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# Influence of lesion size on differential diagnosis of benign and malignant breast lesions by real-time two-dimensional shear wave elastography

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► ***Original article***

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***Keywords:*** *Ultrasound, shear wave, elastography, breast lesions, BI-RADS.*

## ABSTRACT

***Background*:** The aim of this study was to evaluate the influence of lesion size on the performance of real-time two-dimensional shear wave elastography (2D-SWE) in the diagnosis of breast lesions. ***Materials and Methods*:** A total of 118 consecutive female patients with 129 breast lesions (50 malignant and 79 benign) who underwent surgical excision and/or core biopsy were studied. The lesions were categorized into three subgroups according to their size: (1) group 1: < 1.0 $cm^3$; (2) group 2: 1.0–4.0 $cm^3$; (3) group 3: > 4.0 $cm^3$. The maximum elasticity (Emax), mean elasticity (Emean), and their standard deviation (SD) in the three subgroups were compared and analyzed in terms of the cutoff values acquired by pathological results. ***Results*:** The lesion size significantly differed between benign and malignant masses ($P < 0.05$). Malignant lesions exhibited significantly elevated values of Emax, Emean, and SD, compared with benign lesions in the three subgroups. The optimal threshold was higher for larger malignant and benign lesions ($P < 0.05$). In malignant lesions, the SWE parameters in group 1 were significantly different from those in groups 2 and 3. The area under the receiver operating characteristics curve (AUROC) of SD was higher than that of Emax and Emean in all three subgroups. ***Conclusion*:** The values of 2D-SWE parameters increase with the increase in size of a breast mass, and the adjustment of the threshold based on lesion size yields a more accurate diagnosis. Among the SWE parameters, SD has the best diagnostic performance.

## INTRODUCTION

Breast cancer (BC) is considered one of the most common malignant tumors in women worldwide [(1)]. Approximately 252,710 new cases of invasive breast cancer and 40,610 breast cancer deaths occurred among women in the United States in 2017 [(2)]. In China, BC also ranks first among female malignant tumors, with about 279,000 new cases per year; with a mortality rate of 9.9 per 100,000, breast cancer ranks fifth in female cancer mortality [(3)]. Therefore, it is important to correctly distinguish malignant breast masses from benign breast lesions. Mammography (MG) and ultrasound (US) are used as conventional imaging techniques for BC diagnosis. Of note, sensitivity of MG to detect BC is low for breasts with graphically dense radiological images, but MG is highly sensitive to detect microcalcifications in breast lesions. US has many limitations in distinguishing malignant breast lesions, especially for smaller breast lesions [(4)]. Although magnetic resonance imaging (MRI) is more sensitive than MG and US in the diagnosis of BC [(5)], it is not commonly used in detecting breast lesions due to its high cost. Therefore, it is urgent to discover a new imaging technology to improve diagnostic efficiency significantly.

In the past few years, US elastography has been developed for many clinical applications. There are two major elastographic approaches: strain elastography (SE) and shear wave elastography (SWE) [(6-9)]. In SE, a compressive force is applied to the tissue to measure the lesion stiffness. The likelihood of malignancy increases with the increasing stiffness, and the strain ratio of malignant lesions is greater than that of benign lesions. In SE, lesion stiffness is expressed on a color scale for semiquantitative assessment, with poor consistency and repeatability [(7)].

SWE imaging can quantitatively measure tissue stiffness, expressed as Young's modulus; it has advantages over conventional elastography because SWE delivers more quantitative parameters that are free of interobserver variability [(10)]. The maximum elasticity (Emax), mean elasticity (Emean), and standard deviation (SD) are the most common SWE



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parameters. The Emax is the elasticity value of the stiffest part of the mass within the region of interest (ROI). The Emean represents the mean elasticity values within the ROI [11], and the SD is the standard deviation of elasticity. The integration of the elastography technique with conventional US may improve the diagnostic accuracy of breast lesions [12,13] and assist the evaluation of breast lesions based on the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) [14,15]. It has been documented that approximately 32.6%–88% of biopsies of benign lesions can be avoided by combining SWE with conventional US [13,16]. Among the SWE parameters, the Emax is considered the best parameter to evaluate benign and malignant breast lesions [8,12]. However, Emax shows a large difference in the diagnostic threshold of breast lesions, and the value was reported to be 56.0–87.5 kPa in some studies [17,18]. Lesion size has a significant impact on false results, as reported in a previous study [19].

