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Original Article

The value of virtual touch tissue imaging quantification combined with color Doppler ultrasound and CA153 in diagnosing early breast cancer

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Abstract: Objective: To explore the value of virtual touch tissue imaging quantification combined with color Doppler ultrasound and carbohydrate antigen 153 (CA153) in diagnosis of early breast cancer. Methods: Clinical data of 196 patients with breast masses were collected and analyzed proactively. Among these patients, 89 patients were confirmed with malignant breast tumor and 107 patients were confirmed with benign breast tumor according to final pathological report. The breast imaging reporting and data system (BI-RADS) grading quantitative score, transverse shear wave velocity (SWV), and CA153 level of all patients were analyzed. Results: The BI-RADS grading quantitative score, SWV, and CA153 level of the malignant tumor group were all significantly higher than those of the benign tumor group (all $P<0.05$). The area under the receiver operating characteristic curve (AUC) of SWV in diagnosing breast cancer was 0.855, and when SWV was 4.205 m/s, its sensitivity and specificity were 0.640 and 0.981, respectively; The AUC of BI-RADS score in diagnosing breast cancer was 0.797, and when the BI-RADS grading quantitative score was 3.5 points, its sensitivity and specificity were 0.798 and 0.636, respectively. The AUC of CA153 in diagnosing breast cancer was 0.838, and when the CA153 level was 19.99 U/mL, its sensitivity and specificity were 0.663 and 0.981, respectively. In addition, the AUC of SWV combined with BI-RADS grading quantitative score and CA153 in diagnosing breast cancer was 0.978, and its sensitivity and specificity were 0.910 and 0.953, respectively. Conclusion: Virtual touch tissue imaging quantification combined with color Doppler ultrasound and CA153 is of a high value in the diagnosis of breast cancer, so it is worthy of clinical application.

Keywords: Breast cancer, virtual touch tissue imaging quantification, color Doppler ultrasound, carbohydrate antigen 153, diagnostic value

Introduction

Breast cancer is one of the most prevalent malignant tumors that threaten women's health, accounting for 11.4% of all new cases of tumors and 6.6% of tumor-related deaths [1, 2]. It is also the most common malignant tumor that leads to women's death [3]. According to studies, the incidence of breast cancer is increasing annually, and more and more young people suffer from the disease [4, 5]. Early diagnosis and treatment of patients with breast cancer are of great significance to the prognosis of the patients [6, 7]. Ultrasonography has unique advantages in the diagnosis and differential diagnosis of early breast cancer. Color Doppler ultrasound can image blood flow on the basis of conventional ultrasound for qualitative analysis of blood flow, which is clinically called "noninvasive angiography" [8, 9]. However, in the diagnose of blood flow and tissue in the lesion, color Doppler ultrasound is susceptible to external factors such as individual differences and chemotherapy, so it has certain limitations [10]. Being able to judge the elastic hardness of tissues to identify the nature of masses, ultrasonic elastography is more and more widely used in the diagnosis and differential diagnosis of breast cancer in recent years. However, as a qualitative and semi-quantitative technology, it has certain limitations in accuracy and repeatability in clinical application [11-13]. Virtual touch tissue imaging quantification (VTIQ) is a new shear wave velocity imaging method, which can qualitatively and quantitatively analyze the elasticity and hardness of local lesions and predict the malignancy of lesions, but it has not been widely applied to the diagnosis of breast cancer in clinical practice [14]. Carbohydrate antigen 153 (CA153) is recognized as the most specific serum marker in the diagnosis of breast cancer. However, in recent years, the diagnostic value of CA153 in breast cancer has been questioned. One study has found that the sensitivity of CA153 alone in diagnosis of breast cancer is unfavorable [15]. Therefore, this study adopted VTIQ combined with color Doppler ultrasound and CA153 to diagnose patients with breast cancer.

