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Relationship between elasticity and collagen fiber content in breast disease: A preliminary report

Zhi Li Wang [a,*], Lu Sun [b], Ye Li [a], Nan Li [a]

[a] Department of Ultrasound, Chinese People's Liberation Army General Hospital, 28 Fuxing Road, Beijing 100853, China
[b] Department of Pathology, Chinese People's Liberation Army General Hospital, 28 Fuxing Road, Beijing 100853, China

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ABSTRACT

Objective: To investigate the differences in elasticity and collagen fiber content between malignant and benign breast lesions, and to study the relationship between shear wave elasticity and the content of collagen fiber in extracellular matrix (ECM).

Materials and methods: Between May 2012 to May 2013, 106 patients with 116 breast lesions who were referred to our center for ultrasound-guided biopsy of a sonographically apparent breast lesion underwent shear wave elasticity examination. The specimen underwent Van Gieson (VG) dye and Image-Pro Plus 5.1 software was used to quantitatively analyze area of collagen fiber.

Results: Malignant lesions exhibited significantly higher maximum elasticity, mean elasticity, and elasticity ratio between lesions and surrounding parenchyma (140.43 ± 70.16 kPa, 63.11 ± 33.68 kPa, 3.49 ± 1.95) than benign lesions (54.64 ± 48.53 kPa, 34.52 ± 25.23 kPa, 2.25 ± 1.48) ($t = 5.329$, $t = 4.382$, $t = 4.487$, $P < 0.001$). The content of collagen fiber of malignant lesions was significantly higher than that of benign lesions ($t = 8.437$, $p = 0.000$). There was a positive correlation between max elasticity and the content of fiber collagen ($r = 0.746$).

Conclusion: The elasticity of breast lesions has a close correlation with the content of collagen fiber, which might have an important impact on tissue stiffness of breast lesions.

1. Introduction

Elastography is an emerging imaging technique that quantifies the "stiffness" of a breast lesion [1,2]. Studies had shown that the increase of matrix stiffness was one of the characteristics of cancer and stiffness had already been applied in the cancer detection [3,4]. In prior studies, elastography imaging had shown potential for differentiating benign from malignant breast disease and could possibly reduce the overall number of breast biopsies [5,6]. Most of previous studies used elastography scoring (ES) or strain ratio measurement (SR) as the diagnostic parameter, both of which were semi-quantitative parameters. Both of these semi-quantitative parameters were highly dependent on the organ's compressibility limits under stress and on the skill of the operator to correctly compress the tissue [7].

SWE is a new method of obtaining elastography images, where an acoustic pressure wave induces slow-moving shear waves within the tissue, and the speed of propagation of the shear wave is proportional to the tissue's elastic stiffness. Shear waves travel relatively faster in stiffer tissue compared to softer tissues. Ultrafast imaging of the propagation of shear waves allows measurement of small changes in velocity that occur when the waves pass through tissues of different stiffness. The velocity information can be mapped to create an image of the stiffness, with the option of measuring SWE features such as the minimum, mean, and maximum elasticity in a region of interest. Deformation of tissue leading to shear waves is created by an acoustic impulse that is generated electronically. With this method, the radiation force produced by the probe is used generate shear waves. This approach is different from conventional quasi-static elastography where the compression is applied externally by the operator.

The study by Evans et al. [8] demonstrated that shear wave elastography could give quantitative and reproducible information on solid breast lesions with diagnostic accuracy at least as good as conventional ultrasound with BI-RADS classification. Our previous study demonstrated that when optimal cut-off value of 91.53 kPa was used for max elasticity in the differentiation of breast lesions, the diagnostic sensitivity and specificity were 60.9% and 85.3%, respectively [9]. All these studies showed that shear wave elastography could give quantitative elasticity information that potentially could help in breast lesion characterization.

* Corresponding author. Tel.: +86 10 66936848; fax: +86 10 68161218.
E-mail address: wangzhililg@126.com (Z.L. Wang).

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Although malignant breast tumors exhibited stiff properties compared with benign breast tumors, the reasons for this difference remained to be elucidated. The extracellular matrix (ECM) in primary breast cancers was significantly changed compared with normal breast tissue [10,11]. Collagen fiber is the most abundant structural protein in ECM [12], and increased collagen fiber I had been found to facilitate breast tumor formation, invasion, and metastasis [13,14]. Study has demonstrated that, in cancer progression, there were changes of ECM, such as increasing collagen expression, collagen deposition and structure changes [15]. X-ray mammography, which detected dense fibroglandular tissue in the breast, demonstrated that women with high (50–74% versus <5%) breast density have a 4.64-fold increased risk of developing breast carcinoma [16]. Levental discovered that breast tumorigenesis was accompanied by collagen crosslinking, ECM stiffening, and increased focal adhesions. Induction of collagen crosslinking stiffened the ECM, promoted focal adhesions, enhanced PI3 kinase (PI3K) activity, and induced the invasion of an oncogene-initiated epithelium [17]. Studies also had demonstrated that the proportion of collagen fiber areas was the strongest pathologic determinant of mean stiffness in hepatocellular carcinomas [18]. To our knowledge, there are no investigations comparing elasticity with collagen fiber content in breast lesions.

