Original Article

Differential diagnosis of B-mode ultrasound Breast Imaging Reporting and Data System category 3–4a lesions in conjunction with shear-wave elastography using conservative and aggressive approaches

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Background: The high false-positive rates of US Breast Imaging Reporting and Data System (BI-RADS) category 3–4a breast lesions leads to excessive biopsies of many benign lesions, and our aim was to investigate the diagnostic performance achieved by adding a maximum elasticity (Emax) of shear-wave elastography (SWE) to ultrasound (US) to evaluate US BI-RADS category 3–4a breast lesions using conservative and aggressive approaches. We explored the capacity of using this method to avoid unnecessary biopsies without increasing the probability of missing breast cancers.

Methods: A total of 123 breast lesions of 120 patients classified as BI-RADS category 3 or 4a were enrolled from January 2019 to December 2019. The US features were evaluated according to the US BI-RADS lexicon. The maximum diameter measured on the US was defined as the size of the lesion. The Emax was assessed by SWE, and the average Emax of breast lesions on two images were calculated and recorded as the final maximum Young's modulus. The diagnostic performance of the combined B-mode US and SWE approach for BI-RADS category 3–4a breast lesions was tested using a conservative approach and an aggressive approach. In the conservative approach, the lesions were downgraded with Emax of 30 kPa or less and upgraded with Emax of 160 kPa or more. In the aggressive approach, the lesions were downgraded with Emax of 80 kPa or less and upgraded with Emax of 160 kPa or more. Pathologic results were defined as the reference standard.

Results: Among all 123 breast lesions, there were 60 lesions classified as BI-RADS category 3 and 63 lesions classified as BI-RADS category 4a. Compared to the B-mode US, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and area under the receiver operating characteristic (ROC) curve (AUC) of the combined B-mode US and SWE with a conservative approach changed from 88.9% to 94.4%, 55.2% to 60.0%, 25.4% to 28.8%, 96.7% to 98.4%, 60.2% to 65.0%, and 0.721 to 0.772, respectively. The specificity, PPV, and accuracy of combined B-mode US and SWE with an aggressive approach increased from 55.2% to 72.4%, 25.4% to 29.3%, and 60.2% to 71.5%, respectively, but this was accompanied with decreases in the sensitivity from 88.9% to 66.7%, the NPV from 96.7% to

92.7%, and the AUC from 0.721 to 0.695.

Conclusions: The addition of SWE improves the diagnostic performance of breast US. Adding the diagnostic criteria of SWE to the BI-RADS assessment of B-mode US, downgrading the lesions with Emax 30 kPa or less, and upgrading the lesions with Emax 160 kPa or more helped discriminate low suspicion lesions from benign lesions in order to decrease false-positive findings and avoid missing cancer diagnosis.

Keywords: Ultrasound (US); shear-wave elastography (SWE); Breast Imaging Reporting and Data System (BI-RADS); breast lesion; maximum elasticity (Emax)

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Introduction

Breast ultrasound (US) is used as a common screening tool to detect and diagnose breast lesions. Breast lesions can be classified according to the US Breast Imaging Reporting and Data System (BI-RADS), which recommends biopsy of breast lesions with a probability of malignancy of more than 2% (1). However, the high false-positive rates (46.0–85.7%) of US BI-RADS leads to excessive biopsies of numerous benign lesions (2-5). Therefore, it is clinically important to develop an imaging modality that reduces unnecessary biopsies of benign lesions and improves diagnostic efficacy.

In addition to becoming an adjunctive diagnostic tool of breast lesions, US elastography has been adopted by the BI-RADS-US lexicon in the second edition (6). Shear-wave elastography (SWE) is a promising elastographic technique that can provide quantitative parameters to depict tissue stiffness, increase confidence in breast lesion characterization, and provide fine intra- and inter-observer reproducibility (7-10). Previous studies have shown that most malignant lesions are much stiffer than benign lesions (3,11,12).

Previous studies have shown that SWE has advantages in distinguishing benign tumors from malignant tumors, and these studies have indicated that SWE features, including mean elasticity and maximum elasticity (Emax), could improve the specificity of B-mode US from 43.1–61.0% to 65.7–87.7% without resulting in a loss of sensitivity (12-15). However, the most valuable SWE feature and cutoff value have not yet been unified. Some studies have demonstrated that Young's modulus Emax, which correlated with Emax measured in kilopascals, had the best diagnostic performance compared with other quantitative parameters when combined with the conventional US BI-RADS (11,16-18).