To the best of our knowledge, few studies have been carried out using SWE parameters to differentiate breast lesions based on lesion size (volume). Therefore, in this study, we aimed to evaluate the optimal cutoff thresholds of the SWE parameters, including Emax, Emean, and SD, based on different lesion size so as to achieve more accurate distinction between benign and malignant breast lesions.

## MATERIALS AND METHODS

### *Patients*

This was a retrospective study, so informed consent was waived. The study protocol was reviewed and approved by the Clinical Trial Ethics Committee of the Hefei Second People's Hospital (protocol number: 2020-Science and Education Office -015), and it complied with the Declaration of Helsinki for the study of human subjects.

The medical records of 118 consecutive female patients with 129 breast lesions who had undergone surgical resection and/or core needle biopsy from December 2015 to April 2019 were included in the study. The inclusion criteria were as follows: 1) no history of surgery, radiotherapy, or chemotherapy before US examination; 2) solid breast lesions that can be detected by US; 3) available histopathological findings. Conventional US and SWE were performed in all the patients before biopsy and/or surgery.

### *Conventional US examinations*

All the SWE and US images were acquired using the Supersonic Imagine Aixplorer E (Supersonic Imagine, Aix-en-Provence, France) equipped with a linear array transducer with a frequency range of 4–15 MHz. Breast US examinations were performed by two certified sonographers with over 20 years of experience. The sonographers measured the lesion size (calculated as length × width × depth × 0.523) and recorded features observed with conventional US. BI-RADS for US was used for the assessment of each lesion. All the lesions were evaluated by US with the Breast Imaging Reporting and Data System (BI-RADS) of the American College of Radiology.

### *US elastography evaluation*

For SWE imaging, an adequate ROI was set in the system to include the largest portion of the lesion as well as its surrounding breast parenchyma, with the chest wall and skin excluded. The Emax, Emean, and SD were then measured by the system. For large lesions beyond the color overlay range of SWE, the ROI was positioned in the stiffest part displayed by SWE to measure the Emax. The Emean and SD values were measured multiple times across different parts of the lesion to minimize errors. The mean values of the above parameters were calculated in six elastography images with two of the three orthogonal planes of adequate quality (figure 1), which referred to images that clearly displayed abnormal stiffness in the plane and were free of motion or pressure artifacts. Those lesions were categorized into three subgroups according to their size (volume): (1) group 1: < 1.0 $cm^3$; (2) group 2: 1.0–4.0 $cm^3$; (3) group 3: > 4 $cm^3$. The Emax, Emean, and SD were compared and analyzed in terms of the cutoff values acquired by pathological results.

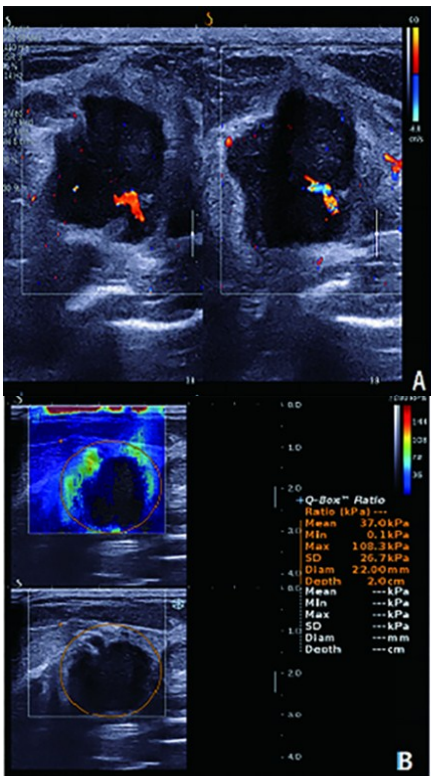


**Figure 1.** B-mode **(A)** US and SWE images **(B)** of invasive ductal carcinoma in a 56-year-old woman. The Emax, Emean, and SD were automatically measured by the system. The ROI was set sufficiently large to include the largest possible part of the mass and the surrounding breast parenchyma tissue. ROI, region of interest; SD, standard deviation; SWE, shear wave elastography; US, ultrasound.



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### Histological evaluation

All the patients received surgical resection and/or core needle biopsy for breast tumors. All specimens were fixed in formalin, embedded in paraffin, and sectioned for hematoxylin and eosin (H&E) staining.

