The impact of preoperative axillary ultrasonography in T1 breast tumors

Poster No.: C-0474
Congress: ECR 2015
Type: Scientific Exhibit
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Keywords: Breast, Lymph nodes, Oncology, Ultrasound, Biopsy, Metastases
DOI: 10.1594/ecr2015/C-0474

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Aims and objectives

Sentinel node biopsy (SNB) has replaced axillary lymph node dissection (ALND) as the method of choice for preoperative axillary staging in patients with clinically negative axillae (cN0)(1). Tumors with negative SNB do not require ALND. SNB results in less morbidity and ALND in these cases does not improve survival (2, 3).

Preoperative axillary ultrasonography (AUS) together with US-guided needle biopsy (UNB), is the method of choice for detecting axillary involvement; when this approach detects axillary involvement, patients undergo ALND without the need for SNB (4). ALND is no longer considered necessary for axillary micrometastases (Nmic) (5), so the practical impact of US increases since micrometastases need not be considered "N positive".

Many studies suggest it may be beneficial to omit ALND in selected patients with positive SNB (3, 6, 7). The prospective multicenter American College of Surgeons Oncology Group (ACOSOG) Z0011 trial randomized SNB-positive patients (1-2 lymph nodes with macrometastases) classified as cT1-T2, cN0, treated with breast-conserving surgery (BCS) and whole-breast radiotherapy (WBRT), to receive ALND vs SLN-only (6, 7). The study found no significant differences in survival or disease-free survival between the two groups, and the authors concluded that ALND was therefore not justified (7). These results have been incorporated into clinical practice, and ALND is avoided in patients who fulfill the ACOSOG Z0011 criteria (8). Consequently, the role of AUS in axillary staging needs to be redefined (9).

In this context, several questions arise: What is the future of SNB? Can an imaging technique predict and select cases with low likelihood of axillary involvement that would not benefit from ALND? With these questions in mind, we aimed to determine whether preoperative AUS can identify patients with limited axillary involvement that could forgo both SNB and ALND.

Our objectives were (a) to estimate the diagnostic validity of AUS in pT1 tumors and to determine whether adding FNA improves the diagnostic performance of the technique, and (b) to assess the negative predictive value (NPV) of AUS in a simulation environment, taking a cutoff of two lymph nodes with macrometastases in patients who fulfill the ACOSOG Z0011 criteria.
Methods and materials

Patients

This was a multicenter, retrospective, cross-sectional study of 873 consecutive histologically diagnosed breast cancers at six public hospitals in Spain in the period comprising March 2010 through August 2011. Fig. 2 on page 7

The study consisted of two substudies:

1- Diagnostic validation of AUS and of AUS plus FNA in pT1 tumors.
2- Diagnostic validation of AUS in a simulation environment for cases that fulfilled the ACOSOG Z0011 criteria except positive SNB (pT1 + BCS + WBRT + nonpalpable lymph nodes).

For both studies, patients were classified in function of the size of the tumor measured at histology (pT) and only pT1 tumors were included in the analyses.

To calculate the diagnostic validity of AUS and AUS plus FNA, we excluded cases in which the histologic status of the axillary lymph nodes was not confirmed (no gold standard), cases in which patients underwent neoadjuvant chemotherapy (NCT), and cases occurring during pregnancy or lactation. For the simulation environment, in addition to patients fulfilling the exclusion criteria above, we excluded those that underwent mastectomy, those that did not undergo WBRT after BCS, and those with palpable lymph nodes.

873 breast cancers were diagnosed at the six centers; 395 (45.2%) of these were classified as T1(pT1) at histology. A total of 40 (10.1%) were excluded: 7 for lack of confirmation about patients' lymph node status (no gold standard) and 33 because the patients underwent neoadjuvant chemotherapy (ypT1). None of the cases occurred during pregnancy or lactation.

The analyses included only cases studied by AUS for which gold-standard data were available (n=355); in 55 (15.5%) cases, FNA was not done, so 300 (84.5%) underwent AUS plus FNA.

The flowchart in Fig. 3 on page 7 shows the patients and data included in the first substudy and in Fig. 4 on page 8 is the flowchart of the second substudy.
Image Acquisition and Analysis

US studies were done by experienced radiologists (4 y - 25 y) dedicated to women's imaging using high frequency (8 MHz - 15 MHz) transducers with various US scanners. US studies examined the axilla ipsilateral to the tumor craniocaudally, reviewing Berg levels I, II, and III.

