manresa between July 2005 and June 2009 with suspected BC or were referred from another center with the diagnosis of BC were screened for eligibility. Patients were enrolled consecutively after diagnosis with core needle biopsy (CB) of BC, or patients with axillary lymphadenopathy as the only clinical finding (study of cancer of unknown origin).

Exclusion criteria were as follows: patients who had undergone axillary node CB as a first procedure, those without subsequent axillary surgery due to clinical contraindications, diagnosis of ductal carcinoma in situ < 4 cm, and recurrent BC.

When bilateral BC was diagnosed or suspected, a bilateral axillary study was performed.

The protocol was approved by the local ethics committee and the patients' written informed consent was obtained.

Axillary Ultrasonography and FNA Procedure

Two ultrasounds with a linear 8-MHz probe (Toshiba-Aplio, Toshiba Medical Systems) and a 7.27–11.43-MHz multifrequency linear probe (Siemens Premium Edition, Acuson Antares) were used interchangeably. The tests were performed by 6 radiologists with 4–15 years of experience in breast imaging.

The morphological characteristics of the node cortex detected during ultrasonography (US) were collected and subsequently classified into 4 groups: type 1 = thin (< 3 mm) hypoechoic cortex, type 2 = hypoechoic cortex thicker than 3 mm, type 3 = focal hypoechoic cortical lobulation, type 4 = totally hypoechoic node with no hilum. Type 1 lymph nodes were considered benign while type 2, 3, and 4 lymph nodes were considered suspicious for malignancy.

FNA was performed when a lymph node was visible, regardless of its morphological characteristics. When more than 1 lymph node was visible, or when all presented benign features, the largest one or the one closest to the breast was selected. 21G needles were used.

Samples were processed in the Pathological Anatomy Service, fixed for a minimum of 30 min, and extensions were stained by Papanicolaou test [14, 15]. The material was processed to form cell blocks. When the US-FNA results were inconclusive due to insufficient material (indeterminate or acellular) and the ultrasound findings were classified as highly suspicious for malignancy, puncture was repeated.

Standard Reference Test

The reference test used to determine the axillary lymph node status was the histology obtained by SLNB or AD.

The criteria for the indication of SLNB were those established by the consensus meetings on sentinel nodes and BC [14, 15].

Intraoperative Sentinel Node Assessment

During the intraoperative assessment of each lymph node, sections of 2 mm were cut and individually studied. Scrape cytology smears of all fresh specimens were assessed: Sections were fixed and stained with the Diff-quik® staining method.

Histological Assessment of Lymph Nodes Obtained by SLNB and/or AD

The lymph nodes obtained by SLNB were fixed in formaldehyde, and sections of approximately 1 mm thickness were cut. From each paraffin-embedded block, 3 tissue sections were cut, separated by 250-μm intervals. Consecutively, 1 section was stained with hematoxylin-eosin, 2 sections with cytokeratins AE1–AE3, and a 4th section with hematoxylin-eosin.

In the case of AD, after fixation in formaldehyde, lymph nodes were isolated from the specimen and separated into the 3 levels identified by the surgeon. A section representative of each was included. The hematoxylin-eosin staining protocol was then used in all sections. In the case of post-primary chemotherapy AD, the pathological response of the Miller-Payne histological grading system [16] was used.

The pathologist who made the diagnosis based on SLNB or AD was blinded to the result of the US-FNA. 3 pathologists with more than 4 years of experience in the technique of SLNB participated in the study.

Patient Management

The Multidisciplinary Breast Cancer Committee of our hospital decided on the best treatment and management for each patient according to the findings obtained from the axillary US and the US-FNA, as well as the results obtained from the other techniques used in the diagnostic workup. For tumors larger than 3 cm, the primary treatment was breast surgery plus AD or chemotherapy/hormonal therapy (these patients later underwent breast surgery plus AD). SLNB was indicated for patients with extensive in situ carcinoma, those with infiltrative BC ≤ 3 cm, when axillary studies did not detect lymph nodes, or when US-FNA of lymph nodes yielded negative results.

AD was indicated when SLNB showed axillary metastasis, and radiotherapy was indicated when internal mammary nodes were affected.

If the axillary US-FNA was positive, no SLNB was performed and patients underwent surgery with AD or primary systemic treatment, depending on the local and regional extension of the tumor.