### Statistical analysis

SPSS software version 20.0 (SPSS, Chicago IL, USA) was employed for statistical analysis in this study. The Wilcoxon Mann–Whitney U test was performed for the comparison of differences in the elasticity values between malignant and benign lesions among the three subgroups. The ROC curve analysis was performed to calculate the optimal cutoff values of the quantitative SWE parameters in each group and to assess the diagnostic performance of each parameter using the final histopathological diagnosis as the reference standard. Then, sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy of the diagnosis were calculated based on the optimal cutoff values of each parameter. The statistically significant difference was determined when $P$ was < 0.05.

## RESULTS

### Population description and lesions' characteristics

To validate the pathological results of 129 breast masses, 118 women underwent surgical resection or needle biopsy of breast masses. The results indicated that 79 masses were benign (61.2%) and 50 were malignant (38.8%). The mean patients' age was 43.5±12.7 years (range, 19–86 years). There was a significant difference in patients' age between benign and malignant lesions (benign: 38.57±10.78 years; malignant: 51.62±11.38 years). The average size of lesions was 3.34±4.52 $cm^3$ (range, 0.041–20.589 $cm^3$; benign lesions: 0.042–20.475 $cm^3$; malignant lesions: 0.041–20.589 $cm^3$). The size of malignant lesions was larger than that of benign lesions, and the difference was statistically significant [benign: 1.15 (0.37–3.58) $cm^3$, malignant: 1.73 (0.81–6.11) $cm^3$, $P$<0.05].

### Pathological diagnosis

The pathological results and the detection rate of lesions are listed in table 1. The most common type of benign lesions was fibroadenoma (40.5%, 32/79), followed by adenosis (29.1%, 23/79). The most common type of malignant lesions was infiltrative ductal carcinoma (64%, 32/50), followed by ductal carcinoma in situ (DCIS) (14%, 7/50). The results of histopathological analysis served as the standard of reference method.

### BI-RADS category of US

The absolute and relative frequencies of each conventional US BI-RADS category are listed in table 2. Of the 79 benign lesions confirmed by histology, 47 (59.5%) were classified as probably benign (BI-RADS 2 or 3) and 22 (40.5%) were classified as suspected malignancy (BI-RADS 4 or 5) on US. Of the 50 malignant lesions confirmed by histology, 48 lesions (96.0%) were classified as suspected malignancy (BI-RADS 4 or 5) and two lesions were classified as probably benign (BI-RADS 3) on US. According to the final pathological results, sensitivity, specificity, PPV, NPV, and diagnostic accuracy were 96%, 40.5%, 50.5%, 94.1%, and 73.6%, respectively, based on the BI-RADS classification.

### SWE parameters of breast lesions in subgroups

The data of the SWE parameters of the breast lesions in different subgroups classified according to lesion size are listed in table 3. In the three subgroups, malignant lesions exhibited significantly higher values of Emax, Emean, and SD compared with those of benign lesions ($P$<0.05 for all) (figure 2). The differences in the values of Emax, Emean, and SD in the three subgroups of benign lesions were not statistically significant, while elevated thresholds were observed in larger malignant and benign lesions. The SWE parameters of malignant lesions in group 1 were significantly different from those in groups 2 and 3 (figure 3).

### Diagnostic performance of SWE parameters

In terms of the SWE parameters, the area under the receiver operating characteristics curve (AUROC) of SD was higher than that of Emax and Emean in all three subgroups. Higher thresholds were also found in the subgroup of larger lesions. The sensitivity, specificity, NPV, PPV, and the diagnostic accuracy of Emax, Emean, and SD calculated with the optimal cutoff values are listed in table 4. The thresholds for the diagnosis of malignant lesions were significantly different among the three subgroups classified according to lesion size.

**Table 1.** Pathological details of benign and malignant lesions.

| Pathological diagnosis | Number of lesions | % |
|---|---|---|
| Benign lesions (79) | | |
| Fibroadenoma | 32 | 40.5 |
| Adenosis | 23 | 29.1 |
| Benign phyllodes tumor | 10 | 12.7 |
| Breast inflammation | 8 | 10.1 |
| Papilloma | 3 | 3.8 |
| Others | 3 | 3.8 |
| Malignant lesions (50) | | |
| Invasive ductal carcinoma | 32 | 64 |
| Ductal carcinoma in situ | 7 | 14 |
| Invasive papillary carcinoma | 3 | 6 |
| Invasive lobular carcinoma | 2 | 4 |
| Mucinous carcinoma | 2 | 4 |
| Others | 4 | 8 |



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**Table 2.** BI-RADS category of US.

| | Total (n = 129) | Benign (n = 79) | NPV | Malignant (n = 50) | PPV |
|---|---|---|---|---|---|
| BI-RADS 2 | 2 | 2 | 100% | | |
| BI-RADS 3 | 47 | 45 | 95.7% | 2 | 4.3% |
| BI-RADS 4 | | | | | |
| 4a | 36 | 26 | | 10 | 27.8% |
| 4b | 19 | 5 | | 14 | 73.7% |
| 4c | 14 | 1 | | 13 | 92.9% |
| BI-RADS 5 | 11 | | | 11 | 100% |

BI-RADS, Breast Imaging Reporting and Data System; NPV, negative predictive values; PPV, positive predictive values; US, ultrasound.

