BREAST

Stiffness of the surrounding tissue of breast lesions evaluated by ultrasound elastography

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Abstract

Objective To evaluate the stiffness of the surrounding tissue of breast lesions using the strain ratio assessment method by ultrasound (US) elastography.

Methods This was an institutional ethics committee approved prospective study. A total of 127 breast lesions in 118 women (mean age 48.23±14.32, range 20–90) were examined with conventional and elastographic US. The strain ratio assessment method was utilized to semi-quantitatively evaluate the stiffness of the breast lesions and the surrounding tissue.

Results Fifty-five lesions were malignant and 72 were benign. The strain ratio of the surrounding tissue was significantly higher in malignant cases (1.49 ± 0.67) than in benign ones (1.17 ± 0.44) (P=0.001), and yielded an Az value of 0.669 in the diagnosis of breast lesions. There was a significant high positive correlation between the strain ratio of the lesion and the strain ratio of the surrounding tissue in the malignant group (r=0.740, P<0.001), and a significant moderate positive correlation in the benign group (r=0.595, P<0.001).

Conclusion The stiffness of the surrounding tissue of malignant breast lesions was higher than that of benign lesions. The strain ratio of the surrounding tissue and the lesions was significantly correlated, and has potential for breast lesion diagnosis.

Key Points

- Stiffness of the surrounding tissue of malignant breast lesions was increased.
- Stiffness of the surrounding tissue correlated with stiffness of breast lesions.
- Stiffness of the surrounding tissue has potential use in diagnosis of breast lesions.

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Introduction

Breast cancer is the most common cancer in both the developing and developed world, and is the leading cause of death among women globally [1]. Mammography, magnetic resonance imaging and ultrasound (US) are the main imaging diagnostic methods employed for characterization of breast lesions and determination of their risk for malignancy [2–5]. The advantage of US is that it can distinguish cystic from solid lesions with a high degree of certainty. However, the inadequate specificity in differentiating benign from malignant solid breast masses has limited the usefulness of breast US [6]. Recently, US elastography has been introduced and allows improved characterization of solid breast lesions with high specificity [7].

Elastography can be used to depict the stiffness or strain of soft tissues [8, 9]. Two types of US elastography are currently available: strain elastography and shear wave elastography [6]. Strain elastography is based on the comparison of echo signals acquired before and after compression of the tissue. The results of the comparison are displayed as an elastographic image, which shows the relative stiffness of the tissues [7, 8, 10, 11]. In contrast, shear wave elastography, including the acoustic radiation force impulse imaging (ARFI) and the supersonic shear-wave imaging (SSI), can provide a quantitative assessment of the stiffness of tissues by measuring the propagation speed of shear waves, which are generated by the acoustic radiation force [12–14].

In strain elastography, the five-point elasticity scoring system yielded a sensitivity of 70.1–98.6 % and a specificity of 45.7–98.5 % in determining malignant breast lesions [7, 15–22], and the strain ratio afforded a sensitivity of 87.1–



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95.0 % and a specificity of 74.0–94.3 % [21, 23–28]; in shear wave elastography, ARFI achieved a sensitivity of 75.6–96.3 % and a specificity of 53.3–95.1 % [29–32], and SSI afforded a sensitivity of 60.9–97.0 % and a specificity of 83.0–93.7 % [33–36].

Studies have shown that many malignant breast lesions exhibited high stiffness not only in the lesion but also in the surrounding tissue, whereas benign breast lesions usually demonstrate low stiffness in both lesion and the surrounding area [7, 37, 38]. In those studies, however, the stiffness of the surrounding tissue of breast lesions was evaluated by subjective visual inspection rather than by quantitative analysis. A semi-quantitative method, referred to as the strain ratio measurement, has been developed and used in an attempt to identify benign and malignant breast lesions [23, 24, 39]. However, limited by the measurement software provided by the manufacturer, the strain ratio only reflects the relative stiffness of the lesion rather than the surrounding tissue.

The high stiffness of the surrounding tissue of malignant breast lesions indicates the infiltration of cancer cells into the peritumoral tissue [7]. Studies have revealed that the peritumoral invasion is an independent prognostic factor significantly associated with increased risk of relapse and death in node-negative breast cancer patients [40, 41]. Therefore, the objective measurement of the stiffness of the surrounding tissue might have clinical importance.

The purpose of this study was to evaluate the stiffness of the surrounding tissue of breast lesions using the strain ratio assessment method with a recently available commercial US system.

Materials and methods

Patients

Our institutional ethics committee approved this prospective study, and informed consent was obtained from each patient. From August 2012 through September 2012, 127 consecutive women with breast lesions on clinical examination and/or imaging underwent conventional and elastographic US of 138 breast lesions. Eleven lesions in nine women were later excluded owing to the following reasons: five lesions without histopathological confirmation, four lesions with simple breast cyst confirmed by conventional US and two lesions without satisfactory elastographic images. Finally, 127 breast lesions in 118 women (mean age 48.23±14.32, range 20–90) were included in the final data analysis.

