Journal of Medical Ultrasonics (2019) 46:459–466
https://doi.org/10.1007/s10396-019-00948-0

ORIGINAL ARTICLE–BREAST & THYROID

The value of virtual touch tissue imaging quantification in the differential diagnosis between benign and malignant breast lesions

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Received: 12 January 2019 / Accepted: 10 April 2019 / Published online: 17 May 2019

Abstract

Purpose To evaluate the value and diagnostic performance of virtual touch tissue imaging quantification (VTIQ) and to determine the optimum cut-off value for differential diagnosis between benign and malignant breast lesions.

Methods Conventional ultrasonography (US) and VTIQ were performed in 454 patients with 466 breast lesions with a Siemens Acuson S3000 ultrasound machine. All lesions were assessed by an ultrasound Breast Imaging Reporting and Data System (BI-RADS) and confirmed by histopathology. The maximum, mean, and minimum shear wave velocity (SWV) values were quantitatively measured in m/s within the regions of interest (ROIs) and ranged from 0.5 to 10 m/s. The sensitivity, specificity, accuracy, and area under the receiver operating curve (AUC) of the VTIQ, BI-RADS, and combined data were compared.

Results Among the 466 breast lesions, 266 were benign and 200 were malignant. All of the SWV values of the malignant lesions were significantly greater than those of the benign ones ($P < 0.05$). The optimal cut-off values for SWVmax, SWVmin, SWVmean, and SWVmax/SWVmin obtained from ROC analysis were 5.37 m/s, 3.08 m/s, 4.04 m/s, and 1.83, respectively. Logistic regression analysis revealed that BI-RADS was an independent risk factor for the differential diagnosis of breast lesions, whereas SWV values were not independent risk factors.

Conclusions VTIQ is useful in the differential diagnosis between benign and malignant breast lesions. The combination of VTIQ and ultrasonic BI-RADS can improve the diagnostic performance.

Keywords Virtual touch tissue imaging quantification · Breast imaging reporting and data system · Shear wave velocity · Diagnostic performance

Introduction

Breast cancer, the leading cause of cancer death among women [1], has increased in incidence and prevalence in recent years. Early and correct diagnosis is particularly important to improve the prognosis of breast cancer patients.

Ultrasound (US) is one of the most powerful techniques for the diagnosis of breast carcinomas. Currently, in addition to B-mode ultrasound and colour Doppler flow imaging (CDFI), elastography has become a noteworthy method for diagnostic ultrasound systems [2–3]. Elastic techniques can be used to measure the stiffness of the tissue. Malignant lesions are often stiffer than benign lesions, which is useful for differential diagnoses. Various methods have become available, including strain elastography (SE) and shear wave elastography (SWE). However, strain elastography is operator dependent, and the results are sometimes inconsistent. In

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contrast, SWE measures the shear wave velocity (SWV) to quantify the tissue stiffness by generating an acoustic radiation force impulse (ARFI), which is more operator independent [4]. When using this technique, the probe generates a longitudinal push pulse that causes minimal localized displacement and is detected by the US instrument. There are two ARFI imaging techniques: virtual touch tissue quantification (VTQ) and virtual touch tissue imaging (VTI). The former is a quantitative technique that provides only a single-point shear wave velocity measurement, while the latter provides ARFI imaging for a qualitative assessment of tissue elasticity. However, VTQ has some limitations. It is impossible to pinpoint the stiffest lesion area. The fixed ROI size makes it unsuitable for small lesions. Moreover, the measurement scale of the SWV is limited (0.5–8.4 m/s). If the stiffness of the tissue is beyond the range of the scale, the SWV will be displayed as "X.XX m/s", which is caused by higher shear wave attenuation or the lack of SW generation [5–7]. Virtual touch tissue imaging quantification (VTIQ) is an improvement over ARFI. It has potential advantages to overcome the above limitations of the relatively wide measurement range (0.5–10 m/s) and small ROI (2 × 2 mm). The maximum, minimum, and mean SWV values can be obtained by the measurement according to a 2-D SWE map as well as qualitative maps for the shear wave quality, travel time, and tissue displacement. The clinical application of VTIQ has been reported in some papers [8–10].

