RESEARCH ARTICLE

Comparative Study of Contrast-Enhanced Ultrasound Qualitative and Quantitative Analysis for Identifying Benign and Malignant Breast Tumor Lumps

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Abstract

Background: To compare the value of contrast-enhanced ultrasound (CEUS) qualitative and quantitative analysis in the identification of breast tumor lumps. Materials and Methods: Qualitative and quantitative indicators of CEUS for 73 cases of breast tumor lumps were retrospectively analyzed by univariate and multivariate approaches. Logistic regression was applied and ROC curves were drawn for evaluation and comparison. Results: The CEUS qualitative indicator-generated regression equation contained three indicators, namely enhanced homogeneity, diameter line expansion and peak intensity grading, which demonstrated prediction accuracy for benign and malignant breast tumor lumps of 91.8%; the quantitative indicator-generated regression equation only contained one indicator, namely the relative peak intensity, and its prediction accuracy was 61.5%. The corresponding areas under the ROC curve for qualitative and quantitative analyses were 91.3% and 75.7%, respectively, which exhibited a statistically significant difference by the Z test (*P*<0.05). Conclusions: The ability of CEUS qualitative analysis to identify breast tumor lumps is better than with quantitative analysis.

Keywords: Ultrasonography - breast nodules - qualitative - quantitative - analysis

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Introduction

The tumor angiogenesis is the development of a new vascular network out of the preexisting vessels and is considered essential towards the progression of solid tumors. The ultrasound imaging of tumor vessel has gained the increasing interest in the tumor search during recent years (Fleischer, 2000; Ricci et al., 2007). The conventional ultrasound (US) is a commonly used imaging modality in the detection of breast lesions (Boonlikit, 2013; Wang et al., 2013). However, the sensitivity of conventional Doppler ultrasound is low towards the detection of flow in small tumor vessels. Breast lesion characterization based on Doppler ultrasound flow measurements has produced mixed results, because of the overlap among the flow measurements in benign and malignant tumors (Taylor et al., 2002).

The contrast-enhanced ultrasound (CEUS) imaging with microbubble contrast agents has created a significant opportunity towards the visualisation of microcirculation, and made it possible to overcome the drawbacks of the conventional US techniques. In particular, the application of second-generation contrast agents, such as SonoVue, could facilitate the continuous and dynamic observation and research of tumor vascular perfusion (Wang et al., 2007). However, the final diagnosis of CEUS still depends on correct image analysis method. Image analysis methods of CEUS include the qualitative analysis and the quantitative analysis. The qualitative analysis is to assess the contrast enhancement patterns of breast lesions, which has the examiner-dependent accuracy. Several studies have shown that CEUS could provide the characteristic enhancement patterns that could be helpful in the differential diagnosis of breast lesions (Zhao et al., 2010; Du et al., 2012). CEUS quantitative parameters are obtained from time-intensity (T/I) curve using dedicated software, which offers an objective and reproducible assessment of lesion vascularisation. Although there are many quantitative researches towards the breast US imaging, and the types of quantization parameters are also plenty (Caproni et al., 2010; Palmowski et al., 2010; Paolo et al., 2011; Wan et al., 2012), the research about the evaluation of diagnostic capability of US quantitative analysis is still rare, this study aimed to investigate and compare the application values of CEUS qualitative and quantitative analysis towards the identification of benign and malignant breast tumor lumps.

Materials and Methods

Study subjects

73 patients with breast tumor lumps, who were treated

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in the affiliated School of Medicine, North Sichuan Medical College, from September 2011 to June 2013, were selected, all the patients were female, aged 19 to 68 years old, with the mean age as 43.5±8.8 years old. All patients were treated by the surgery, and before the surgery, all the patients agreed with the surgery and signed the informed consent before the performance of angiographic examination, the gross specimen observation was performed intraoperatively, and the pathological diagnosis was made by the postoperative frozen sections and paraffin sections, among whom 41 cases were malignant (39 cases of invasive ductal carcinoma and 3 cases of intraductal carcinoma in situ), and 32 cases were benign (19 cases of fibroadenoma, 8 cases of adenosis, 3 cases of inflammatory lesions and 2 cases of cysts).

