

Published: May 31, 2023

Citation: Febles G, Dell'Acqua A, et al., 2023. Current Status of Ultrasonography and Fine-Needle Aspiration Cytology for the Management of the Axilla in Breast Cancer, Medical Research Archives, [online] 11(5). <https://doi.org/10.18103/mra.v11i5.3851>

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DOI
<https://doi.org/10.18103/mra.v11i5.3851>

ISSN: 2375-1924

RESEARCH ARTICLE

Current Status of Ultrasonography and Fine-Needle Aspiration Cytology for the Management of the Axilla in Breast Cancer

Gustavo Febles De León*, Andrés Dell'Acqua, Andrea Cristiani

*febles.gustavo@gmail.com

ABSTRACT

Objective: to analyze whether ultrasonography with fine-needle aspiration cytology of an axillary suspicious node, in patients with breast cancer, could help to differentiate between patients with low involvement of the axilla (up to 2 nodes with macrometastasis) of those with high involvement of the axilla (more than 2 lymph nodes with macrometastasis).

Material and methods: A total of 115 consecutive patients with breast cancer (up to 5 cm in diameter), with clinically negative axilla and pathologically positive axilla. All patients underwent preoperative axillary ultrasound and ultrasound-guided fine-needle aspiration cytology was performed in patients with suspicious nodes. In all patients with positive cytology, lymphadenectomy was performed. In all patients with negative ultrasound and cytology, sentinel lymph node biopsy was performed, and when it was positive, lymphadenectomy was performed. The number of pathological lymph nodes was evaluated after lymphadenectomy.

Results: A total of 61 patients had positive axillary ultrasound and cytology. In 42 of them (69%), there were more than 2 pathological lymph nodes. There were 54 patients with negative axillary ultrasound and cytology. In 49 of them (90%), there were only 1 or 2 pathological lymph nodes. Axillary ultrasound and fine-needle aspiration cytology were able to identify 42 of the 47 patients (89%) with more than 2 pathological lymph nodes.

Conclusion: ultrasound and ultrasound-guided fine-needle aspiration cytology was able to identify, in a preoperative stage, those patients with high axillary involvement (more than 2 lymph nodes with macrometastasis). The latter are the patients who would benefit from lymphadenectomy of the axilla, ignoring the sentinel lymph node biopsy stage.

Introduction

The management of the axilla in breast cancer has been a subject in constant evolution since the replacement of complete axillary dissection began with less aggressive alternatives. Various transformations have occurred both in the diagnostic approach and in the locoregional treatment of the axillary nodes, based on the results of successive international studies.

Currently, sentinel node biopsy (SNB) has been established as the standard technique for axillary staging in cases of clinically negative axillary breast cancer^{1,2}. However, it has been seen that the clinical examination has low precision and can be overcome with the incorporation of axillary ultrasound with the addition of techniques such as fine-needle aspiration cytology (FNAC) or core needle biopsy.

There is currently a consensus that an ultrasound scan of the axilla should be performed in all patients with breast cancer, and if a suspicious lymph node is detected, a puncture, either cytological or histological, should be performed. With this practice, greater precision is achieved in the selection of patients for SNB or axillary lymph node dissection (ALND).³⁻⁸

In this evolution regarding the concepts related to the management of the axilla in breast cancer, it is necessary to highlight the publication of study Z0011 by the American College of Surgeons Oncology Group (ACOSOG) in 2011.⁹

The study analyzed patients with T1 and T2 tumors, clinically negative axilla and SNB with a result of up to 2 nodes with macrometastases, treated with conservative surgery and whole-breast radiotherapy. The results indicated that in this group of patients ALND of the axilla would not generate a benefit in terms of overall survival and locoregional recurrence.

This study was updated with the same conclusions in April 2016 at the annual meeting of the American Surgical Association, with an average follow-up time of 9 years.¹⁰

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial has changed clinical practice in many patients with positive sentinel nodes, saving them from ALND, but the ultrasound and the cytology were not part of the study.

This trend towards axillary surgery reserved only for cases involving more than 2 sentinel nodes with macrometastases, forces us to redefine the role of ultrasound with FNAC of the suspicious nodes.

