Quantitative evaluation of peripheral tissue elasticity for ultrasound-detected breast lesions

Y. Xiao^{a,*}, Y. Yu^{b,*}, L. Niu^a, M. Qian^a, Z. Deng^a, W. Qiu^a, H. Zheng^{a,†}

^a Paul C. Lauterbur Research Center for Biomedical Imaging, Institute of Biomedical and Health Engineering, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China

^b Department of Department of Electronic Engineering, City University of Hong Kong, Hong Kong, China

*These authors contributed equally to this work and are joint first authors.

[†]Guarantor and correspondent: H. Zheng, Paul C. Lauterbur Research Center for Biomedical Imaging, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, 1068 Xueyuan Ave., SZ University Town, Shenzhen, China, 518055. Tel.: +86-755-86392244; fax: 86-755-86392299.

E-mail address: hr.zheng@siat.ac.cn

ABSTRACT

AIM: To evaluate the diagnostic performance of the quantitative measurement of peripheral tissue elasticity using shear-wave elastography (SWE) in differentiating between benign and malignant breast lesions detected by ultrasonography (US).

MATERIALS AND METHODS: This study was approved by institutional review board; informed consent was signed from all patients. From June 2012 to April 2014, conventional B-mode US and SWE were performed in 205 breast lesions (78

malignant, 127 benign) of 205 consecutive women (mean age, 41.9 ± 12.3 years; age range, 18–76 years). For each lesion, a rim around its contour was constructed by using a computer-aided tool, including adequate adjacent peripheral tissue. Quantitative elastographic features of the rim (elasticity mean, maximum, standard deviation, and elasticity ratio) as well as Breast Imaging Reporting and Data System (BI-RADS) categories were assessed according to the final histopathological results. Sensitivity, specificity, positive and negative predictive values, and receiver operating characteristic (ROC) curve analysis were performed to evaluate the diagnostic performances for the three data sets (conventional B-mode US alone, SWE features alone, and combined B-mode US and SWE features).

RESULTS: SWE features of the peripheral tissue differed significantly between benign and malignant breast lesions (mean $\pm$ standard deviation [SD]: elasticity mean, 16.1 ± 6.6 versus 43.6 ± 17.8 ; maximum, 55.4 ± 31.4 versus 150.3 ± 44.6 ; SD, 8.1 ± 4.1 versus 30 ± 13.8 and elasticity ratio, 1.1 ± 0.2 versus 2 ± 0.7 , respectively, all $p < 0.001$), and enabled significantly higher specificities compared with conventional B-mode US alone (92.9%, 84.3%, 94.5%, and 93.7% versus 44.1%, respectively, all $p < 0.001$). The combinations of SWE assessment (including individual features and the logistic regression model of all four features) and conventional B-mode US for BI-RADS 3 and 4a lesions significantly improved the diagnostic performance compared with B-mode US alone, with significantly increased specificity (85%, 82.7%, 81.9%, 86.6%, and 85% versus 44.1%; all $p < 0.001$) and AUC (0.942, 0.940, 0.940, 0.935, and 0.953 versus 0.916, all $p < 0.05$).

CONCLUSION: Quantitative evaluation of the elastic properties of the peripheral tissue exhibited good discriminatory ability in differentiating US-detected breast lesions and could be used to further stratify low-suspicion lesions within BI-RADS

category 3 and 4a to avoid unnecessary biopsy.

INTRODUCTION

In addition to mammography, conventional ultrasonography (US) has become a routine tool to diagnose breast disease; however, low specificity and high false-positive rates limit its utility in differentiating between benign and malignant breast lesions^{1,2}. Shear-wave elastography (SWE) has been developed as a quantitative elastography technique based on the local measurement of shear-wave propagation created by an acoustic radiation force, enabling two-dimensional colour-coded imaging of the elasticity modulus of a biological tissue^{3,4}.

Breast cancers generally cause considerable changes in the elastic properties of soft tissue and, subsequently, induce stiffness. Based on this property, SWE is a valuable adjunct to conventional morphological US for breast lesion differentiation, improving the specificity without loss of sensitivity⁵⁻¹⁰.

To the authors' knowledge, the previously published literature regarding breast SWE investigated quantitative elastographic features of the stiffest area in the region of interest (ROI), and demonstrated that the most common site of maximum lesion-associated stiffness was generally found in the surrounding stroma rather than the lesion itself;⁵⁻¹⁴ however, in these studies, separate analysis of the peripheral tissue was not undertaken. Zhou *et al.*¹⁵ proposed a qualitative visual assessment using the "stiff rim" sign, which was influenced by the elasticity range setting of the colour image, resulting in a biased overestimate for benign lesions. Quantitative evaluation of peripheral tissues that represent the "stiff peripheral tissue" sign have the potential to become an effective marker to characterise malignancy. The present study was undertaken to evaluate the diagnostic performance of the quantitative

measurement of peripheral tissue elasticity using SWE to differentiate between benign and malignant breast lesions detected at US.

MATERIALS AND METHODS

Patients and breast lesions

This study was approved by the institutional review board, and signed informed consent for the scientific analysis of US images and histopathological records was obtained from all included patients. The group consisted of patients with visible hypoechoic lesions detected initially on conventional B-mode US. From June 2012 to April 2014, 229 consecutive women with breast lesions underwent US examinations. Among these 229 patients, two patients with breast implants, 10 patients without complete measurements, and 12 patients with 17 lesions without definitive contours on B-mode US were excluded. In 45 patients with multiple lesions, the most suspicious lesion with the highest Breast Imaging Reporting and Data System (BI-RADS) category was chosen. Finally, a total of 205 patients (mean age, 41.9 ± 12.3 years; age range, 18–76 years) with 205 breast lesions (78 malignant, 127 benign) were collected. Histopathological diagnoses were performed in all breast lesions using core-needle biopsy or surgical excision, by one of two pathologists who had 10–20 years of experience in breast pathology and were blinded to US findings. Final results were used as the reference standard (Table 1).

