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Differentiation of benign and metastatic axillary lymph nodes in breast cancer: additive value of shear wave elastography to B-mode ultrasound

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ABSTRACT

Objectives: The purpose of this study is to evaluate the additive value of shear wave elastography (SWE) for differentiating benign and metastatic axillary lymph nodes (LNs) in breast cancer.
Materials and methods: The area under the receiver operating characteristic curve, sensitivity, and specificity of B-mode US, SWE, and combined modality were compared for 54 suspicious LNs.
Results: After combining information from SWE, sensitivity was significantly higher for combined modality than for B-mode US alone (94.12% vs. 82.35%, $p = 0.046$) without a decrease in specificity.
Conclusion: Combined B-mode US and SWE may improve detection of metastatic axillary LNs in patients with breast cancer.

1. Introduction

Axillary lymph node (LN) status is the most reliable prognostic indicator for disease recurrence and patient survival in breast cancer [1]. Axillary ultrasound (US) is an important means for detecting metastatic LNs. It is moderately sensitive and fairly specific for diagnosing axillary LNs [2]. US-guided fine needle aspiration biopsy (FNAB) for preoperative axillary LNs increases the specificity of axillary US and is the most effective technique for nonsurgical staging [3]. Positive FNAB cytology results may lead to axillary LN dissection (ALND) and reduce the number of unnecessary surgical sentinel LN biopsies (SLNBs) [4]. Negative FNAB results are usually followed by SLNB. However, even with axillary US examinations and FNAB of suspicious LNs, the risk of false negatives is substantial [5]. Nori et al. reported false negatives that did not cause perceptible morphological alterations on US, which were probably due to micrometastasis [6]. False-negative results for FNAB with subsequent positive SLNB results lead to delayed ALND. Therefore, any improvement in the accuracy of axillary US that reduces false-negative US-guided FNAB results could decrease the incidence of delayed ALND.

Elastography may be helpful for differentiating benign and metastatic LNs by measuring tissue elasticity or lesion compressibility [7,8]. The superficial nature of LNs makes them ideal candidates for the elastography technique as tissue deformation can be produced by manual compression [9]. Previous studies examined the diagnostic value of strain elastography in differentiating between benign and metastatic axillary LNs in patients with breast cancer [10–13]. Several studies evaluated strain scoring for differentiating benign and metastatic LNs and identified the added value of strain elastography [11,12]. Choi et al. [11] evaluated 64 LNs (33 benign and 31 metastatic) and suggested that combined B-mode US and elastography showed higher sensitivity (87.1%) than B-mode US alone (74.2%). Tsai et al. [12] evaluated 90 LNs and found that a combination of B-mode US and elastography showed higher sensitivity, specificity, and diagnostic performance than B-mode US alone (sensitivity 80% vs. 84%, specificity 88% vs. 98%, and area under the receiver operating characteristic curve 0.883 vs. 0.951). However, Park et al. [10] reported interpretation difficulty with strain elastography and no significant benefit over conventional B-mode US for evaluating abnormal axilla LNs, contradicting previous strain-elastographic studies. The study evaluated elastogram parameters other than strain scoring, the proportion of black (hard) areas of LNs, and ratios of lesion length on elastography to lesion length on B-mode image (E/B ratio). On strain elastography, images are produced by tissue displacement due to manual compression or a low-frequency US pulse. The relative strain between a lesion and the surrounding tissue is then determined [14]. Data acquisition and interpretation of strain elastography images is largely dependent on examiner experience, and significant interobserver variability has been reported [15,16].

On the other hand, shear wave elastography (SWE) quantitatively measures lesion stiffness [14,17]. SWE has high reported interobserver and intraobserver reproducibility [17]. Several studies measured the

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tissue stiffness (elasticity) of sentinel LNs for differentiating metastatic and nonmetastatic LNs in breast cancer [18,19]. However, these studies evaluated the shear wave values of SLNs from mostly patients with negative axillary examinations and sonographic findings. Therefore, the accuracy of elastography measurements did not reflect the value of customary axillary examinations during preoperative staging US. In addition, relatively few clinical studies have assessed shear wave values for axillary LNs in the clinical setting [20]. Thus, we evaluated suspicious axillary LNs detected on preoperative staging US or postoperative follow-up US in patients with breast cancer. The purpose of our study was to compare the diagnostic performance of SWE with conventional B-mode US and combination of both methods for diagnosing axillary LNs in patients with breast cancer. Final surgical histology was the reference standard.

2. Materials and methods

2.1. Patients

Our institutional review board approved this retrospective study, and the need for informed consent was waived. From May 2014 to August 2016, 66 patients (mean age 54.7, 33–80) were selected based on the following criteria: (i) patients with breast cancer undergoing preoperative staging evaluation or post-treatment follow-up, (ii) patients with suspicious axillary LNs detected on B-mode US who then underwent SWE and FNAB. Among these 66 patients, 13 were excluded because definite histology was not known after benign FNAB results. This was either because the patient underwent preoperative chemotherapy ($n = 4$) or was lost to follow-up if surgery was not performed in our hospital ($n = 9$). Suspicious axillary LNs identified on B-mode US were based on previously published criteria as follows: round shape, loss of echogenic hilum, or > 3 mm thick cortex [21]. A total of 54 axillary LNs in 53 patients with breast cancer were included. Of 49 patients who presented for preoperative ultrasound staging of known breast cancer, 48 patients underwent FNAB of ipsilateral axillary LNs for breast cancer, and one underwent FNAB for ipsilateral and contralateral axillary LNs. Four patients with prior breast cancer underwent FNABs for axillary LNs that were detected with postoperative follow-up; all were on the contralateral side of a previous breast cancer. There was no LN which is located deeper than 30 mm and has a possibility of signal loss with SWE (range of lesion depth, 2.9–18.5 mm).

