ORIGINAL RESEARCH

Confirmed value of shear wave elastography for ultrasound characterization of breast masses using a conservative approach in Chinese women: a large-size prospective multicenter trial

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Purpose: This study aimed to investigate the value of shear wave elastography (SWE) for characterization of breast masses in a Chinese population.

Patients and methods: Two thousand two hundred seventy-three women consented to be prospectively enrolled for the characterization of breast masses with ultrasound and SWE. Breast masses were known from symptoms, palpability, and/or previous imaging screening with mammography and/or ultrasound. Correlation of SWE qualitative and quantitative features with malignancy risk and impact on diagnostic performance of combining SWE features were assessed, and the Breast Imaging Reporting and Data System (BI-RADS) scoring was calculated using histopathology as reference.

Results: Data of 2,262 masses (median size: 13 mm; range: 1.3–50) from 2,262 patients (median age: 43 years; range: 18–91) were investigated, of which 752 (33.3%) were malignant. Sensitivity and specificity of BI-RADS diagnosis were 97.5% (733/752) and 54.8% (827/1,510), respectively. By logistic regression, the combination of maximum elasticity (E_{max}) measurements with BI-RADS assessments increased the area under the receiver operating characteristic curve from 0.908 (95% CI: 0.896–0.920) to 0.954 (95% CI: 0.944–0.962). Using E_{max} of 30 kPa or lower to selectively downgrade BI-RADS 4a masses to follow-up, and E_{max} of 160 kPa or higher to selectively upgrade BI-RADS 3 lesions to biopsy, specificity significantly increased from 54.8% (827/1,510) to 66.1% (998/1,510) ($P<0.001$) while sensitivity decreased nonsignificantly from 97.5% (733/752) to 96.9% (729/752) ($P=0.2891$). Positive predictive value for biopsy recommendation increased from 51.7% (733/1,417) to 58.7% (729/1,241) ($P<0.001$).

Conclusion: Adding SWE maximum stiffness to BI-RADS 3 and BI-RADS 4a breast masses in a Chinese population increased significantly the specificity of breast ultrasonography, without significant change in sensitivity.

Keywords: breast cancer, shear wave elastography, ultrasound, multicenter

Introduction

Ultrasonography (US) has become an indispensable tool in breast imaging. Morphologic descriptors of a given lesion seen on grayscale imaging were standardized by the American College of Radiology (ACR) with the Breast Imaging Reporting and Data System (BI-RADS)-US lexicon.[1] The major advantages of this system are improved reliability and reproducibility of cancer risk assessment,[2,3] high sensitivity (at least 90%), and negative predictive value (NPV; at least 90%) for breast cancer. However, it causes a high incidence of false-positive BI-RADS 4a, which leads to unnecessary biopsy.[4,5]

Mammography is the imaging modality of preference for breast cancer screening, although its sensitivity may decrease to 30%–48% in women with dense breasts,[6,7] leading to insufficient screening accuracy in Asian populations including Chinese.[8,9] The Japan Strategic Anti-cancer Randomized Trial (J-START) reported that US could offer a low cost way to increase the detection of early breast cancer.[10] Another multicenter randomized trial revealed that US was superior to mammography for breast cancer screening in high-risk Chinese women.[11]

Breast US elastography has become a routine tool in addition to diagnostic US, enabling an increase in specificity by selectively reconsidering biopsy for low suspicion, BI-RADS 4a lesions.[12] US elastographic evaluation has been incorporated into the second edition of the BI-RADS-US lexicon,[1,13] and the Korean Society for Ultrasound in Medicine published its guidelines for the use of breast elastography.[14]

ShearWave™ Elastography (SWE™) is commercially available on the Aixplorer® general purpose ultrasound system (SuperSonic Imagine, Aix-en-Provence, France). SWE can provide qualitative and quantitative elastic information in real time and has proven to be highly reproducible.[15]

The clinical utility of SWE in ultrasonic diagnosis of breast lesions was demonstrated in previous studies, including the transatlantic BE1 study, the prospective multicenter, multinational study with the largest sample size published so far based on American and European population.[16–19] It is concluded that adding SWE features, and especially maximum stiffness evaluation to US grayscale imaging could significantly reduce the number of false-positive cases, leading to a specificity increase from 61.1% to 78.5% without any loss in sensitivity. The clinical utility of SWE for ultrasound diagnosis of breast lesions in Asian populations has only been studied in single-center studies to date. The purpose of this prospective multicenter study was to validate the added value of SuperSonic Imagine SWE as proposed by Berg et al for the characterization of breast masses in a Chinese population.[16]

Patients and methods

This prospective Health Insurance Portability and Accountability Act (HIPAA)-compliant study protocol (www.clinical-trials.gov, NCT02226081), funded by SuperSonic Imagine, was approved by Shanghai Fudan Medical University Chinese Ethics Committee (#1405135-3) and conducted from June 2014 to June 2015 in 16 Chinese mainland hospitals. There were 80 investigators in this study who were ultrasound specialists with a minimum experience of 4,000 breast ultrasound cases in the preceding 2 years, and they had a minimum training phase of 20 SWE examinations supervised by SuperSonic Imagine staff.

Ethics, consent, and permission

This study was approved by Shanghai Fudan Medical University Chinese Ethics Committee (#1405135-3). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study.

Consent for publication

Written informed consent for the publication of these details was obtained from all participants.

