BJR

https://doi.org/10.1259/bjr.20200880

Received: 20 July 2020 | Revised: 25 January 2021 | Accepted: 30 January 2021

Cite this article as:
Zhang F, Jin L, Li G, Jia C, Shi Q, Du L, et al. The role of contrast-enhanced ultrasound in the diagnosis of malignant non-mass breast lesions and exploration of diagnostic criteria. *Br J Radiol* 2021; **94**: 20200880.

FULL PAPER

The role of contrast-enhanced ultrasound in the diagnosis of malignant non-mass breast lesions and exploration of diagnostic criteria

[1,2]FAN ZHANG, MD, [2]LIFANG JIN, PhD, [2]GANG LI, MD, [2]CHAO JIA, MD, [2]QIUSHENG SHI, PhD, [2]LIANFANG DU, PhD and [1,2]RONG WU, MD, PhD

[1]Department of Ultrasound, Shanghai General Hospital of Nanjing Medical University, Shanghai, China
[2]Department of Ultrasound, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Address correspondence to: Mrs Rong Wu
E-mail: *wurong7111@163.com*

Objectives: To assess the value of contrast-enhanced ultrasound (CEUS) for diagnosing malignant non-mass breast lesions (NMLs) and to explore the CEUS diagnostic criteria.

Methods: A total of 116 patients with 119 NMLs detected by conventional US were enrolled. Histopathological results were used as the reference standard. The enhancement characteristics of NMLs in CEUS were compared between malignant and benign NMLs. The CEUS diagnostic criteria for malignant NMLs were established using independent diagnostic indicators identified by binary logistic regression analysis. The diagnostic performance of Breast Imaging Reporting and Data System-US (BI-RADS-US), CEUS, and BI-RADS-US combined with CEUS was evaluated and compared.

Results: Histopathological results showed 63 and 56 benign and malignant NMLs. Enhancement degree (OR = 5.75, p = 0.003), enhancement area (OR = 4.25, p = 0.005), and radial or penetrating vessels (OR = 7.54, p = 0.003) were independent diagnostic indicators included to establish the CEUS diagnostic criteria. The sensitivity and specificity of BI-RADS-US, CEUS, and BI-RADS-US combined with CEUS were 100 and 30.2%, 80.4 and 74.6%, and 94.6 and 77.8%, respectively; the corresponding areas under the receiver operating characteristic curve (AUC) were 0.819, 0.775, and 0.885, respectively.

Conclusions: CEUS has a high specificity in malignant NML diagnosis based on the diagnostic criteria including enhancement degree, enhancement area, and radial or penetrating vessels, but with lower sensitivity than BI-RADS-US. The combination of CEUS and BI-RADS-US is an effective diagnostic tool with both high sensitivity and specificity for the diagnosis of malignant NMLs.

Advances in knowledge: In this study, we assessed the diagnostic value of CEUS for malignant NMLs and constructed a feasible diagnostic criterion. We further revealed that the combination of CEUS and BI-RADS-US has a high diagnostic value for malignant NMLs.

INTRODUCTION

Conventional ultrasonography (US), as a convenient imaging tool without the limitation of dense breasts, has been routinely used to detect and diagnose breast cancer. With the aim of reducing operator dependency and facilitating communication between physicians, the American College of Radiology published the breast imaging report and data system (BI-RADS)-US in 2003 and updated it in 2013.[1,2] In the BI-RADS-US, breast masses refer to lesions showing a space-occupying effect in two different planes. However, despite the majority of breast lesions being detected as masses by conventional US, 5–9% of breast lesions do not meet this definition and are thus considered as non-mass breast lesions (NMLs).[3–5] Currently, different words are used by radiologists to describe the ultrasonic images of NMLs owing to a lack of uniform terminology, such as hypoechoic area with or without calcification, architectural distortions, and ductal changes.[5–8] Several studies have shown that BI-RADS categories are sensitive for detecting breast cancer presenting as NMLs, with sensitivity ranging from 95.4 to 100%; however, the specificity is relatively lower, ranging from 6.5 to 42.3%.[5,7–10] High diagnostic sensitivity is necessary for the clinical management of breast cancer, but low diagnostic specificity will lead to an increase in biopsy rate, which may cause patient distress and waste medical resources. Therefore, further evaluation of NMLs detected using conventional US is necessary.

Contrast-enhanced ultrasound (CEUS) using gas-filled microbubbles as the contrast agent is an advanced ultrasonic imaging technique. The gas-filled microbubbles, with a diameter of 3–5 μm, are truly an intravascular contrast agent and cannot penetrate the vascular endothelium. Hence, they afford a unique advantage in the microcirculation imaging for target lesions.[11,12] In the past decades, with the application of second-generation contrast agents and the continuous development of ultrasonic equipment, CEUS has been increasingly used in breast cancer evaluation. However, most current studies have focused on distinguishing benign and malignant breast masses, and to date, limited data are available on the diagnostic value of CEUS for malignant NMLs.[13,14] Hence, in this study, we aimed to explore the imaging characteristics of NMLs in CEUS and determine the diagnostic value of CEUS for malignant NMLs, particularly CEUS diagnostic criteria.

