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Original article

Axillary ultrasound for preoperative nodal staging in breast cancer patients: Is it of added value?

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ABSTRACT

Background: New insights show that an axillary lymph node dissection (ALND) may not always be indicated for metastases detected by ultrasound (pathologically proven). This study investigated whether axillary ultrasound accurately predicts pN0, pN1 and pN2–pN3 status.

Methods: Data were retrospectively collected from all consecutive patients with invasive breast cancer who underwent (primary) surgery between 2008 and 2012. False negative percentages and negative predictive values (NPVs) for sonographic nodal staging were calculated for all patients and again for cT1–2 patients treated by breast conserving therapy (BCT).

Results: A total of 577 axillary ultrasounds were included. After negative ultrasound findings (cN0), pathology showed pN2–pN3 disease in 4.4% of these cases, with an NPV of 95.5% (93.4–97.1%). When cN1 (1–3 suspicious nodes) was predicted, pathology showed pN2–pN3 disease in 41.2%, with an NPV of 58.5% (44.2–71.5%).

In the subgroup of patients with cT1–2 breast cancer that were treated by BCT, pathology showed pN2–pN3 disease in 2.3% after negative ultrasound findings (cN0), with an NPV of 97.7% (94.9–99.0%). When cN1 was predicted ($n = 12$), pathology showed pN2–pN3 disease in 50.0%, with an NPV of 50.0% (22.3–77.9%). A direct ALND was performed in these 12 cN1 cases; pathology showed six patients with pN1 (three patients with one and three with two macrometastases) and six with pN2–pN3 disease (4, 5, 11, 13, 16 or 22 macrometastases, respectively).

Conclusion: In conclusion, a negative axillary ultrasound generally excludes the presence of pN2–pN3 disease. An axillary ultrasound cannot accurately differentiate between pN1 and pN2–pN3. It could be argued that the standard performance of an axillary ultrasound in breast cancer patients is questionable; multidisciplinary discussion could guide decisions on the use of axillary ultrasound for the individual patient.

Introduction

The sentinel lymph node biopsy (SLNB) is regarded as the standard surgical nodal staging technique for clinically node negative breast cancer patients. In the absence of a sentinel lymph node (SLN) metastasis, the SLNB has replaced routine axillary lymph node dissection (ALND) for staging axillary lymph nodes [1], thereby reducing the number of unnecessary ALNDs as well as the morbidity rate (seroma, infection, lymphoedema, arm- and shoulder pain, nerve injury) [2,3]. About 30–40% of newly diagnosed breast cancer patients have nodal metastases [4]. Preoperative axillary ultrasound is widely used for assessing the clinical nodal status in breast cancer. If the patient's axillary evaluation is negative, an SLNB is performed for further staging. If a suspicious lymph node is detected with ultrasound, this node will then be sampled and if pathology shows a metastasis, the SLNB is omitted and an ALND is indicated [5]. The ALND can then be performed

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simultaneously with the tumour excision. This approach prevents 19.8% of patients from having to undergo an additional operation [6].

Several retrospective studies, which included patients treated with mastectomy and breast conserving surgery, assessed the differences in recurrence and survival rates for SLN-positive patients treated by SLNB alone compared to patients who received an SLNB with completion ALND [7–11]. Interestingly, no clinically relevant benefit was demonstrated for completion ALND, although patient selection might be a confounding factor. More evidence can be deduced from several randomized controlled trials. These trials have shown that either performing axillary radiotherapy [12], or omitting further axillary treatment following a positive sentinel lymph node [6,13], does not compromise overall survival, nor disease control. The sentinel lymph node positive breast cancer patients included in these trials had a clinically node negative status by physical examination. One of these trials, the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial demonstrated that omitting the completion ALND after the detection of 1–2 SLN metastases provided neither worsened regional control nor an inferiority of survival in clinically node negative breast cancer patients (cT1–2) treated by breast conserving therapy (BCT). In 97% of the patients, adjuvant systemic therapy was administered and the whole breast was radiated (with possible tangential radiation overlap to the axilla). As the completion ALND specimen contained additional nodal metastases in 27% of the patients in the control arm, patients randomised to the SLNB-alone arm were likely to have important residual non-SLN metastases that were not removed by surgery [13]. This suggests that not all non-SLN metastases develop into clinically detectable disease.