Therefore, the objective of our study was to evaluate the diagnostic performance of VTIQ and to determine the optimal cut-off value for the differentiation between benign and malignant breast lesions.

Methods

Patient population

Between October 2015 and May 2018, a total of 454 women with breast lesions (range age 13–86 years; mean age 41.6 ± 15.2 years) who were willing to sign informed consent were enrolled in this study. They were enrolled based on the following eligibility criteria: (1) solid breast lesions. (2) Ultrasonic data were complete. (3) Final diagnoses for all lesions were proven histopathologically after surgical resection, ultrasound-guided percutaneous biopsy, or mammotome biopsy. The study was approved by our hospital's ethical committee. Signed written informed consent was obtained from all participants.

Ultrasound and touch tissue imaging quantification

All patients were examined with a Siemens Acuson S3000 ultrasound machine equipped with VTIQ software (Siemens Medical Solutions, Mountain View, CA, USA). The 9L4 liner array transducer with a frequency range from 4 to 9 MHz was assigned for the VTIQ examination. Prior to the VTIQ examination, all patients underwent routine tests including palpation, conventional US, and CDFI. Both the conventional ultrasound and the VTIQ examination were performed by one specialist with at least 5 years of breast imaging experience. The US images of breast lesions were simultaneously analysed and classified according to the Breast Imaging Reporting and Data System (BI-RADS). Data and images were reviewed by the same radiologist, who was blind to any pathological results of the lesions.

The VTIQ procedure was started after the optimal grey-scale ultrasound image had been selected. Then, the VTIQ procedure was started. Manual compression on the skin may change the elasticity and make the tissue stiffer [11], so the probe was placed on the skin surface with no manual compression. The angle of the probe was maintained perpendicular to the skin. The VTIQ measurement box was to include the breast lesion and surrounding tissue. Then, the SWE image was obtained while each patient held their breath for 3–5 s. The SW quality mode was first applied to evaluate whether the shear wave was of sufficient magnitude and to determine the signal-to-noise ratio. High-quality images are presented as green, whereas low-quality images are displayed as orange. From the colour-coded SWV map, the shear wave speed varied from red to blue, where red was assigned a high value, green an intermediate value, and blue a low value. Thereafter, some 2 mm square SW regions of interest (ROIs) were distributed among the lesions 5 mm apart to measure the SWV (Figs. 1, 2). The SW-ROI was to include the hardest stiff area and the lowest stiff area. The system automatically calculated SWVmax, SWVmin, and SWVmean. And the value of SWVmax/SWVmin was also obtained. The images and data were reviewed by another radiologist.

Statistical analysis

The data were analysed by statistical software (SPSS 18.0; SPSS, Chicago, IL). Quantitative data were expressed as the mean ± SD. An independent sample *t* test was used to compare each quantitative SWV (SWVmax, SWVmin, SWVmean, and SWVmax/SWVmin) between benign and malignant lesions. A *P* value of less than 0.05 was considered statistically significant. ROC analysis based on the predictive probability was performed to assess the diagnostic accuracy of SWV, BI-RADS, and the combination of the two. The optimal cut-off values for predicting malignancy were obtained by the Youden Index, and the sensitivity, specificity, and area under the curve (AUC) were also calculated. Logistic regression analysis was performed to evaluate the independent risk factor of the differential diagnosis.

