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Shear-wave elastography and immunohistochemical profiles in invasive breast cancer: Evaluation of maximum and mean elasticity values

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ABSTRACT

Purpose: To evaluate the correlations of maximum stiffness (Emax) and mean stiffness (Emean) of invasive carcinomas on shear-wave elastography (SWE) with St. Gallen consensus tumor phenotypes.
Methods: We used an ultrasound system with SWE capabilities to prospectively study 190 women with 216 histologically confirmed invasive breast cancers. We obtained one elastogram for each lesion. We correlated Emax and Emean with tumor size, histologic type and grade, estrogen and progesterone receptors, HER2 expression, the Ki67 proliferation index, and the five St. Gallen molecular subtypes: luminal A, luminal B without HER2 overexpression (luminal B HER2−), luminal B with HER2 overexpression (luminal B HER2+), HER2, and triple negative.
Results: Lesions larger than 20 mm had significantly higher Emax (148.04 kPa) and Emean (118.32 kPa) ($P = 0.005$) than smaller lesions.

We found no statistically significant correlations between elasticity parameters and histologic type and grade or molecular subtypes, although tumors with HER2 overexpression regardless whether they expressed hormone receptors (luminal B HER2+ and HER2 phenotypes) and triple-negative tumors had lower Emax and Emean than the others.

We assessed the B-mode ultrasound findings of the lesions with some of the Emax or Emean values less than or equal to 80 kPa; only four of these had ultrasound findings suggestive of a benign lesion (two with luminal A phenotype and two with HER2 phenotype).
Conclusions: We were unable to demonstrate statistically significant differences among the subtypes of invasive tumors, although there appears to be a trend toward lower Emax and Emean in the aggressive phenotypes.

1. Introduction

In the standard workup for malignant breast tumors, sonography is fundamental in the morphological and anatomical study of the breast. A relatively new sonography technique, sonoelastography, adds complementary information about lesion composition. Sonoelastography aims to determine the degree of stiffness of lesions based on the elastic properties of tissues [1]. Among different sonoelastography techniques, shear-wave elastography (SWE) is the only one that is highly reproducible [2–4]. Athanasiou et al. [5] were the first to report that malignant lesions were stiffer than benign lesions on SWE [2,6]. Later studies found that invasive lesions were stiffer than carcinomas in situ. However, the most reliable elastography parameters and their best cutoff values for classifying lesions remain to be determined. Evans et al. [7] shifted

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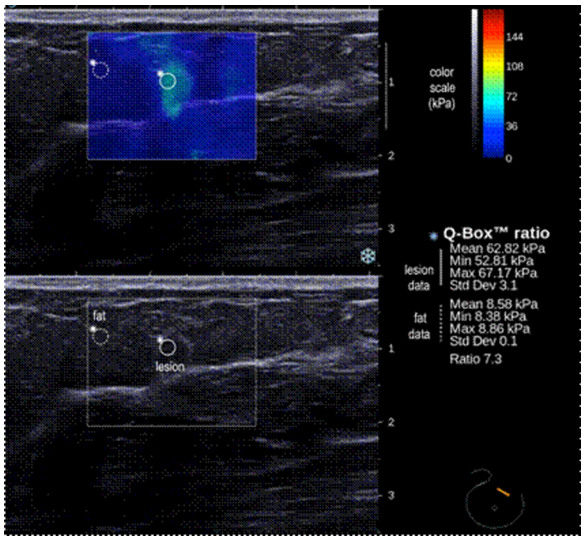

Fig. 1. Procedure for SWE. B-mode (lower image) and elastogram (upper image). An ROI (solid-line circle) is traced in the stiffest area of the lesion, determined by the color scale and another ROI is traced in the adjacent fat (dotted-line circle), then the different parameters for the two ROIs are obtained.

the focus to concentrate only on malignant lesions and specifically on invasive tumors. However, these authors did not take into account the tumor's molecular subtype, an aspect that is becoming increasingly more important in the classification, prognosis, and treatment of breast cancer. More recently, two retrospective studies reported the relation between mean stiffness and the different tumor subtypes [8,9]. We prospectively studied the maximum (Emax) and mean stiffness (Emean) on SWE of the invasive tumor subtypes defined at the St. Gallen Breast Cancer Congress [10]: luminal A, luminal B (HER2−), luminal B (HER2+), HER2, and triple-negative (TN).

2. Materials and methods

From December 2011 through October 2012, we prospectively studied 196 women (mean age, 59.3 years; range, 33–91 years) with 216 histologically confirmed malignant invasive breast lesions (a single lesion in 198, two lesions in 16, and three lesions in 2). There were no exclusion criteria. The institution's review board approved the study.