The question arises as to whether this technique makes it possible to identify, in a pre-surgical stage, those cases that would benefit from an ALND, due to having more extensive involvement of the lymph

nodes in that region, in patients with T1 and T2 tumors and clinically negative axilla.

The objective of this work is, then, to analyze whether ultrasonography with FNAC of an axillary suspicious node, in patients with breast cancer and clinically negative axilla, could help to differentiate between patients with low involvement of the axilla (up to 2 nodes with macrometastasis) of those with high involvement of the axilla (more than 2 lymph nodes with macrometastasis). The latter are the patients who would benefit from ALND, ignoring the SNB.

Material and methods

Retrospectively, 115 consecutive cases of patients with breast cancer up to 5cm in diameter, with clinically negative axilla, were analyzed, in which the presence of metastatic lymph nodes was finally confirmed in the surgical specimen.

The data were obtained from patients diagnosed and treated at the Breast Diagnosis and Treatment Center of the Spanish Association (Montevideo - Uruguay).

In all cases, the axilla ipsilateral to the cancer was explored by ultrasound. A General Electric brand ultrasound machine, Logiq P5 model, with a 10 MHz linear transducer was used.

Axillary nodes were considered suspicious on ultrasound when they presented focal or diffuse cortical thickening greater than 3 mm.

In cases with lymph nodes with a suspicious appearance on ultrasound, FNAC was performed on one of them, with a 21-gauge needle, taking samples from the pathological area of the lymph node. Samples were spread on a glass slide and allowed to air dry. The cytologist evaluated the sufficiency of the samples at the time of puncture. The May Grünwald Giemsa staining technique was used.

In the patients in whom the cytology was positive, ALND was performed directly, without previously performing the SNB. In patients in whom no suspicious lymph node was detected, or when cytology was negative, SNB was performed.

When the result of this SNB showed the presence of macrometastasis, ALND was performed.

For the pathological study of resected lymph nodes, a careful dissection of them was carried out and all were embedded in paraffin. The largest nodes they were hemisectioned and, if commitment was observed grossly evident, a representative fragment was entered in relation to the capsule. Serial cuts were made who were stained with hematoxylin-eosin.

The number of pathological nodes resulting from ALND was compared between the two groups of

patients: those with positive axillary ultrasound and cytology and those with negative ultrasound and cytology but positive SNB. The SPSS software version 12.0 and the EPIDAT version 3.1 were used to carry out the calculations. The chi-square test of association and Fisher's exact test were applied.

Results

The mean age of the included patients was 59 years (range 31 to 85). The histological characteristics of all the cases included in the series can be seen in table 1.

Histology	Cases	%
IDC	61	53
IDC/ DCIS	34	30
ILC	20	17
Total	115	100

IDC: infiltrating ductal carcinoma; DCIS: ductal carcinoma in situ; ILC: infiltrating lobular carcinoma.

The result of the pathological study of the resected lymph nodes in the 115 patients included in the series can be seen in table 2.

Number of pathological nodes	Cases	%
1	48	42
2	20	17
More than 2	47	41

Of the 115 patients with breast cancer and pathologically positive axilla included in the series, 61 had positive axillary ultrasound/cytology (53%), while 54 had negative axillary ultrasound/cytology (47%). Of the 61 patients with positive ultrasound/cytology, in 42 cases (69%) had more than two

pathological lymph nodes according to the result of the final pathological anatomy, while in the group of 54 patients with negative ultrasound/cytology, only in 5 cases (9%) had more than 2 pathological nodes (Table 3). The difference between both groups was statistically significant ($p = 0.00001$).

Number of pathological nodes	FNAC + (%)	FNAC – (%)
1	10 (16)	38 (70)
2	9 (15)	11 (20)
More than 2	42 (69)	5 (9)

FNAC: fine-needle aspiration cytology

In the group of patients with positive ultrasound/cytology the mean number of metastatic nodes was 5.3, while in the group with negative ultrasound/cytology this value was 1.6. Considering all the patients included in the series, axillary ultrasound and cytology of suspicious lymph nodes were able to identify 42 of the 47 cases (89%) with more than 2 pathological lymph

nodes. The sensitivity of the technique was 89%; specificity, 72%; positive predictive value, 69%; and negative predictive value 91%.

Discussion

The importance of preoperatively detecting nodal metastasis has emerged as an active debate, especially in the context of a decreasing role for ALND.

