Efficacy of contrast-enhanced ultrasonography and shear-wave elastography in conjunction with BI-RADS classification for diagnosis of small breast nodules

Yan Shen

Gongli Hospital

Jie He

Gongli hospital

Miao Liu

Gongli hospital

Jiaojiao Hu

Gongli Hospital

Yonglin Wan

Gongli Hospital

Tingting Zhang

Gongli Hospital

Jun Ding

Gongli Hospital

Jiangnan Dong

Gongli Hospital

Xiaohong Fu (✉ fuxiaohong66@126.com)

Research article

Keywords: Small breast nodule, Ultrasound, Contrast-enhanced ultrasound, Shear-wave elastography

Posted Date: June 24th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-36646/v1>

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Abstract

Background

Identification of malignancy in small breast nodules can be difficult using conventional methods, especially in patients with dense breast tissue. Advanced imaging techniques, including contrast-enhanced ultrasound (CEUS) and shear-wave elastography (SWE), may work in conjunction with Breast Imaging Reporting and Data System (BI-RADS) classification to more effectively characterize these nodules. This study aimed to evaluate the use of CEUS and SWE for differentiation of benign from malignant small (≤ 2 cm) breast nodules.

Methods

This retrospective study reviewed the medical records and imaging data of 302 patients who underwent evaluation for 305 small breast nodules from November 2015 to December 2019. BI-RADS classification of nodules and results from CEUS and SWE studies were retrospectively analyzed, and the diagnostic efficacy of these techniques were evaluated by comparison to pathology results. Receiver operating characteristic curves were analyzed based on CEUS patterns and shear wave velocity values of nodules. The sensitivities, specificities, positive and negative predictive values, and accuracies of BI-RADS, CEUS, SWE, and a combination of all methods for identifying benign versus malignant small breast nodules were investigated.

Results

CEUS was effective at diagnosing malignant nodules when at least two out of nine suspicious features were present. Receiver operating curve analysis revealed that the best cut-off value for SWE was 3.7 m/s. The BI-RADS classification of nodules was reduced by one level when both CEUS and SWE diagnosed benign BNs and was unchanged when only CEUS or SWE diagnosed benign BN, with the highest level being category 5 and the lowest level being category 3. Furthermore, when using the combined method, 75.8% (91/120) of small breast nodules with a BI-RADS category 4A classification avoided the need for coarse needle biopsies.

Conclusion

CEUS and SWE can be used as auxiliary methods for clarifying BI-RADS classification of BNs, and a combination of these techniques may provide more diagnostic efficacy for identifying malignancy in small breast nodules.

Background

Breast cancer accounts for the second highest tumor-related mortality rate in women [1], and its morbidity is also trending upwards, especially in patients with early-onset disease. There is general consensus that recognition and treatment of early-stage breast cancer can significantly reduce mortality [2].

Ultrasound technology plays an important role in screening of patients for breast cancer. In recent years, broad use of the Breast Imaging Reporting and Data System (BI-RADS) [3] for conventional ultrasonography has improved the predictive value of breast cancer diagnosis. According to management guidelines, nodules meeting criteria for BI-RADS category 4A are suspected to be malignant in 3–10% of cases, so a biopsy is typically recommended in these patients [4]. However, biopsies are invasive, with underlying risks associated with needle use and increased financial and psychological burden for patients. Therefore, the need for biopsies in patients with low-risk nodules remains controversial.

More advanced technologies, including contrast-enhanced ultrasound (CEUS) and shear-wave elastography (SWE), have recently been introduced and may improve the accuracy of breast nodule (BN) diagnosis. CEUS is a blood pool imaging technique in which a gaseous microbubble of contrast agent with a diameter similar to red blood cells is injected into a surrounding vein. CEUS obtains a large contrast sonogram by leveraging the strong gas-scattering properties and differing acoustic characteristics of human tissues to increase differences in the acoustic impedances of circulating blood or lesions and adjacent tissues [5]. Further, tissue hardness can be determined based on SWE, which measures the propagation velocity of shear waves in tissue and allows for differentiation of benign from malignant lesions.

