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Original Article

Clinical diagnostic value of contrast-enhanced ultrasound combined with ultrasonic elastography in identifying benign and malignant breast tumors

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Abstract: Background: Currently, conventional radiographic examination techniques (conventional ultrasound and mammography) cannot meet the needs of clinical diagnosis of breast cancer and the rate of missed diagnosis or misdiagnosis is relatively high. Objective: The objective of our study was to investigate the diagnostic efficacy and clinical value of contrast-enhanced ultrasound combined with ultrasonic elastography in the diagnosis of benign and malignant breast tumors. Methods: We selected 480 female patients with breast tumors whose BI-RADS classifications were between categories 3-5, with 498 lesions in total, and performed contrast-enhanced ultrasound as well as ultrasonic elastography examinations, respectively. We then used the pattern of multidisciplinary treatment (MDT) of the lesions and performed a combined diagnosis of contrast-enhanced ultrasound and ultrasonic elastography, so that results of the three diagnostic methods were obtained. Pathological examination results were used as the "golden standard" in the qualitative and quantitative analysis of image features and the sensitivity, specificity, positive predictive value, negative predictive value, and the area under the ROC curve of the three diagnostic methods were calculated, respectively. Results: Among 498 lesions, there were 287 malignant tumors (57.63%) and 211 benign tumors (42.37%). The results of contrast-enhanced ultrasound showed that both the initiation time and peak time of the malignant group were earlier than those of the benign group, while the peak intensity was greater than that of the benign group and all of differences were statistically significant ($p<0.05$). The results of ultrasound elastography showed that the score of ultrasound elastography of the malignant group was higher than that of the benign group and the difference was statistically significant ($p<0.001$). The combination of contrast-enhanced ultrasound with ultrasonic elastography, a highly effective method in the diagnosis of benign and malignant breast tumors, resulted with the sensitivity, specificity, positive predictive value, negative predictive value, and the ROC curve area of 95.12% (0.918-0.972), 90.99% (0.861-0.943), 93.49% (0.899-0.960, 93.20% (0.886-0.961), and 0.942 (0.918-0.967), respectively. The above indexes were significantly different from those of the separate use of contrast-enhanced ultrasound or ultrasonic elastography ($p<0.001$). Conclusions: The techniques of contrast-enhanced ultrasound and ultrasonic elastography analyzed the characteristic of breast lesions from different angles and have complementary effects. The combination of them is more conducive to the diagnosis and differential diagnosis of breast tumors and can make up for the shortcomings of either of the single diagnostic method, while significantly improve the accuracy, specificity, and sensitivity of ultrasonic diagnosis of breast lesions. Therefore, combination of the two diagnostic methods has great clinical application prospect and is worthy of application and popularization in clinical practices.

Keywords: Breast tumors, contrast-enhanced ultrasound, ultrasonic elastography, combined diagnosis, diagnostic values

Introduction

Breast cancer is one of the most common malignancies in the females all over the world [1, 2]. The latest data shows that the incidence of breast cancer ranks first among the incidence of malignancy in Chinese women with about 279, 000 new cases each year, while the mortality rate has increased to fifth [3]. Incidence of breast cancer is relatively high and patients are getting younger. It seriously threatens women's physical and mental health and