Materials and methods

General materials

The clinical data of 196 patients with breast masses admitted to the department of breast and thyroid surgery in the Second Affiliated Hospital of Hainan Medical University from January 2017 to January 2020 were collected and analyzed proactively. The patients were between 34 and 72 years old, with an average age of 51.9±8.3 years. Among these patients, 89 patients aged 51.8±9.2 years were confirmed with malignant breast tumor and 107 patients aged 52.3±8.1 years were confirmed with benign breast tumor according to final pathological study. The study was carried out with permission from the Ethics Committee of the Second Affiliated Hospital of Hainan Medical University and informed consent forms signed by all enrolled patients.

Inclusion and exclusion criteria

The inclusion criteria of the study were as follows: patients meeting the diagnostic criteria of breast cancer or benign tumor, patients between 18 and 75 years old, patients who had received radical mastectomy, patients confirmed with benign or malignant tumor according to breast puncture pathology, and those who had received VTIQ, color Doppler ultrasound examination, and CA153 results before diagnosis [16].

The exclusion criteria of the study were as follows: patients without complete clinical data, patients with severe heart, liver, kidney, or other diseases, patients unable to cooperate with the study due to mental diseases or cerebrovascular diseases, patients with other comorbid cancers or non-primary breast cancer, and new-onset patients who were undergoing chemoradiotherapy or had received chemoradiotherapy.

Methods

VTIQ and color Doppler ultrasound: All enrolled patients received VTIQ and color Doppler ultrasound conducted by a Siemens Acuson S3000 (SIEMENS AG, Germany). Firstly, the ultrasound instrument was adopted to carry out color Doppler ultrasound examination for each patient to detect and record the tumor mass nature, size, location, blood supply, their relationships with surrounding tissues, and echo, and the breast imaging reporting and data system (BI-RADS) was adopted to score and grade tumors. Afterwards, with the help of ultrasonic instrument, the maximum section of the breast mass was selected, so that the image of the lesion and surrounding tissues can be clearly displayed on the screen. The patient was required to hold his/her breath, and then the probe was adopted to touch the patient's skin. Then, the mode was switched to the VTIQ mode after stabilization of the image. Under this mode, the quality and speed mode pattern was acquired, and the pattern was switched to speed mode pattern when the image quality reached the highest under the quality and speed mode pattern. Subsequently, the transverse shear wave velocity (SWV) was recorded. Seven times of SWV in each mass position were recorded, and then averaged, and expressed in m/s. The BI-RADS grading quantitative score of each patient was analyzed. The scoring standard of BI-RADS was as follows: 1 point for possible benign lesion without suspicious malignancy, 2 points for probably benign lesion with a low-grade suspicious malignancy, 3 points for benign lesion with a medium-grade suspicious malignancy that requires a short-term follow-up, 4 points for suspicious malignant lesion with a malignant rate higher than 2% and lower than or equal to 95%, and 5 points for high-grade malignant lesion with a malignant rate higher than 95% [17]. A score of 1 to 3 points indicated benign lesion, and a

Table 1. Comparison of general data and baseline data between the two groups

Items	Malignant tumor group (n=89)	Benign tumor group (n=107)	χ^2/t	P
Age (years)	51.8±9.2	52.3±8.1	0.404	0.686
Tumor size (mm)	10.86±2.68	10.48±2.48	1.032	0.304
Distance from tumor to skin (mm)	7.76±1.86	7.49±1.62	1.086	0.279
Distance from tumor to nipple (mm)	4.68±0.68	4.62±0.63	0.640	0.523
Breast thickness (mm)	19.57±2.68	19.23±2.59	0.901	0.369
Body mass index (kg/m^2)	21.36±2.45	21.58±2.19	0.663	0.508
Menopause (≥45 years old)	74	94	0.878	0.349
Abortion history	48	51	0.764	0.382
Smoking history	16	21	0.086	0.769

score higher than 3 points indicated malignant lesion.

CA153 quantification: Venous blood (5 mL) was sampled from each patient with breast masses after 8 hours of fasting on the day before pathological examination, and stored in coagulation-promoting tubes (Zhuhai Kindly Medical Devices Co., Ltd., China). After standing for 30 min, the sampled blood was centrifuged at 4000 rpm to separate serum from it. The level of CA153 in the serum was determined using automatic chemiluminescence immunoassay system (MAGLUMI X8; Shenzhen New Industries Biomedical Engineering Co., Ltd., China). The level of CA153 higher than 25 U/mL indicated positive result. All operations were strictly carried out in accordance with the instrument and reagent instructions.