According to the latest BI-RADS edition, the malignant probability of BI-RADS 3 is less than or equal to 2%, while the probability of BI-RADS 4a is more than 2% with a less than or equal to 10% chance of being malignant (6). Applying SWE could reduce the unnecessary short-term follow-up or biopsy for BI-RADS category 3–4a lesions. Berg *et al.* (11) showed that SWE features changed the treatment of BI-RADS 3 and 4a lesions, but did not influence that of BI-RADS category 2 or BI-RADS category 4c or 5 lesions. They found that BI-RADS 4b lesions and above with suspicious morphology can achieve higher diagnostic accuracy, which remained unchanged when SWE was added to assist treatment decision-making, and biopsy can still be suggested because of patients' requests, breast surgeons' palpation, or suspicious criteria assessed by magnetic resonance imaging (MRI) or mammography.

In previous studies, conservative and aggressive approaches have rarely been used to judge the value of SWE Emax to assist the diagnosis of the special BI-RADS category 3–4a group patients. In addition, most of the existing studies have confirmed that Emax-assisted B-mode US is valuable in the diagnosis of breast lesions, of which the optimal thresholds used mostly came from their samples. Therefore, our study aimed to verify the clinical benefit of adding SWE Emax to B-mode US with conservative and aggressive approaches to differentiate benign and malignant BI-RADS category 3 and 4a lesions, to explore which diagnostic method was more beneficial. We present the following article in accordance with the Standards for Reporting Diagnostic accuracy studies (STARD) reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-21-916/rc).

Methods

Patients

The study was conducted in accordance with the Declaration of (as revised in 2013). The Institutional

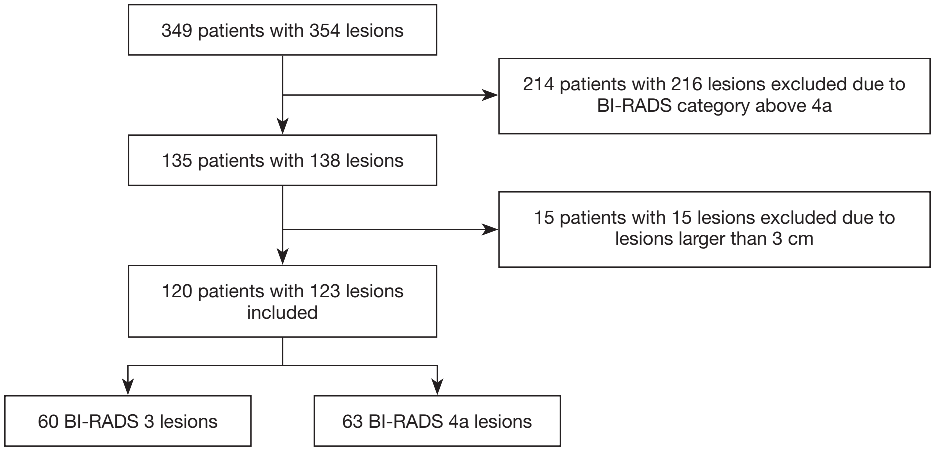

Figure 1 Workflow of the 123 included BI-RADS category 3–4a lesions. BI-RADS, Breast Imaging-Reporting and Data System.

Review Board of Fudan University Shanghai Cancer Center (FUSCC) approved the study (No. 2107238-18), and informed consent was provided by all participants. In this prospective study, from January 2019 to December 2019, a total of 349 consecutive women inpatients with 354 breast lesions classified as BI-RADS 3 to BI-RADS 6 underwent resection of lesions based on the patients' requests or when suspicious features were identified by MRI or mammography. These patients underwent B-mode US and SWE examinations before undergoing surgical resection. The following patients were excluded: 214 patients with 216 lesions, including those breast lesions categorized as BI-RADS category 4b, 4c, or 5 on the US and BI-RADS category 6 as confirmed by pathology; and 15 lesions larger than 3 cm because they did not show changes in the Young's modulus value of surrounding tissue. Finally, a total of 120 patients with 123 breast lesions classified as BI-RADS category 3 or 4a based on B-mode US were enrolled to undergo analysis with SWE (*Figure 1*). Among the 120 patients, 4 patients with breast cancer had a family history of breast cancer, and 1 patient with benign breast lesions had a family history of breast cancer.