Patients

Consecutive female patients of at least 18 years of age deriving from diagnosis who gave written informed consent were recruited and received SWE examinations free of charge. Breast lesions classified BI-RADS 2, 3, 4, or 5 had to be visible on ultrasound. Exclusion criteria included inability to give written informed consent, lesions previously treated or biopsied, multiple lesions, pregnant or breastfeeding women, breast lesions classified as BI-RADS 0 or 6, and women with previous ipsilateral breast surgery and/or with breast implants (More details in Supplementary material).

Data collection

Ultrasound examination

Ultrasound examinations were performed on Aixplorer ultrasound imaging system (SuperSonic Imagine) using the SL15-4 transducer in two orthogonal planes by one of two sonographers with over 10 years' experience in breast imaging. Ultrasound characterization was performed according to the BI-RADS: Ultrasound lexicon.[1] Lesion size was defined as the largest dimension of the maximum diameters measured in both scanning planes.

Three SWE acquisitions of three frozen frames were acquired following the manufacturer recommendations in both scanning planes, using the default maximum color scale of 180 kPa (7.7 m/second). Images were evaluated collectively by two principle investigators who were blinded to each other's findings. Another experienced sonographer was invited to discuss and finally reach a consensus when the two principle investigators did not reach agreement.

Lesion maximum diameter on SWE images was measured encompassing the entire lesion on B-mode images and any stiffness halo immediately adjacent. Qualitative and quantitative SWE features were assessed.[16,20]

Qualitative features

Qualitative features including SWE shape, SWE shape similarity with B-mode images, SWE homogeneity, and SWE color patterns were recorded (Details in Supplementary material).

SWE shapes of breast lesions were identified as three types, including oval, round, and irregular types. By comparing the SWE shapes with B-mode images, we identified the similarity as very similar, reasonably similar, and dissimilar.

SWE homogeneity was evaluated as very homogeneous, reasonably homogeneous, and not homogeneous, by observing the color distribution inside the lesions and between adjacent areas.

Seven color patterns could be demonstrated in this study including no finding, vertical stripes pattern, rim of stiffness pattern, colored lesion pattern, void center pattern, horseshoe pattern, and spots pattern (Figure 1).

Quantitative features

For each of the three SWE acquisitions in both views, elasticity measurements were performed by placing a first built-in "Q-Box™" quantification tool covering as much of the lesion as possible. This Q-Box provided three elasticity measurements: the lesion maximum elasticity value (E_{max}), the lesion average elasticity (E_{mean}), and the lesion elasticity standard deviation (E_{SD}). Additionally, an elasticity ratio (E_{ratio}) was also calculated between the lesion and subcutaneous fatty tissue, by placing a 2 mm diameter Q-Box over the lesion's stiffest area (or immediately adjacent to it) and another 2 mm diameter Q-Box over subcutaneous fatty tissue at distance from the lesion (Figure 2). When needed, the stiffest area on SWE images was identified by gradually lowering the color scale from 180 kPa until the first relevant red area appeared.

Elasticity measurements were recorded on each of the three SWE acquisitions in both views using the "Q-Box" quantification tool. Maximum, average, and SD of lesion stiffness (lesion E_{max}, E_{mean}, E_{SD}) were measured with a Q-Box covering as much as lesion SWE map. Elasticity ratio (E_{ratio}) between the lesion and fatty tissue was calculated with the Q-Box ratio tool, using a 2 mm diameter Q-Box over the lesion's stiffest area (or immediately adjacent) and a second 2 mm diameter Q-Box over subcutaneous fatty tissue at a distance from the lesion (Figure 2). The maximum and aver-

age elasticity values (E_{max}, E_{mean}) of fatty tissue were also recorded. When needed, the stiffest area on SWE images was identified by gradually lowering the color scale from 180 kPa until the first relevant red area appeared.

Reference standard

BI-RADS 2 lesions were considered benign. All the 152 lesions classified as BI-RADS 2 have been followed up for over 2 years until June 2017. For 695 lesions classified as BI-RADS 3 in this study, final pathological diagnosis was available because all the lesions underwent core-needle biopsy, among which 596 lesions underwent surgery, owing to the medical status of China and patients' demand for intervention. BI-RADS 4a lesions or higher were core-biopsied under ultrasound guidance according to routine clinical practice. When surgery was performed, pathological results were collected. Ground truth for biopsied lesion was derived from histopathologic results after core biopsy, surgery, or a combination of these. The final diagnosis was determined from fine-needle aspiration (FNA) alone in eight cases, from core biopsy alone in 418 cases and from surgery and/or surgical biopsy alone in 1,381 cases. One lesion underwent FNA followed by core biopsy, another lesion underwent surgery after a positive FNA for malignancy, and 453 lesions received surgery after core biopsy. A total of 935 benign lesions were diagnosed after surgery (62%).

Statistical analysis

SWE variables were compared between benign and malignant lesions. Categorical variables were compared using chi-squared test and chi-squared test for trend, while continuous variables were compared using the Kruskal–Wallis test. For continuous variables (E_{max}, E_{mean}, E_{SD}, and E_{ratio}), average values were calculated across the three acquisitions in both longitudinal and transverse planes.

