

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

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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), could be used in conjunction with Breast Imaging Reporting and Data System (BI-RADS) classification to characterize these nodules more effectively. This study aimed to evaluate the use of CEUS and SWE for the differentiation of benign and malignant small breast nodules (maximum diameter ≤ 2 cm).

Methods: This retrospective study reviewed the 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 the results of CEUS and SWE were retrospectively analyzed; the diagnostic efficacy of these techniques was evaluated by comparison with pathology results. Receiver operating characteristic curves were analyzed based on the 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 three methods for identifying benign versus malignant small breast nodules were investigated.

Results: CEUS was effective in diagnosing malignant nodules when at least two of the nine suspicious features were present. Receiver operating curve analysis revealed that the best cut-off value for SWE was 3.7 m/s. For the diagnosis of benign breast nodules, the BI-RADS classification was reduced by one level when both CEUS and SWE data were used, and was unchanged when CEUS or SWE alone was used; the highest and lowest levels were category 5 and 3, respectively. Furthermore, when using the combined method, 75.8% (91/120) of small breast nodules with a BI-RADS category 4A did not need coarse needle biopsies.

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

Background

Breast cancer has the second highest tumor-related mortality rate in women [1], and its morbidity is increasing, especially in patients with early-onset disease. There is a consensus that the recognition and treatment of early-stage breast cancer can reduce the mortality rate [2]. However, small breast nodules (maximum diameter ≤ 2 cm) lack the typical clinical characteristics of breast cancer and are easily missed by clinicians; some small malignant breast nodules present ultrasonographic features similar to benign nodules [3]. Ultrasound imaging is important for screening patients with breast cancer. In recent years, the broad use of the Breast Imaging Reporting and Data System (BI-RADS) [4] for conventional ultrasonography has improved the predictive value of breast cancer diagnosis. The BI-RADS is primarily based on a subjective judgment by clinicians; thus, conventional ultrasound

diagnosis remains imperfect [5,6]. As a result, ultrasound-guided breast nodule biopsy must be performed for the diagnosis of early breast cancer. According to management guidelines, nodules that meet the criteria for BI-RADS category 4A are suspected to be malignant in 3% to 10% of cases, and a biopsy is typically recommended in these patients [7]. 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 have recently been introduced and are expected to improve the accuracy of breast nodule diagnosis. These include contrast-enhanced ultrasound (CEUS) and shear-wave elastography (SWE). 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 [8]; the resulting images can provide information regarding the morphology and distribution of blood vessels associated with tumors. SWE can facilitate the differentiation of benign from malignant lesions by measuring the propagation velocity of shear waves in tissue to determine the tissue hardness.

Previous studies have confirmed that multi-mode ultrasound (US combined with CEUS or SWE) can significantly improve the diagnostic efficacy of breast cancer [9], and some studies have confirmed that CEUS combined with SWE can greatly improve the detection rate of small breast cancer [10]. However, few studies have evaluated the efficacy of US combined with CEUS and SWE in the diagnosis of small breast cancer and its value in terms of avoiding unnecessary biopsies. The purpose of this study was to evaluate the diagnostic efficacy of CEUS and SWE for identifying small malignant breast nodules to guide further refinement of the BI-RADS classification system and for 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 breast nodules underwent conventional ultrasound, CEUS, and SWE at our institution. Patients were eligible for inclusion in this study if they had (a) a breast nodule with a diameter of ≤ 2 cm; (b) no treatment for breast nodule before ultrasonography; (c) pathological results obtained from surgical or needle biopsies; and (d) a solid or mostly solid breast nodule (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 breast nodule images that were too poor for analysis. The selection of patients is shown in the flow chart (**Figure 1**).

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 5–12 MHz frequency range. A Siemens Acuson S3000 Ultrasound diagnostic apparatus (Siemens Medical Solutions, Mountain View, CA, USA) equipped with SWE imaging software was used for SWE imaging. It was equipped with a 9L4 linear probe and operated at 4–9 MHz frequency range.

