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Original Article

Values of contrast-enhanced ultrasound combined with BI-RADS in differentiating benign and malignant breast lesions

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Abstract: Background: Conventional ultrasound with breast imaging reporting and data system (BI-RADS) is often used for diagnosing the breast lesions, but has not considered the blood supply of the tumor. This study aimed to investigate the values of contrast enhanced ultrasound (CEUS) combined with BI-RADS in differentiating benign and malignant breast lesions. *Methods:* One hundred and forty-nine patients with 149 breast lesions were enrolled. The conventional ultrasound and CEUS examinations were performed on the breast lesions. The images of conventional ultrasound were analyzed and categorized based on BI-RADS. After CEUS, the BI-RADS categorizing of CEUS was corrected. The sensitivity, specificity and accuracy of each method were calculated, and the receiver operating characteristic (ROC) curve was drawn to determine the diagnostic efficiency. *Results:* In conventional ultrasound, there were 20, 30, 89 and 10 cases with BI-RADS category 2, 3, 4 and 5, respectively. All ultrasound image features had significant difference between benign and malignant groups, including lesion shape, direction, margin, echo type, posterior echo, calcification and Adler grade of blood flow ($P < 0.001$). In CEUS, there were 45, 27, 44 and 33 cases with BI-RADS category 2, 3, 4 and 5, respectively. All the CEUS image features had significant difference between benign and malignant groups, including enhancement intensity, enhancement range, margin after enhancement, contrast agent distribution and tumor nourishing vessel distribution ($P < 0.001$). There was no significant difference of sensitivity between conventional ultrasound and CEUS ($P > 0.05$), but the specificity and accuracy of CEUS were significantly higher than those of conventional ultrasound, respectively ($P < 0.01$). The AUC of CEUS was significantly higher than that of conventional ultrasound ($P < 0.001$). *Conclusion:* CEUS combined with BI-RADS can significantly improve the differentiation ability of breast lesions, and it is worthy of application in clinic.

Keywords: Contrast-enhanced ultrasound, BI-RADS, breast lesions

Introduction

Breast cancer is a cancer in women, and it has the highest incidence worldwide [1]. China is one of the countries with fastest growing incidence of breast cancer [2]. The mortality rate of breast cancer has leapt to the second place in malignant tumors, of which the main reason is that the breast cancer has not obtained effective early diagnosis [3]. Therefore, the early diagnosis and effective treatment has become the key to improve the survival rate of breast cancer patients. Conventional imaging methods for breast lesions include ultrasound, molybdenum target examination and magnetic resonance imaging. Ultrasound, as a non-invasive examination method, has been widely used in clinical diagnosis and treatment due to its non-invasive, convenient, inexpensive, radioactivity-free and high-sensitivity characteristics. It has become the first choice of auxiliary examination for breast lesions [4]. At present, the breast imaging reporting and data system (BI-RADS) formulated by the American College of Radiology (ACR) has been widely used in clinic. It can effectively resolve the consistency problem between clinical and ultrasonic diagnosis of breast lesions [5]. However, BI-RADS is completely based on the classification of two-dimensional ultrasound, without consider-

Table 1. Pathological types of breast lesions

Pathological type	n	Percentage (%)
Invasive ductal carcinoma	31	20.8
Intraductal carcinoma	12	8.1
Invasive ductal carcinoma with intraductal carcinoma	7	4.7
Invasive ductal carcinoma with other cancers	3	2.0
Intraductal papillary carcinoma	3	2.0
Invasive lobular carcinoma	2	1.3
Mucous adenocarcinoma	2	1.3
Carcinoma in situ	1	0.7
Adenoma of adenoma	30	20.1
Adenosis	18	12.1
Cyst	18	12.1
Intraductal papilloma	15	10.1
Plasma cell mastitis	3	2.0
Sclerosing adenosis	3	2.0
Tuberculosis	1	0.7

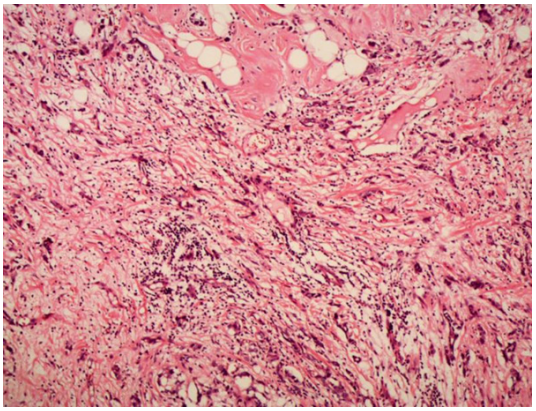

Figure 1. Pathological image of invasive ductal carcinomav (HE, 10×). There was obvious infiltration of fat, with unclear boundary with the surrounding tissue and crisscrossing vessels.