US and SWE examination

For all breast lesion patients, imaging was performed to obtain B-mode US images and SWE images in two orthogonal planes with the US system (Aixplorer V10, SuperSonic Imagine, Aix-en-Provence, France) equipped with an SL15-4 MHz linear array transducer by two radiologists with 4–10 years of experience in breast US and SWE. The US characterizations were assessed based on the US BI-RADS lexicon by two radiologists who were blinded to pathology. The maximum diameter measured in both perpendicular planes on the US was defined as the final size of the lesion.

After B-mode US, participants were asked to hold their breath for at least 3–5 seconds to obtain stable images during the image acquisition process. A semitransparent color map of tissue stiffness overlaid on the B-mode US image indicated regions with the lowest stiffness to the highest stiffness (0–180 kPa) in a range from dark blue to red. The built-in quantification instrument—the region of interest (ROI) (Q-box; SuperSonic Imagine) of the system—had various sizes that were used to include the whole lesions and the adjacent tissue to quantify elasticity for the lesions. Two SWE acquisitions of two frozen frames were acquired with the default maximum color scale of 180 kPa by the same radiologist with no pressure applied. We manually delineated lesions on B-mode US and elastography. The contours of the lesions outlined on elastography included areas of relatively harder breast glandular tissue that surrounded the lesions. The quantitative elasticity values, including the Emax and other elasticity values, were automatically calculated. On the elastic image, the higher Emax of the two sets of SWE parameters was used as the Emax of the lesion. All elastic images and B-mode US images were recorded for review and data analysis. The average Emax of two breast nodule images was calculated and recorded as the final average maximum Young's modulus.

Table 1 Histologic results of lesions confirmed by surgery

Histologic features	No. of lesions
Fibroadenoma	68
Intraductal papilloma	10
Adenosis	17
Benign phyllodes tumor	5
Mastitis	2
Borderline phyllodes tumor	3
Ductal carcinoma *in situ*	6
Invasive ductal carcinoma	11
Solid papillary carcinoma	1
Total	123

Combined US and SWE with conservative and aggressive approaches

The conservative approach was defined as follows: combined with B-mode US, the final US BI-RADS grade of the lesion was downgraded with Emax of 30 kPa or less and upgraded with Emax of 160 kPa or more (11).

The aggressive approach was defined as follows: combined with B-mode US, the final US BI-RADS grade of the lesion was downgraded with Emax of 80 kPa or less and upgraded with Emax of 160 kPa or more (11).

Statistical analysis

Pathologic diagnosis was used as the reference standard. All statistical analyses were performed using the software SPSS 22.0 (IBM Corp., Armonk, NY, USA) and MedCalc (MedCalc Software, Mariakerke, Belgium). All the count data were described as the mean ± standard deviation (SD). The significant differences among different groups were analyzed with the independent-samples *t*-test. The diagnostic performance of US and US combined Emax were evaluated with receiver operating characteristic (ROC) curves.

Results

General information about patients and lesions

In our study cohort, the mean age of patients was 45.9±11.8 (range, 19 to 76) years, and the mean size of the lesion was 14.8±4.8 (range, 5 to 27) mm. *Table 1* shows the histologic results of 123 lesions, including 60 category 3 lesions and 63 category 4a lesions, which were confirmed by surgery.

The sizes of 102 benign lesions, 3 borderline phyllodes tumors, and 18 malignant lesions were 14.9±4.6 (range, 5 to 27), 23.0±1.0 (range, 22 to 24), and 12.7±4.7 (range, 6 to 22) mm, respectively. The mean ages of malignant and benign groups were 54.7±10.3 and 44.4±11.3 years, respectively, and there was no significant statistical difference (P=0.970).

Conventional US evaluation

Among the 123 lesions, 60 were classified as BI-RADS category 3, of which 58 (96.7%, 58/60) were benign, including 47 fibroadenomas, 9 breast adenosis, 1 benign phyllodes tumor, and 1 intraductal papilloma. There were 2 invasive ductal carcinomas, and the malignancy rate was 3.3%. Of the 63 BI-RADS category 4a lesions, 44 (69.8%, 44/63) were benign, which included 21 fibroadenomas, 9 intraductal papillomas, 2 breast mastitides, 8 breast adenosis, and 4 benign phyllodes tumors. Three (4.8%, 3/63) were borderline phyllodes tumors, and 16 (25.4%, 16/63) were malignant tumors, which included 9 invasive ductal carcinomas, 6 ductal carcinomas *in situ*, and 1 solid papillary carcinoma.