Image acquisition

Breast US examinations were performed with a DC-8 diagnostic US system (Mindray Medical International, Shenzhen,

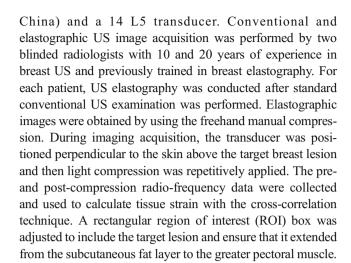


Image analysis

Conventional US images for each lesion were evaluated individually by each radiologist who performed the US examinations when the images were obtained. US Breast Imaging Reporting and Data System (BI-RADS) final assessment categories were assigned independent of mammogram findings, including categories 3, 4a, 4b, 4c or 5 [42, 43].

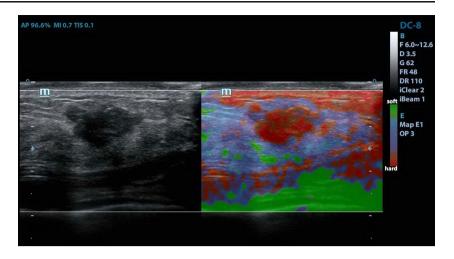
The elastographic image was visualized in a colour-coded mode. No strain areas (hardest areas) were displayed as red, intermediate elasticity areas were displayed as blue and elastic areas (softest areas) were coded as green. Subjective qualitative interpretation of the elastographic images was done using the five-point scoring system [7], which distinguishes five types of lesions: score 1, an even strain for the entire lesion; score 2, strain in most of the lesion; score 3, strain at the periphery with sparing of the centre; score 4, the entire lesion was stiff; score 5, the entire lesion and surrounding tissue were stiff.

For semi-quantitative evaluation of the stiffness of the surrounding tissue of breast lesions, the strain ratio assessment method was utilized by using the embedded software program in the US system. Calculation of the strain ratio of breast lesion or the surrounding tissue was based on determining the average strain of the breast lesion or the surrounding tissue and comparing it to the average strain of the adjacent normal-appearing breast glandular tissue at a depth similar or as close to the depth of the target lesion. Previous studies usually take fatty tissue as the reference normal tissue [44]; however, the breast fatty tissue layer in East Asian women is comparatively thin, sometimes even not visible on ultrasound (Fig. 1). Therefore, glandular tissue was selected as the reference tissue in our study.

The first ROI (A) was manually drawn along the border of the lesion; the second ROI (shell), an area just outside the ROI A with a width of 1 mm, was then automatically created by activating the "shell" button on the control panel of the US



Fig. 1 Intraductal papilloma in a 24-year-old woman. B-mode image shows an irregular hypoechoic mass (*left*). Elastographic image shows that the lesion was scored 4 (*right*). Images show that the breast is composed of glandular tissue, and fatty tissue layer is almost not visible



system. The third ROI (B) was manually drawn at the normal-appearing breast glandular tissue. The average strain within ROI A represented the strain of the lesion and was expressed as A, that within ROI shell represented the strain of the surrounding tissue and was expressed as shell, and that within ROI B represented the strain of the glandular tissue and was expressed as B. Therefore, the stiffness of the lesion can be reflected by the strain ratio B/A, and that of the surrounding tissue by B/S shell.

Both qualitative and semi-quantitative evaluations of the elastographic images were performed individually by each radiologist who performed the US examinations at the time when elasticity images were obtained.

Pathological examination

The final diagnosis was determined by histopathology after surgical excision or US-guided core needle biopsy. All diagnoses were made by a specialized breast pathologist with 25 years of experience, who was blinded to the results of US.

Statistical analysis

Statistical analyses were performed using SPSS version 17.0 (SPSS Inc, Chicago, IL). Receiver operator characteristic (ROC) analysis was performed using Stata software, version 12 (StataCorp, College Station, TX). P<0.05 was considered statistically significant. The nonparametric Mann—Whitney U test or Student's t test was used to compare the elasticity scores and the strain ratios. The correlations between B/A and B/shell, and between elasticity score and B/shell were evaluated by the Spearman correlation coefficient. The strength of the correlation coefficient was set as the following: <0.2, a slight correlation; 0.2–0.4, a low correlation; 0.4–0.7, a moderate correlation; 0.7–0.9, a high correlation; >0.9, a very high correlation [45]. ROC analysis was performed to assess the sensitivity and specificity, and the best cutoff point to achieve the

maximal sum of the sensitivity and specificity was analysed. The areas under the ROC curves (Az) were calculated to compare the diagnostic performances of different elasticity parameters. For the purpose of evaluating the effect of lesion size on the diagnostic accuracy of elasticity parameters, ROC assessment was carried out in two size subgroups: ≤15 mm and >15 mm.