Outcome measures

The diagnostic value and optimal diagnostic cutoff value of BI-RADS grading quantitative score, SWV, and CA153 level for malignancy of breast masses were analyzed, and binary Logistic regression analysis was adopted to calculate the predicted values of diagnosis by combination of the three, on which receiver operating characteristic (ROC) curves of the combination in diagnosis were evaluated.

The benign tumor group and the malignant tumor group were compared in grading quantitative BI-RADS score, SWV, and CA153 level.

Statistical analyses

Statistical analyses were carried out using SPSS 17.0. Measurement data were analyzed using the normality test. Measurement data in normal distribution were expressed as the mean ± standard deviation ($\bar{x}$ ± sd), and others were expressed as the median M (interquartile distance P25 and P75). Measurement data in normal distribution and homoscedasticity were analyzed using the t test, and expressed by t, and others were analyzed using the rank sum test, and expressed by χ^2. Enumeration data were analyzed using the Pearson chi-square test, and expressed by chi-square. In addition, ROC curves of diagnosis were adopted to evaluate diagnostic value, and ROC curves were drawn using Medcalc. $P<0.05$ indicates a significant difference.

Results

Comparison of general data and baseline data between the two groups

There was no significant difference between the two groups in age, tumor size, distance from tumor to skin, distance from tumor to nipple, breast thickness, body mass index, Menopause (≥45 years old), abortion history, and smoking history (all P>0.05). See **Table 1**.

Comparison of BI-RADS grading quantitative score, SWV, and CA153 level between the two groups

The BI-RADS grading quantitative score, SWV, and CA153 level of the malignant tumor group were all significantly higher than those of the benign tumor group (all P<0.05). See **Table 2**.

Diagnostic value of SWV combined with BI-RADS grading quantitative score and CA153 level in breast cancer

According to the ROC curves of SWV combined with BI-RADS grading quantitative score and CA153 level in diagnosing breast cancer, the

Table 2. Comparison of BI-RADS grading quantitative score, SWV, and CA153 level between the two groups

Items	Malignant tumor group (n=89)	Benign tumor group (n=107)	t	P
BI-RADS score	4.16±0.67	2.92±0.74	12.192	<0.001
SWV (m/s)	4.72±1.48	2.79±0.98	10.538	<0.001
CA153 (U/mL)	26.34±16.43	9.89±6.91	9.587	<0.001

Note: BI-RADS: breast imaging reporting and data system; SWV: shear wave velocity; CA153: carbohydrate antigen 153.

area under the ROC curve (AUC) of SWV in diagnosing breast cancer was 0.855, and when SWV was 4.205 m/s, its sensitivity and specificity were 0.640 and 0.981, respectively; the AUC of BI-RADS grading quantitative score in diagnosing breast cancer was 0.797, and when the score was 3.5 points, its sensitivity and specificity were 0.798 and 0.636, respectively; the AUC of CA153 in diagnosing breast cancer was 0.838, and when the CA-153 level was 19.99 U/mL, its sensitivity and specificity were 0.663 and 0.981, respectively; the AUC of SWV combined with BI-RADS score and CA153 level in diagnosing breast cancer was 0.978, and its sensitivity and specificity were 0.910 and 0.953, respectively. Pairwise comparison of the AUCs showed that the AUCs of SWV, CA153, and combination of the three were all significantly better than the AUC of BI-RADS grading quantitative score, and the AUC of the combination of the three was significantly better than that of SWV and CA153, respectively (all P<0.05). See **Table 3** and **Figure 1**.

Ultrasonographic features of VTIQ in the diagnosis of breast cancer

The VTIQ was adopted to diagnose invasive breast cancer and mucinous breast cancer, and the ultrasonographic features of them are shown in **Figures 2** and **3**.

