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Application Value of Contrast-Enhanced Ultrasound in the Diagnosis of Breast Lesions

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Abstract: *Objective:* To explore the value and effect of contrast-enhanced ultrasound in the diagnosis of breast lesions. *Methods:* Seventy-two patients with breast lesions in Shaanxi Provincial People's Hospital from June 2020 to December 2021 were selected as the research subjects. All 72 patients met the diagnostic criteria of breast lesions. Two patients with incomplete clinical data were excluded; hence, there were 70 patients remaining. The diagnostic results of the two examination methods and the diagnostic value of the joint examination for breast lesions were analyzed and compared. *Results:* The results of benign, malignant, missed, and misdiagnosed breast lesions by contrast-enhanced ultrasound were 31, 32, 6, and 1 cases, respectively, accounting for 44.29%, 45.71%, 8.57%, and 1.43%, respectively. The results of benign, malignant, missed, and misdiagnosed breast lesions by ultrasound automatic volume imaging were 21, 24, 17, and 8 cases, respectively, accounting for 30.00%, 34.28%, 24.29%, and 11.43%, respectively. There were statistical differences between the two groups for missed diagnosis and misdiagnosis, but there was no significant difference between the two groups for benign and malignant lesions. The accuracy, sensitivity, and specificity of contrast-enhanced ultrasound were 87.69%, 83.62%, and 83.45%, respectively; the accuracy, sensitivity, and specificity of ultrasound automatic volume imaging were 71.39%, 68.99%, and 74.69%, respectively; the accuracy, sensitivity, and specificity of contrast-enhanced ultrasound combined with ultrasound automatic volume imaging were 96.29%, 92.68%, and 91.78%, respectively. *Conclusion:* Contrast-enhanced ultrasonography has a high clinical application value and a low inspection error rate in the diagnosis of breast lesions. It merits clinical advancement since it helps doctors diagnose and treat breast lesions more effectively.

Keywords: Contrast enhanced ultrasound; Breast lesions; Application value; Ultrasound automatic volume imaging

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1. Background

Breast diseases include inflammatory breast diseases, benign breast diseases, and malignant breast diseases. The early diagnosis and evaluation of breast diseases play an important role in improving the prognosis of patients. In recent years, ultrasound has steadily evolved into an inspection method for the clinical diagnosis of breast diseases. Among them, ultrasound automatic volume imaging and contrast-enhanced ultrasound microvascular imaging have become the mainstream ultrasound approaches. The two methods have good diagnostic values for benign and malignant breast diseases [1]. This study investigated the application value of contrast-enhanced ultrasound combined with automatic volume imaging on breast diseases.

2. Data and methods

2.1. General information

Seventy-two patients with breast lesions in Shaanxi Provincial People's Hospital from June 2020 to

December 2021 were selected as the research subjects. All 72 patients met the diagnostic criteria of breast lesions. Two patients with incomplete clinical data were excluded; hence, there were 70 patients remaining. The diagnostic results of the two examination methods and the diagnostic value of joint examination for breast lesions were analyzed and compared. The patients ranged in age from 32 to 65, with an average of 40.9 ± 5.2 years.

2.2. Methods

(1) Contrast-enhanced ultrasound microvascular imaging

The imaging was performed with a L9-4 probe, PIH contrast conditions, and mechanical index settings of 0.06 to 0.08. Each patient was placed in a supine position with arms raised to expose the breast, and a single point was focused on the deepest part of the breast tissue; 2.2 to 2.5 ml of SonoVue contrast was injected intravenously as a bolus. After starting the contrast timer, the dynamics of the lesion and the trajectory of the contrast microbubble were carefully observed within three minutes of the injection.

(2) Ultrasonic automatic volume imaging

The frequency was set at 5 to 14 MHz, and a 14L5 probe was selected. After exposing the breast, taking the nipple as the center point, and applying sufficient heat couplant near it, ultrasonic scanning was performed following a fan-like arc and instantaneous time direction; the size, location, echo, and blood flow of the scanned focus were carefully observed. The ultrasonic probe was used to scan both breasts. Finally, the ABVS system was used to analyze the image.

2.3. Observation indicators

The diagnostic results of the two groups and the diagnostic value of combined examination for breast lesions were compared.

2.4. Statistical analysis

SPSS 20.0 was used for analysis. The measurement data were expressed in $\bar{x} \pm s$, and t-test was used; the counting data were expressed in n(%), and χ^2 test was carried out to draw the receiver operating characteristic (ROC) curve, so as to evaluate the sensitivity and specificity of contrast-enhanced ultrasound combined with automatic volume imaging for breast lesions. A p value of less than 0.05 was considered to be statistically significant.

