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Original Article

A novel two-dimensional quantitative shear wave elastography for differentiating malignant from benign breast lesions

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Abstract: Objective: The purpose of this study was to evaluate the diagnostic performance of a novel quantitative shear wave elastography (SWE) of virtual touch tissue imaging quantification (VTIQ) in diagnosis of breast lesions. Methods: The conventional ultrasound (US) and VTIQ images of 133 pathologically proven breast lesions in 98 patients were assessed. The breast lesions were classified by US breast imaging reporting and data system (BI-RADS) category. The maximum, minimum, mean and median shear wave velocity (SWV) values on VTIQ in the lesions were obtained. The area under the receiver operating curve (AUC) was computed. Results: Twenty-six of 133 lesions were malignant and 107 were benign. The sensitivity and specificity for US BI-RADS assessment were 96.2% and 62.6% respectively. The SWVs in malignant lesions were all significantly higher than those in benign ones (all $P < 0.001$). The AUC for mean SWV value was slightly higher than AUC for maximum, minimum and median SWV values, whereas no significant differences among them were found (all $P > 0.05$). The cut-off value of mean SWV was 3.68 m/s, with associated sensitivity and specificity of 93.3% and 79.4% respectively. Conclusion: The novel quantitative SWE of VTIQ is helpful in differentiating breast lesions. Adding the quantitative SWE of VTIQ to the US BI-RADS assessment improves the specificity in diagnosing breast lesions without loss of sensitivity.

Keywords: Breast lesion, ultrasound, shear wave elastography, acoustic radiation force impulse, virtual touch tissue imaging quantification, diagnosis

Introduction

Breast cancer is a common cancer of women in most countries and is the leading cause of cancer death among women globally [1]. Although conventional ultrasound (US) in western countries is often used as a supplemental screening test in women with breast disease and in high-risk women [2], in eastern countries, conventional US remains the primary method and the general investigational screening test for breast cancer detection because of high breast density on mammography [3-5]. However, on conventional US, there is a considerable overlap in imaging features between the benign and malignant lesions, thus it is difficult to give an accurate specific diagnosis. Although conventional US using the breast imaging reporting and data system (BI-RADS) criteria provides a high sensitivity in differentiating malignancies, it suffers from low specificity [6]. Therefore, the inadequate specificity in differentiating benign from malignant breast masses has limited the usefulness of breast US [7]. A recent development is US elastography technique, which can reflect the stiffness of tissue [8]. The basic hypothesis of all elastography techniques is that malignant tissue is stiffer than benign tissue. Adding elastography technique to conventional US may help to improve the differentiation of benign and malignant breast lesion [9, 10].

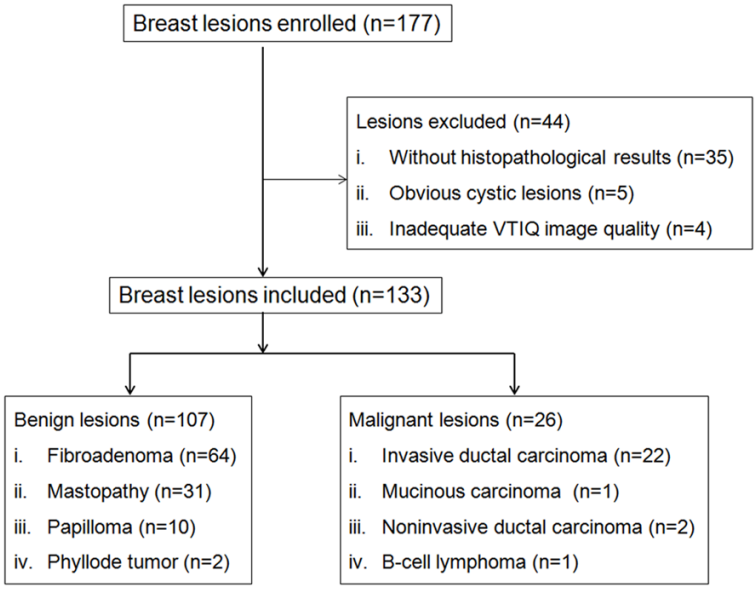

Figure 1. Flowchart of selection of the breast lesions.

