Diagnostic accuracy of virtual touch tissue quantification for patients with breast cancer

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Abstract: Breast cancer remains a significant clinical and societal challenge worldwide. The diagnosis of breast cancer plays a crucial role in determining the treatments and mean survival time. In recent studies, virtual touch tissue quantification (VTTQ) has been widely applied for human breast cancer diagnosis. The study showed that VTTQ velocity was significantly correlated with estrogen receptor (r = -0.342, P < 0.01) and progesterone receptor (r = -0.374, P < 0.01) status of invasive breast cancer. High histological grade (P = 0.001) and C-erbB-2 expression (P = 0.029) were significantly associated with VTTQ velocity (r = 0.316, P < 0.01). Multiple linear regressions revealed that breast tumor size was the pathologic indicator determinant of VTTQ velocity (P < 0.01). In conclusion, these outcomes indicate that VTTQ is markedly associated with clinicopathologic breast nodule, which provides diagnostic information in patients with benign or invasive breast cancer.

Keywords: Breast cancer, VTTQ, diagnosis

Introduction

Breast cancer is one of the most common metastatic tumors, which significantly affects women’s health [1]. Human breast carcinoma remains a highly lethal disease due to local invasion and distant metastasis at diagnosis [2, 3]. Although the potential role of circulating tumor cell detection and monitoring in breast cancer has been explored in the clinic, the lymphatic metastasis and recurrence rate are still high [4, 5]. A systematic review has summarized the current treatments for breast cancer-related lymphedema, which provides potential anti-cancer strategies for patients with breast cancer [6]. Currently, breast cancer is a significant public health problem and the treatment of breast cancer has many side effects for patients [7, 8]. Therefore, reports have concluded that the utilization of diagnostic tools would greatly assist in the modern management of breast cancer.

In recent years, virtual touch tissue quantification (VTTQ) has been widely applied for human cancer diagnosis. Study showed that VTTQ can effectively detect the stiffness of prostate cancer and benign prostatic hyperplasia [9]. A report has indicated that VTTQ could be a valuable clinical tool for estimating breast cancer pathology in a non-invasive fashion [10]. In addition, VTTQ can detect ductal carcinomas in situ and small invasive breast cancers, which may be a useful application for assessing breast tumors [11]. Furthermore, VTTQ were significantly associated with clinicopathologic abnormalities, and may therefore provide prognostic information in patients with invasive ductal breast cancer [12]. However, the association between VTQ and clinicopathologic breast
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nodule has not clearly investigated in patients with breast cancer.

The aims of this randomized study were to analyze the correlation between VTTQ velocities and status of invasive breast cancer, in order to improve early diagnosis. This study also evaluated the relationship between VTTQ velocity and the estrogen receptor and C-erbB-2 expression in patients with breast cancer, which may be one of methods to diagnose the status of breast cancer recurrence or metastasis based on VTTQ velocity.

Materials and methods

Patients

All patients were required to write informed consent for all participants. Between May 2011 and October 2013, we analyzed 128 invasive ductal breast cancer patients including 72 invasive ductal carcinoma, 28 ductal carcinoma, 8 mucinous carcinoma, 14 fibroadenoma and 6 intraductal papilloma using VTTQ. The median age was 43.6 years old (age range, 35.64-54). The study was approved by the Ethics Committee of the Yantai Yu Huang Ding Hospital.

VTTQ assay

In all the patients, VTTQ examinations were performed for diagnosis of breast cancer tissue. VTTQ was used to detect lesions for its elastic properties by using a region-of-interest (ROI) cursor according to manufacturer instrument [13]. Acoustic push pulse and detection pulses in VTTQ were used to analyze the shear wave velocity and calculated by quantitative assessment of the tissue stiffness by wave velocity (m/s). The fastest velocities were defined as the hotspots of these lesions described previously [14].

