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The impact of axillary ultrasound with biopsy in overtreatment of early breast cancer

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ABSTRACT

Purpose: (a) To compare the axillary tumor burden detected by fine-needle aspiration cytology (FNAC) versus sentinel lymph node biopsy (SLNB). (b) To evaluate the relationship between axillary tumor burden and the number of suspicious lymph nodes detected by axillary ultrasonography (US). (c) To calculate the false-positive and false-negative rates for FNAC in patients fulfilling ACOSOG Z0011 criteria.
Methods: Retrospective multicenter cross-sectional study of 355 pT1 breast cancers. SLNB and axillary lymph node dissection (ALND) were gold standards. Low axillary burden (≤2 positive lymph nodes); high burden (> 2 positive lymph nodes). Patients ACOSOG Z0011: false-positive (positive FNAC + low burden), false-negative (negative FNAC + high burden).
Results: High axillary burden: in entire series 38.5% FNAC+ vs. 5.7% SLNB+ ($p < 0.0001$). In subgroup fulfilling ACOSOG Z0011 criteria: 45.5% vs 6.7%, respectively ($p < 0.001$).

61 positive axillary US. With 1 suspicious node on axillary US: 95.6% had ≤2 involved nodes (including pN0); with 2 suspicious nodes: 60% had > 2 involved nodes. In ACOSOG Z0011 patients, with 1 suspicious node, 93.7% had ≤2 involved nodes. Of the 37 FNAC in ACOSOG Z0011patients: 54.5% false-positives for high burden; 3.8% false-negatives.
Conclusions: FNAC-positive tumors have greater axillary burden, even in patients fulfilling ACOSOG Z0011 criteria. Using axillary US/FNAC to triage patients meeting Z0011 criteria may result in axillary overtreatment. The number of suspicious nodes seen in axillary US is related with the final axillary burden and should be taken into account when deciding to do FNAC in patients fulfilling ACOSOG Z0011 criteria.

1. Introduction

Axillary stage is a prognostic factor in breast cancer [1,2]. For many years, axillary lymph node dissection (ALND) was the standard treatment to check for metastatic axillary disease [3]. Sentinel lymph node biopsy (SLNB) has become the technique of choice for axillary staging, replacing ALND in patients with clinically negative axillae [4]. Because the prevalence of axillary involvement and axillary recurrence in tumors with negative SLNB findings are low, patients can forgo ALND, reducing morbidity without affecting survival [5]. Moreover, in 40% to 65% of cases with positive SLNB findings, the sentinel node is the only lymph node involved, and ALND is not necessary in these cases either

Abbreviations: ALND, axillary lymph node dissection; US, ultrasonography; UNB, US-guided needle biopsy; FNAC, fine-needle aspiration cytology; SLNB, sentinel lymph node biopsy

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[6]. The role of ALND among lymph node positive patients continues to evolve.

Many studies provide evidence of the benefits of omitting ALND in selected patients with positive SLNB findings [7,8]. In cases where SLNB is positive for micrometastases (pNmi), ALND increases morbidity without improving survival [9]. The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial, a prospective multicenter study, randomized patients classified as cT1-T2, cN0 with positive SLNB (1–2 tumor-involved lymph nodes with either micro or macrometastatic disease) treated with breast conserving surgery (BCS) and whole-breast radiotherapy (WBRT) to receive ALND vs SLNB only [10,11]. Finding no significant differences in overall or disease-free survival, the authors concluded that ALND is not justified in this group of patients [10,11]. This trial has had a significant impact on clinical practice [12], but it did not consider the use of axillary ultrasonography (US). Thus, the usefulness of US in these patients must be reassessed.

The sensitivity and specificity of axillary US is moderate when the technique is used alone, but increases considerably when combined with US-guided needle biopsy (UNB), especially in patients with larger tumors and greater axillary involvement [13,14]. Combined axillary US/UNB is the preoperative study of choice to identify patients with axillary involvement, who could undergo ALND directly, obviating the need for SLNB [15]. This approach seems clear in patients who do not meet the ACOSOG Z0011 criteria [16], but the role of axillary US/UNB is controversial in patients who meet the criteria.

Axillary US/UNB promises to be useful in patients meeting the ACOSOG Z0011 criteria provided it could accurately identify patients with heavy axillary burden who would benefit from ALND.