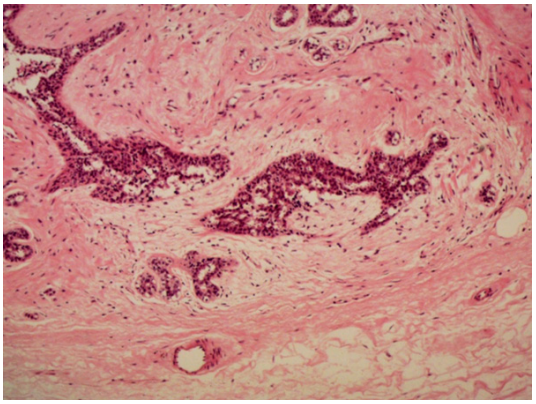

Figure 2. Pathological image of adenoma of adenoma (HE, 10×). The lesion had clear boundary with surrounding tissue, with slightly large vessels around. The intratumoral nourishing vessels were tiny.

ing the blood supply of the tumor. The application of microbubble ultrasound contrast agent can enhance the vascular signals in ultrasonic imaging, which is helpful to improve the ability of ultrasonic evaluation of breast lesions, and differentially diagnose the benign and malignant breast lesions [6-8]. The effective combination of above two techniques can greatly increase the differentiation ability of breast lesions. In this study, the conventional ultrasound and contrast-enhanced ultrasound (CEUS) were applied to the patients with breast lesions. Their diagnostic results on benign and malignant breast lesions based on BI-RADS categories were analyzed. The objective was to provide a basis for further application of CEUS to diagnosis of breast lesions.

Subjects and methods

Subjects

One hundred and forty-nine patients with 149 breast lesions receiving breast mass surgery in Zhejiang Xiaoshan Hospital (Hanzhou, China) from June 2013 to September 2016 were enrolled in this study. Al patients were female. The age was 24-65 years, with average age of 41.5 ± 6.9 years. The patient came to visit with the breast pain and finding or touching of breast masses. All patients underwent conventional ultrasound and CEUS examination of breast lesions before surgery. All the excised lesions underwent the pathological examination. All patients had no liver, kidney, major cardiovascular or cerebrovascular disease. The study protocol was approved by the Ethics Committee of Zhejiang Xiaoshan Hospital. Informed consent was obtained from all participants after explanation of the procedure and purpose of the study to all of them.

Examination methods

MyLab™ ClassC ultrasonic diagnostic instrument (Esaote Inc., Genoa, Italy) was used for the ultrasound examination. The probe type

Table 2. BI-RADS categories by conventional ultrasound and pathological findings

BI-RADS category	n	Pathological finding [n (%)]	
		Benign	Malignant
2	20	20 (100)	0 (0)
3	30	29 (96.7)	1 (3.3)
4A	34	27 (79.4)	7 (20.6)
4B	30	11 (36.7)	19 (63.3)
4C	25	1 (4)	24 (26)
5	10	0 (0)	10 (100)

BI-RADS, breast imaging reporting and data system.

Table 3. Image features of conventional ultrasound and pathological findings

Image features	Pathological finding (n)		X^2	P
	Benign	Malignant		
Shape			44.59	< 0.001
Circular	10	3		
Oval	60	12		
Irregular	18	46		
Direction			45.44	< 0.001
Parallel	80	24		
Vertical	8	37		
Margin			31.62	< 0.001
Clear	48	7		
Vague	17	32		
Leaflet	15	16		
Burr	8	6		
Echo type			17.15	0.002
No	16	0		
High	3	1		
Low	51	52		
Equal	5	1		
Mixed	13	7		
Posterior echo			45.15	< 0.001
Enhanced	25	7		
Attenuated	12	41		
No obvious change	51	13		
Calcification			16.35	< 0.001
No calcification	63	30		
Coarse calcification	17	9		
Micro calcification	8	22		
Adler grade of blood flow			40.86	< 0.001
0	29	5		
1	33	12		
2	23	19		
3	3	25		

was LA523 and LA522, respectively, with the probe frequency of 5-12 MHz and 3-9 MHz, respectively. Firstly, the conventional two-dimensional ultrasound examination was performed to observe the conditions of lesion including lesion size, shape, direction, margin, echo, posterior echo, calcification and blood flow distribution. The ultrasound images were saved. Then, the largest viewing section was selected for CEUS examination. The instrument was adjusted to double contrast mode. SonoVue ultrasound contrast agent (4.8 ml; Shanghai Bolaike Xinyi Pharmaceutical Co., Ltd., Shanghai, China) was bolusly injected into the elbow vein of patients, followed by injection of 5 ml 0.9% sodium chloride solution. The time was recorded from the starting of contrast agent injection. The dynamic images of the entire CEUS process were saved.