Statistical Analysis

In order to obtain a precision of 10% in the estimation of the sensitivity of US-FNA to detect lymph node metastases in BC patients, with 95% confidence interval (CI) and assuming a sensitivity of 75% compared with axillary surgery (SLNB and/or AD) as reference standard [2], 72 patients with positive US-FNA should be included. Assuming a 40% prevalence of axillary metastasis, 180 patients with BC and axillary assessment by US-FNA have to be recruited.

In cases of bilateral BC, the findings on each tumor and homolateral axilla were considered as independent data.

Quantitative data are shown as mean and standard deviation (SD), while categories are listed in terms of absolute and relative frequencies (%).

Based on the histological findings of SLNB and/or AD as reference tests, we determined the sensitivity, specificity, PPV, NPV, and the diagnostic accuracy of US-FNA. Measures of diagnostic accuracy are presented with 95% CI.

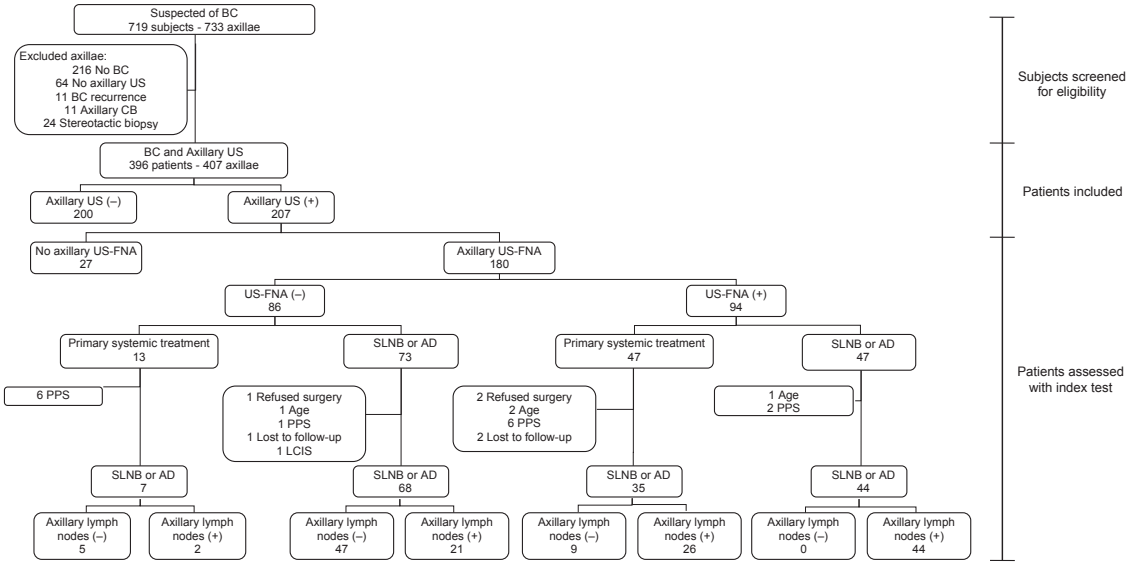

Fig. 1. Flowchart of the screening process, recruitment, and assessment with the index test. BC = Breast cancer, US = ultrasonography, CB = core biopsy, US-FNA = US-guided fine-needle aspiration, SLNB = sentinel lymph node biopsy, AD = axillary dissection, PPS = poor performance status, LCIS = lobular carcinoma in situ.

The number of patients who avoided unnecessary SLNB was determined as the ratio between the total number of positive axillae initially candidates for SLNB and the total number of axillary assessments with US-FNA initially candidates for SLNB. Candidate patients for SLNB were patients with unifocal or multifocal tumors < 3 cm in diameter.

The programs SPSS for Windows v.17 and STATA v.10 were used for statistical analysis.

Results

Patient Inclusion

A total of 719 patients (733 axillary studies) with clinical or radiological suspicion of BC or BC confirmed by histology in another center were assessed for eligibility. Of these, 396 patients (407 axillae) with BC and US were included in the study. The other 326 axillae (44.5%) were excluded: 216 (66.2%) for not presenting infiltrative BC, 64 (19.6%) for not having undergone axillary ultrasound, 11 (3.4%) for BC recurrence, 11 (3.4%) for axillary CB and 24 (7.4%) for stereotactic biopsies of in situ carcinomas of < 4 cm. Of the 396 patients (407 axillae) included, no lymph nodes were observed in 200 axillae (49.2%). US-FNA was performed in 180 (86.9%) of the 207 axillae (50.8%) where lymph nodes were visualized. In 27 cases where lymph nodes were visualized by axillary ultrasound, the radiologist decided not to perform US-FNA; 23 (85.2%) of the 27 most suspicious lymph nodes visualized in these patients were classified as types 1 and 2. Of these 27 patients, 18 were operated, 3 (16.6%) of which were positive for metastasis (fig. 1).