3. Results

3.1. Comparison of diagnostic results of contrast-enhanced ultrasound and automatic volume imaging

The results of benign, malignant, missed, and misdiagnosed breast lesions by contrast-enhanced ultrasound were 31, 32, 6, and 1 cases, respectively, accounting for 44.29%, 45.71%, 8.57%, and 1.43%, respectively. The results of benign, malignant, missed, and misdiagnosed breast lesions by ultrasound automatic volume imaging were 21, 24, 17, and 8, respectively, accounting for 30.00%, 34.28%, 24.29%, and 11.43%, respectively. There were significant differences between the two groups for missed diagnosis and misdiagnosis, but there were no significant differences between the two groups for benign and malignant lesions, as shown in **Table 1**.

Table 1. Comparison of diagnostic results of contrast-enhanced ultrasound and automatic volume imaging for breast lesions

Group	Benign lesion	Malignant lesion	Missed diagnosis	Misdiagnosis
Contrast-enhanced ultrasound (n = 70)	31 (44.29)	32 (45.71)	6 (8.57)	1 (1.43)
Ultrasonic automatic volume imaging (n = 70)	21 (30.00)	24 (34.28)	17 (24.29)	8 (11.43)
χ^2	3.0594	1.9048	6.2951	4.2748
p	0.0803	0.1675	0.0121	0.0387

3.2. Comparison of diagnostic value between contrast-enhanced ultrasound and automatic volume imaging

The accuracy, sensitivity, and specificity of contrast-enhanced ultrasound were 87.69%, 83.62%, and 83.45%, respectively; whereas the accuracy, sensitivity, and specificity of automatic ultrasound volume imaging were 71.39%, 68.99%, and 74.69%, respectively; the accuracy, sensitivity, and specificity of contrast-enhanced ultrasound combined with automatic ultrasound volume imaging were 96.29%, 92.68%, and 91.78%, respectively, as shown in **Table 2**.

Table 2. Comparison of diagnostic value between contrast-enhanced ultrasound and automatic volume imaging (%)

Group	Accuracy	Sensitivity	Specificity
Contrast-enhanced ultrasound (n = 70)	87.69	83.62	83.45
Ultrasonic automatic volume imaging (n = 70)	71.39	68.99	74.69
Joint examination (n=70)	96.29	92.68	91.78

4. Discussion

Among female patients with malignant tumors, breast cancer has the highest incidence rate and mortality worldwide. According to the data provided by the International Agency for Research on Cancer (IARC), in 2012, there were 1.671 million new cases of breast cancer worldwide, with 522,000 deaths. In China, the age of onset for breast cancer among females is 10 years younger than that in western countries, and its incidence rate and mortality are still increasing [1], making cancer prevention and control a dire condition. Since the implementation of the two approaches of cancer screening in 2009, an increasing number of breast lesions have been detected. These cases were followed-up or managed surgically [2]. Finding an accurate, reliable, and non-invasive examination method to guide clinical decision-making has become the common goal of the majority of patients and clinicians. Traditional breast imaging modalities include magnetic resonance imaging (MRI), mammogram (MG), and conventional ultrasound (CUS). MRI provides good soft tissue resolution and is clearly superior in diagnosing multiple and small breast lesions. However, it has little value in the diagnosis of early breast cancer because it is not sensitive to microcalcification. Moreover, this technology is complex, time-consuming, and costly, with many contraindications. It is mainly used as a follow-up investigation for Mg and CUS patients with problematic diagnoses [3-5]. MG is recommended as the primary choice for breast cancer screening by the American Cancer Society. Its detection of microcalcification is better than CUS and MRI. However, it is impossible to observe the blood supply to the focus with this imaging modality. The specificity of diagnosis in Asian women with dense breast is low, and the false positive rate can even be as high as 65% [6]. Small lesions located at the edge or deep within the breast are often affected by the patient's position and the overlapping shadow of surrounding tissues, resulting in missed diagnosis [7]. In addition, the examination brings discomfort and risks to patients due to pressure radiography and ionizing radiation; hence, this imaging modality is poorly accepted among patients. In China, CUS is the first choice for breast cancer screening. It has several advantages, including real-time, simplicity, no radiation, high repeatability, and low cost. It is superior to MG in locating and evaluating cystic and solid lesions in dense breast. However, the two-dimensional morphological characteristics of benign and malignant breast lesions may result in the phenomenon of "different symptoms with the same image, different images with the same disease." The color Doppler also has limitations in displaying small and low-speed blood flow signals, resulting in low diagnostic specificity. Many benign lesions are misdiagnosed as BI-RADS 4 or 5 (suspicious or highly suggestive of malignancy), resulting in unnecessary puncture and surgery [8,9]. Contrast-enhanced ultrasound (CEUS) is a new imaging modality that uses contrast agents to enhance the contrast between blood vessels and the surrounding tissues, so as to improve the display of microvessels. SonoVue, a second-generation contrast agent used in CEUS, is a sulfur hexafluoride microbubble wrapped in a lipid shell. It forms a strong loud impedance difference through liquid-air interface, and its shell oscillation generates nonlinear harmonics, which enhance the backscatter signal, thus improving the blood flow display rate. It can display blood flow in microvessels (< 10 um) at low-speed (< 1 mm/s), which cannot be detected by CUS in real time; it can also provide information about microcirculation perfusion in the focus as well as the number, thickness, shape, spatial distribution, and other neovascularization characteristics [10-12], which is extremely useful in differentiating benign and malignant diseases. Its contrast agent has a high safety profile [13]. It is metabolized by the lungs and eliminated via respiration within five minutes, having no impact on liver and kidney functions. It has a wide range of clinical applications. At present, it is widely used in the qualitative diagnosis of liver and other abdominal organ tumors [14]. The microbubble contrast agent in the vascular system enhances the backscatter of ultrasound, thereby amplifying the blood flow signal and acquiring information about the lesions' blood supply. Since tumor angiogenesis is the basis for tumor growth and development into invasive cancer and metastasis, CEUS can improve the efficacy of differential diagnosis by qualitative and quantitative evaluation of perfusion morphology and microcirculation.