Results

Pathological diagnoses

Fifty-five of the 127 lesions were diagnosed as malignant and 72 as benign. The diameters of benign lesions and malignant lesions were 7.60-50.9 mm (22.41 ± 9.99 mm) and 6.50-59.20 mm (17.23 ± 8.76 mm), respectively. There were 55 lesions sized ≤15 mm (16 malignant, 39 benign), 72 lesions sized ≥15 mm (39 malignant, 33 benign). Final pathological diagnoses are shown in Table 1. The most common type of benign lesion was fibroadenoma (53, 73.6%), and the most common type of malignant lesion was invasive ductal carcinoma (IDC) (43, 78.2%), Among the 43 cases of IDCs, one was IDC grade 1(IDC 1), 31 were IDC grade 2 (IDC 2) and 11 were IDC grade 3 (IDC 3).

Diagnostic performance of conventional US

The final assessment of BI-RADS categories of the 127 lesions is shown in Table 2. The optimal cutoff was between category 4a and 4b, which yielded a sensitivity of 83.6 %, a specificity of 87.5 % and an Az value of 0.908.

Elastography results

The mean elasticity score, the mean B/A and the mean B/A in malignant and benign breast lesions according to the BI-



Table 1 Pathological diagnoses in 127 breast lesions

Malignant lesions	N	Benign lesions	N
Invasive ductal carcinoma	43	Fibroadenoma	53
Invasive lobular carcinoma	5	Intraductal papilloma	9
Ductal carcinoma in situ	4	ANDI	7
Mucinous carcinoma	1	Complicated cyst	2
Metaplastic carcinoma	1	Lipoma	1
Adenoid cystic carcinoma	1		

ANDI aberrations of normal development and involution without fibroadenoma

RADS assessment category are shown in Table 2. The mean elasticity score was significantly higher for malignant lesions (4.35 ± 0.80) than for benign ones (2.54 ± 0.84) (P<0.001); the mean B/A was significantly higher for malignant lesions (2.34 ± 1.15) than for benign ones (1.45 ± 0.62) (P<0.001); and the mean B/shell was significantly higher for malignant lesions (1.50 ± 0.67) than for benign ones (1.16 ± 0.44) (P=0.001) (Table 3, Figs. 2 and 3).

As shown in Fig. 4, significant positive correlations were found between B/A and B/shell in the malignant group, the benign group and the total group (r=0.740, r=0.595 and r=0.689, respectively; P<0.001 for all). There were no correlations between elasticity score and B/shell in the malignant group and the benign group (r=0.251 and r=0.084, respectively; P>0.05 for both), whereas there was a significant positive correlation in the total group (r=0.310, P<0.001).

In the malignant group, 29 (52.7 %) malignant lesions had a score of 5, and 26 (47.3 %) malignant lesions had a score of 2–4. The mean B/shell was significantly higher for malignant lesions scored 5 (1.67±0.74) than for malignant ones scored 2–4 (1.31±0.53) (P=0.042). In addition, the mean elasticity score, the mean B/A and the mean B/shell were higher for IDC 3 lesions than for IDC 1 and IDC 2; however, these differences were not significant (P>0.05 for all) (Table 4).

Diagnostic performance of elasticity parameters

In the total group (Table 5), the Az value for elasticity score (0.917) was comparable with that for conventional US (0.908, P=0.702), and significantly higher than that for B/A (0.786; P<0.001) and B/shell (0.669; P<0.001). The Az value for B/A was significantly higher than that for B/shell (P=0.003).

There were no significantly differences of the Az values of the three elasticity parameters between the lesions \leq 15 mm and the lesions \geq 15 mm (P=0.397 for elasticity score, P=0.499 for B/A and P=0.671 for B/Shell).



assessment category parameters in malignant and benign lesions according to the BI-RADS a Elasticity Fable 2

Parameters	BI-RADS 3		BI-RADS 4a		BI-RADS 4b		BI-RADS 4c		BI-RADS 5	
	M(n=0)	A(n=0) B $(n=17)$	M (<i>n</i> =9)	B (<i>n</i> =46)	M(n=12)	B (n=7)	M(n=10)	B $(n=2)$	M (n=24)	B (n=0)
Elasticity	NA	2.24 ± 0.66	3.78 ± 0.97	2.54 ± 0.86	4.25 ± 0.87	3.00 ± 0.82	4.30 ± 0.82	3.50 ± 0.71	4.63 ± 0.58	NA
B/A	NA	1.33 ± 0.57	2.19 ± 1.00	1.44 ± 0.65	2.19±0.89	1.57 ± 0.62	2.73±1.55	1.72 ± 0.86	2.30±1.14	NA
B/shell	NA	(0.65-2.99) 1.17 ± 0.65	$(1.15-3.84)$ 1.35 ± 0.67	(0.61-4.06) 1.17±0.36	(1.52-3.80) 1.56 ± 0.65	(0.94-2.83) 1.05 ± 0.22	(0.7/-3.83) 1.60 ± 0.52	(1.11-2.55) 1.45 ± 0.72	(0.48-3.62) 1.49 ± 0.75	NA
		(0.56-3.12)	(0.35-2.34)	(0.48-2.17)	(0.69-2.92)	(0.80-1.50)	(0.80-2.44)	(0.94-1.96)	(0.36 - 3.69)	

