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Original Article

Characteristics of benign and malignant tumor shown on three-dimensional ultrasound and contrast-enhanced ultrasound and their diagnostic efficacy

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Abstract: Objective: The goal of this study was to evaluate three-dimensional ultrasound (3D-US) and contrast-enhanced ultrasound (CEUS) and whether combining the two was more effective in diagnosing benign and malignant breast lumps. Methods: Breast tumor patients admitted by our hospital from February 2016 to August 2017, 47 benign and 47 malignant, were enrolled in this study. 3D-US and CEUS were then applied to both groups and test results were analyzed. A comparison was made between the three approaches, 3D-US, CEUS and the combination of both, in terms of accuracy in determining whether a breast tumor is benign or malignant. Results: Imaging from 3D-US of benign and malignant breast nodules showed statistical significance in margins, shape, aspect ratio, internal and after-discharge echo and calcification between benign and malignant nodules ($P<0.05$). Imaging from CEUS of benign and malignant breast tumor showed statistical significance in enhanced patterns, margins-enhanced patterns and the degree of enhancement ($P<0.05$) while there was no statistical significance in regressed patterns between the two ($P>0.05$). CEUS was superior to 3D-US in sensitivity, specificity, Youden index and likelihood ratio, but the difference was insignificant ($P>0.05$). No statistical significance was found between the combined approach and individual tests in sensitivity, specificity, Youden index and likelihood ratio ($P>0.05$). Conclusion: 3D-US and CEUS are equivalent in determining whether a breast lump is malignant or benign, and combining the two does not improve the sensitivity, specificity and accuracy of determining breast lump malignancy.

Keywords: Benign and malignant breast lump, three-dimensional ultrasound, contrast-enhanced ultrasound, diagnostics

Introduction

Breast cancer is one of the most common malignant tumors among women clinically and its morbidity and mortality both rank the first in all malignant tumors affecting women. Due to the fact that breast cancer is latent at its first stage where patients show little symptoms, it is usually diagnosed at the middle and the advanced stage, where patients have missed the window of opportunity for a complete surgical removal, which poses a great threat to their life and health [1]. Therefore, timely and effective diagnosis is crucial for improving the survival rate of breast cancer patients. Conventional ultrasonograph used to be the main approach to determine whether a breast lump is benign or malignant; however, its accuracy is influenced by many factors, including skills of the operator, which makes conventional ultrasonograph less ideal. As medicine advances and ultrasonograph develops in recent years, three-dimensional ultrasound (3D-US) and contrast-enhanced ultrasound (CEUS) are being used in diagnosing benign and malignant tumors. Compared to two-dimensional ultrasound (2D-US), 3D-US captures tissue mass by volume imaging and increases diagnosis information by slicing or pulling from different angles, which yields imaging of the tissue mass from different angles, including vector, cross and coronal sections [2]. CEUS is a commonly-used diagnostic approach to detect breast cancer and benign breast lumps, a non-invasive method that offers quality imaging of the breast anatomy in its entirety [3]. This paper aims to

discuss the effectiveness of 3D-US, CEUS and the combined use of both in determining whether a breast lump is malignant.

Materials and methods

Selection of study subjects

Under the approval of the hospital's ethics committee, a retrospective case-control study was conducted. Forty-seven patients with malignant breast tumor who visited our hospital from February 2016 to August 2017 were enrolled in the case group and 47 with benign breast tumor enrolled in the control group.

Inclusion criteria: All patients had undergone surgical pathology diagnostic procedures that yielded a confirmed diagnosis; all patients were given 3D-US and CEUS test, which were performed according the protocol and gave a preliminary diagnosis on whether the tumor in question was malignant and were documented properly.

Exclusion criteria: Women in pregnancy or lactation period; patients who had trouble expressing themselves and couldn't provide medical history; patients who had radiotherapy or chemotherapy before the surgery; patients who didn't have post-surgical pathology diagnosis.