The diagnostic value of the combination of the BI-RADS classification with each SWE variable was assessed by stepwise logistic regression, in which a model fit P-value <0.05 was used to identify features that contributed to the prediction of the outcome. The best-performing SWE variable was then selected to implement reclassification of initially BI-RADS 3 and 4a lesions according to reclassification rules proposed by Berg et al.[16]

Ultrasound tests (original BI-RADS and modified BI-RADS) were considered positive for malignancy for scores 4 and 5 and negative for scores 2 and 3. Diagnostic performances of ultrasound tests [sensitivity, specificity, positive predictive value (PPV), NPV, and accuracy] were calculated and compared using appropriate tests: the McNemar test for comparison of paired proportions and the chi-squared test
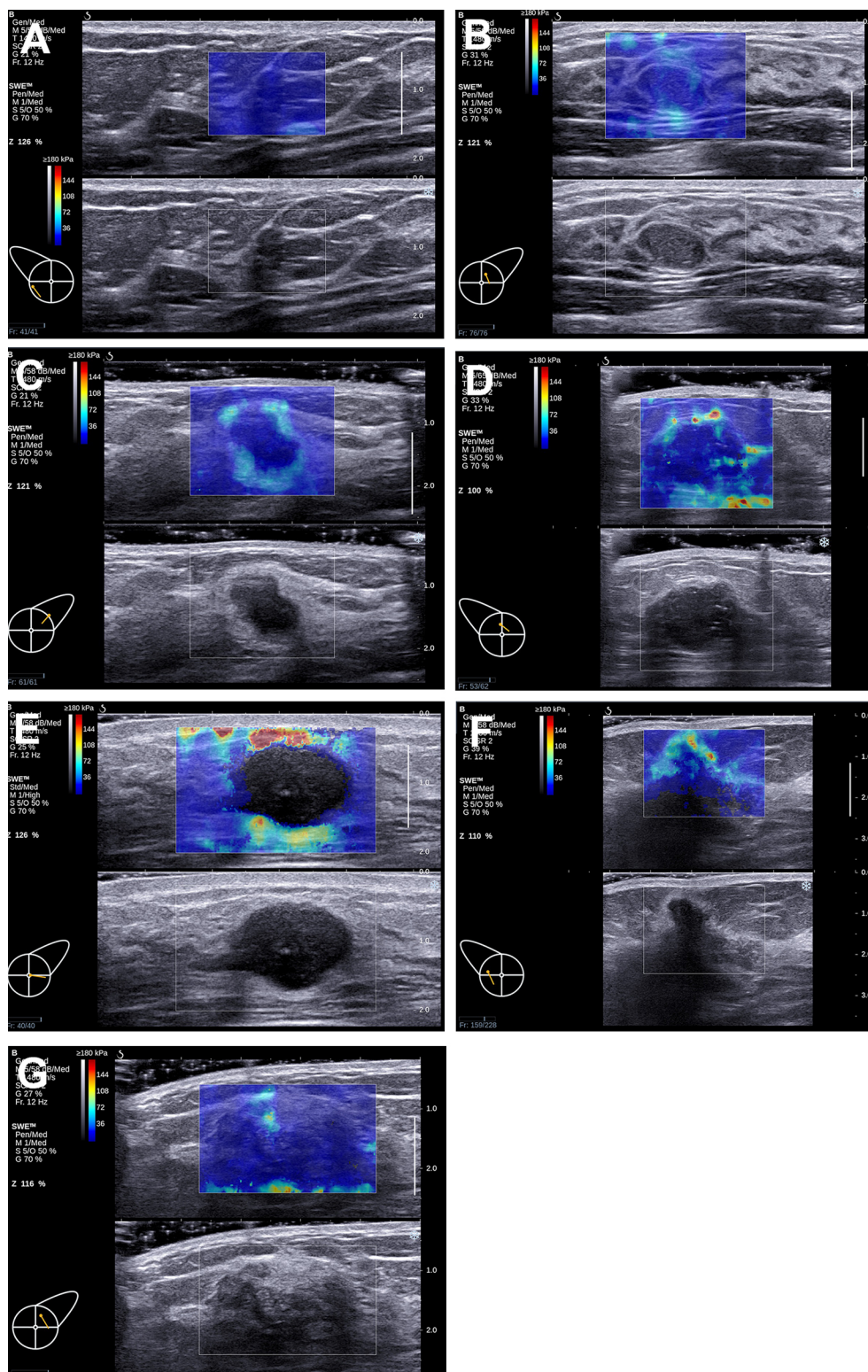
Figure 1 Seven patterns could be demonstrated on the images acquired in ShearWave™ Elastography (SWE).
Notes: (**A**) No findings: No difference is observed at the margin of or inside the lesion with the color around the lesion (homogeneously blue). (**B**) Vertical stripes pattern: A color is observed at the margin of or inside the lesion, which differs from the color around the lesion. The differing color extends beyond the lesion and continues vertically in cords on the cutaneous side and/or the thoracic wall. (**C**) Rim of stiffness pattern: A localized colored area appears at the margin of the lesion and creates a continuous closed circle. (**D**) Colored lesion pattern: Colored areas are heterogeneously visible inside the lesion. (**E**) Void center pattern: There is a lack of SWE signal inside the lesion. The rest of the SWE Box fills correctly. (**F**) Horseshoe pattern: A localized colored area appears at the margin of the lesion and creates an open circle. (**G**) Spots pattern: Colored areas are visible above and/or below the lesion.
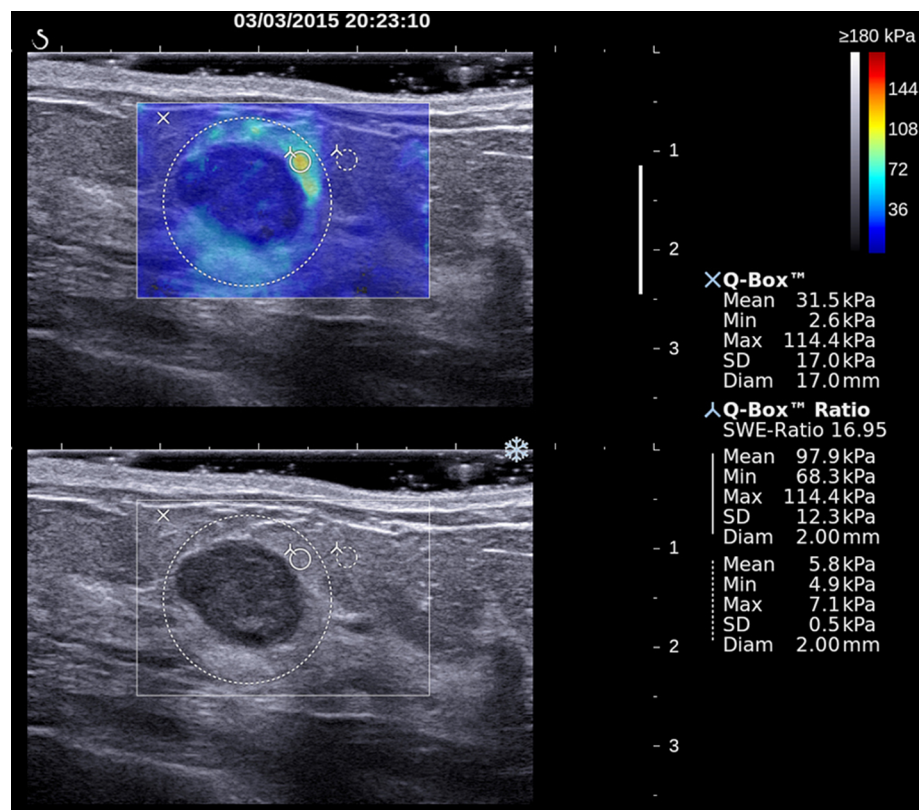
Figure 2 Two-dimensional grayscale ultrasound image (bottom) of a breast lesion in a 51-year-old female patient.
Notes: According to morphological signs, the lesion was classified as probably benign (BI-RADS 3). Upper image shows the SWE semitransparent map that overlays the grayscale anatomical image. The largest dotted line circular region of interest (ROI) marked with an "X" was used to quantify global lesion stiffness values, reported on the right-hand side under "XQ-Box™." The two smallest ROIs were used to calculate the elasticity ratio between the stiffest area within the lesion or surrounding stiffness halo and breast fatty tissue used as a reference. The SWE features of this lesion were suspicious for malignancy. Pathological outcome from breast biopsy was a mixed papillocarcinoma with mixed ductal carcinoma.
Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; SWE, shear wave elastography.