Histological analysis

Surgical specimens were isolated and fixed in neutral 10% formalin. Breast cancer tissues were then embedded in paraffin and cut into 4 mm sections. Tumor sections were stained using hematoxylin and eosin, and avidin-streptavidin immunoperoxidase method using antibody targeting of estrogen receptor (1:1000, ab32063, Abcam), progesterone receptor (1:1000, ab2765, Abcam), Ki-67 (1:1000, ab156956, Abcam) and C-erbB-2 (1:1000, ab194979, Abcam) in an automated immunostainer (Benchmark System; Ventana). Horse-radish peroxidase-conjugated anti-rabbit IgG (Bio-Rad, Hercules, CA, USA) was used at a 1:5000 dilution and detected using a Western blotting luminol reagent. Histopathologic evaluations were performed based on the World Health Organization histologic classification of tumors of breast [15]. Expression levels of progesterone receptor, estrogen receptor, Ki-67, and C-erbB-2 were determined by nuclear staining and was graded from 0 to 8 using the Allred score, with positive cases defined as a score of 3 [16].

Statistical analysis

All data are presented as mean ± standard deviation (SD) of triplicate and analyzed by SPSS 19.0 statistical software (SPSS Inc. Chicago, IL, USA). Comparison of means among multiple groups was performed by one-way analysis of variance (ANOVA) followed by Tukey post hoc pairwise comparisons. The optimal cutoff value for VTTQ to distinguish breast cancer tissue was selected using the histologic subtype of the lesions, by minimizing the sum of the observed false-positive and false-negative errors with the bootstrapping methodology [17]. Linear regression analyses were performed to investigate the degree of correlation between VTTQ and progesterone receptor, estrogen receptor, Ki-67 and C-erbB-2. Statistical significance was defined when P < 0.05.

Results

Patient characteristics

A total of 128 invasive ductal breast cancer patients were recruited and measured using VTTQ. Breast cancer patients including 72 cases of invasive ductal carcinoma, 28 cases of ductal carcinoma, 8 cases of mucinous carcinoma, 14 cases of fibroadenoma and 6 cases of intraductal papilloma were analyzed in this study. The mean age for breast cancer patients was 43.6 years old. Table 1 shows the patient characteristics.

Efficacy of VTTQ on diagnosis of breast cancer

The efficacy of VTTQ on diagnosis of breast cancer was analyzed in this study. VTTQ velocities were statistically higher in malignant cases than in benign cases (Figure 1, P < 0.01). The
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**Table 1. Patients characteristic**

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Age</th>
<th>Tumor size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>128</td>
<td>35.64-54.00</td>
<td>14.2 (0-60)</td>
</tr>
<tr>
<td><strong>Histologic types</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Invasive ductal carcinoma</td>
<td>72</td>
<td>36.4-48.2</td>
<td>16.2 (3-56)</td>
</tr>
<tr>
<td>Ductal carcinoma</td>
<td>28</td>
<td>40.3-50.2</td>
<td>7.8 (6.4-34.5)</td>
</tr>
<tr>
<td>Mucinous carcinoma</td>
<td>8</td>
<td>37.48-52.16</td>
<td>18.2 (10-54.3)</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>14</td>
<td>41.24-50.62</td>
<td>22.8 (14.4-60)</td>
</tr>
<tr>
<td>Intraductal papilloma</td>
<td>6</td>
<td>38.4-47.50</td>
<td>19.2 (13-52.6)</td>
</tr>
<tr>
<td><strong>Histopathologic characteristcs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ki-67 (median)</td>
<td>17</td>
<td>1 (1-80)</td>
<td></td>
</tr>
<tr>
<td>C-erbB-2</td>
<td>12</td>
<td>1 (1-50)</td>
<td></td>
</tr>
<tr>
<td>Estrogen receptor</td>
<td>18</td>
<td>1 (1-60)</td>
<td></td>
</tr>
<tr>
<td>Progesterone receptor</td>
<td>20</td>
<td>1 (1-70)</td>
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</table>

Relationships between VTTQ and Ki-67 expression

Figure 2 shows the relationship between VTTQ velocities and tumor size for lesions of invasive breast cancer (Mann-Whitney test, P = 0.0015). VTTQ velocities were positively corrected with breast cancer volume (r = 0.368, and P < 0.01, Figure 3). Outcomes revealed that VTTQ velocity were statistically significant correlations with the Ki-67 labeling index (r = 0.405, and P < 0.01, Figure 4).