We classified lymph nodes according to the morphologic criteria proposed by Bedi (10):

1- Negative AUS: a - No visible node; b - "Nonspecific" node: hyperechoic hilum with either no cortex visible or a uniform cortex < 3mm thick (Bedi 1 and 2) (10). 2- Positive AUS: a- diffuse cortical thickening > 3mm; b- generalized cortical lobulation; c- focal cortical lobulation; d- hypoechochogenic node without a fatty hilum (Bedi 3-6)(10).

Pathology Techniques

FNA was done with standard 21G or 22G needles. Smears were air dried and stained with May-Grünwal-Giemsa stain, and liquid-based cell preparations were stained with Papanicolaou stain.

In SNB, the radiotracer (99mTc) was injected into or around the tumor under US guidance. When there was no migration to regional nodes, a second intratumoral or peritumoral injection or a subcutaneous periareolar injection was administered. ALND was done in all cases when no migration was seen after two injections.

At one center, SNBs were processed by one-step nucleic acid amplification (OSNA), with the following cutoffs: macrometastases (> 5 x 103 copies of mRNA/ml), micrometastases (between 2.5 x 102 and 5 x 103 copies of mRNA/ml), and the absence of metastasis (< 2.5 x 102 copies of mRNA/ml).

At the other centers, SNB specimens were frozen intraoperatively and later sectioned (maximum thickness, 3mm) at different levels and stained with hematoxylin and eosin (H&E) stain. In uncertain cases, the study was completed with immunohistochemical techniques for AE1/AE3, CK 7, and CK19. In H&E-stained specimens, we used the following cutoffs: for macrometastases, diameter ≥ 2 mm; for micrometastases, diameter between 0.2mm and 2mm or > 200 tumor cells in a single tissue section; and for isolated
tumor cells, diameter #0.2 mm or < 200 tumor cells in a single tissue section. The finding of isolated tumor cells (N0+) was considered pN0.

Axillary Management

FNA was done when at least one axillary lymph node was visible, regardless of the US appearance of the node. When more than one suspicious node was present, FNA targeted the node with the greatest number of suspicious morphological characteristics; when no node had more suspicious morphological characteristics than the others, FNA was done on the most accessible node.

When FNA was negative or provided insufficient material for diagnosis, SNB was performed. ALND was done when: FNA was positive, when SNB was positive, and when FNA was negative and there was no migration to regional nodes on SNB.

We compiled the following information for each case: demographics, date of diagnosis, histologic type and grade, tumor phenotype (according to Cheang et al. (11), bilaterality, axillary palpation, US appearance of the axillary node, morphological sign, FNA findings, SNB findings, number of nodes studied by SNB, number of metastatic nodes on SNB, ALND findings, number of nodes studied on ALND, number of metastatic nodes in ALND, pT, pN, M, surgical treatment, SAT, WBRT, local recurrence, axillary recurrence, remote recurrence, and date of last follow-up.

Statistical Analysis

We did a descriptive analysis of the main variables in the two series of tumors analyzed in the two substudies.

SNB and ALND were considered gold standards.

To calculate the diagnostic accuracy of AUS plus FNA, we classified cases in which one or both of the techniques was positive as "positive" and cases in which both techniques were negative as "negative". Cases in which FNA yielded insufficient material for diagnosis were considered "FNA negative", as these patients then underwent SNB.
In the first substudy, we calculated the diagnostic performance of AUS and of AUS plus FNA separately in the patients who underwent FNA. We also determined the diagnostic validity considering cases with only micrometastases to be 'N negative'.

In the second substudy in patients fulfilling ACOSOG Z0011 criteria except positive SNB, we used a cutoff of more than two lymph nodes involved by macrometastases.

For all the cases analyzed, we estimated the sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and diagnostic accuracy, together with their respective 95% confidence intervals (95% CI).

We calculated the PPV (95% CI) of US for predicting pN2 and pN3 metastatic axillary disease.
Fig. 2

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Fig. 3: Flow diagram for the entire series. NVLN: Nonvisible lymph node; NGS: Non-Gold-Standard; NCT: neoadjuvant chemotherapy.

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Fig. 4: Flow diagram for the ACOSOG Z0011 simulation series. BCS: breast conserving surgery; WBRT: whole-breast radiotherapy, NPLN: nonpalpable lymph node.

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Results

Substudy for the diagnostic validation of AUS and of AUS plus FNA

Table 1 on page 12 reports the descriptive demographics, tumor characteristics, and treatment in the populations of the two substudies.

Axillary metastases (pNmic-pN3) were found in 81 (22.8%) cases, being micrometastases in 30 (37.0%) of these.