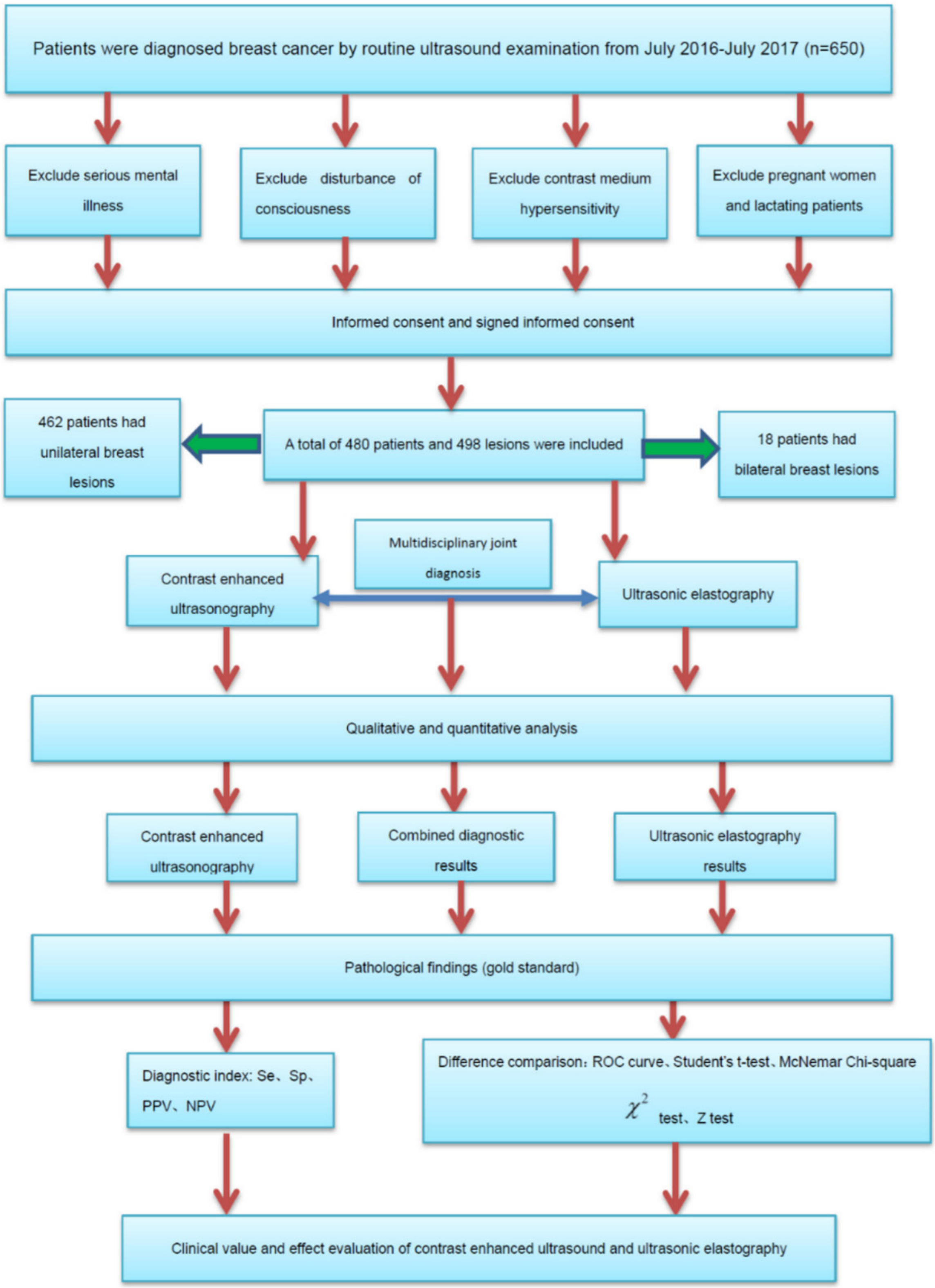

Figure 1. The research flow chart.

therefore is a major public health problem worldwide [4, 5]. Currently, there is no effective primary prevention method for breast cancer, thus early detection and treatment are very important for prevention and treatment of the disease. Early diagnosis and treatment of breast cancer will improve the survival rate of the patients and reduce the fatality rate [6].

Accurate identification of benign or malignant breast tumors is of great significance. It determines the therapeutic regimen and surgical procedures for the patients and even affects the prognosis and survival rate of the patients [6]. Therefore, it has always been the focus of clinical research [7]. At present, the most common imaging methods for diagnosis of breast cancer are ultrasound and mammography and the combination of these two methods is highly sensitive (ranging from 92.6% to 94.4%) [8, 9]. However, due to the radioactivity of mammography, it cannot precisely locate the lump or confirm the blood supply status of the breast lump and it often misses or misdiagnoses atypical small breast cancer or lesions near the chest wall. Conventional ultrasound examinations show poor display of the invasion boundary of the tumor with small calcification, lack of blood supply, or with no blood supply while it has high operating requirements for tumors with a diameter below 1cm. The rate of misdiagnosis was relatively high [10, 11]. Although both CT and MRI have certain diagnostic efficacy [12, 13], they are not conventional imaging methods for breast diseases.

