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● *Original Contribution*

PRE-OPERATIVE ULTRASONOGRAPHIC EVALUATION OF AXILLARY LYMPH NODES IN BREAST CANCER PATIENTS: FOR WHICH GROUP STILL OF ADDITIONAL VALUE AND IN WHICH GROUP CAUSE FOR SPECIAL ATTENTION?

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Abstract—A non-invasive and widely available method for pre-operative evaluation of the axilla is axillary ultrasonography (US). The purpose of this study was to evaluate the diagnostic accuracy of axillary US and fine-needle aspiration cytology in a large cohort of breast cancer patients. The sensitivity and specificity of US and fine-needle aspiration cytology in our cohort of 1124 patients were 42.2% and 97.1%, respectively. As the number of axillary nodes increased, sensitivity increased. The percentage of false-negative US results was 18.9%; patients in this subgroup were significantly younger, had larger tumors, more often had lymph vascular invasion and were more likely to have estrogen receptor-positive tumors. Ultrasonography in combination with fine-needle aspiration cytology is useful in the pre-operative workup of breast cancer patients, especially patients with three or more nodal metastases. Special attention should be paid to younger women with larger tumors in whom a larger percentage of false-negative results are obtained. (E-mail: y.moorman@zgt.nl) © **2015 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Breast cancer, Pre-operative staging, Axillary ultrasonography, Fine-needle aspiration cytology, Sentinel lymph node biopsy, Axillary lymph node dissection, False-negative ultrasonography.**

INTRODUCTION

Over the years there has been growing interest in the development of clinical prediction tools to estimate the risk of patients with breast cancer having axillary nodal metastases, thereby making it possible to plan specific therapies. Sentinel lymph node biopsy (SLNB) has become the standard method of axillary lymph node staging in patients with invasive breast cancer. It has replaced axillary lymph node dissection (ALND), as it is associated with significantly lower morbidity (Purushotham et al. 2005). However, SLNB is still an invasive method and has a 4%–14% rate of complications such as lymphedema, seroma, paresthesia, chronic pain and immobility (Temple et al. 2002). When node metastases are found with SLNB, ALND is still warranted, which means that the patient has to undergo a second operation. Not only is this an inconvenience for the patient, but it also results in more operating time, space and costs (Boughey et al. 2010).

A non-invasive and widely available screening method is axillary ultrasonography (US). Pre-operative axillary US, with or without fine-needle aspiration cytology (FNAC) of lymph nodes suspicious for metastases, is now routinely performed in many breast cancer centers (Glynn et al. 2010). The utility of axillary US in detecting nodal metastases has been studied extensively. The results vary widely, especially in patients with early-stage breast cancer (Alvarez et al. 2006; Garcia Fernandez et al. 2011; Mainiero et al. 2010). The sensitivity and specificity of axillary US range between 40% and 92%, and between 56% and 100%, respectively. Specificity increases to 100% with the use of FNAC. However, as with all US procedures, the sensitivity and specificity of axillary US depend strongly on the experience of the ultrasonographer and the reference standard for malignancy used. The majority of previous studies on axillary US and FNAC

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have studied small patient groups (<500 patients) and have used different morphologic criteria for detecting nodal metastases: palpable versus non-palpable nodes, inclusion or exclusion of micrometastases and differences in the prevalence of axillary nodal burden (Alvarez et al. 2006; Bonnema et al. 1997; Cho et al. 2009; de Freitas et al. 1991; Jung et al. 2010; Motomura et al. 2001; Rajesh et al. 2002; Vaidya et al. 1996; Verbanck et al. 1997; Yang et al. 1996).

The aim of this study was to evaluate the utility and diagnostic accuracy of axillary US and US with FNAC in detecting axillary lymph node metastases in a large cohort of breast cancer patients.

METHODS

Patients

This retrospective cohort study was conducted in the Hospital Group Twente, a large teaching hospital located in Almelo and Hengelo, The Netherlands. Approval from the institutional review board was not required because this was a non-interventional retrospective study using known data. From January 2007 until July 2011, 1124 consecutive primary breast cancer patients were selected. These patients were both screen detected and/or symptomatic. All patients underwent pre-operative axillary US and subsequent surgery with SLNB and/or ALND according to current Dutch guidelines. Patients with palpable axillary disease, clinical and radiologic T4 status, ipsilateral recurrent breast malignancy and neo-adjuvant chemotherapy were excluded.

Pre-operative ultrasonography and fine-needle aspiration

All patients underwent routine mammography, ultrasonography of the breast and ipsilateral ultrasonography of the axilla by a trained radiologist or a radiology resident under the supervision of a trained radiologist. Two commercial ultrasound scanners were used; the Acuson X300/VF13-5 transducer (Siemens, Seongnam, South Korea), with a frequency bandwidth of 4.4–13.0 MHz and a maximum field of display of 61 mm, and the Aloka Prosound Alpha 7/UST-5412 transducer (Aloka, Tokyo, Japan), with a frequency bandwidth of 5–13 MHz and maximum field of display of 60 mm. These were located at different sites, so the ultrasound scanner used was the one available in the hospital where patients presented. A lymph node was classified as suspicious if its cortical thickness was >2.3 mm or if it had an irregular nodular cortex and/or a diminished or absent hilum (Deurloo et al. 2003). When suspicious nodes were found, US-guided FNAC was performed using a 21-gauge needle, and the aspirate was sent to the pathology department for cytologic analysis. If needed, a second attempt was made. FNAC analysis was carried out after Giemsa and Papanicolaou staining (Surepath).

SLNB and ALND protocol

The study protocol is summarized in Figure 1. Patients with non-suspicious nodes after axillary US and those with no malignant cells after FNAC (or from whom insufficient material was obtained for diagnosis after several attempts) were scheduled for SLNB. Sentinel lymph nodes (SLNs) were harvested after scintigraphy and patent blue dye injection during or immediately before surgery by one of our experienced breast surgeons or by a surgical trainee under the strict supervision of an experienced breast surgeon. A sentinel node was identified as any blue-staining node, hot node or node with at least 10% of the highest hot node count. Pathologic examination classified SLNs as macrometastases (>2 mm), micrometastases (0.2–2 mm) or isolated tumor cells (<0.2 mm). If US-guided FNAC proved positive for malignant cells, ALND was performed. Complete ALND was routinely performed when a metastasis was present in the SLN. In this study, we focused on macrometastases, because micrometastases do not normally alter the morphology of the lymph node and are thereby difficult to detect (Garcia-Ortega et al. 2011).

Patient and tumor characteristics were retrieved from the original patient files. The final pathology results, based on SLNB and/or ALND, were correlated with axillary US alone or US in combination with FNAC.

Statistical analysis

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for axillary US alone and axillary US in combination with FNAC, with the final pathologic findings with SLNB and/or ALND as gold standard. The utility of US and US with FNAC was assessed by determining the positive and negative likelihood ratios. The correlation between clinic and pathologic variables and false negativity of axillary ultrasonography was analyzed using the χ^2 test. A p value < 0.05 was considered to indicate statistical significance.

RESULTS

Patient and tumor characteristics

During the observational period from January 2007 until July 2011, 1178 patients were treated for primary invasive breast cancer in the Hospital Group Twente, The Netherlands. Of these patients, 20 had palpable axillary lymph nodes and 34 patients, did not undergo the routine workup for other reasons, leaving 1124 patients for further analysis. All patients had solitary tumors. The median age of the patients was 61 y