The protocol of 3D-US test was listed as followed: Logiq9/e9 Color Doppler Ultrasound system (GE Company, USA) was used to perform the test with the probe's frequency set at 6-8 MHz; the contrast medium was SonoVue (Bracco Company, Italy) [4]. 3D imaging mode was chosen to conduct multi-mode two-dimensional gray-scale and energy doppler on the lesion area; the patient was required to hold her breath during the test, the result of which was analyzed using the software 4DVIEW. A standard plain scan was conducted to determine the area, size, margins and number of lesions and other parameters of 2D imaging. A color doppler imaging was superimposed on the 2D imaging simultaneously to observe hemodynamics of the lesion area [5].

3D-US results were graded based on Breast Imaging Reporting and Data system developed by American College of Radiation in 1992: level 1, negative; level 2, benign lesion; level 3, probability of benign tumor>98%; level 4, 95%> malignancy probability ≥ 2% (divided into three sub-levels: level 4a, 8% ≥ malignancy ≥ 2%; level 4b, 49% ≥ malignancy ≥ 9%; level 4c, 95% ≥ malignancy ≥ 50%). Levels 1, 2, 3 and 4a are deemed as benign and levels 4b, 4c and 5 as malignant nodules [6].

CEUS criteria for benign and malignant nodules are listed as followed: breast nodules were scored from 1 to 5 as Itoh and others proposed. Score of 1-3 was deemed as a benign breast nodule and 4-5 as malignant [7]. Diagnostic criteria for the combined use of 3D-US and CEUS: if results from both were benign, the diagnosis from combined approach was benign; if both were malignant, the diagnosis from combined approach was malignant; if the two showed different results and any of the following criteria was met, the tumor was deemed malignant: CEUS showed uneven enhancement within the lesion or clear entry of radiography bubbles; substantive hypoechoic lumps with ill-defined margins and abundant blood flow were detected, PI ≥ 1.5 or RI ≥ 0.7; if any of the following criteria was met, the tumor was deemed benign: CEUS didn't show enhanced echoes in lesion; substantive lumps with defined margins and limited blood flow were detected.

Data collection

The retrospective case control study was conducted and relevant data were collected, which included 1) general information, including at the age of 25-78, on average 46.7±10.3 years old; 2) information on breast nodules: 50 on the left and 44 on the right with diameter ranging from 0.5 to 4.9cm, on average 2.1±0.8 cm; 3) pathology results from surgeries: 47 malignant cases, including 39 cases of invasive ductal carcinoma , 3 cases of invasive lobular carcinoma, 3 cases of ductal carcinoma in situ and 2 cases of medullary carcinoma; 47 benign cases, including 21 cases of fibroadenoma, 18 cases of adenosis, 5 cases of cysts and 3 cases of inflammation; 4) test results from 3D-US and CEUS and diagnosis of malignant or benign.

Indicators for observation

Imaging results of two tests were analyzed based primarily on pathology diagnostic results. False positive rate, false negative rate, sensitivity, specificity and accuracy of 3D-US, CEUS and the combination of both were compared and coefficient of consistency was calculated.

Table 1. Imaging results of benign and malignant nodules from 3D-US (n, %)

3D-US		Malignant nodules (n=47)	Benign nodules (n=47)	χ^2	P
Margin	Defined	8 (17.02)	31 (65.96)	23.182	0.000
	Ill-defined	39 (82.98)	16 (34.04)		
Shape	Irregular	38 (80.85)	25 (53.19)	8.134	0.004
	Regular	9 (19.15)	22 (36.81)		
Depth-width ratio	<1	17 (36.17)	40 (85.11)	23.578	0.000
	>1	30 (63.83)	7 (14.89)		
Internal echo	Even	7 (14.89)	28 (59.57)	20.075	0.000
	Uneven	40 (85.11)	19 (40.43)		
Posterior echo	Without regression	26 (55.32)	39 (82.98)	8.428	0.004
	With regression	21 (44.68)	8 (17.02)		
Calcification	Yes	22 (46.81)	6 (12.77)	13.022	0.000
	No	25 (53.19)	41 (87.23)		

Note: 3D-US, three-dimensional ultrasound.