Ultrasound examinations

Conventional B-mode US and SWE examinations were performed using an Aixplorer system (SuperSonic Imagine, Aix en Provence, France) equipped with a 4–15 MHz linear array probe, by one of three radiologists who had 6–25 years of experience in

breast US and at least 4 months of experience in acquiring and interpreting SWE images. The radiologists were instructed to avoid pressing and moving the transducer to minimise unintentional pre-compression otherwise artefactual areas of stiffness radiating from skin surface were produced¹⁶. The probe was held still for a few seconds during a breath-hold period to obtain a stabilised image. Once an imaging plane that showed the largest diameter of a breast lesion was located on the B-mode image, a ROI box was set centred on the target lesion and the surrounding tissue was adequately imaged (including subcutaneous fat, parenchyma, and pectoral muscle). After a standard scan, both B-mode and SWE images were simultaneously displayed on a monitor, with the greyscale B-mode image on the bottom and the translucent 256-colour coded SWE image superimposed on the corresponding B-mode image on the top. The probe was removed and re-applied between each acquisition by the same radiologist in the same imaging plane. Three separate and representative US images of each lesion were captured and recorded, with BI-RADS assessment categories¹⁷ (category 3, probably benign; category 4a, low suspicion; category 4b, intermediate suspicion; category 4c, moderate suspicion; category 5, highly suggestive of malignancy; BI-RADS categories 4a or higher are considered as positive for malignancy) and visual assessments (lesion size, shape and orientation).

Image evaluation

The SWE image was evaluated by one radiologist using a computer-aided tool after an interval (mean, 7 days; range, 0–32 days), who was blinded to the histopathological results. Quantitative elastographic features were measured using MATLAB software (The Math Works, Natick, MA, USA), programmed by the investigator who had 6 years of experience in computer-aided diagnosis (CAD) applied to breast US. The procedure

was conducted as follows: first, a combined US image in red–green–blue (RGB) format was opened and the elasticity modulus of each pixel inside the ROI was reconstructed using the method proposed in previous studies^{18,19}. Second, the hypoechoic area of the lesion on the B-mode image was located and its complete contour was outlined by the radiologist. A circle of 2-mm diameter was placed on the normal fatty tissue (Fig. 1a). Then both the contour of the lesion and the circle were automatically mapped onto the corresponding SWE image. Third, a morphological dilating algorithm was used to create a rim of 3-mm width around the contour of the segmented lesion, including the adjacent peripheral tissue (Fig. 1b). Finally, a series of quantitative elastographic features that represent the elastic properties of the peripheral tissue within the rim were automatically calculated by the computer: elasticity mean (E_{mean}), maximum (E_{max}), standard deviation (E_{std}), and elasticity ratio (E_{rat}), which is the ratio of mean elasticity within the rim to that in the normal fatty tissue within the 2-mm circle (Fig. 1c). Three separate measurements of each lesion were performed by the same observer. The mean value of the three measurements was calculated and used for the final analysis.

Observer variability evaluation

In the group of 205 patients, agreement among the three measurements of SWE features by the same observer was initially assessed for evaluating intra-observer variability. To evaluate interobserver variability, a second observer, who had 16 years of experience in breast US and was blinded to the previous US and histopathological results, performed an independent review of the previous US images after an interval of 2 months. One image was arbitrarily chosen from the group of the three measurements. Then the SWE features were measured and recorded by the new

observer using the computer-aided tool. Agreement between the two measurements by the different observers was evaluated.

Evaluation for combining B-mode US and SWE

The combination of conventional B-mode US assessment category and SWE features was evaluated against B-mode US alone. According to BI-RADS assessment, category 3 lesions are probably benign and have a <2% likelihood of malignancy, whereas category 4 is noted for lesions that do not have classic appearances of malignancy but are sufficiently suspicious and require biopsy; these lesions have a broad likelihood of malignancy of 2–95%. To further indicate a radiologist's level of suspicion for malignancy, category 4 has been subdivided into the subcategories 4a, 4b, and 4c, which represent 2–10%, 10–50%, and 50–95% likelihood of malignancy, respectively. BI-RADS category 3 and 4 lesions were analysed. Quantitative SWE features were added to upgrade category 3 lesions with stiff peripheral tissue or downgrade category 4a lesions with soft peripheral tissue to avoid unnecessary biopsy and improve patient management.

Statistical analysis

The median values and interquartile range (IQR) of quantitative SWE features for each histopathological subtype were calculated according to the final histopathological results. Agreements among continuous SWE features within or across observers were evaluated using intraclass correlation coefficients (ICCs). Each SWE feature was divided into various categories according to the malignancy risks and threshold values. Odds ratios and rates for malignancy with established BI-RADS categories were calculated. Optimal threshold values were the points with maximum Youden's index

values. Diagnostic performances were evaluated and compared with sensitivity, specificity, positive (PPV) and negative (NPV) predictive values, and receiver operating characteristic (ROC) curve analysis for the three data sets (conventional B-mode US alone, SWE features alone, and combined B-mode US and SWE features). The logistic regression model was used to perform analysis of all combinations of SWE features and B-mode US.

