Am J Transl Res 2021;13(12):13941-13949
www.ajtr.org /ISSN:1943-8141/AJTR0138219

Original Article

Value of ultrasound elastography combined with contrast-enhanced ultrasound and micro-flow imaging in differential diagnosis of benign and malignant breast lesions

Zuopeng Ding[1], Weiyong Liu[1], Nianan He[1], Xiaopeng Ma[2], Lili Fu[3], Lei Ye[1]

[1]Department of Ultrasound Medicine, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei 230036, Anhui, China; [2]Department of Breast Surgery, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei 230036, Anhui, China; [3]Department of Ultrasound Medicine, Guoyang County People's Hospital, Bozhou 233600, Anhui, China

Received August 11, 2021; Accepted October 19, 2021; Epub December 15, 2021; Published December 30, 2021

Abstract: Objective: Breast cancer is one of the most common malignant tumors in women and shows a rising incidence at younger ages. Therefore, early diagnosis is of great significance for treatment and prognosis. This study aimed to compare the value of ultrasound elastography (UE) combined with contrast-enhanced ultrasound (CEUS) and micro-flow imaging (MFI) in differential diagnosis of benign and malignant lesions of the breast. Methods: The sonographic characteristics of UE and CEUS as well as the vascular characteristics of MFI of 109 breast lesions categorized as Breast Imaging Reporting and Data System (BI-RADS) category 4, confirmed by surgical or biopsy pathology were retrospectively analyzed. Receiver operating characteristic (ROC) curves were used to compare the diagnostic efficacy of the three examination modalities, either alone or in combination. Results: Of the 109 breast lesions, 78 lesions were pathologically diagnosed as malignant and 31 as benign. At diagnosis, the area under the ROC curve (AUC), sensitivity, specificity, and accuracy of UE were 0.8495, 65.38%, 83.87% and 83.34%, respectively. The AUC, sensitivity, specificity and accuracy of MFI were 86.29%, 70.51%, 87.10% and 85.56%, respectively. The AUC, sensitivity, specificity and accuracy of CEUS were 90.84%, 88.46%, 74.19% and 89.16%, respectively. The AUC, sensitivity, specificity and accuracy of the combined diagnosis of UE, MFI, and CEUS were 93.90%, 85.90%, 90.32%, and 92.07%, respectively. Conclusions: The combination of UE, CEUS and MFI has the highest specificity and accuracy in the differential diagnosis of benign and malignant breast lesions compared to any one used singly.

Keywords: Ultrasound elastography, contrast enhanced ultrasound, micro-flow imaging, diagnostic value, accuracy

Introduction

Breast cancer is one of the most common malignancies in women [1, 2]. According to the data revealed by Global Cancer in 2020 (GLOBOCAN), female breast cancer ranks the first by representing 11.7% of all cancer new cases among 185 countries worldwide with the new cases numbering 2,261,419 [3]. Breast cancer has the highest incidence and mortality among malignant diseases in Chinese women, with a mortality rate of approximately 6.9% [4]. Due to the lack of early screening and detection methods along with the expensive cost of therapy, breast cancer is one of the most serious disease burdens [5, 6].

Clinically, the characteristics and signs of breast cancer are diverse. Most patients first see a doctor because they accidentally palpate a breast lump [7]. However, the mass is insufficient for the establishment of a breast cancer diagnosis. Breast masses can be either benign or malignant lesions. Benign lesions include fibroadenoma, hyperplasia, hamartoma, and inflammation [8, 9]. Malignant lesions include intraductal breast cancer, lobular carcinoma, and mucinous carcinoma [10, 11]. In addition to this, the onset of breast cancer is complicated and has a long incubation period [12]. Further diagnosis of breast cancer patients requires the combination of ultrasound, mammography, MRI, and other auxiliary examinations [13-15]. Nevertheless, the "gold standard" for the final diagnosis of breast cancer is undoubtedly pathologic diagnosis.

The preferred imaging modality for breast cancer screening is mammography, but it is limited by its low diagnostic sensitivity in patients with dense breast tissues due to the involvement of ionizing radiation [16]. MRI is relatively too expensive and not suitable for large-scale screening or multiple repeated examinations, and also shows low specificity for examination [17]. Ultrasonography is not only unaffected by the patient's gland density, but also has a good ability to distinguish breast tissue without radiological damage. Meanwhile, it is easy and convenient to operate, with significant advantages in the examination of breast lesions [18]. In recent years, contrast-enhanced ultrasound (CEUS) combined with ultrasound elastography (UE) have been developed as an advanced technique in the diagnosis of breast cancer, which can provide micro perfusion and texture information for differentiating benign and malignant tumors [19, 20]. Micro-flow imaging (MFI) is a vascular imaging technology applied in CEUS mode, which can not only observe the perfusion of contrast agent microbubbles to the lesion with blood flow, but also more intuitively display the overall microvascular characteristics of the lesion [21]. Studies have demonstrated that the combination of CEUS and UE significantly improved the accuracy in the diagnosis of diseases such as thyroid carcinoma [22], and evaluated the response of breast cancer patient to neoadjuvant chemotherapy [23]. However, there are no reports on the combination of CEUS, UE, and MFI in the diagnosis of diseases, especially in the identification of benign and malignant breast lesions. Thus, the innovation of this study was to apply these three diagnostic modalities for the diagnosis of benign and malignant tumors of the breast, to observe their performance, either alone or in combination.