**Table 3.** Breast lesion size and corresponding SWE parameters.

| Variable | Median (quartile 1–quartile 3) | | *P* value |
|---|---|---|---|
| SWE parameters | Benign (n = 79) | Malignant (n = 50) | |
| Lesions < 1.0 $cm^3$ | n = 36 | n = 15 | |
| Emax (kPa) | 32.15 (27.63–37.75) | 53.30 (33.70–66.00) | 0.001 |
| Emean (kPa) | 19.27 (16.86–21.97) | 19.78 (14.44–31.80) | 0.420 |
| SD (kPa) | 4.30 (2.91–5.32) | 9.77 (7.60–11.30) | 0.000 |
| Lesions 1–4.0 $cm^3$ | n = 25 | n = 19 | |
| Emax (kPa) | 39.22 (24.75–47.50) | 101 (77.6–108.30) | 0.000 |
| Emean (kPa) | 22.03 (15.69–29.80) | 38.0 (27.20–78.10) | 0.001 |
| SD (kPa) | 5.10 (3.06–8.94) | 20.0 (13.70–26.30) | 0.000 |
| Lesions > 4.0 $cm^3$ | n = 18 | n = 16 | |
| Emax (kPa) | 41.45 (30.15–47.94) | 117.95 (86.00–210.80) | 0.000 |
| Emean (kPa) | 22.04 (17.32–27.01) | 42.24 (29.49–131.40) | 0.001 |
| SD (kPa) | 5.60 (4.11–7.81) | 29.90 (17.49–35.68) | 0.000 |

Emax, maximum elasticity; Emean, mean elasticity; SD, standard deviation; SWE, shear wave elastography.

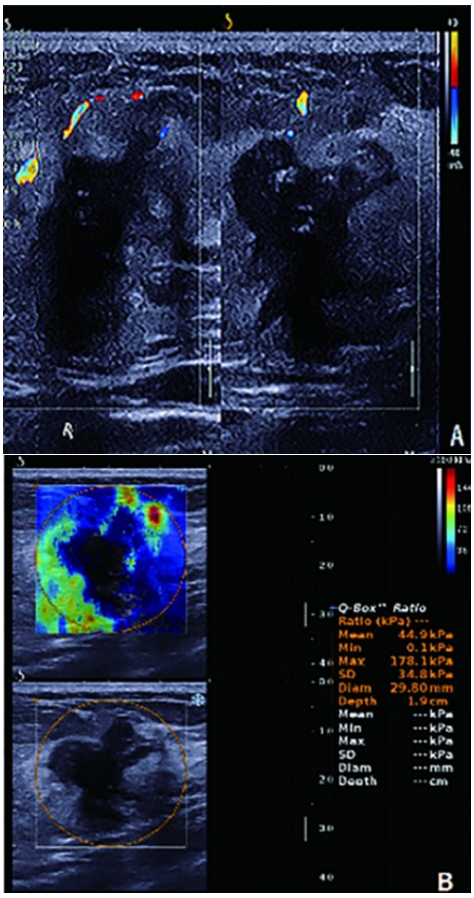


**Figure 2.** Images of a 48-year-old woman with pathohistologically confirmed invasive ductal carcinoma. B-mode images **(A)** and SWE **(B)** showed a 25-mm-large and irregular red mass with heterogeneous elasticity. b. The Emean, Emax, and SD of elasticity values were measured in kPa by placing a sufficiently large ROI including the largest portion of the lesion. ROI, region of interest; SD, standard deviation; SWE, shear wave elastography.