Discussion

Based on the popularization of medical education, women have acquired a certain understanding of breast cancer, but due to the lack of typical clinical manifestations in the early stage, breast cancer is usually found late, resulting in the missing of the optimal treatment timing [18]. Ultrasonography for breast cancer is improving, and BI-RADS grading is adopted for lesions of different natures after ultrasonography in clinical practice, so the malignancy of lesions can be judged more objectively [19]. Moreover, BI-RADS grading can be adopted to describe the characteristics of breast masses such as edge, internal echo, and morphology, which is helpful for clinicians to judge the breast masses and determine the further treatment plan for patients [20]. VTIQ is a novel clinical ultrasonic diagnostic technique with real-time, quantitative, qualitative, and high-accuracy characteristics [21]. One study has revealed that VTIQ can be adopted for quantitative and qualitative analysis on the elastic hardness of lesion areas, which is more objective and accurate [22]. CA153 is a common serum marker for clinical detection of breast cancer [23]. One study believes that the prognosis of breast cancer can be well predicted by monitoring the level of CA153 [24]. In this study, we analyzed 196 patients with breast lesions, and found that the BI-RADS grading quantitative score and CA153 level of patients with breast cancer confirmed by pathology were both higher than those of patients with benign breast lesions. We further compared the SWV in VTIQ between the two groups of patients, and found that the SWV of patients with breast cancer was also higher than that of patients with benign lesion. These differences may be due to the fact that cancer cells of breast cancer patients infiltrate into tissue stroma, resulting in proliferation of fibrous tissue of tumor stroma and increase in the hardness and brittleness of tumor site. Higher malignancy is presented by stronger infiltration ability. It was previously reported that SWV in VTIQ can reflect the hardness difference of masses [25]. In VTIQ, after ultrasonic wave is emitted from the probe, a thrust is generated to contact and compress the mass, and the hardness of the mass is sensed through acoustic palpation, and then quantified to reflect SWV, which can reflect the hardness of the mass in real time and accurately [26]. Notably, a previous study has found that the SWV of 110 patients with breast cancer examined by VTIQ increases with the increase of tumor malignancy [27].

According to one study, the specificity of BI-RADS grading combined with elastosonography

Table 3. Comparison of AUCs of SWV, BI-RADS grading quantitative score, and CA153 in predicating breast cancer

Indicators	Cut off value	AUC	Sensitivity	Specificity	Standard error	95% CI
SWV (m/s)	4.205	0.855	0.640	0.981	0.026	0.803-0.907
BI-RADS score (point)	3.500	0.797**	0.798	0.636	0.031	0.737-0.857
CA153 (U/mL)	19.990	0.838#	0.663	0.981	0.029	0.781-0.895
Combination of the three		0.978***,###,&&&	0.910	0.953	0.010	0.960-0.997

Note: Compared with the AUC of SWV, **P<0.01; ***P<0.001; compared with the AUC of BI-RADS, #P<0.05; ###P<0.001; compared with the AUC of CA153, &&&P<0.001. CA153: carbohydrate antigen 153; BI-RADS: breast imaging reporting and data system; SWV: shear wave velocity; AUC: area under the curve; CI: confidence interval.