Materials and methods

General information

The clinical data of 109 patients with breast lesions hospitalized for treatment in the First Affiliated Hospital of University of Science and Technology of China from January 2019 to June 2021 were retrospectively analyzed. All patients were aged between 30 and 77 years old, with an average of (48.5±10.4) years old. Inclusion criteria: patients with lesions classified as Breast Imaging Reporting and Data System (BI-RADS) category 4 on routine preoperative ultrasound; patients with preoperative UE, CEUS, and MFI examinations; patients without any treatment or tissue biopsy before examination; patients who underwent surgery or biopsy, with complete clinicopathological data. Exclusion criteria: pregnant or lactating women; patients with a history of breast trauma or surgery; patients who also had other malignancies; patients with other endocrine system diseases that may affect the results of this study; patients with immune system disorders, severe cognitive impairment or history of psychiatric disorders. This study was approved by the institutional review board at our hospital with code number (2021-RE-096).

Instruments and examination methods

Instruments: Mindray Resona 8 color Doppler ultrasound system. The probe used for 2-D and elastography was 5-14 MHz. The probe used for contrast and MFI was 3-9 MHz. The instruments were equipped with UE and CEUS analysis software. SonoVue (Bracco, Italy) was used as the contrast agent.

Routine ultrasound examination: The patient was placed in a supine position with both arms raised to sufficiently expose the breast and axilla for ultrasound examination. After the detection of lesions, the morphology, boundaries, internal echogenicity of the lesions were recorded for BI-RADS classification. Irregular morphology, vertical growth, bordered hyperechogenic halo, edge opacity, microcalcification, and posterior echo attenuation were considered as indicators of malignancy. Lesions meeting 1, 2 and 3 indicators were classified as Class 4a, 4b, and 4c respectively, while those meeting 4 indicators or above were classified as Class 5. CEUS, UE, and MFI were performed on lesions with BI-RADS category 4.

UE examination was performed using strain elastography (STE) and shear-wave elastography: the probe touched the skin lightly without applying extra pressure and the probe was kept perpendicular to the skin. After starting the STE mode, the size and location of the area of interest were adjusted and the mass was placed in the center of the elastic imaging area. The area of interest covered some normal glands or adipose tissue around the mass. The patient was asked to hold her breath until there was a stable elastic image with no obvious artifact. Elastic data measurement: press "Measure", select "Young's modulus (E)". After tracing the mass area, the system automatically calculates the Emean, Emax, Emin and Esd. By adjusting the corresponding knob to select Shell (1 mm, 2 mm, 3 mm, etc.), the system automatically calculates Emean, Emax, Emin and Esd of Shell around the tumor area. Care was taken to keep the bump sufficiently distant from the boundary of the elastic region of interest so that the Shell did not go beyond the zone of interest border.

CEUS and MFI were performed as follows: The cut surface with the most abundant blood flow and well-characterized vascularity of the lesion were selected to start the CEUS CnTI, which was performed in a double amplitude contrast mode with rapid bolus injection of 4.8 mL of contrast agent by the antecubital vein, followed by injection of 5.0 mL of 0.9% sodium chloride solution into the punch tube. Continuous video recording (at least 2 minutes) was performed as soon as the timer was started, and images were saved for analysis. The patient was instructed to breathe calmly during the contrast procedure, and the operator placed the probe lightly on the skin in front of the lesion to avoid undue pressure affecting the contrast agent microvascular imaging. The enhancing time, intensity, uniformity, boundary, morphology and the change of lesion extent were observed.

Image analysis and diagnostic criteria

Two sonographers with specialized training and more than five years of experience in ultrasound were selected to do image analysis. A third highly experienced physician was consulted once there was a disagreement, and a final decision was made upon discussion. The patient data and the pathologic results of the lesions were all unknown to the diagnostic physicians.

Elastography was measured according to the elastic diagnostic reference standard: shear-wave elastography Shell 2 mm: Emax value >98 kPa indicates malignancy and Emax value <98 kPa indicates benign.