Over the past five years, both CEUS and SWE results have been integrated into auxiliary protocols for the BI-RADS classification system in our hospital. The purpose of this study was to evaluate the diagnostic efficacy of CEUS and SWE for identifying malignant small BNs in order to guide further refinement of the BI-RADS classification system and to provide better management of individual cases.

Methods

Ethical statement

This study was carried out in accordance with the Declaration of Helsinki, and written informed consent was obtained from all patients. The protocol was approved by the Ethics Committee of Gong Li Hospital. The need for written informed consent from patients was waived due to the retrospective nature of this study.

Patients

From November 2015 to December 2019, 676 patients with BNs underwent conventional ultrasound, CEUS, and SWE at our institution. Patients were eligible for inclusion in this study if they had: (a) a BN with a diameter of ≤ 2 cm; (b) no prior treatment for BN before ultrasonography; (c) pathological results obtained from surgical or needle biopsies; and (d) a solid or mostly solid BN (cystic portion of less than

25% of the total volume). Patients were excluded from this study if they: (a) were pregnant or lactating or (b) had only low-quality BN images that were too poor for analysis.

Imaging instruments

A Philips iU Elite and EPIQ 5 Ultrasound diagnostic apparatus equipped with CEUS software was used for CEUS imaging (Philips Medical Systems, Bothell, WA, USA). The apparatus was equipped with a L12-5 linear probe and operated at a frequency ranging from 5 to 12 MHz. A Siemens Acuson S3000 Ultrasound diagnostic apparatus (Siemens Medical Solutions, Mountain View, CA, USA) equipped with SWE imaging software was used for SWE imaging. This apparatus was equipped with a 9L4 linear probe and operated at a frequency ranging from 4 to 9 MHz.

Imaging techniques and analysis

For ultrasonography, each patient was placed in a supine position with her hands raised above her head. To detect the lateral breast, the patient was turned onto her side, with both breasts fully exposed. Parameters like gain and depth were adjusted according to the position and size of the breast mass. Operators recorded information about nodular features, including location, size, shape, orientation, margin, echo pattern, posterior acoustic features, calcification, and vascularity, and the lesion was then categorized based on the BI-RADS classification system. For patients with multiple nodules, the BI-RADS classification was based on the nodule in the highest category.

The SWE technique, which assesses quality, velocity, and image retention, was then performed, with nodules imaged where they were most clear. After identifying the maximum longitudinal section, selected nodules were imaged within regions of interest (ROIs). The size was adjusted at least two times, and the patient was instructed to hold her breath for a few seconds after image stabilization. The quality of images obtained after assessment of shear wave elasticity distributions were graded from high to low based on a color-coded system ranging from green to yellow to red. Images with a uniform distribution and a regional 'green' area were defined as good quality; otherwise, images were considered to be of poor quality.

After identification of high-quality images, SWV was measured. SWE speed mode can be used to obtain SWV values directly within the two-dimensional space distribution of the SWE imaging map, with the SWV displayed as red, yellow, green, or blue to depict speeds ranging from fast to slow. The SWV range was gradually adjusted (maximum of 10.0 m/s) when the internal region of nodules was red or yellow with surrounding blue or green. ROIs were positioned within different areas inside the nodules (upper, lower, middle, and periphery, at highest and lowest speeds), with a minimum ROI size of 1 mm × 1 mm. SWV data measurements (generally 5-7 groups) were performed in the effective measurement areas, and average SWV values (m/s) for each nodule were obtained.