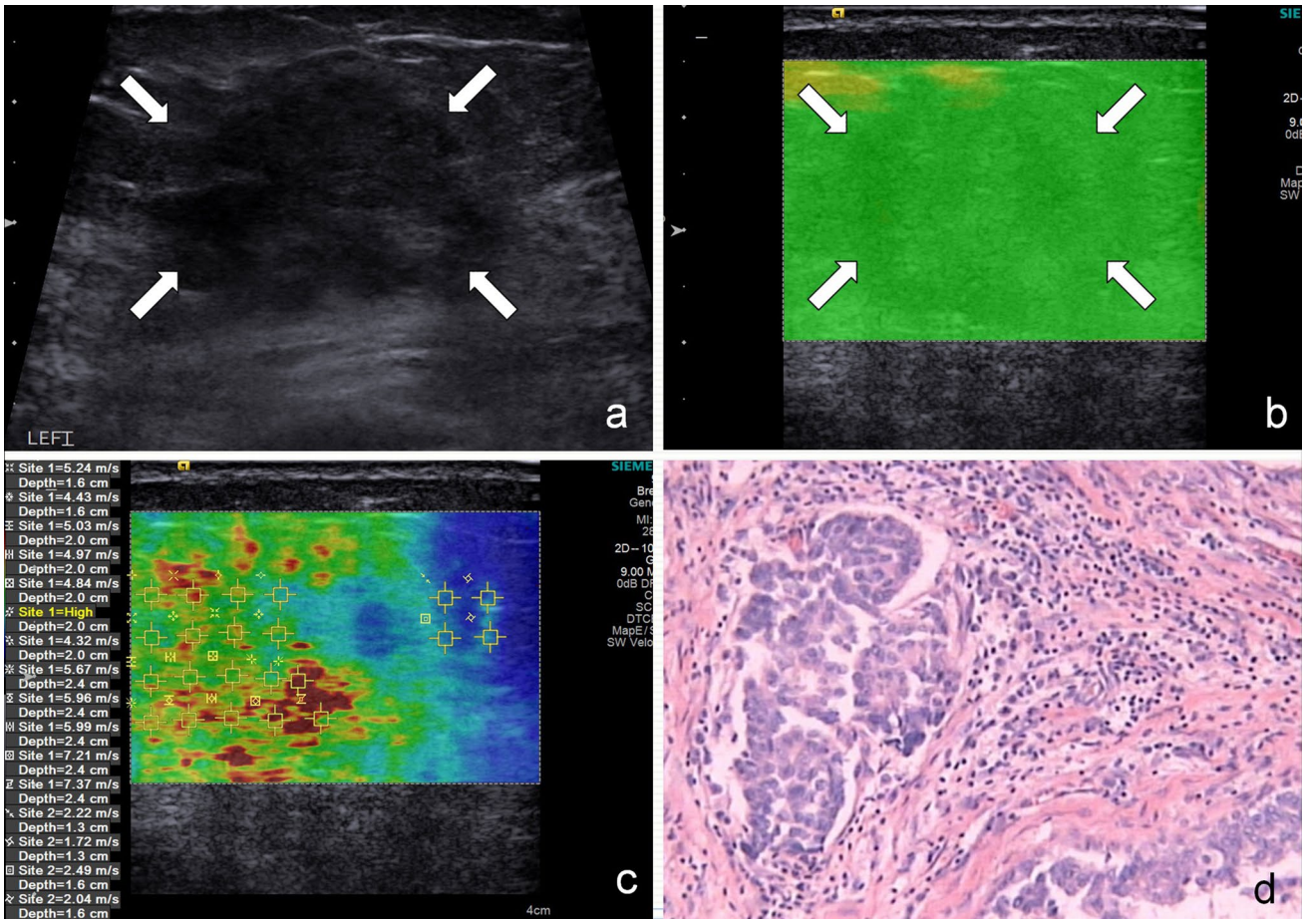

Fig. 1 A hypoechoic mass with an irregular shape and obscure boundary (**a**). It may be classified as BI-RADS 4c. The quality of the SWE image was good (**b**). In VTIQ velocity mode, the mass almost showed red or green areas, representing higher SWVs. The highest and mean SWVs were 7.37 m/s and 5.45 m/s, respectively (**c**). Pathological examination confirmed the diagnosis of an IDC (**d**)

Results

A total of 466 lesions were ultimately enrolled in this study. Two hundred (42.9%) lesions were pathologically confirmed as malignant, including invasive ductal carcinoma (IDC) ($n=164$), ductal carcinoma in situ (DCIS) ($n=14$), lobular carcinoma ($n=4$), and other types of malignancy ($n=18$), whereas 266 (57.1%) benign lesions were identified, including fibroadenoma ($n=264$) and benign phyllodes tumour ($n=2$). The lesion diameter ranged from 0.7 to 10.4 cm with a mean diameter of 2.1 ± 1.2 cm. The mean size of the malignant lesions was often larger than that of the benign lesions (2.6 ± 1.5 cm vs. 1.8 ± 0.7 cm, $P<0.05$). The mean patient age was significantly higher in patients with malignant lesions than in those with benign lesions (51.8 ± 11.7 years vs. 32.4 ± 10.1 years, $P<0.05$).