However, conventional US strain elastography relies on manual compression and decompression applied by the examiner [11, 12], which leads to inconsistent results and examiner dependency. Acoustic radiation force impulse (ARFI) technology, as a shear wave elastography (SWE) technique, is based on the assessment of elastic properties by acoustic pulse [13-17]. When the ARFI is initiated, the probe emits a short-duration acoustic pulse which causes vertical pressure and lateral local displacement. The time to peak displacement at each lateral location is defined as shear wave velocity (SWV). SWV in soft tissue is slower than that of hard tissue, which provides an objective indicator of the tissue stiffness [16-19]. Thus in theory, ARFI may avoid the limitations of conventional US elastography techniques; it may be more reproducible and provide quantitative information of tissue stiffness [16, 17, 20-25]. In spite of that, conventional ARFI of virtual touch tissue quantification (VTQ) (Siemens Medical Solutions, Mountain View, CA, USA) suffers from the following shortcomings: the ROI is fixed (i.e. 6.5 mm) thus it is not suitable for small lesions; the SWV measurement range (i.e. 0.5-8.4 m/s) is limited thus it is not suitable for extremely hard or soft tissues; the imaging quality is hard to know that sometimes the SWV is not measurable because of inappropriate placement of ROI in the lesion. The latest quantitative SWE technique, virtual touch tissue imaging quantification (VTIQ) method (Siemens Medical Solutions, Mountain View, CA, USA) of ARFI, has the potential to technically overcome the limitations thus it may be more accurate to depict the real elasticity of the tissue quantitatively and may be applicable for more patients. The purpose of our study was to prospectively evaluate the diagnostic performance of VTIQ for differentiating breast lesions found in screening US.

Materials and methods

Patients

From June 2014 to August 2014, 134 consecutive women with 177 breast lesions on standard US with BI-RADS category 2 to 5 were enrolled in the study. The patients were referred by the clinicians after a standard clinical examination. The patients included those for screening US examination, for surveillance of an already existing breast mass, or for clarifying clinical symptoms. Forty-four lesions in 36 women were later excluded owing to the following reasons: 35 lesions in 31 women without histopathological confirmation, five lesions in 3 women with simple breast cyst since shear wave does not propagate in non-viscous fluid, and four lesions in 2 women without satisfactory VTIQ images. Finally, 98 women with 133 breast masses were enrolled in the study (**Figure 1**). Multiple breast lesions were found in 10 women and single breast lesion was present in 88 women. All the lesions were confirmed by pathological results with the specimens from surgery or US guided core biopsy.

The study was performed in strict accordance with the ethical guidelines of the Helsinki Declaration. Informed consent was obtained from the patients. The Ethics Committee of the University Hospital approved the prospective study and the consent procedures.