M malignant, B benign, NA not available

 Table 3 Elasticity parameters in malignant and benign lesions

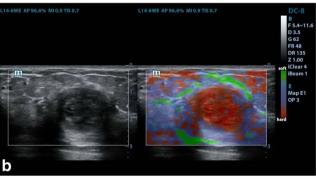
Data are mean \pm standard deviation, and numbers in parentheses are range

Parameters	Malignant lesions (<i>n</i> =55)	Benign lesions (<i>n</i> =72)	P value	
Elasticity score	4.35±0.80 (2-5)	2.54±0.84 (1-5)	< 0.001	
B/A	2.34±1.15 (0.48-5.83)	1.45±0.62 (0.61-4.06)	< 0.001	
B/shell	$1.50\pm0.67~(0.35-3.69)$	1.16±0.44 (0.48–3.12)	0.001	

Discussion

The phenomenon of increased stiffness in the surrounding tissue of malignant breast lesions has been found by both strain elastography and shear wave elastography. In strain elastography, a larger tumour size at elasticity imaging than at B-mode image is a specific characteristic of malignant breast lesions according to the size criteria, which is mainly based on the algorithm method utilized by the Siemens and Philips US elastographic systems [38, 46–48]. Additionally,





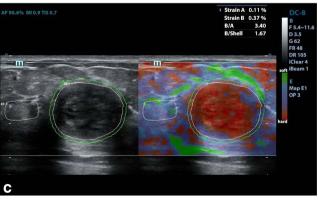
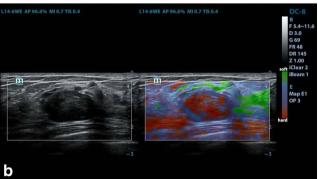


Fig. 2 Invasive ductal carcinoma grade 3 in a 57-year-old woman. B-mode image shows a regular hypoechoic mass with scattered cystic areas (a). Elastographic image shows that the lesion was scored 4 (b). The strain ratio of the lesion was 3.40, and the strain ratio of the surrounding tissue was 1.67 (c)





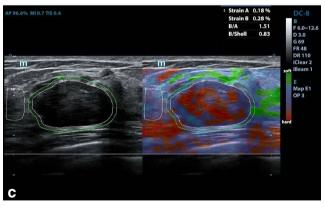
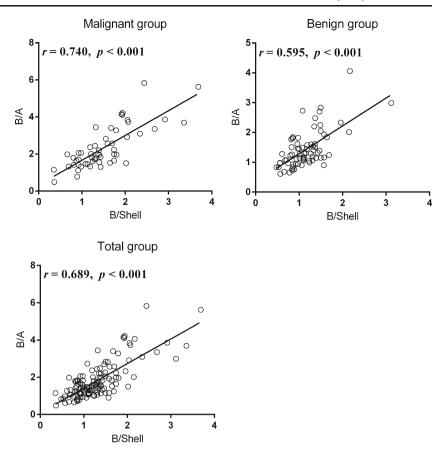


Fig. 3 Fibroadenoma in a 44-year-old woman. B-mode image shows a regular hypoechoic mass (a). Elastographic image shows that the lesion was scored 2 (b). The strain ratio of the lesion was 1.51, and the strain ratio of the surrounding tissue was 0.83 (c)



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Fig. 4 High positive correlation between the stiffness of the lesions (B/A) and the stiffness of the surrounding tissue of the lesions (B/Shell) in the malignant group (r=0.740, P<0.001), moderate positive correlations in the benign and the total group (r=0.595, and r=0.689, respectively; P<0.001 for both)



the entire lesion in the majority of malignant lesions, sometimes along with the surrounding tissue, is stiffer than normal breast tissue according to the stiffness criteria, which is applicable to almost all of the commercially available US elastographic systems [7, 20, 21, 37, 49–52]. In shear wave elastography, many studies, using the SSI technique, revealed that some malignant breast lesions showed typical peritumoral stiffness in the colour elastic map [35, 53–55].

To our knowledge, however, no studies have yet specifically evaluated the stiffness of the surrounding tissue of breast lesions by semi-quantitative strain elastography. This is the first application of on-line strain ratio measurement to assess the stiffness of the surrounding tissue. Our results revealed that the strain ratio of the surrounding tissue was significantly higher in malignant cases (1.49 ± 0.67) than in benign ones (1.17 ± 0.44) (P=0.001). Thus, consistent with the previous studies mentioned above, our study semi-quantitatively confirmed that the stiffness of the surrounding tissue of malignant

breast lesions was increased. Moreover, our study demonstrated that the stiffness of the surrounding tissue was significantly higher for malignant lesions scored 5 (1.67 \pm 0.74) than for malignant ones scored 2–4 (1.31 \pm 0.53) (P=0.042), which was due to score 5 indicating that the surrounding tissue was stiff. In addition, our results showed that both the elasticity score and the strain ratio were significantly higher in malignant lesions than in benign ones (P<0.001 for both), which was consistent with previous studies [28, 39, 56].