2.2. Pathology analysis

US-guided fine needle aspiration biopsy using 25-gauge needles was performed on all 54 axillary LNs. Surgery was performed on 32 axillary LNs from 31 patients that underwent axillary LN dissection ($n = 16$), sentinel LN biopsy ($n = 15$), and excision ($n = 1$). Excision was done under US guidance with a skin marking to ensure radiologic-pathologic correlation. Axillary LN dissection or sentinel LN biopsy were performed without skin markings. Surgery was performed by a single breast surgeon. Based on physical examinations and radiologic findings, the surgeon removed 5–28 nodes during axillary LN dissection.

Patients received 3–4 injections of 30 MBq (0.8 mCi) Tc 99m-antimony trisulfide colloid in 1.0 ml saline in the subareolar and intradermal area. In the operating room, radioactive SLNs were detected with a gamma probe (Neo 2300, Devicor Medical Products, Incorporation, Cincinnati, OH, USA) and assessed for residual radioactivity after surgery.

Histopathological diagnosis was considered the reference standard. Of 34 metastatic LNs detected by sonographically guided FNAB, 15 were referred for surgery and the remaining 19 were lost to follow-up. Of 20 benign LNs by FNAB, 17 were negative on SLNB. The remaining 3 LNs were all found in post treatment patients in the side contralateral to the treated cancer. All 3 of these LNs had decreased in size and had no evidence of metastasis on follow up US for 12 to 36 months after breast surgery. Histological breast cancer types included invasive ductal carcinoma ($n = 50$), papillary carcinoma ($n = 1$), medullary carcinoma ($n = 1$), and ductal carcinoma in situ ($n = 1$).

2.3. Image acquisition and analysis

B-mode US and SWE were performed using an Aixplorer system (Supersonic Imagine, Aix en Provence, France) equipped with a 4–15 MHz linear array transduce. One of two radiologists with 10 years and 6 years of experience in breast imaging performed B-mode US and SWE. After B-mode US, the same radiologist obtained shear wave elastography images before biopsy with no pressure induced by the transducer. SWE was performed prospectively but was not used to determine the need for FNAB of axillary nodes. Patients were positioned identically for imaging as in standard breast US: in the supine oblique position with the ipsilateral arm elevated. After identifying the most suspicious LNs on B-mode US, long-axis and short-axis diameter, long/short axis diameter ratios, maximal cortical thickness, and cortical thickening morphology (concentric, eccentric, or no fatty hilum) of LNs were evaluated. In the absence of a hilum, cortical thickening morphology could not be assessed [20]. SWE was performed with minimum compression from the probe. Elasticity values were measured from the stiffest color-coded area by defining a circular region of interest 3 mm in diameter. Elastographic data included elasticity index (in kPa) maximum, mean, and minimum, standard deviation, and elasticity ratio between lesion and fatty tissue in the axillary area. Two radiologists analyzed B-mode US and SWE images by consensus. Both radiologists were blinded to the pathology results.

2.4. Statistical analysis

Fisher's exact test was used to analyze qualitative variables for sonography, and Mann-Whitney U test was used to compare mean values of all quantitative variables for B-mode US and SWE. Receiver operating characteristic (ROC) curves were plotted to determine the discriminatory power of groups. Cutoff points yielding the maximal sum of sensitivity and specificity for B-mode US and shear-wave elastography were calculated. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for findings were calculated. Among the features of B-mode US and shear-wave elastography, cortical thickness and maximum stiffness showed the highest areas under the receiver operator characteristic curve (AUC). Thus, these values were used to obtain the diagnostic performance of combined B-mode US and shear-wave elastography. To evaluate the additional value of combined modality (cortical thickness + maximum stiffness) compared with B-mode US only (cortical thickness), sensitivity, specificity, and accuracy were compared with chi-square tests. Sensitivity is the probability of true positives between true positives and false negatives. Specificity is the probability of true negatives between true negatives and false positives. Accuracy is the probability of true results (true positives and true negatives) among all patients. p Values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS (IBM SPSS statistics 23).

3. Results

Of 54 LNs, 20 were benign and 34 were malignant. Table 1 shows B-mode US features of cortical thickening morphology, cortical thickness, long-axis and short-axis diameter, and long/short axis diameter ratio, elastographic values for elasticity index (in kPa) maximum, mean, minimum and standard deviation, and elasticity ratio between lesion and fatty tissue in the axillary area. Long-axis and short-axis diameter, cortical thickness, maximum, mean, minimum, standard deviation, and elasticity ratio were significantly higher in metastatic LNs compared to benign LNs. However, there is no significant difference in the long/short axis diameter ratios between benign and malignant LNs.