Accuracy of Sonographic Elastography in the Differential Diagnosis of Enlarged Cervical Lymph Nodes: Comparison with Conventional B-Mode Sonography

OBJECTIVE. The purpose of our study was to evaluate the diagnostic performance of sonographic elastography and B-mode sonography individually and combined in the differentiation of reactively and metastatically enlarged cervical lymph nodes.

SUBJECTS AND METHODS. Eighty-five lymph nodes (metastatic, \(n = 53\); reactive, \(n = 32\)) from 37 patients were examined by both elastography and B-mode sonography in this prospective study. Elastographic patterns were determined on the distribution and percentage of the lymph node area with high elasticity (hard), with pattern 1 being an absent or very small hard area to pattern 5, a hard area occupying the entire lymph node. The cutoff line for reactive versus metastatic was set between patterns 2 and 3; patterns 3–5 were considered metastatic. B-mode sonographic diagnosis was based on the sum of scores for five criteria: short-axis diameter, shape, border (regular or irregular), echogenicity (homogeneous or inhomogeneous), and hilum (present or absent). The cutoff line for reactive versus metastatic was set between scores 6 and 7; scores 5 and 6 were considered reactive, and scores 7–10, metastatic.

RESULTS. Sensitivity, specificity, and accuracy of B-mode sonography were 98%, 59%, and 84%, respectively; 83%, 100%, and 89% for elastography; and 92%, 94%, and 93% for the combined evaluation.

CONCLUSION. The combination of highly specific elastography with highly sensitive conventional B-mode sonography has the potential to further improve the diagnosis of metastatic enlarged cervical lymph nodes.

Elastography. Elastography is a mechanical tissue characteristic that prevents tissue displacement under pressure. It varies in different types of tissue (fat, collagen, and so forth) and in the same tissue in different pathologic states (inflammatory, malignant). During the past few years, sonographic elastography, MR elastography [1, 2], and some other techniques have performed digital measurements of tissue hardness. In sonographic elastography, image representation of tissue hardness can be obtained using a conventional sonography machine with special software and a conventional ultrasound probe [3, 4].

In brief, sonographic elastography works in the following steps: first, elastography receives digitized radiofrequency echo lines from the tissue; second, it gives slight compression to the tissue by the transducer along the radiation axis to make some displacement; and third, it receives a second, post-compression digitized radiofrequency echo line from the same tissue [4]. Then the data from these two echo lines undergo processing, and ultimately an elastographic image (elastogram) appears on the monitor. There are two types of elastograms, gray-scale and color. The hard and soft areas (i.e., areas of high and low elasticity, respectively) appear in the gray-scale elastogram as dark and bright [5, 6]. In the color elastogram, increasing tissue hardness appears in ascending order as red, yellow, green, and blue. These colors represent the relative hardness of the tissues in the elastogram.

Sonographic elastography has been used to examine several organs: the breast [7, 8], thyroid [5], prostate [9], cervix [10], liver [11], and so forth. Recently, an article relating their initial experience in the diagnosis of cervical lymph node metastasis using gray-scale sonographic elastography was published by Lyschik et al. [6]. To our knowledge, however, no English-language articles have documented the evaluation of cervical lymph nodes using color sonographic elastography.
Of the 400–450 lymph nodes in the human body, the head and neck contain 60–70. These nodes show reactive enlargement due to infection (e.g., infection of upper aerodigestive tract). They also undergo enlargement when they are secondarily involved in head and neck cancer. Sometimes metastatic cervical lymphadenopathy appears as the first symptom in patients having malignancy in the head and neck, lung, breast, and so forth. Differentiation between reactive and metastatic lymphadenopathy is vital, and one of the differentiating criteria is hardness (elasticity) of the lymph node.

The purpose of this study was to investigate the accuracy of conventional sonography, sonographic elastography, and their combined evaluation for the differentiation between reactive and metastatic enlarged cervical lymph nodes.

Subjects and Methods

Patients

This was a prospective study. From January to November 2006, 109 lymph nodes of 59 consecutive patients who were referred for sonography of enlarged cervical lymph nodes were enrolled. Written informed consent was received from all patients for undergoing both conventional B-mode sonography and elastography. The 85 lymph nodes (reactive, n = 32; metastatic, n = 53) from 37 patients (25 males, 12 females; mean age ± SD, 55 ± 22 years old; age range, 11–92 years) with (n = 25) and without (n = 12) malignancy in which the final diagnosis was known, were used for evaluation.

