VIRTUAL TOUCH TISSUE IMAGING QUANTIFICATION SHEAR WAVE ELASTOGRAPHY: PROSPECTIVE ASSESSMENT OF CERVICAL LYMPH NODES

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Abstract—The goal of this study was to prospectively evaluate the diagnostic performance of Virtual Touch tissue imaging quantification (VTIQ) shear wave elastography in the discrimination of benign and malignant cervical lymph nodes in routine clinical practice. Shear wave velocity was analyzed using VTIQ in 100 patients with 100 histologically proven cervical lymph nodes. Diagnostic performance was evaluated using receiver operating characteristic curve analysis and leave-one-out cross-validation. Agreement between measurements was assessed with intra-class correlation coefficients. The mean shear wave velocity was significantly higher in metastatic lymphadenopathy (4.46 ± 1.46 m/s) than in benign lymphadenopathy (2.71 ± 0.85 m/s) (p < 0.001) at a cutoff level of 3.34 m/s. The cross-validated accuracy, sensitivity and specificity were 77%, 78.9% and 74.4%, respectively. Agreement of measurements with VTIQ was excellent (intra-class correlation coefficient 5 0.961). VTIQ shear wave elastography may be a feasible quantitative imaging method for differentiating benign and malignant cervical lymph nodes.

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Key Words: Head and neck, Malignant, Lymph nodes, Ultrasound, Shear wave elastography, Virtual Touch tissue imaging quantification.

INTRODUCTION

Assessment of nodal metastases is the most important clinical aspect of oncologic staging because it predicts prognosis and helps in the selection of treatment. Different imaging modalities such as gray-scale ultrasonography (US), US-guided fine-needle aspiration cytology, computed tomography (CT) and magnetic resonance imaging have been used to evaluate cervical lymph nodes (Atula et al. 1997; de Bondt et al. 2007; Sumi et al. 2003). Recently, US elastography has emerged as a complementary tool for the detection of metastatic cervical lymph nodes with promising results (Choi et al. 2013, 2015; Lo et al. 2013; Tan et al. 2010).

Strain elastography (Ophir et al. 1991), the first commercialized elastography technique, uses unquantifiable freehand compression, which requires continuous transducer compression or external mechanical compression and displays qualitative results of tissue stiffness (Bhatia et al. 2010). Acoustic stress elasticity imaging, such as acoustic radiation force impulse (ARFI) imaging, is a new elastography technique that reduces operator dependency and improves reproducibility because of the addition of automated tissue compression (Fujiwara et al. 2013; Meng et al. 2013; Nightingale et al. 2002). This technique uses focused high-intensity, short-duration acoustic pulses from a US transducer and makes localized tissue displacements producing shear waves in the region of interest (ROI), providing quantitative assessment of tissue stiffness based on tracking of the shear wave propagation caused by the pushing pulse (Balleyguier et al. 2013; Sarvazyan et al. 1998). The more stiff a tissue is, the more shear wave velocity it produces. Virtual Touch tissue imaging quantification (VTIQ) is a new measurement technique that uses ARFI imaging technology to gently displace tissue for qualitative visualization and quantitative evaluation of tissue stiffness. The VTIQ shear wave technique uses multiple push pulses across the transducer face at multiple depths and provides an
elastogram of tissue stiffness based on shear wave speed. Multiple ROIs can be placed on the elastogram, which detects pulse sequences that can measure localized shear wave velocity from 0.5 to 10 m/s in multiple locations (Matsuzuka et al. 2015).