According to the BI-RADS classification, 210 lesions of benign cases were category 3, 44 were category 4a, seven were category 4b, four were category 4c, and one was category 5. Of the malignant cases, two lesions were category 3, nine were category 4a, 23 were category 4b, 68 were category 4c, and 98 were category 5 (Table 1).

The SWVmax, SWVmin, SWVmean, and SWVmax/SWVmin of the malignant lesions were 7.0 ± 2.3 m/s, 3.5 ± 1.4 m/s, 5.1 ± 1.7 m/s, and 2.2 ± 1.0, respectively (Fig. 3). All of the SWV values were higher than those of the benign lesions (3.6 ± 1.3 m/s, 2.3 ± 0.7 m/s, 2.9 ± 0.9 m/s, and 1.6 ± 0.4, respectively), with significant difference ($P<0.01$) (Table 2) (Figs. 1, 2).

The optimal cut-off values for SWVmax, SWVmin, SWVmean, and SWVmax/SWVmin obtained from ROC analysis were 5.37 m/s, 3.08 m/s, 4.04 m/s, and 1.83, respectively. All of the SWV values had a moderate sensitivity and fairly high specificity (SWVmax: 74.0%, 92.1%; SWVmin: 59.0%, 86.5%; SWVmean: 71.5%, 90.2%; SWVmax/SWVmin: 58.5%, 82.3%). The AUCs of SWVmax, SWVmin, SWVmean, and SWVmax/SWVmin were 0.884, 0.781, 0.871, and 0.720, respectively (Fig. 4). The diagnostic performance of SWVmax was a little higher than other SWV values, with an accuracy of 66.1% (Table 3).