**Table 4.** Diagnostic performance of the Emax, Emean, and SD in different groups.

| Parameter | Group | AUC (95% CI) | Threshold | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy |
|---|---|---|---|---|---|---|---|---|
| Emax (kPa) | < 1.0 $cm^3$ | 0.821 (0.675–0.967) | 44.55 | 73.30 | 91.70 | 78.57 | 89.19 | 44/51 (86.27%) |
| | 1–4.0 $cm^3$ | 0.964 (0.919–1.00) | 58.50 | 100.0 | 84.00 | 82.61 | 100.0 | 40/44 (90.91%) |
| | > 4.0 $cm^3$ | 0.927 (0.812–1.00) | 63.50 | 93.80 | 94.40 | 93.75 | 94.44 | 32/34 (94.12%) |
| Emean (kPa) | < 1.0 $cm^3$ | 0.572 (0.376–0.768) | 22.61 | 46.70 | 80.60 | 50.00 | 78.38 | 36/51 (70.59%) |
| | 1–4.0 $cm^3$ | 0.787 (0.647–0.927) | 26.12 | 84.20 | 68.00 | 66.67 | 85.00 | 33/44 (75.00%) |
| | > 4.0 $cm^3$ | 0.795 (0.628–0.963) | 28.01 | 81.20 | 83.30 | 81.25 | 83.33 | 28/34 (82.35%) |
| SD (kPa) | < 1.0 $cm^3$ | 0.849 (0.701–0.997) | 7.465 | 80.00 | 88.90 | 75.00 | 91.43 | 45/51 (88.24%) |
| | 1–4.0 $cm^3$ | 0.971 (0.931–1.00) | 10.28 | 94.70 | 88.00 | 85.71 | 95.65 | 40/44 (90.91%) |
| | > 4.0 $cm^3$ | 0.938 (0.836–1.00) | 14.97 | 87.50 | 100.0 | 100.0 | 90.00 | 32/34 (94.12%) |

AUC, area under the curve; CI, confidence interval; Emax, maximum elasticity; Emean, mean elasticity; SD, standard deviation; NPV, negative predictive values; PPV, positive predictive values.



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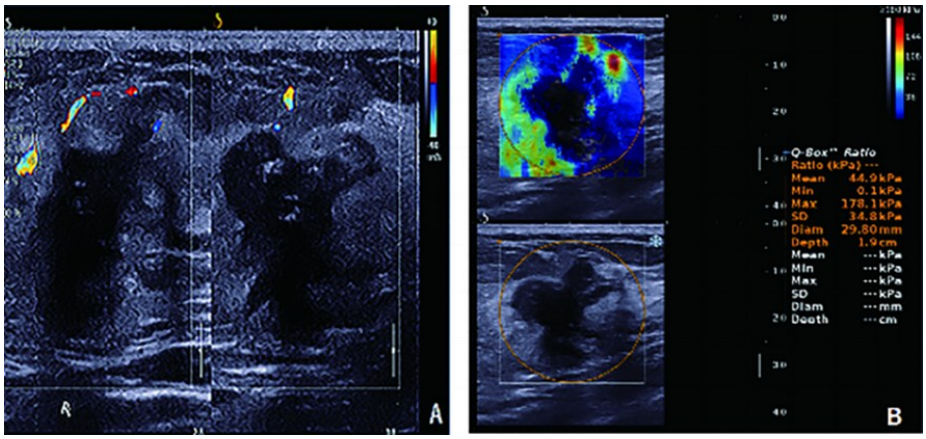


**Figure 2.** Images of a 48-year-old woman with pathohistologically confirmed invasive ductal carcinoma. B-mode images **(A)** and SWE **(B)** showed a 25-mm-large and irregular red mass with heterogeneous elasticity. b. The Emean, Emax, and SD of elasticity values were measured in kPa by placing a sufficiently large ROI including the largest portion of the lesion. ROI, region of interest; SD, standard deviation; SWE, shear wave elastography.

## DISCUSSION

SWE is a new method of US elastography providing stiffness information in real time for clinical practice. Some studies have shown that the addition of SWE features can improve the specificity of conventional US examination of breast masses and avoid unnecessary biopsies of BI-RADS 4a masses [18]. The European Federation Societies for Ultrasound in Medicine [20] and the World Federation of Ultrasound in Medicine and Biology [21] recommend the addition of elastography to conventional US to improve diagnostic accuracy. Therefore, it is recommended to use SWE as a supplemental approach to conventional US imaging.

In the present study, malignant lesions exhibited significantly higher values of Emax, Emean, and SD compared with those of benign lesions in the three subgroups. Most importantly, the result of this study indicated that the SWE parameters increased with the increasing size of benign and malignant lesions, and the optimal thresholds (Emax, Emean, SD) were higher for larger lesions ($P$<0.05). These results suggest that size is an important factor affecting the elasticity of breast masses. It may be necessary to establish different SWE diagnostic thresholds according to the size of breast lesions.