For CEUS imaging, sections with rich blood flow, large blood vessels, or irregular shapes were selected, and sections with large calcifications accompanied by wide sound shadows were avoided. After

switching to breast CEUS mode, dual real-time displays were used to continuously track and observe two-dimensional images, allowing the radiologist to maintain image stabilization on the same section. The depth was adjusted so that enough normal breast tissue was present around the nodule for comparison. The focal point was set behind the nodule with a mechanical index of 0.07. Twenty-five mg of the contrast agent (SonoVue, Bracco SpA, Milan, Italy) was suspended in 5 mL of a 0.9% sodium chloride solution and shaken by hand. The probe was then gently placed against the skin in front of the nodule to avoid applying excessive pressure. A rapid intravenous bolus injection was performed with 4.8 mL of the contrast agent suspension followed by 5 mL of the 0.9% sodium chloride solution. Video recording commenced concurrently with contrast agent injection, and the dynamic perfusion process of the nodule was continuously observed for at least three minutes. During the entire angiography process, the patient was asked to breathe normally and to remain still. The probe was always maintained at the same section to avoid human interference.

The following nine variables were evaluated during CEUS examinations: 1. enhancement intensity (low enhancement, equal enhancement, high enhancement); 2. order of enhancement (concentricity, non-concentricity); 3. change (difficult to distinguish, shrinking, unchanged, expanding); 4. enhancement uniformity (uniform, non-uniform); 5. enhancement defects (present or absent); 6. morphology after enhancement (regular, difficult to distinguish, irregular); 7. enhanced posterior boundary (clearly distinguishable, difficult to distinguish, unclear); 8. claw sign (present or absent); and 9. nourishing blood vessels (present or absent). When evaluations were inconsistent, two ultrasound physicians discussed features to reach consensus.

All conventional ultrasound, CEUS, and SWE images were stored on the hard drive of the ultrasonic instrument for further analysis. All SWE image acquisition and data analyses were completed by two radiologists (JH & YW) with more than 3 years of experience in SWE and 10 years of experience in breast ultrasonography. CEUS images were collected by two radiologists (ML & TZ) with more than 3 years of experience in breast CEUS and more than 10 years of experience in breast ultrasonography. CEUS images were evaluated by two radiologists (YS & JH) with more than five years of experience in CEUS and 10 years of experience in routine ultrasound examinations.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) software (version 22.0, SPSS Inc., Chicago, IL, USA) and MedCalc software (version 19.0.7, Mariakerke, Belgium) were used for statistical analyses. Continuous variables were expressed as mean $\pm$ standard deviation or range and compared using the independent-samples *t*-test. Categorical data were expressed as numbers with percentages and compared using the chi-squared test or the Fisher's exact test. Receiver-operating characteristic (ROC) curves were used to analyze the diagnostic value of classifying small BNs using each of the four diagnostic methods (BI-RADS, CEUS, SWE, combined method). The areas under the curve (AUCs) for the diagnostic ability of the four methods were calculated, and the Cochran *Q*-test and *z*-test were used for statistical analysis. The best cut-off values were obtained from ROC analysis, and the corresponding

sensitivities (SEN), specificities (SPE), positive predictive values (PPV), negative predictive values (NPV), and accuracies (ACC) were calculated. Two-sided *P*-values of < 0.05 were considered statistically significant.

Results

General characteristics

A total of 302 female patients with 305 BNs and a mean age of 49.2 ± 16.4 years (18-84) met eligibility criteria and were enrolled in this study. Of the 305 small BNs assessed, 192 (63.0%) were determined to be benign based on pathologic examinations, including 83 (43.2%) fibroadenomas, 41 (21.4%) adenopathies, 39 (20.3%) adenopathies with fibroadenomas, 17 (8.9%) intraductal papillomas, nine (4.7%) cases of inflammation or abscesses, one (0.5%) tubular adenoma, and one (0.5%) cavernous hemangioma. The other 113 nodules (37.0%, 113/305) were determined to be malignant, including 78 (69.0%) invasive ductal carcinomas, five (4.4%) invasive lobular carcinomas, 11 (9.7%) ductal carcinomas *in situ*, 11 (9.7%) papillary carcinomas, two (1.8%) mucinous carcinomas, one (0.9%) invasive adenocarcinoma, and five (4.4%) mixed cancers.