METHODS AND MATERIALS

Patients

This retrospective study was approved by our hospital's institutional review board, and informed consent was obtained from all patients. From January 2017 to April 2020, 135 consecutive patients with NMLs who underwent both conventional US and CEUS were identified after searching a US database. Lesions without a space-occupying effect in two different planes, such as a hypoechoic area, architectural distortions, and ductal changes, were defined as NMLs. Patients who met the following criteria were excluded: (1) inadequate data ($n = 6$); (2) lack of histopathological confirmation (surgery specimen or breast biopsy) ($n = 4$); (3) previous neoadjuvant chemotherapy, radiotherapy, biopsy, or breast surgery ($n = 9$). Finally, 116 patients with 119 NMLs (patient age: from 21 to 90 years, mean age: 48.9 ± 13.8 y) were included. A total of 113 patients had a unilateral lesion and three had bilateral lesions; 93 patients presented with palpable lesions; 12 patients presented with nipple discharge; and one 31-year-old patient had a family history of breast cancer. The lesion size (maximal diameter) ranged from 0.7 to 5.8 cm (mean diameter: 2.5 ± 1.3 cm). A total of 107 lesions were confirmed by surgical excision, and 12 lesions were confirmed by core-needle biopsy. Histopathology results of the specimens obtained by surgery or biopsy were used as the reference standard. The interval between the histopathological examination and US was less than 2 weeks.

US imaging

A Toshiba-Aplio 500 system (Toshiba Medical Systems Corporation, Tokyo, Japan) equipped with a 14L5 linear array probe was used for conventional US and CEUS. All US scanning was performed by one of two radiologists with 12 and 7 years of experience, respectively, in breast US.

Conventional B-mode and color Doppler US were initially performed to assess lesion characteristics. The color scale of the Doppler US was preset to a low velocity to capture the intralesional blood-flow signal with minimal background noise. Subsequently, we selected the plane with the most abundant blood supply for CEUS. The technique used in CEUS was contrast pulse sequencing with a low mechanical index (0.02), and images were displayed in dual mode with conventional US and CEUS. Regarding CEUS, continuous imaging was immediately performed after a bolus injection of 5.0 ml of contrast agent SonoVue (Bracco, Milan, Italy) followed by flushing with 5 ml of normal saline. Real-time dynamic images were stored at least 3 min for further analysis.

Image interpretation

Two radiologists with more than 10 years of experience in breast US retrospectively reviewed the conventional US and CEUS data. They were blinded to other imaging and pathology results. Any disagreement was resolved by involving a third radiologist (R.W., with more than 20 years of experience in breast US) to discuss and reach a consensus. The above three radiologists received formal training in BI-RADS US, fifth edition. The lesions that did not meet the definition of a breast mass in conventional US were recognized as NMLs by consensus.

We first evaluated the morphological features and blood supply of NMLs in conventional US. The blood supply of NMLs detected by color Doppler US was classified into four grades based on Adler's classification system: Grade 0, scarce blood supply; Grade 1, moderate blood supply; and Grades 2 and 3, rich blood supply.[15] The NMLs were classified into BI-RADS 3–5 according to the fifth edition of BI-RADS-US.[2]

After an interval of 1 month, we analyzed the following enhancement features of each NML in CEUS. The enhancement indicators of CEUS used for analysis were derived from previous studies and our clinical experience: wash-in time/wash-out time of the contrast agent compared to surrounding breast tissue (earlier, synchronous, or later); enhancement degree compared to the surrounding breast tissue at the peak time (hyper-. iso-, or hypo-enhancement); enhancement sharpness (regular or irregular), round or oval lesions were considered regular in sharpness; enhancement margin (clear or unclear), more than 50% of the lesion circumference being clearly visible was described as a clear margin; enhancement distribution (homogeneous or heterogeneous), homogeneity was defined by equal enhancement of the whole lesion, and the other enhancement patters were categorized as heterogeneous; enhancement direction (centripetal, centrifugal, or diffuse), contrast agent perfusion from the periphery of the lesion to the center was called centripetal enhancement, and perfusion from the center of the lesion to the periphery is called centrifugal enhancement; perfusion defects in the lesion after contrast agent injection (present or absent); radial or penetrating vessels extending from the surrounding tissue to the lesion (present or absent); and enhancement area (enlarged or not). The criterion for enhanced area enlargement was defined as the maximum transverse or longitudinal diameter of the lesion in CEUS being larger than 3 mm compared to that in gray-scale US.[16]

Statistical analysis

All data were analyzed with SPSS v.20.0 software. $p < 0.05$ was considered statistically significant. Quantitative data were expressed as mean ± SD (standard deviation) values, and its normal distribution was assessed using the Kolmogorov–Smirnov test. An independent t-test was used to compare

Table 1. Characteristics of NMLs determined using conventional US and CEUS: comparison between malignant and benign lesions

	Benign (n = 63)	Malignant (n = 56)	P
Age (years)	45.2 ± 13.8	53.3 ± 12.5	0.006
Conventional US			
Lesion size (cm)	2.3 ± 1.2	2.7 ± 1.3	0.062
Intralesional echo			
Hypo-echo	63 (100)	56 (100)	
Other echoes	0 (0)	0 (0)	
Lesion sharpness			0.373
Round	0 (0)	0 (0)	
Oval	4 (6)	1 (1.8)	
Irregular	59 (94)	55 (98.2)	
Lesion margin			0.374
Clear	31 (49.2)	23 (41.1)	
Unclear	32(50.8)	33 (58.9)	
Spiculated	5 (15,6)	7 (12.1)	
Angular	27 (84.4)	26 (87.9)	
Orientation			0.101
Non-parallel	0 (0)	3 (5.4)	
Parallel	63 (100)	53 (94.6)	
Calcifications			<0.001
Present	6 (9.5)	22 (39.3)	
Absent	57 (90.5)	34 (60.7)	
Color Doppler			0.002
Grade 0	25 (39.7)	7 (12.5)	
Grade 1	24 (38.1)	25 (44.6)	
Grades 2 and 3	14 (22.2)	24 (42.8)	
Posterior echo			0.229
Attenuation	8 (12.3)	10 (16.3)	
Enhancement	1 (1.6)	4 (6.1)	
No change	54 (85.7)	42 (77.6)	
CEUS			
Wash-in time			<0.001
Early	18 (28.6)	42 (75)	
Synchronous	24 (38.1)	12 (21.4)	
Later	21 (33.3)	2 (3.6)	
Enhancement degree			<0.001
Hyper-enhancement	25 (39.7)	49 (87.5)	
iso-/hypo-enhancement	38 (60.3)	7 (12.5)	
Enhancement sharpness			0.404
Regular	18 (28.6)	12 (21.4)	
Irregular	45 (71.4)	44 (78.6)	
Enhancement margin			0.043