CEUS positive indicators: 1. High enhancement when peaking; 2. Heterogeneous enhancement or with filling defect; 3. The lesion begins to enhance earlier than the peripheral breast tissue; 4. Enlarged lesion area after enhancement; 5. Edge irregular or burr-like after enhancement; 6. Radiating or twisting vessels can be seen around or inside the lesion. CEUS negative indicators: 1. Low, equal or none enhancement when peaking; 2. Homogeneous enhancement; 3. The lesion begins to enhance equal or later than the peripheral breast tissue; 4. The lesion area stays unchanged or decreased after enhancement; 5. Smooth edge of lesion after enhancement; 6. The lesion shows capsular enhancement. Each positive indicator was scored 1 point, and negative indicators were scored 0 point with a total score of 0-6 points.

The following vascular characteristics were observed by MFI: the number of vessels in the lesion, perforating vessels, the angle between the trunk and branches, the course of the vessel, and the microangioconstruction (blood supply, vessel morphology).

Statistical analysis

All data were analyzed using SPSS 20.0 software. With pathological results as the "gold standard", the sensitivity, specificity, accuracy of UE, CEUS, MFI and UE + CEUS + MFI in the diagnosis of BI-RADS category 4 lesions were calculated by constructing receiver operating characteristic (ROC) curves. Categorical data were expressed as n (%) and compared using a Chi-Square test. The differences between the areas under the ROC curves were compared using the Z test. $P<0.05$ was considered significant.

Results

Pathologic results of breast lesions

Postoperative histopathology confirmed 31 benign and 78 malignant lesions out of 109 breast lesions. Malignancies included invasive carcinoma (n=58), intraductal carcinoma (n=4), invasive lobular carcinoma (n=3), intraductal papillary carcinoma (n=2), high-grade intraductal carcinoma (n=2), intermediate grade ductal carcinoma (n=1), papillary carcinoma with ductal in situ (n=1), invasive micropapillary carcinoma with intraductal carcinoma (n=1),

Table 1. Contrast-enhanced ultrasound features of breast lesions

Enhancement characteristic	Pathologic findings		χ^2/t	P
	Benign	Malignant		
Enhancement rate			13.8920	0.0010
Slow progression	2	0		
Meanwhile	14	15		
Fast forward	15	63		
Augmentation sequence			8.6592	0.0132
Centrifugation	1	5		
Diffusivity	22	31		
Tropism	8	42		
Degree of enhancement			8.0613	0.0448
None	2	1		
Low	7	8		
Median	10	18		
High	12	51		
Lesion borders			4.8641	0.0274
Clear	17	25		
Blurring	14	53		
Contrast agent distribution			9.8781	0.0017
Uniformity	21	27		
Uneven	10	51		

invasive poorly differentiated carcinoma (n=1), invasive carcinoma with surrounding intraductal carcinoma (n=1), high grade ductal adenocarcinoma in situ (n=1), high-grade ductal carcinoma in situ (n=1), poorly differentiated carcinoma (n=1), and ductal hyperplasia with local carcinomatosis (n=1).

CEUS features of breast lesions

The contrast enhancement characteristics of malignant and benign lesions were compared according to the postoperative histopathologic results. Th results showed that there were significant differences in contrast enhancement characteristics between 78 malignant lesions and 31 benign lesions ($P<0.05$), as shown in **Table 1**.

Vascular features on MFI of breast lesions

The comparison of angiographic imaging vessel characteristics between 78 malignant lesions and 31 benign lesions showed significant differences in the number of vessels, perforators, genotyping of the main stem to branch angle, vessel course, and blood supply methods in the microvasculature ($P<0.05$), as shown in **Table 2**.

Comparison of adjusted BI-RADS between CEUS and UE

BI-RADS categories before and after adjustment were analyzed by comparing pathological outcomes. Among the 78 malignant lesions, 11 were classified by routine ultrasound as BI-RADS category 4a, 43 as category 4b, and 24 as category 4c; the Diagnostic results of UE + CEUS revealed 0 cases of BI-RADS category 3 and 4a, 4 cases of category 4b, 5 cases of category 4c and 69 cases of category 5. Among the 31 patients with benign lesions, 20 were classified as BI-RADS category 4a, 11 as category 4b, and 0 as category 4c by routine ultrasound. According to the results of UE + CEUS, there were 22 cases of BI-RADS category 3, 6 cases of category 4a, 0 case of category 4b, 3 cases of category 4c, and 0 cases of category 5, as shown in **Table 3**.