for unpaired proportions. Aggressive and conservative reclassification rules of BI-RADS 3 and 4a lesions as proposed by Berg et al were also tested (Supplementary material).

Statistical analyses were performed using statistical analysis software MedCalc®, version 14.12.0–64 bit for Windows XP/Vista/7/8 (MedCalc Software bvba), with a *P*-value of <0.05 indicating statistical significance.

Results
Population description and lesions' characteristics
Two thousand two hundred seventy-three breast lesions from 2,273 patients were recruited, from which 11 were excluded (nine with missing final pathology, one with no SWE acquisition, and one nonbreast lesion). The final study population consisted of 2,262 patients (median age: 43 years old; IQR: 35–51; range: 18–91), with 2,262 breast lesions, of which 752 were malignant (33.3%). All the 152 lesions classified

as BI-RADS 2 had been followed up for over 2 years until June 2017. Characteristics of patients and breast lesions were described in Table 1.

Diagnostic performance of conventional ultrasound in breast lesions
Malignancy rates in the BI-RADS 2, 3, 4a, 4b, 4c, and 5 categories were 0/152 (0%), 19/694 (2.7%), 87/611 (14.2%), 147/267 (55.1%), 267/301 (88.7%), and 232/237 (99.7%), respectively. The sensitivity, specificity, PPV, and NPV for ultrasound characterization of breast lesions were 97.5% (733/752), 54.8% (827/1,510), 51.7% (733/1,417), and 97.8% (827/846), respectively. The diagnostic accuracy of breast ultrasound was 69% (1,560/2,262).

SWE evaluation
Qualitative SWE features (homogeneity, shape, and dissimilarity of lesion shape between B-mode and SWE imaging)

Table 1 Description of the study population and lesion characteristics

		Total	Benign	Malignant	P-value[a]
Age (year)	Median	43	40	50	
	IQR	31–51	31–46	43–58	
	Range	18–91	18–91	20–84	
	N	2261[b]	1,509 (66.7%)	752 (33.3%)	P<0.001
Depth of lesions (mm)	Median	6.0	6.2	6.0	
	IQR	4.0–9.0	4.0–9.0	4.0–8.3	
	Range	0.0–39.5	0.0–34.1	0.0–39.5	P=0.189
Lesion longest axis (mm)	Median	13.0	11.6	16.0	
	IQR	9.0–17.6	8.1–16.0	12.0–20.4	
	Range	1.3–50.2	1.3–50.2	2.2–40.0	P<0.001
Symptoms	Yes	437 (19.3%)	321 (73.5%)	116 (26.5%)	
	None	1,825 (80.7%)	1,189 (65.2%)	636 (34.8%)	P=0.001
Palpability	Yes	1,609 (71.1%)	948 (58.9%)	661 (41.1%)	
Mobile	Yes	857 (53.3%)	734 (85.4%)	125 (14.6%)	
	No	752 (46.7%)	215 (28.6%)	537 (71.4%)	P<0.001
	No	653 (28.9%)	562 (86.1%)	91 (13.9%)	P<0.001
Patient's history of breast cancer	Yes	141	100 (70.9%)	41 (29.1%)	
	Family history	109 (4.8%)	80	29	
	Previous history	32 (1.4%)	20	12	
	None	2,121 (93.8%)	1,411 (66.5%)	710 (33.5%)	P=0.438
Total		2,262	1,510 (66.8%)	757 (33.2%)	P<0.001