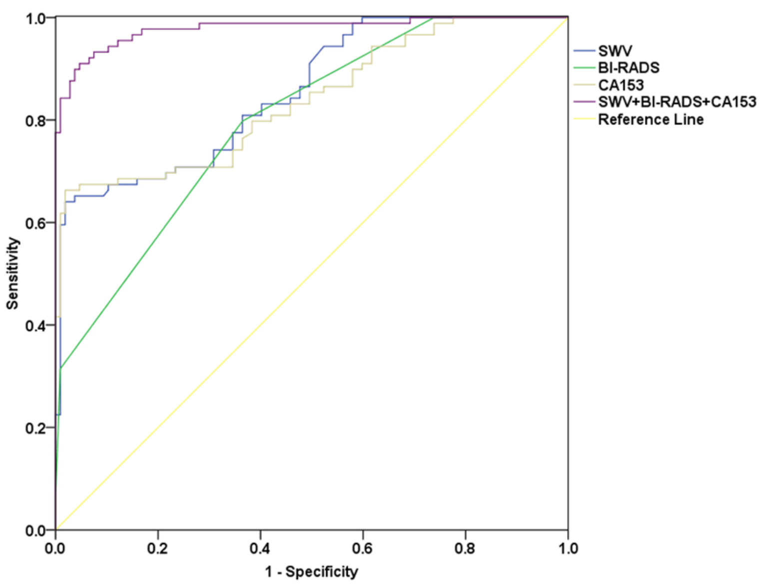

Figure 1. ROC curve of SWV combined with BI-RADS grading quantitative score and CA153 in diagnosing breast cancer. CA153: carbohydrate antigen 153; BI-RADS: breast imaging reporting and data system; SWV: shear wave velocity; ROC: receiver operating characteristic.

in the diagnosis of breast cancer can reach 99.45%, while the sensitivity of it is only 43.44% [28]. One other study has shown that the optimal cutoff value of VTIQ for the diagnosis of triple negative breast cancer is average SWV (≥4.279 m/s), and the diagnostic efficiency of VTIQ is higher than that of ultrasonic elastography and conventional ultrasonic imaging [29]. At present, there is no report on VTIQ combined with BI-RADS and CA153 for diagnosis. This study found that the optimal cutoff value of VTIQ for the diagnosis of breast cancer was 4.205 m/s, which was consistent with the above research results. Further application of VTIQ combined with BI-RADS and CA153 for diagnosis showed that diagnosis by the combination of the three can effectively improve the diagnostic sensitivity and specificity to breast cancer, which reached up to 0.910 and 0.953, respectively, suggesting that clinical ultrasound combined with blood index assay can improve the diagnostic efficiency of early breast cancer.

The deficiencies and prospects of the study are as follows: the sample size of this study is small, so it can be further expanded. In addition, this study is a retrospective study that may have selection bias due to many external factors. Therefore, a multi-center randomized controlled study can be further carried out.

To sum up, VTIQ combined with color Doppler ultrasound and CA153 is of a high value in the diagnosis of breast cancer, so it is worthy of clinical application.

Disclosure of conflict of interest

None.

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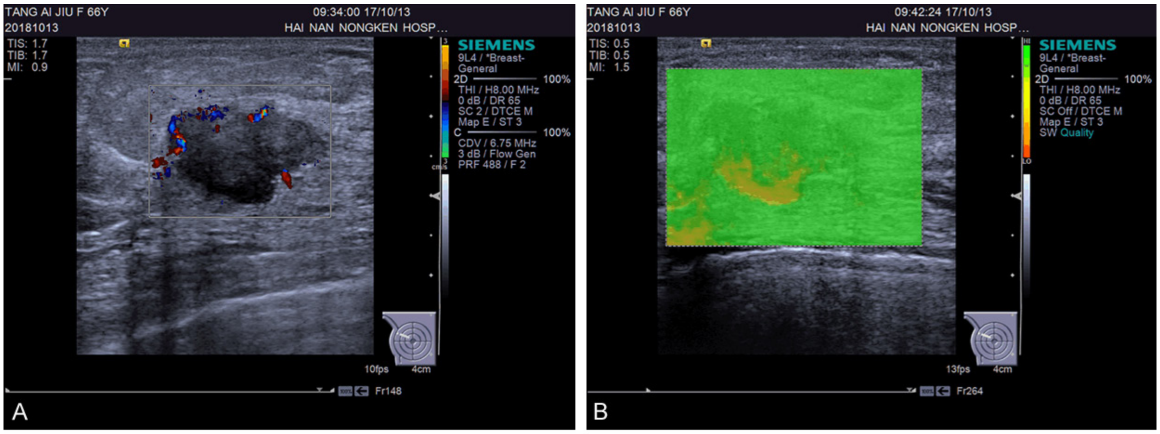