Differences between continuous values of two independent groups were compared using the Mann–Whitney *U*-test. Proportions were compared using the McNemar test. Differences between the normalised areas under the ROC curve (AUCs) were compared using *Z*-values²⁰. A two-tailed *p*-value <0.05 indicated a statistically significant difference and 95% confidence intervals (CIs) were used. The ROC analysis was performed using MedCalc software (MedCalc Software, Mariakerke, Belgium). Statistical analyses other than ROC analysis were performed using SPSS version 19.0 software (SPSS, Chicago, IL, USA)²¹.

RESULTS

Conventional B-mode US

Of the 205 patients with BI-RADS assessment, 59 cases (28.8%) were category 3 with the lowest malignant likelihood of 5.1% (3 of 59) and 29 cases (14.1%) were category 5 with highest malignant likelihood of 100% (29 of 29). Of the 117 cases (57.1%) classified as category 4, increased malignancy rates were observed from low (category 4a, 11.5% [7 of 61]), intermediate (category 4b, 58.1% [18 of 31]) to moderate (category 4c, 84% [21 of 25]) (Table 2). The overall sensitivity of BI-RADS assessment was 96.2% (75 of 78; 95% confidence interval [CI]: 89.2%, 99.2%), specificity was 44.1% (56 of 127; 95% CI: 35.3%, 53.2%), PPV was 51.4% (75 of 146;

95% CI, 43%, 59.7%) and NPV was 95% (56 of 59; 95% CI: 85.9%, 99%). The AUC was 0.916 (95% CI: 0.869, 0.950) for conventional B-mode US alone (Table 3).

SWE features of peripheral tissue

SWE features of peripheral tissue (elasticity mean [E_{mean}]; maximum [E_{max}]; standard deviation [E_{std}] and elasticity ratio [E_{rat}]) all significantly differed between overall benign ($n=127$) and malignant ($n=78$) breast lesions (all $p<0.001$; Table 1, Fig. 2). The adjacent peripheral tissue of benign lesions was softer (Fig. 3) than that of malignancies (Fig. 4), with a median E_{mean} of 15.6 kPa (IQR, 11–20.1) versus 41.6 kPa (IQR, 27.1–57.4; $p<0.001$). Values of the E_{mean} for invasive breast carcinomas ($n=68$) were significantly higher than those for non-invasive carcinomas ($n=10$; $p<0.001$). The median value of E_{max} was 47.9 kPa (IQR, 35.2–66.8) for benign lesions and 180 kPa (IQR, 116.6–180) for malignancies ($p<0.001$). Of note, among benign lesions, there were 20 cases (15.7% [20 of 127]) with an E_{max} of >80 kPa (Fig. 5). Malignancies had a higher level of heterogeneous elasticity, with a median E_{std} of 28.3 kPa (IQR, 19.3–40.4) compared with 7.7 kPa (IQR, 4.8–11.1) for benign lesions. As a semi-quantitative ratio index, the E_{rat} exhibited the best discriminating ability. Peripheral tissues of benign lesions had comparable stiffness to normal fatty tissues ($p=0.208$), with a median E_{rat} of 1 (IQR, 0.9–1.2). Among malignancies, there were 71 lesions (91% [71 of 78]) with an E_{rat} of >1.4, with a median E_{rat} of 1.8 (IQR, 1.6–2.2). In particular, for relatively soft non-invasive carcinomas, nine of 10 (90%) cases had an E_{rat} of >1.4.

Compared with conventional B-mode US, SWE features of peripheral tissues showed significantly higher overall specificities (E_{mean} , 92.9%; E_{max} , 84.3%; E_{std} , 94.5%; and E_{rat} , 93.7% versus 44.1%, respectively, all $p<0.001$) and PPVs (87.5%; 77.8%; 90.5%

and 89.9% versus 51.4%, respectively, all $p<0.001$; Table 3). There was no significant difference in the AUC between the E_{mean} with an optimal cut-off value of 25 kPa and B-mode US (0.941 versus 0.916, $p=0.300$) due to the significantly lower sensitivity (80.8% versus 96.2%, $p<0.01$). The E_{max} with an optimal cut-off value of 80 kPa also provided insignificant improvement in the AUC (0.936 versus 0.916, $p=0.394$), with the lowest specificity of 84.3% among all SWE features. The best-performing feature, E_{rat} , with an optimal cut-off value of 1.4, enabled a significantly improved diagnostic performance than that of B-mode US alone, with a significantly increased AUC (0.975 versus 0.916, $p<0.05$), higher specificity (93.7% versus 44.1%, $p<0.001$) and sustained sensitivity (91% versus 96.2%, $p=0.344$).

Observer agreements of SWE features

Intra-observer agreements of the SWE features among three separate measurements by the same observer were substantial to almost perfect (ICC: E_{mean} , 0.85; E_{max} , 0.90; E_{std} , 0.83; E_{rat} , 0.72; respectively). Interobserver agreements between two separate measurements of the same US image by the different observers were almost perfect (ICC: E_{mean} , 0.91; E_{max} , 0.94; E_{std} , 0.87; E_{rat} , 0.81; respectively).