Ultrasound performance in benign and malignant lesions

Benign lesions: Routine ultrasound showed a hypoechoic mass in the outer upper quadrant of the right breast with irregular morphology, which was classified as BI-RADS category 4a, as shown in **Figure 1A-(1)**. Elastography showed that most of the lesions and surrounding tissues were completely blue, and the CEUS showed that the enhancement started earlier than the peripheral breast tissue, with low enhancement at the peak, as shown in **Figure 1A-(2)** and **1A-(3)**. MFI suggested that the blood flow signal was abundant, the angle between the main stem and the branch was not at a right angle, and the vessel went off center, as shown in **Figure 1A-(4)**. Pathology suggested adenosis.

Malignant lesions: Routine ultrasound showed an extremely hypoechoic mass in the lower quadrant of the right breast inner quadrant with irregular morphology and rough edge, classified as BI-RADS category 4a, as shown in **Figure 1B-(1)**. Elastography showed that the lesions were mostly blue and surrounding tissues were red. CEUS showed that the beginning of enhancement was earlier than that of

Table 2. Vascular features on micro-flow imaging of breast lesions

Indicators of vascular characteristic	Pathologic findings		χ^2/t	P
	Benign	Malignant		
Number of vessels			4.6811	0.0305
Not enriched	7	6		
Abundance	24	72		
Penetrating vessel			17.8410	<0.0001
No	25	27		
Yes	6	51		
The angel between the main stem and branches of the vessels			37.6010	<0.0001
Non-orthogonal	26	16		
Right angle	5	62		
Blood vessel orientation			9.6421	0.0019
Acentric	29	50		
Centric	2	28		
Blood supply mode			54.3850	<0.0001
Non-blood supply	4	1		
Peripheral vascular	16	1		
Direct vascular branching	7	46		
Penetrating vascular branching	2	18		
Penetrating vascular	2	6		
Central large vascular	0	6		
Vascular morphology			66.2740	<0.0001
Non-vascular	4	1		
Linear	7	1		
Treelike	13	1		
Residual roots	7	47		
Crab foot	0	28		

Table 3. Comparison of adjusted BI-RADS between CEUS and UE

Diagnosis	Number	Pathology results	
		Benign	Malignant
BI-RADS			
4a	31	20	11
4b	54	11	43
4c	24	0	24
Adjusted BI-RADS			
3	22	22	0
4a	6	6	0
4b	4	0	4
4c	8	3	5
5	69	0	69

the peripheral breast tissue, the peak was hyperenhanced, the extent of the lesion was increased after enhancement, the margin was spiculated, and radial vascular shadow was seen around it, as shown in **Figure 1B-(2)** and **1B-(3)**. MFI suggested abundant blood flow signals, penetrating from the periphery of the lesion into the interior, with the mainstem at a right angle to the branch angle, and the vessel coursing centrally, as shown in **Figure 1B-(4)**. Pathology suggested invasive carcinoma.

Diagnostic values of UE, CEUS, MFI, and UE + CEUS + MFI

ROC curves showed that the AUC values of UE, CEUS, MFI, and UE + CEUS + MFI for diagnosis were 0.8495, 0.8629, 0.9084, and 0.9390, respectively, which suggested a high diagnostic accuracy of the combination of the three modalities, as shown in **Figure 2** and **Table 4**.

Diagnostic efficacy of UE, CEUS, MFI, and UE + CEUS + MFI

The sensitivity, specificity, and accuracy of UE, CEUS, MFI and UE + CEUS + MFI were as follows: 65.38%, 70.51%, 88.46%, 85.90%;