Notes: [a]P-value for statistical significance of difference between benign and malignant lesions using Kruskal–Wallis test (continuous variables) or the chi-squared test (categorical variables). [b]Total population of 2,262 masses in 2,262 patients. Age was missing in one patient.

were correlated with increased malignancy risk (Table 2). A single SWE pattern was reported in 1,049 (46.4%) lesions, of which 674 (64.3%) lesions were malignant. Patterns "Spots" and "Vertical stripes" failed to predict malignancy (OR 1.18; P=0.3692 and 0.52, P=0.004, respectively); all other patterns were predictive of malignancy: "Rim of stiffness" (OR 20.31; P<0.001), "Horseshoe pattern" (OR 10.61; P<0.001), "Colored lesion" (OR 3.45; P<0.001), and "Void center" (OR 3.45; P<0.001). When no specific SWE pattern was reported, the malignancy rate was low: 59/1,191 (4.95%). A combination of two or more SWE patterns was described in 22 cases (0.9%), of which 19 (86.4%) were malignant. All combinations involving any of "Rim of stiffness," "Horseshoe," or "Colored lesion" were highly predictive of malignancy (100%), with 12/12, 7/7, and 6/6 lesions being malignant, respectively.

All stiffness measurements, including those performed in subcutaneous fat tissue, were significantly higher in breasts with malignant lesions in both scanning planes (Table 3).

Diagnostic value of SWE variables

The diagnostic value of SWE features alone was described in Table 4. When combining SWE variables with original

Table 2 Rates of malignancy according to qualitative shear wave elastography features

Homogeneous	Benign	Malignant	Total
Very homogeneous	705 (96.8%)	23 (3.2%)	728
Reasonably homogeneous	617 (84.8%)	111 (15.2%)	728
Not homogeneous	188 (23.3%)	618 (76.7%)	806
Shape			
Oval	899 (92.0%)	78 (8.0%)	977
Round	81 (74.3%)	28 (25.7%)	109
Irregular	530 (45.1%)	646 (54.9%)	1,176
Vs B-mode lesion shape dissimilarity			
Very similar	814 (91.9%)	72 (8.1%)	886
Reasonably similar	581 (56.0%)	457 (44.0%)	1,038
Very dissimilar	115 (34.0%)	223 (66.0%)	338
Total	1,510	752	2,262

Notes: The chi-squared test for trend statistically significant (P<0.001) for difference between benign and malignant lesions for all three qualitative features. Data reported as total numbers and percentages per line.

BI-RADS assessment by stepwise logistic regression, SWE homogeneity, SWE shape, "Rim of stiffness" color pattern, as well as all quantitative variables (E_{max}, E_{mean}, E_{ratio}, and E_{SD}) significantly increased the area under the receiver operating characteristic curve (AUC) (P<0.001) (Table 5), among which E_{max} yielded the highest AUC (0.954).

Table 3 Shear wave elastography measurements performed in both scanning planes in the masses or their surrounding and in the reference fatty tissue

	Total (N=2,262)			Benign (N=1,510)		Malignant (N=752)		P-value[a]
	Median	IQR	Range	Median	IQR	Median	IQR	
Average values in longitudinal plane								
E_{max}	39.9	24.1–82.5	4.6–300.0	29.0	20.5–42.9	112.8	64.2–178.2	<0.001
E_{mean}	17.3	12.0–26.6	1.9–254.0	14.4	10.6–19.7	30.1	18.7–49.8	<0.001
E_{ratio}	3.5	2.1–6.7	0.2–55.9	2.7	1.8–3.9	8.2	5.4–11.3	<0.001
E_{SD}	7.1	4.0–14.2	0.5–83.9	5.0	3.2–7.6	18.4	11.6–30.0	<0.001
Fat E_{max}	10.5	7.5–14.7	2.5–300.0	10.0	7.3–13.7	11.9	8.4–17.1	<0.001
Fat E_{mean}	7.4	5.5–10.1	1.1–90.5	7.1	5.4–9.5	8.0	5.9–11.2	<0.001
Average values in transverse plane								
E_{max}	41.1	24.7–84.6	5.0–300.0	29.7	20.8–44.2	113.1	67.3–176.8	<0.001
E_{mean}	18.0	12.5–28.3	2.3–221.6	15.1	11.0–20.8	30.8	20.1–50.9	<0.001
E_{ratio}	3.5	2.1–6.6	0.3–36.0	2.6	1.8–3.9	7.7	5.1–11.1	<0.001
E_{SD}	7.0	3.9–14.6	0.4–90.3	4.9	3.2–7.5	17.9	11.6–30.1	<0.001
Fat E_{max}	10.8	7.8–14.9	1.7–300.0	10.3	7.5–13.8	12.0	8.5–17.7	<0.001
Fat E_{mean}	7.7	5.6–10.4	1.3–99.2	7.4	5.5–9.8	8.3	6.1–11.8	<0.001

Notes: [a]P-value for statistical significance of difference between benign and malignant lesions using the Kruskal–Wallis test.

