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Original Article

Diagnostic value of contrast-enhanced ultrasonography supplied in breast tumor

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Abstract: Objective: To study the imaging features of contrast-enhanced ultrasonography (CEUS) in benign and malignant breast tumors, and explore its clinical value in the differential diagnosis of benign and malignant breast tumors. Method: From March 2012 to December 2015, 200 female patients with breast tumor aged from 20 to 65 years old were selected for this study. Definite diagnosis couldn't be obtained by clinical conventional ultrasound technology, so CEUS was then used, and in addition, histopathological results of biopsy or surgical resection were obtained. In all, 200 tumor lesions were analyzed and Siemens Sonoline ultrasound machine was used with SonoVue as the ultrasonic contrast media. Real-time dual-frame contrast-enhanced ultrasound mode was selected in imaging; real-time dynamic image storage technology was uses in the whole process for whole recording; the images were played back after imaging for analysis frame by frame; the imaging features of CEUS were finally compared with histopathological results with the normal breast tissues surrounding lesions as reference samples. Results: In 200 cases of breast tumors, 80 cases of them were malignant tumors, and 120 cases of them were benign tumors. The imaging characteristics of malignant tumors such as the shape of lesions, vessels running, boundary of lesion, distribution of lesion contrast media and contrast media washout pattern, were compared with those of benign tumors, and the result showed significant differences between them ($P<0.05$), in addition, there was statistically significant difference in average maximum diameter of malignant tumor before and after the CEUS ((19.3±6.8) mm *vs.* (22.4±7.5) mm, $P<0.05$). Conclusions: The imaging of malignant breast tumors was characterized by irregular shape and irregular vessel running, uneven distribution of contrast media within the lesions, fast clearance mode, and unclear lesion boundaries; in addition, the maximum diameter after CEUS was significantly larger than that before CEUS. These features are expected to provide the basis for distinguishing the difference of benign and malignant breast tumors.

Keywords: CEUS, contrast media, breast tumor

Introduction

Breast carcinoma is a malignant tumor that occurs in the breast ductal epithelial cells and the peripheral ductal epithelial cells. In recent years, the incidence of breast carcinoma has increased year by year and tends to occur on younger population. Breast carcinoma has become the second most common female malignant tumors, only secondary to cervical cancer, and it has seriously endangered women's health and life [1-3]. Therefore, early detection, early diagnosis and early treatment of breast carcinoma will help to improve the survival rate of patients with breast carcinoma.

Tumor pathology results of breast carcinoma showed that gene mutation occurred in lobes of mammary gland epithelial cells and ductal epithelial cells under the effects of carcinogenic factors, resulting in abnormal biological behavior of cells and runaway malignant growth [4]. The unlimited proliferation of tumor cells would not only infiltrate and destruct the surrounding normal tissues, but also secrete tumor vascular growth factors to stimulate neovascularization. Neovascularization is an important pathological basis for tumor growth, invasion and transfer. At present, tumor pathological changes are regarded as the basis in the clinical imaging techniques to distinguish the benign and malignant breast tumors. The commonly used auxiliary examination methods for breast carcinoma include molybdenum target X-ray, ultrasound, CT, PET-CT, infrared imaging instrument, MRI and radionuclide imaging, etc. The most commonly used methods in clinic are molybdenum target X-ray and ultrasound. Molybdenum target X-ray is easy to result in misdiagnosis or missed diagnosis of near chest wall lesions and atypical small breast carcinoma, and cannot provide the status of blood supply for breast tumors [5]. Conventional ultrasound has limitations in displaying low velocity blood flow and micro-vessels, so it has limitations for the diagnosis of tumors with small volume, insufficient blood supply or infiltrated boundaries [6]. In recent years, with the development of contrast-enhanced ultrasonography (CEUS), its value in tumor diagnosis and differential diagnosis attracts more and more attention. CEUS can show the blood flow signals and neovascularization of the breast tumors, and is helpful to understand the distribution and the characteristics of the micro-vessels in the breast tumors [7, 8]. As a new method of imaging techniques, CEUS plays a more and more important role in the early diagnosis, clinical treatment and prognosis of breast cancer. The study of CEUS begins late in the breast studies, and its accuracy on diagnosis of benign and malignant tumors is still controversial [9, 10].