The BI-RADS category 3 lesions were classified as benign and the BI-RADS 4a lesions were classified as malignant according to the standard. The US BI-RADS category had a sensitivity of 88.9%, specificity of 55.2%, positive predictive value (PPV) of 25.4%, negative predictive value (NPV) of 96.7%, and an accuracy of 60.2% (*Table 2*).

SWE quantitative evaluation

The average elasticity values of the benign, malignant, and borderline phyllodes tumor groups were 73.5±56.3 (range, 65.3 to 300.0), 133.9±67.3 (range, 65.3 to 300.0), and 171.0±115.3 (range, 77.9 to 300.0) kPa, respectively. The average Emax in malignant tumors and borderline phyllodes tumor groups was significantly higher than that in benign lesions (P<0.001 and P=0.006, respectively; *Table 3*; *Figures 2-4*). The Emax of malignant lesions was significantly higher than that of adenosis [82.2±69.7 (range, 9.0 to 225.0) kPa; P=0.010] and fibroadenoma [64.5±50.8 (range, 10.5 to 234.3) kPa; P=0.000]. The Emax of borderline phyllodes tumors was higher than that of benign phyllodes tumors (80.1±26.8 kPa; P=0.036), adenosis (P=0.017), and fibroadenoma (P=0.003). The Emax of intraductal

Table 2 Diagnostic performances of US and combined US and SWE

Different methods	Sen (%)	Spe (%)	PPV (%)	NPV (%)	Accuracy (%)	AUC	SE	95% CI
US	88.9	55.2	25.4	96.7	60.2	0.721	0.0452	0.633–0.798
Conservative approach	94.4	60.0	28.8	98.4	65.0	0.772	0.0367	0.688–0.843
Aggressive approach	66.7	72.4	29.3	92.7	71.5	0.695	0.0612	0.606–0.775

US, ultrasound; SWE, shear-wave elastography; Sen, sensitivity; Spe, specificity; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the receiver operating characteristic curve; SE, standard error; CI, confidence interval.

Table 3 Clinical and Emax results of breast lesions confirmed by surgery

Histologic features	Number of lesions	Emax (kPa), mean ± SD [range]	Size (mm), mean ± SD [range]	Age (years), mean ± SD [range]
Fibroadenoma	68	64.5±50.8 [10.5–234.3]	14.9±4.1 [7–25]	42.6±11.2 [19–65]
Intraductal papilloma	10	113.4±58.6 [34.3–206.4]	14.7±4.4 [9–21]	51.6±15.0 [36–76]
Adenosis	17	82.2±69.7 [9.0–225.0]	13.8±6.0 [5–27]	48.5±8.8 [31–69]
Benign phyllodes tumor	5	80.1±59.9 [33.5–148.2]	20.2±2.6 [17–23]	41.0±4.6 [38–49]
Mastitis	2	113.4±58.6 [87.2–94.8]	13.5±5.0 [10–17]	41.5±0.7 [41–42]
Borderline phyllodes tumor	3	171.0±115.3 [77.9–300.0]	23.0±1.0 [22–24]	43.3±18.0 [25–61]
Breast cancer	18	133.9±67.3 [65.3–300.0]	12.7±4.7 [6–22]	54.7±10.3 [38–69]
Total	123	–	–	–

Emax, maximum elasticity; SD, standard deviation.

papillomas [113.4±58.6 (range, 34.3 to 206.4) kPa] was higher than that of fibroadenoma (P=0.015), but no differences were found between breast cancers and borderline phyllodes tumors (P=0.312), mastitis [91.0±5.4 (range, 87.2 to 94.8) kPa; P=0.329], and intraductal papillomas (P=0.379).

Diagnostic performance of combined US and SWE

Figure 5 shows the changes of the final BI-RADS assessment after applying the combination of B-mode US and SWE. When using the conservative approach in this study, adding the SWE Emax feature to B-mode US improved the diagnostic performance of breast lesion assessment (*Table 2*). Compared to the B-mode US, the sensitivity, specificity, PPV, NPV, accuracy, and area under the ROC curve (AUC) of the combined US and SWE method changed from 88.9% to 94.4%, 55.2% to 60.0%, 25.4% to 28.8%, 96.7% to 98.4%, 60.2% to 65.0%, and 0.721 to 0.772, respectively.

Using the conservative approach, none of the 17 cancers were downgraded. One cancer with Emax 300 kPa was upgraded from BI-RADS category 3 to 4a, which shown to have avoided misdiagnosis. Out of the 47 false-positive lesions diagnosed by US, 17.0% (8/47) were properly downgraded from category 4a to 3 and recommended to be followed up.