Table 2. Analysis of imaging results of benign and malignant breast nodules from CEUS (n, %)

CEUS		Malignant nodules (n=47)	Benign nodules (n=47)	χ^2	P
Enhanced pattern	Partially enhanced	36 (76.60)	12 (25.53)	24.522	0.000
	Entirely enhanced	11 (23.40)	35 (74.47)		
Margin-enhanced pattern	Defined margins	9 (19.15)	37 (78.72)	33.377	0.000
	Ill-defined margins	38 (80.85)	10 (21.28)		
Level of enhancement	Levels 0-2	10 (21.28)	25 (53.19)	10.242	0.001
	Level 3	37 (78.72)	22 (46.81)		
Regressed pattern	Even	20 (42.55)	24 (51.06)	0.684	0.408
	Uneven	27 (57.45)	23 (48.94)		

Note: CEUS, contrast-enhanced ultrasound.

Statistics approach

The software SPSS20.0 was chosen and data was expressed as mean±standard deviation. Sensitivity=positive cases after screening/confirmed positive cases * 100%; specificity=negative cases after screening/confirmed negative cases * 100%; misdiagnosis rate=1 - specificity; missed diagnosis rate=1 - sensitivity. Data was shown in (n, %) and χ^2 test and χ^2 partition tests (there is a statistical significance when P<0.017) were conducted and compared. Based on pathology diagnostic results, the golden standard, the diagnostic results of the three approaches, 3D-US, CEUS and the combined were compared and a difference of P<0.05 was deemed to have statistical significance.

Results

Imaging results of benign and malignant nodules from 3D-US

Imaging from 3D-US of benign and malignant breast nodules showed statistical significance in margin, shape, depth-width ratio, internal and after-discharge echo and calcification between benign and malignant nodules (P< 0.05). See **Table 1**.

Analysis of imaging results of benign and malignant breast nodules from CEUS

Imaging from CEUS of benign and malignant breast tumor showed statistical significance in enhanced patterns, margin-enhanced patterns and the degree of enhancement between benign and malignant lumps (P<0.05). See **Table 2** and **Figure 1**.

Diagnostic effectiveness of CEUS and 3D-US

CEUS was superior than 3D-US in terms of sensitivity, specificity, Youden Index and likelihood ratio; however, the difference was not significant (P>0.05). In other words, CEUS had an advantage over conventional ultrasonograph but a limited one. No statistical significance was found between the combined approach and individual tests in sensitivity, specificity,