Combined B-mode US and SWE features

Each SWE feature was divided into several categories and higher odds ratios and rates for malignancy were obtained in the categories with increased elasticity values (Table 2). Within BI-RADS categories 3 and 4a (Figs. 3–4), all SWE features enabled further classification of lesions according to the level of malignancy risk (Fig. 6). In particular, for BI-RADS category 4a benign lesions ($n=54$), there were 54 (100% [54 of 54]) cases with an E_{mean} of <30 kPa, 51 (94.4% [51 of 54]) cases with an E_{max} of <120

kPa, 51 (94.4% [51 of 54]) cases with an E_{std} of <15 kPa, and 54 (100% [54 of 54]) cases with an E_{rat} of <2. Using aggressive strategies at the highest thresholds with malignancy rates of >90%, adding any individual SWE feature to B-mode US for BI-RADS 3 and 4a lesions maintained overall sensitivities (E_{mean} , 96.2%; E_{max} , 96.2%; E_{std} , 96.2%; and E_{rat} , 93.6% versus 96.2%, respectively, all $p>0.05$) while significantly improving specificities (85%; 82.7%; 81.9% and 86.6% versus 44.1%, respectively, all $p<0.001$) compared with B-mode US alone. Use of the E_{mean} provided the best improvement with an aggressive cut-off value of 30 kPa. All 54 benign lesions regarded as BI-RADS category 4a were accurately downgraded to category 3 and one malignancy regarded as category 3 was upgraded to category 4a. The specificity insignificantly increased from 44.1% (56 of 127) for BI-RADS assessment alone to 85% (108 of 127, $p<0.01$) for combining E_{rat} with BI-RADS and the AUC was statistically improved (0.942 versus 0.916, $p<0.05$; Table 3). The ROC analyses of the logistic regression model were performed by combining B-mode US with all four SWE features. The model had the best AUC of 0.953 (95% CI: 0.914, 0.978), with both improved sensitivity (98.7% versus 96.2%) and specificity (85% versus 44.1%, $p<0.001$) compared with B-mode US alone.

DISCUSSION

Malignancy-associated increased stiffness in the peripheral tissue of a lesion is regarded as a positive finding at breast SWE. Increased stiffness may be due to: (1) changes in the stroma due to abnormal stiff collagen secreted by cancer-associated fibroblasts, or (2) infiltration of cancer cells into the interstitial tissues or the intraductal component^{7,9,14-15}. This study proposed a quantitative measurement for the elastic properties of the peripheral tissue that could represent the

“stiff peripheral tissue” sign more accurately and objectively than qualitative visual assessment¹⁵. Using a computer-aided tool applied to the Aixplorer system, the rim of the ROI including sufficient peripheral tissue was located on the B-mode image and quantitative elastographic features of the rim were calculated from the colour SWE image. With combined morphological and elastic information from both conventional B-mode and elastography US images, the proposed SWE features provided further characterisation of breast lesions. Moreover, the use of peripheral tissue elasticity could be expected to avoid the intrinsic “black-hole” artefact of the SWE technique, which mostly presents in the interior portion of a lesion and may be mistaken as a soft region⁴. Thus the elastic characteristics of the peripheral tissue of a lesion should be more reliable.

There was no direct manual evaluation for the SWE image in this study: the radiologists determined the contour of the lesion and the position of the normal fatty tissue using greyscale B-mode US image. Therefore, the intra- and interobserver reproducibility was at least as good as that of B-mode assessment. The most reproducible SWE feature was $E_{\max}$, which was consistent with a previous study²². E_{rat} showed the worst agreement because of differing selections of fatty tissue positions by different observers.

For the present cohort, the proposed SWE features of peripheral tissue were useful in breast lesion differentiation, with significantly different values between benign and malignant lesions (all $p < 0.001$). The experimental values were lower than those in previous studies⁵⁻¹³. This is because initial investigations have so far evaluated the stiffest portion of the elastography image rather than mapping out the extent of the area with abnormal stiffness. Compared with conventional B-mode US alone, individual SWE features of the peripheral tissue alone all showed significantly higher

overall specificities and PPVs (all $p < 0.001$). In practice, the stiffest region was generally found in the extent of the peripheral tissue and the SWE feature $E_{\max}$ could be used to represent maximum elasticity as in previous studies⁵⁻¹³. Values of the $E_{\max}$ were significantly influenced by local stiffness artefact, resulting in false-positive findings (Fig 4). Factors producing local stiffness artefact may include: excessive pre-compression by the radiologist¹⁶, reflection of the pushing beam at the margin of the lesion⁴, large lesion size²³⁻²⁶, unintentional vertical band of stiffness extended over the abnormalities,^{14,24} and the effect of the thoracic wall next to the lesion. Therefore, when applying the $E_{\max}$, the false-positive rates of benign lesions were significantly higher than those of other features (E_{std} and E_{rat}) using more available elastic information of the whole peripheral tissue (15.7% versus 5.5% and 6.3%, respectively, all $p < 0.05$) with comparable false-negative rates of malignancies (10.3% versus 14.1% and 9%, respectively, all $p > 0.05$), which indicated peripheral tissue elasticity enhanced the diagnostic confidence compared with maximum elasticity, especially for benign lesion characterisation. The best-performing feature was the elasticity ratio (E_{rat}), which enabled differentiation of softer malignancies from normal fatty tissue and reduced the effect of compression on the elastic properties of the tissue¹¹. In particular, for softer non-invasive carcinomas, nine of 10 (90%) cases had an E_{rat} of > 1.4 . The individual E_{rat} with an optimal cut-off value of 1.4 alone yielded better diagnostic performance than that of conventional B-mode US alone, with the AUC up to 0.975 (95% CI: 0.944, 0.992; $p < 0.05$).