(Continued)

Table 1. (Continued)

	Benign (n = 63)	Malignant (n = 56)	P
Clear	33 (52.4)	19 (33.9)	
Unclear	30 (47.6)	37 (66.1)	
Enhancement distribution			0.383
Homogeneous	21 (33.3)	23 (41.1)	
Heterogeneous	42 (66.7)	33 (58.9)	
Enhancement direction			0.943
Centripetal	24 (38)	23 (41.1.)	
Centrifugal	2 (3.2)	2 (3.6)	
Diffuse	37 (58.7)	31 (55.3)	
Perfusion defects			0.025
Present	12 (19.0)	22 (39.3)	
Absent	51 (81)	34 (60.7)	
Radial or penetrating vessels			<0.001
Present	4 (6.3)	20 (35.7)	
Absent	59 (93.6)	36 (64.3)	
Enhancement area			<0.001
Enlarged	18 (28.6)	42 (75)	
Non-enlarged	45 (71.4)	14 (25)	
Wash-out time			<0.001
Early	25 (39.7)	47 (83.9)	
Synchronous	32 (50.8)	8 (14.3)	
Later	6 (9.5)	1 (1.8)	

Quantitative data are presented as mean ± SD (standard deviation) values.
Categorical data are presented as the number of NMLs with percentages in parentheses.
To compare differences between benign and malignant NMLs, an independent t-test was used for quantitative variables and chi-square or Fisher's exact test was used for categorical variables.

quantitative variables, while the chi-square or Fisher's exact test was used to evaluate categorical variables. To optimize the CEUS diagnostic criteria for non-mass breast cancer, binary logistic regression analysis was performed to explore the enhancement indicators associated with the diagnosis of malignant NMLs. Next, we re-evaluated the BI-RADS categories of NMLs according to the logistic regression results. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the receiver operating characteristics curve (AUC) were calculated for BI-RADS-US, CEUS, and BI-RADS-US combined with CEUS to distinguish between malignant and benign NMLs. The McNemar test was used to compare the sensitivity and specificity, of the three methods; the Z-test was used to compare the AUC values. The cut-off value for distinguishing benign and malignant NMLs was placed between BI-RADS categories 3 and 4a.

RESULTS

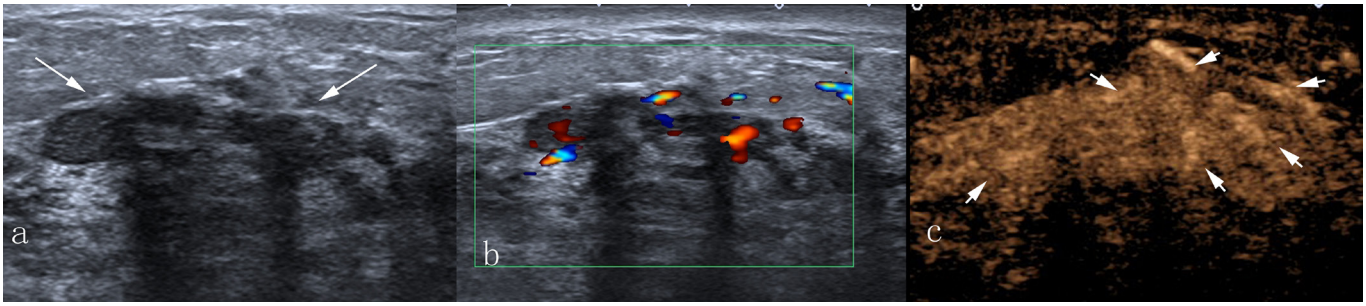
Patient clinical data

The mean age of patients with malignant and benign NMLs was 53.3 ± 12.5 years and 45.2 ± 13.8 years, respectively (p = 0.006). The mean size of malignant and benign NMLs was 2.7 ± 1.3 cm and 2.3 ± 1.2 cm, respectively (p = 0.063). Histopathological assessments revealed that 56 (47.1%) NMLs were malignant and 63 (52.9%) NMLs were benign. Among the malignant lesions, ductal carcinoma *in situ* (DCIS) (n = 25, 15 lesions with microinvasion) was the most common histopathological type, followed by invasive ductal carcinoma (IDC) (n = 11), IDC +DCIS (n = 14), invasive lobular carcinoma (n = 3), intraductal papillary carcinoma (n = 1), mucinous carcinoma (n = 1), and solid papillary carcinoma (n = 1). The benign lesions included adenosis (n = 37, four lesions with interstitial collagenization, eight lesions with fibroadenoma formation, 10 lesions with ductal epithelial hyperplasia), inflammation (n = 12), sclerosing adenosis (n = 5), intraductal papilloma (n = 5), and duct ectasia (n = 4).