Image analysis and diagnosis

Conventional ultrasound images were classified by BI-RADS. The CEUS images were read, and the features of lesion were described. The observed image features included enhancement intensity, enhancement range, enhancement margin, contrast agent distribution and tumor nourishing vessels. The malignant lesions were determined based on the signs as follows: i) the lesions presented rapid and obvious high enhancement; ii) the enhancement range was larger than conventional ultrasound; iii) the enhancement margin was irregular; iv) the contrast agent distribution was heterogeneous; v) there were twisted nourishing vessels in or around the lesions. The BI-RADS categories were adjusted after CEUS. The BI-RADS category of cases with 3 or more malignant signs was upgraded by one category, and that with one malignant sign was degraded by one category. The BI-RADS category with 1-2 malignant signs was maintained at the original category. The category 2 and 5 were maintained at the original categories even if

Table 4. BI-RADS categories by CEUS and pathological findings

BI-RADS category	n	Pathological finding [n (%)]	
		Benign	Malignant
2	45	45 (100%)	0 (0%)
3	27	27 (100%)	0 (0%)
4A	17	14 (82.4%)	3 (17.6%)
4B	8	1 (12.5%)	7 (87.5%)
4C	19	1 (5.3%)	18 (94.7%)
5	33	0 (0%)	33 (100%)

BI-RADS, breast imaging reporting and data system.

they met the degrading and upgrading condition, respectively. Category 4 and above were determined as positive diagnostic values. The sensitivity, specificity and accuracy of each method were calculated, and the receiver operating characteristic (ROC) curve was drawn to determine the diagnostic efficiency.

Statistical analysis

SPSS 22.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The enumeration data were presented as number. The image features between benign and malignant breast lesions were compared using X^2 test. The sensitivity, specificity and accuracy of conventional ultrasound and CEUS were compared using X^2 test. The diagnostic efficiencies of two methods were analyzed using ROC curve, and the area under curve (AUC) between two methods was compared using Z test. $P < 0.05$ was considered as statistically significant.

Results

Basic information of patients

In 149 cases of breast lesions, the pathological examination confirmed 61 cases of malignant lesions and 88 cases of benign lesions. The pathological types of breast lesions were shown in **Table 1**. The representative pathological images of invasive ductal carcinoma and adenoma of adenoma were shown in **Figures 1** and **2**, respectively.

BI-RADS categories by conventional ultrasound and pathological findings

BI-RADS categories by conventional ultrasound and pathological findings were shown in **Table 2**. The image features of conventional ultrasound and pathological findings were shown in **Table 3**. All the image features of conventional ultrasound had significant difference between benign and malignant groups, including lesion shape, direction, margin, echo type, posterior echo, calcification and Adler grade of blood flow ($P < 0.001$).

BI-RADS categories by CEUS and pathological findings

BI-RADS categories by conventional ultrasound combined with CEUS and pathological findings were shown in **Table 4**. The distribution to lesions with BI-RADS category corrected from conventional ultrasound to CEUS was shown in **Table 5**. The image features of CEUS and pathological findings were shown in **Table 6**. All the image features of CEUS had significant difference between benign and malignant groups, including enhancement intensity, enhancement range, margin after enhancement, contrast agent distribution and tumor nourishing vessel distribution ($P < 0.001$). The benign lesions presented homogeneous low or equal enhancement and clear margin, unexpanded enhancement range. There was no obvious nourishing vessel inside or around the lesions (**Figure 3**). The malignant lesions presented the irregular and burr margin. The lesion range after enhancement was expanded, and the enhancement intensity was significantly improved, with a mixture of high enhancement zone and low enhancement zone. The contrast reagent was heterogeneously distributed in the lesions. There were twisted tumor nourishing vessels inside or around to the lesions (**Figure 4**).