Conventional US and VTIQ examinations

A standard conventional US examination, including B-mode US and color Doppler US

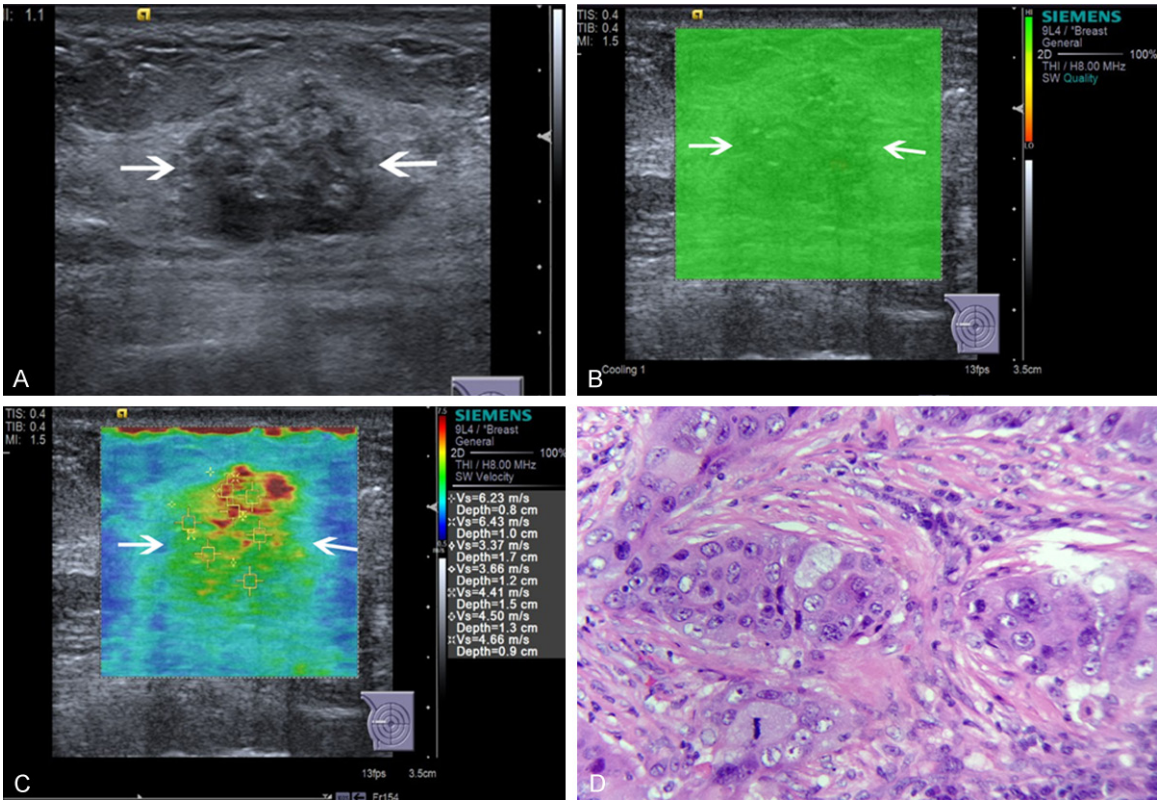

Figure 2. Invasive ductal carcinoma seen on US (A) as a BIRADS 4c hypoechoic mass (arrows). A high quality image map of VTIQ shows homogeneous green picture of the lesion (arrows) (B). In VTIQ shear wave velocity mode (C), SWV values in the lesion (arrows) are measured and repeated for seven times. The highest and lowest measurements are recorded as 6.43 m/s and 3.37 m/s; the median value is 4.5 m/s; and the mean SWV is calculated to be 4.75 m/s. The pathological examination confirms the diagnosis of invasive ductal breast carcinoma (Hematoxylin-eosin stain, ×100) (D).

examinations, were performed to all the patients. Firstly, the patients were asked to take the supine position with the breast fully exposed. The transducer was gently placed on the breast with light pressure. The patients were asked to hold breath. Meanwhile, the conventional US scanning was performed and the US features of the lesion were evaluated. Conventional US assessment was completed after the routine clinical examination by the consultant physician.

The VTIQ elastography was performed after conventional US examination with Siemens S3000 US scanner and a 9L4 linear array transducer (transducer frequency range of 4-9 MHz). VTIQ function was built in the imaging machine. The US image was adjusted to ensure the lesion was placed in the center of the screen, and then VTIQ was initiated in the longitudinal section of the breast lesion with the VTIQ box including the lesion and sufficient surrounding tissue. The transducer generates a longitudinal push pulse which causes minimal localized displacement and transverse shear-wave (SW) propagation. VTIQ measures the speed of the transverse SWs by detection pulses. The SWV can be quantitatively measured in meters per second (m/s) within the region of interest (ROI), up to 10 m/s [26-28]. VTIQ provides several imaging modes, such as SW quality mode, SW velocity mode, SW displacement mode and SW time mode. In each mode, a color coded map gives information of the tissue stiffness. In VTIQ SW quality mode, the image quality is shown as different colors from high (green), intermediate (yellow), to low quality (red). Then the imaging mode was shifted to SW velocity mode following SW quality mode, and the ROI was placed on the sites corresponding to the green areas on SW quality mode and the yellow or red areas on SW quality mode were avoided, which ensures effective SWV measurement. The ROI can be as small as 1.1 mm