Table 4 Cutoff value determined by the Youden index and associated performances of SWE feature

	AUC	95% CI AUC	P-value	Cutoff value	Sensitivity	Specificity
Qualitative variables						
SWE shape	0.762	0.744–0.779	<0.0001	1–2/3	85.8	64.9
SWE homogeneity	0.877	0.863–0.890	<0.0001	1–2/3	82.2	87.6
SWE rim pattern	0.715	0.696–0.734	<0.0001	0/1	47.3	95.8
SWE horseshoe pattern	0.565	0.544–0.586	<0.0001	0/1	14.6	98.4
SWE vs B shape similarity	0.755	0.737–0.773	<0.0001	1/2–3	90.4	53.9
Quantitative variables						
E_{max}	0.918	0.906–0.929	<0.0001	60	84.8	85.1
E_{mean}	0.832	0.816–0.847	<0.0001	25.2	70	82.6
E_{ratio}	0.893	0.879–0.905	<0.0001	7.5	79	88
E_{SD}	0.914	0.902–0.926	<0.0001	11.2	83.3	85.4

Abbreviations: AUC, area under the receiver operating characteristic curve; SWE, shear wave elastography.

Table 5 Impact of combining SWE characteristics with the BI-RADS classification on the global diagnostic performance (AUC) of the BI-RADS classification alone

	AUC	95% CI AUC	P-value[a]
Qualitative SWE feature added to BI-RADS			
None	0.908	0.896–0.920	
SWE shape	0.936	0.925–0.945	<0.001
SWE homogeneity	0.940	0.930–0.950	<0.001
SWE rim pattern	0.942	0.932–0.952	<0.001
SWE horseshoe pattern	0.910	0.897–0.922	<0.001
SWE vs B shape similarity	0.924	0.912–0.934	<0.001
Quantitative SWE feature added to BI-RADS			
None	0.908	0.896–0.920	
Max E_{max}	0.954	0.944–0.962	<0.001
Max E_{mean}	0.949	0.939–0.958	<0.001
Max E_{ratio}	0.949	0.939–0.958	<0.001
Max E_{SD}	0.951	0.942–0.960	<0.001

Notes: [a]P-value for statistical significance of AUC.
Abbreviations: AUC, area under the receiver operating characteristic curve; BI-RADS, Breast Imaging Reporting and Data System; SWE, shear wave elastography.

Confirming reclassification rules for BI-RADS category 3 and 4a lesions

When the conservative reclassification rule defined by BE1 study was applied to this study population,[16] using E_{max} as the reclassifying SWE variable, the sensitivity, specificity, PPV, and NPV of the ultrasound diagnostic test would have changed from 97.5% (733/752) to 96.9% (729/752) (P=0.2891), 54.8% (827/1510) to 66.1% (998/1510) (P<0.001), 51.7% (733/1,416) to 58.7% (729/1,241) (P<0.001), and 97.8% (827/846) to 97.7% (998/1,021) (P=0.883), respectively. Using the more aggressive rule to downgrade the BI-RADS 4a masses would have led to a higher increase in specificity: from 54.8% (827/1,510) to 86.4% (1,305/1,510) (P<0.001), along with a significant decrease in sensitivity: from 97.5% (733/752) to 91.5% (688/752) (P<0.001), and NPV: from 97.8% (827/846) to 95.3% (688/893) (P=0.005) (Table 6).

Focus on low suspicion masses

Low suspicion masses can be defined as BI-RADS 3 and 4a lesions showing oval shape, circumscribed margins, no posterior shadowing, or any other suspicious feature on gray-scale imaging. A subset of 519 low suspicion masses could be extracted, of which 20 (3.9%) were cancers.

Using BE1 conservative reclassification rule, no cancer would be downgraded from BI-RADS 4a to follow-up nor upgraded from BI-RADS 3 to biopsy. Forty-three percent (43/99) of initial false-positive masses would be properly downgraded to follow-up, while no benign masses would be upgraded to biopsy, increasing nonsignificantly the positive biopsy rate from 9.2% (10/109) to 15.2% (10/66)

(P=0.232671). The malignancy rate among BI-RADS 3 low suspicion lesions would decrease nonsignificantly from 2.4% (10/410) to 2.2% (10/453) (P=0.825447).

Discussion

To the best of our knowledge, this study was the first investigation into the clinical use of SWE in a prospective multi-center cross-sectional study in a Chinese population. Previous studies performed in China investigated the diagnostic value of strain elastography for breast lesion characterization,[21–23] and only one yielded potential improvement of diagnostic performance of ultrasound by combining elastography information to grayscale evaluation.[21] The main findings of SWE in this study were the reduction of false positives and improvement in specificity.