The purpose of this study was to investigate the differences in elasticity and collagen fiber content between malignant and benign breast lesions, and to study the relationship between shear wave elasticity and the content of collagen fiber in ECM.

2. Material and methods

2.1. Patients

Between March 2012 to March 2013, a prospective study was conducted at our institute. The study population consisted of consecutive patients referred to our center for ultrasound-guided biopsy of a sonographically apparent breast lesion. Subjects were included following their consent for the index testing. We excluded pregnant and lactating women, those with breast implants, women receiving chemotherapy or radiotherapy for any cancer, skin masses and any which had been biopsied, and patients with a history of ipsilateral breast surgery. Pathologic diagnosis was used as the reference standard.

One hundred and six consecutive patients with one hundred and sixteen solid lesions were included in this study. Of these 106 women, 61 women were asymptomatic, 45 women presented with a palpable mass, and two showed nipple discharge. The age of the patients was 22–82 years (mean age ±standard deviation, 51.8 ± 28.3 years). Of these patients, 96 patients had a single nodule, and 10 patients had two nodules. The maximum diameter of the nodules ranged from 0.7 to 4.6 cm (mean diameter ± standard deviation, 2.1 ± 2.0 cm).

Informed consent was obtained from all patients, and the study was approved by our local Ethics Committee. Written informed consent was obtained from every patient at enrollment.

2.2. US examination and SWE examination

US examination and SWE examination were performed with Aixplorer® ultrasound system (SuperSonic Imagine, Aix en Provence, France) with the center frequency of the probe was 12 MHz.

The ultrasound images underwent American College of Radiology Breast Imaging Reporting and Data System (ACR BI-RADS) [14] classification by two breast radiologists (Zhi Li Wang and Nan Li) who have twelve years and ten years experience in breast ultrasound, respectively.

After the ultrasound examination, the radiologist switched to the elastography model. The probe was applied as light as possible to give no pressure to the lesion. The probe needs to be kept still for 10–20 s during acquisition of the elastography images (due to a slow frame rate) and this was often best done during a breath hold. The elastography views selected were those most clearly displaying abnormal stiffness within the plane but with the absence of movement or pressure artifact, such as the red area under the probe. After the stable image was obtained, the image was recorded and region of interest (ROI) was chosen to calculate the elasticity value. The ROI was chosen as large as possible to cover the whole lesion including calcification potentially present and the edge of the lesion. Because the ROI box was circle, it was hard to cover the whole lesion, especially for the lesions with irregular edge. But we tried our best to cover most part of the lesion, especially for the hardest part of the lesion. Another ROI in peripheral parenchyma was selected to be at a similar depth to that of the breast lesion. For each patient, three ROIs in the lesion and peripheral parenchyma, respectively, were selected and the mean value was regarded as the final value. The ROI in peripheral parenchyma was made as much as possible to be of the same size and depth of the corresponding breast lesion. The maximum value within the ROI, called max elasticity, the mean elasticity, the minimum value within the ROI, called min elasticity and elasticity ratio between lesions and surrounding parenchyma were recorded.

Table 1
Maximum, mean and minimum elasticity and elasticity ratio between lesions and surrounding parenchyma of malignant and benign lesions.

	Max elasticity (kPa)	Mean elasticity (kPa)	Min elasticity (kPa)	Elasticity ratio
Malignant lesions	140.43 ± 70.16	63.11 ± 33.68	25.48 ± 19.85	3.49 ± 1.95
Benign lesions	54.64 ± 48.53	34.52 ± 25.23	18.86 ± 15.95	2.25 ± 1.48
t test	6.329	5.382	0.567	4.487
p-value	0.000	0.000	0.356	0.001

Table 2
Maximum, mean and minimum elasticity and elasticity ratio between lesions and surrounding parenchyma among different pathology lesions.

Pathological diagnosis	Maximum elasticity (kPa)	Mean elasticity (kPa)	Minimum elasticity (kPa)	Mean elasticity ratio
IDC (n = 51)	142.45 ± 68.37	64.12 ± 33.97	26.31 ± 21.76	3.51 ± 1.89
DCIS (n = 19)	134.17 ± 61.45	60.62 ± 36.59	25.15 ± 19.11	3.35 ± 1.68
ILC (n = 5)	138.89 ± 64.78	61.38 ± 29.43	25.01 ± 20.45	3.26 ± 1.73
Fibroadenoma (n = 19)	53.25 ± 49.63	35.03 ± 29.78	17.58 ± 10.94	2.04 ± 1.22
Fibroadenoses (n = 12)	55.14 ± 50.69	30.84 ± 27.82	23.13 ± 29.31	2.43 ± 1.94
Papillomas (n = 6)	63.62 ± 75.02	40.24 ± 45.47	24.63 ± 21.74	2.57 ± 2.13
Inflammation (n = 4)	44.26 ± 39.47	33.72 ± 33.48	13.58 ± 10.32	2.28 ± 2.14