Diagnostic value of virtual touch tissue imaging quantification for benign and malignant breast lesions with different sizes

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Abstract: The study was to explore diagnostic value of the virtual touch tissue imaging quantification (VTIQ) in distinguishing benign and malignant breast lesions of variable sizes. We performed conventional ultrasound and VTIQ in 139 breast lesions. The lesions were categorized into three groups according to size (group 1, ≤ 10 mm; group 2, 10-20 mm; and group 3, > 20 mm), and their mean, min, and max shear wave velocities (SWVs) were measured. Diagnoses were confirmed by pathological examination after surgery or needle biopsy. Receiver-operating characteristic curves (ROC) were constructed to determine the optimum cut-off values, calculate the area under curve (AUC), the sensitivity, specificity and accuracy for each velocity. For all groups, the mean, min, and max SWVs of malignant lesions were significantly higher than those of benign lesions (P < 0.05). The cut-off values of mean, min, and max SWVs were not significantly different among the three groups. In addition, the diagnostic performance of mean, min, and max SWV values is analogous, regardless of lesion size. In conclusion, VTIQ is a strong complement to conventional ultrasound, which is a promising method in the differential diagnosis of the breast lesions with different sizes. Further studies validate our results as well as reduce the number of unnecessary biopsies, regardless of size is warranted.

Keywords: Diagnostic value, virtual touch tissue imaging quantification (VTIQ), breast lesions, different sizes

Introduction

Because of consistent environmental and lifestyle changes, breast cancer has become the main public health concern in women. Approximately 1 million new patients are diagnosed with breast cancer every year. The annual death toll is estimated at 478000 [1]. Therefore, early diagnosis and treatment of breast cancer are particularly important.

Ultrasonography and mammography are commonly used diagnostic tools for breast cancer that can also help in distinguishing benign and malignant lesions [2-5]. Nevertheless, breast lesions are very complex, and the differential diagnosis of benign and malignant lesions is sometimes complicated by the absence of specific markers [6]. Recent advancements in elastography have led to the development of acoustic radiation force impulse (ARFI) imaging. ARFI imaging is a novel ultrasound elastography-based technique that allows three types of diagnosis: virtual touch tissue imaging (VTI), virtual touch tissue quantification (VTQ), and virtual touch tissue imaging quantification (VTIQ) [7-9]. Thus, it offers a combination of qualitative and quantitative clinical diagnostic tools.

Tumor size is thought to be a strong predictor of breast cancer prognosis. As the tumor size increases, tumor stage also increases, and the prognosis of patients significantly worsens [10]. VTIQ can measure the shear wave velocity (SWV) of the tumor lesion at up to 10 m/s within the region of interest (ROI) [11]. Thus, benign and malignant lesions can often be distinguished on the basis of differential tissue stiffness. Although the application of VTIQ in diag-
agnosis of breast lesions is well known, the effect of lesion size on the actual diagnosis remains unclear. The aim of this study was to determine the diagnostic value of VTIQ, including the mean, min, and max shear wave velocity (SWV), for the assessment of breast lesions with different sizes.

Materials and methods

Patients and study design

From June 2014 to September 2014, 325 patients with breast lesions underwent conventional ultrasound examination followed by VTIQ at the Tenth People’s Hospital of Tongji University. All the lesions were confirmed by needle biopsy or histopathology after surgery. All the pathological diagnoses were made by a single experienced pathologist. The flowchart of the study design is shown in Figure 1. Patients (1) in whom cystic lesions were identified by conventional ultrasound; (2) who did not undergo VTIQ; (3) in whom benign vs malignant pathology remained unconfirmed; and (4) who underwent treatment for the lesions were excluded from the study. Eventually, 130 women with 139 lesions, including 53 malignant lesions and 86 benign lesions, met the inclusion criteria. The lesions diameters ranged from 4 mm to 86 mm. The mean age of patients was 44.74 ± 14.77 years (range 16-84 years).

Both conventional ultrasound and VTIQ elastography were performed by a single consultant specialist, with at least 15 years of experience in breast imaging. The consultant was trained to handle a SIEMENS sonography device.

This study was approved by the ethical and scientific review board of the Tenth People’s Hospital of Tongji University. Verbal informed consent was acquired from all participating patients.