Breast cancer is a vascular dependent disease. Newly formed blood vessels not only provide nutrition for the proliferation of cancer cells, but also act as an important channel for their invasion and metastasis. Previous studies have found that when the volume of the cancer focus reaches more than 1 to 2 mm^3 and exceeds the maximum dispersion distance, the cancer cells begin to secrete a variety of active factors represented by endothelial growth factors, which in turn stimulate the formation of a large number of endothelial cells and arrange them in a single layer to provide nutrients for neovascularization. Newly formed blood vessels lack the support of smooth muscles and intact basement membrane. They have high permeability and large blood flow, thus easily forming arteriovenous anastomoses, vascular rings, and venous lakes. As the tumor volume continues to increase, the number of new blood vessels increases, but they are distended and disordered. A large number of cancer cells are released to the blood through the vascular space for distant metastases. The degree of vascularization in the central region of the tumor is lower than that in the marginal region. The sparse blood vessels in the central region are subjected to high interstitial compression; hence, with low blood perfusion, the central region is prone to ischemia and necrosis. However, the nutrition supply of benign lesions, such as fibroadenoma, intraductal papilloma, and adenosis is largely dependent on the proliferation and expansion of normal blood vessels in the glands, with normal vascular structure and venous reflux. The vascular heterogeneity of benign and malignant breast lesions is the pathological basis of imaging. Vascular morphology has emerged as the most accurate diagnostic indicator for distinguishing between benign and malignant lesions.

In breast cancer, the mesenchymal cells in the tumor microenvironment secrete various active factors to regulate tumor neovascularization [5,6], which is uncoordinated in time and space [7], resulting in vascular heterogeneity [8,9]. The vascular morphology can be characterized as follows: (1) abnormal wall structure, lack of smooth muscle and basement membrane support, as well as high blood flow and permeability; (2) tortuous in shape, irregular spatial distribution, varying diameters, and presence of venous lakes and arteriovenous anastomosis; (3) increased blood vessel density, mainly in the marginal area, with relatively rare blood vessels in the central area, which has poor blood perfusion and is prone to ischemia and necrosis. Vascular morphology assessment is currently the best method for differentiating benign and malignant lesions [10]. Other studies have reported that the changes in the composition and quantity of extracellular matrix are related to the hardness of the tumor [11,12]. In higher degrees of malignancies, fibroblasts are activated and synthesize a large amount of collagen, which supports formation of extracellular matrix and collagen fibers; as a result, the hardness increases.

In conclusion, contrast-enhanced ultrasound has high clinical application value and low inspection error rate in the diagnosis of breast lesions. It merits clinical advancements as it helps doctors diagnose breast lesions more effectively.

Disclosure statement

The authors declare no conflict of interest.

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