Ultrasonographic predictors of malignancy

There were no significant differences in patient age ($t = 0.693$, $P = 0.406$), BN size ($t = 2.452$, $P = 0.118$), or BN location ($\chi^2 = 0.759$, $P = 0.226$) between benign and malignant nodules. Compared to benign BNs, a higher proportion of malignant nodules had irregular shapes (82.3%, 93/113), nonparallel orientations (60.2%, 68/113), and distinct boundaries (83.2%, 94/113). Other features were also more commonly observed in malignant lesions, including calcification (46.0%, 52/113), presence in intramammary ducts (6.2%, 7/113), internal vascularity (54.9%, 62/113), and lymph node metastasis (11.5%, 32/113) (Table 1, Fig. 1).

Diagnostic efficacy

A total of 162 nodules were classified as BI-RADS category 3 (15.4%, 25/162) or category 4A (84.6%, 137/162) and therefore considered low risk. A total of 143 nodules were classified as BI-RADS category 4B (54.5%, 78/143), category 4C (42.0%, 60/143), or category 5 (3.5%, 5/143) and therefore considered high risk. Of the 162 low-risk nodules, 145 were confirmed to be benign, while 17 were found to be malignant using pathologic testing. Of the 143 high-risk nodules, 96 (67.1%, 96/143) were determined to be malignant, while 47 (32.9%, 47/143) were determined to be benign using pathologic testing. The cut-off value for the BI-RADS classification system was determined to be category 4B, with a SEN, SPE, PPV, NPV, ACC, and AUC of 82.3%, 74.5%, 65.5%, 87.7%, 77.4%, and 78.4%, respectively.

When at least two out of nine suspicious malignant signs manifested at the same time on CEUS, malignant nodules could be identified using this modality, with a SEN, SPE, PPV, NPV, and ACC of 83.2%, 87.5 %, 79.7%, 89.8%, and 85.9%, respectively. The diagnostic efficacy of SWE was determined according

to mean SWV values. The mean SWV was 5.2 ± 1.6 m/s for malignant nodules, which was significantly higher than the mean SWV of 3.1 ± 1.1 m/s for benign nodules. Based on ROC curve analysis, the cut-off value for SWV was 3.7 m/s, with a SEN, SPE, PPV, NPV, ACC, and AUC of 86.7%, 82.8%, 74.8%, 91.4%, 84.3%, and 84.8%, respectively.

Using the combined method, the BI-RADS classification of nodules was shown to be increased by one category when both CEUS and SWE diagnosed malignant nodules and was shown to be reduced by one category when both CEUS and SWE diagnosed benign nodules. If only CEUS or SWE diagnosed benign nodules, the BI-RADS classification remained unchanged. The SEN, SPE, PPV, NPV and ACC for the combined method of diagnosis was 88.5%, 87.0%, 80.0%, 92.8%, and 87.5%, respectively.

The Cochran *Q* test revealed significant differences between the four methods (Cochran *Q* = 19.573, $P < 0.01$). The AUCs for the ROC curves for diagnostic efficacy of BI-RADS, CEUS, SWE, and the combined method were 78.4%, 85.3%, 84.8% and 87.7%, respectively, with the combined diagnostic method having a significantly higher AUC (*z*-value 4.553, $P < 0.01$; Tables 2, 3; Fig. 2).

Discussion

In this study, we have demonstrated that....