Conventional ultrasound and VTIQ elastography

Conventional ultrasound and VTIQ were performed with Siemens Acuson S3000 ultrasound machine. A linear array transducer 10L12 with 4-9 MHz multi frequency was used for conventional ultrasound examination and 4-9 MHz multi frequency, 9L4 transducer (Acoustic Radiation Force Impulse, Virtual Touch IQ, Siemens) was used for VTIQ examination. The shear-wave elastography mode was available on a Siemens S3000 ultrasound unit equipped with the VTIQ software. The patient was asked to lie in the supine position with the breast and axillary glands fully exposed. The conventional ultrasound device scanned the breast radially from the center starting with the nipples. The lesion sizes were recorded. The ultrasound device was then switched to the
Diagnostic value of VTIQ for benign and malignant breast lesions

VTIQ mode. Color-coded qualitative and quantitative maps developed with the SWV values were used. With adjacent color spectrum as reference, red and green areas were found to correspond to high and low relative SWV values, respectively. The ROIs were marked within the lesions, while avoiding calcified areas, cystic areas, and necrotic tissue (Figures 2 and 3). A longitudinal push pulse is generated by the probe to cause minimal localized tissue displacement, and the speed of the perpendicular shear waves is tracked by a detection pulse during VTIQ [1, 11, 12]. The speed of the shear waves propagating through the tissue is proportional to the stiffness of the tissue; a color-coded map of the ROIs helps determine tissue stiffness in a specific ROI [13, 14]. ROIs were defined by the sonographer, and SWV values for the targeted area were measured. Qualitative maps of shear waves that display green coloring for SWV values were considered reliable. In addition, tissue displacement images (dark and light blue for low and high displacement, respectively) and travel time map (red and blue for high and low SWVs, respectively) were also obtained. SWV values were quantitatively measured in m/s within the ROIs and ranged from 0.5 to 10 m/s [11]. From high to low to resize SWV ranges (maximum 10 m/s), with surrounding background as light blue or light green, the lesions appeared red or yellow within the VTIQ velocity model for the standard at the end to the image. For each effective measured area under the VTIQ velocity color

Figure 2. Ultrasound and pathological findings of an invasive ductal carcinoma. (A) B-mode ultrasound image and (B) VTIQ quality map showing defined areas in green. The high quality of generated shear waves supported the all findings. (C) VTIQ velocity map displaying relative shear wave velocities (SWVs) according to the reference color spectrum; red areas are consistent with higher velocities. Seven repetitive measurements were obtained for each lesions to test the re-test reliability of VTIQ. Any given SWV was measured at the center of the lesion (mean = 8.24 m/s, max = 8.89 m/s and min = 7.27 m/s). (D) Histopathological image confirming the diagnosis of an invasive ductal carcinoma.
overlay, we obtained seven repetitive measure-
ments for each lesion to test the retest reliabil-
ity of VTIQ. The ROIs within lesions were defined
according to their color intensities on the VTIQ
two-dimensional color-coded map as areas
with highest SWV (red areas), those with lowest
SWV (blue areas). The lesions were divided into
three groups according to size: Group 1: maxi-
mum diameter, ≤ 10 mm; group 2: maximum
diameter, 10-20 mm; and group 3: maximum
diameter, > 20 mm. The max, min, and mean
cut-off values of SWV were used to assess the
sensitivity, specificity and accuracy for the
lesions of different sizes.

Statistical analysis

Statistical analysis was performed using the
SPSS software version 17.0. The SWV values
were expressed as mean (max, min) ± standard
development (SD). We used the independent sam-
ple t test to compare the max, min, and mean
values of benign vs malignant tumors. Receiver-
operating characteristic (ROC) curves were con-
structed in order to determine the acceptable
cut-off values for max, min, and mean SWV val-
ues. The areas under the curves (AUCs) for
mean, min, and max SWVs were compared by
using z test for the inter- and intra-group. $P < 0.05$ was considered as statistically signi-
ficant.