There was a moderate correlation between the stiffness of the lesion (B/A) and the stiffness of the surrounding tissue (B/A) shell) in the benign group, whereas there was a high correlation in the malignant group. The moderate correlation in the benign group might be due to more obvious surrounding fibrotic and sclerosing tissue changes occurring in stiffer benign lesions. A possible reason for the high correlation in the malignant group was that high stiffness malignant lesions might have more obvious desmoplastic reaction or cancerous

Table 4 Elasticity parameters in IDC lesions

Data are mean ± standard deviation, and numbers in parentheses are range

Parameters	IDC 1 plus IDC 2 (<i>n</i> =32)	IDC 3 $(n=11)$ P var	
Elasticity score	4.38±0.75 (3-5)	4.64±0.67 (3-5)	0.342
B/A	$2.31\pm0.99~(0.77-4.22)$	$2.77 \pm 1.67 \ (0.48 - 5.83)$	0.283
B/shell	1.42±0.59 (0.35–3.36)	1.77±0.94 (0.36–3.69)	0.164



Table 5 Diagnostic Performances of elasticity parameters according to different size groups

Total (n=127)	>3			
	- 3	83.6	87.5	0.917
$\leq 15 \text{ mm } (n=55)$	>3	87.5	87.2	0.946
>15 mm (<i>n</i> =72)	>3	82.1	87.9	0.910
Total $(n=127)$	>1.29	92.6	54.2	0.786
$\leq 15 \text{ mm } (n=55)$	>1.39	100	56.4	0.839
>15 mm (<i>n</i> =72)	>1.60	71.8	78.8	0.786
Total $(n=127)$	>1.64	38.2	93.1	0.669
≤15 mm (<i>n</i> =55)	>1.64	62.5	92.3	0.735
>15 mm (n=72)	>1.18	69.2	69.7	0.690
	\leq 15 mm (n =55) >15 mm (n =72) Total (n =127)	\leq 15 mm (n =55) $>$ 1.39 $>$ 15 mm (n =72) $>$ 1.60 Total (n =127) $>$ 1.64 \leq 15 mm (n =55) $>$ 1.64	\leq 15 mm (n =55) $>$ 1.39 100 >15 mm (n =72) $>$ 1.60 71.8 Total (n =127) $>$ 1.64 38.2 \leq 15 mm (n =55) $>$ 1.64 62.5	$\leq 15 \text{ mm } (n=55)$ >1.39 100 56.4 $>15 \text{ mm } (n=72)$ >1.60 71.8 78.8 100 10

infiltration in the peritumoral region. Many studies found that higher lesion stiffness values correlated with high histological grades of breast cancer [29, 57–59]. Consequently, it is reasonable to believe that the stiffness of the surrounding tissue might have potential use in predicting the outcome of breast cancer patients. The elasticity score, the stiffness of the lesion and the stiffness of the surrounding tissue were higher for IDC 3 lesions than for IDC 1 and IDC 2. However, those differences were not significant (P>0.05 for all), which might be due to the relatively small sample size in our study.

Elasticity score showed the best diagnostic performance, followed by B/A and B/shell. As compared with conventional US, elasticity score has similar diagnostic performance (Az, 0.917 vs. 0.908, p=0.702). Our result were consistent with data from a meta-analysis [60], which showed that the application of elasticity score as a single test was not superior to conventional US alone (Az, 0.91 vs. 0.92). Meta-analysis also showed that the sensitivity and specificity values for the strain ratio of lesions were 88.3 % and 81.4 %, respectively, which were similar to those for elasticity score, namely 83.4 % and 84.2 %, respectively [61]. However, our study revealed that elasticity score yielded satisfactory sensitivity (83.6 %) and specificity (87.5 %), whereas the strain ratio of lesions (B/A) showed high sensitivity (92.6 %) but poor specificity (54.2 %). This discordance may be in part because fatty tissue was used as the reference normal tissue in previous studies, whereas glandular tissue was used in our study owing to the smaller area of breast fatty tissue in East Asian women [62]. The stiffness of glandular tissue was significantly higher than that of fatty tissue [63], which can explain the low value of the strain ratio of lesions (B/A) in our study compared with previous studies [44]. Whereas the diagnostic value of strain ratio of the surrounding tissue was never reported in previous studies, our study found that the strain ratio of the surrounding tissue (B/shell) provided an Az value of 0.669, a specificity of 93.1 % and a sensitivity of 38.2 %.

There were no significant differences in the diagnostic performances of elasticity parameters between the lesions ≤15 mm and >15 mm. These results can be compared to the meta-analysis by Sadigh et al. [64] which concluded that the performance of elastography does not significantly vary with lesion size.