A total of 26 axillae (14.4%) that underwent US-FNA were not candidates for axillary surgery (4 due to advanced age, 15 due to poor performance status (PPS), 3 due to rejecting surgery, 3 due to loss of follow-up, and 1 in situ lobular carcinoma).

In the diagnostic accuracy analysis, 154 axillary studies with US-FNA and axillary surgery (SLNB and/or AD) were included, 79 (51.3%) of which were positive for metastasis on US-FNA. 42 (27.8%) of the 154 patients received chemotherapy or hormonal therapy as a first treatment, while 109 (72.2%) underwent surgery. The mean age was 62.6 years (SD 14.1 years) and 98.0% were women (tables 1 and 2).

Table 1. Characteristics of the 151 patients assessed with axillary US-FNA and SLNB/AD

Patients (N = 151)	
Mean age, years	62.6 (SD = 14.1)
	n (%)
Sex	
Women	148 (98.0)
Men	3 (2.0)
Origin	
General practice	110 (72.8)
Breast cancer screening program	20 (13.2)
Emergencies	13 (8.6)
Other	8 (5.3)
Bilateral	
No	148 (98.0)
Yes	3 (2.0)
Primary treatment	
Chemotherapy	32 (21.2)
Hormone therapy	10 (6.6)
Surgery	109 (72.2)

SD = Standard deviation.

Outcome Assessment

Mammography, CB of the primary tumor, and axillary US-FNA were performed on the same day in 91.2% of the patients. In the remaining 8.8%, no decision was made until the results of the CB of the primary tumor were obtained. The mean delay for US-FNA was 9.5 calendar days.

Eleven punctures, in 5.8% (9/154) of the patients, were repeated for insufficient material (indeterminate or acellular), finally yield-

Table 2. Histologic features of the tumors in 154 axillary assessments

Clinicopathologic features	n (%)
Histological type	
Ductal	133 (86.4)
Lobular	11 (7.1)
Mucinous	5 (3.2)
Tubular	1 (0.6)
Mixed	2 (1.3)
Others	2 (1.3)
Ductal carcinoma	
In situ	10 (7.5)
Invasive	123 (92.5)
Nuclear-grade ductal carcinomaa	
I	6 (5.0)
II	59 (49.6)
III	54 (45.4)
Stage	
0	5 (3.8)
I	25 (18.8)
IIA	40 (30.1)
IIB	30 (22.6)
IIIA	16 (12.0)
IIIB	5 (3.8)
IIIC	5 (3.8)
IV	4 (3.0)
Tx	3 (2.3)
Mean primary tumor size, mm	20.1 (SD = 13.6)

SD = Standard deviation.
a14 missing values.

ing 6 negative results, 4 positive ones, and 1 insufficient result. In 5 US-FNAs with insufficient material, puncture was not repeated as the lymph nodes presented benign US features. The total of results with insufficient material in our series was 6 (3.9%).

AD showed no evidence of residual tumor in 9 patients with axillary US-FNA positive for malignancy, who subsequently received primary chemotherapy. This suggests pathologic complete response of the axillary metastasis. Complete pathologic response of the primary tumor in the breast surgical specimen was also observed. Assuming that the US-FNA method gives no false-positive results, these axillae were considered as positive surgery for the calculation of the diagnostic accuracy of US-FNA.

The diagnostic accuracy of US-FNA to detect metastasis in axillary lymph nodes in patients with BC was 85.1% (95% CI: 78.4–90.3%), with a sensitivity of 77.5% (95% CI: 68.1–85.1%) and an NPV of 69.3% (95% CI: 57.6–79.5%) (table 3).

A total of 23 (14.9%) false-negative US-FNA was obtained. Overall, axillary lymph node involvement was rare in these cases; 4 (17.4%) were affected by pN1mic, 18 (78.3%) by pN1, and 1 (4.3%) by pN2. The primary tumor size was pT1 in 13 patients (56.5%) and pT2 in 10 (43.5%). Likewise, the ultrasound features were benign in 11 patients (47.8%) and suspicious in 12 (52.2%).