Results

Patient characteristics

A total of 139 lesions in 130 patients were ana-
lyzed. Of the 53 malignant lesions (38.1%), 42
Table 1. Histological findings

<table>
<thead>
<tr>
<th>Lesion findings</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>53</td>
<td>38.1</td>
</tr>
<tr>
<td>Invasive ductal carcinoma</td>
<td>42</td>
<td>30.2</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>9</td>
<td>6.5</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Papillary carcinoma</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>Benign</td>
<td>86</td>
<td>61.9</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>65</td>
<td>46.8</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>11</td>
<td>7.9</td>
</tr>
<tr>
<td>Intraductal papilloma</td>
<td>7</td>
<td>5.0</td>
</tr>
<tr>
<td>Benign phyllodes tumor</td>
<td>3</td>
<td>2.2</td>
</tr>
</tbody>
</table>

were invasive ductal carcinomas. Of the 86 benign lesions (61.9%), 65 were fibroadenomas. The specific histological findings are presented in Table 1. Comparison of shear wave velocities of benign and malignant lesions of different sizes.

The mean, max, and min SWV values obtained from seven measurements of each lesion are shown in Table 2. The mean, min, and max SWV values of benign lesions were 3.39 ± 1.25 m/s (range, 2.14-4.64 m/s), 2.61 ± 0.97 m/s, and 4.00 ± 1.65 m/s, respectively. The mean, min, and max SWV values of malignant lesions were 5.27 ± 1.83 m/s (range, 3.44-7.10 m/s), 4.09 ± 1.59 m/s, and 6.64 ± 2.21 m/s, respectively. Thus, all SWV values of malignant lesions were significantly higher than those of the benign lesions ($P < 0.01$). The mean, min, and max values for both malignant and benign lesions were also compared by lesion size. For each group, the mean, min, and max SWV values of malignant lesions were significantly higher than those of benign lesions ($P < 0.05$).

**Diagnostic performance of VTIQ**

ROC curves were constructed to determine the mean, min, and max SWV values that can act as optimal cut-off values in the differentiation of malignant and benign breast lesions (Table 3). For all lesions (malignant and benign), the cut-off value for mean SWV was 3.36 m/s, and it was associated with sensitivity of 88.7%, specificity of 66.3%, and an AUC of 0.818 (95% CI, 0.744-0.893). The cut-off value for min SWV was 2.7 m/s, and it was associated with sensitivity of 86.8%, specificity of 64.0%, and an AUC of 0.796 (95% CI, 0.720-0.873). The cut-off value for max SWV was 5.37 m/s, which was associated with sensitivity of 71.7%, specificity of 86%, and an AUC of 0.828 (95% CI, 0.756-0.901). The sensitivity, specificity, accuracy, AUC, and 95% CI for all groups are shown in Table 3. No significant differences were observed between the AUC values for mean, min, and max SWV in inter- and intra-group ($P > 0.05$). Thus, the diagnostic performance of mean, min, and max SWV values is comparable, regardless of lesion size. In group 1, the cut-off values of mean SWV were associated with a sensitivity of 81.8% and specificity of 76.0%. In group 2, the cut-off values of mean SWV were associated with a sensitivity of 88.9% and specificity of 61.4%. In group 3, the cut-off values of mean SWV were associated with a sensitivity of 83.3% and specificity of 94.1%.

**Discussion**

The incidence and prevalence of breast cancer have been continuously increasing in recent years [15]. In order to improve the prognosis and life expectancy, early diagnosis of breast cancer is particularly important. Although B-mode ultrasound is commonly used in breast cancer screening, this technique suffers from low specificity [16]. To overcome this limitation, elastography was developed [17]. Elastography in combination with B-mode ultrasound can help improve the differentiation of benign and malignant lesions [1, 18, 19]. Elastography is a noninvasive imaging modality that can evaluate the stiffness of breast tissues [20]. VTIQ, an elastography-based technique, is advantageous because it is less investigator-dependent and has high specificity and sensitivity [21, 22]. VTIQ allows the measurement of target area stiffness, a parameter that reflects the properties of breast lesions. Quantifiable SWVs values yielded by VTIQ can be directly used for comparison with tissue pathology. Indeed, elasticity values from high to low in the order were invasive ductal carcinoma, noninvasive ductal carcinoma, fibroadenoma, breast tissue, and fat tissue by pathological types [23-26].