Comparison of diagnostic efficiency between conventional ultrasound and CEUS

Diagnosis results of conventional ultrasound and CEUS were compared. Using BI-RADS category 4 and above as the positive diagnostic values, the sensitivity, specificity and accuracy of conventional ultrasound and CEUS were calculated (**Table 7**). There was no significant difference of sensitivity between conventional ultrasound and CEUS ($P > 0.05$), but the specificity and accuracy of CEUS were significantly higher than those of conventional ultrasound, respectively ($P < 0.01$). The ROCs of conventional ultrasound and CEUS were shown in

Table 5. Distribution to lesions with BI-RADS categories corrected from conventional ultrasound to CEUS

BI-RADS category in conventional ultrasound	BI-RADS category in CEUS	n
3	2	25
3	4A	1
4A	3	23
4B	4A	5
4B	4C	17
4C	5	23

BI-RADS, breast imaging reporting and data system. CEUS, contrast-enhanced ultrasound.

Table 6. Image features of CEUS and pathological findings

Image feature	Pathological finding (n)		χ^2	P
	Benign	Malignant		
Enhancement intensity			81.96	< 0.001
High	9	51		
Equal	47	6		
Low	17	4		
No	15	0		
Enhancement range			69.41	< 0.001
Expanded	7	45		
Shrunk	6	0		
Equal	75	16		
Margin			75.21	< 0.001
Clear	47	5		
Burr	4	21		
Irregular	7	30		
No obvious margin	30	5		
Contrast agent distribution			15.14	< 0.001
Homogeneous	53	17		
Heterogeneous	35	44		
Tumor nourishing vessel			50.09	< 0.001
No vessel	33	7		
Smooth	43	11		
Twisted	12	43		

CEUS, contrast-enhanced ultrasound.

Figure 5. The AUC and the test result were shown in **Table 8**, which indicated that, the CEUS had higher diagnostic efficiency compared with conventional ultrasound.

Discussion

Breast cancer is a disease depending on the angiogenesis [9]. The vascular anatomy and hemodynamics are different between benign and malignant tumors, which has provided a pathophysiological basis for Doppler ultrasound of breast lesions. However, as an important examination method, the color Doppler ultrasound has limitation in displaying the intratumoral vessels [10]. As a new technique of ultrasonic imaging, CEUS has been widely carried out in the abdomen and the heart examination. SonoVue is a pure blood-pool contrast agent, of which the microbubble diameter (2.5 μm) is smaller than the capillary diameter, so it can well reflect the distribution of microvascular network in the lesion [11]. It has provided a new method for detecting micro vascular perfusion status. In the present study, based on the difference in vascular microcirculation of benign and malignant tumors, the CEUS was applied to differentiating the benign and malignant breast lesions. Results of this study has provided a basis for further application of CEUS to diagnosis of breast lesions.

ACR has proposed that, the lesions with BI-RADS category 2 are benign. The lesions with category 3 may be benign, and the malignant rate is generally less than 2%. It is suggested to make a short-term follow-up. The lesions with category 4 can be included in suspected cases, and the positive rate is 3%-94%, so the further biopsy is needed. The lesions with category 5 are highly suspected malignant, with a positive rate greater than 95%, and the appropriate clinical measures should be taken [12]. The BI-RADS category 4 and above are used as the boundary of positive diagnosis. The conventional ultrasound has high sensitivity, but the specificity and accuracy are low. Improving the specificity is the key for diagnosis without reducing the sensitivity. In this study, after CEUS there were 23 lesions of BI-RADS category 4C upgrading to category 5 and 1 lesion of category 3 upgrading to category 4A. They were all pathologically confirmed as malignant. In these 24 cases, CEUS displayed typical high