The lymph node involvement in the surgical staging was correlated with the size of the primary tumor. The sensitivity of US-FNA increased with the size of the primary tumor from 67.5% in

Table 3. Diagnostic accuracy of axillary US-FNA with histological assessment of the lymph nodes obtained by SLNB or AD (N = 154)

	SLNB/AD		
US-FNA	Positive	Negative	Total
Positive	79	0	79
Negative	23	52	75
Total	102	52	154
	%	95% confidence interval	
Sensitivity	77.5	68.1–85.1	
Specificity	100	93.2–100	
Positive predictive value	100	95.4–100	
Negative predictive value	69.3	57.6–79.5	
Diagnostic accuracy	85.1	78.4–90.3	

T1 tumors to 100% in T4 tumors (table 4). 6 patients with extensive in situ ductal carcinoma underwent SLNB, which was negative. With respect to the clinical utility of US-FNA, in our prospective series of 154 axillary assessments with US-FNA, SLNB was determined as the first therapeutic option in 108 axillae. Of these, US-FNA was positive in 51 (47.2%) axillae and the therapeutic approach was changed to AD, primary chemotherapy, or hormone therapy. AD was positive in all the cases.

From the total number of axillary ultrasounds performed in women with BC, 281 were candidates for SLNB as a first therapeutic option and 60 for AD, depending on the size of the primary tumor (> 3 cm). US-FNA allowed the detection of 51 cases of axillary metastasis among the 281 axillae candidates for SLNB, thus avoiding the performance of SLNB, which corresponds to a reduction of 18.1%.

Adverse Effects

No serious complications occurred during or immediately after the procedure, except for mild discomfort during puncture. All the patients were visited by the surgeon to collect the results of the US-FNA within a maximum of 1 week, and no complications were referred (hematoma, infection).

Discussion

Our study is one of the largest prospective series in the literature that preoperatively determines the presence of axillary lymph node metastasis in BC patients by US-FNA. Our results show a sensitivity of 77.5%, a specificity of 100%, and a PNV of 69.3%. This allows us to preoperatively select the group of patients in which SLNB can be avoided for the diagnosis of axillary metastasis. In a meta-analysis of 31 studies with US-guided needle biopsy (including FNA and CB), Houssami et al. [17] show a sensitivity of 79.6% and a specificity of 98.3%. Our series includes a total of 341 axillary ultrasound examinations, corresponding to 332 patients with localized BC as candidates for surgery. Of these, 281 were to undergo SLNB to determine the presence of axillary lymph node involvement. The per-

Table 4. Diagnostic accuracy of axillary US-FNA with final surgical results (SLNB/AD) according to the primary tumor size

	Tx		Tis		T1		T2		T3		T4	
Number of axillae	3		6		71		60		9		5	
Surgery	+	–	+	–	+	–	+	–	+	–	+	–
US-FNA +	3	0	0	0	27	0	36	0	8	0	5	0
US-FNA –	0	0	0	6	13	31	10	14	0	1	0	0
Total	3	0	0	6	40	31	46	14	8	1	5	0
Sensitivity, %	100 (29.2–100)		–		67.5 (50.9–81.4)		78.2 (63.6–89.0)		100 (63.1–100)		100 (47.8–100)	
Specificity, %	–		100 (54.1–100)		100 (88.7–100)		100 (76.8–100)		100 (25.0–100)		–	
PPV, %	100 (29.2–100)		–		100 (87.2–100)		100 (90.2–100)		100 (63.1–100)		100 (47.8–100)	
NPV, %	–		–		70.4 (54.8–83.2)		58.3 (36.6–77.9)		100 (25.0–100)		–	
Diagnostic accuracy, %	100 (29.2–100)		100 (54.1–100)		81.7 (70.7–89.9)		83.3 (71.5–91.7)		100 (66.4–100)		100 (47.8–100)	

Data correspond to the number of axillae. Data in brackets are the 95% CI.
PPV = Positive predictive value, NPV = negative predictive value.
pT was modified for patients on primary systemic therapy for whom the clinical tumor size was considered.

formance of US-FNA allowed the diagnosis of 51 cases of axillary metastasis, thus avoiding SLNB (18.1%). The percentage of avoiding SLNB reported in the meta-analysis of Houssami et al. [17] was 19.8%. In this regard, it should be noted that the meta-analysis concludes that the sensitivity and specificity of CB (4 studies) are slightly higher than those of FNA (24 studies), but this was not statistically significant.