Imaging features

The characteristics of NMLs in conventional US and CEUS are listed in Table 1. In conventional US, all the included NMLs appeared as hypoechoic lesions, calcifications (39.3% *vs* 9.5%, p < 0.001) and abundant blood supply (42.8 *vs* 22.2%, p = 0.002) were more common in malignant NMLs than in benign NMLs.

Figure 1. A 49-year-old female diagnosed as showing invasive ductal carcinoma +ductal carcinoma *in situ* by surgical excision. (a) The B-mode US image shows a 47.6 mm non-mass breast lesion in the outer upper quadrant of the left breast (arrows). (b) The color Doppler US image shows abundant blood supply. (c) In CEUS, the lesion exhibited hyper-enhancement with an enlarged area and radial or penetrating vessels (short arrows). The lesion was classified as BI-RADS 4b in conventional US and reevaluated as BI-RADS five with CEUS information.



The CEUS analysis indicated most malignant NMLs were characterized by early wash-in time (75% *vs* 28.6%, $p < 0.001$), hyper-enhancement degree (87.5% *vs* 39.7%, $p < 0.001$), unclear enhancement margin (66.1% *vs* 47.6%, $p = 0.043$), enlarged enhancement area (75% *vs* 28.6%, $p < 0.001$), and early wash-out time (83.9% *vs* 39.7%, $p < 0.001$) (Figure 1). Meanwhile, the predominant characteristics of benign NMLs were the absence of radial or penetrating vessels (93.6% *vs* 64.3%, $p < 0.001$) and perfusion defects (81% *vs* 60.7%, $p = 0.025$) (Figure 2). No significant difference was found in enhancement sharpness, distribution, and direction between malignant and benign NMLs.

Results of logistic regression analysis

As shown in Table 2, the univariate analysis showed six enhancement characteristics (wash-in time, enhancement degree, perfusion defects, enhancement area, radial or penetrating vessels and wash-out time) in CEUS were significantly associated with the diagnosis of malignant NMLs. And in the multivariate analysis with stepwise forward variable selection method, three enhancement characteristics (enhancement degree, enhancement area, and radial or penetrating vessels) were identified in the final step as independent diagnostic indicators for the prediction of malignant NMLs.

Evaluation of diagnostic performance

On the basis of these three independent diagnostic indicators, we established a CEUS diagnostic criterion for malignant NMLs: lesions presenting with two or three independent indicators were classified as malignant, while others were classified as benign. Similarly, in the combination of BI-RADS-US and CEUS, the BI-RADS category of NMLs was upgraded when the lesion exhibited two or three independent indicators, otherwise it was downgraded. In particular, lesions with or without all of three three independent indicators were directly reevaluated as BI-RADS 5 or 3.

The re-evaluation of BI-RADS category and the diagnostic performance of BI-RADS-US, CEUS and their combination are illustrated in Tables 3 and 4. The BI-RADS category with conventional US showed substantially higher sensitivity (56/56, 100%) in the diagnosis of malignant NMLs, but its specificity (19/63, 30.2%) was obviously low, since the BI-RADS category of 44 (69.8%) benign NMLs had been overestimated while no malignant NMLs had been underestimated. When using CEUS alone, the specificity was significantly higher than that with BI-RADS-US (74.6% *vs* 30.2%, $p < 0.001$), but sensitivity was lower than that with BI-RADS-US (80.4% *vs* 100%, $p =$

Figure 2. A 54-year-old female diagnosed as showing breast adenosis with interstitial collagenization by surgical excision. (a) The B-mode US image shows a 22.8 mm non-mass breast lesion with calcifications in the inner upper quadrant of the right breast (arrows). (b) The color Doppler US image shows slight blood supply. (c) In CEUS, the lesion exhibited hypo-enhancement without an enlarged area and radial or penetrating vessels. The lesions was classified as BI-RADS 4b in conventional US and re-evaluated as BI-RADS three with CEUS information.

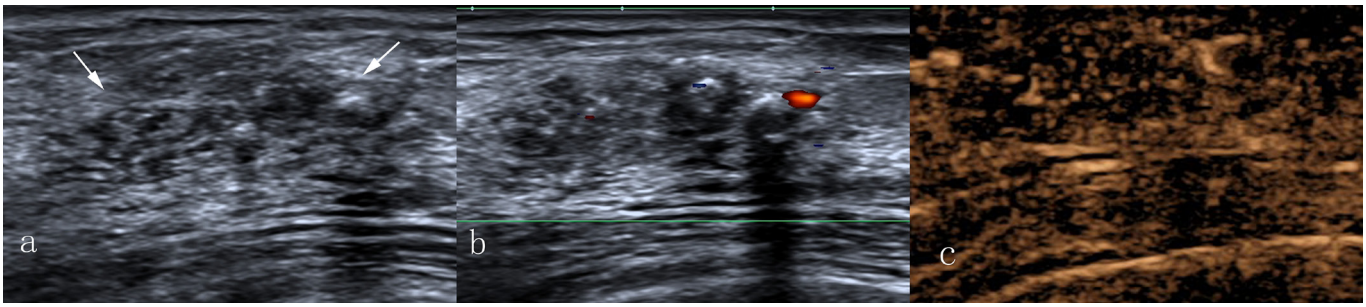


Table 2. Indicators of CEUS for predicting malignant NMLs: logistics regression results