This raises the question what the added value is of performing a preoperative evaluation of the axilla by ultrasound, and whether ALND is indicated for every metastasis detected by ultrasound. Consequently, preoperative axillary ultrasound might only be useful if it can differentiate between patients with limited axillary disease (defined as pN1) and those with advanced axillary disease (defined as pN2 or pN3). This would prevent the need for direct ALNDs in patients with limited nodal disease and facilitate the direct performance of ALNDs in patients with advanced nodal disease.

The aim of this retrospective study was to determine whether preoperative axillary ultrasound can distinguish between pN0, pN1 and pN2–pN3 disease.

Materials and methods

Study population and data collection

Due to the retrospective nature of this study, a certified medical ethics committee waived the requirement of informed consent. Between 2008 and 2012, all consecutive patients with operable primary invasive breast cancer were retrospectively included. Data concerning age; sex; diagnostic work-up; surgical procedures; and pathology reporting of tumour type, grade, size, receptor status and lymph nodes were retrospectively collected.

Clinical nodal status

Clinical nodal status was based on results of physical examination and axillary ultrasound, and classified according to the *number* of suspicious lymph nodes imaged by ultrasound, that is, cN1 is 1–3, cN2 is 4–9 and cN3 is >9 suspicious axillary lymph nodes. Tissue sampling was generally performed in axillae suspicious for malignancy on ultrasound using 16–18 gauge core needle biopsy. When core needle biopsy was technically challenging, for example due to the proximity of a blood vessel, fine needle aspiration cytology was used. In cases of multiple suspicious nodes, only the most suspicious node was sampled, and the number of suspicious nodes reported. The total number of suspicious and non-suspicious nodes was not reported. The axillary ultrasound was performed in every patient by dedicated breast radiologists (regardless of the results of physical examination) using an ATL-HDI5000 system, which in 2011 was replaced by an iU22-xMATRIX ultrasound system in combination with a high-frequency linear array transducer (Philips Medical Systems, Best, the Netherlands). If the sampled tissue contained no tumour cells or the ultrasound was negative, an SLNB was performed; otherwise an ALND was performed directly.

Surgical techniques

The SLN was identified by using a triple technique consisting of lymphoscintigraphy (using 80 MBq Technetium-99m nanocolloid injected peri-areolar), blue dye to detect lymphatic vessels (Bleu Patente V; Guerbet, Aulnay-sous-Bois, France), and gamma probes to detect radioactivity. After the SLNB, a palpation of the axilla was performed to identify and remove suspicious non-SLNs. After the detection of one or more (micro-)metastasis, a completion level I–II ALND was performed.

Pathological technique

Core biopsies were routinely processed after formalin fixation. Sections stained with haematoxylin and eosin (H&E) were assessed and additional immunohistochemical analyses were performed. Fine needle aspiration cytology was routinely processed: air-dried smears were stained with May-Grünwald–Giemsa and liquid-based thin-layer cell preparations were stained with Papanicolaou and used for immunocytochemistry. SLNs were sliced with a maximum thickness of 3 mm and embedded in paraffin after formalin fixation. Each paraffin block was step sectioned at 500-μm intervals at three levels and stained with haematoxylin and eosin. If no metastasis was detected with haematoxylin and eosin, immunohistochemical staining was performed with a mouse anti-human MNF116 antibody (Dako).

All ALND lymph nodes were embedded in paraffin after formalin fixation. Lymph nodes larger than 5 mm were sliced with a maximum thickness of 3 mm. All slides were stained with haematoxylin and eosin. Each node was recorded as either benign or as an isolated tumour cell (ITC) (pN0(i+)) ($\leq$0.2 mm), micrometastasis (pN1mi) (0.2 $\leq$ 2.0 mm) or macrometastasis (pN+) (>2.0 mm).

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (Version 19.0, Chicago, Illinois, USA). The false negative percentages and negative predictive values (NPVs) for axillary nodal staging with ultrasound were calculated for each nodal status in general and for cT1–2 patients treated by BCT in particular. Data were summarised as means with standard deviations (SD). Chi-square tests were used to analyse categorical data and independent-samples *t*-tests were used to analyse continuous data. *P*-value $<$ 0.05 was considered statistically significant.

Results

Patient demographics and tumour characteristics

During the study period, 647 patients were diagnosed with primary invasive breast cancer, 18 of whom had bilateral breast cancer, resulting in 665 possibly affected axillae. Clinical nodal status was based on axillary ultrasound (±tissue sampling), and