With the development of imaging equipment and diagnostic techniques as well as clinical experiences, the technology of ultrasound elastography and contrast-enhanced ultrasound have been considerably improved in our hospital while more and more of these technologies have been applied to clinical diagnosis and treatment of breast diseases. In clinical practice, we found that the combination of several new ultrasonic technologies is beneficial in making up for the deficiencies and shortcomings of these techniques when used alone and can further improve accuracy of diagnosis and differential diagnosis of breast cancer. In this study, we performed combined diagnosis of breast lumps by the combination of contrast-enhanced ultrasound and ultrasound elastography in order to explore the accuracy, specificity, and sensitivity of this method, which confirmed the diagnostic value of the combination of contrast-enhanced ultrasound with ultrasound elastography in the determination of benign or malignant lesions of breast tumor.

Materials and methods

Research objectives

Six-hundred and fifty female patients diagnosed with breast lesions by routine breast ultrasound in our hospital from July 2016 to July 2017 were randomly selected as research objectives. None of the patients received surgery, radiotherapy, chemotherapy, or any other treatments. Exclusion criteria included: patients with severe mental disorders, consciousness disorders, allergies to ultrasound contrast agents, and pregnancy or lactating. Finally, 480 patients agreed to participate in the research (with a total of 498 lesions while 18 of the patients were detected with 1 lesion in both sides of the breast) were included in this study. This study was approved by the Ethics Committee of Cangzhou Central Hospital. All of the patients were informed with the content.

The 498 lesions were classified between categories 3-5 by BI-RADS. 482 patients were aged 17-91 years with the mean age of (53.2 ± 9.7) years. The diameters of the lesions were 4.9 mm-145.8 mm with average diameter of 42.8 mm. All of the lesions were examined by contrast-enhanced ultrasound and ultrasonic elastography before surgery in order to decide operation and treatment methods. The diagnoses for all these 498 lesions were confirmed by histopathologic examination with specimens obtained by a surgical resection or biopsy. The histopathological diagnosis was considered as the gold standard. The workflow is presented in **Figure 1**.

Examination methods

Contrast-enhanced ultrasound: We chose the SIEMENS ACUSON-S2000 color Doppler ultrasonic diagnostic instrument for ultrasound, with the probe model of 4C1 and the frequency of 2.5-5 MHz. SonoVue (Bracco Corporation, Italy) was used as ultrasound contrast agent and the microbubbles were six sulfur hexafluoride (SF_6) of phospholipid microcapsules with average diameter of 2.5 μm and good stability. The patients were in supine position or semi supine position with both hands stretched out to fully expose the breast. Routine ultrasound and color Doppler ultrasound were performed. The sections with most abundant blood flow were selected as the ultrasonic contrast section. We switched to the contrast condition and turned on the double real-time display mode which would show the two-dimensional gray scale image and the contrast-enhanced ultrasound image of the same section, simultaneously. After adjusting the gray scale, depth, and focus according to the size and position of the lesion, we rapidly injected 4.8 mL of the prepared contrast agent (SonoVue) solution from the cubital vein followed by rapid injection of 5 mL normal saline to flush the tube, while switching on the original dynamic data storage button and the screen timer. During the examination, the patient should keep quiet breathing and the position and angle of the probe should be fixed to ensure that the section with the most abundant blood flow in the entire imaging process remains unchanged. The storage time was 180 seconds and the ultrasound sonogram of the lesion should be observed during the examination, observing for 6 minutes if necessary. The patient stayed for observation for 15 to 20 minutes after the contrast examination. The examination was then complete if no adverse reaction occurred.

After the imaging process, saved dynamic images were stored in Dicom format and image analysis and data measurement were carried out. Qualitative observation indexes included: enhancement intensity, enhancement phase, enhancement sequence, enhancement uniformity, crab paw sign, nourishing blood vessel, enhancement posterior border, and enhanced morphology. Quantitative analysis was performed using time-intensity curve (TIC) analysis. The parameters included: arrival time (AT), time to peak (TTP), and peak intensity (PI) [14].