Univariate logistic regression			Multivariate logistic regression		
	P	OR (95% CI)		*P*	OR (95% CI)
Wash-in time	0.000	3.60 (2–6.49)	Enhancement degree	0.003	5.75 (1.84–18.02)
Enhancement sharp	0.555	1.31 (0.53–3.25)	Radial or penetrating vessels	0.003	7.54 (2.16–39.06)
Enhancement degree	0.000	12.67 (4.73–33.95)	Enhancement area	0.005	4.25 (1.56–11.61)
Enhancement margin	0.227	1.56 (0.76–3.22)			
Enhancement distribution	0.383	1.39 (0.66–2.94)			
Enhancement direction	0.807	0.96 (0.66–1.38)			
Perfusion defects	0.027	2.55 (1.11–5.85)			
Radial or penetrating vessels	0.000	11.11 (3.08–40.04)			
Enhancement area	0.000	8.26 (3.62–18.90)			
Wash-out time	0.000	6.59 (2.88–15.12)			

0.001). With the combination of BI-RADS-US and CEUS, 33 (52.4%) benign NMLs overestimated as BI-RADS four or five by conventional US were downgraded to BI-RADS category 3. The combined approach showed substantially higher specificity (77.8% *vs* 30.2%, $p < 0.001$) and high sensitivity (94.6% *vs* 100%, $p = 0.25$) compared to BI-RADS-US. The combined AUC of BI-RADS-US and CEUS was the highest among these three methods, although there was no statistical difference in AUC between BI-RADS-US and the combination assessment (0.885 *vs* 0.819, $Z = 1.582$, $p > 0.05$) (Figure 3). Additionally, 14 benign NMLs were overestimated to BI-RADS four or 5 (two intraductal papillomas, three sclerosing adenosis, and nine inflammation lesions) and three malignant NMLs were underestimated to BI-RADS 3 (one IDC +DCIS and two DCIS) in this combined method.

DISCUSSION

Non-mass lesions on conventional US are lesions without a space-occupying effect. Many studies have suggested that some types of breast cancer, especially DCIS, often present as NMLs in conventional US.[17–19] Thus, a definitive distinction between malignant and benign NMLs is essential.

In this study, calcifications and abundant blood supply were detected more frequently in malignant NMLs. These results were consistent with the findings of previous articles.[6–9] Besides, although more than 50% of malignant breast masses have been reported to show a tendency of longitudinal growth (aspect ratio >1),[20–22] we found that the transverse diameter of almost all NMLs was parallel to the mammary gland (aspect ratio <1). Since assessment of breast lesions by the current BI-RADS-US system is primarily based on the morphology and blood supply differences between benign and malignant breast lesions, these overlapping imaging features observed between malignant and benign NMLs would hinder its diagnostic accuracy in breast cancer.

The differences in the histologic structure and hemodynamics in the microcirculation of benign and malignant breast lesions are the foundation of CEUS imaging.[23] With a bolus injection of gas-filled microbubbles, physicians can determine the nature of the target lesions by monitoring the distribution characteristics and perfusion sequence of the contrast agent. Two previous studies have shown that malignant NMLs tend to exhibit early wash-in/out time of the contrast agent, hyper-enhancement, enlarged area, and radial or penetrating vessels in CEUS.[12,14] In this study, we systematically observed 10 enhancement indicators of NMLs in CEUS. The results suggested that in addition to the above enhancement characteristics, malignant NMLs also tended to show unclear margins and perfusion defects in CEUS. These enhancement characteristics of malignant NMLs were similar to those of malignant breast masses, which might be caused by the increased neovascularization in malignant breast lesions and the structural, functional, and distributional characteristics of this neovascularization.[24–26] However, unlike the homogeneous enhancement often observed in benign breast masses,[27–30] more than 50% benign NMLs showed heterogeneous enhancement. Heterogeneous enhancement in benign breast lesions has been reported to correspond to loose cell proliferation in a more sclerotic stroma.[31] Meanwhile, in comparison with breast masses that often showed centripetal or centrifugal enhancement,[27–30] regardless of benign or malignant NMLs, the most common enhancement direction was diffuse enhancement.

A definite diagnostic criterion is critical for the application of an imaging examination in clinical practice. After screening the optimized diagnostic indicators of CEUS for malignant NMLs using logistic regression analysis, enhancement degree, enhancement area, and radial or penetrating vessels were chosen to design the diagnostic criterion. When the diagnostic criterion was applied in the diagnosis of malignant NMLs, the specificity of CEUS was significantly improved, but at the cost of decreasing sensitivity compared to BI-RADS-US, resulting in a reduction in diagnostic efficiency (AUC = 0.775 vs. AUC = 0.819). The reason might be that CEUS is not suitable for displaying the morphological features of breast lesions as clearly as conventional US, which leads to loss of diagnostic information. To overcome this defect of CEUS, we attempted to combine CEUS and BI-RADS-US for

Table 3. Re-evaluation of BI-RADS categories with established CEUS diagnostic criteria

	BI-RADS 3		BI-RADS 4a		BI-RADS 4b		BI-RADS 4c		BI-RADS 5	
	Benign	Malignant	Benign	Malignant	Benign	Malignant	Benign	Malignant	Benign	Malignant
BI-RADS-US	19	0	30	15	10	20	4	10	0	11
BI-RADS-US+CEUS	49	3	0	7	6	10	6	9	2	27

BI-RADS, Breast imaging reporting and data system; CEUS, Contrast-enhanced ultrasound; US, Ultrasonography.