Inspection method

The iU22 ultrasound instrument (Philips) was used, with L9-3 broadband linear array probe, as well as the conditions of pulse reversed phase harmonic contrasting, the mechanical index was 0.07. the ultrasound contrast agent was Sonovue (Bracco Milan, Italy), which was oscillation-diluted with 5ml saline before the usage. During the examination, the patient was placed in the supine position, exposing the chest, then the high-frequency L9-3 broadband linear array probe was used to scan the bilateral breasts, respectively, which started from the outer upper quadrant and performed the spoke-like scanning from the periphery to the nipple and along the clockwise direction, the suspicious lesion was performed the bilateral comparison, the gray and color Doppler and spectral Doppler images were gathered, meanwhile, the lesion areas of interest were performed CEUS, 3ml contrast medium was intravenously bolus-injected through the medial cubital vein, and 3-min continuous dynamic US images were synchronously and dynamically stored in the instrument.

Image analysis

The stored image data were performed the offline analysis, and the features of enhanced contrasting lesion area were then carefully observed, including 6 indicators: contrast perfusion mode (rapid or slow perfusion), enhanced homogeneity of lesion areas (homogeneous, heterogeneous), whether or not the lesion diameter expanded when the contrast agent reached the peak (expansion, non expansion), enhanced type of lesion edge, whether or not the edge was clear (clear, not clear), and lesion intensity at the peak (low or Iso-Enhanced, highly enhanced), the above indicators were used as the qualitative diagnosis basis of lesions; the QLAB analysis software was also opened and performed the sampling towards the lesion regions and surrounding normal tissues that had the richest blood flow imaging, respectively, then the time - intensity curve towards the interested region could be obtained, and the perfusion parameters towards different regions could also be obtained through the curve, including the peak intensity, area under the curve, peak time, increasing slope, decreasing slope, increasing-start time, relative peak intensity, relative area under the curve, relative peak time, relative increasing slope, relative decreasing slope and relative increasing-start time, these total 12 indicators were used as the quantitative diagnosis basis of lesions.

For statistical methods

The SPSS 11.5 statistical software was used, the measurement data were performed the normality test,

Table 1. Results of CEUS Qualitative Analysis of 73 Breast Tumour Cases

Group	Cases	Contrast Perfusion Mode*		Enhanced Characteristic Of Lesions		Diameter Expansion At The Peak*	
		Rapid	Slow	Homogeneous	Heterogeneous	Non-Expansion	Expansion
Benign	32	12	20	25	7	28	4
Malignant	41	38	3	15	26	5	36
x^2		10.03		12.52		41.15	
P		0.002		0		0	
Group	Cases	Types Of Enhanced Lesion Edge		Border Edge		Lesion Intensity Grade At The Peak*	
		Radiated	Non-Feature	Clear	Not Clear	Low Or Iso-Enhanced	Highly Enhanced
benign	32	1	31	16	16	19	13
malignant	41	19	22	8	33	4	37
x^2		16.88		7.57		20.505	
P		0		0.006		0	

Note: *: Continuous correction X^2 test; without *: Pearson X^2 test.

Table 2. Results of CEUS Quantitative Analysis of 73 Breast Tumour Cases (x^2±s)