Despite general agreement on diagnostic value of SWE evaluation within ultrasound assessment of breast masses,[16,17,19,24–30] consensus on the most valuable SWE feature(s) and cutoff value(s) has not been reached yet.[31] Evans et al[26] and Chang et al[25] proposed to use $E_{mean} \geq 50$ kPa and ≥ 80.17 kPa as suspicious signs, respectively. In the study by Ko et al,[32] the optimal E_{mean} cutoff value (41.6 kPa) was lower than those determined by other published studies on solid breast masses.[25,26,28] Other studies demonstrated best diagnostic performance for E_{max} when combining with the BI-RADS score: Berg et al,[16] Lee et al,[28] and Yoon et al[20] used an E_{max} of 80–82.8 kPa while Zhou et al[30] reported that both an E_{SD} of 6.3 kPa and an E_{max} of 49.57 kPa had significantly better performance than any other quantitative measurements. Park et al[31] demonstrated that E_{max} provided the best AUC

Table 6 Diagnostic performance of combining SWE E_{max} with the BI-RADS classification according to conservative and aggressive reclassification rule from the BE1 study

	BI-RADS alone			BI-RADS + E_{max} Rule #1			BI-RADS + E_{max} Rule #2		
	Benign	Malignant	Total	Benign	Malignant	Total	Benign	Malignant	Total
Test <0	828	19	847	999	23	1,022	1,305	64	1,369
Test >0	683	734	1,417	512	730	1,242	206	689	895
Total	1,511	753	2,264	1,511	753	2,264	1,511	753	2,264

	BI-RADS alone	BI-RADS + E_{max} Rule #1	P-value[a]	BI-RADS + E_{max} Rule #2	P-value[b]
Sensitivity	97.5	96.9	0.2891	91.5	<0.001
Specificity	54.8	66.1	<0.001	86.4	<0.001
PPV	51.8	58.8	0.0003	76.9	<0.001
NPV	97.8	97.7	1	95.3	0.004
Accuracy	69.0	76.4	<0.001	88.1	<0.001

Notes: BI-RADS test is considered to be Test >0 for BI-RADS 4 and 5 and Test <0 for BI-RADS 2 and 3; Rule #1: the conservative reclassification rule from the BE1 study (Supplementary material); Rule #2: the aggressive reclassification rule from the BE1 study (Supplementary material); [a]P-value for statistical significance of difference between BI-RADS + E_{max} Rule #1 and BI-RADS alone using the chi-squared test. [b]P-value for statistical significance of difference between BI-RADS + E_{max} Rule #2 and BI-RADS alone using the chi-squared test.
Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; NPV, negative predictive value; PPV, positive predictive value; SWE, shear wave elastography.

compared with other quantitative parameters and determined the optimal cutoff value to be 45.1 kPa.[32]

Patterns "Spots" and "Vertical stripes" failed to predict malignancy because they were related with artifact produced by pressure of the probe. Results of this study confirmed that SWE homogeneity, SWE shape, the "Rim of Stiffness" sign, and the "Horse Shoe" pattern were indicative of malignancy risk. Evans et al,[26] Tozaki et al,[33] and Zhou et al[30] showed that the "stiff rim" sign was a predictor of malignancy. Data of this study suggested that lesions presenting with a combination of two SWE patterns (1% of the sample population), including "Rim of Stiffness," "Horse Shoe," or "Colored Lesion" patterns, had a 100% malignancy rate. Desmoplastic reaction or infiltrating cancer cells have been proposed as explanations of the "Rim of Stiffness" or the "Horse Shoe."[12,26] As to the other patterns, low shear wave amplitudes and/or noise within malignant lesions have been presented as other possible explanations,[32] which might be caused by the attenuation of the shear waves from lesion surrounding tissue.[33]

Lesion maximum stiffness (E_{max}) was found to be the best-performing stiffness measurement combined with the BI-RADS score, similar to findings from other experiences.[16,17,19,24–30] In this study, we found that the BE1 conservative reclassification rule[16] significantly increased the specificity of breast ultrasound to a slightly higher extent than that observed in the BE1 study (11.3 points from 54.8% to 66.1% compared with 4.6 points from 61.1% to 65.7%, respectively), providing a higher increase in PPV for biopsy recommendation (7 points higher in the BE3 population compared with 3.4 points in the BE1 population). However, the implementation of the BE1 aggressive reclassification rule to the studied Chinese population significantly decreased sensitivity by 6 points (from 97.5% to 91.5%). Therefore, we assume that the BE1 conservative rule is applicable to Chinese population, but not the aggressive rule, which legitimates the fact that both a conservative rule and an aggressive rule were initially developed. This study population could be used in future works to determine specific cutoff values for this population, for example, by randomly splitting it into two independent cohorts, one to determine new cutoffs values and the other to validate such new reclassification rules. As initially suggested by Berg et al,[16] the benefit of conservative reclassification rule was confirmed in this study when applied to low suspicion masses. However, because no low suspicion masses initially classified as BI-RADS 3 had stiffness values over 160 kPa, none of the false-negative cases could be upgraded to biopsy by using SWE information.

The different outcome of the BE1 aggressive reclassification rule applied to this study population could be explained by populations' differences. Increased breast tissue density in Asian patients may be one of the reasons; patients' median age in this population was lower than the BE1 population (43 vs 50 years old), theoretically in line with a younger average age of highest incidence of breast cancer in Asian populations. Palpable masses were more common in this population (70% vs 40%), with an apparently similar malignancy rate among palpable lesions (41% vs 43%, respectively); median E_{max} values seemed to be lower in this population of benign (30 vs 41 kPa) and malignant (113 vs 179 kPa) lesions. On the contrary, no differences were found for median lesion size and malignancy rates in BI-RADS classes.

The study has some limitations. First, combinations of several SWE features added to BI-RADS classification were not evaluated in this study because such combinations were proved to be useless.[16,29] Second, this study design was not comparative, and patients' management was not prospectively modified as a consequence of SWE evaluation. In such a comparative design, the upfront comparison of the number of biopsies performed, malignancy rates in each of the BI-RADS classes, and number of false negatives and false positives in both arms would probably provide the definitive proof of the benefit of SWE in the ultrasound characterization of breast masses. Third, owing to the patients' requests, surgeons' decisions, and the size of masses over 2 cm, there was a high number of BI-RADS 3 masses underwent surgery and finally confirmed as benign.