further evaluation of NMLs. After reevaluation of BI-RADS category, eight (14.3%) malignant NMLs in our study that showed only one diagnostic indicator in CEUS were not missed, because of the obvious malignant tendency in conventional US. Moreover, the misdiagnosis rate of benign NMLs decreased from 69.8 to 23.8%, which implied a significant reduction in the need for biopsy. We indicated that the combined specificity and sensitivity were both high (77.8 and 94.6%, respectively) for the diagnosis of malignant NMLs, and the diagnostic efficiency of this combined assessment was better than that of BI-RADS-US (AUC = 0.885 vs. AUC = 0.819). These results supported the assumption that CEUS combined with BI-RADS-US had good performance in the diagnosis of malignant NMLs. Compared to the study by Zhang et al[13], our results revealed a higher combined sensitivity and specificity (94.6% *vs* 90%, 78% *vs* 58.1%). This disparity might be caused by the different diagnostic criteria in these two studies. In Zhang's study, the diagnostic criterion for re-evaluating the BI-RADS category was a mixture of multimodal US diagnostic indicators, and only enhancement degree in CEUS was included, which cannot fully represent the diagnostic value of CEUS.[12] However, the combined specificity was lower in our study than in the study by Xu et al. (77.8% *vs* 0.89%). In addition to the different diagnostic criteria, the different sample sizes might also be the reason for the difference.[14] Furthermore, NMLs of BI-RADS category 4a were regarded as benign in the two previous studies, which might be another source for the difference in diagnostic performance.

Of the three false-negative NMLs in this study, one (middle-grade IDC +DCIS) only exhibited one enhancement indicator (hyper-enhancement) in CEUS and the remaining 2 NMLs (one low-grade DCIS and one low and middle-grade IDC +DCIS) did not show any of the three diagnostic indicators. These observations are in agreement with outcomes reported by Lehotska et al. They revealed that malignant breast lesions with a lower degree of nuclear atypia could show atypical images in CEUS.[32] Among the 14 false-positive NMLs, we visualized similar enhancement characteristics to malignant NMLs: two intraductal papilloma, three sclerosing adenosis, and nine inflammatory lesions showed two diagnostic indicators (hyper-enhancement and enlarged area) in CEUS, while one sclerosing adenosis and two inflammation lesion showed all of the three indicators (hyper-enhancement, enlarged area, and radial or penetrating vessels). As illustrated in previous studies,[13,22,33] benign breast lesions of the above histopathological types often show overlapping CEUS images with malignant breast lesions, which are difficult to differentiate. The reason may be related to cellular proliferation, hyperplasia, and inflammatory response.

This retrospective study had the following limitations. First, we only included NMLs that were detected by conventional US and confirmed by pathology; therefore, the results may not fully reflect the NMLs group. Second, there is unavoidable subjectivity in the interpretation of morphological features, blood supply, and enhancement characteristics of NMLs. In our study, two radiologists reached a consensus on the imaging features of NMLs. Thus, the intra- and inter-observer bias could not be calculated. Third, although there was little overlap between the

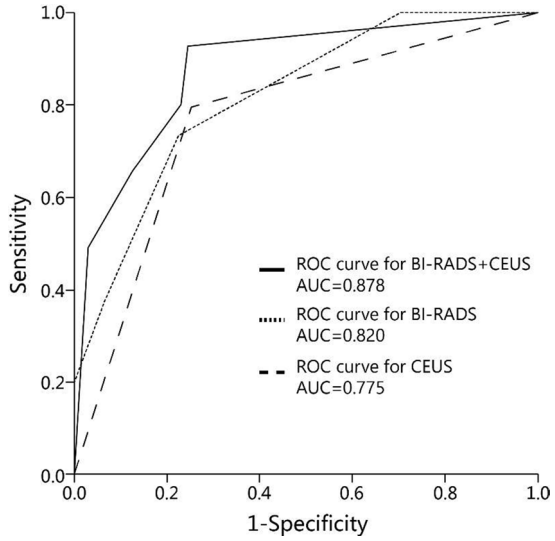
Table 4. Comparison of the diagnostic performance of BI-RADS-US, CEUS, and BI-RADS-US combined with CEUS

	BI-RADS-US	CEUS	*P*a	BI-RADS-US+CEUS	*P*b
AUC	0.819	0.775	0.432	0.885	0.114
Sensitivity (%)	100	80.4	0.001	94.6	0.25
Specificity (%)	30.2	74.6	<0.001	77.8	<0.001
NPV (%)	100.0	81	/	92.5	/
PPV (%)	56	73.8	/	77.3	/

AUC, Area under the receiver operating characteristics curve; BI-RADS, Breast imaging reporting and data system; CEUS, Contrast enhanced ultrasound; NPV, Negative predictive value; PPV, positive predictive value; US, Ultrasonography.
[a]Difference in the diagnostic performances between BI-RADS-US and CEUS.
[b]Difference in the diagnostic performance between BI-RADS-US and combined assessment.

diagnostic indicators used in conventional US and CEUS, the time interval for radiologists to review the data of these two methods was short, and there was no random ordering, which might cause recall bias. Fourth, the quantitative analysis of CEUS was not performed in this study. Several previous studies have suggested that the diagnostic accuracy of qualitative CEUS in breast cancer is comparable to or even higher than that of quantitative CEUS.[34–36] However, with advancements in image processing algorithms, quantitative analysis of CEUS could be added in further studies.

Figure 3. Receiver operating characteristic (ROC) curves of BI-RADS, CEUS, and BI-RADS combined with CEUS for malignant NMLs.



