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Original Article

Study on the role of contrast-enhanced ultrasonography in diagnosis of breast tumor

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Abstract: Objective: To investigate the diagnostic value of contrast-enhanced ultrasonography in malignant breast tumors. Method: From January 2017 and December 2019, 210 patients with breast tumor were enrolled in this study. All patients underwent conventional ultrasound and contrast-enhanced ultrasonography prior to histopathological results of biopsy or surgical resection. The diagnostic value and BI-RADS classification were compared between conventional ultrasound and contrast-enhanced ultrasonography. And the character of image in contrast-enhanced ultrasonography for malignant breast tumors was also analyzed. Results: The diagnostic sensitivity and accuracy of contrast-enhanced ultrasonography for malignant breast tumors were higher than those of conventional ultrasound, and there were significantly statistical differences ($P<0.05$). And there was no significant difference in diagnostic specificity between conventional ultrasound and contrast-enhanced ultrasonography. The significant difference was also found in the diagnosis of BI-RADS 4b class and 5 class for breast tumors between conventional ultrasound and contrast-enhanced ultrasonography ($P<0.05$). In contrast-enhanced ultrasonography, the image features of benign breast tumor and malignant breast tumor showed significantly statistical differences in the term of distribution of contrast agents, degree of enhancement, enhanced margins, and enhancement sequence. Moreover, the maximum intensity (IMAX) and time to peak (TTP) detected by contrast-enhanced ultrasonography showed remarkably statistical differences among different molecular types malignant breast tumors. Conclusions: Contrast-enhanced ultrasonography significantly increased the diagnostic sensitivity and accuracy of malignant breast tumors and modify BI-RADS classification, compared to that of conventional ultrasound. The image features of malignant breast tumors in contrast-enhanced ultrasonography were characterized by uneven distribution of contrast agents, marked degree of enhancement, indistinct enhanced margins, and centripetal enhancement direction. And contrast-enhanced ultrasonography also has significant values in the diagnosis of different molecular types of malignant breast tumors.

Keywords: Contrast-enhanced ultrasonography, conventional ultrasound, malignant breast tumor, diagnostic value

Introduction

In recent years, the incidence of breast cancer has increased year by year and tends to occur in younger population. Breast cancer has been the most frequently diagnosed cancer in women, which has seriously threatened women's life quality and physical and psychological health [1, 2]. Most of patients with breast masses were diagnosed as benign pathologic results by the methods of biopsies, however, It was reported that 15%-40% of screening mammograms with abnormal results and 25%-50% of palpable lumps recommended for biopsy will result in the diagnosis of malignant breast tumors [3]. Therefore, early diagnosis of tumorous types is very important for patients with breast masses, which will help to improve the prognosis of patients with breast cancer [4].

At present, the auxiliary detection methods for breast tumor include ultrasound, MRI, molybdenum target X-ray, CT, PET-CT, and radionuclide imaging, etc. The most commonly used method and the standard of breast imaging is ultrasound examination. Conventional ultrasound

Table 1. The basic information of patients in this study

Parameters	Values
Age (years)	52.4±8.6
Diameter (mm)	28.5±10.1
BMI (kg/m^2)	21.3±0.8
Benign breast tumor (cases)	110
Intraductal papilloma	24
Fibroadenoma	52
Denosis	19
Chronic granuloma	5
Malignant breast tumor (cases)	100
Tissue typing	
Intraductal carcinoma	13
Invasive lobular carcinoma	10
Invasive ductal carcinoma	77
Molecular typing	
Luminal subtype	42
Her-2 overexpression subtype	26
TN subtype	32

Note: BMI: Body mass index; Her-2: Human epidermal growth factor receptor-2; TN: Triple negative.

has its limitations in the diagnosis of tumors with small volume, and displaying low velocity blood flow and micro-vessels [5]. In the last decade, the development of advanced techniques occurs in the ultrasound imaging, contrast-enhanced ultrasonography is one of them, using intravenous contrast medium with microbubbles and a dedicated software for deep analysis [6]. It has many advantages such as fast, no radiation, without nephron- or hepatotoxicity and so on [7]. The role of this method in tumor diagnosis and differential diagnosis attracts more and more emphases [8]. It was reported that the role of contrast-enhanced ultrasonography in the management of focal liver lesions was widely recognized [9]. In term of diagnosis of breast tumor, the exact quantitative and qualitative contrast-enhanced ultrasonography parameters still remain controversial [10]. It was reported that the results regarding sensitivity and specificity of contrast-enhanced ultrasonography for breast tumors differed widely [11]. In this context, this study was performed to explore the diagnostic value of contrast-enhanced ultrasonography for breast tumors and to identify the image features of breast lesions that could be the source of negative findings and of diagnostic difficulties. The results of this study might contribute to reduce the misdiagnosis in patients with breast masses.