Using the aggressive approach, out of the 47 false-positive lesions diagnosed by US, 44.7% (21/47) were properly downgraded from category 4a to 3, which avoided unnecessary biopsies. Five out of 18 cancerous lesions (27.8%) were underestimated and downgraded from BI-RADS category 4a to 3 (*Figure 6*). Compared to the B-mode US, the specificity, PPV, and accuracy of the combined B-mode US and SWE method increased from 55.2% to 72.4%, 25.4% to 29.3%, and 60.2% to 71.5%, respectively. However, this was accompanied with a decrease in sensitivity from 88.9% to 66.7%, decrease in NPV from 96.7% to 92.7%, and decrease in AUC from 0.721 to 0.695 (*Table 2*).

One cancer with an Emax of 75.8 kPa was diagnosed as BI-RADS category 3 using B-mode US alone and with the combination of US and SWE using the conservative approach or the aggressive approach.

Figure 7 shows the diagnostic performances of B-mode

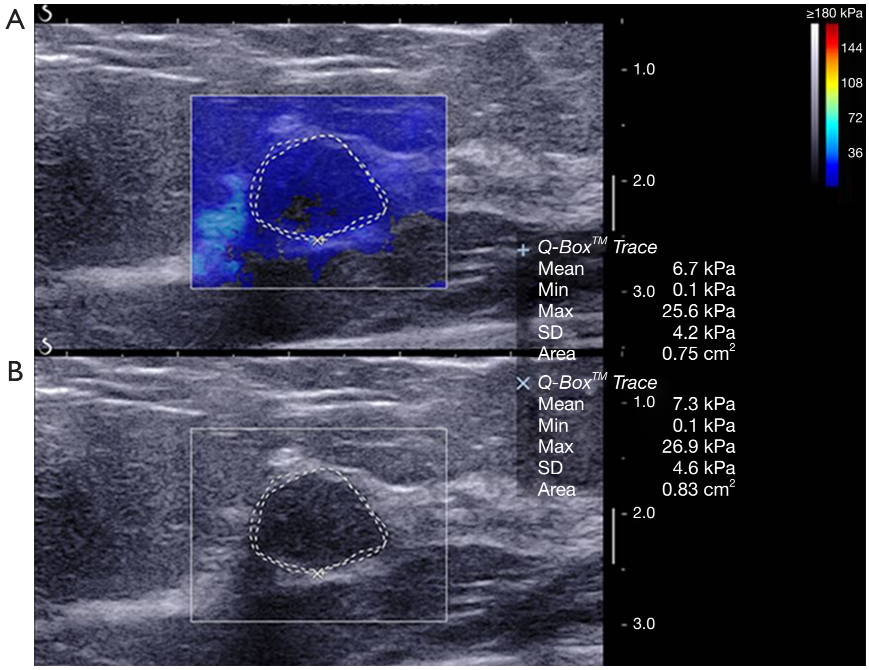

Figure 2 A 54-year-old woman with a 14 mm fibroadenoma. The US shows (B) a circumscribed, wider than taller, hypoechoic nodule assessed as BI-RADS category 3, while the corresponding SWE (A) shows an oval homogeneous mass with blue color and Emax of 26.9 kPa. SD, standard deviation; US, ultrasound; BI-RADS, Breast Imaging-Reporting and Data System; SWE, shear-wave elastography; Emax, maximum elasticity.