In our study, the area just outside a lesion with a width of 1 mm, i.e. the "shell", was defined as the surrounding tissue region. This definition was basically consistent with the criteria proposed in pathological research, in which peritumoral region meant the area adjacent to, but outside, the margin of the breast tumour with a width of one highpower microscopic field or more, i.e. 0.5 mm or more [41]. The presence of high stiffness of the surrounding tissue in malignant lesions might be caused by the desmoplastic reaction or the infiltration of cancer cells into the peritumoral tissue [7, 35, 65]. Several studies have shown that both peritumoral stroma and peritumoral invasion played a critical role in the spreading and metastasis of breast cancer [40, 41, 66, 67]. Therefore, even though the diagnostic value of strain ratio of the surrounding tissue was inferior to the strain ratio of lesion and elasticity score, it is reasonable to believe that the objective measurement of the stiffness of the surrounding tissue is of clinical significance. Further prospective study with a large population is warranted, with an emphasis on the relationship between the stiffness of the surrounding tissue of breast cancer and the histological prognostic features such as tumour type, histological grade, vascular invasion status and lymph node status.

There were some limitations to this study. First, we did not evaluate the interobserver and intraobserver variability in data acquisition and interpretation. Second, our study was influenced by sampling bias. Because our institution is a referral centre, patients usually present with suspicious breast lesions and typically require surgical exploration. Consequently, the malignancy percentage was higher in our study. Third, we drew the borders of lesions manually; thus, lesions with ill-defined borders might have more inaccurate measurements for both B/A and B/shell. Forth, the sample size was relatively small. Thus, further studies with larger sample sizes are



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required to clarify the value of the semi-quantitative evaluation of the stiffness of the surrounding tissue of breast lesions.

In conclusion, our study, by using semi-quantitative measurement methods, showed that the stiffness of the surrounding tissue of malignant breast lesions was higher than that of benign ones. The stiffness of the surrounding tissue showed significant high correlation with the lesion stiffness in the malignant group, and showed significant moderate correlation in the benign group. Additionally, the strain ratio of the surrounding tissue has potential use in the diagnosis of breast lesions.

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References

- Benson JR, Jatoi I (2012) The global breast cancer burden. Future Oncol 8:697–702
- Kriege M, Brekelmans CT, Boetes C et al (2004) Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. N Engl J Med 351:427–437
- Warner E, Plewes DB, Hill KA et al (2004) Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. JAMA 292:1317–1325
- Kolb TM, Lichy J, Newhouse JH (1998) Occult cancer in women with dense breasts: detection with screening US—diagnostic yield and tumor characteristics. Radiology 207:191–199
- Schaefer FK, Waldmann A, Katalinic A et al (2010) Influence of additional breast ultrasound on cancer detection in a cohort study for quality assurance in breast diagnosis-analysis of 102,577 diagnostic procedures. Eur Radiol 20:1085–1092
- 6. Hooley RJ, Scoutt LM, Philpotts LE (2013) Breast ultrasonography: state of the art. Radiology 268:642–659
- Itoh A, Ueno E, Tohno E et al (2006) Breast disease: clinical application of US elastography for diagnosis. Radiology 239:341–350
- Ophir J, Cespedes I, Ponnekanti H, Yazdi Y, Li X (1991) Elastography: a quantitative method for imaging the elasticity of biological tissues. Ultrason Imaging 13:111–134
- Ophir J, Garra B, Kallel F et al (2000) Elastographic imaging. Ultrasound Med Biol 26(Suppl 1):S23–29
- Balleyguier C, Ciolovan L, Ammari S et al (2013) Breast elastography: the technical process and its applications. Diagn Interv Imaging 94:503–513
- Goddi A, Bonardi M, Alessi S (2012) Breast elastography: a literature review. J Ultrasound 15:192–198
- Nightingale K, McAleavey S, Trahey G (2003) Shear-wave generation using acoustic radiation force: in vivo and ex vivo results. Ultrasound Med Biol 29:1715–1723
- Nightingale KR, Zhai L, Dahl JJ, Frinkley KD, Palmeri ML (2006)
 Shear wave velocity estimation using acoustic radiation force

- impulsive excitation in liver in vivo. Proc 2006 I.E. Ultrasonics Symposium 1156–1160.
- Bercoff J, Tanter M, Fink M (2004) Supersonic shear imaging: a new technique for soft tissue elasticity mapping. IEEE Trans Ultrason Ferroelectr Freq Control 51:396–409
- Tan SM, Teh HS, Mancer JF, Poh WT (2008) Improving B mode ultrasound evaluation of breast lesions with real-time ultrasound elastography