Material and methods

Subjects

From January 2017 and December 2019, 210 women with breast masses were examined and enrolled in this study. And this study was approved by Hospital Ethics Committee and written informed consent was obtained from all the included patients. The inclusion criteria were as follows: The age of patients was over 18-year old; Patients had only a solitary lesion; Patients voluntarily underwent tumor biopsy or surgical resection and histopathological results were obtained; Patients received both conventional ultrasound and contrast-enhanced ultrasonography; Patients had complete medical records and were able to cooperate in this study. The exclusion criteria were as follows: Patients had previous therapy, radiotherapy and chemotherapy for treatment of breast masses; Patients were hypersensitive to contrast agents; Patients were pregnant or had breast implants, histories of ipsilateral breast cancer, other malignant tumors, severe renal and hepatic insufficiency, cardio-and cerebrovascular disease and mental disorder. All the patients receiving conventional ultrasound were informed about the need of pathological examination of the breast lesions and about the examination of contrast-enhanced ultrasonography conducted prior to the biopsy or surgery.

As seen in **Table 1**, the average age of patients included in this study is 52.4±8.6 years and diameter of tumors is 28.5±10.1 mm. Among 210 patients with breast masses, 100 patients were pathologically diagnosed with breast cancer including 13 cases of intraductal carcinoma, 10 cases of invasive lobular carcinoma and 77 cases of invasive ductal carcinoma. Among 100 patients with breast cancer, there were 42 patients with Luminal subtype breast cancer, 26 patients with human epidermal growth factor receptor-2 (Her-2) overexpression subtype breast cancer, and 32 patients with triple negative (TN) subtype breast cancer. In addition, 110 patients were definitely diagnosed with benign breast tumor including 24 cases of

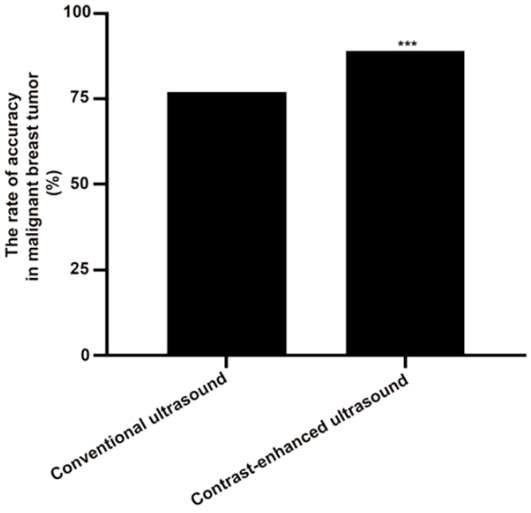

Figure 1. Comparison of the rate of accuracy in malignant breast tumor between conventional ultrasound and contrast-enhanced ultrasound. Compared with conventional ultrasound, ***P=0.001.

intraductal papilloma, 52 case of fibroadenoma, 19 cases of adenosis and 5 cases of chronic granuloma.