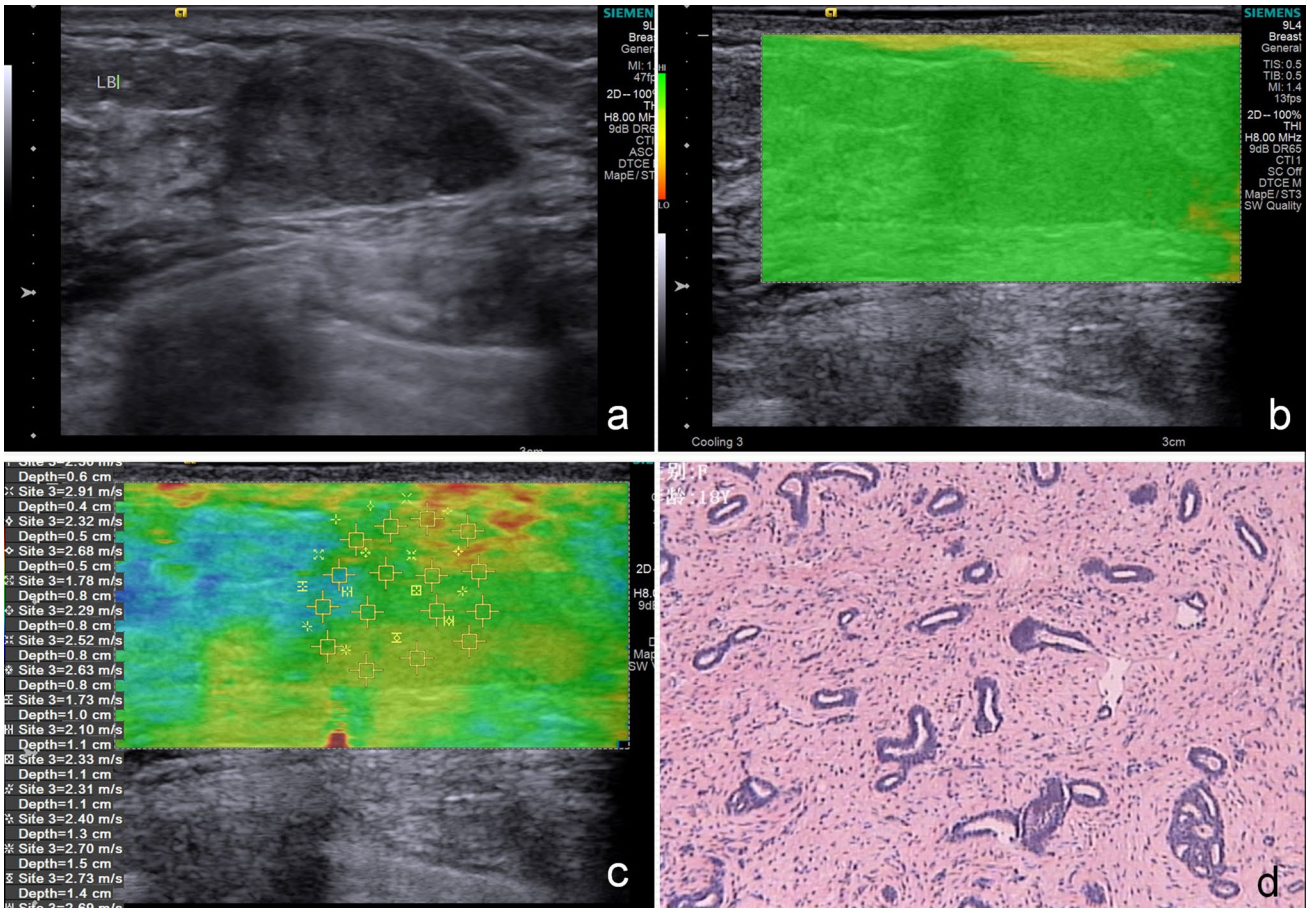

Fig. 2 A breast lesion classified as BI-RADS 3 on US shows a regular hypoechoic mass (**a**). A high-quality VTIQ image in which the whole lesion appears green is shown (**b**). In the VTIQ shear wave velocity mode, the SWV values in the lesion were relatively low (**c**). Pathological examination confirmed the diagnosis of fibroadenoma (**d**)

Table 1 The basic characteristics of patients and breast lesions

Characteristics	Total	Benign	Malignant	*P* value
No. of lesions	466	266	200	
Mean age (years)	41.6 ± 15.2	32.4 ± 10.2	51.8 ± 11.7	< 0.01
Nodule size (cm)	2.1 ± 1.2	1.8 ± 0.7	2.6 ± 1.5	< 0.01
BI-RADS classification				
3	212	210	2	
4a	53	44	9	
4b	30	7	23	< 0.01
4c	72	4	68	
5	99	1	98	

With category 4a as the optimal cut-off value, the sensitivity, specificity, and accuracy of BI-RADS in differentiating benign and malignant breast tumours was 94.5%, 95.5%, and 90.0%, respectively. Logistic regression analysis revealed that BI-RADS was an independent risk factor for the differential diagnosis of breast lesions, whereas SWVmax, SWVmin, SWVmean, and SWVmax/SWVmin were not independent risk factors (Table 4). However, the combination of VTIQ cannot significantly improve the diagnostic performance compared with BI-RADS alone (Table 5).

Discussion

The accurate prediction of malignant breast lesions remains a challenging problem. As a novel elastography technique, VTIQ can qualitatively and quantitatively measure the tissue stiffness to provide objective information for the differential diagnosis of breast lesions.