Elastic evaluation using SWE was a valuable adjunct to conventional B-mode morphological assessment to reduce false-positive findings and subsequently avoid unnecessary biopsy. SWE features were applied to distinguish lesions of BI-RADS category 3 and 4a with relatively low malignancy rates (category 3, 5.1% and category

4, 11.5%). The results showed that lesions of BI-RADS categories 3 or 4a with soft peripheral tissues were likely to be benign, and lesions with stiff peripheral tissues were likely to be malignant, similar to many previously published studies²⁷⁻³⁰. The combination of any individual SWE feature and B-mode US could be used to upgrade category 3 lesions and downgrade category 4a lesions, leading to significantly increased AUCs than that of B-mode US assessment alone (all $p < 0.05$), maintaining sensitivities (all $p > 0.05$) while significantly improving specificities (all $p < 0.001$). The logistic regression model combining all the four features and B-mode US category that made full use of the US information produced the best diagnostic performance with an AUC value up to 0.953 (95% CI: 0.914, 0.978). When applying the combined model to BI-RADS categories 3 and 4a lesions, 52 (40.9% [52 of 127]) benign lesions avoided unnecessary biopsies, and 77 (98.7% [77 of 78]) malignancies could be correctly recommended for biopsy. There were still three false results, including two benign lesions (a 26-mm fibroadenoma and a 22-mm abscess) that remained as BI-RADS category 4a and one malignancy (a 9-mm invasive ductal carcinoma) that remained as BI-RADS category 3. Note that the two benign lesions both had larger lesion sizes of >20 mm, while the malignancy had a smaller lesion size of 9 mm. Lesion size had a significant effect on elasticity values with benign lesions of larger size showed higher values than the small ones and more false-positive SWE findings, which is supported by the previous studies²³⁻²⁶.

The present study had several limitations. First, an elasticity modulus map of the ROI was decoded to calculate quantitative SWE features using a computer-aided tool. The reconstructed values according to the colour bar were affected by its maximum measurement range and had quantisation errors¹⁸⁻¹⁹. Second, representative images were analysed in one view only. Orthogonal plane or three-dimensional images may

be more appropriate to reduce technical errors and may provide more information for lesion characterisation. Third, the factors influencing SWE image quality (such as pre-compression, lesion depth, size, orientation, and so on) were not assessed^{16, 23-26}. Fourth, the group only consisted of screening US-detected breast lesions with contours that could be outlined entirely. Fifth, there were a few cases showing SWE findings that did not fit the final histopathological results and could not be differentiated correctly. Sixth, in some countries, such as the UK, many BIRADS 3 lesions would undergo biopsy to prove benignity at the first visit, thus avoiding multiple follow-up appointments. Consequently, the use of elastography does not have the same potential to reduce biopsies. Moreover, this was a small, single-centre study. In particular, the number of malignancies within BI-RADS category 3 was small. The diagnostic criteria were determined according to the limited group. To verify the reliability and generalisability of peripheral tissue elasticity, similar studies should be performed in multiple centres on a large numbers of patients with symptomatic and screening US-detected lesions.

In summary, the results of the present quantitative analysis using a computer-aided tool, demonstrated that increased stiffness present in the peripheral tissue of a lesion could be used for breast lesion characterisation. The proposed quantitative SWE features of the peripheral tissue exhibited good discriminatory ability in the differential diagnosis of US-detected breast lesions and could improve the diagnostic confidence of low-suspicion breast lesions of BI-RADS category 3 and 4a to avoid unnecessary biopsy, with significantly improved specificity while maintaining sensitivity compared with conventional US alone. Further studies on larger numbers of patients and guidelines on the clinical use are needed to verify the reliability and generalisability of the present study.

ACKNOWLEDGEMENTS

The work was supported by National Science Foundation Grants (grant no. 61302039, 11272329).

REFERENCES

1. Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. *Radiology* 2002; 225(1):165-175.
2. Lee SH, Chang JM, Kim WH, et al. Added value of shear-wave elastography for evaluation of breast masses detected with screening US imaging. *Radiology* 2014; 273(1): 61-69.
3. Bercoff J, Tanter M, Fink M. Supersonic shear imaging: a new technique for soft tissue elasticity mapping. *IEEE Trans Ultrason Ferroelect Freq Control* 2004; 51(4): 396-409.
4. Bamber J, Cosgrove D, Dietrich C.F., Fromageau J, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: basic principles and technology. *Ultraschall Med* 2013; 34(3): 169-184.
5. Berg WA, Cosgrove DO, DoréCJ, Schäfer FKW et al. Shear-wave elastography improves the specificity of breast US: the BE1 Multinational Study of 939 masses. *Radiology* 2012; 262(2):435-449.
6. Itoh A, Ueno E, Tohno E, et al. Breast disease: clinical application of US elastography for diagnosis. *Radiology* 2006; 239(2): 341-350.