Group	Cases	Increasing Slope	Decreasing Slope	Increasing-Start Time(s)	Peak Time(s)	Peak Intensity(db)	Area Under The Curve(db*s)
Benign	32	0.70±0.30	0.09±0.05	15.66±5.40	18.00±5.40	4.36±1.68	220.11±18.25
Malignant	41	0.80±0.29	0.06±0.02	15.35±5.48	53.00±23.00	5.40±2.02	265.00±158.02
X^2		-1.142	0.46	1.06	0.85	-2.03	-1.27
P		0.26	0.64	0.29	0.41	0.04	0.21
Group	Cases	Relative Increasing Slope	Relative Decreasing Slope	Relative Increasing-Start Time (s)	Relative Peak Time (s)	Relative Peak Intensity (db)	Relative Area Under The Curve (db*s)
Benign	32	0.12±0.39	-0.01±0.02	-0.20±4.11	1.75±6.37	0.97±1.50	60.8±73.6
Malignant	41	0.24±0.48	-0.02±0.05	-3.40±5.66	36.20±21.3	2.57±1.82	43.5±160.4
X^2		-0.98	1.7	2.55	-0.81	-0.36	-2.63
P		0.33	0.09	0.01	0.43	0.01	0.01

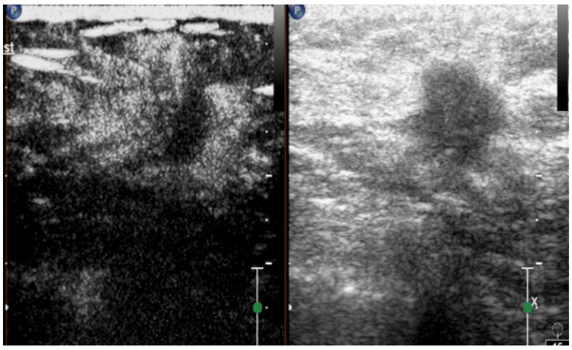

Figure 1. CEUS Manifests of Malignant Lesions: Rapid Perfusion, High Enhancement, Heterogeneous Enhancement, Diameter Expanded, Unclear Boundary, Peripheral Radial Enhancement

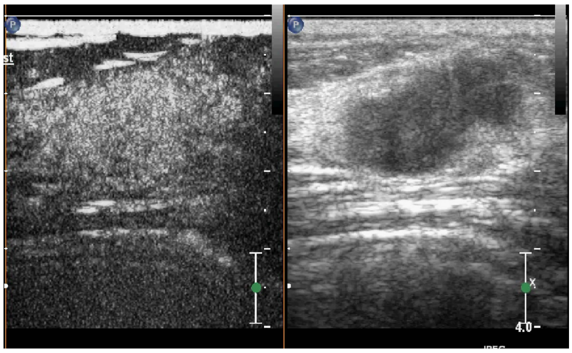

Figure 2. CEUS Manifests of Benign Lesions: Rapid Perfusion, Homogeneous Enhancement, High Enhancement, Clear Boundary, Diameter Non-expanded, without Peripheral Radial Enhancement

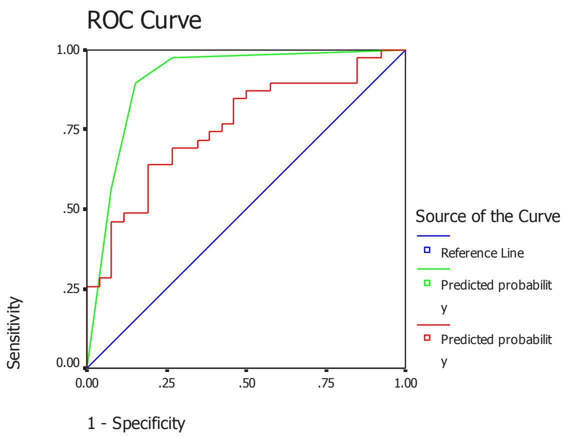

Figure 3. Comparison of Area under the ROC Curve Between the Qualitative Analysis and Quantitative Analysis, the Red Curve Was the Quantitative Analysis ROC Curve, the Green Curve was the Qualitative Analysis ROC Curve

Table 3. Multivariate Analysis of CEUS Qualitative Indicators

Regression parameter	B	S.E.	Wald	df	Sig.	Exp(B)
Enhanced feature	1.912	0.765	6.245	1	0.012	6.766
Diameter expansion	-3.254	0.694	22.006	1	0	0.039
Peak intensity grade	1.571	0.53	8.778	1	0.003	4.3811