On the one hand, it enables differentiation between tumors with low axillary burden (many of which would not benefit from surgical staging including SLNB) and those with high axillary burden, which should be directly treated with ALND [6,17]. On the other hand, tumors in patients with axillary disease detected by UNB have a worse prognosis, with a greater axillary burden [18,19]. Some authors consider that the ACOSOG Z0011 criteria would not apply to these tumors [19]. It remains to be determined whether all patients with UNB-positive tumors would benefit from ALND. If the answer is no, then doing UNB in all patients who meet the ACOSOG Z0011 criteria who have positive findings on axillary US could result in overtreatment by indicating ALND when it does not benefit the patient. The key question is whether axillary US can identify which patients would benefit from UNB and which would not.

We aimed to compare the axillary tumor burden detected by positive fine-needle aspiration cytology (FNAC) versus positive SLNB, to analyze the relationship between axillary tumor burden and the number of suspicious lymph nodes seen on axillary US, and to calculate the false-positive and false-negative rates for FNAC in patients who meet the ACOSOG Z0011 criteria.

2. Material and methods

2.1. Patients

This retrospective cross-sectional study included consecutive patients with histologically confirmed breast cancer attended at six public hospitals in Spain between March 2010 and August 2011. The ethics committees at each institution approved the study and waived the requirement for informed consent due to the retrospective nature of the study.

Cases were classified according to tumor size on pathology study (pT); only cases with pT1 were analyzed.

The current study comprises three substudies with the following specific aims:

1. To compare the final axillary burden, defined as the number of affected lymph nodes detected in the histologic study (SLNB + ALND), detected by positive FNAC versus positive SLNB.
2. To analyze the relationship between the number of suspicious lymph nodes identified on axillary US and the final axillary burden.
3. To calculate the percentage of false-positive and false-negative FNAC findings in patients meeting the ACOSOG Z0011 criteria (pT1 + cN0 + BCS + WBRT) using a cutoff of > 2 tumor-involved lymph nodes.

2.2. Exclusion criteria

In all three substudies, we excluded tumors without histologic axillary staging (no gold standard), tumors treated with neoadjuvant chemotherapy, and tumors detected during pregnancy or lactation. In the first substudy, tumors with negative axillary findings at histology (pN0) were excluded. In the second substudy, tumors with negative findings on axillary US were excluded. In the third substudy, we excluded patients with mastectomies, patients who did not undergo whole-breast radiotherapy after breast-conserving surgery, patients with palpable lymph nodes, and tumors with negative axillary US findings.

2.3. Image acquisition

For axillary US examinations, radiologists with 4–25 years' experience in breast imaging used different ultrasound scanners: Supersonic Imagine's Aixplorer (Hologic, Bedford, USA); Acuson S2000, Acuson Sequoia, and Acuson Antares (Siemens Medical Systems, Erlangen, Germany); Aplio XG (Toshiba Medical Systems Europe, Zoetermeer, The Netherlands); Logiq 700 (General Electric Medical System, Milwaukee, USA) with high frequency linear multi-frequency transducers (8–15 MHz) to study the axilla ipsilateral to the tumor caudocranially, reviewing Berg levels I, II, and III.

Negative axillary US was defined as no visible lymph nodes or normal nodes (hyperechoic hilum with no visible cortex or a uniformly thin (< 3 mm) cortex); positive axillary US was defined as the presence of a suspicious lymph node (diffuse cortical thickening (> 3 mm), generalized cortical lobulation, focal cortical lobulation, hypoechoic nodule without a fatty hilum).

2.4. Axillary management

Cases with positive axillary US were studied with FNAC. When more than one suspicious lymph node was present, FNAC was done on the most suspicious node. Cases with negative or indeterminate findings on FNAC were studied with SLNB. ALND was performed in cases with positive FNAC, positive SLNB, or negative FNAC with no migration in SLNB.

2.5. Pathology techniques

FNAC specimens were obtained with standard 21G or 22G needles. Smears were air dried and stained with May-Grünwald-Giemsa stain; liquid-based cell preparations were stained with Papanicolaou stain.

For SLNB, the tracer (^{99m}Tc) was injected into or around the tumor under US guidance. If no migration was observed, a second intratumoral or peritumoral injection or a subcutaneous periareolar injection was done. If no migration was observed after the second injection, ALND was done.

In one center, SLNBs were processed by one-step nucleic acid amplification (OSNA), with the following cutoffs: macrometastases (> 5 × 103 copies of mRNA/μl), micrometastases (between 2.5 × 102 and 5 × 103 copies of mRNA/μl), and no metastases (< 2.5 × 102 copies of mRNA/μl).

At the other centers, SLNB specimens were frozen intraoperatively and later sectioned (≤3 mm) at different levels and stained with hematoxylin and eosin (H&E). The cutoff values for H&E specimens were