Imaging techniques and analysis

For ultrasonography, each patient was placed in the supine position with their hands raised above their head. To detect the lateral breast, the patient was turned onto their side, with both breasts fully exposed. Parameters such as gain and depth were adjusted according to the position and size of the breast mass. Operators recorded information about nodular features, including the location, size, shape, orientation, margin, echo pattern, posterior acoustic features, calcification, and vascularity; 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.

Subsequently, SWE, which assesses the quality, velocity, and image retention, was performed; nodules were imaged where they were most clear. After identifying the maximum longitudinal section, selected nodules were imaged within the sampling frame. The size was adjusted at least two times, and the patient was instructed to hold their breath for a few seconds after image stabilization. The quality of the images obtained after assessment of shear-wave elasticity distributions was 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 having good quality; otherwise, images were considered to be of poor quality.

After the identification of high-quality images, shear-wave velocity (SWV) was measured to determine the tissue stiffness. The SWE speed mode was used to obtain SWV values directly within the two-dimensional space distribution of the SWE imaging map, with the SWV displayed as either red, yellow, green, or blue to depict speeds ranging from fast to slow. The SWV range was gradually adjusted (maximum 10.0 m/s) when the internal regions of the nodules were red or yellow with the surrounding being blue or green. Multiple (generally 5–7) regions of interest (ROIs) were positioned within different areas inside the nodules (upper, lower, middle, and periphery, at the highest and lowest speeds). SWV measurements were recorded 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 the two-dimensional images, allowing the radiologist to stabilize the image on the same section. The depth was adjusted such 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. Next, 25 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. An intravenous bolus was rapidly injected with 4.8 mL of the contrast agent suspension, followed by 5 mL of 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 3 min. During the entire angiography process, the patient was asked to breathe normally and to remain still. The probe was maintained at the same section to avoid human interference.

According to a previously published article [11] and our experience, 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 the evaluations were inconsistent, two ultrasound physicians discussed the features to reach a consensus.

All conventional ultrasound, CEUS, and SWE images were stored on the hard disk 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 and 10 years of experience in SWE and breast ultrasonography, respectively. CEUS images were collected by two radiologists (ML & TZ) with more than 3 and 10 years of experience in breast CEUS and breast ultrasonography, respectively. CEUS images were evaluated by two radiologists (YS & JH) with more than 5 and 10 years of experience in CEUS and routine ultrasound examinations, respectively. All the ultrasound images were read and asserted two ultrasound specialists who did not participate in the collection of contrast images, and the contrast features of the lesions were classified after reaching an agreement. The two ultrasound specialists were blinded to patients' clinical data before image analysis. Therefore, consistency between the two radiologists' evaluation of CEUS images was ensured.

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 are expressed as mean \pm standard deviation or range and were compared using the

independent-samples *t*-test. Categorical data are expressed as numbers with percentages and were 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 breast nodules using each of the four diagnostic methods (BI-RADS, CEUS, SWE, and the 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 sensitivity (SEN), specificity (SPE), positive predictive value (PPV), negative predictive value (NPV), and accuracy (ACC) were calculated. Two-sided *P*-values of < 0.05 were considered statistically significant.

Results

Pathology

A total of 302 patients were enrolled in the study. Among these, three patients had two nodules with the same highest BI-RADS classification, thus accounting to a total of 305 enrolled nodules. The average age of the patients was 49.2 ± 16.4 years (range, 18–84 years). Of the 305 small breast nodules 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 remaining 113 nodules (37.0%, 113/305) were determined to be malignant, including 78 (69.0%) invasive ductal carcinomas, 11 (9.7%) ductal carcinomas in situ, 11 (9.7%) papillary carcinomas, five (4.4%) invasive lobular carcinomas, five (4.4%) mixed cancers, two (1.8%) mucinous carcinomas, and one (0.9%) invasive adenocarcinoma.

Ultrasonographic predictors of malignancy

There were no significant differences in the patient age, breast nodule size, breast nodule location, and echo pattern between benign and malignant nodules. However, there were significant differences in the shape, orientation, and margin between benign and malignant nodules. Other features, including calcification, presence of intramammary ducts, internal vascularity, and lymph node metastasis, were more commonly observed in malignant lesions than in benign lesions (**Table 1, Figure 2**).