In order to improve investigator independence and reproducibility and to evaluate the diagnostic performance of VTIQ on breast lesions of different sizes, VTIQ employs automatically generated acoustic radiation force impulses (ARFI) to
induce shear waves within the targeted area. It is not dependent on the examiner’s ability to apply appropriate mechanical pressure to the breast tissue. Golatta et al. found a high positive inter-examiner correlation with VTIQ ($r = 0.93$) [27]. In the present study, we obtained seven repetitive measurements of each lesion to test the re-test reliability of VTIQ, improve intra-rater correlation, and reduce selection bias. Although some overlap was observed between the SWV values of benign and malignant lesions, the mean, min, and max SWV values of malignant lesions were significantly higher than those of benign lesions. These results were consistent with those of three previous clinical reports on the use of VTIQ for breast lesions [27-29].

Ours is the first study to yield good diagnostic values with VTIQ for breast lesions of variable sizes. Our results demonstrate that mean, min, and max SWV values of malignant lesions are higher than those of benign lesions, regardless of size. Recently, Yao et al. demonstrated that the sensitivity of VTQ in lesions of size < 10 mm was relatively low (33.33%) [30]. In our study,

### Table 2. Comparison of shear wave velocities of benign and malignant lesions of variable sizes

<table>
<thead>
<tr>
<th>Groups</th>
<th>Benign No.</th>
<th>SWV (m/s)</th>
<th>Malignant No.</th>
<th>SWV (m/s)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10 mm</td>
<td>25 Max</td>
<td>3.56 ± 1.81</td>
<td>11 Max</td>
<td>5.39 ± 2.19</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>2.54 ± 1.06</td>
<td>Min</td>
<td>3.94 ± 1.59</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>3.04 ± 1.40</td>
<td>Mean</td>
<td>4.56 ± 1.83</td>
<td>0.027</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>4.06 ± 1.60</td>
<td>Max</td>
<td>6.33 ± 2.16</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>10-20 mm</td>
<td>44 Min</td>
<td>2.71 ± 1.00</td>
<td>18 Min</td>
<td>4.07 ± 1.91</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>3.37 ± 1.23</td>
<td>Mean</td>
<td>5.08 ± 2.04</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>4.49 ± 1.44</td>
<td>Max</td>
<td>7.45 ± 2.02</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&gt; 20 mm</td>
<td>17 Min</td>
<td>2.48 ± 0.78</td>
<td>24 Min</td>
<td>4.17 ± 1.38</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>3.54 ± 1.02</td>
<td>Mean</td>
<td>5.73 ± 1.58</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>4.00 ± 1.65</td>
<td>Max</td>
<td>6.64 ± 2.21</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total</td>
<td>86 Min</td>
<td>2.61 ± 0.97</td>
<td>53 Min</td>
<td>4.09 ± 1.59</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>3.31 ± 1.25</td>
<td>Mean</td>
<td>5.27 ± 1.83</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

### Table 3. Receiver operating characteristic curves for max, min and mean cutoff values of shear wave velocities (SWV) in the differentiation of benign and malignant lesions of variable sizes

<table>
<thead>
<tr>
<th>Groups</th>
<th>No.</th>
<th>Cutoff value</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
<th>*AUC</th>
<th>95% CI</th>
<th>$z$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10 mm</td>
<td>36 Mean</td>
<td>3.27</td>
<td>0.818</td>
<td>0.760</td>
<td>0.778</td>
<td>0.742</td>
<td>0.550-0.934</td>
<td>2.469</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>Max</td>
<td>3.88</td>
<td>0.818</td>
<td>0.760</td>
<td>0.778</td>
<td>0.756</td>
<td>0.570-0.943</td>
<td>2.695</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>2.62</td>
<td>0.818</td>
<td>0.720</td>
<td>0.750</td>
<td>0.767</td>
<td>0.589-0.945</td>
<td>2.934</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>3.36</td>
<td>0.889</td>
<td>0.614</td>
<td>0.694</td>
<td>0.771</td>
<td>0.643-0.900</td>
<td>4.106</td>
<td>0.001</td>
</tr>
<tr>
<td>10-20 mm</td>
<td>62 Max</td>
<td>4.53</td>
<td>0.778</td>
<td>0.727</td>
<td>0.742</td>
<td>0.808</td>
<td>0.687-0.929</td>
<td>4.968</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>2.48</td>
<td>0.944</td>
<td>0.500</td>
<td>0.629</td>
<td>0.737</td>
<td>0.601-0.873</td>
<td>3.435</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>4.37</td>
<td>0.833</td>
<td>0.941</td>
<td>0.878</td>
<td>0.873</td>
<td>0.748-0.997</td>
<td>5.921</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&gt; 20 mm</td>
<td>41 Max</td>
<td>5.77</td>
<td>0.833</td>
<td>0.941</td>
<td>0.878</td>
<td>0.897</td>
<td>0.761-0.997</td>
<td>6.317</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>3.06</td>
<td>0.875</td>
<td>0.824</td>
<td>0.854</td>
<td>0.886</td>
<td>0.785-0.987</td>
<td>7.423</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>3.36</td>
<td>0.887</td>
<td>0.663</td>
<td>0.820</td>
<td>0.818</td>
<td>0.744-0.893</td>
<td>8.368</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total</td>
<td>139 Max</td>
<td>5.37</td>
<td>0.717</td>
<td>0.860</td>
<td>0.806</td>
<td>0.828</td>
<td>0.756-0.901</td>
<td>8.865</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Min</td>
<td>2.7</td>
<td>0.868</td>
<td>0.640</td>
<td>0.784</td>
<td>0.796</td>
<td>0.720-0.873</td>
<td>7.590</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