Note: B: regression coefficient; SE: standard error of regression coefficients; Wald: test statistic of partial regression coefficient; df: degrees of freedom; Sig : significant level; Exp(B): regression coefficient index

followed by the two independent sample t test; the counting data were performed the chi-square or rank sum test, with P<0.05 set as the test standard, and considered as the statistical significance. The Binary Logistic process was used to perform the Logistic regression forward stepwise analysis towards the qualitative and quantitative indicators, respectively, and found the Logistic regression equation; the new variables, pre-1 and pre-2, which contained the individual prediction probability, were generated from the SPSS data table, the ROC curve process of SPSS was then used , with the new variables as the independent variables, and the pathological diagnostic results as the dependent variables (benign value: 0, malignant value: 1), to perform the ROC curve analysis, the areas under the 2 curves were performed the Z test, with p<0.05 set as the test standard, and considered as the statistical significance.

Results

Univariate analysis

Among the qualitative indicators, such indicators as enhanced type of lesion edge, contrast perfusion mode, enhanced homogeneity of lesion areas, diameter expansion at the peak, lesion intensity at the peak and whether or not the edge was clear had the statistically significant differences between the benign and malignant groups (p <0.05) , the CEUS qualitative analysis results were shown in Table 1 and Figures 1 and 2. Among the quantitative indicators, such indicators as lesion intensity at the peak, relative peak intensity, relative area under the curve and relative increasing-start *time* between the two groups had statistically significant differences (p <0.05), the quantitative analysis results were shown in Table 2.

Multivariable analysis

Logistic regression analysis of qualitative indicators: the qualitative indicators that had the statistical significance were put into the logistic regression, and those that finally entered the equation were lesion enhanced homogeneity, lesion diameter expansion and peak intensity grading. the equation accuracy towards the prediction of benign and malignant tumors diagnosis was 91.8%, the multivariate analysis of qualitative indicators were shown in Table 3.

The logistic regression analysis of quantitative indicators: the quantitative indicators that eventually entered the Logistic regression equation were only the relative peak intensity, with the regression coefficient as 0.383, and the Wald test value was 10.26, P=0.001, and the equation accuracy towards the prediction of benign and malignant tumors diagnosis was only 61.5%.

Comparison of areas under the ROC curves (Figure 3) the area under the ROC of pre-1, new variable generated by the qualitative analysis, was 91.3%,, while that of pre-2 generated by the quantitative analysis was 75.7%, the Z test revealed that Z = 2.113 and P = 0.0346, and the difference was statistically significant, indicating that the qualitative indicators were better in the diagnosis of benign and malignant breast tumor lumps than the quantitative indicators.

Discussion

The breast ultrasound examination has become a popular clinical examination, and with the development of CEUS techniques, the diagnostic accuracy has been greatly improved than the conventional US (Ricci et al., 2007; Barnard et al., 2008). The results of this study indicated that among the quantitative indicators, the peak intensity was higher in the malignant breast tumor lumps, while among the qualitative indicators, the enhancement degree mainly showed the high enhancement in the malignant group, the above enhancement degree indicators reflected the consistent substance, i.e., the blood vessel density of malignant lesions was higher. The quantitative analysis could display the differences inside the qualitative indicators with a value- quantization way, thus it would be more intuitive and comparable (Du et al., 2012). In addition, this study also introduced the relative parameter study, aiming to eliminate the patients' individual differences, reduce the interference factors that would affect the quantitative analysis, thus it would be more stable than the simple use of lesion parameters. The results showed that the relative peak intensity, relative area under the curve and relative increasing- start time had the difference between the benign and malignant groups, indicating that the contrast agent appeared in the malignant tumors much more earlier than in the benign tumors, and the enhancement was much more stronger, the accumulation of microbubbles per unit time was much more. The multivariate analysis showed that the relative peak intensity exhibited a greater role and influence than the other quantitative indicators in predicting the benign and malignant breast tumor lumps, but the corresponding area under the ROC curve was only 75.7%, so that its prediction ability was only moderate and limited. The reason might lie in the fact that the parameters and indexes of quantitative analysis might be interfered by many extrinsic and intrinsic factors (Ignee et al., 2010; Gauthier et al., 2011). Such intrinsic factors included the patient's heart rate, blood vessel flexibility, mental status in the examination, which would directly affect the speed and concentration of contrast agent distribution and diffusion *in vivo*; the extrinsic factors included the dosage of contrast agent injected, injection speed, size and location of the interested region, which would affect the parameters ,such as peak time, peak intensity and area under the curve, etc. The study also confirmed that though the application of time-intensity curve for the quantitative parameter had the objective comparability, it was still interfered by many unknown factors presently, which would affect the stability of parameters, and still needed a lot of objective researches to further improve the quantitative analysis.