Diagnostic efficacy

The BI-RADS categories of BNs are shown in **Table 2**. The cut-off value for the BI-RADS classification system was determined to be category 4B, with SEN, SPE, PPV, NPV, ACC, and AUC of 82.3%, 74.5%, 65.5%, 87.7%, 77.4%, and 78.4%, respectively.

The details of the nine suspected malignant characteristics of BNs by CEUS are shown **Table 3**. Malignant nodules could be identified using CEUS when at least two out of nine suspicious malignant

signs manifested at the same time, with 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 the 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 ($P \leq 0.001$). Based on ROC curve analysis, the cut-off value for SWV was 3.7 m/s, and the SEN, SPE, PPV, NPV, ACC, and AUC was 86.7%, 82.8%, 74.8%, 91.4%, 84.3%, and 84.8%, respectively.

Using combined CEUS and SWE, the BI-RADS classification of the nodules was increased by one category and reduced by one category when diagnosing malignant nodules and benign nodules, respectively. If either CEUS or SWE alone was used to diagnose 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 among the four methods (Cochran $Q = 19.573$, $P < 0.01$). The AUCs of the ROC curves for the 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 than the rest (z -value 4.553, $P < 0.01$; **Table 4**; **Table 5**; **Figure 3**).

Discussion

Imaging examinations, especially molybdenum target radiography, magnetic resonance imaging, and ultrasonography, play an important role in the early screening and diagnosis of breast diseases. Over the past 3 years, studies outside of China have suggested that large-scale breast cancer screening programs can reduce the overall breast cancer mortality by 20% and early breast cancer mortality by 60% [12]. However, compared to women of other ethnicities, Chinese women generally have relatively small breast volumes with higher proportions of dense breast tissue; these characteristics can reduce the sensitivity of mammography for identifying malignant breast lesions. In these cases, ultrasound is a more effective method for characterizing suspicious lesions [13].

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 occasionally share overlapping characteristics, especially in patients with small breast tumors. The BI-RADS classification system, which standardizes breast ultrasonography reporting worldwide [14], has improved the sensitivity of identifying malignant masses; however, the false-positive rate remains high [15].

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 both false positives and false negatives. For example, some ductal carcinomas in situ with small and atypical nodules do not display hyperechoic halos or burr signs—which may therefore be misdiagnosed as benign nodules. In this study, three cases of ductal carcinomas in situ were diagnosed as benign nodules, and in one case, CEUS and SWE suggested the possibility of malignancy, which is why the BI-RADS category was upgraded from 4A to 4B. Moreover, some small invasive ductal carcinomas, mucinous carcinomas, and papillary carcinomas manifest with clear boundaries, few lobes, and parallel growth, leading to false negative results. In this study, two cases of invasive ductal carcinomas of less than 1 cm diameter were diagnosed as benign nodules, including one with a diameter of 0.9 cm. SWE suggested that SWV was less than the truncation value, and CEUS suggested malignancy; finally, the BI-RADS category remained unchanged at 4A. The other nodule was 0.8 cm in diameter. SWE suggested that SWV was less than the truncation value, and CEUS also suggested benign nodules; thus, the BI-RADS category was downgraded from 4A to 3. Additionally, two nodules were less than 1 cm in diameter and showed low hardness. The malignant signs in one case were not obvious. Therefore, they were identified as benign nodules, leading to false negative results. Finally, some sclerosing adenoses, intraductal papillomas with inflammation, and other benign lesions exhibited obscure boundaries, leading to false infiltration and false positive results. In this study, 35 cases of benign nodules were diagnosed as malignant by ultrasound. Therefore, the use of conventional ultrasonography, which relies on the recognition of distinctive morphological features, can be problematic during the evaluation of small breast nodules.

In addition to morphological features, other tumor characteristics have been evaluated for their applicability in imaging-based diagnoses. For example, previous studies have shown that angiogenesis plays an important role in tumor growth and metastasis [16]. 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 [17]. On the other hand, real-time CEUS can provide more accurate information about the morphology and distribution of blood vessels associated with tumors [16]. Moreover, SWE can quantitatively evaluate the hardness of breast nodules [18,19]. Therefore, conventional ultrasound combined with CEUS and SWE techniques can comprehensively evaluate nodules based on the shape, micro-blood flow, and hardness of nodules to improve the diagnostic efficacy.

