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Three-dimensional versus two-dimensional shear-wave elastography: Associations of mean elasticity values with prognostic factors and tumor subtypes of breast cancer

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ABSTRACT

Purpose: To explore associations between prognostic factors and subtypes of invasive breast cancer (IBC) and elasticity values using three-dimensional (3D) and two-dimensional (2D) shear-wave elastography (SWE).
Materials and methods: Mean elasticity values (kPa) of 121 IBCs were measured using both 3D and 2D SWE. Associations between these values and prognostic factors and subtypes were analyzed using linear regression model.
Results: In both 3D and 2D SWE, larger size and presence of lymphovascular invasion were independent factors influencing higher mean elasticity on multivariate analyses (all p values < 0.05).
Conclusions: Using either 3D or 2D SWE, higher mean elasticity values are associated with poor prognostic factors of IBC.

1. Introduction

Breast cancer is a heterogeneous disease with various clinical, histological, and molecular characteristics, which affect its prognosis and treatment [1]. In clinical practice, immunohistochemical (IHC) classification based on expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) is used as a surrogate for the intrinsic molecular subtypes as well as to categorize breast tumors into three major subtypes: ER-positive (i.e., ER-positive, HER2-negative, PR may be positive or negative), HER2-positive (i.e., HER2-positive; ER and PR may be positive or negative), and triple-negative (i.e., ER-negative, PR-negative, and HER2-negative) [2]. Previous studies have focused on identifying imaging biomarkers that can aid in distinguishing these tumor subtypes.

Shear-wave elastography (SWE) allows quantitative measurement of lesion stiffness in kilopascals (kPa) or meters per second. SWE is a reproducible technique [3], and when combined with B-mode ultrasound (US), it can improve the diagnostic performance for differentiating benign from malignant breast lesions, potentially reducing unnecessary biopsies [4,5]. According to the results of a recent meta-analysis, the sensitivity and specificity of SWE using mean elasticity values were 94% and 71%, respectively [6]. Furthermore, SWE stiffness values are associated with known prognostic factors of breast cancer, such as tumor size, lymph node status, and histological grade [7–11]. However, results regarding tumor subtypes have been inconsistent, with Chang et al. [12] reporting that tumor subtype is an independent factor influencing SWE stiffness, and Youk et al. [7] failing to show an independent association.

Three-dimensional (3D) US offers 3D volumetric reconstruction with a single sweep of the US beam, acquiring comprehensive information for all aspects of lesions, and thus it allows for a more accurate assessment of disease and surrounding anatomic structures, as well as treatment response [13,14]. Compared to conventional two-dimensional (2D) US, 3D US provides equivalent or better accuracy for differentiating benign from malignant solid breast masses [15,16]. Furthermore, a recent study showed that 3D US features such as retraction pattern in the coronal plane and intratumoral vascularization index were useful for predicting prognosis in patients with breast cancer [17]. From this perspective, 3D SWE may provide more complete 3D elastographic volume data regarding tissue stiffness of breast lesions. As breast cancer is a heterogeneous disease, our hypothesis is that tumor stiffness values for entire breast tumors acquired from 3D

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SWE may be different from the values quantified in the representative plane of the lesion from 2D SWE, and if so, 3D SWE features may reflect actual tumor biology and provide additional prognostic information beyond that obtained with 2D SWE. However, only a few studies to date have investigated the diagnostic performance of 3D SWE for breast masses [18,19]; no studies have focused on the associations between mean elasticity values derived from 3D SWE and histological prognostic factors or tumor subtypes.

Therefore, the purpose of the present study was to explore possible associations between prognostic factors and tumor subtypes of invasive breast cancer and the quantitative elasticity values acquired using 3D SWE compared with those acquired using 2D SWE.

2. Materials and methods

2.1. Patients

The institutional review board of our institution approved this retrospective study and did not require informed consent from patients. Between April 2015 and January 2016, 148 consecutive women who had been diagnosed with invasive breast cancer by core needle biopsy underwent 2D and 3D SWE along with B-mode US prior to curative surgery. Among these patients, 12 who underwent neoadjuvant chemotherapy before surgery, 8 who had breast lesions larger than the field of view on 3D SWE, and 7 who had inadequate SWE images for the analysis were excluded. For women with multifocal or multicentric cancer, the largest tumor was included, and for women with bilateral cancer, the more dominant tumor was included. Finally, 121 breast tumors in 121 women (mean age, 52.2 years; range, 24–78 years) were included in the analyses. Of these, 56 were asymptomatic and 65 had symptoms; 60 had lumps, 4 had breast pain, and 1 had nipple discharge. The tumors included infiltrating ductal carcinoma (n = 107, 88.4%), infiltrating lobular carcinoma (n = 5, 4.1%), mucinous carcinoma (n = 6, 5.0%), metaplastic carcinoma (n = 2, 1.7%), and invasive micropapillary carcinoma (n = 1, 0.8%).

