Eur Radiol
DOI 10.1007/s00330-014-3152-7

BREAST

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

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Received: 27 October 2013 / Revised: 24 January 2014 / Accepted: 12 March 2014

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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Keywords Ultrasound · Elastography · Stiffness · Strain ratio · Breast

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–

Published online: 05 April 2014

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, China) and a 14 L5 transducer. Conventional and elastographic US image acquisition was performed by two blinded radiologists with 10 and 20 years of experience in breast US and previously trained in breast elastography. For each patient, US elastography was conducted after standard conventional US examination was performed. Elastographic images were obtained by using the freehand manual compression. During imaging acquisition, the transducer was positioned perpendicular to the skin above the target breast lesion and then light compression was repetitively applied. The pre- and post-compression radio-frequency data were collected and used to calculate tissue strain with the cross-correlation technique. A rectangular region of interest (ROI) box was adjusted to include the target lesion and ensure that it extended from the subcutaneous fat layer to the greater pectoral muscle.

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

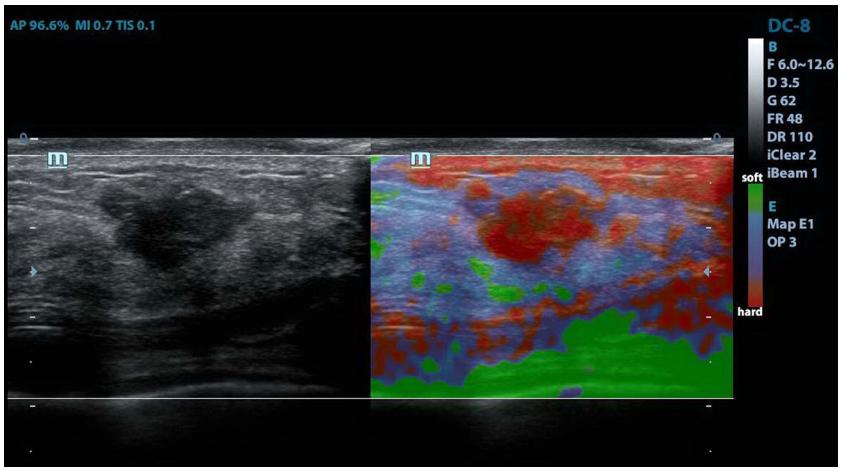

Fig. 1 Intraductal papilloma in a 24-year-old woman. B-mode image shows an irregular hypoechoic mass (*left*). Elastographic image shows that the lesion was scored 4 (*right*). Images show that the breast is composed of glandular tissue, and fatty tissue layer is almost not visible

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*/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*/shell 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 ≤15 mm and the lesions >15 mm ($P=0.397$ for elasticity score, $P=0.499$ for *B*/*A* and $P=0.671$ for *B*/shell).

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

Parameters	BI-RADS 3		BI-RADS 4a		BI-RADS 4b		BI-RADS 4c		BI-RADS 5	
	M ($n=0$)	B ($n=17$)	M ($n=9$)	B ($n=46$)	M ($n=12$)	B ($n=7$)	M ($n=10$)	B ($n=2$)	M ($n=24$)	B ($n=0$)
Elasticity score	NA	2.24±0.66 (1–3)	3.78±0.97 (2–5)	2.54±0.86 (1–5)	4.25±0.87 (3–5)	3.00±0.82 (2–4)	4.30±0.82 (3–5)	3.50±0.71 (3–4)	4.63±0.58 (3–5)	NA
B/*A*	NA	1.33±0.57 (0.65–2.99)	2.19±1.00 (1.15–3.84)	1.44±0.65 (0.61–4.06)	2.19±0.89 (1.32–3.86)	1.57±0.62 (0.94–2.83)	2.73±1.55 (0.77–5.83)	1.72±0.86 (1.11–2.33)	2.30±1.14 (0.48–5.62)	NA
B/shell	NA	1.17±0.65 (0.56–3.12)	1.35±0.67 (0.35–2.34)	1.17±0.36 (0.48–2.17)	1.56±0.65 (0.69–2.92)	1.05±0.22 (0.80–1.50)	1.60±0.52 (0.80–2.44)	1.45±0.72 (0.94–1.96)	1.49±0.75 (0.36–3.69)	NA

M malignant, *B* benign, *NA* not available

Table 3 Elasticity parameters in malignant and benign lesions

Parameters	Malignant lesions (n=55)	Benign lesions (n=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±0.67 (0.35–3.69)	1.16±0.44 (0.48–3.12)	0.001