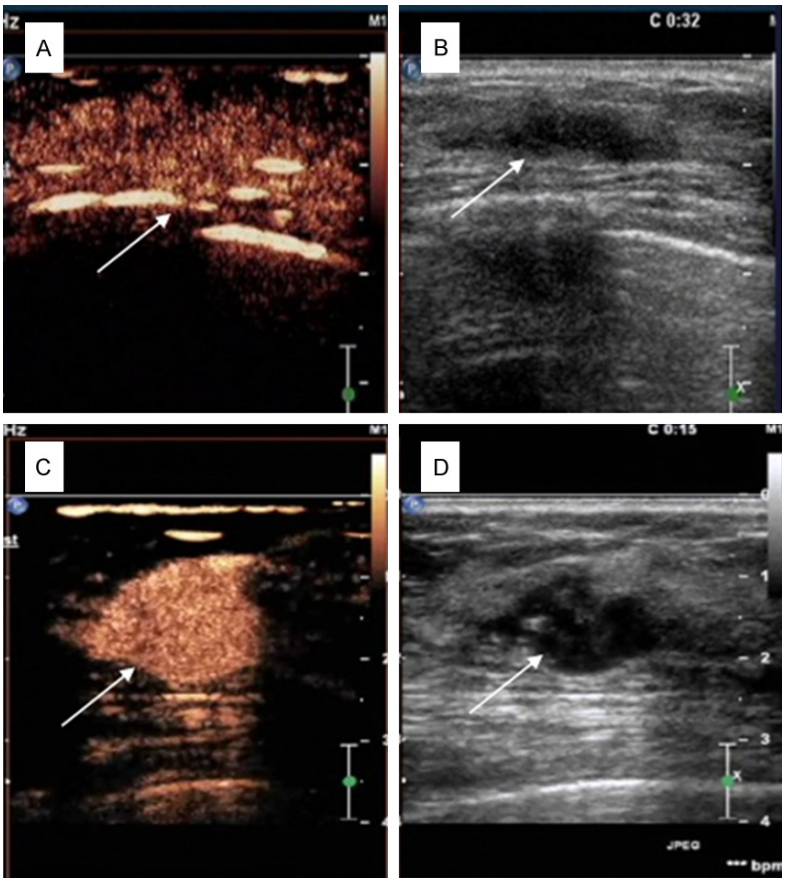

Figure 1. Two-dimensional ultrasonograph and CEUS of malignant and benign breast tumors. CEUS, contrast-enhanced ultrasound. A: CEUS shows a malignant tumor which is a lump with uneven and partial enhancement; B: Two-dimensional color ultrasonograph shows a malignant tumor which is a lump with ill-defined margins; C: CEUS shows a benign tumor - the size of the lump after contrast medium entered is the same as its size on the two-dimensional imaging; D: Two-dimensional color ultrasonograph shows a benign tumor which is a lump with defined margins.

Youden index and likelihood ratio (P>0.05). See **Tables 3**-**5**.

Discussion

Breast cancer is a common malignant tumor in China and the morbidity rate has been increasing every year. A common malignant tumor among women, it is one of the deadliest malignant tumor for women. Early symptoms of breast cancer are mainly painless and isolated small nodules in the affected breast. Due to its atypical symptoms, it is not rare that a malignant tumor is misdiagnosed as a benign one, causing the patient to miss the window of opportunity for the most effective treatment. Therefore, detection, diagnosis and treatment at an early stage are crucial for improving the survival rate and quality of patients.

Radiology tests, including mammograms, ultrasonograph, infrared and MRI, play an important role in diagnosing breast diseases. Conventional ultrasound tests are one of the commonly used approaches in diagnosing breast tumors and have certain advantages, for example high-frequency two-dimensional ultrasonograph has high resolution and precise location. Using 3D-US to observe breast tumors provides three-dimensional images that more truthfully reflect the tumor in question on top of images and information from two-dimensional ultrasonograph, including shape, location, internal echo, margins, calcification and blood flow distribution. In addition, it shows the coronal section unavailable in two-dimensional ultrasonograph, which adds another detection technique to the breast tumor diagnostics arsenal [8].

A benign breast lump is manifested as a lesion with defined margins, even enhancement, invariable area and enhanced patterns in envelop, due to the fact that benign tissue has even distribution of blood and moderate amount of growth. 3D-US prevents misdiagnosis of benign breast diseases [9-13]. This study shows difference in margins, shapes, depth-width ratio, internal echo, posterior echo and calcification between benign and malignant tumors shown on CEUS, which indicates the effectiveness of CEUS in distinguishing benign and malignant breast nodules, a finding that is fundamentally in line with results from other studies [14]. The main reasons: 3D-US allows observation of any section by moving and choosing the section needed for a better understanding of the lesion's anatomy; it also conducts effective analysis of

Table 3. 3D-US and CEUS three-way Chi-square test

Three-way Chi-square test		+ (True positive)			- (True negative)		
		3D-US			3D-US		
		+ (Positive)	- (Negative)	Total	+ (Positive)	- (Negative)	Total
CEUS	+ (Positive)	25	9	34	8	4	12
	- (Negative)	4	9	13	12	23	35
	Total	29	18	47	20	27	47
		3D-US		CEUS	χ^2		P
Sensitivity		0.617		0.723	1.265		0.234
Specificity		0.574		0.744	1.593		0.198
Youden index		0.191		0.467	3.248		0.053
Consistency rate		59.60%		73.40%	2.037		0.107
Positive likelihood rate		1.448		2.824	3.189		0.062
Negative likelihood rate		0.667		0.372	3.223		0.055

Note: 3D-US, three-dimensional ultrasound; CEUS, contrast-enhanced ultrasound.