 –a clinical approach. Breast 17:252

 –257
- Thomas A, Kummel S, Fritzsche F et al (2006) Real-time sonoelastography performed in addition to B-mode ultrasound and mammography: improved differentiation of breast lesions? Acad Radiol 13:1496–1504
- 17. Zhi H, Ou B, Luo BM, Feng X, Wen YL, Yang HY (2007) Comparison of ultrasound elastography, mammography, and sonography in the diagnosis of solid breast lesions. J Ultrasound Med 26: 807–815
- Zhu QL, Jiang YX, Liu JB et al (2008) Real-time ultrasound elastography: its potential role in assessment of breast lesions. Ultrasound Med Biol 34:1232–1238
- Parajuly SS, Lan PY, Yan L, Gang YZ, Lin L (2010) Breast elastography: a hospital-based preliminary study in China. Asian Pac J Cancer Prev 11:809–814
- Lee JH, Kim SH, Kang BJ et al (2011) Role and clinical usefulness of elastography in small breast masses. Acad Radiol 18:74–80
- Mansour SM, Omar OS (2012) Elastography ultrasound and questionable breast lesions: does it count? Eur J Radiol 81:3234–3244
- 22. Zhi H, Xiao XY, Ou B et al (2012) Could ultrasonic elastography help the diagnosis of small (</ = 2 cm) breast cancer with the usage of sonographic BI-RADS classification? Eur J Radiol 81:3216–3221
- Thomas A, Degenhardt F, Farrokh A, Wojcinski S, Slowinski T, Fischer T (2010) Significant differentiation of focal breast lesions: calculation of strain ratio in breast sonoelastography. Acad Radiol 17: 558–563
- Cho N, Moon WK, Kim HY, Chang JM, Park SH, Lyou CY (2010) Sonoelastographic strain index for differentiation of benign and malignant nonpalpable breast masses. J Ultrasound Med 29:1–7
- Fischer T, Peisker U, Fiedor S et al (2012) Significant differentiation of focal breast lesions: raw data-based calculation of strain ratio. Ultraschall Med 33:372–379
- Zhao QL, Ruan LT, Zhang H, Yin YM, Duan SX (2012) Diagnosis of solid breast lesions by elastography 5-point score and strain ratio method. Eur J Radiol 81:3245–3249
- Parajuly SS, Lan PY, Yun MB, Gang YZ, Hua Z (2012) Diagnostic potential of strain ratio measurement and a 5 point scoring method for detection of breast cancer: Chinese experience. Asian Pac J Cancer Prev 13:1447–1452
- Zhi H, Xiao XY, Yang HY, Ou B, Wen YL, Luo BM (2010) Ultrasonic elastography in breast cancer diagnosis: strain ratio vs 5point scale. Acad Radiol 17:1227–1233
- Zhou J, Zhan W, Chang C et al (2013) Role of acoustic shear wave velocity measurement in characterization of breast lesions. J Ultrasound Med 32:285–294
- Jin ZQ, Li XR, Zhou HL et al (2012) Acoustic radiation force impulse elastography of breast imaging reporting and data system category 4 breast lesions. Clin Breast Cancer 12:420–427
- Bai M, Du L, Gu J, Li F, Jia X (2012) Virtual touch tissue quantification using acoustic radiation force impulse technology: initial clinical experience with solid breast masses. J Ultrasound Med 31: 289–294
- 32. Meng W, Zhang G, Wu C, Wu G, Song Y, Lu Z (2011) Preliminary results of acoustic radiation force impulse (ARFI) ultrasound imaging of breast lesions. Ultrasound Med Biol 37:1436–1443
- Chang JM, Moon WK, Cho N et al (2011) Clinical application of shear wave elastography (SWE) in the diagnosis of benign and malignant breast diseases. Breast Cancer Res Treat 129:89–97



- Wang ZL, Li JL, Li M, Huang Y, Wan WB, Tang J (2013) Study of quantitative elastography with supersonic shear imaging in the diagnosis of breast tumours. Radiol Med 118:583–590
- Evans A, Whelehan P, Thomson K et al (2010) Quantitative shear wave ultrasound elastography: initial experience in solid breast masses. Breast Cancer Res 12:R104
- 36. Chang JM, Won JK, Lee KB, Park IA, Yi A, Moon WK (2013) Comparison of shear-wave and strain ultrasound elastography in the differentiation of benign and malignant breast lesions. AJR Am J Roentgenol 201:W347–356
- 37. Yi A, Cho N, Chang JM, Koo HR, La Yun B, Moon WK (2012) Sonoelastography for 1,786 non-palpable breast masses: diagnostic value in the decision to biopsy. Eur Radiol 22:1033–1040
- Adamietz BR, Meier-Meitinger M, Fasching P et al (2011) New diagnostic criteria in real-time elastography for the assessment of breast lesions. Ultraschall Med 32:67–73
- Yerli H, Yilmaz T, Kaskati T, Gulay H (2011) Qualitative and semiquantitative evaluations of solid breast lesions by sonoelastography. J Ultrasound Med 30:179–186
- Colleoni M, Rotmensz N, Maisonneuve P et al (2007) Prognostic role of the extent of peritumoral vascular invasion in operable breast cancer. Ann Oncol 18:1632–1640
- 41. de Mascarel I, Bonichon F, Durand M et al (1998) Obvious peritumoral emboli: an elusive prognostic factor reappraised. Multivariate analysis of 1320 node-negative breast cancers. Eur J Cancer 34:58–65
- American College of Radiology (ACR) (2003) ACR BI-RADS Ultrasound ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas. American College of Radiology, Reston
- 43. American College of Radiology (ACR) (2003) ACR BI-RADS Mammography ACR Breast Imaging Reporting and Data System, Breast Imaging Atlas. American College of Radiology, Reston
- Sadigh G, Carlos RC, Neal CH, Dwamena BA (2012) Accuracy of quantitative ultrasound elastography for differentiation of malignant and benign breast abnormalities: a meta-analysis. Breast Cancer Res Treat 134:923–931
- De Muth JE (2006) Correlation. In: De Muth JE (ed) Basic statistics and pharmaceutical statistical applications. Chapman & Hall/CRC, Boca Raton, pp 311–342
- Barr RG, Destounis S, Lackey LB II, Svensson WE, Balleyguier C, Smith C (2012) Evaluation of breast lesions using sonographic elasticity imaging: a multicenter trial. J Ultrasound Med 31:281–287
- Regner DM, Hesley GK, Hangiandreou NJ et al (2006) Breast lesions: evaluation with US strain imaging—clinical experience of multiple observers. Radiology 238:425–437
- Alhabshi SM, Rahmat K, Abdul Halim N et al (2013) Semiquantitative and qualitative assessment of breast ultrasound elastography in differentiating between malignant and benign lesions. Ultrasound Med Biol 39:568–578
- Raza S, Odulate A, Ong EM, Chikarmane S, Harston CW (2010)
 Using real-time tissue elastography for breast lesion evaluation: our initial experience. J Ultrasound Med 29:551–563
- Navarro B, Ubeda B, Vallespi M, Wolf C, Casas L, Browne JL (2011)
 Role of elastography in the assessment of breast lesions: preliminary results. J Ultrasound Med 30:313–321