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

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,

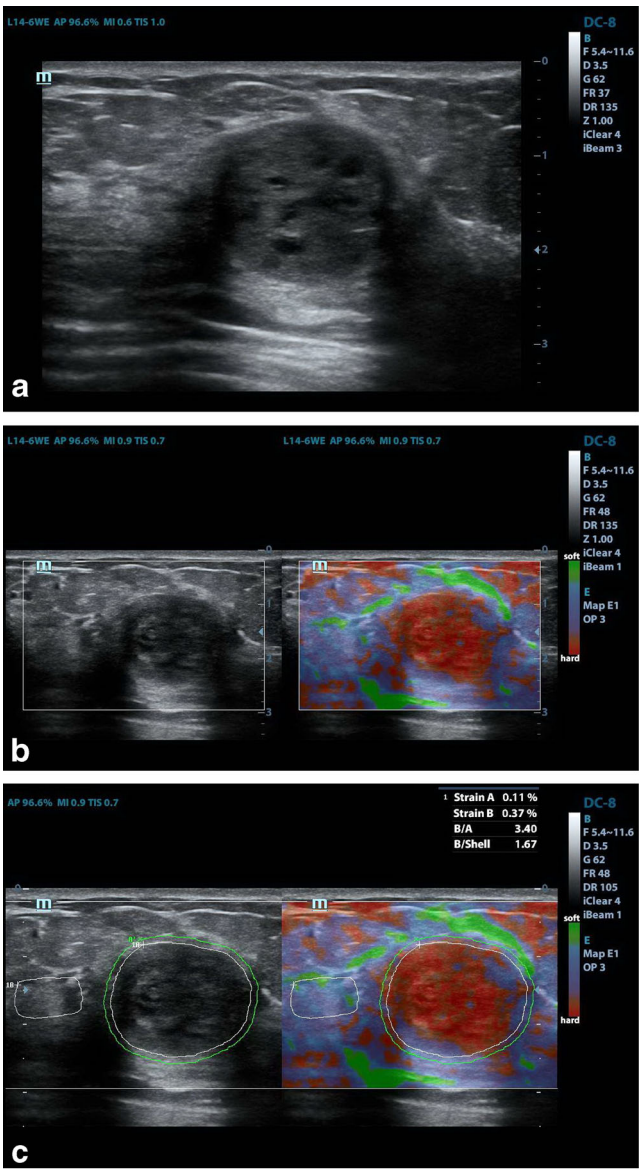

Fig. 2 Invasive ductal carcinoma grade 3 in a 57-year-old woman. B-mode image shows a regular hypoechoic mass with scattered cystic areas (**a**). Elastographic image shows that the lesion was scored 4 (**b**). The strain ratio of the lesion was 3.40, and the strain ratio of the surrounding tissue was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

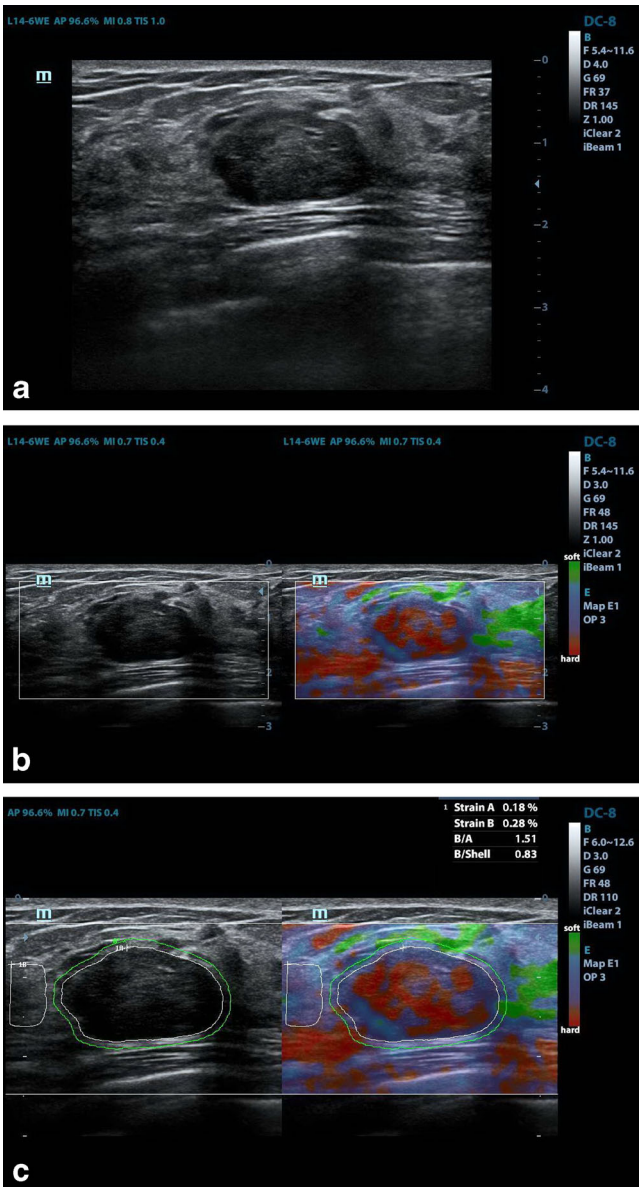

Fig. 3 Fibroadenoma in a 44-year-old woman. B-mode image shows a regular hypoechoic mass (**a**). Elastographic image shows that the lesion was scored 2 (**b**). The strain ratio of the lesion was 1.51, and the strain ratio of the surrounding tissue was 0.83 (**c**)