Ultrasonic elastography examinations: Ultrasonic elastography examinations were performed using Hitachi HV-900 with a 5-13 MHz linear transducer (Hitachi Medical, Tokyo, Japan). The patients were in supine position and bilateral breast areas were fully exposed. First, conventional ultrasound examinations were performed to determine the position of the lesion. We placed the probe at the site of the lesion, noting that the direction of the probe force should be perpendicular to the skin. We controlled the pressure and held the probe against the lesion with slight vibrations. We then captured and saved the image when the pressure was 2-4 on the display screen of the controller. We then analyzed and classified the breast lesions according to the color of the lesion in the elastographic images. The scoring system described by Itoh was used to score the elastograms of lesions from 1 to 5 [15]: benign lesions <3 points while malignant lesions ≥ 4 points. Meanwhile, elastic strain ratio [16] was used to compare the results: SR$\leq$3.48 was considered benign while SR$\leq$3.48 was considered malignant.

Image processing and analysis

The contrast-enhanced ultrasound data and ultrasonic elastography data of the lesions were analyzed and recorded in detail by 2 ultrasound imaging physicians (not the operator of either of the examinations) with 15-20 years of experience, respectively, without knowing the clinical symptoms, pathological findings, and other imaging data. Then multidisciplinary diagnosis and treatment (MDT) model was adopted. The operators of the examinations and the imaging physicians underwent joint consultation to make a comprehensive analysis of the imaging features and to make a joint diagnosis. If both diagnoses were consistent, the diagnosis was used as the combined diagnostic result. If the diagnoses were inconsistent, another experienced physician was invited to make an independent diagnosis. Each investigator clarified the reasons for making the diagnoses and a consensus was reached in cases of discrepancies.

Statistical methods

SPSS 20.0 was used for statistical analysis. Enumeration data were expressed by mean (percentage) and the difference of image features between benign and malignant contrast-enhanced ultrasound images were analyzed by Chi-square test. Quantitative data (the parameters in the time-intensity curve) were expressed by mean ± standard deviation and t-test was used to analyze the difference between the benign group and malignant group. The pathological results of operation or puncture were used as the gold standard and sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) of the diagnosis of benign or malignant breast lesions by contrast-enhanced ultrasound, ultrasonic elastography, or the combination of the two examinations were calculated. McNemar's Chi-square test was used to compare diagnos-

Table 1. The pathological diagnosis of 498 lesions

Tumor property	Types	Case (n)	Ratio (%)
Malignant	Invasive ductal carcinoma	146	29.32%
	Ductal carcinoma in situ	61	12.25%
	Invasive lobular carcinoma	38	7.63%
	Mixed infiltrating carcinoma	17	3.41%
	Medullary carcinoma	14	2.81%
	Mucinous adenocarcinoma	11	2.21%
Benign	Fibroadenoma (13.86%)	69	13.86%
	Adenosis of breast (9.24%)	46	9.24%
	Hyperplasia of mammary glands	31	6.22%
	Inflammatory nodule	27	5.42%
	Intraductal papilloma	15	3.01%
	Lipoma	14	2.81%
	Breast cyst	9	1.81%
Summation		498	100%

tic effects of the three diagnostic methods. Diagnostic efficiency of the three methods was analyzed by ROC curve analysis. Confidence intervals for area under the ROC curve (Az) values were estimated on the basis of a 95% confidence level. Inspection level $\alpha=0.05$, $p<0.05$ represents statistical significance.

Results

Pathological diagnosis

Tissue specimens of 498 breast lesions were obtained either from surgical resection (n=452) or from a needle biopsy (n=47). According to the pathological findings, there were 287 malignant tumors (57.63%) and 211 benign tumors (42.37%). Among the malignant lesions, 146 were invasive ductal carcinomas (29.32%), 61 were ductal carcinomas in situ (12.25%), 38 were invasive lobular carcinomas (7.63%), 17 were mixed invasive carcinomas (3.41%), 14 were medullary carcinomas (2.81%), and 11 were mucinous adenocarcinomas (2.21%). Among the benign lesions, 69 were fibroadenomas (13.86%), 46 were adenosis of mammary glands (9.24%), 31 were hyperplasia of mammary glands (6.22%), 27 were inflammatory nodules (5.42%), 15 were intraductal papillomas (3.01%), 14 were lipomas (2.81%), and 9 were breast cysts (1.81%), as shown in **Table 1**.