In addition to detecting shear wave velocity, VTIQ can also display shear wave quality. This is useful in interpreting whether the shear wave was of sufficient magnitude with an adequate signal-to-noise ratio to accurately estimate shear wave velocity in the shear wave velocity display, and is also valuable in understanding whether the shear wave was adequately formed (Tozaki et al. 2013). VTIQ shear wave elastography has been widely used for the assessment of breast diseases (Golatta et al. 2013; Ianculescu et al. 2014; Tozaki et al. 2013), testicular lesions (Trottmann et al. 2014), liver disease (Leschied et al. 2015) and bowel wall fibrosis (Dillman et al. 2014) and has been found to be effective in differentiating between benign and malignant lesions and in evaluating tissue hardness. However, to our knowledge, VTIQ shear wave elastography has not been used in the discrimination of benign and malignant cervical lymph nodes. The purpose of this study was to prospectively determine the diagnostic performance of VTIQ shear wave elastography in differentiating between benign and malignant cervical lymph nodes.

**METHODS**

This prospective study protocol was reviewed and approved by the institutional review board of our hospital. Written informed consent for routine US was obtained from all patients before each US examination.

**Study patients**

This study was conducted at a single tertiary referral center between July 2014 and February 2015. We enrolled consecutive patients who were referred for US-guided biopsy based on the following criteria: (i) neck lymph nodes undergoing US-guided fine-needle aspiration for cytology (FNAC) or US-guided core needle biopsy (CNB) in routine clinical practice; (ii) neck lymph nodes >5 mm in minimal axial diameter; and (iii) cytopathologically confirmed benign or metastatic lymph nodes. Criteria for a referral US-guided biopsy were as follows: (i) discomfort and palpable symptoms in the cervical region suspicious for lymphadenopathy, or a lymph node detected on CT or [18 F]FDG PET and/or (ii) malignant US or CT findings, including loss of hilar fat, cortical heterogeneous echogenicity, echogenic dots or calcification, cystic or necrotic area, long-to-short axis diameter ratio <2.0 and peripheral cortical vascularity (Choi et al. 2013; Meng et al. 2013; Teng et al. 2012; Yoon et al. 2009). When none of these criteria was met, the largest lymph node was selected as a target lymph node.

**VTIQ examinations**

During routine clinical practice, each study patient underwent VTIQ shear wave elastography using the Acuson S3000 ultrasound system (Siemens Medical Solutions, Erlangen, Germany) equipped with a linear array transducer (Siemens Medical Solutions) with a bandwidth of 4–9 MHz. The detection pulse transmits at 6.15 MHz with a pulse repetition frequency in the range 7 to 10 kHz depending on depth. The total tracking duration was around 10 ms for each shear wave excitation. All US examinations were performed by a radiologist with 4 y of experience who had been trained by a VTIQ applications specialist.

Each patient was placed in a supine position with the neck slightly extended over a pillow. The radiologist located the probe vertical to the skin and applied the probe with minimal pressure to create complete contact with the cervical lymph node while letting the patient hold his or her breath. Elastography color maps were displayed on the box, and a ROI was identified in the cortex, avoiding cystic and calcified components. A ROI was determined in the target area on the color-coded 2-D maps to obtain the shear wave velocity, which was quantitatively measured in meters per second (m/s). The shear wave quality map was obtained before measuring shear wave velocity. On VTIQ, high-quality regions are displayed as green, low-quality regions as orange and marginal-quality regions as yellow (Tozaki et al. 2013). VTIQ shear wave elastography was performed twice in a single session by one observer, was blind to the velocity measurement value during the examination. The shear wave velocity value was defined as the average of two-time measurements.

For analysis of patients with multiple lymph nodes, we selected a target lymph node that exhibited at least one of the following criteria: (i) increased uptake on [18 F]FDG PET and/or (ii) malignant US or CT findings, including loss of hilar fat, cortical heterogeneous echogenicity, echogenic dots or calcification, cystic or necrotic area, long-to-short axis diameter ratio <2.0 and peripheral cortical vascularity (Choi et al. 2013; Meng et al. 2013; Teng et al. 2012; Yoon et al. 2009). When none of these criteria was met, the largest lymph node was selected as a target lymph node.