Most patients were referred directly from our hospital (gynecology and surgery outpatient clinics or breast cancer screening program). The rest were referred from two other centers in the metropolitan areas for which our unit is the reference center. All patients underwent SWE at our unit.

We used an ultrasound system (Aixplorer; SuperSonic Imagine; Aix en Provence, France) equipped with a 50 mm linear probe (bandwidth, 4–15 MHz) with B-mode and SWE capabilities.

We acquired at least one SWE image for each lesion. In a few cases multiple SWE images were acquired, but only the ones with extreme values were considered. The maximum diameter in the B-mode image was taken into account for SWE measurements. Measurements were shown by means of a color scale with a maximum range of 180 kPa. Measurements were obtained from two 2 mm^2 regions of interest (ROI): one located in the stiffest part of the lesion (in function of the color scale, which assigned red to the stiffest areas and blue to the softest areas) and the other in adjacent adipose tissue. In cases where the image appeared saturated (absence of color), the ROI also included the adjacent breast tissue (Fig. 1).

We recorded the following parameters: maximum stiffness (Emax), mean stiffness (Emean), minimum stiffness (Emin), and lesion-to-fat elasticity ratio (E-ratio); however, we only considered Emax and Emean, because they are the most reliable [2–6,11–13].

SWE studies were done by five experienced breast radiologists (more than 5 years); all SWE studies were supervised by a breast radiologist (S.G.) with 6 years' experience in elastography at that time.

After SWE, 14G core biopsy or 9G vacuum-assisted biopsy specimens were obtained from all lesions, regardless of the results of the SWE studies. The criteria for indicating a biopsy were based on the findings at mammography, B-mode ultrasound, and/or MRI). Histologic study confirmed malignancy and determined the histologic type of invasive cancer, histologic grade (according to the Elston modification of the Scarff–Bloom–Richardson criteria), estrogen and progesterone receptors, HER2 expression, and the Ki67 proliferation marker (determined by standard immunohistochemistry techniques). The cutoff for hormone receptor positivity was 10%, and Ki67 ≥ 14% was considered a high proliferation index. Immunohistochemistry was taken into consideration in classifying HER2. Tumors scoring 0 or 1+ were considered negative, and those scoring 3+ were considered positive. Tumors scoring 2+ were sent for fluorescence in situ hybridization (FISH). Tumors with HER2 amplification were considered positive when the ratio of the HER2 gene signal to chromosome 17 signal was greater than or equal to 2. Based on the immunohistochemistry results and the St. Gallen criteria [10], tumors were classified into five molecular subtypes: luminal A (estrogen receptor positive (ER+), progesterone receptor positive (PR+) or negative (PR−), HER2 negative, and low Ki67 expression), luminal B without HER2 overexpression (ER+, PR+ or PR−, HER2 negative, and high Ki67), luminal B with HER2 overexpression (ER+, PR+ or PR−, HER2 positive), HER2 (ER− and PR−, HER2 positive), and triple negative (TN) (ER−, PR−, and HER2 negative).

As values below 50 kPa or 80 kPa are considered to reflect low stiffness and thus benignity [2,6,11,13], we reviewed the B-mode images for all lesions that had Emax or Emean ≤80 kPa and classified them according to the BI-RADS criteria for ultrasound [14].

2.1. Statistical analysis

We did a descriptive analysis of all variables. We used Student's *t*-test or one-way ANOVA to compare Emax and Emean in function of tumor-related variables. Significance was set at $P < 0.05$. We used SPSS 20.0 (IBM Corp.) for all analyses.

3. Results

Table 1 provides a detailed summary of the results.

3.1. Size

Lesions measuring greater than 20 mm ($n = 85$) had significantly higher Emax (148.04 kPa) and Emean (118.32 kPa) ($P = 0.005$) than lesions measuring 1–10 mm ($n = 41$) (105.12 and 85.83 kPa), respectively, and than lesions measuring 11–20 mm ($n = 90$) (123.45 and 100.16 kPa, respectively).

3.2. Histology

Most lesions (176/216; 81.48%) were classified as invasive carcinoma of no special type (NST); the remaining lesions (40/216) consisted of lobular carcinomas (25/216; 11.6%), mucinous carcinomas (10/216), tubular carcinomas (3/216), and medullary carcinomas (2/216). Although no statistically significant differences were found, Emax was moderately higher for lobular carcinomas