CEUS is an advanced technique for microperfusion imaging using a safe contrast medium. It can dynamically display the microperfusion of tumors, lymph nodes, and surrounding tissues in real-time, and plays significant roles in the diagnosis and targeted therapy of breast diseases, detection of metastatic sentinel lymph nodes, and evaluation of the efficacy of neoadjuvant chemotherapy. CEUS can qualitatively characterize benign and malignant lesions by identifying the homogeneous and centripetal enhancement of benign lesions. In addition, it can quantitatively characterize lesions by creating time-

intensity curves and obtaining a series of quantitative parameters, including rise time, peak time (time to peak), peak intensity, mean transit time, and the 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 many proliferative and active cells at the perimeter of malignant tumors, as well as numerous abnormal capillary networks with disordered structures and increased microvessel densities. At the same time, perfusion disruptions can lead to increased microcirculation flow and velocity [20]. In addition, the peripheral regions of malignant breast tumors are often associated with breast hyperplasia and precancerous lesions at different stages. With the progression of these precancerous lesions to breast cancer, neovascularization and blood vessel density also increase [21].

In this study, adenoses generally manifested without pseudocapsules and exhibited an irregular shape after enhancement, which was often low or equally distributed, with a focus that either remained unchanged, became narrowed, or was completely integrated with the surrounding glands after enhancement. Further, 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 qualitatively and quantitatively distinguish benign from malignant lesions. The elastic coefficient or hardness of the tissue is closely associated with the biological characteristics of lesions. The stroma of benign tumors, such as breast fibroadenomas, are rich in loose mucopolysaccharides; thus, their hardness is reduced compared to that of malignant tumors such as invasive ductal carcinomas, in which the stroma is denser and harder due to fibrous tissue components [22]. In general, tumors are softer if they have a higher proportion of parenchyma than stroma. Tumor tissues can also soften when undergoing necrosis and harden 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 other studies 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 SEN and SPE for BI-RADS category 4 nodules and small breast tumors. These findings are consistent with those of other studies from China and elsewhere [23,24]. 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 [25, 26]. Tumor cells can infiltrate the surrounding stroma and cause changes in the connective tissue, increasing collagen cross-linking and the corresponding density of surrounding tissues. Using color gradients, SWE can demonstrate the hardness of areas surrounding the lesions, with high-density areas displaying "hard ring signs" [27]. 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. The SWV values for intraductal carcinomas with low tumor cell atypia, reduced proliferation of fibrous tissue, and no obvious infiltration into surrounding tissues have also been shown to be below the cut-off value. 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 the diagnostic accuracies for benign and malignant breast nodules. Sclerosing adenoses were most commonly identified to be false-positives, with some cases showing irregular morphologies due to 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 as 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 uniform, 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 aged less than 60 years with a higher risk of malignancy due to family history should be followed closely, and further puncture biopsies should be performed if necessary.

The BI-RADS classification system is not without flaws, especially in patients with category 4 nodules (with a malignancy probability greater than 2% but less than 95%) [28]. 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 the 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 [26]. 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 the 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 the CEUS and SWE results were not considered.

The current study had several limitations. First, as a retrospective study, the potential bias in the selection of the participants could not be eliminated. Second, the sample size was small; therefore, studies on larger datasets with long-term follow-ups are required.

Conclusions

In summary, the BI-RADS classification system in combination with CEUS and SWE techniques exhibited a high diagnostic efficacy and applicability for differentiating benign from malignant small breast nodules. Furthermore, this combined diagnostic method optimized the classification of BI-RADS category 4A masses, although further research on 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; NPV, negative predictive value; PPV, positive predictive value; SEN, sensitivity; SPE, specificity; SWE, shear-wave elastography; SWV, shear-wave velocity

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

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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				59.354	<0.001
Parallel	159(82.8)	45(39.8)	204		
Non-parallel	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		
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 a mass	35(18.2)	52(46.0)			
Calcification outside a 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		

Data in parentheses are percentages.

Table 2. The BI-RADS categories of BNs.