**Final diagnosis**

After US elastography, all lymph nodes underwent US-guided FNAC or CNB. The final diagnosis was based on adequate cytopathology results. US-Guided FNACs were performed routinely with a disposable 23-gauge needle. Capillary or aspiration technique was used according to the characteristics of each nodule. US-Guided CNBs were performed with a 1.1- or 1.6-cm excursion, disposable, 18-gauge, double-action, spring-activated needle.
(TSK Ace-Cut, Create Medic, Yokohama, Japan) after administering local anesthesia using 1% lidocaine.

**Statistical analysis**

Demographic data are presented as means and standard deviations for continuous variables and as number of patients (percentages) for categorical variables. Student’s t-test was used to analyze differences in shear wave velocity between benign and metastatic lymph nodes. Receiver operating characteristic (ROC) curves were constructed to determine the threshold of shear wave velocity values that differentiates between benign and metastatic lymph nodes. Leave-one-out cross-validation was used to evaluate the performance of VTIQ measurements of shear wave velocity. In each round of the leave-one-out cross-validation, one participant was selected as a testing sample. The remaining participants were used as training samples to construct the classifier. The testing sample was then grouped with the trained classifier. This procedure was repeated until each participant was tested once. The performance of shear wave velocity was evaluated in terms of sensitivity and specificity. To evaluate the intra-observer agreement of shear wave velocity measurement, the intra-class correlation coefficient (ICC) was used. Agreement was classified as poor (ICC = 0.00–0.20), fair to good (ICC = 0.40–0.75) or excellent (ICC > 0.75) (Fleiss 2011). The unit of analysis was the number of patients. All statistical analyses were performed using MedCalc for Windows, Version 14.0 (MedCalc Software, Ostend, Belgium), with p-values <0.05 considered statistically significant.

**RESULTS**

**Patients and lymph nodes**

A comparison of the demographic data between included patients with benign and metastatic lymph nodes is provided in Table 1. Fourteen lymph nodes from 14 consecutive patients were excluded from our study series. All of these lymph nodes were metastatic lymph nodes that yielded low-quality VTIQ images. Finally, a total of 100 lymph nodes from 100 consecutive patients (51 men and 49 women; age: 52.7 ± 16.2 y, range: 14–80 y) were included in our study series. Of these 100 nodes, 57 (57%) were metastatic and 43 (43%) were benign. Histopathologic analysis revealed that among patients with benign lymph nodes, 28% (n = 28) had reactive hyperplasia, 9% (n = 9) had Kikuchi disease and 6% (n = 6) had tuberculous lymphadenitis. Among patients with metastatic lymph nodes, 22% (n = 22) had lung cancer; 6% (n = 6) had ovarian cancer; 5% (n = 5) had thyroid cancer; 4% (n = 4) had esophageal cancer; 3% (n = 3) each had tongue cancer, tonsil cancer, laryngeal cancer and gastric cancer; 2% (n = 2) had nasopharyngeal carcinoma; and 1% (n = 1) each had cancer of unknown primary, gall bladder cancer, melanoma, colon cancer, uterine cancer and urinary bladder cancer. The mean minimum axial diameter of the lymph nodes was 1.16 ± 0.68 cm (range: 0.5–4.9 cm). Among benign lymph nodes, 13% (n = 13) occurred in the level V region, 12% (n = 12) in the level II region, 9% (n = 9) in the supravacular region, 5% (n = 5) in the level IV region, 3% (n = 3) in the level I region and 1% (n = 1) in the level III region. Among metastatic lymph nodes, 36% (n = 36) occurred in the supraclavicular region, 11% (n = 11) in the level II region, 6% (n = 6) in the level IV region and 4% (n = 4) in the level III region.