- 51. Houelleu Demay ML, Monghal C, Bertrand P, Vilde A, Brunereau L (2012) An assessment of the performance of elastography for the investigation of BI-RADS 4 and BI-RADS 5 breast lesions: correlations with pathological anatomy findings. Diagn Interv Imaging 93: 757–766
- 52. Stachs A, Hartmann S, Stubert J et al (2013) Differentiating between malignant and benign breast masses: factors limiting sonoelastographic strain ratio. Ultraschall Med 34:131–136
- Tozaki M, Fukuma E (2011) Pattern classification of shear wave elastography images for differential diagnosis between benign and malignant solid breast masses. Acta Radiol 52:1069–1075
- Kim H, Youk JH, Gweon HM, Kim JA, Son EJ (2013) Diagnostic performance of qualitative shear-wave elastography according to different color map opacities for breast masses. Eur J Radiol 82:e326–331
- Lee EJ, Jung HK, Ko KH, Lee JT, Yoon JH (2013) Diagnostic performances of shear wave elastography: which parameter to use in differential diagnosis of solid breast masses? Eur Radiol 23:1803–1811
- Kumm TR, Szabunio MM (2010) Elastography for the characterization of breast lesions: initial clinical experience. Cancer Control 17: 156–161
- 57. Youk JH, Gweon HM, Son EJ, Kim JA, Jeong J (2013) Shear-wave elastography of invasive breast cancer: correlation between quantitative mean elasticity value and immunohistochemical profile. Breast Cancer Res Treat 138:119–126
- Chang JM, Park IA, Lee SH et al (2013) Stiffness of tumours measured by shear-wave elastography correlated with subtypes of breast cancer. Eur Radiol 23:2450–2458
- Evans A, Whelehan P, Thomson K et al (2012) Invasive breast cancer: relationship between shear-wave elastographic findings and histologic prognostic factors. Radiology 263:673–677
- Sadigh G, Carlos RC, Neal CH, Dwamena BA (2012) Ultrasonographic differentiation of malignant from benign breast lesions: a meta-analytic comparison of elasticity and BIRADS scoring. Breast Cancer Res Treat 133:23–35
- 61. Gong X, Xu Q, Xu Z, Xiong P, Yan W, Chen Y (2011) Real-time elastography for the differentiation of benign and malignant breast lesions: a meta-analysis. Breast Cancer Res Treat 130:11–18
- Maskarinec G, Meng L, Ursin G (2001) Ethnic differences in mammographic densities. Int J Epidemiol 30:959–965
- Golatta M, Schweitzer-Martin M, Harcos A et al (2013) Normal breast tissue stiffness measured by a new ultrasound technique: virtual touch tissue imaging quantification (VTIQ). Eur J Radiol 82:e676–679
- 64. Sadigh G, Carlos RC, Neal CH, Wojcinski S, Dwamena BA (2013) Impact of breast mass size on accuracy of ultrasound elastography vs. conventional B-mode ultrasound: a meta-analysis of individual participants. Eur Radiol 23:1006–1014
- 65. Garra BS, Cespedes EI, Ophir J et al (1997) Elastography of breast lesions: initial clinical results. Radiology 202:79–86
- Wernicke M, Roitman P, Manfre D, Stern R (2011) Breast cancer and the stromal factor. The "prometastatic healing process" hypothesis. Medicina (B Aires) 71:15–21
- Auvinen P, Tammi R, Parkkinen J et al (2000) Hyaluronan in peritumoral stroma and malignant cells associates with breast cancer spreading and predicts survival. Am J Pathol 156:529–536