	Total n=305	Benign n=192	Malignant n=192	Malignant rate%
BI-RADS 3	25	25	0	0.0
BI-RADS 4A	137	120	17	12.4
BI-RADS 4B	78	45	33	42.3
BI-RADS 4C	60	2	58	96.7
BI-RADS 5	5	0	5	100.0

Table 3. Details of the nine suspected malignant characteristics of BNS by CEUS

	Total	Benign	Malignant	Malignant rate%
High enhancement	188	108	80	42.6
Centripetal enhancement	99	28	71	71.7
Inhomogeneous enhancement	166	82	84	50.6
Filling defect	25	2	23	92
Irregular shape after enhancement	164	70	94	57.3
Volume expansion	72	8	64	88.9
Unclear boundary after contrast enhancement	134	38	96	71.6
Crab foot sign	29	1	28	96.6
Nourishing vessel sign	57	8	49	86.0

TABLE 4 Comparison of diagnoses of malignant nodules based on the four examination methods

Category	Final 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		

TABLE 5 Diagnostic efficacy of the 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

Figures

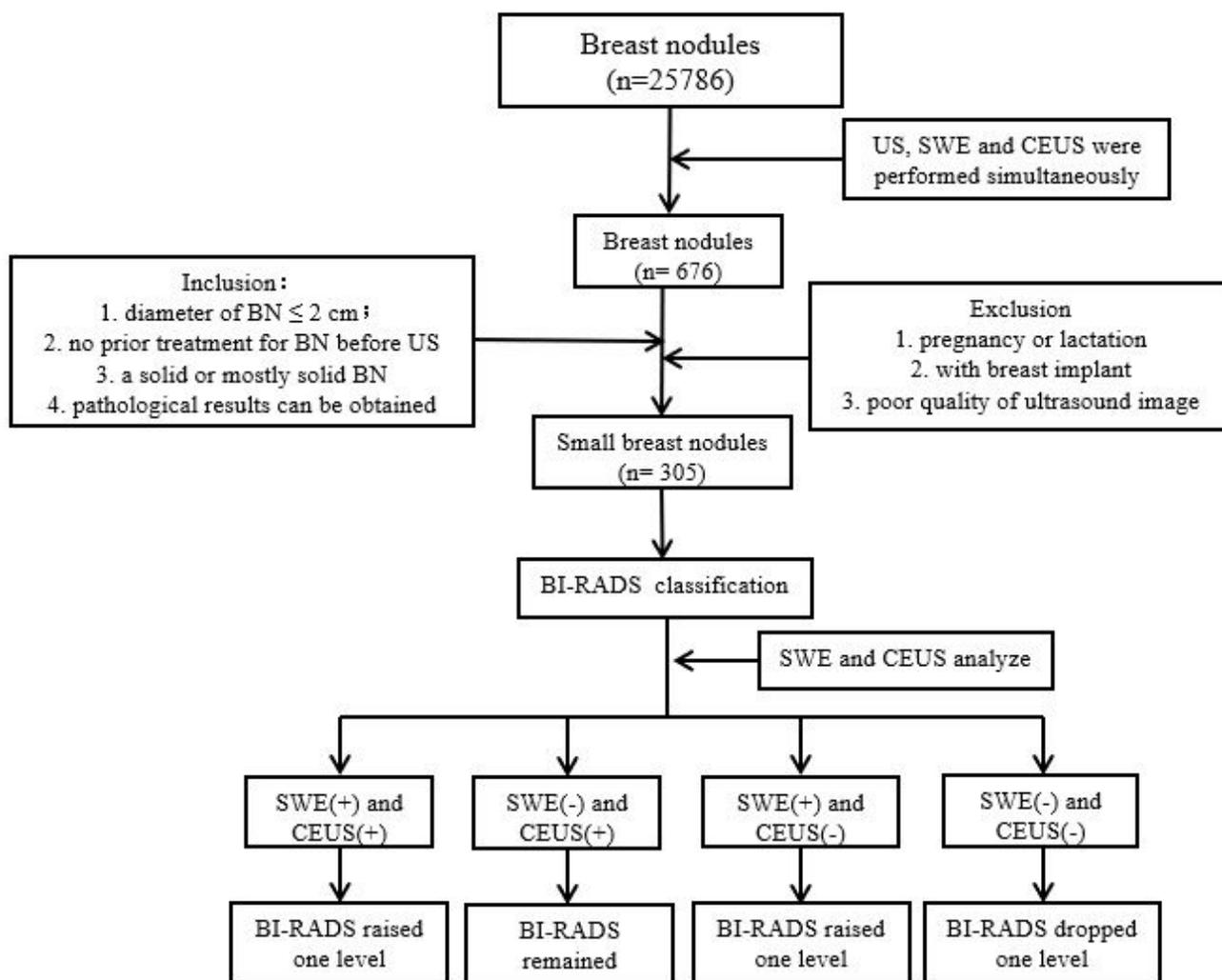


Figure 1

Flow chart of patients' selection.

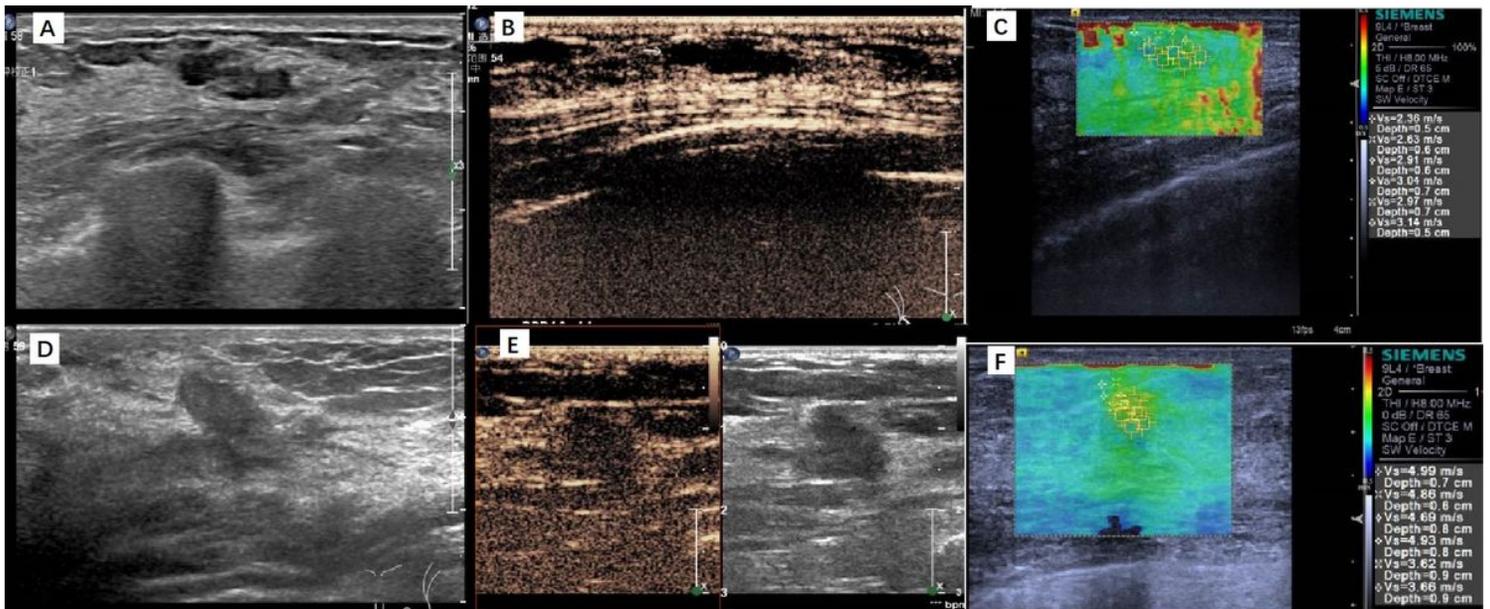


Figure 2

(A) The nodule is irregular and not circumscribed. The nodule was classified as BI-RADS is 4A. (B) CEUS showed no significant enhancement of nodules, and the volume decreased after enhancement. (C) The average SWV of SWE was 2.8 m / s, which is less than the cut-off 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. The nodule is classified as BI-RADS 4A. (E) CEUS showed unevenness and centripetal enhancement, and the volume increased after enhancement. (F) The average SWV of SWE was 4.1 m / s, which is more than the cut-off 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 carcinomas in situ.