Final Diagnosis

Lymph nodes were determined to be reactive on the basis of histopathologic findings or on the basis of clinical findings such as enlarged tender lymph node, increased C-reactive protein, leukocytosis, decreased size of the lymph node after antibiotic treatment, and the absence of known malignancy. The reference standard for the final diagnosis of metastatic lymph nodes was histopathologic findings or imaging findings suggesting central necrosis—that is, hypodensity on contrast-enhanced CT [12] or hypointensity on contrast-enhanced T1-weighted MRI in patients with malignancy.

Equipment and Scanning

One radiologist who had 18 years’ experience with conventional sonography and was a novice in elastography performed the sonography. The patients underwent both B-mode and elastographic sonography in the supine position with a digital sonography scanner (EUB 8500, Hitachi Medical) equipped with the Real-time Tissue Elastography software (Hitachi Medical); the probe was a conventional linear probe with a 13-MHz transducer (EUP-L65, Hitachi Medical).

For each lymph node, B-mode images were obtained first. Then, changing the system into the elastography mode, real-time handheld elastography was performed using the same probe for an additional 1–2 minutes. For elastography, compression with light pressure followed by de-compression was repeated until a stable image was obtained—that is, nearly the same size and color distribution of the target area in several consecutive images. Direction of the compression was upward and downward (along the radiation axis). Frequency of compression appeared on a scale on the monitor. Real-time elastographic and B-mode images simultaneously appeared as a two-panel image. Figure 1 shows a typical image displayed on the monitor during elastography, in which the elastogram appears in a region-of-interest (ROI) box. The size of the box was determined to be the target lymph node including surrounding tissue in almost the same proportion while avoiding tissues (bone, blood vessel) that might disturb the appropriate analysis of the relative hardness of the target lymph node. To maintain unbiased reading, 85 sets of elastograms and corresponding B-mode images without any patient information were collected into two separate slide shows (Microsoft PowerPoint, 2003) in random order.

Evaluation

To minimize recall bias, 1 month after data collection was completed, score-based reevaluation of B-mode and elastographic images was done by one of the authors who was blinded to other information. Less than 1 minute was required for the evaluation of each image (elastography and B-mode).

B-mode evaluation—B-mode images were evaluated on the criteria of size, shape, border, echogenicity, and hilum. Size and shape were evaluated per region. Regional distribution was determined according to the 1997 American Joint Committee on Cancer (AJCC) criteria for lymph nodes [13], in which neck lymph nodes are divided into seven levels. Lymph nodes in level 7 were excluded because scanning them was not possible with sonography. For the criterion of size, the short-axis diameter (in mm) of the lymph nodes was evaluated. For shape, the ratio of the short-axis diameter to the long-axis diameter (S/L axis ratio) was used. For each lymph node, we determined the cutoff values of short-axis diameter and S/L axis ratio that gave the best accuracy. In cases of level 4 (AJCC classification) lymph nodes in which two cutoff values had the highest accuracy, we used receiver operating characteristic (ROC) curve analysis to select one for our purposes. Scores were determined for five criteria: the short-axis diameter (diameter ≤ cutoff value, score of 1; diameter > cutoff value, score of 2), the S/L axis...
ratio (ratio ≤ 0.6, score of 1; > 0.6, score of 2), the border (regular, 1; irregular, 2), echogenicity (homogeneous, 1; inhomogeneous, 2), and hilum (present, 1; absent, 2) [6, 12–21]. The score for each lymph node was determined by summing scores for all criteria. A statistically supported cutoff line between reactive and metastatic was set between scores 6 and 7, depending on the best accuracy. Scores 5 and 6 were determined to be reactive, and scores 7–10, metastatic.

Elastogram evaluation—After observing all the elastograms, two authors together subjectively decided five patterns for the elastograms depending on the distribution of the blue (i.e., hard) area in the lymph node. Elastographic patterns were determined on the distribution and percentage of the lymph node area with high elasticity (hard): pattern 1, an absent or very small hard (i.e., blue) area; pattern 2, hard area < 45% of the lymph node; pattern 3, hard area ≥ 45%; pattern 4, peripheral hard and central soft areas; pattern 5, hard area occupying entire lymph node with or without a soft rim. The patterns 1, 2, 3, 4, and 5 were assigned scores of 2, 4, 6, 8, and 10, respectively. The outline of the lymph node was drawn, and the percentage of blue area was measured on an off-line computer using image analysis software “Image J” developed by the National Institutes of Health [22]. On average, approximately 1–2 minutes was required for the measurement of the blue area of each lymph node. A statistically supported cutoff line at 45% blue between patterns 2 and 3 was obtained from the ROC curves were calculated.