CONCLUSIONS

In conclusion, our study indicates that enhancement degree, enhancement area, and radial or penetrating vessels could be used to construct a diagnostic criterion of CEUS for the diagnosis of malignant NMLs. CEUS exhibit a higher diagnostic specificity in the diagnosis of malignant NMLs, but the decreased sensitivity may limit the clinical demand of CEUS. However, the combination of CEUS and BI-RADS-US has both high sensitivity and specificity in the differential diagnosis of malignant NMLs, which could be an effective diagnostic tool in clinical practice.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (Grants No. 82071931), program for Shanghai Outstanding Medical Academic Leaders (2019LJ18), the interdisciplinary program of Shanghai Jiaotong university (ZH2018ZDA17) , and the program from Science and Technology Commission of Shanghai Municipality (No. 20Y11912400).

REFERENCES

1. Mendelson E, Baum J, Berg W, Merritt C, Rubin E. *Breast imaging reporting and data system, BI-RADS: Ultrasound*. Reston: American College of Radiology; 2003.
2. Mendelson EB, Böhm-Vélez M, Berg WA. et al.*ACR BIRADS® Ultrasound. In: ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System*. Reston: American College of Radiology; 2013.
3. Park JW, Ko KH, Kim E-K, Kuzmiak CM, Jung HK. Non-mass breast lesions on ultrasound: final outcomes and predictors of malignancy. *Acta Radiol* 2017; **58**: 1054–60. doi: https://doi.org/10.1177/0284185116683574
4. Kim SJ, Park YM, Jung HK. Nonmasslike lesions on breast sonography: comparison between benign and malignant lesions. *J Ultrasound Med* 2014; **33**: 421–30. doi: https://doi.org/10.7863/ultra.33.3.421
5. Wang ZL, Li N, Li M, Wan WB. Non-mass-like lesions on breast ultrasound: classification and correlation with histology. *Radiol Med* 2015; **120**: 905–10. doi: https://doi.org/10.1007/s11547-014-0493-x
6. Uematsu T. Non-mass-like lesions on breast ultrasonography: a systematic review. *Breast Cancer* 2012; **19**: 295–301. doi: https://doi.org/10.1007/s12282-012-0364-z
7. Li L, Zhou X, Zhao X, Hao S, Yao J, Zhong W, et al. B-Mode ultrasound combined with color Doppler and strain elastography in the diagnosis of Non-mass breast lesions: a prospective study. *Ultrasound Med Biol* 2017;