Conclusion

Results of this study confirmed several aspects of the use of ultrasound and SWE for the characterization of breast lesions in a large Chinese population. The ability of SWE features to improve the diagnostic performances of breast ultrasound, especially maximum stiffness (E_{max}), was confirmed, in particular in low suspicion masses. It was confirmed that SWE could be used as an additional criterion to reduce false positives of breast ultrasound characterization, and therefore improve diagnostic confidence.

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Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

1. **To illustrate the patient selection process in detail, the inclusion and exclusion criteria were supplemented as follows:**

Inclusion Criteria

Patients eligible for participation in the study must:

- Be female,
- Be aged 18 years old or more,
- Already known breast lesion that has not been treated or biopsied,
- Have been referred to a breast ultrasound because of a breast mass found on at least one of the following examinations: physical palpation, mammography, ultrasound examination, or MRI.

Exclusion Criteria

The following patients must also be excluded:

- Women who are unwilling or unable to provide informed consent,
- Women whose breast lesions have been managed or treated or biopsied,
- Women with breast implants,
- Women who are pregnant or breastfeeding,
- Women in whom all lesions are diagnostically categorized as Breast Imaging Reporting and Data System (BI-RADS) 0 or 6,
- Women with previous ipsilateral breast surgery,
- Women with no visible breast mass on ultrasound examination,
- Women with multiple lesions,
- Women with axillary metastatic lymph nodes only,
- Women with foreign body in the breast.

2. **In order to analyze the diagnostic performance of shear wave elastography (SWE), both qualitative and quantitative SWE features were documented. These SWE features will be described on a SWE image with default maximum display setting of 180 kPa (7.7 m/second). Here is a detailed explanation of all SWE features of interest in this study.**

Table S1 List of qualitative features acquired in ShearWave™ Elastography (SWE)

SWE feature	Labeling	Definition
SWE shape	Oval	A mass that is elliptical or egg shaped (may include two or three undulations, ie, gently lobulated or macrolobulated).
	Round	A round mass is one that is spherical, ball-shaped, circular, or globular. It has an anteroposterior diameter equal to its transverse diameter.
	Irregular	The lesion shape is neither round nor oval.
SWE homogeneity	Very homogeneous	The elastography image has a smooth and consistent color appearance throughout or very subtle color differences relating to small changes on the color scale are observed.
	Reasonably homogeneous	The elastography image has a slightly "patchy" appearance. The image may consist of larger (2–5 mm) subregions within the lesion boundary that are homogeneous or the color differences between adjacent areas within the lesion are small.
	Not homogeneous	The elastography image that is inhomogeneous has a "mottled" or "patchy" appearance throughout. Large scale Elastography differences in color are observed in adjacent 1 mm regions within the boundaries of the lesion.
SWE pattern (as defined by Tozaki et al[1])	No findings	No difference is observed at the margin of or inside the lesion with the color around the lesion (homogeneously blue)
	Vertical stripes	A color is observed at the margin of or inside the lesion, which differs from the color around the lesion. The differing color extends beyond the lesion and continues vertically in cords on the cutaneous side and/or the thoracic wall.
	Rim of stiffness	A localized colored area appears at the margin of the lesion and creates a continuous closed circle.
	Colored lesion	Colored areas are heterogeneously visible inside the lesion.
Other SWE pattern (as defined by BE1 investigators)[2]	Void area inside the lesion	There is a lack of SWE signal inside the lesion. The rest of the SWE Box fills correctly.
	Horse shoe pattern	A localized colored area appears at the margin of the lesion and creates an open circle.
	Spots above/below	Colored areas are visible above and/or below the lesion.

Table S2 List of quantitative features acquired in ShearWave™ Elastography (SWE)

SWE features	Labeling	Definition
Lesion SWE elasticity	E_{max}, E_{mean}, E_{SD}	By using a region of interest (ROI) covering as much as the entire lesion on the SWE images, we measured the lesion E_{max}, E_{mean}, E_{SD} on each of the three acquisitions in both longitudinal and transverse views and calculated the averages.
Reference SWE elasticity	E_{max}, E_{mean}	ROI of 3×3 mm was placed over the tissue of reference (subcutaneous fatty tissue if possible) at distance from the lesion. The averages of the control tissue E_{max} and E_{mean} on each of the three acquisitions were calculated.
SWE elasticity ratio	E_{ratio}	The Q-Box™ ratio quantification tool was used, with the same ROI of 2×2 mm placed on the stiffest portion of the lesion (or its immediately adjacent tissue) and the fatty tissue, respectively.

Notes: Quantitative SWE features were measured on each of the three SWE images of two orthogonal views using the quantification tool "Q-Box" built in Aixplorer US system. The measurement of maximum diameter of the lesion on SWE images included the entire mass on B-mode images and any stiff areas immediately adjacent to the lesion.

3. Aggressive and conservative reclassification rules

Rule #1

If Max E_{max} would be added to the BI-RADS test to help classify BI-RADS 3 and 4a masses, using the conservative reclassification rule from the BE1 study:
- Downgrade BI-RADS 4a below 30 kPa
- Upgrade BI-RADS 3 above 160 kPa

Rule #2

If Max E_{max} would be added to the BI-RADS test to help classify BI-RADS 3 and 4a masses, using the aggressive reclassification rule from the BE1 study:

- Downgrade BI-RADS 4a below 80 kPa
- Upgrade BI-RADS 3 above 160 kPa

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