Imaging examinations play an important role in the early screening and diagnosis of breast diseases, especially molybdenum target radiography, magnetic resonance imaging, and ultrasonography. Over the past three years, studies outside of China have suggested that large-scale breast cancer screening programs can reduce overall breast cancer mortality by 20% and early breast cancer mortality by 60% [6]. However, in comparison to women of other ethnicities, Chinese females generally have relatively smaller breast volumes with higher proportions of dense breast tissue, characteristics that can lead to a poorer sensitivity of mammography for identifying malignant breast lesions. In these cases, ultrasound is a more effective method for characterizing suspicious lesions [7].

Conventional ultrasound can clearly show a variety of breast lesion characteristics, including location, number, size, shape, orientation, perimeter, internal echo, rear features, calcification, blood supply, and associated axillary lymph nodes. In clinical practice, however, two-dimensional ultrasound manifestations of benign and malignant nodules sometimes share overlapping characteristics, especially in patients with small breast tumors. The BI-RADS classification system, which standardizes breast ultrasonography reporting worldwide [8], has been shown to improve the sensitivity of identifying malignant masses; however, the false-positive rate remains high [9].

Based on years of clinical experience, we believe that the biological characteristics of small breast cancers are less commonly manifested and that signs of malignancy in these small tumors are more difficult to observe using two-dimensional ultrasound imaging. Even color Doppler imaging cannot adequately detect obvious differences in blood flow for benign nodules, making differential diagnosis even more difficult. In addition, the pathological characteristics of breast cancer tissues are diverse, which

can lead to false positives and false negatives. For example, some *in situ* cancers with small and atypical nodules do not display hyperechoic halos or burr signs. Also, some small invasive ductal carcinomas, mucinous carcinomas, and papillary carcinomas manifest with clear boundaries, few lobes, and parallel growth, leading to false negatives. Finally, some sclerosing adenoses, intraductal papillomas with inflammation, and other benign lesions exhibit obscure boundaries, leading to false infiltration and false positives. Therefore, use of conventional ultrasonography, which relies on recognition of distinctive morphological features, can be problematic during evaluation of small BNs.

In addition to morphological features, other tumor characteristics have been evaluated for their application to imaging-based diagnoses. For example, previous studies have shown that angiogenesis plays an important role in tumor growth and metastasis [10]. Tumor blood flow has been evaluated using Doppler ultrasound with some success; however, this modality can only identify a blood flow signal above the threshold of large vessels and the wall filter [11]. Real-time CEUS, on the other hand, can provide more accurate information about the morphology and distribution of the blood vessels associated with tumors [10]. In addition, SWE can quantitatively evaluate the hardness of breast nodules [12,13]. Therefore, conventional ultrasound combined with CEUS and SWE technology can comprehensively evaluate nodules based on the shape, micro-blood flow, and hardness of nodules in order to improve diagnostic efficacy.

CEUS is an advanced technique for microperfusion imaging using a safe contrast medium. This technique can dynamically display microperfusion of tumors, lymph nodes, and surrounding tissues in real-time, and it plays significant roles in the diagnosis and targeted therapy of breast diseases, detection of metastatic sentinel lymph nodes, and evaluation of neoadjuvant chemotherapy efficacy. CEUS can qualitatively characterize benign and malignant lesions by identifying homogeneous and centripetal enhancement of benign lesions. In addition, it can quantitatively characterize lesions by creating time-intensity curves (TIC) and obtaining a series of quantitative parameters, including rise time (RT), peak time (time to peak [TTP]), peak intensity (PI), mean transit time (MTT), and AUC under the ROC curve.

The present study found that most fibroadenomas and intraductal papillomas manifested with true capsules or pseudocapsules caused by expansive growth; accordingly, if there was high enhancement on CEUS, the boundary was clear and the enhancement was well distributed. Malignant lesions of the breast, on the other hand, often lacked a capsule, and the boundary and size of the tumor, as well as the shape of nutrient angiography, could only be seen after enhancement. Since angiogenesis is a risk factor for invasion and metastasis of solid tumors, there are generally a large number of proliferative and active cells at the perimeter of malignant tumors, as well as a large number of abnormal capillary networks with disordered structures and increased microvessel densities. At the same time, perfusion disruptions can lead to increased microcirculation flow and velocity [14]. In addition, the peripheral regions of malignant breast tumors are often associated with breast hyperplasia and precancerous lesions at different stages. With progression of these precancerous lesions to breast cancer, neovascularization and blood vessel density also increase [15].