7. Evans A, Whelehan P, Thomson K, et al. invasive breast cancer: relationship between shear-wave elastographic findings and histologic prognostic factors. *Radiology* 2012; 263(3):673-677.
8. Taylor K, Keefe SO, Britton PD, et al. Ultrasound elastography as an adjuvant to conventional ultrasound in the preoperative assessment of axillary lymph nodes in suspected breast cancer: a pilot study. *Clin Radiol* 2011, 66(11): 1064-1071
9. Evans A, Whelehan P, Thomson K, et al. Quantitative shear wave ultrasound elastography: initial experience in solid breast masses. *Breast Cancer Res* 2010; 12:R104.
10. Bamber J, Cosgrove D, Dietrich C.F., et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 2: clinical applications. *Ultraschall Med* 2013; 34(3): 238-253.
11. Lee EJ, Jung HK, Ko KH, Lee JT, Yoon JH. Diagnostic performances of shear wave elastography: which parameter to use in differential diagnosis of solid breast masses? *Eur Radiol* 2013; 23(7):1803–1811
12. Chang JM, Park IA, Lee SH, et al. Stiffness of tumours measured by shear-wave elastography correlated with subtypes of breast cancer. *Eur Radiol* 2013; 23(9):2450-2458.
13. Sim YT, Vinnicombe S, Whelehan P, Thomson K, Evans A. Value of shear-wave elastography in the diagnosis of symptomatic invasive lobular breast cancer. *Clin Radiol* 2015; 70(6):604-609
14. Mitsuhiro Tozaki, Eisuke Fukuma. Pattern classification of shear wave elastography images for differential diagnosis between benign and malignant solid breast masses. *Acta Radiol* 2011; 52(10): 1069-1075.

15. Zhou JQ , Zhan WW, Chang C, et al. Breast lesions: evaluation with shear wave elastography, with special emphasis on the “stiff rim” sign. *Radiology* 2014; 272(1):63-72.
16. Barr RG, Zhang Z. Effects of precompression on elasticity imaging of the breast. *J Ultrasound Med* 2012; 31:895-902.
17. American College of Radiology. *Breast Imaging Reporting and Data System (BI-RADS). Ultrasound*. Reston, VA: American College of Radiology; 2003.
18. Wang CZ, Zhang J, Huang ZP, et al. Influence of measurement depth on the stiffness assessment of healthy liver with real-time shear wave elastography. *Ultrasound Med Biol* 2014; 40(3):461-469.
19. Xiao Y, Zeng J, Niu LL, et al. Computer-aided diagnosis based on quantitative elastographic features with supersonic shear wave imaging. *Ultrasound Med Biol* 2014; 40(2):275-286.
20. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; 44(3):837-845
21. Field AP. *Discovering statistics using SPSS*, 3rd edn. Los Angeles: SAGE; 2009.
22. Cosgrove DO, Berg WA, Doré CJ, et al. Shear wave elastography for breast masses is highly reproducible. *Eur Radiol* 2012; 22:1023-1032.
23. Yoon JH, Jung KJ, Lee TJ, Ko KH. Shear-wave elastography in the diagnosis of solid breast masses: what leads to false-negative or false-positive results? *Eur Radiol* 2013; 23(9): 2432-2440.
24. Chang JM, Moon WK, Cho N, Kim SJ. Breast mass evaluation: factors influencing the quality of US elastography. *Radiology* 2011; 259(1):59-64.

25. Cho N, Moon WK, Chang JM et al. Aliasing artifact depicted on ultrasound (US)-elastography for breast cystic lesions mimicking solid masses. *Acta Radiol* 2011; 52(1): 3-7.
26. Yoon JH, Kim MH, Kim EK, Moon HJ, Kwak JY, Kim MJ. Interobserver variability of ultrasound elastography: how it affects the diagnosis of breast lesions. *AJR Am J Roentgenol* 2011; 196(3):730-736.
27. Chang JM, Won JK, Lee KB, Yi a, Moon WK. Comparison of shear-wave and strain ultrasound elastography in the differentiation of benign and malignant breast lesions. *AJR Am J Roentgenol* 2013; 201(2):W347-56.
28. Schaefer FK, Heer I, Schaefer PI, et al. Breast ultrasound elastography: results of 193 breast lesions in a prospective study with histopathologic correlation. *Eur J Radiol* 2011; 73(3):450-456.
29. Youk JH, Gweon HM, Song EJ, Han KH, Kim JA. Diagnostic value of commercially available shear-wave elastography for breast cancers: integration into BI-RADS classification with subcategories of category 4. *Eur Radiol* 2013; 23(10):2695-2704.
30. Richard G, Zheng Z. Shear-wave elastography of the breast: value of a quality measure and comparison with strain elastography. *Radiology* 2015; 275(1):45-53.

Figure 1. An invasive ductal carcinoma in a 45-year-old woman. (a) The contour of a segmented lesion (yellow line) and a 2-mm circle of fatty tissue (blue line) on the greyscale B-mode image. (b) The lesion contour and a 2-mm circle of normal fatty tissue mapped on the colour SWE image and the ROI rim of peripheral tissue between the two yellow lines. (c) The constructed rim including peripheral tissue and normal fatty tissue within a 2-mm circle.

Figure 2: Box plots for quantitative SWE features of peripheral tissue between benign and malignant breast lesions. (a) Elasticity mean: E_{mean} , (b) elasticity maximum: E_{max} , (c) elasticity standard deviation: E_{std} , and (d) elasticity ratio: E_{rat} .

Figure 3: A fibroadenoma regarded as BI-RADS category 4a in a 49-year-old woman. Left: The contour of a segmented lesion on the greyscale B-mode image. Right: The rim including peripheral tissue around the lesion contour on the colour SWE image. In this case, $E_{mean}=9.8$ kPa, $E_{max}=35.2$ kPa, $E_{std}=5.3$ kPa, $E_{rat}=1.0$. The lesion with soft peripheral tissue was downgraded to category 3.