Few reports have evaluated the impact of mass volume on the values of SWE parameters. In this study, higher thresholds showed a better diagnostic performance in group 3. The results indicated that the thresholds of SWE parameters suitable for larger breast masses may not be suitable for smaller breast lesions. DCIS and invasive cancer with a small size (≤ 10 mm) and a low grade may show low elasticity values [17]. The reason for the differential stiffness of lesions might lie in tissue heterogeneity in breast lesions of different sizes. In fact, it has been reported that tumors tend to be stiffer during their growth due to the increasing ratio of fibrosis [22].

In this study, the Emax showed remarkable diagnostic performance. The results were consistent with the values reported in previous studies [9, 12], which obtained various thresholds of Emax, probably because Emax is susceptible to various factors including lesion size, breast thickness, lesion depth, breast composition, pathological grade, lymph vascular invasion, ethnicity, and/or US instrument [23,24]. In addition, some factors that affect the image quality could also affect the values of SWE. Indeed, larger benign breast lesions are likely to affect image acquisition. In addition, lesions larger than 40 mm may not be completely covered in the color overlay range of SWE, which may hinder image acquisition and/or result interpretation [25].

It has been reported that the diagnostic performance of the Emean was not significantly different than that of the Emax (P>0.21) [26]. Several studies obtained different optimal cutoff values using the Emean. This is probably because the Emean is significantly influenced by the size of the ROI, especially in malignant masses with higher heterogeneity [8]. The cutoff values of the Emean in the present study are consistent with the results obtained in previous studies that used cutoff values in the range from 21.37 kPa to 102 kPa [27]. In the present study, the Emean showed poor diagnostic performance for tumors of <1 $cm^3$ and good diagnostic performance for tumors in the 1–4-$cm^3$ group and those >4 $cm^3$ with the aforementioned cutoff values. Smaller cancers are softer than larger ones [16], so they tend to show a lower Emean value.

Currently, heterogeneity in tumors has been considered as a hallmark of cancer. The heterogeneity of the tumor microenvironment leads to nonuniform distribution of hardness within the lesion [28]. Areas with more fibrosis and collagen matrix proliferation usually show higher elasticity, while areas with tumor cell proliferation and necrosis show lower stiffness on elastography [22]. Therefore, malignant lesions are highly heterogeneous, while benign lesions grow slower and



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usually are homogeneous. Previous studies have shown that the assessment of tumor heterogeneity plays an important role in diagnosing cancer, predicting metastasis, monitoring treatment response, and assessing prognosis [29]. SD can serve as a measure of lesion heterogeneity [30] and has shown good diagnostic performance in two-dimensional shear wave elastography (2D-SWE), comparable to that of Emax measurements [14, 31]. Tian *et al.* found that the 3D-SWE-derived SD showed better stability than Emax in effectively identifying benign and malignant breast masses [31]. In this study, SD exhibited the largest area under the curve (AUC) in all three subgroups. In addition, it has been reported in the literature that the "black hole" phenomenon may appear in the signal void area or large tumors with gross necrosis [9], which may be the reason why SD was shown to be more effective in diagnosing malignant masses in this study.

We showed that the Emean had poor diagnostic performance for tumors of <1 $cm^3$, while SD and Emax showed good diagnostic values for tumors <1 $cm^3$ based on the adjusted threshold. Therefore, the adjustment of thresholds based on the lesion size might improve the effectiveness of SWE in the diagnosis of breast masses, especially for improving the detection rate of early (<1 $cm^3$) breast cancer.

There are some limitations to this retrospective, single-center study. This study only analyzed the effect of the size of breast mass on the diagnostic accuracy of SWE in a limited number of patients. Many factors affect the results of SWE. A comprehensive analysis and further research on a larger sample size might be necessary. With the development of imaging technology, SWE can be combined with other imaging modes, which will certainly increase the sensitivity and specificity of diagnosis in the future.

In conclusion, the adjustment of thresholds based on lesion size yields more accurate diagnosis. The SD showed the best diagnostic performance, comparable to that of the Emax in all three subgroups of this study.

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***Author contributions*:** Data curation: Wenjuan Qu, Xiaolei zheng, Data analyses: Wenjuan Qu, Nianan He, Guiping zhang,Funding acquisition: Xiao Yang, Investigation: Changhe Yuan, Jie Wei, Writing-original draft: Wenjuan Qu, Nianan He, Writing-English translation: Wenjuan Qu, Nianan He.

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