2.2. Ultrasound examination

B-mode US and SWE images were obtained by one breast radiologist (J. Y. K., with 7 years of experience in breast US and elastography) using the Aixplorer® US system (SuperSonic Imagine, Aix-en-Provence, France) equipped with a 4–15 MHz linear-array transducer. No histopathological information was provided, although the radiologist was aware that all patients had been diagnosed with invasive breast cancer.

After B-mode US acquisition, SWE images were obtained in the same imaging planes without changing the patient's position. First, 2D SWE was performed with a linear transducer without manual compression. Only the minimal pressure required to maintain contact with the skin over the lesion was applied. The built-in region of interest (ROI) (Q-box; SuperSonic Imagine) of the system was focused on the target lesion and was adjusted to include the surrounding area from the subcutaneous fat layer to the superficial portion of the pectoralis muscle layer.

After a few seconds of immobilization to obtain stable images, a representative SWE image considered most appropriate for interpretation was saved. Tissue elasticity represented by Young's modulus in kPa was color-coded for each pixel and displayed as an overlay on the B-mode image with a range from 0 (dark blue; soft) to 180 kPa (red; hard) (Fig. 1(a)). Quantitative elasticity was measured in each SWE image using the built-in quantification tool (Q-box; SuperSonic Imagine) of the system. Fixed 2 mm circular ROIs were placed by the investigator on the stiffest portion of the lesion, including immediately adjacent stiff tissue in the SWE image. The system automatically calculated and displayed the quantitative elasticity values for the breast lesions, including minimum, maximum, and mean elasticity values in kPa.

Next, 3D SWE was performed with a 5–16 MHz dedicated volume transducer (SuperSonic Imagine). 3D volumetric SWE data of approximately 3 × 3 × 2.5 cm were acquired and reconstructed simultaneously in three orthogonal planes (transverse, sagittal, and coronal images) (Fig. 1(b)). Similar to the procedure followed with 2D SWE, a semitransparent color overlay map, which also ranged from 0 to 180 kPa, was obtained using the Q-Box. The quantitative elasticity values were obtained by positioning 2-mm circular ROIs in all three orthogonal planes of 3D SWE. Once the quantification was completed, the acquired 3D volume data were saved on the US system. Acquisition of both 2D and 3D SWE data took < 5 min per case.

2.3. Clinicopathological data

Mastectomy (n = 42) or breast conservation surgery (n = 79) was performed for all breast cancers. Patient medical records and surgical pathology reports were reviewed. All invasive breast cancers were graded using the Nottingham combined histologic grading system [20]. ER, PR, HER2, Ki-67, and p53 were evaluated using the avidin-biotin complex IHC technique. ER and PR expression status were assessed using the Allred scoring system [21], which is the sum of the proportion score and intensity score of positively stained tumor cells. Tumors with Allred scores ≥ 3 were considered positive. The HER2 staining intensity was scored as 0, 1 +, 2 +, or 3 +. Tumors with a score of 3 + were classified as HER2-positive and tumors with a score of 0 or 1 + were classified as HER2-negative. Tumors with a score of 2 + were further evaluated using fluorescence in situ hybridization (FISH). If the ratio of the HER2 gene signal to the chromosome 17 probe signal was > 2.2, the tumor was considered HER2-positive. Ki-67 was reported as the percentage of immunoreactive cells among 2000 randomly selected tumor cells, and a Ki-67 labeling index ≥ 14% was considered high-level expression. For p53, nuclear staining ≥ 10% was considered positive.

Tumors were stratified by ER, PR, and HER2 status and classified into three tumor subtypes, as follows: ER-positive (i.e., ER-positive and/or PR-positive and HER2-negative), HER2-positive (i.e., ER-negative, PR-negative, and HER2-positive), and triple-negative (i.e., ER-negative, PR-negative, and HER2-negative).

2.4. Data and statistical analysis

The medical records and radiological studies of 121 patients were retrospectively reviewed. Among the multiple quantitative elasticity values obtained with SWE, mean elasticity values were used and recorded for this analysis, because these values showed the highest reliability in a previous study [3]. For 3D SWE, the highest mean elasticity values were selected among three orthogonal planes of 3D SWE.

The relationships between mean elasticity values, as measured by 3D and 2D SWE, and clinicopathological variables were investigated using the Mann–Whitney U test and the Kruskal–Wallis test. The mean elasticity values in 3D and 2D SWE images were correlated with prognostic factors and tumor subtypes using univariate linear regression analyses. Multivariate linear regression analyses were performed to identify variables independently associated with the mean elasticity values by including factors that showed significance (p < 0.05) in univariate analyses.

All statistical analyses were performed using SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered statistically significant.

3. Results

The mean tumor size of 121 invasive breast cancers was 2.0 ± 1.5 cm (range, 0.5–3.0 cm). The mean elasticity value was 123.66 ± 48.59 kPa (range, 18.6–279.8 kPa) using 3D SWE, which was not significantly different from the mean elasticity value of 125.04 ± 62.35 kPa (range, 20.7–285.3 kPa) obtained using 2D SWE