Relationships between VTTQ and breast cancer markers

VTTQ velocity negatively correlated with the estrogen receptor (r = -0.342, P < 0.01) expression in breast cancer cases (Figure 5). Figure 6 demonstrated that VTTQ velocity also negatively correlated with progesterone receptor (r = -0.374, P < 0.01) status of invasive breast cancer.

Relationships between VTTQ and histological grade

The relationships between VTTQ and histological grade were further analyzed. As shown in Figure 7, VTTQ velocity is correlated with the histological grade (r = 0.326, P < 0.01). VTTQ velocity was correlated C-erbB-2 expression (r = 0.364, P < 0.01, Figure 8).

Discussion

The VTTQ diagnosis of breast cancer plays crucial role in determining treatments and mean survival time. Evidence has shown that VTTQ is highly reliable and reproducible in diagnosing benign and malignant lesions [13]. In this study, the impact of VTTQ on breast imaging was investigated, demonstrating that VTTQ has the value in diagnosing of malignant cases and benign cases. VTTQ was associated with clinicopathologic breast nodule, which may provide diagnostic information in patients with benign or invasive breast cancer. The associations between VTTQ and breast tumor size, as well as Ki-67 labeling index, C-erbB-2, estrogen recep-

**best cutoff value of VTTQ velocity was > 2.94 m/s in malignant cases and it was < 2.74 m/s in benign cases.**
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Figure 3. VTTQ velocities are positively corrected with breast cancer volume.

Figure 4. VTTQ velocity is significantly correlated with Ki-67 labeling index ($r = 0.405$).

Figure 5. VTTQ velocity is negatively correlated with the estrogen receptor ($r = -0.342$) expression in breast cancer cases.

Figure 6. VTTQ velocity is negatively correlated with progesterone receptor ($r = -0.374$) status of invasive breast cancer.

tor and progesterone receptor were investigated in this clinical study.

Currently, VTTQ is valuable to differentiate benign from malignant breast imaging-reporting and data system category 4 lesions, which might be useful for patient selection before biopsy [18]. VTTQ could detect patients with benign, invasive breast cancer and normal breast tissue. Previous study has showed that VTTQ imaging and quantification is a helpful and reproducible tool for predicting thyroid malignancy [19]. In this study, VTTQ velocity was correlated with the histological grade ($r = 0.326, P < 0.01$) that is essential for the tumor eradication, treatment and prognostic analysis. In addition, VTTQ imaging quantification was efficient in differential diagnosis of metastatic and non-metastatic cervical lymph nodes [20]. Furthermore, VTTQ imaging can be used to evaluate thyroid nodules [21]. The best cutoff value of VTTQ velocity was found to be $> 2.94$ m/s in malignant cases and it was $< 2.74$ m/s in benign cases.

Ki-67 labeling index, C-erbB-2, estrogen receptor and progesterone receptor are associated with the progression of breast cancer [22-25]. Study has found that Ki-67 is involved in promoting the genesis and development of breast cancer by affecting the proliferation and migration of cancer cells [26]. VTTQ velocity was correlated with the Ki-67 labeling index. Arslan et al. has showed that expression of c-erbB-2 is overexpressed and associated with the progression of patients with breast cancer [27]. VTTQ velocity value was shown here to be positively correlated with estrogen receptor expres-
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Malkov et al. have suggested that estrogen receptor is positively correlated with cancer [28]. Reports also indicated that progesterone receptor loss identifies hormone receptor-positive breast cancer subgroups at higher risk of relapse [29, 30]. In this study, VTTQ velocity was negatively correlated with progesterone receptor in patients with breast cancer. Multiple linear regressions revealed that breast tumor size is the pathologic indicator determinant of VTTQ velocity.

In conclusion, the breast lesion could be quantitatively assessed by VTTQ in patients with invasive ductal breast cancer. VTTQ appears to be a promising method in the differential diagnosis of the malignant breast lesion. These findings indicate that VTTQ is a potential method in assessing breast tumors in early phase. However, further studies were warranted to improve the sensitivity of VTTQ assessment in breast cancer patients in a large number population.

Disclosure of conflict of interest

None.

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