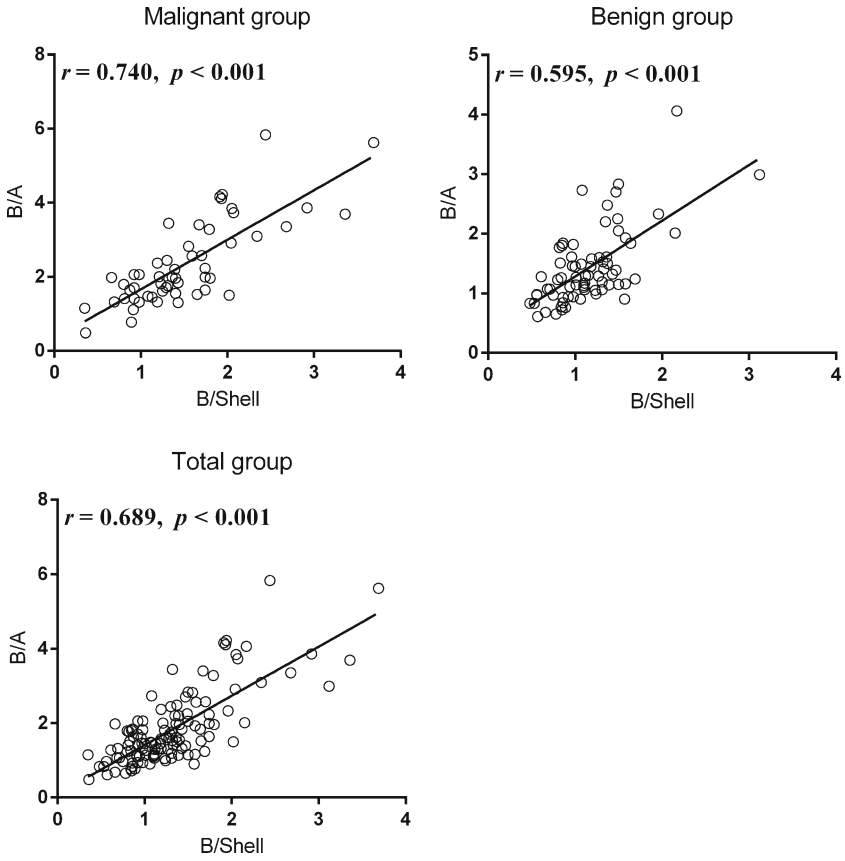

Fig. 4 High positive correlation between the stiffness of the lesions (*B*/*A*) and the stiffness of the surrounding tissue of the lesions (*B*/shell) in the malignant group (r=0.740, P<0.001), moderate positive correlations in the benign and the total group (r= 0.595, and r=0.689, respectively; P<0.001 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±0.74) than for malignant ones scored 2–4 (1.31±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*/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

Parameters	IDC 1 plus IDC 2 (n=32)	IDC 3 (n=11)	P value
Elasticity score	4.38±0.75 (3–5)	4.64±0.67 (3–5)	0.342
B/*A*	2.31±0.99 (0.77–4.22)	2.77±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

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

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

Parameters	Group	Threshold	Sensitivity (%)	Specificity (%)	Az
Elasticity score	Total (n=127)	>3	83.6	87.5	0.917
	≤15 mm (n=55)	>3	87.5	87.2	0.946
	>15 mm (n=72)	>3	82.1	87.9	0.910
B/*A*	Total (n=127)	>1.29	92.6	54.2	0.786
	≤15 mm (n=55)	>1.39	100	56.4	0.839
	>15 mm (n=72)	>1.60	71.8	78.8	0.786
B/shell	Total (n=127)	>1.64	38.2	93.1	0.669
	≤15 mm (n=55)	>1.64	62.5	92.3	0.735
	>15 mm (n=72)	>1.18	69.2	69.7	0.690

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 high-power 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

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.

Acknowledgements The scientific guarantor of this publication is WeiWei Zhan. The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article. The authors state that this work has not received any funding. No complex statistical methods were necessary for this paper. Institutional review board approval was obtained. Written informed consent was obtained from all subjects (patients) in this study. No study subjects or cohorts have been previously reported. Methodology: Prospective, case-control study, performed at one institution.

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