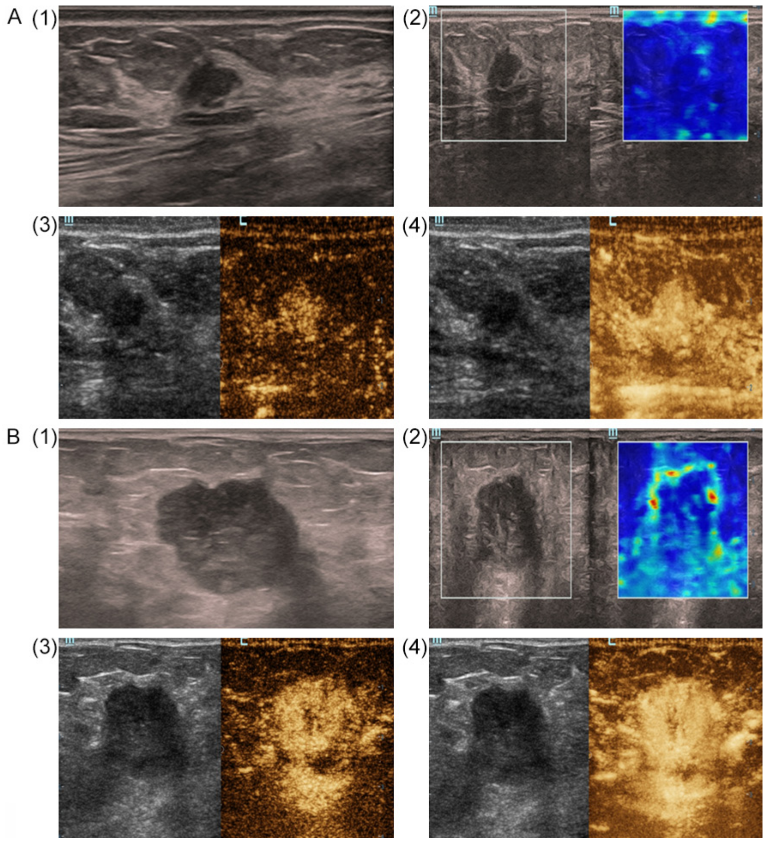

Figure 1. Ultrasound images of benign and malignant lesions. A: Sonographic images of benign lesions using different techniques; B: Sonographic images of malignant lesions (1) Conventional ultrasound; (2) Ultrasound elastography; (3) Contrast enhanced ultrasound; (4) Micro-flow imaging.

83.87%, 87.10%, 74.19%, 90.32%; 83.34%, 85.56%, 89.16%, 92.07%; as shown in **Table 5**.

Discussion

The BI-RADS classification has been widely used in the diagnosis of breast disease, and its accurate judgment is essential for clinical diagnosis and treatment [24]. The results of this study showed that the combination of ultrasound elastography (UE), contrast-enhanced ultrasound (CEUS), and MFI can improve the preoperative diagnostic efficacy of BI-RADS classification, which will provide valuable information for more accurate and personalized clinical treatment.

Long-term clinical studies have found that the stiffness of lesions is related to their benign or malignant properties, and increased stiffness suggests an elevated risk of malignancy [25]. UE is a technique that can obtain the information of tissue stiffness based on the histobiologic changes of tissue caused by pathologic structure changes, and the tissue stiffness is closely related to the pathologic structure within it [26]. It is now extensively applied to superficial organs such as thyroid and breast. Malignant lesions usually have a greater stiffness than benign lesions due to increased extracellular matrix components [27, 28]. UE can provide high-quality images and has advantages in diagnosing the nature of breast masses. It can obtain contrast-enhanced images by exploiting the non-linear effect of gas microbubbles in the blood in the acoustic field and the resulting intense backscatter. Also, it can comprehensively display breast morphology and intralesional blood flow by utilizing the elastography difference between lesional tissue and adjacent normal tissue, which benefits the evaluation of the nature and prognosis of breast masses [29, 30]. Our study showed that the AUC, sensitivity, specificity, and accuracy of UE for the diagnosis were 0.8495, 65.38%, 83.87%, and 83.34% respectively. Nevertheless, there might be some overlap in the elastic coefficients of tissues in different cases. Lesions that are too deep or have some fluid in them may cause a UE diagnosis deviation.

CEUS is one of the sensitive methods to diagnose breast masses, which can enhance the blood flow signal by injecting contrast agent which can create an air-liquid interface of contrast microbubbles to enhance the Doppler signal of blood flow. This enables an increase in the contrast of tissue blood flow in ultrasound images for the detection of low-velocity blood flow [31]. Through the acoustic scattering characteristics of contrast agent microbubbles, it can increase the acoustic impedance difference between lesion tissue and surrounding normal tissue, clearly showing the abnormal blood perfusion of lesion tissue that cannot be