In our study, we attempted to determine the optimal cut-off values to improve the specificity and sensitivity of diagnosis using various SWV parameters (SWVmax, SWVmin, and SWVmean). We also used the value of SWVmax/SWVmin, which may represent the heterogeneity of the tumour texture. We found that the diagnostic performance

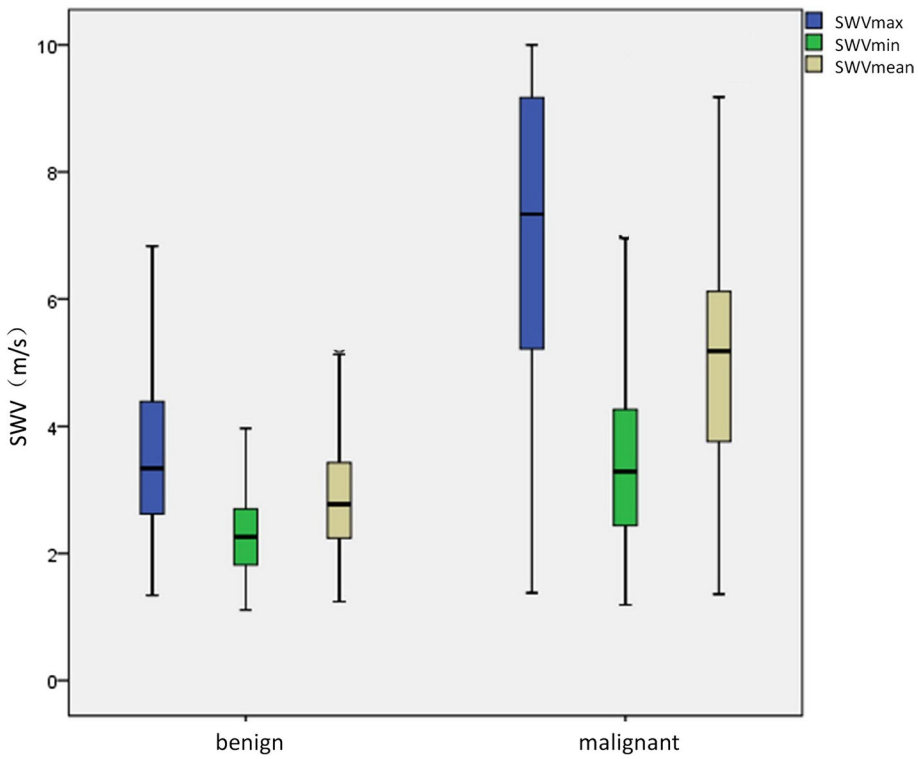

Fig. 3 Boxplot showing the range of SWVs in benign and malignant lesions

Table 2 The SWV of benign and malignant breast lesions

	Malignant	Benign	*t* value	*P* value
SWVmax (m/s)	7.0 ± 2.3	3.6 ± 1.3	12.721	< 0.01
SWVmin (m/s)	3.5 ± 1.4	2.3 ± 0.7	11.081	< 0.01
SWVmean (m/s)	5.1 ± 1.7	2.9 ± 0.9	16.771	< 0.01
SWVmax/SWVmin	2.2 ± 1.0	1.6 ± 0.4	8.231	< 0.01

of SWVmax was a little higher than that of the other SWV parameters, with an accuracy of 66.1%. SWVmean, SWVmin, and SWVmax/SWVmin were less valuable, in that order. When using 5.37 m/s as the SWVmax cut-off value, we found a sensitivity of 74.0% and a specificity of 92.1%. For SWVmean, this resulted in a cut-off of 4.04 m/s, yielding a sensitivity of 71.5% and a specificity of 90.2%. However, the optimal cut-off values for SWV were different in the literature. A study of 116 breast lesions showed an optimal cut-off value of 3.49 m/s with a sensitivity of 87.2% and a specificity of 82.6% [12]. Tozaki et al. [13] reported a cut-off value for malignant lesions of 4.14 m/s, and the sensitivity and specificity for the diagnosis of breast lesions were 88% and 93%, respectively. Golatta et al. [14] chose 5.18 m/s as the optimal cut-off value, which yielded a sensitivity of 98% and a specificity of 68% [10]. Another study of 296 breast lesions reported a value of 4.39 m/s with a sensitivity of 67.9% and a specificity of 86.3%. The differences among these studies might be due to the patient inclusion criteria, technical factors, pathological factors, or some unknown factors. For example, seven measurements were performed for each lesion in some reports, whereas in some studies, only one SWV measurement was performed. Multi-point measurements were adopted in our study, and a 2 mm square SW-ROI was distributed among the lesions 5 mm apart to measure the SWV. Thus, a different measurement method may result in different cut-off values.