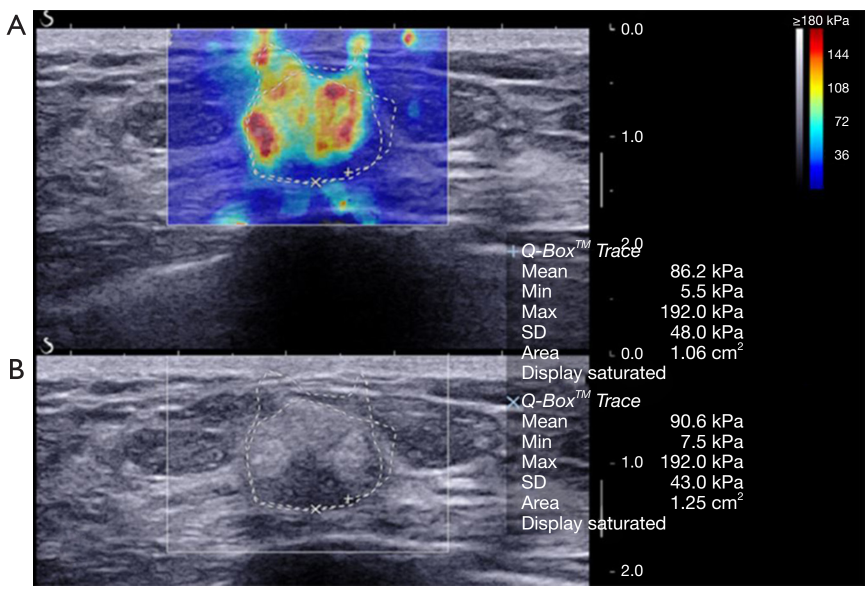

Figure 3 A 64-year-old woman with a grade II invasive ductal carcinoma. US image (B) shows a 14 mm hypoechoic mass with an indistinct margin classified as BI-RADS category 4a. SWE image (A) shows Emax of 192.0 kPa. The mass would be upgraded to BI-RADS category 4b by using the aggressive and conservative approaches. SD, standard deviation; US, ultrasound; BI-RADS, Breast Imaging-Reporting and Data System; SWE, shear-wave elastography; Emax, maximum elasticity.

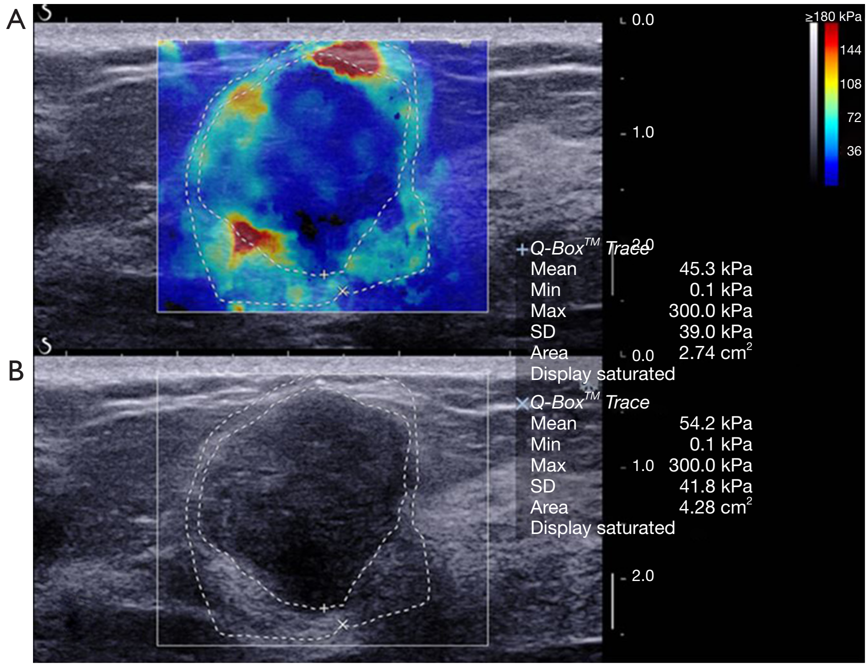

Figure 4 A 61-year-old woman diagnosed with a 22 mm, borderline phyllodes tumor. The lesion was assessed as BI-RADS category 4a on US image (B), the SWE image (A) shows Emax of 300.0 kPa. The lesion would be upgraded to BI-RADS category 4b by using the aggressive and conservative approaches with combined assessment of US and SWE. SD, standard deviation; BI-RADS, Breast Imaging-Reporting and Data System; US, ultrasound; SWE, shear-wave elastography; Emax, maximum elasticity.