In this study, adenoses generally manifested without pseudocapsules and often exhibited an irregular shape after enhancement, which was often low or equally distributed, with a focus that remained unchanged, became narrowed, or was completely integrated with the surrounding glands after enhancement. In addition, few nutrient vessels and filling defects were manifested. These features can be helpful for differential diagnosis; however, some special adenoses exhibit uneven enhancement and unclear boundaries and can, therefore, easily be misdiagnosed as malignant nodules. Some inflammatory lesions also showed malignant signs after enhancement, including uneven high enhancement, irregular shapes, and unclear boundaries, which likely resulted from irregular infiltration of inflammatory cells into the surrounding tissue.

Real-time SWE can indicate differences in tissue hardness by measuring the propagation velocity of shear waves in tissues and can also qualitatively and quantitatively distinguish benign from malignant lesions. The elastic coefficient or hardness of tissue is closely associated with biological characteristics of lesions. The stroma of benign tumors, such as breast fibroadenomas, are rich in loose mucopolysaccharides, so their hardness is reduced in comparison to malignant tumors like invasive ductal carcinomas, in which the stroma is denser and harder due to fibrous tissue components [16]. In general, tumors are softer if they have higher proportions of parenchyma than stroma. Tumor tissues can also become softer when undergoing necrosis and can become harder when calcareous deposition or bone formation occurs. Real-time SWE is a relatively easy, noninvasive, and objective method to evaluate tissue hardness, and this study, as well as others, have demonstrated that it can effectively be used to differentiate benign from malignant breast tumors.

Consistent with our previous study, we found that SWE had a high diagnostic sensitivity and specificity for BI-RADS category 4 nodules and small breast tumors. These findings are also consistent with other studies, both based in China and elsewhere [17,18]. In addition, many studies have shown that tissue density information obtained by SWE can predict the degree of vascular infiltration, which is a predictor of lymph node metastasis [19,20]. Tumor cells can infiltrate the surrounding stroma and cause changes to connective tissue, increasing collagen cross-linking and the corresponding density of surrounding tissues. Using color gradients, SWE can demonstrate the hardness of areas surrounding lesions, with high-density areas dubbed to display "hard ring signs" [21]. Unfortunately, this technique can also lead to misdiagnosis, as some malignant lesions undergo liquefactive necrosis, which results in decreased SWV values and false-negative diagnoses. SWV values for intraductal carcinomas have also been shown to be below the cut-off value, with low tumor cell atypia, reduced proliferation of fibrous tissue, and no obvious infiltration into surrounding tissues. Some sclerosing benign breast lesions may also lead to an increase in the elastic modulus of tissues, resulting in false-positive diagnoses.

In our study, the combined use of CEUS, SWE, and BI-RADS led to adjustments in the BI-RADS classification for some breast nodules, with improvements in diagnostic accuracies for benign and malignant BNs. Sclerosing adenoses were most commonly identified to be false positives, with some cases showing irregular morphologies due to significant interstitial fiber hyperplasia that was sometimes mixed with inflammation. In these instances, the SWV value was higher than the cut-off value and CEUS

showed uneven regions of high contrast enhancement. The malignant features of small breast carcinomas identified to be false negatives were not as obvious on two-dimensional ultrasonography, showing only large lobulation, homogeneous echo patterns, and no changes or enhancement in posterior features. The ultrasound images resembled those of benign tumors, with SWE values lower than the cut-off value and CEUS showing only uniformly low contrast enhancement. Therefore, it is necessary to comprehensively analyze many images for nodules with these features, with close follow-up recommended. In addition, patients who are less than 60 years of age with a higher risk of malignancy due to family history should be followed closely, and further puncture biopsies should be carried out if necessary.