Figure 4: A mucinous carcinoma regarded as BI-RADS category 3 in a 30-year-old woman. Left: The contour of a segmented lesion on the greyscale B-mode image. Right: The rim including peripheral tissue around the lesion contour on the colour SWE image. In this case, $E_{mean}=47.8$ kPa, $E_{max}=180$ kPa, $E_{std}=31.8$ kPa, $E_{rat}=1.9$. The lesion with stiff peripheral tissue was upgraded to category 4a.

Figure 5: A fibrocystic change regarded as BI-RADS category 4b in a 59-year-old woman. Left: The contour of a segmented lesion on the greyscale B-mode image. Right: The rim including peripheral tissue around the lesion contour on the colour SWE image. In this case, $E_{mean}=17.5$ kPa, $E_{max}=180.0$ kPa, $E_{std}=17.7$ kPa, $E_{rat}=1.2$.

Figure 6: Bar graph demonstrates distribution of SWE features for benign and malignant lesions within BI-RADS category 3 and 4a. Numbers on bars indicate the number of lesions. (a) Elasticity mean: E_{mean} , (b) elasticity maximum: E_{max} , (c) elasticity standard deviation: E_{std} , and (d) elasticity ratio: E_{rat} .

Table 1 Quantitative shear-wave elastography (SWE) features to histopathological results for 205 breast lesions

Histopathological results	No.	SWE feature [Median(IQR)] ^a			
		E_{mean} (kPa)	E_{max} (kPa)	E_{std} (kPa)	E_{rat}
Benign	127	15.6(11–20.1)	47.9(35.2–66.8)	7.7(4.8–11.1)	1(0.9–1.2)
Fibroadenoma	61	15.9(11.4–20.4)	51.5(39.2–70)	8.2(5.1–11.6)	1(0.9–1.2)
Adenosis	29	14.9(9.1–20.7)	43.2(30.3–57.2)	5.4(3.9–10.4)	1.1(1–1.2)
Fibrocystic change	15	14.2(11–15.9)	40.4(35.2–46.7)	4.8(6.4–7.3)	1(0.9–1.1)
Benign phyllodes tumour	10	20.1(15.7–24.8)	66.1(50.1–75.9)	9.7(9.3–14.8)	1(1–1.2)
Abscess or mastitis	6	13.8(9.4–23.8)	46.3(22.2–100.7)	9.3(3.3–14.3)	1.2(1–1.4)
Papilloma	5	23.9(11–28.9)	52.2(37.9–79.1)	7.8(4.8–10)	1(1–1.3)
Hamartoma	1	5.1	27.5	2.2	0.9
Malignant	78	41.6(27.1–57.4)	180(116.6–180)	28.3(19.3–40.4)	1.8(1.6–2.2)
Invasive ductal carcinoma	62	46.1(36.4–58)	180(151.2–180)	29.6 (22–42)	1.9(1.6–2.2)
Invasive lobular carcinoma	4	21(20.2–31)	86(57.5–155.3)	11.3(10.3–31.4)	1.7(1.6–1.9)
Ductal carcinoma in situ	8	24.4(18.9–27.2)	75.6(66.6–121.9)	16.1(10.9–21.2)	1.7(1.5–1.8)
Mucinous carcinoma	2	27.3,47.8	180,180.0	15.2,31.8	1.5,1.9
Papillary carcinoma	2	14.6,27.5	43.6,103.6	9.3,14.8	2.1,2.1
p -Value ^b		<0.001	<0.001	<0.001	< 0.001

Data are medians. Data in parentheses are the 25th and 75th percentiles of the data.

^aElasticity mean, maximum, standard deviation within the rim which was a 3-mm width band around the lesion contour, and elasticity ratio which was the ratio of the mean elasticity value within the rim to that in the normal fatty tissue within a 2-mm circle.

^b p -Value indicates that there is significantly different between those values of overall benign and malignant breast lesions.

Table 2 Malignancy rates and odds ratios: classified shear-wave elastography (SWE) features to BI-RADS categories

Malignancy Rate							Odds ratio for malignancy ^a
SWE Parameter	Overall	BI-RADS Category 3	BI-RADS Category 4a	BI-RADS Category 4b	BI-RADS Category 4c	BI-RADS Category 5	
None	78/205(38)	3/59(5.1)	7/61(11.5)	18/31(58.1)	21/25(84)	29/29(100)	
E_{mean} (kPa)							
≤15	2/59(3.4)	0/24(0)	1/27(3.7)	0/6(0)	1/2(50)	NA	1
>15 to ≤20	4/40(10)	0/20(0)	0/13(0)	2/4(50)	1/2(50)	1/1(100)	3.1(0.5, 17.7)
>20 to <30	15/44(34.1)	2/12(16.7)	0/15(0)	6/9(66.7)	2/3(66.7)	5/5(100)	14.7(3.2, 68.9)
≥30	57/62(91.9)	1/3(33.3)	6/6(100)	10/12(83.3)	17/18(94.4)	23/23(100)	324.9(60.5, 1774.1)
E_{max} (kPa)							
≤60	5/93(5.4)	1/41(2.4)	1/39(2.7)	2/10(20)	1/3(33.3)	NA	1
>60 to ≤80	4/24(16.7)	1/9(0)	0/8(0)	1/5(20)	1/1(100)	1/1(100)	3.5(0.9, 14.3)
>80 to <120	10/23(43.5)	0/6(0)	0/5(0)	3/3(100)	1/3(33.3)	6/6(100)	13.5(4, 45.9)
≥120	59/65(90.8)	1/3(33.3)	6/9(66.7)	12/13(92.3)	18/18(100)	22/22(100)	173.1(50.5, 593.2)
E_{std} (kPa)							
≤10	4/91(4.4)	1/39(2.6)	1/40(2.5)	1/9(11.1)	1/3(33.3)	NA	1
>10 to ≤15	7/40(17.5)	1/16(6.3)	0/12(0)	4/8(50)	1/3(33.3)	1/1(100)	4.6(1.3, 16.8)
≥15	67/74(90.5)	1/4(25)	6/9(66.7)	13/14(92.9)	19/19(100)	28/28(100)	208.2(58.5, 740.6)
E_{rat}							
≤1	1/55(1.8)	0/27(0)	0/19(0)	0/6(0)	1/2(50)	NA	1
>1 to ≤1.4	6/71(8.5)	0/29(0)	0/29(0)	2/8(25)	1/2(50)	3/3(100)	5(0.6, 42.7)
>1.4 to <2	43/51(84.3)	3/3(100)	2/8(25)	9/10(90)	16/17(94.1)	13/13(100)	290.3(34.9, 2411.2)