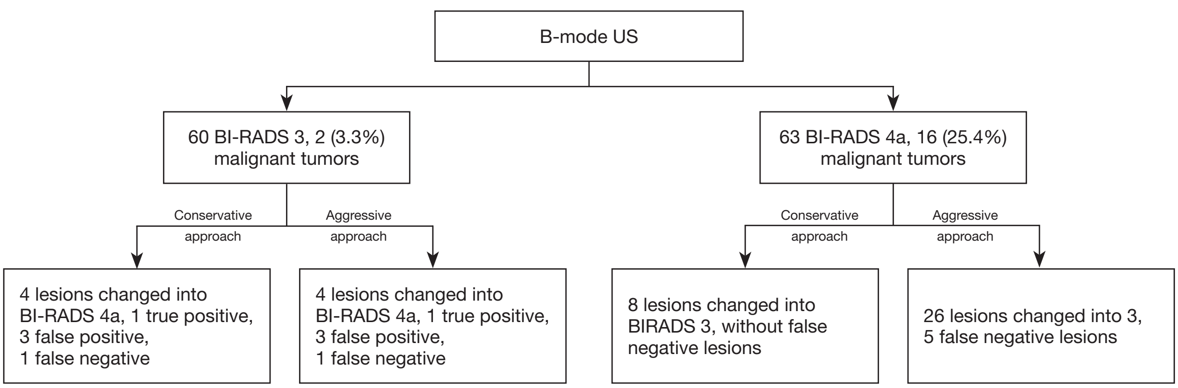

Figure 5 BI-RADS classification of breast lesions by US and US combined with SWE using the conservative and aggressive approaches after and before. US, ultrasound; BI-RADS, Breast Imaging-Reporting and Data System; SWE, shear wave elastography.

US only and the combined B-mode US and SWE method using the conservative and aggressive approaches.

Discussion

As a complementary modality to B-mode US, SWE can quantify the elasticity of breast lesions. The addition of SWE to B-mode US yields better diagnostic performance than using B-mode US alone, especially when identifying the Emax in low suspicion masses (13,18,19). Previous studies have shown that SWE can downgrade the BI-RADS category of some lesions that have a low likelihood of malignancy, which can reduce unnecessary biopsies (20-22). We showed that a combination of B-mode US and SWE

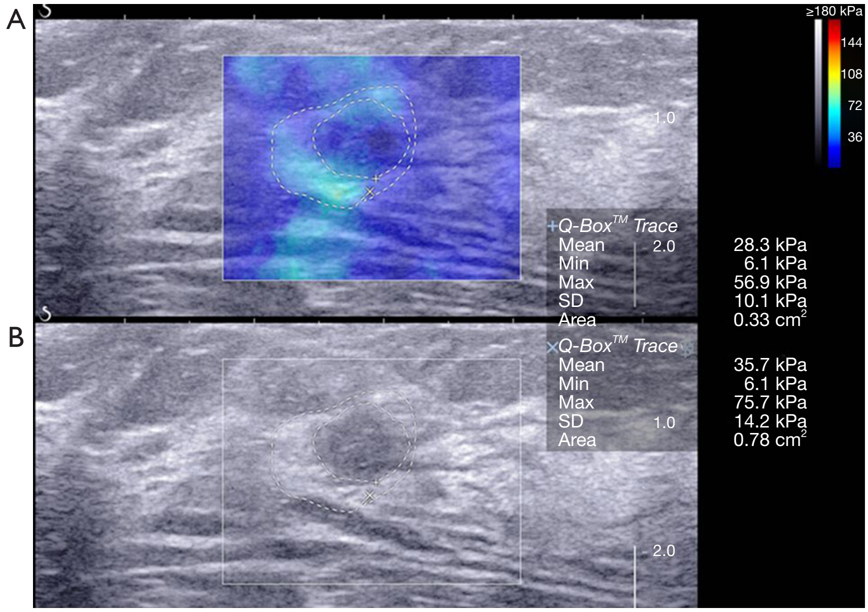

Figure 6 A 38-year-old woman diagnosed with grade II invasive ductal carcinoma. The US image (B) shows a 10 mm lesion assessed as BI-RADS category 4a, the SWE image (A) shows an Emax of 75. 7kPa. The lesion would be categorized BI-RADS category 4a by using the conservative approach with combined assessment of US and SWE, but it would be downgraded to BI-RADS category 3 by using the aggressive approach, resulting in a false-negative finding. SD, standard deviation; US, ultrasound; BI-RADS, Breast Imaging-Reporting and Data System; SWE, shear-wave elastography; Emax, maximum elasticity.

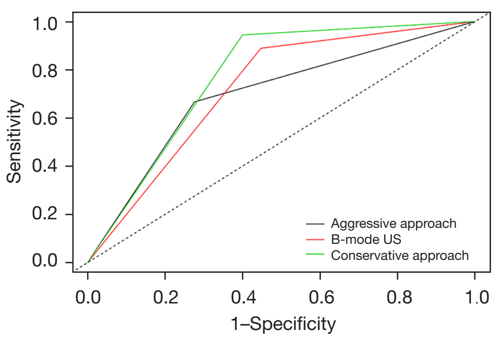

Figure 7 The diagnostic performance of B-mode US and B-mode US combined with SWE using the conservative and aggressive approaches. US, ultrasound; SWE, shear-wave elastography.