Contrast-enhanced ultrasonographic features of benign and malignant breast tumors

The contrast-enhanced ultrasonographic features of typical malignant breast tumors were high enhancement (98.0%), increased phase forward (95.5%), enlarged range of lesions after enhancement (91.6%), centripetal enhancement (54.0%), inhomogeneous enhancement (75.6%), crab paw signs (60.3%), nourishing blood vessels (63.8%), unclear boundary after enhancement (61.3%), and irregular morphology after enhancement (80.5%). The above contrast-enhanced ultrasonographic features of the malignant group were significantly different from those of the benign group ($p<0.001$), as shown in **Table 2**. By comparing quantitative parameters of the time-intensity curve, it can be concluded that the initiation time and peak time of the malignant group were earlier than those of the benign group, while the peak intensity was greater than that of the benign group. All of the differences were statistically significant ($p<0.05$), as shown in **Table 3**. The contrast-enhanced ultrasonographic curve of the malignant group usually showed an ascending steep peak which lasted for a long time. There could be a long period of "platform" that descended slowly, thus the overall pattern of the curve was "fast-up and slow-down".

Ultrasonic elastography features of benign and malignant breast tumors

In this study, we used an ultrasonic elastography scoring method for the differential diagnosis of benign and malignant breast tumors. Among the malignant lesions diagnosed by pathology, 154 were scored 4 points (55.0%) and 10 were scored 5 points (36.8%). Among the benign lesions, 89 were scored 1 point (40.3%), 68 were scored 2 points (30.8%), and 33 were scored 3 points (14.9%). Ultrasonic elastographic scores of the malignant group were higher than those of the benign group and the differences were statistically significant ($p<0.001$), as shown in **Table 4**.

Comparison of the three methods in diagnosis efficiency of benign and malignant breast lesions

The pathological examination results were used as the "golden standard" to compare diagnosis efficiency of benign and malignant breast

Table 2. Comparison of contrast-enhanced ultrasonographic features of benign and malignant breast tumors

Factor	Benign lesion group (n=211)	Malignant lesion group (n=287)	X^2	P
Strength enhancement			71.72*	<0.001
Hyperechoic	152 (72.0%)	281 (98.0%)		
Isoechoic	30 (14.2%)	3 (1.0%)		
Hypotonic	29 (13.7%)	3 (1.0%)		
Enhancement phases			98.35*	<0.001
Increased phase forward	126 (59.7%)	274 (95.5%)		
Phase forward	64 (30.3%)	10 (3.5%)		
Slow forward	21 (10.0%0	3 (1.0%)		
Enhanced range of lesions			269.91*	<0.001
Enlarged range of lesions after enhancement	40 (19.0%)	263 (91.6%)		
No change	127 (60.2%)	16 (5.6%)		
Reduced	18 (8.5%)	3 (1.0%)		
Difficult to distinguish	26 (12.3%)	5 (1.7%)		
Enhancement order			34.94*	<0.001
Centripetal enhancement	58 (27.5%)	155 (54.0%)		
Non directional	153 (72.5%)	132 (46.0%)		
Enhanced uniformity				
Uniformity	148 (70.1%)	70 (24.4%)	103.42*	<0.001
Inhomogeneous enhancement	63 (29.9%)	217 (75.6%)		
Crab paw signs			146.29*	<0.001
No	196 (92.9%)	114 (39.7%)		
Yes	15 (7.1%)	173 (60.3%)		
Nourishing blood vessels			126.97*	<0.001
No	183 (76.7%)	104 (36.2%)		
Yes	28 (13.3%)	183 (63.8%)		
Boundary after enhancement			75.43*	<0.001
Clear	123 (58.3%)	106 (36.9%)		
Unclear	55 (26.1%)	176 (61.3%)		
Indistinguishable	33 (15.6%)	5 (1.8%)		
Morphology after enhancement				
Regular	150 (71.1%)	50 (17.4%)	215.09*	<0.001
Irregular	30 (14.2%)	231 (80.5%)		
Indistinguishable	31 (14.7%)	6 (2.1%)		

Legends: *represents statistically significant differences between the benign group and the malignant group (p<0.001).

lesions by contrast-enhanced ultrasound, ultrasonic elastography, or the combination of the two methods. As shown in **Table 5**, 295 malignant lesions were diagnosed by contrast-enhanced ultrasound and 37 benign lesions were misdiagnosed. The misdiagnosis rate was 17.5%. Meanwhile, 203 benign lesions were diagnosed and 29 malignant lesions were missed. The rate of missed diagnosis was 10.1%. As for ultrasonic elastography, 275 malignant lesions were diagnosed and 29 benign lesions were misdiagnosed. The misdiagnosis rate was 13.7%, while 223 benign lesions were diagnosed and 41 malignant lesions were missed. The rate of missed diagnosis was 14.3%. The combination of contrast-enhanced ultrasound and ultrasonic elastography diagnosed 292 malignant lesions and misdiagnosed 19 benign lesions. The misdiagnosis rate was 9.0%, while it diagnosed 206