Table 4. Three-way Chi-square test of CEUS and the combination of CEUS and 3D-US

Three-way Chi-square test		+ (True positive)			- (True negative)		
		Combined test			Combined test		
		+ (Positive)	- (Negative)	Total	+ (Positive)	- (Negative)	Total
CEUS	+ (Positive)	28	6	34	7	5	12
	- (Negative)	5	8	13	9	26	35
	Total	33	14	47	16	31	47
		Combined test		CEUS	χ^2		P
Sensitivity		0.702		0.723	0.215		0.432
Specificity		0.66		0.744	1.247		0.238
Youden index		0.362		0.467	1.548		0.196
Consistency rate		68.09%		73.40%	1.768		0.164
Positive likelihood rate		2.065		2.824	1.451		0.062
Negative likelihood rate		0.452		0.372	2.113		0.095

Note: CEUS, contrast-enhanced ultrasound.

Table 5. Three-way Chi-square test of 3D-US and the combined use of 3D-US and CEUS

Three-way Chi-square test		+ (True positives)			- (True negatives)		
		3D-US			3D-US		
		+ (Positive)	- (Negative)	Total	+ (Positive)	- (Negative)	Total
Combined test	+ (Positive)	26	7	33	10	6	16
	- (negative)	3	11	14	10	21	31
	Total	29	18	47	20	27	47
		Combined test		3D-US	χ^2		P
Sensitivity		0.702		0.617	1.119		0.087
Specificity		0.66		0.574	1.288		0.198
Youden index		0.362		0.191	2.976		0.087
Consistency rate		68.09%		59.60%	2.124		0.094
Positive likelihood rate		2.065		1.448	3.004		0.085
Negative likelihood rate		0.452		0.667	3.113		0.078

Note: 3D-US, three-dimensional ultrasound; CEUS, contrast-enhanced ultrasound.

detailed structures within the lesion by ultrasound tomography, which improves diagnostics efficacy [15]. Advantages of 3D-US over two-dimensional ultrasonograph include clearer margins, good envelope integrity and hypoechoic margins. When there is ambiguity between a benign and malignant lesion, a malignant tumor might appear to have defined and intact margins in two-dimensional ultrasonograph and a benign tumor irregular, affecting diagnostics.

Unlimited growth of malignant tumor cells is dependent on the incessant growth of stromal blood vessels, therefore evaluating newly grown blood vessels within a tumor is conducive to distinguishing benign from malignant [16]. Some scholars believe that malignant breast lesions usually have multiple blood vessels that show even or uneven enhancement whereas benign lesions have less blood vessels and have uneven enhancement around their margins [17]. In this study, the comparison between imaging results of CEUS and other approaches showed statistical significance in enhanced patterns, margin-enhanced patterns and degree of enhancement, which indicated the effectiveness of CEUS in diagnosing benign and malignant nodules. It is worth noting that postsurgical pathology tests of three cases in this study indicated benign inflammation. These three cases later showed overall enhancement of above level 3, which was due to the fact that degree of enhancement of a lesion is mainly influenced by vascular density within the lesion, not dependent on whether it is benign or malignant [18]. Some inflammatory lesions have abundant blood flow, which might be similar [19] to malignant lesions in terms of microvascular structures and microcirculation. That makes diagnosing more difficult, which reminds us to have further discussions about whether CEUS is able to distinguish tumors from inflammation effectively, among other issues [20].

In addition, effectiveness of the two methods were compared based on pathology test results, which indicated CEUS being superior over 3D-US in sensitivity, specificity, Youden index and likelihood ratio, but the difference was not significant ($P>0.05$). In other words, CEUS had advantages over conventional ultrasonograph, but limited at that.

This is an exploratory study with inadequacies listed as follows: 1) criteria needs to be optimized and given more details to prevent overlapping imaging results among benign and malignant lesions, in order to improve specificity and accuracy of diagnostics; 2) a prospective study with a bigger sample volume is needed for further verification; 3) this study chose sections with abundant blood low or in irregular shapes as the sole CEUS section for observation, but a single section does not provide a full picture of a lesion.

In conclusion, 3D-US and CEUS are equivalent in determining whether a breast lump is malignant or benign, and combining the two does not improve the sensitivity, specificity and accuracy of determining breast lump malignancy.

Disclosure of conflict of interest

None.

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