The BI-RADS classification system is not without flaws, especially in patients with category 4 nodules (with a malignant probability greater than 2% but less than 95%) [22]. In the United States, most BI-RADS category 4 lesions (69%–95%) undergo puncture biopsies, even though only 22% to 33% of these lesions are malignant. A meta-analysis of studies from Europe and the United States showed that the overdiagnosis rate of breast cancer lesions using molybdenum target mammography was 52% with the current BI-RADS classification system [21]. In the present study, 120 nodules were initially evaluated as BI-RADS category 4A, with 67 cases adjusted to BI-RADS category 3 after consideration of CEUS and SWE results. This finding indicates that 55.8% (67/120) of BI-RADS 4A nodules would have undergone unnecessary puncture biopsies after conventional ultrasound if not combined with CEUS and SWE results.

Conclusions

In summary, the BI-RADS classification system in combination with CEUS and SWE technology exhibited high diagnostic efficacy and applicability for differentiating benign from malignant small breast masses. Furthermore, this combined diagnostic method optimized classification of BI-RADS category 4A masses, though further research related to this topic is warranted.

Abbreviations

ACC, accuracy; AUC, area under the curve; BI-RADS, Breast Imaging Reporting and Data System; CEUS, contrast-enhanced ultrasound; CI, confidence interval; MTT, mean transit time; NPV, negative predictive value; PPV, positive predictive value; RT, rise time; SEN, sensitivity; SPE, specificity; SWE, shear-wave elastography; SWV, shear wave velocity; TIC, time-intensity curves; TTP, time to peak time

Declarations

Ethics approval and consent to participate: The protocol was approved by the Ethics Committee of Gong Li Hospital. The need for informed patient consent was waived due to the retrospective nature of this study.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request.

Competing interests: The authors declare that they have no competing interests

Funding: None

Authors' Contributions: (I) Conception and design: YS and XHF; (II) Administrative support: YS and XHF; (III) Provision of study materials or patients: YS, XHF, JND; (IV) Collection and assembly of data: JH, ML, JJH, YLW, TTZ, JD, JND; (V) Data analysis and interpretation: YS and JH; (VI) Manuscript writing: YS, JH, JND, XHF; (VII) Final approval of manuscript: All authors

Acknowledgments: Not applicable

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Tables

Table 1
Summary of demographic and ultrasonographic features

Parameter	Pathological result		Total	t/χ^2	P-value
	Benign	Malignant			
No. of nodules	n = 192	n = 113	n = 305		
Age, years				0.693	0.406
Mean	42 ± 14	60 ± 12			
Range	18–83	36–84			
Tumor size (mm)				2.452	0.118
Mean	13.8 ± 4.3	14.5 ± 3.8			
Range	4–20	5–20			
Location				0.759	0.226
Right breast	88 (45.8)	46 (40.7)	134		
Left breast	104 (54.2)	67 (59.3)	173		
Shape				57.455	< 0.001
Oval	106 (55.2)	13 (11.5)	119		
Round	8 (4.2)	7 (6.2)	15		
Irregular	78 (40.6)	93 (82.3)	171		
Orientation					
Parallel	159 (82.8)	45 (39.8)	204		
Nonparallel	33 (17.2)	68 (60.2)	101		
Margin				91.450	< 0.001
Circumscribed	141 (73.4)	19 (16.8)	160		
Not circumscribed	51 (26.6)	94 (83.2)	145		
Echo pattern				3.093	0.542
Hypoechoic	169 (88.0)	101 (89.4)	270		
Heterogeneous	7 (3.6)	5 (4.4)	12		
Complex cystic and solid	15 (7.8)	7 (6.2)	22		
Hyperechoic	1 (0.5)	0 (0.0)	1		

Data are presented as mean ± SD or number (percentages).