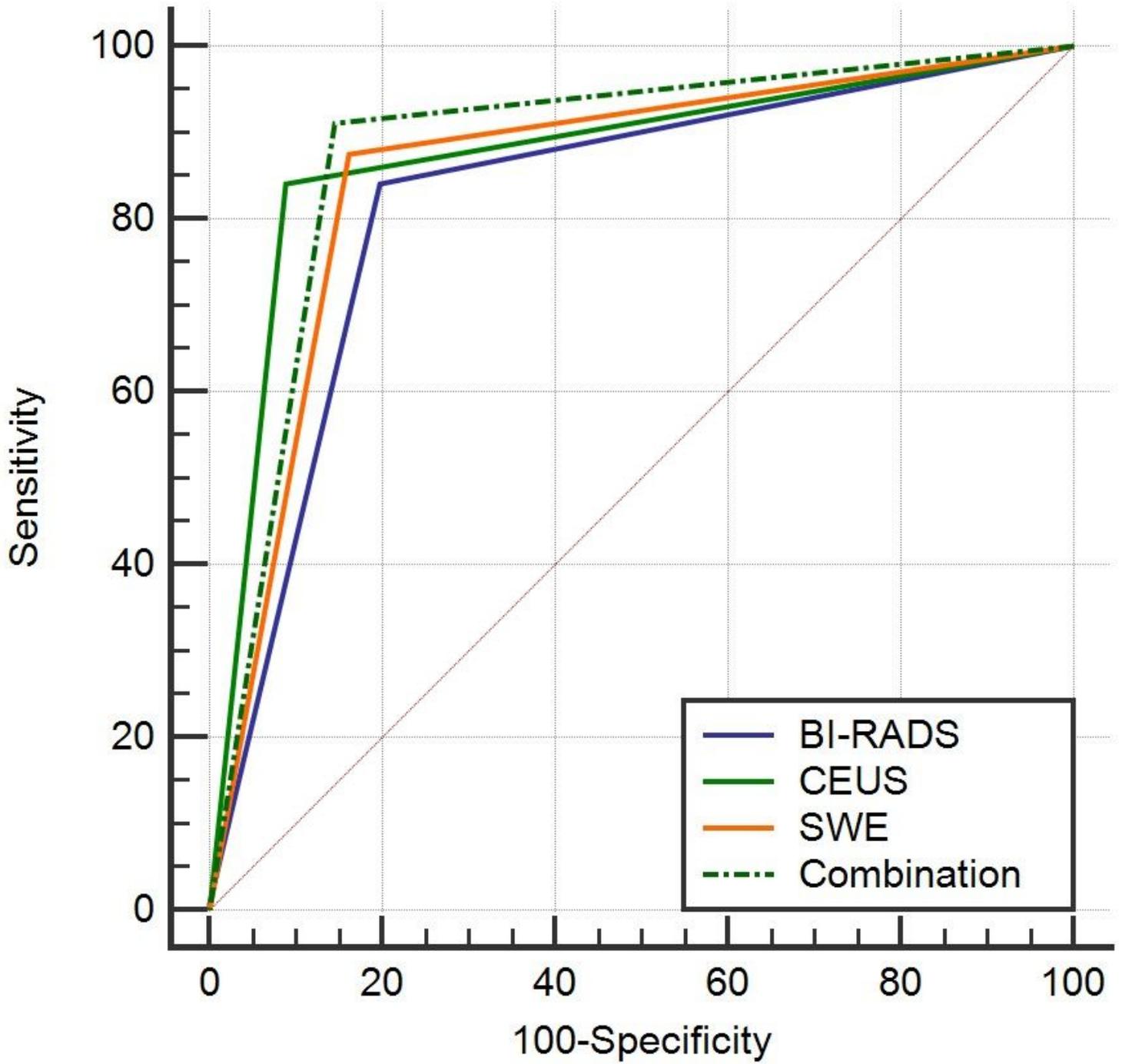


Figure 3

Analysis of the receiver operating characteristic curves of the four methods.

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