≥ 2 28/28(100) NA 5/5(100) 7/7(100) 3/3(100) 13/13(100) NA
 Numbers in parentheses are percentages. Percentages were rounded. Data are no. of malignancies/no. of lesions (%).
^a Numbers in parentheses are 95% CIs.
 BI-RADS, Breast Imaging Reporting and Data System; NA, not applicable.

Table 3 Diagnostic performance of conventional B-mode ultrasound (US), individual shear-wave elastography (SWE) feature and B-mode US combined with SWE

Item		Sensitivity (%)	Specificity (%)	PPV(%)	NPV (%)	AUC (95% CI)	p-Value [†]
B-mode category	US	96.2(89.2, 99.2)[75/78]	44.1(35.3, 53.2)[56/127]	51.4(43, 59.7)[75/146]	95(85.9, 99)[56/59]	0.916(0.869,0.950)	
E_{mean}		80.8(70.3, 88.8)[63/78]	92.9(87, 96.7)[118/127]	87.5(77.6, 94.1)[63/72]	88.7(82.1, 93.6)[118/133]	0.941(0.899,0.969)	0.300
E_{max}		89.7(80.8, 95.5)[70/78]	84.3(76.7, 90.1)[107/127]	77.8(67.8, 85.8)[70/90]	93(86.8, 97)[107/115]	0.936(0.893,0.965)	0.394
E_{std}		85.9(76.2,92.7) [67/78]	94.5(89,97.8) [120/127]	90.5(81.5, 96.1)[67/74]	91.6(85.5, 95.7)[120/131]	0.962(0.926,0.984)	0.026
E_{rat}		91(82.4,96.3) [71/78]	93.7(88,97.2) [119/127]	89.9(81, 95.5)[71/79]	94.4(88.9,97.7) [119/126]	0.975(0.944,0.992)	0.013
$+E_{\text{mean}}$ ^a		96.2(89.2,99.2) [75/78]	85(77.6,90.8) [108/127]	79.8(70.3, 87.4)[75/94]	97.3(92.3,99.4) [108/111]	0.942(0.900,0.970)	0.022
$+E_{\text{max}}$ ^b		96.2(89.2,99.2) [75/78]	82.7(75,99.2) [105/127]	77.3(67.7, 85.2)[75/97]	97.2(92.1,99.4) [105/108]	0.940(0.899,0.969)	0.027
$+E_{\text{std}}$ ^c		96.2(89.2,99.2) [75/78]	81.9(74.1,88.2) [104/127]	76.5(66.9, 84.5)[75/98]	97.2(92,99.4) [104/107]	0.940(0.898,0.968)	0.029
$+E_{\text{rat}}$ ^d		93.6(85.7,97.9) [73/78]	86.6(79.4,92.0) [110/127]	81.1(71.5, 88.6)[73/90]	95.7(90.2,98.6) [110/115]	0.935(0.892,0.965)	0.040

+all features ^e	SWE	98.7(93.1,99.9) [77/78]	85(77.6,90.8) [/127]	80.2(70.8,87.6) [77/96]	99.1(95,99.9) [/109]	0.953(0.914,0.978)	0.006
----------------------------	-----	---------------------------	------------------------	---------------------------	------------------------	---------------------	-------

Categories 4a or higher are considered as positive for malignancy. For sensitivity, specificity, PPV and NPV, data are percentages. Percentages are rounded. Data in parentheses are 95% CIs and data in brackets are raw data. For AUC, data in parentheses are 95% CIs.

^a BI-RADS category 3 was upgraded to category 4a if the E_{mean} was ≥ 30 kPa; category 4a was downgraded to category 3 if the E_{mean} was < 30 kPa.

^b BI-RADS category 3 was upgraded to category 4a if the E_{max} was ≥ 120 kPa; category 4a was downgraded to category 3 if the E_{max} was < 120 kPa.

^c BI-RADS category 3 was upgraded to category 4a if the E_{std} was ≥ 15 kPa; category 4a was downgraded to category 3 if the E_{std} was < 15 kPa.

^d BI-RADS category 3 was upgraded to category 4a if the E_{rat} was ≥ 2 ; category 4a was downgraded to category 3 if the E_{rat} was < 2 .

^e Logistic regression model are used to perform analysis of combining B-mode US with all four SWE features.

^f p -Value indicates that there is significantly different between the AUC values of conventional B-mode US and other assessments (SWE features alone and B-mode US combined SWE features).

AUC, area under the ROC curve; BI-RADS, Breast Imaging Reporting and Data System; PPV, positive predictive value; NPV, negative predictive value.

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6