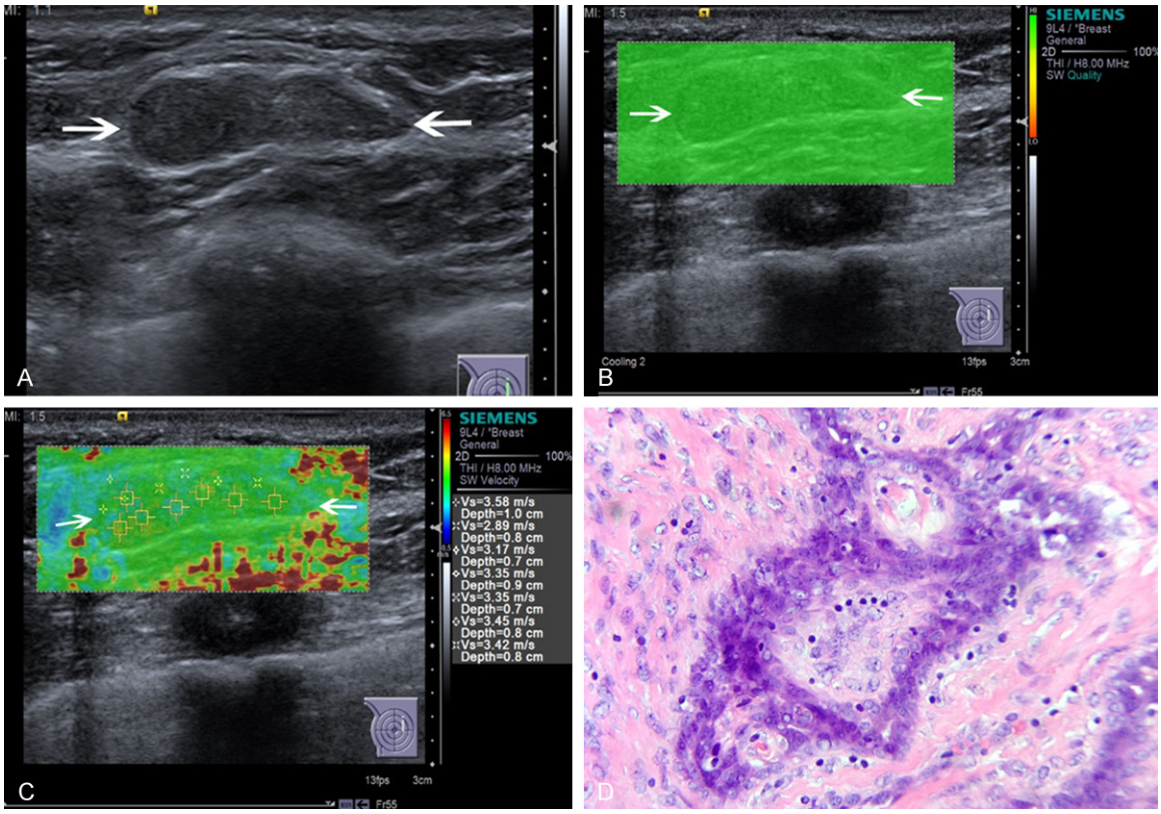

Figure 3. Breast fibroadenoma classified as BI-RADS 3 on US (A) shows a regular hypoechoic mass (arrows). A high quality image of VTIQ is shown that the whole lesion (arrows) appears as green (B). In VTIQ shear wave velocity mode (C), SWV values in the lesion (arrows) are measured and repeated for seven times. The highest and lowest measurements are recorded as 3.58 m/s and 2.89 m/s; the median value is 3.35 m/s; and the mean SWV is calculated to be 3.32 m/s. The pathological examination confirms the diagnosis of fibroadenoma (Hematoxylin-eosin stain, ×100) (D).

thus it is suitable even for small lesions. In VTIQ velocity mode, the speed distribution in the lesion is shown in different colors from high SWV (red), intermediate SWV (yellow or green), to low SWV (blue). The ROIs were placed on different locations in the lesion, including the high SWV area and low SWV area. In general, 5 to 7 measurements were performed (**Figures 2**, **3**). All data were recorded and stored to internal memory of the US machine for further analysis. Both US examinations and VTIQ measurement were performed by the same operator.