Table 3. Comparison of the quantitative parameters in the time-intensity curve of the benign and malignant groups

Pathological findings	Case (n)	Initiation time of enhancement (s)	Time of reaching peak (s)	Peak intensity (dB)
Benign	211	12.45±2.26	23.84±3.19	12.38±3.80
Malignant	287	11.94±2.51	22.71±3.17	20.31±2.65
T		2.377	3.934	-27.422
P		0.018	<0.001	<0.001

Table 4. Comparison of the ultrasonic elastographic scores of benign and malignant tumors (n, %)

Pathological findings	Case (n)	Score of USE					X^2	P
		1	2	3	4	5		
Benign	211	86 (40.8%)	64 (30.3%)	32 (15.2%)	21 (10.0%)	8 (3.8%)	288.07	<0.001
Malignant	287	3 (1.0%)	8 (2.8%)	30 (10.5%)	146 (50.9%)	100 (34.8%)		

Table 5. Comparison of the diagnosis results of benign and malignant breast tumors by contrast-enhanced ultrasound, ultrasonic elastography, or the combination of the two methods (n)

Methods of examination	Inspection result	Pathological findings		McNemar x^2	P
		Malignant	Benign		
CEUS	Malignant	258	37	0.742	0.389
	Benign	29	174		
USE	Malignant	246	29	1.729	0.189
	Benign	41	182		
Combined	Malignant	273	19	0.485	0.486
	Benign	14	192		

benign lesions and missed 14 malignant lesions. The rate of missed diagnosis was 4.9%. The results of the three methods were compared with pathological diagnosis results by McNemar's test, the *P* values were all >0.05. This suggested that the differences were not statistically significant, indicating that all the three methods were of good diagnostic value for breast tumors.

Comparison of the diagnostic efficacy of contrast-enhanced ultrasound, ultrasonic elastography, and the combination in the diagnosis of breast lesions

Table 6 shows the ratio of diagnostic efficacy of the three diagnostic methods (%) and 95% CI. It can be concluded that the sensitivity of contrast-enhanced ultrasound combined with ultrasonic elastography in the diagnosis breast tumors was 95.21% (0.918-0.972), the specificity was 90.99% (0.861-0.943), the positive predictive value was 93.49% (0.899-0.960), and the negative predictive value was 93.20% (0.886-0.961). All the indexes of the combined group were higher than that of the contrast-enhanced ultrasound group or the ultrasonic elastography group. The Chi-square test showed that the *P* values were less than 0.05, indicating that the differences were statistically significant.

Comparison of the ROC curve of contrast-enhanced ultrasound, ultrasonic elastography, and combination in the diagnosis of breast lesions

The pathological (or puncture) examination results were used as the "golden standard". ROC curves were obtained from the diagnosis of 498 breast lesions by contrast-enhanced ultrasound, ultrasonic elastography, or the combination of them while the areas under the ROC curves were calculated. The area under the curve of the combined group was 0.942 (0.918-0.967), which was larger than the area of 0.867 (0.832-0.902) in the contrast-enhanced ultrasound group as well as the area of 0.852 (0.815-0.889) in the ultrasonic elastography group (Z=3.457, p=0.001 and Z=4.005, p<0.001, respectively). This indicates that contrast-enhanced ultrasound combined with ultrasonic elastography is of high diagnostic value for breast tumors (Area >0.9) and that separate use of contrast-enhanced ultrasound

Table 6. Comparison of the diagnostic efficacy of contrast-enhanced ultrasound, ultrasonic elastography, and combination of them in the diagnosis of breast lesions (95% CI)