In this study, CEUS was used for the diagnosis of breast cancer that cannot be diagnosed by conventional ultrasound. The clinical value of CEUS in differentiating benign and malignant tumors was investigated through its imaging features analysis from micro-vascular perfusion characteristics of breast tumors tissues, to provide the experimental basis for the differential diagnosis of benign and malignant tumors.

Material and methods

Subjects

200 female patients with breast tumors that could not be diagnosed by conventional ultrasound in our hospital between March 2012 and December 2015 were included into this study. They were 20-65 years old, with a mean age of (42.2±10.5) years old, and 200 lesions were analyzed. Histopathological results were obtained from all patients who underwent tumor biopsy or surgical resection.

Main equipment and reagents

Siemens Sonoline ultrasonic diagnostic apparatus, 9L4 linear array probe, with an application frequency of 4-9 MHz, and 3.5-5.0 MHz under contrast model, mechanical index of 0.07-0.10, built-in contrast pulse sequencing technology. Contrast medium SonoVue was purchased from Bracco Company in Italy.

Inspection method

In supine position, the lesions of patients were examined by conventional ultrasound mode. 2.4 ml contrast medium SonoVue was injected into the elbow vein in patients, then 5 ml normal saline was quickly injected for tube flushing. The patients were instructed to breathe calmly. We then determined the most optimal interesting areas, step into contrast mode, and kept the probe stable to avoid pressure. The video was real-time dynamically stored during the whole process of CEUS, observed for 6 mins, and injected again after 15 min if necessary. The images were played back frame by frame for analysis by two senior doctors that blinded to this study. The process of CEUS was divided into early stage (0-1 min after injection), medium stage (1-4 min after injection) and late stage (4-6 min after injection). The observing indices were as follows: (1) Lesion shape; (2) Lesion boundary; (3) Vascular running of lesions; (4) Contrast medium distribution in the lesions (including filling defect or local reinforcement of contrast medium); (5) Clearance mode of contrast medium within the lesions (including whether retention was present in contrast medium clearance). (6) Comparison of lesion size before and after CEUS. Finally, the results of the CEUS and pathohistology results were compared.

Statistical treatment

SPSS 17.0 statistical software was used for data analysis. Mean ± standard deviation was used to express measurement data, and t test was used to compare the results of two groups; rate was used to express count data, and χ^2 test was used to compare the results of two groups. $P<0.05$ was used to indicate significant difference.

Table 1. Histopathological examination results in patients with breast lumps

Classification	Malignant tumor				Benign tumor			
	Ductal carcinoma	Lobular carcinoma	Carcinoma in situ	Other types	Fibroadenoma	Papilloma	Breast hyperplasia	Other disease
Number of cases	61	9	4	6	64	14	19	23
Total	80				120			

Table 2. Comparison of age distribution for benign and malignant breast tumors

Groups	Number of cases	<30 years old	30-39 years old	40-50 years old	>50 years old
Malignant tumor	80	4	25	42	9
Benign tumor	120	15	70	30	5

Results

Histopathological results of breast tumors

In 200 cases of breast tumor tissues, 80 cases were pathologically diagnosed of breast carcinoma, including 61 cases of invasive ductal carcinoma, 9 cases of invasive lobular carcinoma, 4 cases of ductal carcinoma in situ, 1 case of mucinous carcinoma, and 5 cases of intraductal carcinoma. Benign breast tumor was diagnosed in 120 cases, including 64 cases of fibroadenoma, 14 cases of intraductal papilloma, 2 cases of chronic granuloma, 3 cases of duct ectasia with inflammatory granuloma, 19 cases of breast hyperplasia lesions, and 18 cases of fibroadenoma with adenosis. See **Table 1** for details.

Among the breast tumor patients in the study, the average age of patients with benign tumor was (40.5±8.7) years old, and the average age of patients with malignant tumor was (45.7±11.2) years old. See **Table 2** for the distribution of various types of tumors in the age.