However, the application of qualitative analysis could get a much more accurate diagnostic result. The results of this study showed that six indicators of qualitative analysis exhibited the differences in the benign and malignant groups, which reflected that the malignant breast tumor lumps were often rapid perfused, with heterogeneous enhancement, when reaching the peak, they exhibited the high enhancement and expanded diameters, the borders were not clear, and the edges would exhibit the feature of radial enhancement; while the benign tumor exhibited the slow perfusion progress, homogeneous enhancement, equal or low enhancement when reaching the peak, clear boundary, non-expanded diameter, and no radial enhanced edge. the multivariate analysis revealed that the enhanced homogeneity, expanded diameter or not, as well as the peak intensity grade were the main factors, and the enhanced homogeneity were the most prominent factor, indicating that the enhanced homogeneity would play the most role in determining the benign and malignant tumors, similar to the previous studies (Caproni et al., 2010; Zhao et al., 2010; Du et al., 2012). The relative pathophysiological basis lied in that the tumor cells would often secrete a large number of vascular endothelial growth factor (VEGF), thus generating a large number of fresh tiny blood vessels, but due to the vigorous growth of malignant cells, the tiny blood vessels could not supply the sufficient nutrients needed by the tumor cells, so the tumors would occur the internal necrosis, furthermore, the metastasis of tumor cells would often block these new blood vessels, further causing the tumor internal ischemia (Metz et al., 2003; Du et al., 2008), followed by the appearance of uneven distribution or filling defect of contrast agent inside the malignant tumors. Du et al (2012) studied and indicated that the characteristic of filling-defected regions within the lesions exhibited the high specificity towards the diagnosis of breast cancer, and this study still classified the characteristics of filling defect into the features of inhomogeneous enhancement, whether the diagnostic specificity was the highest still needed the further analysis. In addition, the malignant tumors often appeared the characteristics of enhanced posterior diameter expansion and high peak intensity. The pathological basis of these characteristics still lied in the fact the malignant cells secreted VEGF, thus promoting the generation of a large number of peripheral and internal microvessels (Drevs et al., 2008), these tiny blood vessels were often not detectable in the conventional US examination, but they would emerge by the contrast enhanced method, thus resulting in the visual illusion of tumor diameter expansion. And also because of the presence of the large number of new capillaries, the pathways of contrast agent entering the tumor would be increased, the large number of contrast agent would then gather within the tumor, leading to the characteristics of significantly high peak intensity.

The application of the above qualitative indicators towards the prediction of benign and malignant breast lesions exhibited the corresponding area under the ROC curve as 91.3%, significantly higher than that of the quantitative indicators, and the Logistic regression prediction could achieve the diagnostic accuracy as 91.8%, which was also significantly higher than the prediction accuracy of quantitative indicators.

In summary, the qualitative analysis of US imaging could not only quickly and accurately obtain the diagnostic information, but also its prediction ability was significantly better than the quantitative analysis, thus it was a clinical diagnostic method worthy of generalization.

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