43: 2582–90. doi: https://doi.org/10.1016/j.ultrasmedbio.2017.07.014
8. Ko K-H, Hsu H-H, Yu J-C, Peng Y-J, Tung H-J, Chu C-M, et al. Non-mass-like breast lesions at ultrasonography: feature analysis and BI-RADS assessment. *Eur J Radiol* 2015; **84**: 77–85. doi: https://doi.org/10.1016/j.ejrad.2014.10.010
9. Choi JS, Han B-K, Ko EY, Ko ES, Shin JH, Kim GR. Additional diagnostic value of shear-wave elastography and color Doppler us for evaluation of breast non-mass lesions detected at B-mode us. *Eur Radiol* 2016; **26**: 3542–9. doi: https://doi.org/10.1007/s00330-015-4201-6
10. Wang ZL, Li Y, Wan WB, Li N, Tang J. Shear-wave elastography: could it be helpful for the diagnosis of Non-Mass-Like breast lesions? *Ultrasound Med Biol* 2017; **43**: 83–90. doi: https://doi.org/10.1016/j.ultrasmedbio.2016.03.022
11. Wilson SR, Burns PN. Microbubble-Enhanced us in body imaging: what role? *Radiology* 2010; **257**: 24–39. doi: https://doi.org/10.1148/radiol.10091210
12. Unnikrishnan S, Klibanov AL. Microbubbles as ultrasound contrast agents for molecular imaging: preparation and application. *AJR Am J Roentgenol* 2012; **199**: 292–9. doi: https://doi.org/10.2214/AJR.12.8826
13. Zhang W, Xiao X, Xu X, Liang M, Wu H, Ruan J, et al. Non-Mass breast lesions on ultrasound: feature exploration and multimode ultrasonic diagnosis. *Ultrasound Med Biol* 2018; **44**: 1703–11. doi: https://doi.org/10.1016/j.ultrasmedbio.2018.05.005
14. Xu P, Yang M, Liu Y, Li Y-P, Zhang H, Shao G-R. Breast non-mass-like lesions on contrast-enhanced ultrasonography: feature analysis, breast image reporting and data system classification assessment. *World J Clin Cases* 2020; **8**: 700–12. doi: https://doi.org/10.12998/wjcc.v8.i4.700
15. Adler DD, Carson PL, Rubin JM, Quinn-Reid D. Doppler ultrasound color flow imaging in the study of breast cancer: preliminary findings. *Ultrasound Med Biol* 1990; **16**: 553–9. doi: https://doi.org/10.1016/0301-5629(90)90020-D
16. Zeggelink WFAK, Deurloo EE, Bartelink H, Rutgers EJT, Gilhuijs KGA. Reproducibility of the assessment of tumor extent in the breast using multiple image modalities. *Med Phys* 2003; **30**: 2919–26. doi: https://doi.org/10.1118/1.1621136
17. Wang LC, Sullivan M, Du H, Feldman MI, Mendelson EB. Us appearance of ductal carcinoma in situ. *Radiographics* 2013; **33**: 213–28. doi: https://doi.org/10.1148/rg.331125092
18. Kim HR, Jung HK. Histopathology findings of non-mass cancers on breast ultrasound. *Acta Radiol Open* 2018; **7**: 205846011877495. doi: https://doi.org/10.1177/2058460118774957
19. Sotome K, Yamamoto Y, Hirano A, Takahara T, Hasegawa S, Nakamaru M, et al. The role of contrast enhanced MRI in the diagnosis of non-mass image-forming lesions on breast ultrasonography. *Breast Cancer* 2007; **14**: 371–80. doi: https://doi.org/10.2325/jbcs.14.371
20. Elverici E, Barça AN, Aktaş H, Özsoy A, Zengin B, Çavuşoğlu M, Aktas H, et al. Nonpalpable BI-RADS 4 breast lesions: sonographic findings and pathology correlation. *Diagn Interv Radiol* 2015; **21**: 189–94. doi: https://doi.org/10.5152/dir.2014.14103
21. Gao J-xi, Yu X-qin, Yao L-hui. Value of BI-RADS ultrasonic scores of direct and indirect ultrasonographic signs in diagnosis of solid breast lesions. *Zhonghua Zhong Liu Za Zhi* 2011; **33**: 465–9.
22. Liu G, Zhang M-K, He Y, Liu Y, Li X-R, Wang Z-L. Bi-Rads 4 breast lesions: could multi-mode ultrasound be helpful for their diagnosis? *Gland Surg* 2019; **8**: 258–70. doi: https://doi.org/10.21037/gs.2019.05.01
23. Nakopoulou L, Stefanaki K, Panayotopoulou E, Giannopoulou I, Athanassiadou P, Gakiopoulou-Givalou H, et al. Expression of the vascular endothelial growth factor receptor-2/Flk-1 in breast carcinomas: correlation with proliferation. *Hum Pathol* 2002; **33**: 863–70. doi: https://doi.org/10.1053/hupa.2002.126879
24. Schneider BP, Miller KD. Angiogenesis of breast cancer. *J Clin Oncol* 2005; **23**: 1782–90. doi: https://doi.org/10.1200/JCO.2005.12.017
25. Forsberg F, Piccoli CW, Merton DA, Palazzo JJ, Hall AL. Breast lesions: imaging with contrast-enhanced subharmonic US--initial experience. *Radiology* 2007; **244**: 718–26. doi: https://doi.org/10.1148/radiol.2443061588
26. Du J, Li F-H, Fang H, Xia J-G, Zhu C-X. Correlation of real-time gray scale contrast-enhanced ultrasonography with microvessel density and vascular endothelial growth factor expression for assessment of angiogenesis in breast lesions. *J Ultrasound Med* 2008; **27**: 821–31. doi: https://doi.org/10.7863/jum.2008.27.6.821
27. Wang Y, Fan W, Zhao S, Zhang K, Zhang L, Zhang P, et al. Qualitative, quantitative and combination score systems in differential diagnosis of breast lesions by contrast-enhanced ultrasound. *Eur J Radiol* 2016; **85**: 48–54. doi: https://doi.org/10.1016/j.ejrad.2015.10.017
28. Quan J, Hong Y, Zhang X, Mei M, You X, Huang P. The clinical role of contrast enhanced ultrasound in differential diagnosis of BI-RADS 4 breast disease. *Clin Hemorheol Microcirc* 2019; **72**: 293–303. doi: https://doi.org/10.3233/CH-180495
29. Zhao Y-X, Liu S, Hu Y-B, Ge Y-Y, Lv D-M. Diagnostic and prognostic values of contrast-enhanced ultrasound in breast cancer: a retrospective study. *Onco Targets Ther* 2017; **10**: 1123–9. doi: https://doi.org/10.2147/OTT.S124134
30. Lee SC, Tchelepi H, Grant E, Desai B, Luo C, Groshen S, et al. Contrast-Enhanced ultrasound imaging of breast masses: adjunct tool to decrease the number of false-positive biopsy results. *J Ultrasound Med* 2019; **38**: 2259–73. doi: https://doi.org/10.1002/jum.14917
31. Liu H, Jiang Y-X, Liu J-B, Zhu Q-L, Sun Q, Chang X-Y. Contrast-Enhanced breast ultrasonography: imaging features with histopathologic correlation. *J Ultrasound Med* 2009; **28**: 911–20. doi: https://doi.org/10.7863/jum.2009.28.7.911
32. Lehotska V, Rauova K, Vanovcanova L. Pitfalls of contrast enhanced ultrasound (CEUS) in determination of breast tumor biological dignity. *Neoplasma* 2018; **65**: 124–31. doi: https://doi.org/10.4149/neo_2018_170116N43
33. Zhang J-xing, Cai L-shan, Chen L, Dai J-long, Song G-hui, Cai LS. CEUS helps to rerate small breast tumors of BI-RADS category 3 and category 4. *Biomed Res Int* 2014; **2014**: 1–8. doi: https://doi.org/10.1155/2014/572532
34. Wan C, Du J, Fang H, Li F, Wang L. Evaluation of breast lesions by contrast enhanced ultrasound: qualitative and quantitative analysis. *Eur J Radiol* 2012; **81**: e444–50. doi: https://doi.org/10.1016/j.ejrad.2011.03.094
35. Wang Y, Fan W, Zhao S, Zhang K, Zhang L, Zhang P, et al. Qualitative, quantitative and combination score systems in differential diagnosis of breast lesions by contrast-enhanced ultrasound. *Eur J Radiol* 2016; **85**: 48–54. doi: https://doi.org/10.1016/j.ejrad.2015.10.017
36. Liu J, Gao Y-H, Li D-D, Gao Y-C, Hou L-M, Xie T. Comparative study of contrast-enhanced ultrasound qualitative and quantitative analysis for identifying benign and malignant breast tumor lumps. *Asian Pac J Cancer Prev* 2014; **15**: 8149–53. doi: https://doi.org/10.7314/APJCP.2014.15.19.8149