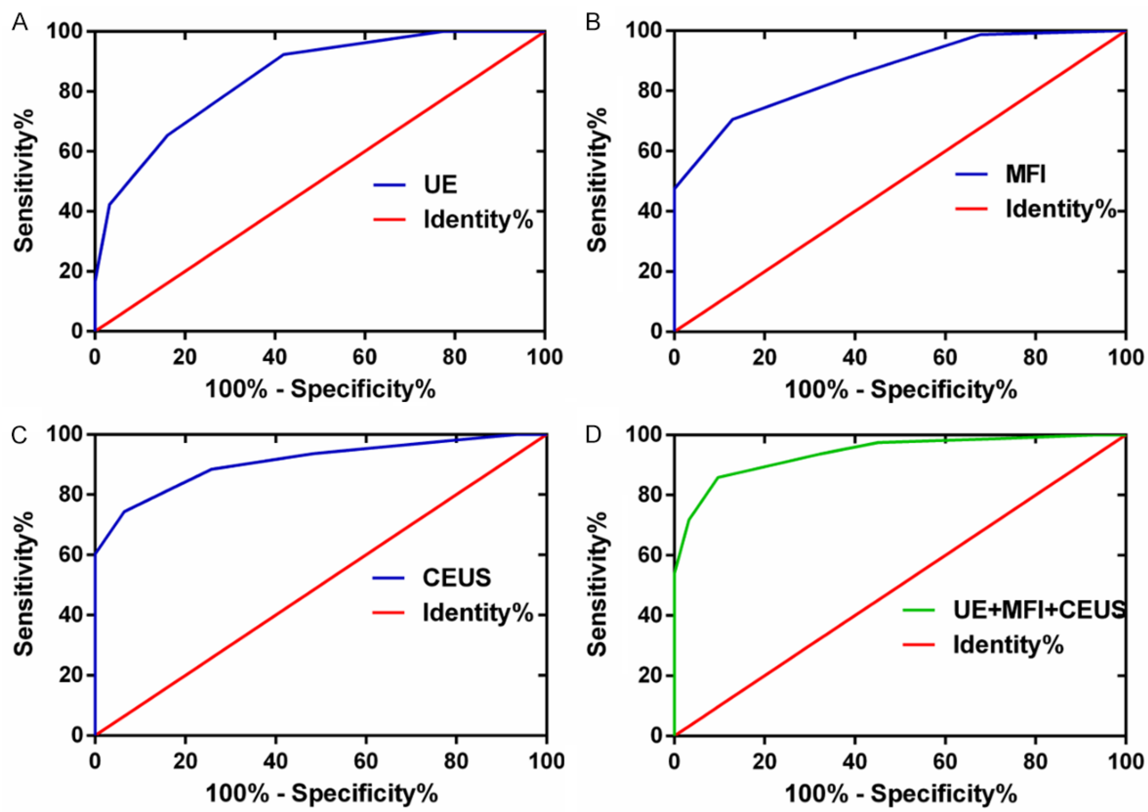

Figure 2. ROC curves of UE, CEUS, MFI, and UE + CEUS + MFI. A: The sensitivity and specificity for diagnosis using ultrasound elastography; B: The sensitivity and specificity for diagnosis using micro-flow imaging; C: The sensitivity and specificity for diagnosis using contrast enhanced ultrasound; D: The sensitivity and specificity for diagnosis using the combination of UE, MFI and CEUS.

Table 4. Area under the ROC curve

	AUC	SE	P	95% HR
UE	0.8495	0.0398	<0.0001	0.7715 to 0.9274
MFI	0.8629	0.0346	<0.0001	0.7951 to 0.9308
CEUS	0.9084	0.0272	<0.0001	0.8550 to 0.9618
UE + MFI + CEUS	0.9390	0.0219	<0.0001	0.8960 to 0.9820

Table 5. Diagnostic efficacy

	Sensitivity (%)	Specificity (%)	Accuracy (%)
UE	65.38	83.87	83.34
MFI	70.51	87.10	85.56
CEUS	88.46	74.19	89.16
UE + MFI + CEUS	85.90	90.32	92.07

visualized by conventional high-frequency color Doppler ultrasound, thus improving the diagnostic accuracy. In our study, the AUC, sensitivity, specificity, and accuracy of CEUS were 0.9084, 88.46, 74.19, and 89.16% respectively; But CEUS has its limitations because of its lower sensitivity to small vessels and microvessels compared to larger vessels. The MFI technique, on the other hand, can visualize the microvessels of lesions. By displaying the blood perfusion images of the lesions superposed over time, it can more comprehensively and intuitively present the microvascular structure of breast lesions [21]. This study also showed that the diagnostic accuracy of MFI was higher than that of UE and CEUS with the AUC, sensitivity, specificity, and accuracy of 0.8629, 70.51%, 87.10%, and 85.56% respectively. Chao et al. [32] found that about 85% of benign and 95% of malignant lesions of the breast can be detected through their blood flow signals. Tumor development requires the formation of new blood vessels [33]. Blood vessels are generated in both benign and malignant lesions, but their morphology is not consistent. The vessels in benign lesions are mostly evenly distributed and of uniform vascular diameter, while in malignant lesions, the vessels are long, meandering and thick with many branches and irregular morphology [34]. The mammary gland is a superficial organ with insufficient blood supply, and the diameter of the lesion is generally thinner, resulting in a slower blood velocity [35]. Because of this, CEUS is not an ideal choice for detecting microvessels. In the present study, the diagnostic sensitivity, specificity, and accuracy of the combination of the three diagnostic modalities were found to be 85.90%, 90.32%, and 92.07% respectively. The result suggests that the combination of three can acquire better sensitivity and accuracy, which can effectively improve the diagnostic ability for breast lesions. As a consequence, it might help patients to avoid needle biopsy for some BI-RADS category 4 lesions that do not require clinical intervention. At the same time, it does not delay the optimal treatment interval for some malignant lesions, which is an ideal non-invasive method for clinical diagnosis.