**Table 1. Demographic data of the study patients**

<table>
<thead>
<tr>
<th></th>
<th>Benign lymph node</th>
<th>Metastatic lymph node</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (M/F)</td>
<td>16/27</td>
<td>35/22</td>
</tr>
<tr>
<td>Age</td>
<td>43.6 ± 17.5*</td>
<td>59.6 ± 11.0*</td>
</tr>
<tr>
<td>Lymph node size (cm)</td>
<td>0.84 ± 0.33*</td>
<td>1.51 ± 0.77*</td>
</tr>
<tr>
<td>Biopsy (FNAC/CNB)</td>
<td>18/25</td>
<td>15/42</td>
</tr>
</tbody>
</table>

CNB = core needle biopsy; FNAC = fine-needle aspiration cytology. * Mean ± SD.

**VTIQ examinations**

All shear wave velocity values were numeric, ranging from 1.68 to 8.24 m/s (mean ± SD: 3.71 ± 1.51 m/s), and the shear wave quality maps all indicated high quality. The shear wave velocity value was significantly higher for metastatic (4.46 ± 1.46 m/s; range, 1.91–8.24 m/s) than for benign (2.71 ± 0.85 m/s; range: 1.68–5.64 m/s) lymph nodes (p < 0.001) (Fig. 1). ROC curve analysis revealed that the estimated shear wave velocity cutoff level for distinguishing between benign and metastatic lymph nodes was 3.34 m/s (area under the ROC curve: 0.855, 95% confidence interval [CI]: 0.770–0.917), when all patients were regarded as a training set. Leave-one-out cross-validation tests with shear wave velocity revealed that the accuracy, sensitivity and specificity for differentiation between benign and metastatic lymph nodes were 77%, 78.9% and 74.4%, respectively. Shear wave velocities of lymph nodes according to diagnosis pooled for benign and metastatic pathologic conditions are listed in Table 2. Representative cases are detailed in Figures 2 and 3.

Among benign lymph nodes, 25.6% (11/43) gave false-positive results, with shear wave velocities ranging from 3.23 to 5.64 m/s. These cases included 5 cases of Kikuchi disease, 3 of tuberculous lymphadenitis and 3 of reactive hyperplasia (Fig. 4). In addition, 12 (21.1%) of the 57 metastatic lymph nodes were false negative, with shear wave velocity values ranging from 1.91 to 3.16 m/s. The intra-observer agreement for shear wave velocity (ICC = 0.961, 95% CI: 0.943–0.974) was excellent.
Whiskers extend from minimal to maximal values. The upper quartiles; the dent’s t-test and benign (2.71 ± 0.59 m/s) lymph nodes (p < 0.001, Student’s t-test). Each box represents the values of the lower to upper quartiles; the central line represents the median; and the whiskers extend from minimal to maximal values. The circle represents a case of tuberculous lymphadenitis.

### DISCUSSION

To the best of our knowledge, the use of ARFI imaging evaluation for cervical lymph nodes based on VTIQ shear wave elastography has not been reported previously. In our study, we prospectively assessed the ability of VTIQ shear wave elastography to distinguish between metastatic and benign lymph nodes in routine clinical practice. Our findings indicate that the VTIQ shear wave velocity values were significantly higher for metastatic than for benign lymph nodes, which is similar to results of previous studies on shear wave-based elastography (Fujiwara et al. 2013; Meng et al. 2013). Our study data had a diagnostic accuracy of 77%, sensitivity of 78.9% and specificity of 74.4% using cross-validation.

Different elastography techniques have been used to evaluate cervical lymph nodes, with sensitivity ranging from 41.9% to 98.1% and specificity from 57.1% to 100% for differentiating between benign and malignant cervical lymph nodes (Bhatia et al. 2012; Choi et al. 2013; Ishibashi et al. 2012; Lo et al. 2013; Teng et al. 2012). Shear wave-based elastography is a new elastographic technique that allows measurement of tissue stiffness without external manual compression and can offer better reproducibility than strain elastography (Cosgrove et al. 2012). In our study, there was excellent intra-observer agreement for shear wave velocity measurements using the VTIQ technique, which is similar to the reported findings of previous studies (Golatta et al. 2013, 2014). In addition, we used leave-one-out cross-validation to test our predictive models to prevent overfitting. Cross-validation was not used in previous reports on US elastography evaluation of cervical lymph nodes. The main advantage of cross-validation is to prevent the negative impact of outliers over a small-sized test set and to avoid substantial overestimation of diagnostic accuracy (Majos et al. 2004; Refaeilzadeh et al. 2009). In our study, diagnostic accuracy remained robust, which indicated that we could validate our results to hypothetical unknown data sets to obtain more consistent similar results in our present data set. Hence, our current results suggest that US elastography using the VTIQ shear wave technique may be a feasible method for differentiating between benign and malignant cervical lymph nodes.