US and VTIQ image analysis

In US images, the lesions were assigned and classified corresponding to BI-RADS categories of 2, 3, 4a/b/c and 5. The assignment and classification were performed by two independent readers and disagreement was solved by consensus. The readers were blind to the related clinical information and the results of mammography. The expected malignancy rates of BI-RADS categories are as follows: category 2 (benign finding), non-malignancy; category 3 (probably benign), 2% likelihood of malignancy or less; category 4a (low suspicion of malignancy), greater than 2% to 10% likelihood of malignancy; category 4b (intermediate suspicion of malignancy), greater than 10% to 50% likelihood of malignancy; category 4c (moderate suspicion of malignancy), greater than 50% to 95% likelihood of malignancy; and category 5 (highly suggestive of malignancy), 95% or greater likelihood of malignancy [6, 24, 28].

VTIQ is an absolute measurement which cannot be influenced by the prior BI-RADS assessment; therefore it can be read by the same examiner without the risk of a bias. For each lesion, the maximum, minimum, median, and mean SWV values on VTIQ were recorded or computed.

Table 1. The size of the breast lesions on conventional US

Diameter (mm)*	Malignant (n=26)	Benign (n=107)	*P* value
Total	22.5±14.7 (3.4-53.3)	13.1±8.3 (9.7-81)	< 0.001#
< 10 mm	2 (7.7%)	21 (19.7%)	0.28
10-20 mm	13 (50%)	53 (49.5%)	
> 20 mm	11 (42.3%)	33 (30.8%)	

*Data are means ± standard deviations, with ranges in parentheses. #Indicates statistically significant difference.

Table 2. Absolute and relative frequencies of each conventional US BI-RADS category

	Total (n=133)	Benign (n=107)	NPV	Malignant (n=26)	PPV
BI-RADS 2	11 (8.3%)	11 (10.3%)	100%	0	-
BI-RADS 3	57 (42.9%)	56 (52.3%)	98.2%	1 (3.8%)	-
BI-RADS 4					
4a	33 (24.8%)	32 (29.9%)	-	1 (3.8%)	3.0%
4b	11 (8.3%)	6 (5.6%)	-	5 (19.3%)	45.5%
4c	18 (13.5%)	2 (1.9%)	-	16 (61.6%)	88.9%
BI-RADS 5	3 (2.2%)	0	-	3 (11.5%)	100%

Note: NPV: negative predictive value; PPV: positive predictive value; -, not applicable.

Statistical analysis

SPSS 17.0 (SPSS Inc, Chicago, IL, USA) was applied for statistical analysis. The quantitative data were expressed in the form of mean ± standard deviation. Differences in quantitative data between the malignant and benign groups were compared with independent *t*-test. Receiver operator characteristic (ROC) analysis was performed to assess the diagnostic performance. The best cut-off value was determined when the maximal sum of the sensitivity and specificity was achieved. The areas under the ROC curves (AUC) were calculated to compare the diagnostic performances of different SWV parameters and the AUC was compared using the *z* test. $P < 0.05$ was considered as statistical significance.

Results

Pathological results

Ninety-eight women with 133 breast lesions were involved in the study. Pathological results showed that 26 lesions were malignant and 107 lesions were benign. The 107 benign lesions included 64 of fibroadenoma, 31 of mastopathy, 10 of papilloma, 2 of phyllodes tumor; and the 26 malignant lesions included 22 of invasive ductal carcinoma, 2 of noninvasive ductal carcinoma, 1 of mucinous carcinoma and 1 of diffuse large B-cell lymphoma. The mean ages were 56.3±12.2 years (range: 40-84 years) for patients with malignant lesions and 40.8±13.4 years (range: 16-79 years) for those with benign lesions ($P < 0.001$). The mean sizes were 22.5±14.7 mm (range: 3.4-53.3 mm) for malignant lesions and 13.1±8.3 mm (9.7-81 mm) for benign lesions ($P < 0.001$) (**Table 1**).

Diagnostic performance of conventional US

Table 2 listed the absolute and relative frequencies of each conventional US BI-RADS category of 2, 3, 4a/b/c and 5. If the lesions of BI-RADS category 4a/b/c or 5 were regarded as malignant and the lesions of BI-RADS category 2, 3 were regarded as benign, conventional US BI-RADS category achieved 96.2% (25/26) of sensitivity, 62.6% (67/107) of specificity, 38.5% (25/65) positive predictive value (PPV), 98.5% (67/68) of negative predictive value (NPV), and 69.2% (92/133) of diagnostic accuracy, with the histological and pathological results as the reference standard.