Methods of examination	Sensitivity	Specificity	Positive predictive value	Negative predictive value
CEUS	89.90% (0.857-0.930)	82.46% (0.765-0.872)	87.46% (0.830-0.909)	85.71% (0.780-0.901)
USE	85.71% (0.810-0.894)	86.26% (0.807-0.905)	89.45% (0.851-0.927)	81.61% (0.758-0.863)
Combined	95.12% (0.918-0.972)	90.99% (0.861-0.943)	93.49% (0.899-0.960)	93.20% (0.886-0.961)
X^2	14.485	6.632	6.227	12.737
P	0.001	0.036	0.044	0.002

Table 7. Comparison of the ROC curve area of contrast-enhanced ultrasound, ultrasonic elastography, and combination of them in the diagnosis of breast lesions

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Ultrasound Elastography	0.852*	0.019	0.000	0.815	0.889
Contrast-enhanced Ultrasound	0.867*	0.018	0.000	0.832	0.902
Combined CEUS and UE	0.942	0.012	0.000	0.918	0.967

The test result variable(s): Ultrasound Elastography, Contrast-enhanced Ultrasound, Combined CEUS, and UE has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. [a]Under the nonparametric assumption. [b]Null hypothesis: true area =0.5. *Significantly different from the Combined CEUS and UE (P<0.05).

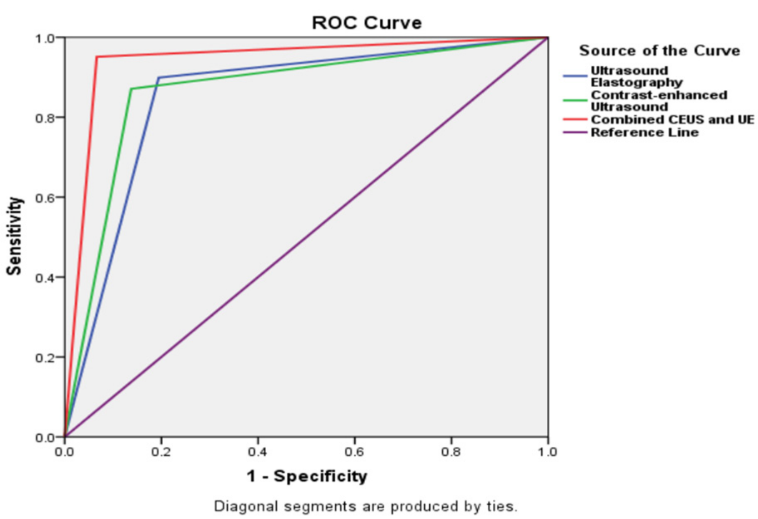

Figure 2. The ROC curves of contrast-enhanced ultrasound, ultrasonic elastography, and the combination in the diagnosis of breast lesions.

or ultrasonic elastography also has certain diagnostic values, which are of moderate diagnostic values (Area >0.7). See **Table 7** and **Figure 2** for details.

Discussion

There are many histopathological types of breast tumors. In the 498 lesions included in this study, there were 6 types of malignant tumors. The major types were invasive ductal carcinoma (29.32%) and ductal carcinoma in situ (12.25%). There were 7 types of benign tumors, the major types were fibroadenoma (13.86%) and adenosis of mammary glands (9.24%). Imaging features of breast tumors are closely related to histopathological characteristics, while ultrasonographic differences of different types of breast cancer is closely related to the structure of mammary glands, the size of cancer cells, as well as infiltration and secretion of the stroma. Currently, the most commonly used imaging methods for diagnosis of benign and malignant breast tumors are based on the morphological changes of the tumors [17, 18]. Meanwhile, malignant breast tumor cells can induce angiogenesis *in vivo* by releasing vascular endothelial growth factors (VEGF) and neovascularization is an important basis for identifying benign or malignant breast tumors. Active neovascularization is the pathological diagnosis basis for the rapid growth, invasion, and metastasis of breast cancer cells [19-21]. Therefore, it has always been our goal to seek for a diagnostic method that not only displays the morphological characteristics of breast tumors but also detects small blood vessels with low flow velocity and low flow capacity, in order to carry out comprehensive diagnoses of breast diseases and to improve diagnosis accuracy.