Table 2 on page 12 shows the diagnostic accuracy of AUS in the entire series and of AUS and AUS plus FNA in the patients who underwent FNA. Separate analyses were done considering pNmic "N positive" and "N negative".

In the 11 (3.1%) cases with pN2-pN3 axillary involvement, AUS was positive in 10, with a 90.9% (95%CI: 73.9-100) PPV.

Of the 355 AUS studies, 294 (82.8%) were negative; the false-negative rate was 14.6% (43 studies, of which 26 (60.5%) were due to micrometastases). In 43 (12.1%) AUS studies, no nodes were seen; 5 of these cases had metastatic involvement (4 with micrometastases). A total of 61 (17.2%) AUS studies were positive; 38 (62.2%) of these cases had axillary involvement, which was due to micrometastases in 4 (10.5%) cases.

In the 300 cases studied by FNA, AUS was negative in 239 (80%); only 2 (0.8%) of these were positive at FNA. AUS plus FNA detected metastatic axillary involvement in 26/300 (8.6%) cases, these 26 cases represent 32% (26/81) of all cases with metastatic axillary involvement. These patients underwent ALND without undergoing SNB. There were no false-positive FNA findings. When pNmic was considered "N positive", FNA's false-negative rate was 18.2% (50/274), and when pNmic was considered "N negative", it was 12.0% (33/274).

Table 3 on page 13 reports the analysis of the predictive values of the morphological characteristics of the lymph nodes (Bedi) and their 95% CI, both considering pNmic as "N positive" and as "N negative". As reported in other studies (12-16), the morphological characteristic with the highest PPV for metastatic lymph node involvement was the absence of a fatty hilum: 100% of the nodes with this characteristic had metastases, both in the analysis that considered pNmic negative and in the one that considered pNmic positive.
Table 4 on page 14 shows the results of the study for the diagnostic validation of AUS according to tumor phenotype with their respective 95% CI, both considering pNmic as "N positive" and as "N negative".

SNB was done in 314 (88.4%) cases; the median number of lymph nodes resected was 1 (range: 1-5). A total of 53 (16.8%) were positive; among these, ALND was done in 41 (77.3%) and ALND was not done in 12 (22.6%). Only 3 (1.1%) of the patients with negative SNB underwent ALND; all were pN0. Moreover, ALND was done in 8 (2.5%) cases in which the radiotracer did not migrate and was negative in all.

ALND was done in 93 (26.2%) patients; the median number of lymph nodes resected was 16 (range: 5-42). A total of 69 (74.2%) had metastatic axillary involvement, being pNmic in 20 (28.9%).

During a mean follow-up of 32 months, 4 (1.1%) cases had local recurrence and only 1 (0.3%) had axillary recurrence. There were no cases of distant recurrence.

Six patients died, but only one (the only patient with axillary recurrence) died of breast cancer.

Fig. 5 on page 16 shows the clinical management of the cases in the series.

Substudy for the Diagnostic validation of AUS in a simulation environment for cases that fulfilled the ACOSOG Z0011 criteria except positive SNB

Of the 355 cases, a total of 67 (18.9%) cases were excluded: 54 (15.2%) because patients underwent mastectomy, 8 (2.6%) because patients did not undergo WBRT, and 5 (1.6%) because patients had palpable lymph nodes. Thus, 288 cases were included; all of these had AUS, BCS, WBRT, and negative axillary palpation; moreover, 286/293 (99.3%) were treated with systemic adjuvant therapy.

Table 5 on page 15 shows the diagnostic accuracy of AUS using a cutoff of more than two lymph nodes with macrometastases.
### Table 1: Demographics, histologic findings, and treatment for the patients in the two substudies. There were no significant differences between the two populations.

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Table 2: When Nmic is considered "N negative", the practical impact of AUS increases. Performing FNA in all visible nodes brought no added benefit to axillary management.

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Table 3: The absence of a fatty hilum was the US sign with the highest positive predictive value for metastatic involvement: 100% regardless of whether pNmic was considered negative or positive.
**Table 4:** The sensitivity for the Her2+ phenotype was 100%, but the small sample (n=11) precludes conclusions.

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Table 5: The high negative predictive value made it possible to identify cases that would not benefit from surgical axillary staging (axillary lymph node dissection or sentinel node biopsy).

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Fig. 5: Clinical management for the entire series.

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Conclusion

In our series, AUS alone had 46.9% sensitivity and 91.6% specificity. The sensitivity in our series was lower than in other series (16) because our series consisted of consecutive tumors rather than selected cases, and our patients had smaller tumors (<20mm) and a low prevalence of axillary metastases (22.8%). Nevertheless, the sensitivity in our series was higher than that found in Diepstraten et al.'s meta-analysis where the sensitivity of AUS plus biopsy for studies with <40% prevalence was only 38% (15).