However, there are some limitations in this study. The sample size of this study might be small and the pathologic types were not comprehensive enough, lacking some rare types of tumor such as medullary carcinoma, mucinous carcinoma, neuroendocrine carcinoma, and hemangioma. In addition, this study was only a retrospective analysis. Therefore, a well-designed randomized controlled trial with prospective data collection and sample size calculation is warranted to make the findings in our study more objective and convincing.

In summary, the diagnostic value of CEUS, UE, and MFI for breast cancer lesions varies, but their combined diagnosis outperforms the sole detection by each one and they are complementary. This can effectively improve the diagnostic accuracy of breast lesions, which may provide more information for clinical diagnosis and treatment.

Acknowledgements

This work was supported by major science and technology project of Anhui Province (No. 201903a07020013).

Disclosure of conflict of interest

None.

Address correspondence to: Lei Ye, Department of Ultrasound Medicine, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, No. 1 Swan Lake Road, New District of Government and Culture, Hefei 230036, Anhui, China. Tel: +86-15905694936; E-mail: ylultras888@163.com

References

[1] Kamińska M, Sygit K, Budny A, Surdyka D, Kukiełka-Budny B and Burdan F. Primary and secondary prevention of breast cancer. Ann Agric Environ Med 2017; 24: 549-553.

[2] Peairs KS, Choi Y, Stewart RW and Sateia HF. Screening for breast cancer. Semin Oncol 2017; 44: 60-72.

[3] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71: 209-249.

[4] Chen W, Zheng R, Baade P and Zhang S. Zeng h, Bray F, Jemal A, Yu XQ and He J. Cancer statistics in China. CA Cancer J Clin 2016; 66: 115-132.

[5] Ginsburg O, Bray F, Coleman MP, Vanderpuye V, Eniu A, Kotha SR, Sarker M, Huong TT, Allemani C, Dvaladze A, Gralow J, Yeates K, Taylor C, Oomman N, Krishnan S, Sullivan R, Kombe D, Blas MM, Parham G, Kassami N and Conteh L. The global burden of women's cancers: a grand challenge in global health. Lancet 2017; 389: 847-860.

[6] Barrios CH, Reinert T and Werutsky G. Global breast cancer research: moving forward. Am Soc Clin Oncol Educ Book 2018; 38: 441-450.

[7] Bendifallah S and Canlorbe G. Common benign breast tumors including fibroadenoma, phyllodes tumors, and papillary lesions: guidelines. J Gynecol Obstet Biol Reprod (Paris) 2015; 44: 1017-1029.

[8] Meretoja T and Leidenius M. Nuoren naisen rintakyhmy. Duodecim 2015; 131: 1353-1359.

[9] Sevim Y, Kocaay AF, Eker T, Celasin H, Karabork A, Erden E and Genc V. Breast hamartoma: a clinicopathologic analysis of 27 cases and a literature review. Clinics 2014; 69: 515-523.

[10] Badve SS and Gökmen-Polar Y. Ductal carcinoma in situ of breast: update 2019. Pathology 2019; 51: 563-569.

[11] Tsagkaraki IM, Kourouniotis CD, Gomatou GL, Syrigos NK and Kotteas EA. Orbital metastases of invasive lobular breast carcinoma. Breast Dis 2019; 38: 85-91.