The development of contrast-enhanced ultrasound (CEUS) technology has made up for the blank of ultrasound imaging technique in detecting neovascularization of tumors. According to the characteristics of rich blood vessels and large circulation perfusion in breast cancers [22], CEUS can perform real-time dynamic tracking of the whole process of contrast medium perfusion in tumor tissues and blood vessels and clearly displays the distribution and shape of vessels in the lesion [23]. With the advent of the second generation of contrast agents, the sensitivity of detecting small vessels has been improved for CEUS which makes up for the lack of good display of small blood vessels [24]. In this study, contrast-enhanced ultrasound was used to differentiate benign and malignant breast tumors. Combining qualitative and quantitative analysis results showed that: sensitivity, specificity, positive predictive value, negative predictive value, and the ROC curve area of CEUS diagnosis of benign and malignant tumors were 89.90% (0.857-0.930), 82.46% (0.765-0.872), 87.46% (0.830-0.909), 85.71% (0.780-0.901), and 0.867 (0.832-0.902), respectively, showing high diagnostic value. The study of 225 female patients by Q Si et al. [25] showed that sensitivity and specificity of contrast-enhanced ultrasound in the diagnosis of benign and malignant tumors were 89% and 91.8%, indicating that CEUS was of high diagnostic value in the diagnosis and differential diagnosis of breast tumors.

Ultrasonic elastography (UE) is a new technique developed in recent years that has been gradually used in clinical diagnosis. According to the principle of different elastic coefficients between the diseased tissue and surrounding normal tissue, UE can identify benign and malignant tumor tissues by comparing ultrasonic signals before and after compression in combination with the technology of digital signaling and image processing [26, 27]. In this study, the sensitivity, specificity, positive predictive value, negative predictive value, and the ROC curve area of UE diagnosis of benign and malignant tumors were 85.71% (0.810-0.894), 86.26% (0.807-0.905), 89.45% (0.851-0.927), 81.61% (0.758-0.863), and 0.852 (0.815-0.889), respectively, showing high diagnostic value as CEUS. The study of Zhi H and Ko K.H. et al. also showed that ultrasound elastography had good specificity and accuracy in diagnosis of benign and malignant breast tumors and provided more information and assistance for clinical diagnosis [28, 29].

Contrast-enhanced ultrasound and ultrasonic elastography are of great value in the diagnosis of benign and malignant breast tumors but there are obvious false positive rates and false negative rates when the two methods are used separately. The observation objects of CEUS are microvasculature of breast lumps. The enhancement patterns of some benign and malignant tumors (such as fibroadenoma, inflammatory mass, intraductal carcinoma etc.) are overlapping, thus easily leading to misdiagnosis. In this study, 27 malignant lesions were missed by CEUS while 37 malignant lesions were misdiagnosed. Because the elastic coefficients of different breast tissues may have a certain degree of overlap, especially for the malignant lesions with hemorrhage and necrosis, the hardness will change which can have a certain impact on the UE results [30], resulting in misdiagnosis and missed diagnosis of some lesions. In this study, 29 cases of benign lesions were misdiagnosed by ultrasound elastography, while 41 malignant lesions were missed. Since the technologies of contrast-enhanced ultrasound and ultrasonic elastography analyze the characteristics of breast lumps from different angles and have complementary effects, we performed contrast-enhanced ultrasonography combined with ultrasonic elastography for the clinical diagnosis and differential diagnosis of breast tumors in this study. The results show that the combination of the two methods has diagnostic efficacy in the diagnosis of benign and malignant breast tumors with the sensitivity, specificity, positive predictive value, negative predictive value, and the ROC curve area of 95.12% (0.918-0.972), 90.99% (0.861-0.943), 93.49% (0.899-0.960), 93.20% (0.886-0.961), and 0.942 (0.918-0.967), respectively. The above indexes are statistically significantly different compared with those in the separate use of CEUS or UE ($p<0.001$).

Overall, this study demonstrates that contrast-enhanced ultrasound and ultrasonic elastography provide a better means of diagnosis for benign and malignant breast tumors. The technology of UE integrates the techniques of pathology and imaging and biomechanics, which solves the important problem of the determination of the hardness of the diseased tissue. CEUS reveals the characteristics of microvessel growth and distribution in breast tumors, which can be quantitatively analyzed by time-intensity curves. The combination of the two methods can be more conducive to the diagnosis and differential diagnosis of breast tumors, making up for the shortcomings of either of the single diagnosis method and improves the accuracy, specificity, and sensitivity of ultrasonic diagnosis of breast diseases. Therefore, it is worthy of application and popularization in clinical practice.

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Disclosure of conflict of interest

None.

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