Ultrasound examination

Patients were maintained at supine position. The conventional ultrasound and contrast-enhanced ultrasonography included in this study were conducted with the Philips IU22 ultrasound equipment and QLAB-Advanced Ultrasound Quantification Software (version 8.1.2) was used for further image analysis. All the detection was conducted by two senior doctors that blinded to this study. The system of ultrasound was switched into the model of contrast-enhanced ultrasonography when the conventional ultrasound of each patient was finished. The parameters of contrast-enhanced ultrasonography system were as follows: mechanical index of 0.1-0.4 and 5-20 frames per second for frame rate. 2.4 ml contrast medium SonoVue (Bracco Company, Italy) were injected into the elbow vein of each patient, then 5 ml normal saline was quickly followed for tube flushing. The transducer was fixed over the lesions and regions of interest. The images were real-time dynamically stored for 3 min. And contrast medium was injected again after 15 min if necessary. Through revie wing the images, parameters including time to peak (TTP) and a maximum intensity (IMAX) were calculated. In addition, The degree of enhancement was confirmed as mild (less than 10% increase in intensity at the peak time compared to precontrast images), moderate (10%-50% increase in intensity at the peak time compared to precontrast images) and marked (more than 50% increase in intensity at the peak time compared to precontrast images). Enhancement direction (centripetal or centrifugal), Enhanced margins (Clear, indistinct or speculated), and distribution of contrast agents (even or uneven) were also recorded.

Statistical analysis

SPSS 21.0 statistical software was used for data analysis. Continuous variables were presented as Mean ± standard deviation, and t test was used to compare the results between two groups; Categorical variables were presented as percentages or frequencies. χ^2 test was used to compare the results between two groups. P<0.05 indicated significantly statistical difference.

Results

Comparison of diagnostic value between contrast-enhanced ultrasound and conventional ultrasound

The degree of accuracy in contrast-enhanced ultrasound for malignant breast tumor was significantly higher than that in conventional ultrasound (89.0% vs 77.1%, χ^2=10.590, P=0.001), as seen in **Figure 1**. The sensitivity for detection of malignant breast tumor in contrast-enhanced ultrasound was significantly higher than that in conventional ultrasound (χ^2=9.634, P=0.002), and the significant difference was not found in specificity for detection of malignant breast tumor between conventional ultrasound and contrast-enhanced ultrasound (χ^2=2.841, P=0.091), as shown in **Table 2**.

Comparison of BI-RADS classification between contrast-enhanced ultrasound and conventional ultrasound

The significant differences were manifested in the BI-RADS 4b class (χ^2=4.339, P=0.037) and 5 classes (χ^2=3.991, P=0.043) between contrast-enhanced ultrasound and conventional ultrasound. And there was no significant difference in the overall BI-RADS classification between contrast-enhanced ultrasound and

Table 2. Comparison of assessment results between contrast-enhanced ultrasound and conventional ultrasound

Methods	Pathological examination		Sensitivity	Specificity
	Benign masses	Malignant masses		
Conventional ultrasound			79.0%	75.5%
Benign masses	83	21		
Malignant masses	27	79		
Contrast-enhanced ultrasound			94.0%	84.5%
Benign masses	93	6		
Malignant masses	17	94		

Table 3. Comparison of BI-RADS classification between contrast-enhanced ultrasound and conventional ultrasound

Methods	2 class	3 class	4 class			5 class
			a	b	c	
Conventional ultrasound	9	83	10	50	20	38
Contrast-enhanced ultrasound	7	84	9	33*	22	55*
χ^2 value	0.260	0.010	0.055	4.339	0.106	3.991
P value	0.610	0.921	0.814	0.037	0.745	0.046

Note: Compared with conventional ultrasound, *P<0.05.

Table 4. Analysis on character of image for breast tumors in contrast-enhanced ultrasound

Feature	Benignancy (n=110)	Malignancy (n=100)	χ^2 value	*P* value
Distribution of contrast agents			11.470	<0.001
Even	71	15		
Uneven	39	85		
Degree of enhancement			14.080	<0.001
Mild enhancement	52	9		
Moderate enhancement	33	19		
Marked enhancement	25	72		
Enhanced margins			18.030	<0.001
Clear	85	20		
Indistinct	20	50		
Spiculated	5	30		
Enhancement direction			49.650	<0.001
Centripetal	26	69		
Centrifugal	84	31		

conventional ultrasound (P>0.05), as shown in **Table 3**.

Character of image in contrast-enhanced ultrasound for patients with breast tumors

Contrast-enhanced ultrasound results showed that there were statistically significant differences for imaging characteristics in distribution of contrast agents, degree of enhancement, enhanced margins, and enhancement sequence between benign breast masses and malignant breast masses (all P<0.001), as shown in **Table 4**.