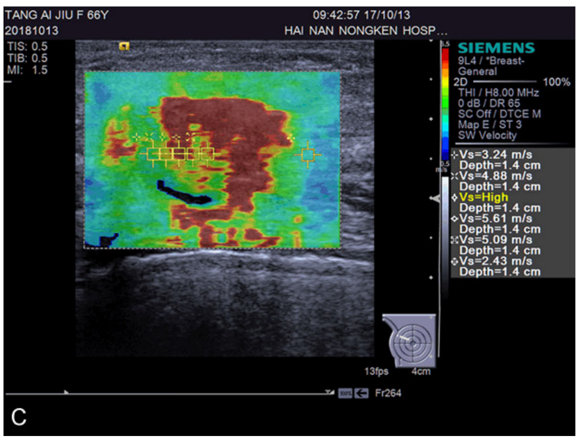
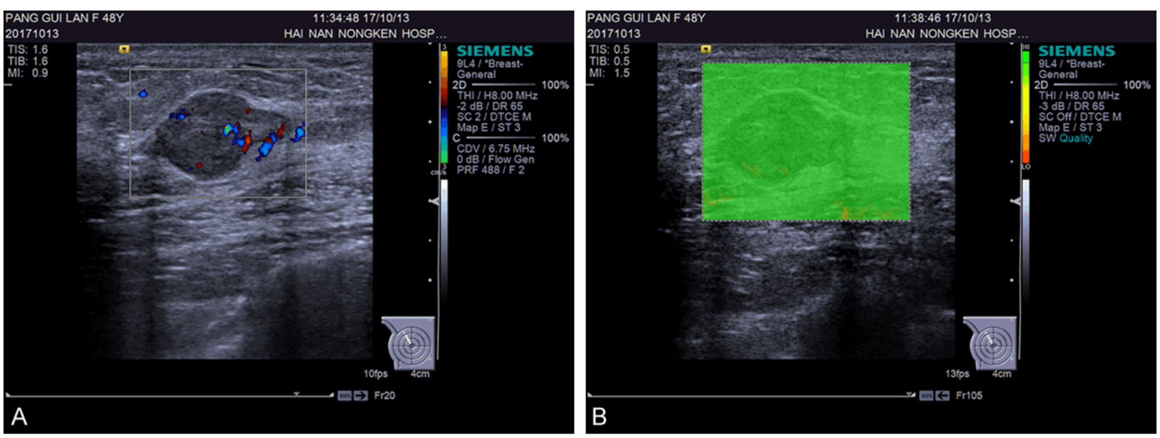


Figure 2. Ultrasonographic features of invasive breast cancer. (A) shows the tumor size and tumor blood flow distribution under B type ultrasound. (B) shows the quality mode pattern in VTIQ. (C) shows that the average SWV of invasive breast cancer was 4.71 m/s in VTIQ. VTIQ: virtual touch tissue imaging quantifcation; SWV: shear wave velocity.



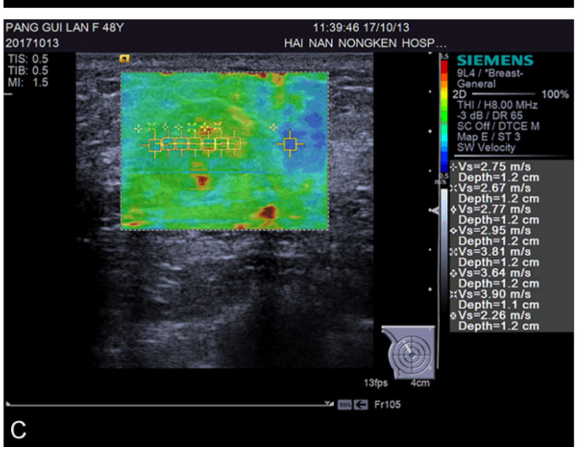


Figure 3. Ultrasonographic features of mucinous breast cancer. (A) shows the tumor size and tumor blood flow distribution under B type ultrasound. (B) shows the quality mode pattern in VTIQ. (C) shows that the average SWV of mucinous breast cancer was 3.21 m/s in VTIQ. VTIQ: virtual touch tissue imaging quantifcation; SWV: shear wave velocity.

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