Comparison of contrast-enhanced ultrasound features of breast benign tumors and malignant tumor

In normal mammary gland tissues, CEUS showed slightly stronger enhanced echo, uniform, and even distribution of micro-vessels. In terms of tumor shapes, as compared with the normal breast tissues, crab-like enhancement was seen in 80 cases of malignant tumor, 63 cases (78.8%) with horn-like enhancement, radial-like enhancement and petal-like enhancement, and the other 17 cases (21.2%) with circular enhancement; while in 120 cases of benign tumors, the shape was regular in 98 cases (81.7%), and irregular in 22 cases (18.3%). There was significant difference between two groups ($P<0.05$) in tumor shapes. In terms of lesion boundary, it was clear in 26 cases (32.5%) among 80 cases of malignant tumor, and unclear in 54 cases (67.5%). While in 120 cases of benign tumors, it was clear in 59 cases (49.2%) and unclear in 61 cases (50.8%). There was significant difference in lesion boundaries between two groups ($P<0.05$). In terms of vascular running within the lesions, earthworm-like vascular running within the tumor lesions or in the peripheral areas, local stenosis or vessel dilation, twisting-like vascular running, clumps-like vascular running or diaphragmatic blood flow were seen in 71 cases (88.8%) among 80 cases of malignant tumors, and normal vascular running was seen in 9 cases (11.2%); while among 120 cases of benign tumors, vascular running was regular in 109 cases (90.8%) and irregular in 11 cases (9.2%), with significant difference between two groups ($P<0.05$). In terms of distribution of contrast medium in the tumor, uneven distribution of contrast medium was present in 68 cases among 80 cases of malignant tumors (85%), and even distribution in 12 cases (15%); while in 120 cases of malignant tumors, uneven distribution was present in 25 cases (20.8%), and even distribution in 95 cases (79.2%), with statistical difference between two groups ($P<0.05$). In terms of contrast medium clearance mode within the lesions, as compared with the surrounding normal breast tissues, fast out accounted for 67.5% (54/80 cases) in 80 cases of malignant tumors, and synchronization or slow out accounted for 32.5% (26/80); while in 120 cases of benign tumors, fast out mode accounted for 12.5% (15/120), synchronization or slow out account-

Table 3. Comparison of CEUS imaging characteristics for benign and malignant breast tumors

CEUS imaging characteristics		Malignant tumor (cases)	Benign tumors (cases)	Statistics (P)
Lesions shape	Regular	17	98	<0.05
	Irregular	63	22	<0.05
Vessels running	Regular	9	109	<0.05
	Irregular	71	11	<0.05
Distribution of contrast medium	Even	12	95	<0.05
	Uneven	68	25	<0.05
Clearance	Slow out or synchronous	26	105	<0.05
Mode	Fast out	54	15	<0.05
Lesion boundary	Clear	26	59	<0.05
	Unclear	54	61	<0.05

Table 4. Comparison of average maximum diameter before and after CEUS for benign and malignant breast tumors

	Number of cases	Diameter before CEUS (mm)	Diameter after CEUS (mm)	T value	*P* value
Malignant tumors	80	19.3±6.8	22.4±7.5	0.327	<0.05
Benign tumors	120	18.6±7.1	19.1±6.9	2.786	>0.05

ed for 87.5% (105/120), with significant difference between two groups ($P<0.05$). In terms of lesion size before and after contrast medium injection, the average maximum diameter of malignant tumors was 19.3±6.8 mm before CEUS and 22.4±7.5 mm after the CEUS, with significant difference before and after CEUS ($P<0.05$); the average maximum diameter of benign tumors was (18.6±7.1) mm before the CEUS, and (19.1 ±6.9) mm after the CEUS, with no statistical difference ($P>0.05$), as shown in **Tables 3**, **4** and **Figures 1**, **2**.

Specificity and sensitivity of CEUS for breast malignant tumors

CEUS imaging characteristics were used as the standard to differentiate benign and malignant breast tumors. Specificity and sensitivity were shown in **Table 5**. Among them, the irregular vessel running had high sensitivity and specificity of 87.9% and 90.5% respectively, and unclear boundary had lower sensitivity and specificity of 63.5% and 46.4% respectively.