Comparison of maximum intensity (IMAX) and time to peak (TTP) in contrast-enhanced ultrasound between different molecular types malignant breast tumor

As shown in **Figure 2**, in patients with malignant breast tumors detected by contrast-enhanced ultrasound, IMAX in Her-2 overexpression subtype cases was obviously higher than that in luminal subtype cases and TN subtype cases (P<0.001). And IMAX in TN subtype cases was remarkably higher than that in luminal subtype cases (P<0.001). TTP in Her-2 overexpression subtype cases was significantly lower than that in luminal subtype cases and TN subtype cases (P<0.001). And TTP in TN subtype cases was

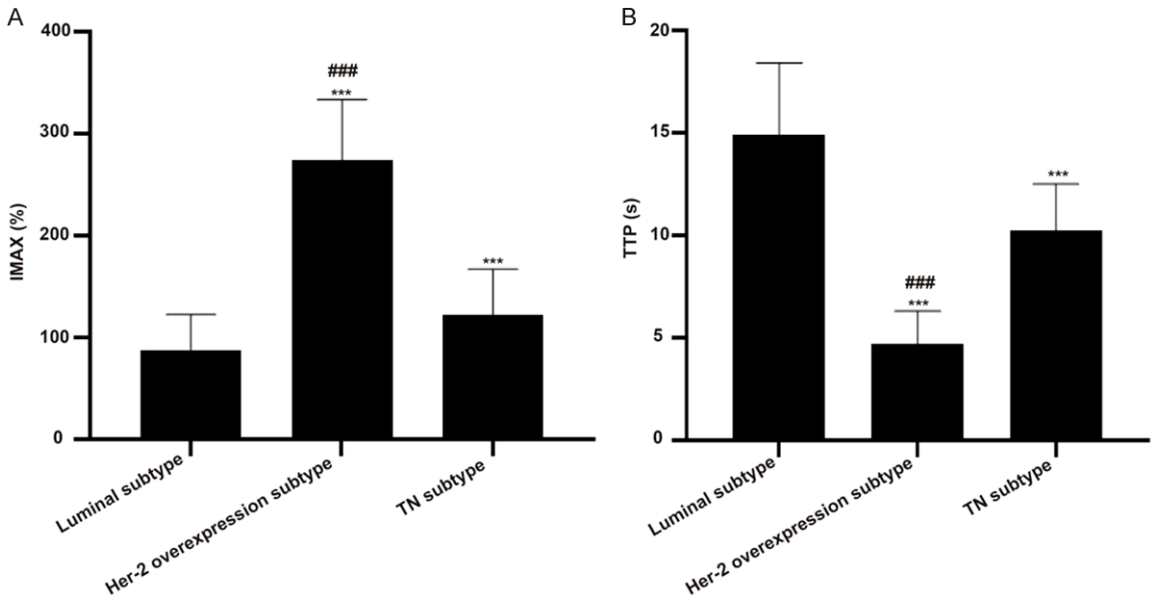

Figure 2. Comparison of IMAX and time to peak (TTP) in contrast-enhanced ultrasound among different molecular subtypes malignant breast tumors. A: IMAX detection; B: TTP detection. Compared with luminal subtype, ***P<0.001; Compared with TN subtype, ###P<0.001. Note: IMAX: Maximum intensity; TTP: Time to peak; Her-2: Human epidermal growth factor receptor-2; TN: Triple negative.

significantly lower than that in luminal subtype cases (P<0.001).

Discussion

Breast carcinoma is a malignant tumor that occurs in the breast ductal epithelial cells and the peripheral ductal epithelial cells. Most of the patients with early-stage breast cancer do not show obvious clinical manifestations. These patients are usually diagnosed by self-detecting or physical examination. When the clinical symptoms occur, it is commonly diagnosed as advanced stage [12]. Therefore, it is of great significance for early detection of breast cancers.