[12] Rodgers KM, Udesky JO, Rudel RA and Brody JG. Environmental chemicals and breast cancer: an updated review of epidemiological literature informed by biological mechanisms. Environ Res 2018; 160: 152-182.
[13] Guo R, Lu G, Qin B and Fei B. Ultrasound imaging technologies for breast cancer detection and management: a review. Ultrasound Med Biol 2018; 44: 37-70.
[14] Zhang Y, Ma AD and Jia HX. Correlation between molybdenum target mammography signs and pathological prognostic factors of breast cancer. J Biol Regul Homeost Agents 2016; 30: 219-225.
[15] Heck L and Herzen J. Recent advances in X-ray imaging of breast tissue: from two-to three-dimensional imaging. Physica Medica 2020; 79: 69-79.
[16] Houssami N, Turner RM and Morrow M. Meta-analysis of pre-operative magnetic resonance imaging (MRI) and surgical treatment for breast cancer. Breast Cancer Res Treat 2017; 165: 273-283.
[17] Lo G, McLaughlin A, Jacques A, Dhillon R, Porter G, Jayaratne T, Bose S and Bourke A. Does Medicare-eligible high-risk breast cancer screening MRI target the right women? J Med Imaging Radiat Oncol 2020; 64: 220-228.
[18] Geisel J, Raghu M and Hooley R. The role of ultrasound in breast cancer screening: the case for and against ultrasound. Semin Ultrasound CT MR 2018; 39: 25-34.
[19] Fang K, Wang L, Huang H, Lan M, Shen D, Dong S and Guo Y. Construction of nucleolin-targeted lipid nanobubbles and contrast-enhanced ultrasound molecular imaging in triple-negative breast cancer. Pharm Res 2020; 37: 145.
[20] Wang XD, Jiang W, Wu W and Liu YN. The value of ultrasonic elastography combined with serum ATF5 in predicting the efficacy of neoadjuvant chemotherapy in breast cancer. Am J Ther 2021; 28: e509-e511.
[21] Du J, Li FH, Fang H, Xia JG and Zhu CX. Microvascular architecture of breast lesions: Evaluation with contrast-enhanced ultrasonographic micro flow imaging. J Ultrasound Med 2008; 27: 833-842.
[22] Li F, Wang Y, Bai B, Wang S and Liu S. Advantages of routine ultrasound combined with contrast-enhanced ultrasound in diagnosing papillary thyroid carcinoma. Ultrasound Q 2017; 33: 213-218.
[23] Wang B, Jiang Ta, Huang M, Wang J, Chu Y, Zhong L and Zheng S. Evaluation of the response of breast cancer patients to neoadjuvant chemotherapy by combined contrast-enhanced ultrasonography and ultrasound elastography. Exp Ther Med 2019; 17: 3655-3663.
[24] Mercado CL. Bi-rads update. Radiol Clin North Am 2014; 52: 481-487.
[25] Pheiffer TS, Thompson RC, Rucker DC, Simpson AL and Miga MI. Model-based correction of tissue compression for tracked ultrasound in soft tissue image-guided surgery. Ultrasound Med Biol 2014; 40: 788-803.
[26] Zhang X, Xiao Y, Zeng J, Qiu W, Qian M, Wang C, Zheng R and Zheng H. Computer-assisted assessment of ultrasound real-time elastography: initial experience in 145 breast lesions. Eur J Radiol 2014; 83: e1-e7.
[27] Yan CX, Luo ZY, Liu XM, Huang PT, Mo GQ, Hong YR, Wen Q, Pan MQ and Weng HF. Ultrasonic scores of conventional ultrasound and ultrasound elastography in the diagnosis of thyroid nodular lesions. Zhonghua Yi Xue Za Zhi 2013; 93: 1630-1633.
[28] Qu XX, Song Y, Zhang YH and Qing HM. Value of ultrasonic elastography and conventional ultrasonography in the differential diagnosis of non-mass-like breast lesions. Ultrasound Med Biol 2019; 45: 1358-1366.
[29] Hao SY, Ou B, Li LJ, Peng YL, Wang Y, Liu LS, Xiao Y, Liu SJ, Wu CJ, Jiang YX, Parajuly SS, Xu P, Hao Y, Li J, Zhi H and Luo BM. Could ultrasonic elastography help the diagnosis of breast cancer with the usage of sonographic BI-RADS classification? Eur J Radiol 2015; 84: 2492-2500.
[30] Zhi H, Xiao XY, Yang HY, Ou B, Wen YL and Luo BM. Ultrasonic elastography in breast cancer diagnosis: strain ratio vs 5-point scale. Acad Radiol 2010; 17: 1227-1233.
[31] Audrey S and Procter S. Employers' views of promoting walking to work: a qualitative study. Int J Behav Nutr Phys Act 2015; 12: 12.
[32] Chao TC, Lo YF, Chen SC and Chen MF. Color Doppler ultrasound in benign and malignant breast tumors. Breast Cancer Res Treat 1999; 57: 193-199.
[33] Szala S and Jarosz M. Tumor blood vessels. Postepy Hig Med Dosw (Online) 2011; 65: 437-46.
[34] Kim ES, Seo BK, Park EK, Woo OH, Jung K, Cho KR, Song SE and Cha J. Significance of microvascular evaluation of ductal lesions on breast ultrasonography: influence on diagnostic performance. Clin Imaging 2018; 51: 252-259.
[35] Jiang Y, Chen W, Luo B, Peng Y, Wang Z, Xu J, Zhou J, Zhou Q, Bao L, Chen L, Chen L, Chen Q, Cong S, Cui K, Cui X, Fang Q, Li F, Li H, Li J, Li J, Li J, Li Q, Li T, Li T, Li Y, Li Z, Liu J, Liu Y, Luo J, Ma B, Ma Z, Nie F, Peng C, Sui X, Sun H, Wang H, Wang J, Wang Y, Wu C, Xiao Y, Xiong H, Xu D, Xue E, Xue L, Yan S, Yang L, Yong Q, Zhan W, Zhang S, Zhang X, Zhang J, Zhou X, Lin X, Yin S and Zhao Q. Chinese association of ultrasound in medicine and engineering, superficial organs and peripheral vessels committee expert consensus on clinical frequently asked questions in breast ultrasonography, June 2018. J Cancer Res Ther 2018; 14: 1463-1468.