ALND is no longer considered necessary for micrometastases (5). This change in management allows us to consider pNmic equivalent to "N negative", which increases AUS's rate of true negatives and thus its impact in clinical decision making. In our study considering pNmic to be "N negative" increased the sensitivity of AUS from 46.9% to 66.7% without affecting specificity.

In our study, AUS plus FNA obviated the need for SNB in 26/300 (8.6%) cases. This percentage is lower than in Houssami et al.'s meta-analysis (4), in which needle biopsy (core biopsy or FNA) obviated the need for SNB in 13.8% of tumors; this discrepancy might be explained by the low prevalence of axillary involvement in our series.

In the cases with nodes suspicious at AUS, FNA not only increases the sensitivity of AUS, but it also increases its specificity to nearly 100% (4, 15, 16). By contrast, when done on all visible nodes, FNA increased the sensitivity compared to AUS alone only slightly and did not affect the specificity, both whether Nmic was considered "negative" or "positive".

After ACOSOG Z0011, the role of AUS plus biopsy has become controversial. It is no longer enough to know whether metastatic axillary involvement is present: now we need to be able to quantify the axillary load.

Various guidelines recommend that when AUS plus biopsy confirms axillary involvement, ALND should be done (1, 4). Although we know that patients with negative AUS findings have a lower axillary metastatic load (15), positive findings at AUS do not allow us to discriminate patients with only one or two lymph nodes with macrometastases from patients with greater loads. Caudle et al. (9) reported that 45% of cases in which AUS studies identified < 2 suspicious nodes had # 3 positives at ALND. In our series, 18% of the positive AUS studies had > 2 nodes with macrometastases, whereas only 0.7% of the negative studies had > 2 macrometastes at gold-standard.

In Diepstraten et al.'s meta-analysis (15), the false-negative rate for both AUS alone and AUS plus needle biopsy was 25%. In our series, the false-negative rate for AUS alone
was 14.6% when we considered Nmic "N positive"; 60.4% of the false-negatives were due to micrometastases, so when we considered Nmic "N negative", the false-negative rate was only 5.7%. Furthermore, the reported NPV of AUS ranges from 58% to 84% (mean, 67.4%) (4, 16). However, the NPV of AUS in our series was 85.3% when Nmic was considered "N positive" and 94.2% when Nmic was considered "N negative".

When we analyze the diagnostic accuracy of AUS in our series using a cutoff of >2 nodes with macrometastases in patients fulfilling ACOSOG Z0011 criteria, the implications are different. In these patients, the sensitivity of AUS is 75.0%, the specificity is 88.9%, and the NPV is 99.2%. This means that when AUS is "negative" only 0.8% of the cases have more than two nodes with macrometastases. These data are similar to those reported by Moorman et al. (17), who analyzed a retrospective series of 1060 T1-T2 tumors with negative axillary palpation studied by AUS. Of the 879 cases with negative findings at AUS, only 4.2% of the cT1-T2 tumors and only 2.2% of the pT1-T2 tumors had more than two nodes with macrometastases. If only T1 tumors are analyzed, these values decrease to 0.96% (NPV 99%) in cT1 tumors and to 0.87% (NPV 99.1%) in pT1.

Given these results, negative findings at AUS in patients with T1 tumors who are candidates for tumorectomy, chemotherapy, and radiotherapy would make it possible to select cases with a low axillary metastatic load that would reap no additional benefits from surgical staging (including SNB). However, more studies with more cases would be necessary to determine the potential impact of this approach on locoregional outcome and survival.

Our study has several limitations. AUS is operator dependent and findings can also vary among institutions. Moreover, our series had a somewhat larger percentage (12.1%) of nodes that could not be viewed than in other series (14). Likewise, the percentage of FNA that obtained insufficient material for diagnosis (10.3%) was higher than the mean percentage among the studies included in Houssami et al.'s (16) meta-analysis (4.1%); these FNA studies were considered "negative" and patients underwent SNB, leading to an underestimation of the sensitivity of AUS plus FNA.

In conclusion, AUS has moderate sensitivity in T1 tumors. As ALND is not necessary in cases with micrometastases, not having to consider micrometastases "N positive" increases the practical impact of AUS.

It is not necessary to do FNA in all visible nodes, because the contribution of this approach to the diagnostic accuracy of AUS is scant.

In our series of patients who fulfilled the ACOSOG Z0011 criteria, AUS alone was able to predict the cases that would not benefit from ALND.
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