In the present study, there were 11 false-positive results based on VTIQ shear wave elastography. Of particular note, 50% of tuberculous lymphadenitis cases (3/6), 55.6% of Kikuchi disease cases (5/9) and 10.7% of reactive hyperplasia cases (3/28) produced false-positive results. Therefore, the diagnostic performance of VTIQ shear wave velocity seems weak in Kikuchi disease and tuberculous lymphadenitis, but strong in reactive hyperplasia for the discrimination of benign and malignant cervical lymph nodes. The differential diagnosis between tuberculous lymphadenitis and metastatic lymphadenopathy is a diagnostic challenge of elastography (Fu et al. 2014; Tan et al. 2010), Teng et al. (2012) reported that only 31% of tuberculous lymphadenitis cases were correctly diagnosed by US elastography. In our current analyses, 50% (3/6) of tuberculous lymphadenitis cases were correctly diagnosed by VTIQ shear wave elastography. Various structures such as calcification and fibrosis with adhesions to adjacent tissues in tuberculous lymphadenitis may contribute to false positivity. More than half of the Kikuchi disease cases had false-positive results in our present study, indicating the stiff nature of the detected lymph nodes in those cases. However, a recent case report documented the use of strain elastography in detecting Kikuchi disease, which is suggestive of benign lesions because of its soft appearance (Lee and Ryu 2014). This discrepancy could be explained by application of different US elastography

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**Table 2. VTIQ shear wave velocity values of the 100 lymph nodes analyzed according to final diagnosis**

<table>
<thead>
<tr>
<th>Cytopathological diagnosis</th>
<th>Number of lymph nodes</th>
<th>VTIQ shear wave velocity (m/s)</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign diagnosis</td>
<td>43</td>
<td>2.71 ± 0.85</td>
<td>1.68–5.64</td>
<td></td>
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<tr>
<td>Reactive hyperplasia</td>
<td>28</td>
<td>2.35 ± 0.59</td>
<td>1.68–3.76</td>
<td></td>
</tr>
<tr>
<td>Kikuchi disease</td>
<td>9</td>
<td>3.40 ± 0.61</td>
<td>2.39–4.17</td>
<td></td>
</tr>
<tr>
<td>Tuberculous lymphadenitis</td>
<td>6</td>
<td>3.38 ± 1.24</td>
<td>1.94–5.64</td>
<td></td>
</tr>
<tr>
<td>Metastatic diagnosis</td>
<td>57</td>
<td>4.46 ± 1.46</td>
<td>1.91–8.24</td>
<td></td>
</tr>
</tbody>
</table>

VTIQ = Virtual Touch tissue imaging quantitation.
techniques (i.e., shear wave elastography vs. strain elastography) or a small study sample size. Therefore, further evaluations in larger populations are required to determine the diagnostic value of elastography performed in the same way as US elastography for Kikuchi disease.