To differentiate benign breast lesions from malignancy, an optimal cut-off value with high sensitivity and specificity is necessary. However, the specificity of all types of SWV value was relatively high in our study, whereas the sensitivity was low. For example, 52 malignant lesions showed a lower SWVmax than the cut-off value of 5.37 m/s. This meant some malignancies would be missed if we used SWV values alone. However, most of these lesions were classified as BI-RADS 4b (13/52), 4c (19/52), or 5 (15/52). With regard to the type of pathology, 75% of lesions were IDC, 15.4% were DCIS, 3.8% were mucinous carcinoma, and 5.8% were solid papillary carcinoma (SPC). The reason that DCIS has a lower SWV is due to the absence of a desmoplastic reaction, thus causing significant tissue stiffness. A mucinous carcinoma often contains a substantial amount of a jelly like substance, and thus may be softer than other kinds of breast cancers [15]. SPC is a rare type of breast carcinoma with abundant tumour cells and small blood vessels. It tends to be soft because of the lack of fibrosis. In the false-negative cases of IDC, no special characteristics of lesions

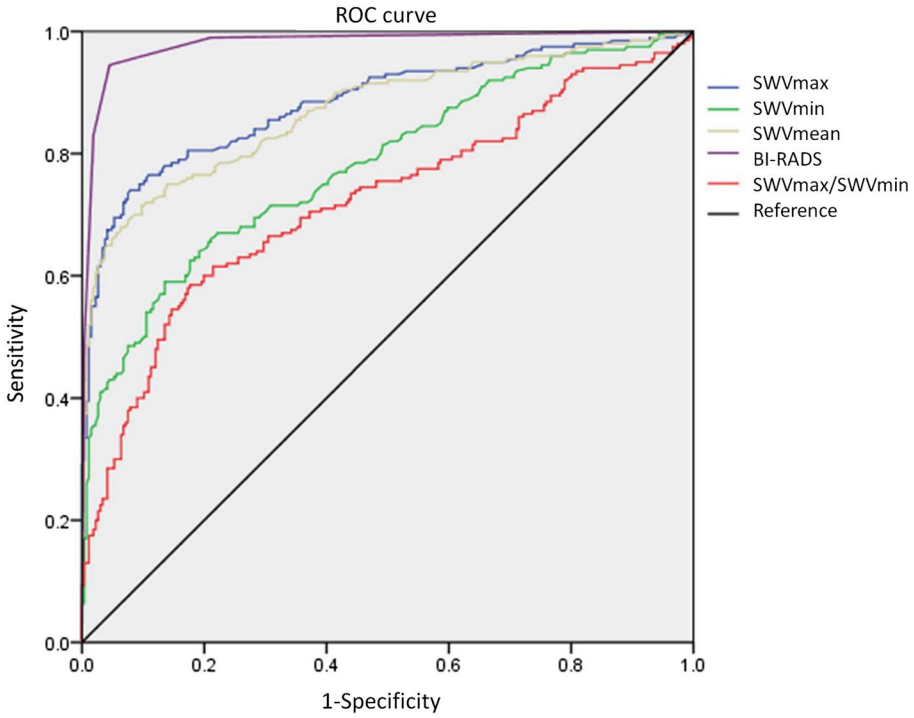

Fig. 4 Receiver operator characteristics (ROC) curve of SWVmax, SWVmean, SWVmin, SWVmax/SWVmin, and BI-RADS

Table 3 The diagnosis performance of various SWV between malignant and benign lesions

	SWVmax	SWVmin	SWVmean	SWVmax/SWVmin	BI-RADS
Cut-off value	5.37	3.08	4.04	1.83	4a
Sensitivity	74.0%	59.0%	71.5%	58.5%	94.5%
Specificity	92.1%	86.5%	90.2%	82.3%	95.5%
PPV	87.6%	76.6%	84.6%	71.3%	94.0%
NPV	82.5%	73.7%	80.8%	72.5%	95.9%
Accuracy	66.1%	45.5%	61.7%	40.8%	90.0%
AUC	0.884	0.781	0.871	0.720	0.980

were observed, also including lesion size. This phenomenon may limit the value of VTIQ when using elastography alone.