Current debate questions whether there is a benefit to diagnosing metastasis with ultrasound-guided needle biopsy as this may lead to more axillary node dissections in an era of its decreasing role.¹¹ In general, most studies show that ultrasound-guided needle biopsy is able to identify those patients with high metastatic nodal burden, which would make them ineligible for Z0011 management.

However, there were some opinions contrary to this interpretation of the issue, coming from the working group of the Memorial Sloan Kettering Cancer Center.

In 2016, Pilewskie et al. published a study whose objective was to determine whether abnormal ultrasound images of the axilla were an indicator of the need to perform ALND in a series of patients who met the clinical selection criteria for the ACOSOG Z0011.¹²

In this work, 425 patients with clinically negative axillary breast cancer up to 5 cm in diameter were included. All underwent SNB and ALND was performed in cases with more than two sentinel nodes with metastases. In cases with two or less than two metastatic sentinel nodes, it was not performed. Subsequently, the axillary images of the patients in both groups were retrospectively analysed. It was observed that 71% of the patients with abnormal axillary images were in the group that did not require ALND. The conclusion was that abnormal preoperative axillary images are not a reliable indicator of the need for ALND.

However, it is a study with multiple methodological limitations, recognized by the authors themselves. Images were not available for all patients. In the cases in which images were available, in several cases these were studies that had not been specifically carried out to evaluate the axilla. Axillary ultrasound was not used in all patients. The physicians who analyzed the studies were aware that they were patients with pathologically positive axillary breast cancer. Puncture was performed only in 18 cases with abnormal images in the axillary nodes and it is not specified what method was used.

This same work was cited by Dr. Morrow in a communication to update the subject, addressed to health professionals, but does not refer to the methodological limitations mentioned above.^{13,14}

These controversies should not detract from the validity of the axillary ultrasound method with preoperative puncture, in patients with breast cancer, even with clinically negative axilla. The evidence indicates that the method is able to identify with good precision the patients with more than 2 pathological nodes, which are those who would benefit from ALND.

Most studies have focused primarily on the ability of ultrasonography with cytology to detect axillary disease, which is no longer disputed. Some studies, on the other hand, evaluate the tumor load in the axilla by comparing two groups of patients: those with metastases lymph nodes in the axilla detected by ultrasound and cytology preoperative, with those with nodal metastases detected by SLNB (with negative ultrasound and cytology).

Evaluating the tumor load in the axilla to help make decisions would be the current role of ultrasound with axillary cytology.

Caudle et al. published a study in which a group of 190 patients with breast cancer with lymph node metastases in the axilla detected by ultrasound and preoperative cytology were compared with a group of 518 patients with axillary metastases detected by SLNB. In the echo/FNAC group there were more pathological nodes than in the SLNB group (mean 4.1 versus 2.2; $p = 0.0001$). More than 2 pathological nodes were detected in 48% of the patients in the echo/FNAC group, compared with 19% in the SNB group.¹⁵

Farrel et al. compared 169 patients with axillary metastases detected by echo/FNAC with 127 patients with axillary metastases detected by SLNB. In the echo/FNAC group there was a mean of 7.3 pathological nodes, while the mean was 2.2 in the SLNB group.¹⁶

Boone et al. compared 199 patients with axillary metastases detected by echo/FNAC with 434 patients with axillary metastases detected by SLNB. The average number of pathological nodes in the positive echo/FNA group was 5.7 and in the SLNB positive group was 2.5. Also, in the eco/ FNAC group positive, there was a higher incidence of axillary stage N2 (33.2 vs.12.4%) and N3 (17.1 vs. 3.9%).¹⁷

In the study by Van Wely et al., in patients with positive echo/FNAC, the mean number of pathological nodes was 4 (1 to 30). In patients with positive SLNB, the mean number of pathological nodes was 2 (1 to 38). They conclude that patients with positive echo/FNAC have significantly more pathological lymph nodes than patients with positive SLNB (in whom axillary ultrasound and puncture had been negative).¹⁸

Verheuel et al. compared 139 patients with axillary metastases detected by echo/FNAC with 163 patients with axillary metastases detected by SLNB. The mean of pathological lymph nodes in the group with positive echo/FNA it was 4, while it was 1 in the group with positive SLNB. Also in the group with a positive echo/FNAC, the free survival of disease at 5 years was lower in relation to the other group (72.6 vs. 87.7%).¹⁹

Del Riego et al. evaluated the efficacy of ultrasound axillary and preoperative FNAC, to detect patients with breast cancer and more than two metastatic nodes, in 288 patients who met the selection criterion of ACOSOG Z0011.²⁰

The results were as follows: sensitivity 83%, specificity 80.6%, positive predictive value 45.4%, negative predictive value 96.1%.