*The areas under the curves (AUCs) of mean SWV, min SWV, and max SWV for each group were compared by using the z test; $P$ values were > 0.05. a. Compared with the AUC of Mean SWV with the size 10-20 mm, $z = 0.245$, $P = 0.806 > 0.05$; b. Compared with the AUC of Mean SWV with the size > 20 mm, $z = 1.118$, $P = 0.264 > 0.05$; c. Compared with the AUC of Mean SWV with the size ≤ 10 mm, $z = 1.124$, $P = 0.261 > 0.05$. 
we selected a mean cut-off wave velocity of 3.27 m/s for lesions with ≤ 10 mm diameter. Relying on this threshold for the differentiation of malignant and benign lesions, we reached a sensitivity of 81.8%, which is 48.5% higher than that of VTQ. The ROI in VTIQ has fixed dimensions of 1 mm × 1 mm. Therefore, the regions surrounding the breast lesion are mostly excluded when the ROI of a breast lesion is mapped. Moreover, VTIQ provides two-dimensional color coded maps for ROIs and seven repetitive velocity measurements, whereas VTQ only provides a single velocity value for any given ROI at a fixed dimension of 5 mm × 6 mm.

Yoon et al. previously reported that elastography is unsuitable for the diagnosis of the lesions of size < 10 mm and ≥ 20 mm and argued that interpretation of image ROIs for small lesions is challenging and application of homogeneous compression to large breast lesions is difficult [31]. In our study, the cut-off values set for mean SWV for > 20 mm size lesions yielded a sensitivity of 83.3% and specificity of 94.1%. No significant differences were observed between the AUC values for mean, min, and max SWV among the three groups. Thus, our analysis yielded the best diagnostic performance for breast lesions of size > 20 mm. Because the ROI in VTIQ is small, calcified areas, liquefied necrotic parts, edges of the breast lesions, and normal breast tissue can be excluded. We could obtain numerical values for SWV in the range of 0.5-10 m/s for all lesions analyzed in the study. The narrow velocity measurement range (0.5-8.4 m/s) in VTQ could produce X.XX m/s. While, SWV values which is shown “X.XX m/s” were not obtained in our study. Our study has a number of limitations. First, VTIQ should be interpreted on the basis of B-mode ultrasound. Second, application of external pressure on lesions could have affected the results. Third, misdiagnosis is sometimes possible with VTIQ and may be related to the pathology of the breast lesion. Fourth, interrater correlation coefficients were not estimated in this study. Finally, the numbers of investigators employed in the analysis and the sample size, in particular, were small. Multicentric studies employing a large number of patients with symptomatic and screen-detected breast lesions will be required to validate the findings of the present study.

In conclusion, our findings confirm that VTIQ can be a promising alternative to conventional ultrasound because of its high diagnostic value in the differential diagnosis of breast lesions of different sizes. Our results also confirmed that malignant lesions would be stiffer in each group. Moreover, the diagnostic performance of mean, min, and max SWV values is comparable, regardless of lesion size. Additional studies will be required to validate the findings of our study such that the number of unnecessary biopsies can be avoided in the future.

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Disclosure of conflict of interest

None.

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