It is worth noting that five malignant lesions with SWVmean values lower than 5.37 m/s were classified as BI-RADS 4a or 3, which may often mimic benign lesions. These lesions included three IDCs (smaller than 1 cm), one DCIS, and one mucinous carcinoma. Some researchers have suggested that some lesions categorized as BI-RADS 3 or 4a with a lower SWV value may not require percutaneous biopsy or short-term follow-up. Giannotti et al. [16] analysed 694 breast lesions with conventional ultrasound and shear wave elastography. They found that none of the cancers had benign characteristics on both grey-scale ultrasound and SWE. However, we thought some early or special types of breast cancer may also have characteristics of benign lesions, so the diagnosis of these lesions needs further investigation.

The statistical results of our study demonstrate that the false-positive rate of VTIQ is relatively low (21/266, 7.9%). There were 21 benign lesions with a greater SWVmax values than the cut-off value of 5.37 m/s. Most of them were classified as BI-RADS 3 ($n=10$) or 4a ($n=6$). False positives may be caused by the nature of some benign lesions, such as a fibroadenoma with a predominant fibrous component, scar tissue, fat necrosis, or calcification [14, 15, 17].

Table 4 The result of Logistic regression analysis

	B	SE	Wals	Sig	Exp (B)	95% CI
SWVmax	−0.487	0.664	0.538	0.463	0.615	0.167–2.256
SWVmin	0.044	0.965	0.002	0.964	1.045	0.157–6.932
SWVmean	1.174	0.908	1.673	0.196	3.235	0.546–19.165
SWVmax/SWVmin	0.605	1.239	0.238	0.626	1.831	0.161–20.776
BI-RADS	2.167	0.241	80.701	0	8.729	5.441–14.004

Table 5 The diagnosis performance of BI-RADS and in combination with SWV values

	Sensitivity (%)	Specificity (%)	Accuracy (%)	AUC
BI-RADS	94.5	95.5	90.0	0.980
BI-RADS + SWVmax	95.5	95.5	91.0	0.986
BI-RADS + SWVmin	95.5	95.1	90.6	0.985
BI-RADS + SWVmean	96.0	95.5	91.5	0.987
BI-RADS + SWVmax/SWVmin	94.5	95.5	90.0	0.981

The combination of VTIQ and BI-RADS in our study seemed not to obviously improve the sensitivity and specificity compared with conventional US alone. This result may have been due to the relatively high diagnostic accuracy of BI-RADS. Logistic analysis also revealed that the SWV was not an independent parameter for the diagnosis of breast lesions. Therefore, we cannot rule out the help of conventional US for evaluating breast lesion characteristics. VTIQ provides only information about the tissue stiffness, and the final diagnosis should be made using a combination of VTIQ with the BI-RADS classification standard. Using the combination of BI-RADS and SWVmean, about 91.5% of lesions can be correctly diagnosed. It seems to be an encouraging result.

There were several limitations in our study. First, the conventional ultrasound imaging and SWE results were analysed by only one doctor, which may have resulted in operator-related bias. Another limitation of our study was the relatively few types of breast lesions investigated. Except for a few other types of breast cancer, most types of breast cancer are IDCs. Therefore, other types of lesions, especially DCIS, require further investigation and discussion. Third, although VTIQ can yield the mean and median SWV of breast lesions, it only reflects two dimensions, and thus can result in a slice selection bias. However, three-dimensional quantitative SWE acquisition is not available at present.

Conclusion

The results of our study suggest that VTIQ is a valuable complement to conventional US. The combination of VTIQ and ultrasonic BI-RADS can improve the diagnostic performance for breast lesions, a finding that is consistent with several recent studies. This study did have some limitations, so a large prospective study should be performed in the future to provide additional clinical application value.

Funding This study was funded by the National Natural Science Foundation of China (81671701) and the Nanjing Medical Science and Technique Development Foundation.

Compliance with ethical standards

Conflict of interest There are no conflicts of interest.

Ethical statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients for being included in the study.

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