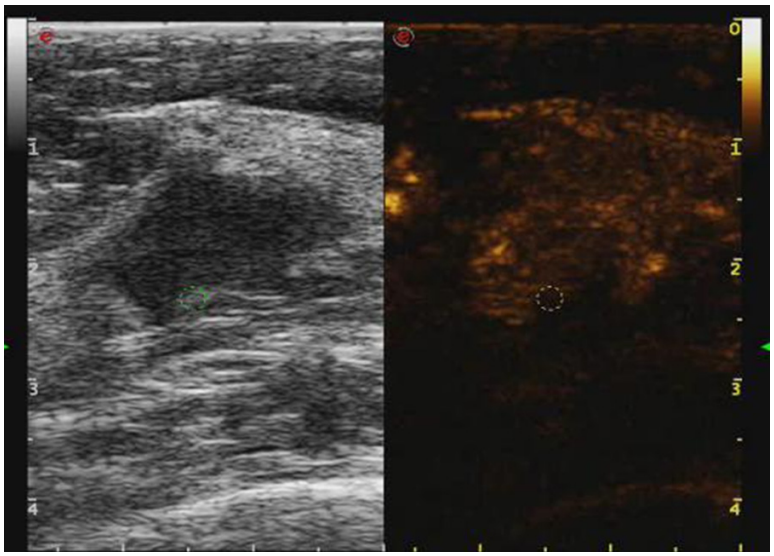

Figure 3. Double-image synchronous display of benign breast lesion by contrast-enhanced ultrasound. The right contrast image showed homogeneous low enhancement and clear margin, with non-enlarged lesion area compared with the left two-dimensional image.

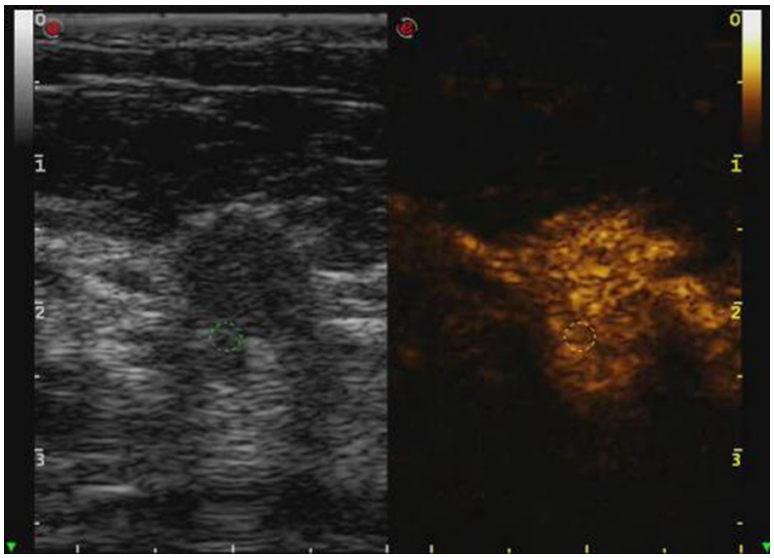

Figure 4. Double-image synchronous display of malignant breast lesion by contrast-enhanced ultrasound. The right contrast image showed heterogeneous high enhancement and burr margin, with significantly enlarged lesion area compared with the left two-dimensional image.

enhancement, expanded enlargement range, burr margin, homogeneous contrast agent distribution and tumor nourishing vessels, which were similar to the results of previous study [13]. In 23 lesions, the BI-RADS category was graded from 4A to 3, and the final pathology confirmed as benign. In these 23 cases, the conventional ultrasound presented the suspicious malignant signs such as irregular shape, vertical growth, heterogeneous internal echo and microcalcification. However, the CEUS showed homogeneous equal or low enhancement, unexpanded enhancement range, clear margin and no obvious tumor vessels.

Morphological characteristics of blood vessels in breast cancer are uneven thickness of internal diameter, tortuous expansion of shape and arteriovenous fistula formation. On the contrary, the blood vessels of the benign breast tumor present regular internal diameter and regular shape. These features are the vascular anatomical basis of CEUS features for benign and malignant breast lesions [14]. Results of the present study prove that, CEUS can accurately reflect the different perfusion modes caused by the difference in internal vascular structure between benign and malignant tumors, thus identifying the benign and malignant breast lesions.

In this study, there were 2 cases of lesion with BI-RADS category 4C not grading to category 5. In 1 case, the pathological result indicated sclerosing adenosis. The conventional ultrasound showed unclear and burr margin, no obvious capsule, unclear boundary to the surrounding tissue, invasive performance, attenuated posterior echo, micro calcification in lesion and grade Adler 1 blood flow. CEUS showed the homogeneous equal enhancement, no obvious boundary of enhancement margin, expanded enhancement range, and no tumor vessel. In the other case, the pathological result indicated the carcinoma muciparum. The conventional ultrasound showed irregular

Table 7. Sensitivity, specificity and accuracy of conventional ultrasound and CEUS

Index	Conventional ultrasound	CEUS	X^2	P
Sensitivity	98.4%	100%	1.613	0.204
Specificity	55.7%	81.8%	15.853	< 0.001
Accuracy	73%	89%	8.3171	0.004

CEUS, contrast-enhanced ultrasound.