Parameter	Pathological result		Total	t/χ^2	P-value
	Benign	Malignant			
Posterior acoustic features				16.015	0.001
No. of posterior acoustic features	172 (89.6)	94 (83.2)	266		
Enhancement	10 (5.2)	1 (0.9)	11		
Shadowing	7 (3.6)	17 (15.0)	24		
Combined pattern	3 (1.6)	1 (0.9)	4		
Calcification				43.308	< 0.001
None	156 (81.3)	54 (47.8)			
Calcification inside mass	35 (18.2)	52 (46.0)			
Calcification outside mass	1 (0.5)	0 (0.0)			
Intraductal calcification	0 (0.0)	7 (6.2)			
Vascularity				35.871	< 0.001
Absent	136 (70.8)	44 (38.9)			
Internal vascularity	43 (22.4)	62 (54.9)			
Vessels in rim	11 (5.7)	4 (3.5)			
Internal + vessels in rim	2 (1.0)	3 (2.7)			
Lymph node metastasis				60.745	< 0.001
Normal	192 (100.0)	79 (69.9)	271		
Metastasis	1 (0.0)	34 (30.1)	35		
<i>Data are presented as mean $\pm$ SD or number (percentages).</i>					

Table 2
Diagnosis of benign and malignant nodules using four evaluation methods and pathology

Category	Pathologic diagnosis		Total	χ^2	P-value
	Benign	Malignant			
No. of nodules	n = 192	n = 113	n = 305		
BI-RADS				92.171	< 0.001
Benign	143	20	163		
Malignant	49	93	142		
CEUS				149.838	< 0.001
Benign	168	19	187		
Malignant	24	94	118		
SWE				143.380	< 0.001
Benign	159	15	174		
Malignant	33	98	131		
Combination				167.533	< 0.001
Benign	167	13	180		
Malignant	25	100	125		
Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; CEUS, contrast-enhanced ultrasound; SWE, shear-wave elastography					
Data are presented as number of nodules.					

Table 3
Diagnostic efficacy of four examination methods

Parameter	SEN (%)	SPE (%)	PPV (%)	NPV (%)	ACC (%)	AUC (%)	95% CI (%)
BI-RADS	82.3	74.5	65.5	87.7	77.4	78.4	73.3–82.9
CEUS	83.2	87.5	79.7	89.8	85.9	85.3	80.9–89.1
SWE	86.7	82.8	74.8	91.4	84.3	84.8	80.2–88.6
Combination	88.5	87.0	80.0	92.8	87.5	87.7	83.5–91.2
Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; CEUS, contrast-enhanced ultrasound; SWE, shear-wave elastography; SEN, sensitivity; SPE, specificity; PPV, positive predictive value; NPV, negative predictive value; ACC, accuracy; AUC, area under the curve; CI, confidence interval							

Figures

Figure 1

Analysis of the receiver operating characteristic curves of the four methods

Figure 2

(A) The nodule is irregular and not circumscribed. BI-RADS is classified as 4A nodules. (B) CEUS showed no significant enhancement of nodules, and the volume decreased after enhancement. (C) The average SWV of SWE is 2.8 m / s, which is less than the cutoff value, indicating that the texture of the nodules is soft. After BI-RADS combined CEUS and SWE, BI-RADS was downgraded to BI-RADS 3. The final pathological result is breast adenopathy. (D) The nodule is not circumscribed and not parallel. BI-RADS is classified as 4A nodules. (E) CEUS showed unevenness and centripetal enhancement, and the volume increased after enhancement. (F) The average SWV of SWE is 4.1 m / s, which is more than the cutoff value, indicating that the nodules is hard. After BI-RADS combined CEUS and SWE, BI-RADS was downgraded to BI-RADS 4B. The final pathological result is Ductal carcinoma in situ.

Supplementary Files

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- [consortchecklist.doc](#)