Twelve of the metastatic lymph nodes we analyzed had false-negative results, including 6 cases of metastasis...
Fig. 3. Images obtained on examination of a 51-y-old woman with malignant melanoma in the nasal cavity presenting with a right neck mass that was cytopathologically diagnosed as a metastatic lymph node (true-positive case). (a) Gray-scale ultrasound image reveals a lobulated lymph node with heterogeneous cortical echogenicity at the right, level II (arrows). (b) Virtual Touch tissue imaging quantitation (VTIQ) revealed a shear wave velocity of 5.28 m/s in the node. (c) The VTIQ quality map display is green, indicating good VTIQ estimates throughout the lesion.
from lung cancer, 3 cases from thyroid cancer and one case each from uterine cancer, esophageal cancer and laryngeal cancer. The possible causes may be microscopic necrosis-induced softening of metastatic lymph nodes or the heterogeneous histology of the metastatic lymph nodes. Sebag et al. (2010) also reported wide

Fig. 4. Images obtained on examination of a 43-y-old man with a left neck mass that was cytopathologically diagnosed as tuberculous lymphadenitis (false-positive case). (a) Gray-scale ultrasound image reveals an oval lymph node at the left supraclavicular region (arrows). (b) Virtual Touch tissue imaging quantitation (VTIQ) revealed a shear wave velocity of 3.50 m/s in the node. (c) The VTIQ quality map is green, indicating good VTIQ estimates throughout the lesion.
CONCLUSIONS

Acoustic radiation force impulse imaging with the VTIQ shear wave technique is a feasible modality for the analysis of cervical lymph nodes. Although the VTIQ value of metastatic lymph nodes was found to be significantly higher than that of benign lymph nodes, there is a significant false-positive rate among cases of tuberculous lymphadenitis and Kikuchi disease, and not all malignant lesions appear to be stiff. On the basis of these results, the usefulness and added value of the VTIQ shear wave technique for evaluating cervical lymph nodes should be further evaluated in large multicenter studies.

REFERENCES


variation in stiffness measurements using elastography for malignant thyroid lesions of different histologies. Although the VTIQ shear wave technique has a considerable false-negative rate, when used in addition to US findings suggestive of metastatic lymph nodes (i.e., loss of hilar fat, cortica! heterogeneous echogenicity, echogenic dots or calcification, cystic or necrotic area, long-to-short axis diameter ratio <2.0 and peripheral cortical vascularity), VTIQ shear wave elastography may improve the characterization of cervical lymph nodes. Future studies in large populations are required to determine the added value of VTIQ shear wave elastography for evaluating cervical lymph nodes.

Our study had some limitations. First, our sample series was relatively small, with evaluations made at a single institution. However, our findings exhibited significance in differentiating metastatic from benign lymph nodes, and we believe that our findings provide important background data for future large-scale prospective studies. Second, the proportion of malignant cases (57%) in our series was high, which may have introduced a bias. We prospectively enrolled consecutive patients with neck lymph nodes larger than 5 mm in minimal axial diameter. Our institution is a tertiary referral institution, and because the proportion of patients at our hospital with cancer is high, the malignancy rate is inevitably high. Previous preliminary studies on US elastography for cervical lymph nodes also reported high proportions of malignancy (range: 53%–62%) (Alam et al. 2008; Lenghel et al. 2012; Rubaltelli et al. 2009). Because histologic confirmation is an inclusion criterion in many studies, our study samples may have had a bias, as patients who did not have tissue proof of diagnosis were excluded. A third limitation of our study was the use of patients with various histologic types of metastatic lymph nodes, with most metastatic lymph nodes being present in patients with lung cancer. The usefulness of shear wave-based elastography in patients with different histologic types of malignancies should be determined in future studies. Fourth, multiple measurements, rather than two measurements, would have been a more desirable study design for the assessment of measurement agreement, as illustrated in previous studies of the liver (Bota et al. 2012; Woo et al. 2015), so future studies are needed to explore this area. Finally, we did not compare conventional US imaging with the VTIQ shear wave technique. Although ARFI imaging with the VTIQ shear wave technique had high diagnostic accuracy on analysis of shear wave velocity, the context in which the VTIQ shear wave technique provides additional diagnostic value to conventional US findings remains unknown. However, we believe that our study provides important background data for future evaluations of the added value of the VTIQ shear wave technique in larger populations.