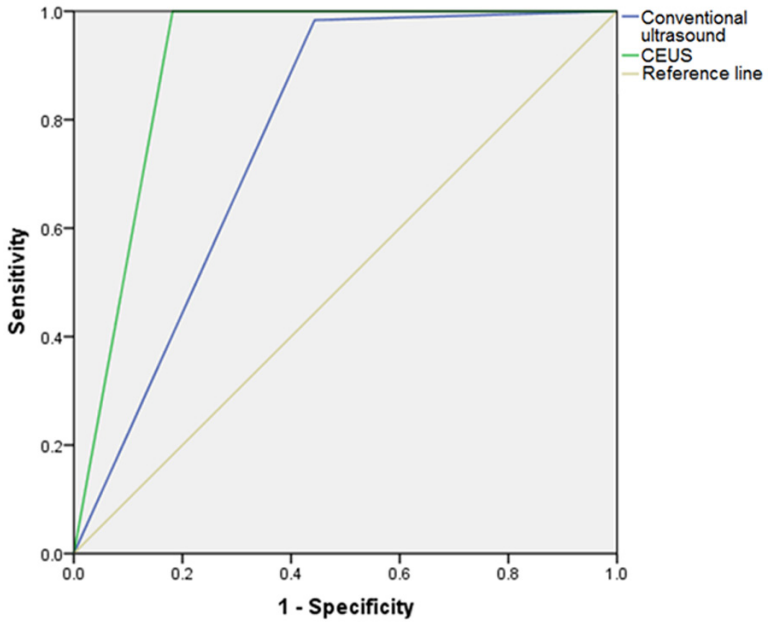

Figure 5. Receiver operating characteristic curves of conventional ultrasound and CEUS. CEUS, contrast-enhanced ultrasound.

Table 8. Area under curve and test result of conventional ultrasound and CEUS

Method	AUC	SE	95% CI	Z	P
Conventional ultrasound	0.770	0.038	0.695-0.845	5.569	< 0.001
CEUS	0.909	0.025	0.859-0.959		

CEUS, contrast-enhanced ultrasound.

shape, vertical growth, homogeneous low echo, no change of posterior echo, slight calcification, and grade Adler 1 blood flow. CEUS showed homogeneous high enhancement, clear enhancement margin, unexpanded enhancement range and access of tumor vessels. It did not contain all the typical malignant features. Above two cases illustrate that, there is the neovascularization in some benign and malignant borderline tumors, which is similar to the malignant tumors. In addition, in some malignant tumors with special pathological type, there is less neovascularization. Therefore, there is no typical benign or malignant manifestation in CEUS images, which makes it difficult to identify the lesion type.

In this study, there were 17 lesions with BI-RADS category 4B grading to category 4C after CEUS. Among these cases, 1 lesion was with plasma cell mastitis. The conventional ultrasound presented heterogeneous low echo, no capsule, irregular shape and rich blood flow, so it was easy to be misdiagnosed as breast cancer [15, 16]. The inflammatory lesions have a variety of manifestations, and CEUS has different manifestation in different stages of disease. In this case, CEUS showed heterogeneous high enhancement, expanded enhancement range, irregular margin and tumor nourishing vessels. It has brought difficulty to the identification, and this needs to be further investigated.

In general, compared with conventional ultrasound, in CEUS the number of lesions with BI-RADS category 5 is increased, based on which the diagnosis of malignant tumor is more explicit. The number of lesions with category 4 is decreased, which can avoid the unnecessary biopsies, thus reducing the psychological and economic burden of patients. The number of lesions with category 3 and below is increased, which can increase the number of patients included in the follow-up observation. There was no significant difference of sensitivity between conventional ultrasound and CEUS, but the specificity and accuracy of CEUS were significantly higher than that of conventional ultrasound. The AUC in CEUS was significantly higher than that of conventional ultrasound. This indicates that, the CEUS has higher diag-

nostic efficiency than conventional ultrasound in differentiating benign and malignant breast lesions.

This study still has some limitations. First of all, due to the insufficient sample size, this study has not investigated the angiographic characteristics of benign and malignant lesions, especially the inflammatory lesions, benign lesions with malignant tendency and malignant lesions with special pathological types. Secondly, this study only observed the qualitative indexes of lesions. The quantitative indexes including enhancement peak value, time reaching peak, extinction time and so on are not included in the research. This needs to be further investigated. In conclusion, CEUS combined with BI-RADS can significantly improve the differentiation ability of breast lesions, and it is worthy of application in clinic.

Disclosure of conflict of interest

None.

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