Buzzato et al. in 2021 published a study that evaluated if axillary ultrasound coupled with FNAC can accurately predict clinically relevant node metastasis in patients with breast cancer, and thus assist clinical decisions. This study included 241 individuals with unilateral operable breast cancer who were submitted to preoperative axillary assessment by physical exam, US and FNAC if suspicious nodes by imaging. Only 2.7% of the patients with normal axillary US had more than 2 metastatic nodes in the axillary lymph node dissection, against 57% of the patients with suspicious lymph nodes in the US and positive FNAC. They concluded that axillary US coupled with FNAC can sort patients who have a few metastatic nodes at most from those with heavy axillary burden.²¹

Hieken et al. found that patients with a suspicious ultrasound and positive needle biopsy often had more than two positive axillary nodes, larger nodal metastasis, and a higher presence of extranodal extension compared with those having a negative needle biopsy.²²

The results of our work coincide with the previously mentioned articles, since in our series the average number of pathological nodes was 5.3 in the group with positive echo/FNAC and 1.6 in the group with negative echo/FNAC. Also, we have observed that in the group of patients with positive ultrasound and cytology, in 69% of the cases there were more than two metastatic lymph nodes, while in the group of patients with negative ultrasound and cytology, this occurred only in 9 % of the cases. The technique made it possible to detect 42 of the 47 cases that would benefit from ALNB, ignoring SLNB

This information is useful in decision-making in relation to surgical conduct in the axilla, and we believe that it is still valid with the advancement of new trends towards increasingly restrictive axillary surgery.

The absence of neoplastic cells on FNAC in ultrasound suspicious nodes did not exclude completely a malignant node. In our study, we had 54/115 (47%) patients with metastatic nodes in the surgical specimen that had a false-negative FNAC result. This situation does not limit the value of axillary ultrasound and cytology for staging of the

axilla. We affirm this since in 81% of the cases that turned out to be false negatives of the echo/FNAC there were no more than 2 involved nodes in the surgical specimen. In all these cases, SLNB would have been the procedure of choice. In other words, the negativity of the echo/FNAC continues to be an indicator of low tumor involvement in the axilla.

Finally, although it is not the objective of this work, it is necessary to mention that ultrasound with cytology of a suspicious lymph node helps to improve the accuracy of SLNB after neoadjuvant chemotherapy in node-positive breast cancer. Preoperative chemotherapy can convert node-positive disease to pathologic complete response (pCR) in 40-60% of cases, making the role of ALND controversial. Removal of the clipped metastatic node at the same time as the SLNB (termed "targeted axillary dissection") further improves the false-negative rate of the procedure.

Within the limitations of our work, it can be pointed out that we should incorporate a greater number of cases to support our concepts, that we have not quantified by ultrasound the number of lymph nodes of pathological and that in all cases a single puncture is ganglion. No relationship was established between the number of sonographically suspicious nodes and the number of resected metastatic nodes.

Conclusion

The evidence indicates that in patients with breast cancer and clinically negative axilla, axillary ultrasound with FNAC of suspicious lymph nodes plays an important role in assessing tumor burden in the axilla.

Patients with suspicious ultrasound and positive FNAC were more likely to have a higher disease burden than those with positive sentinel nodes alone and therefore represent a distinct patient population that should be addressed carefully.

This technique makes it possible to accurately identify those patients with high involvement of the axilla (more than 2 lymph nodes with macrometastases), who would benefit from ALND. Even in patients with clinically negative axillary breast cancer, in order to make the decision to ignore the ALND, it is necessary that an axillary ultrasound was performed in the preoperative stage and that the FNA of a suspicious lymph node be negative.

Conflict of interests.

The authors declare that there is no conflict of interest.

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