Discussion

Breast carcinoma is a mammary epithelial tissues carcinoma with high incidence in the world. According to the current epidemiological survey, the incidence of breast carcinoma has been in a rising trend year by year since the late 1970 s, and now it has become the female tumors with second highest incidence in the world. Most of the early breast carcinoma doesn't have special clinical manifestations. Most of the patients are found or diagnosed during self-detecting or physical examination. When the clinical symptoms of breast carcinoma come to light, it is usually diagnosed as mid-term or advanced stage. Therefore, early detection and diagnosis of breast mass can improve the differentiation of malignant and benign breast tumors, as well as the quality of life and survival rate of patients.

Conventional radiography would cause certain damages to female's body. The location of the breast tumors is superficial at most cases. Ultrasound diagnosis can clearly show the tumor's shape, boundary, size, internal echo and blood flow, etc., and the operation is simple, without damages to body, so now it has became one of the common methods to check breast carcinoma. With the continuous development of ultrasound contrast medium, it provides a new way for the differential diagnosis of benign and malignant breast tumors. Breast CEUS has overcome the limitations of power Doppler ultrasonography and color Doppler ultrasound in the detection effects for micro-vessels, the blood vessels with low velocity and the vessels within less than 1 cm lesion; it can directly enter the micro-vessels, and increase the displaying level to the micro-vessel level

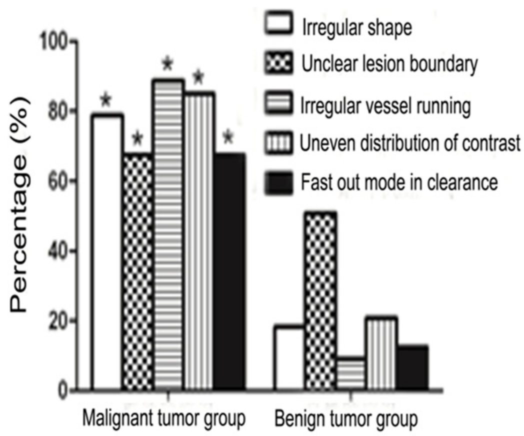

Figure 1. Comparison of CEUS characteristics between malignant tumors and benign tumors. *$P<0.05$, in comparison with benign tumors.

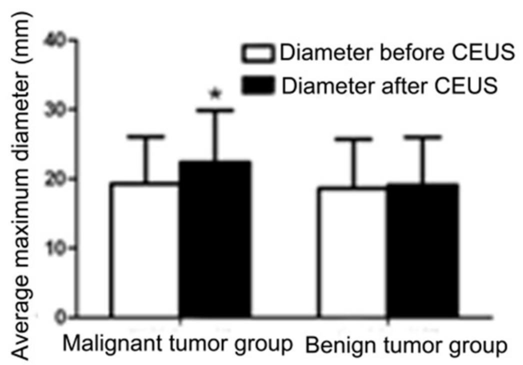

Figure 2. Comparison of average maximum diameter before and after CEUS for breast tumors. *$P<0.05$, in comparison with those before CEUS.

[11, 12]. Studies have shown that ultrasound imaging technology, as one of the reliable methods to evaluate tumor micro-vascular circulation, can show the structure of 20-29 μm diameter micro-vessels [13, 14]. Another study reported that the vascular morphology after CEUS is the best standard to diagnose benign and malignant breast tumors; its vascular detection rate has increased from 22% to 95% for malignant lesions after ultrasonography, and increased from 14% to 21% for benign lesions [15, 16]. Obviously, CEUS not only reflects the anatomical structure and physiological function of tumor tissue vessels, but also plays an important role in the staging of tumors, evaluation of therapeutic effects and prevention of recurrence [17].