For patients with breast tumors, conventional radiography would lead to certain damages to the body. And most of the breast tumors in patients are relatively shallow in position. The boundary, shape, size, blood flow and internal echo of breast masses could be clearly displayed using ultrasound. This method as a non-invasive examination has become one of the common methods to check breast masses. But, conventional ultrasound has its limitations [13]. With the development of contrast medium, contrast-enhanced ultrasound as a new method, has overcome the limitations of conventional ultrasound in the detection effects for solid tumors [14]. However, it was reported that contrast-enhanced ultrasound also has pitfalls and limitations such as special dedication to software, movement artifacts, the necessity of peripheral venous access and the need for experienced physicians. The limitations of contrast-enhanced ultrasound may lead the differential diagnostic problems. However, most of previous studies are following the contribution of contrast-enhanced ultrasound in evaluation of dignity of lesions. In this study, the degree of accuracy and sensitivity of contrast-enhanced ultrasound was 89% and 94%, respectively. And both of them were significantly higher than those in conventional ultrasound. The specificity of contrast-enhanced ultrasound for malignant breast tumors was slight higher than that in conventional ultrasound, and there was no significant difference. These results are similar with those reported by Noro et al [15].

The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) has been considered as the standards and norms for diagnosis of breast tumors [16, 17]. Some studies reported that BI-RADS 3 class has a less than 2% chance of malignancy and it was appropriate for patients to follow up within

a short time, while BI-RADS 4 has a 2%-95% chance of malignancy and it was recommended for tissue sampling [18]. Compared with conventional ultrasound, contrast-enhanced ultrasound could better use the parameters of vessel signal of blood flow in tumors [19]. The results of this study showed that contrast-enhanced ultrasound had significant advantages of distinguish breast tumors at BI-RADS 4 class and BI-RADS 5 class. This is because that contrast-enhanced ultrasound could display the microvascular density of lesions and provide information regarding perfusion of tumor [20].

The role of contrast-enhanced ultrasound in breast cancer is still at the exploratory stage, and the results reported by previous studies are not unified [21]. In this study, it was showed that the contrast agent was unevenly distributed in 35.5% of benign breast tumor lesions and 85% of malignant breast tumor lesions. This was because of uneven distribution of fibrosis, necrosis and neovascularization in malignant breast tumor, which is consistent with what has previously reported [22]. Degree of enhancement was the second analyzed sign. This study showed that the majority of the malignant breast tumors were presented by marked enhancement, while the mild enhancement was mainly observed in benign breast tumors. Statistical differences between benign and malignant breast tumors appeared in degree of enhancement. The same results were found when analyzing the degree of enhancement in contrast-enhanced ultrasound [23]. This parameter was also correlated with neovasculature density. This study also revealed that most of malignant breast tumors expressed indistinct enhanced margins and centripetal enhancement direction and there were significant differences between benign and malignant breast tumors. These observations were in accordance with outcomes of Saracco et al [24]. From these outcomes, it is indicated that the specific histopathologic features of malignant breast tumors could be translated into their qualitative sonographic appearance [25]. Contrast-enhanced ultrasound could be considered as a promising tool for evaluating benign and malignant breast lesions.

The molecular subtype plays an important role in assessment of prognosis in patients with malignant breast tumor. The molecular subtype of malignant breast tumor includes Luminal subtype, Her-2 overexpression subtype and TN subtype. It was reported that patients with Luminal subtype breast cancer had better prognosis and patients with TN subtype breast cancer had worse prognosis comparatively [26]. This study showed that IMAX in Luminal subtype breast cancer was lower than that in other subtypes and TTP in Her-2 overexpression subtype cases was significantly lower than that in other subtypes. The reasons were as follows: there was low microvascular density in Luminal subtype tumors, leading to hypoperfusion in the process of radiography. VEGF overexpression in Her-2 overexpression subtype breast tumor could promote neovascularization to grow from the edge to the center, which could cause contrast agent quickly entering into the centre of lesions. These results were basically consistent with the ones Altundag et al have reported [27].

In conclusion, contrast-enhanced ultrasound as an additional tool in conjunction with conventional ultrasound has the potential to differentiate between benign and malignant breast tumor. And this study also provides the image characteristics of malignant breast tumor in contrast-enhanced ultrasound and demonstrates that contrast-enhanced ultrasound is superior to conventional ultrasound in term of the diagnosis of malignant breast tumor. However, there were still some limitations existing in this study, such as small sample, and single-center study. Subsequent studies will focus on the collection of an increased number of patients, and the multi-center prospective study. Moreover, more parameters of contrast-enhanced ultrasound for malignant breast tumor should be investigated, requiring further experimental confirmation.

Disclosure of conflict of interest

None.

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