Diagnostic performance of VTIQ

The comparisons of SWV on VTIQ between the benign and malignant breast lesions were shown in **Table 3**. For the whole lesions, the maximum, minimum, mean and median SWVs of the malignant lesions were all significantly higher than those of benign lesions (all $P < 0.001$). The cut off values for the maximum, minimum, mean and median SWV were 5.04 m/s, 2.95 m/s, 3.68 m/s, and 3.58 m/s, respectively. According to the ROC analysis, the diagnostic performances in terms of Az were 0.912, 0.937, 0.942, and 0.914, respectively, for the maximum, minimum, mean and median SWVs. The diagnostic performance of the mean value of SWV was slightly higher than other three SWV values, whereas the differences

Table 3. Diagnostic performance of various SWV values in diagnosis benign and malignant breast lesions

	Pathological results			Diagnostic performance						
	Malignant (N=26)	Benign (N=107)	*P value*	Cut-off value	AUC	95% CI	*P* value	Sensitivity	Specificity	Youden's index
SWVmax	6.95±2.03 m/s (3.36-9.96)	3.68±1.34 m/s (1.69-7.97)	< 0.001	5.04 m/s	0.912*	0.851~0.973	< 0.001	80.8%	65.6%	0.464
SWVmin	5.05±1.58 m/s (2.77-8.62)	2.54±0.80 m/s (1.08-4.61)	< 0.001	2.95m/s	0.937**	0.890~0.984	< 0.001	93.2%	70.4%	0.636
SWVmean	5.98±1.79 m/s (3.18-9.17)	3.10±1.02 m/s (1.43-6.32)	< 0.001	3.68 m/s	0.942	0.895~0.987	< 0.001	93.3%	79.4%	0.727
SWVmedian	5.89±1.92 m/s (3.02-9.43)	3.09±1.04 m/s (1.39-6.70)	< 0.001	3.58 m/s	0.914***	0.856~0.972	< 0.001	92.3%	66.5%	0.588

Note: Data are means ± standard deviations, with ranges in parentheses. *Compared with the AUC of SWVmean value, z=0.02, P > 0.05. **Compared with the AUC of SWVmean value, z=0.003, P > 0.05; ***Compared with the AUC of SWVmean value, z=0.02, P > 0.05.

among them were not significant (all $P > 0.05$). For the mean SWV, the associated sensitivity and specificity were 93.3% and 79.4% respectively.

Discussion

SWE has been increasingly used in clinical practice with an aim to reduce inter-and intra-observer variability happened in conventional strain elastography and to provide a quantitative evaluation of tissue stiffness. Until currently, for superficial organs, there are two major types of US-based SWE techniques. One is the so-called point SWE, in that a small measurement box (usually 5 × 6 mm) is placed in the tissue and the shear wave speed is given. The other is two-dimensional (2D) SWE that a color-coded map of the shear wave speed is displayed with sequential multiple pushing and measurement of the acoustic radiation force impulse [15, 21, 25-29].

As a point SWE technique, conventional VTQ has been used in breast imaging in recent years [13, 15-17, 21, 25, 30]. For conventional VTQ of ARFI (i.e. point-SWE), the liquefaction or necrosis area in the breast lesion may lead to failing of SWV measurement, which was always shown as "X.XX m/s" [13, 15-17, 21, 25, 30]. On the other hand, when the stiffness is beyond the measurement range (0.5~8.4 m/s) or the elasticity difference in ROI is remarkable, the SWV value was also shown as "X.XX m/s". Other reasons for absence of shear wave signals include that the tissue is not vibrated enough, the amplitude of the shear wave is too weak and is lost in noise, or the interrogating beam cannot penetrate in the deeper parts of extremely hard cancers. All the above-mentioned factors would result in an invalid measurement result (i.e. X.XX m/s). In previous studies, a solution for this was to replace the value of X.XX m/s by 0 m/s or 8.4-9.0 m/s, depending on the stiffness visualized on strain elastography [13, 15-17, 21, 20, 25, 30]. It is not an ideal solution since other factors are ignored, which might also lead to measurement bias.