The application value of CEUS in breast carcinoma is still at the exploratory stage, and the reported results are not unified. In this study, 78.8% of malignant lesions and 18.3% of benign lesions showed irregular shapes. Irregular shape was a relatively specific imaging feature for malignant breast tumors, with a sensitivity and specificity of 81.3% and 77.6% respectively in diagnosis of malignant lesions. The causes of irregular lesions may be mainly associated with vascular dense at the edge of malignant tumor lesions, non coating, irregular invasive growth and traction at the edge of vascular network [18, 19]. With unclear boundary as an index for differentiating benign and malignant breast tumors, it has a lower sensitivity and specificity of 63.5% and 46.4%. In this study, clear lesion boundaries accounted for 32.5% in 80 cases of malignant tumors, and unclear lesion boundaries accounted for 67.5%; while clear lesion boundaries accounted for 49.2%, and unclear boundaries accounted for 50.8% in 120 cases of benign tumor. Some benign breast tumors and surrounding glands may show enhancement after CEUS, so it is difficult to identify the tumor boundaries; although malignant breast tumors show invasive property, the normal glandular tissues around lesions show significant enhancement after CEUS, while the tumor boundaries are clearly visible on the contrary, so unclear boundaries are not highly valuable for the diagnosis of malignant breast tumors after the CEUS. Earthworm-like vascular running within the tumor lesions or in the peripheral areas, local stenosis or vessel dilation, twisting-like vascular running, clumps-like vascular running or diaphragmatic blood flow were seen in 71 cases (88.8%) among 80 cases of malignant tumors, and normal vascular running was seen in 9 cases (11.2%); while among 120 cases of benign tumors, vascular running was regular in 109 cases (90.8%) and irregular in 11 cases (9.2%). The sensitivity and specificity of irregular vessels was 87.9% and 90.5% respectively for the diagnosis of breast carcinoma, basically consistent with previous research reports [20, 21]. The irregular vessel running is a specific sign of malignant breast tumor. This study showed that the contrast medium was unevenly distributed in 85% of malignant tumor lesions, and in 20.8% of the benign tumor lesions. This may be related to the uneven distribution of neovascularization in

Table 5. Diagnostic value of CEUS characteristics for malignant tumors in 200 cases of breast tumors

CEUS imaging characteristics	Specificity	Sensitivity
Irregular shape	77.6%	81.3%
Irregular vessel running	90.5%	87.9%
Uneven distribution of contrast medium	81.7%	84.2%
Unclear boundary	46.4%	63.5%
Fast out mode for contrast medium	89.5%	66.4%

the malignant breast tumors or necrosis and fibrosis in the tumors, thus causing uneven distribution of contrast medium in malignant lesions at the time of perfusion. However, blood vessels were not abundant in parenchymal lesions of benign tumors except cystic lesions, with less microcirculation perfusion and even distribution of blood vessels [22]. In this study, fast out of contrast medium accounted for 67.5% in 80 cases of malignant tumors, and synchronization or slow out accounted for 32.5%; while in 120 cases of benign tumors, fast out mode accounted for 12.5%, and synchronization or slow out accounted for 87.5%, with significant difference between two groups. The reason may be that the malignant breast tumors destroyed the structure of a large number of normal vessels, arteriovenous fistula formed in new blood vessels, and caused a large number of micro bubbles in vascular beds, large flow volume and high flow rate, showing faster out than the surrounding tissues [23]. The difference in the average maximum diameter of the malignant breast tumors before and after the CEUS may be due to the invasive tumors growth to the surrounding areas, and angiogenesis of malignant breast tumors is usually earlier than morphological changes, so that conventional ultrasound cannot effectively differentiate the malignant and benign tumors. In addition, CEUS can display the whole process of tumor microvascular perfusion, so it can accurately detect the outermost edge of the malignant tumors' invasive growth.

To sum up, there were differences in CEUS imaging between benign breast tumors and malignant breast tumors. In this study, CEUS imaging characteristics of malignant breast tumors included irregular shape of lesions, irregular vessel running, uneven distribution of contrast medium in lesions, fast out mode in clearance, and maximum diameter significantly larger than before CEUS. These imaging features had a certain sensitivity and specificity. This study would provide some experimental evidence for the differential diagnosis of benign breast tumor and malignant breast tumor.

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Disclosure of conflict of interest

None.

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