increased the specificity of B-mode US alone from 55.2% to 72.4% using the aggressive approach and to 60.0% using the conservative approach, which was consistent with previous studies (18). Adding the quantitative Emax value in SWE modified US BI-RADS category 4a to US BI-RADS category 3 for 8 lesions using the conservative approach and 21 lesions using the aggressive approach. This meant that biopsy could be avoided in 17.0% and 44.7% of 47 false-positive cases based on the conservative and aggressive approach, respectively. Although the specificity was improved, the sensitivity of the combination of B-mode US and SWE using the aggressive approach was lower than that of B-mode US alone. As a result, 27.8% (5/18) of breast cancers (Emax from 65.3 to 75.8 kPa) were missed. This phenomenon is not acceptable in clinical practice. However, the sensitivity of the combination of B-mode US and SWE using the conservative approach was higher than that of US, without missing any cancerous lesions.

We found that malignant breast lesions had higher stiffness than benign breast lesions. Similar results have been reported in other studies (23,24). Among the malignant breast lesions, invasive ductal carcinomas (11/18) were the most common pathological type in our study. Of the 18 confirmed breast cancers, 16 breast lesions were correctly diagnosed by B-mode US, while the diagnosis of 1 cancer misdiagnosed using B-mode US alone was corrected using the combination of B-mode US and SWE (Emax 300 kPa) with both the conservative and aggressive approaches. One cancer was incorrectly classified as a benign lesion (BI-RADS category 3) with benign characteristics on the US and had low stiffness (Emax 75.8 kPa) shown by SWE with both the conservative and aggressive approaches.

Fibroadenomas were the most common and the softest benign breast tumors, with an Emax of 64.5±50.8 kPa in our study, which was similar to the report by Hari *et al.* (25). Among the benign lesions, some chronic inflammation and intraductal papillomas often mimic malignant lesions and pose diagnostic challenges (26-28). Two chronic inflammatory masses and 9 intraductal papillomas displayed malignancy features on US, which lead to their misclassification as malignant, but the addition of Emax to B-mode US resulted in two intraductal papillomas being properly classified as BI-RADS category 3 on the US with the aggressive approach; however, other inflammatory masses and intraductal papillomas with higher Emax values were still misdiagnosed with this approach. Borderline phyllodes tumors demonstrated higher Emax than other benign lesions, which were wrongly classified as malignant by the combined B-mode US and SWE. This might be because borderline phyllodes tumors are larger than other benign tumors. Furthermore, Chamming's *et al.* (29) reported that tissue stiffness showed excellent correlation with tumor size in mice.

The combination of B-mode US with SWE improved the diagnostic performance of B-mode US alone. The AUC of B-mode US and B-mode US combined with SWE using the conservative and aggressive approaches were 0.721, 0.772, and 0.695, respectively. These results indicated that B-mode US combined with SWE using the conservative approach yielded the best diagnostic efficacy for breast lesions, and this finding was consistent with other studies (30).

There were several limitations to our study. First, as a single institutional study, our cohort included a relatively small number of malignant lesions. Furthermore, the low malignancy rate of 14.6% (18/123) may have led to a lower PPV. Second, Emax showed the best diagnostic performance, therefore only the diagnostic efficacy of B-mode US combined with the Emax of SWE was considered, and other SWE parameters were omitted. In addition, intraductal papillomas have an increased risk of breast cancer, therefore lesions suspected to be intraductal papillomas were classified as BI-RADS 4a and recommended for biopsy, so there was a higher rate of misdiagnosis. Moreover, the use of BI-RADS was too conservative, which led to a higher positive rate of BI-RADS 4a. In the future, we will correct our BI-RADS category norms. Finally, our study only included patients hospitalized for surgery. Future study should also be extended to outpatients.

Conclusions

The addition of SWE improves the diagnostic performance of breast US. Adding diagnostic criteria of SWE to the BI-RADS assessment of B-mode US, downgrading the lesion of Emax 30 kPa or less, and upgrading the lesion of Emax 160 kPa or more, would help discriminate low suspicion lesions from benign lesions to decrease false-positive findings and avoid missing cancer diagnoses.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-21-916/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-21-916/coif). All authors report that this work was supported by The National Natural Science Foundation of China (No. 81801701 to WZ; No. 81901749 to HZ; No. 81901703 to CY; No. 81830058 to CC). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of (as revised in 2013). This study was approved by the Ethical Review Committee of the Fudan University Shanghai Cancer Center (No. 2107238-18), and informed consent was provided by all the patients.

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