The prevalence of axillary metastasis in patients with ultrasound axillary assessment (341 axillae) was 44.3%. Nevertheless, in the group of 154 axillae with US-FNA, the prevalence of axillary metastasis increased to 51.3%, while results published in the literature range between 21% and 63% [11, 13] and 47.2% in the meta-analysis [17]. The wide discrepancies observed in the results of US-FNA between different series may be due to several factors: procedures performed by different radiologists with different instruments [18–20]; the time spent on exploration [21]; the method used for cytological study [22]; the criteria used to define the degree of suspicion of lymph nodes [21]. Also, some studies are based on selected series (either non-consecutive subjects or consecutive subjects selected for the test) [17]. Finally, other factors include the criteria used for lymph node US-FNA, only for suspicious nodes [21] or in all visualized lymph nodes [1, 4].

Regarding the group of patients presenting lymph nodes with benign ultrasound features (n = 47), 10.6% (n = 5) of the metastases were detected by US-FNA. García-Ortega et al. refer 6.9% [19], Britton et al. 12% [23], and Koelliker et al. [24] 13%. All 5 patients had tumors between 13 and 25 mm and the primary therapeutic option was changed in all cases. Although the percentage of positivity in benign-looking lymph nodes is low, it is not negligible; we therefore suggest that US-FNA should be performed in all patients with visible lymph nodes.

The main cause of false-negative US-FNA results referred in the literature is due to the small size of the metastasis (between 25–60% of false-negatives) [11, 23, 25] or to the scarce number of metastatic lymph nodes [13]. In our study, out of the 75 axillary assessments with negative US-FNA, 23 showed lymph node metastasis in SNLB (false-negatives in cytology), and 4 of these corresponded to pN1mic (17.4%), 18 to pN1 (78.3%), and 1 to pN2 (4.3%). The ultrasound features of the lymph nodes were suspicious in 12 axillary studies (52.2%), and repetition of US-FNA should have been considered. Likewise, in 56.5% of the false-negatives, the primary tumor size was pT1, which suggests a correlation between tumor size and nodal involvement.

In this context, it is considered that US-FNA has no false-positives [1–3, 10]. The causes of false-positive results described in the literature are mainly due to an incorrect interpretation of the cell type obtained from the puncture or to the inadequate sampling of lymph nodes [11, 13, 26]. Likewise, the initial diagnosis of all positive cases was confirmed by a revision of the histopathology.

In our study, the final percentage of insufficient material was 3.9%. 11 of these were due to insufficient material, and a second puncture that resulted diagnostic was performed. The percentage of cases in the literature where insufficient material was obtained for diagnosis ranges between 1% and 30% [11, 24, 26–28]. The sensitivity of US-FNA increased with the size of the primary tumor, from 67.5% in T1 to 100% in T4 [1, 24, 29]. US-FNA may be more sensitive for the detection of lymph node metastasis in patients with larger tumors as metastatic nodes tend to be larger and a greater number of lymph nodes are affected. Yet, although sensitivity decreases in smaller tumors, a sensitivity of 67.5% is acceptable as over half of the patients included in this group will not have to undergo SLNB. In our study, the percentage of lymph node metastasis in T1 (56.3%) is relatively high compared to that reported in the literature. Thus, Ciatto et al. [26] yielded 33% of positive lymph nodes, Koelliker et al. 56% [24], and Garcia-Ortega et al. 27% [19].

Another advantage of US-FNA is that it allows identifying patients who are candidates for systemic primary treatment (in our

series 44.3% (35/79), and 23.1% in the series reported by Garcia-Ortega et al. [19]) and detecting axillary involvement by other tumors [19]. The total number of suspected BCs in our series included 1 lymphoma, 1 ovarian metastasis, and 6 melanomas.

A strength of our study is its prospective design with a consecutive series of patients treated at a hospital that centralizes the preoperative evaluation process and surgery of patients with suspicion of BC. Explorations were performed by 6 radiologists with 4–15 years of experience in breast imaging. A limitation of our study is that it is a single-center study with a possible bias related to external validity. Likewise, we were unable to perform a direct correlation between lymph nodes submitted to US-FNA and those obtained in axillary surgery (SLNB and/or AD). On the other hand, some patients with lymph nodes visualized by ultrasound did not undergo US-FNA due to protocol deviation.

Conclusion

The axillary study of patients affected with BC by US allows detecting involved lymph nodes in a high percentage of cases (50.8%). The US-FNA procedure is a well-tolerated, easy, fast, and reproducible technique that allows the diagnosis of metastasis in this area. This technique allows clinicians to modify the clinical approach and to avoid unnecessary procedures and morbidity. We suggest that this procedure should be addressed in BC management clinical protocols. Further multicenter studies should be conducted to assess the external validity of our results.

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Disclosure Statement

The authors declare that they have no conflict of interest.

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