Unlike conventional VTQ of ARFI, VTIQ is a 2D-SWE technique. VTIQ synthesizes the stiffness information from up to 256 sequential acquisition beam lines in a 2D user defined region, which facilitates qualitative and quantitative map of SWVs. With VTIQ, the SW quality mode facilitates visualization of the imaging quality of SWE that the ROI can be placed on the areas showing good quality whereas the insufficient quality areas are avoided. In addition, VTIQ allows wider SWV measurement range (0.5~10 m/s) so that the extreme hard tissue is also measurable. The small ROI can also reduce the elasticity difference in ROI. Therefore, the immeasurable result was seldom found in the current study and there was no need to allocate a certain SWV value to it, which led to a more accurate SWV measurement. Therefore, compared to VTQ (i.e. point-SWE), VTIQ (i.e. 2D-SWE) has several advantages, for example, the smaller ROI, the higher accuracy of SWV value, and the wider measurement range. In addition, the SW quality mode of VTIQ makes it unique even in comparison with other 2D-SWE techniques since the quality mode is absent for them [26-28].

In the current study, VTIQ can assess the tissue stiffness qualitatively and quantitatively, which shows excellent performance in differentiating the breast lesion and provides more objective assessment. Although the technique of VTIQ has been used for breast examination initially in previous studies, the measurement was limited to 8.4 m/s due to the software version [26-28]; however, the upper limit of SWV measurement is 10 m/s in the current study, which may suggest that the results in the current study were more accurate. In fact, the maximal SWV measurement was 9.96 m/s in the current study. In addition, the maximum, minimum, mean and median SWV values of malignant lesions were significantly higher than those of benign lesions, which were firstly evaluated in the literatures with VTIQ [26-28]. The mean SWV value achieved the highest diagnostic performance in terms of AUC, although no significant differences were present among them. The cut-off value of mean SWV was 3.68 m/s, and the associated sensitivity and specificity were 93.3% and 79.4% respectively. In comparison with the conventional US BI-RADS results, the specificity increased up to 16.8% (62.6% for conventional US) without significant loss of sensitivity (down 3% vs. conventional US). In another prospective study of around 1000 patients using a different quantitative 2D-SWE (SSI, SuperSonic Imagine, Aix-en-Provence, France), the specificity increased from 61.1% for conventional US to 78.5% for 2D-SWE without loss of sensitivity [7]. The cut-

off value of maximum shear wave speed was about 5 m/s (80 KPa) using 2D-SWE of SSI, similar with the cut-off SWVmax value of 5.04 m/s using 2D-SWE of VTIQ in the current study. Using VTIQ, Ianculescu et al reported a sensitivity of 92% and a specificity of 73% in BIRADS 4a breast lesions [28]; Golatta et al reported a cut-off maximum SWV value of 5.18 m/s with associated sensitivity of 98% and specificity of 68% (in comparison with 30% for US BI-RADS) in diagnosing breast lesions [27]. Therefore, the diagnostic performance of the 2D-SWE techniques of VTIQ and SSI is similar with a nearly same cut-off SWV value thus both techniques are acceptable in clinical practice. On the other hand, in the studies using point-SWE of VTQ, the cut-off value of SWV was 2.9-6.4 m/s, with the associated sensitivity of 76-91% and specificity of 81-95% [13, 19, 21, 31]. The wide variability of VTQ may partly attribute to the inappropriate management for the invalid measurement result of X.XX m/s or the variability in placing ROI in the lesion. The 2D-SWE of VTIQ may provide more consistent results compared with point-SWE of VTQ.

There were several limitations to our study. Firstly, as a new elastography technology, VTIQ technology cannot be completely separated from conventional ultrasound, which would lead to a reading bias. Secondly, conventional US and elastography examinations were performed by only one operator. This limitation could result in operator-related selection bias. Thirdly, it was a single institutional study and included a relatively small number of screening US-detected malignancies. Fourthly, almost all the malignant lesions included in our study were invasive ductal carcinomas, with only four other types of carcinomas. Therefore, additional studies including a greater variety of breast tumors in a larger cohort will be needed. Finally, the decision to perform biopsy or follow-up in the clinical practice of patient management should be evaluated in the future.

In conclusion, VTIQ is useful in differentiating malignant from benign breast lesions. Adding VTIQ to the conventional US BI-RADS assessment improves the specificity for diagnosis of breast lesions without loss of sensitivity.

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Disclosure of conflict of interest

None.

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