Results

Final Diagnosis

The prevalence of lymph node metastasis was 62% (53/85). Among the metastatic lymph nodes, 36 had primary squamous cell carcinoma (SCC), 13 had primary thyroid carcinoma, two had their primary site in the breast, one was in the lung, and one was unknown. The lymph nodes were finally diagnosed as reactive histopathologically (n = 2) and clinically (n = 30). The lymph nodes were diagnosed as metastatic by histopathology (n = 26), CT (n = 24), and MRI (n = 3). By AJCC levels, 17 nodes were in level 1, 26 in level 2, 21 in level 3, nine in level 4, and 12 in level 5.

B-Mode Sonography

Cutoff short-axis diameters according to AJCC levels were 11 mm in level 1, 13 mm in level 2, 5 mm in level 3, 9 mm in level 4, and 7 mm in level 5. The cutoff S/L axis ratio was 0.6; ≤ 0.6 was reactive and > 0.6 was metastatic. The accuracy for individual B-mode criteria was 84% for size, 56% for S/L axis ratio, 67% for border, 86% for hilum, and 78% for echogenicity (Table 2).

Elastography

During elastography, compression at a frequency of 3 or 4 on the frequency scale was needed to obtain stable elastographic features. In elastogram evaluation, all 32 reactive lymph nodes showed patterns 1 and 2 (reactive). Among 53 metastatic lymph nodes, and elastographic scores. A statistically supported cutoff line between metastatic and reactive was set between scores 12 and 13, depending on the best accuracy. Scores 7–12 were determined to be reactive, and scores 13–20, metastatic.

Combined evaluation—The combined score for each lymph node was the sum of the B-mode and elastographic scores. A statistically supported cutoff line between metastatic and reactive was set between scores 12 and 13, depending on the best accuracy. Scores 7–12 were determined to be reactive, and scores 13–20, metastatic.

Combined evaluation—The combined score for each lymph node was the sum of the B-mode

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**TABLE 1: Patterns and Scoring System on Elastographic Findings**

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Score</th>
<th>Description</th>
<th>Elastographic Diagnosis</th>
<th>Figure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>Absent or very small blue area(s)</td>
<td>Reactive</td>
<td>2, 3</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>Small scattered blue areas, total blue area &lt; 45%</td>
<td>Reactive</td>
<td>2, 4</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>Large blue area(s), total blue area ≥ 45%</td>
<td>Malignant</td>
<td>2, 5</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>Peripheral blue area and central green area,</td>
<td>Malignant</td>
<td>2, 6</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>Blue area with or without a green rim</td>
<td>Malignant</td>
<td>2, 7</td>
</tr>
</tbody>
</table>

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**Fig. 2—Drawings show typical diagrammatic appearance of five patterns of lymph nodes. Elastographic patterns were determined on distribution and percentage of lymph node area having high elasticity (hard): pattern 1, absent or small hard area; pattern 2, hard area < 45% of lymph node; pattern 3, hard area ≥ 45%; pattern 4, peripheral hard and central soft areas; pattern 5, hard area occupying entire lymph node. Increasing tissue hardness appears in ascending order as red, yellow, green, and blue.**
Sonographic Elastography of Cervical Lymph Nodes

44 (83%) had patterns 3, 4, and 5 (metastatic). Two (4%) and seven (13%) metastatic lymph nodes showed patterns 1 and 2, respectively. Concerning elasticity pattern 4 (i.e., suggestive of central necrosis), 12 of 13 (92%) lymph nodes were metastasized from SCC and one (8%) from an unknown origin.

**Diagnostic Performance**

The diagnostic performances of B-mode sonography, elastography, and the combined test are shown in Table 3. B-mode sonography showed sensitivity of 98% (95% CI, 94–100%), specificity of 59% (42–76%), and accuracy of 84% (76–91%). Elastography showed sensitivity of 83% (73–93%), specificity of 100% (100–100%), and accuracy of 89% (83–96%). The combined evaluation showed sensitivity of 92% (85–100%), specificity of 94% (85–100%), and accuracy of 93% (88–98%). The ROC curves for B-mode, elastography, and the combined evaluation are shown in Figure 5.

Fig. 3—Transverse sonogram of level 1 lymph node in 30-year-old man with left submandibular lymphadenopathy. Elastography image on left shows pattern 1, absent or small hard area. B-mode sonographic image on right shows score of 5, reactive. Final diagnosis from clinical and serologic findings was reactive lymph node.

Fig. 4—Longitudinal sonogram of level 2 lymph node in 33-year-old woman with left posterior auricular lymphadenopathy. Elastography image on left shows pattern 2, hard area < 45% of node. B-mode sonographic image on right shows score of 5, reactive. Final diagnosis from clinical and serologic findings was reactive lymph node.

Fig. 5—Transverse sonogram of level 2 lymph node in 79-year-old man with laryngeal carcinoma. Elastography image on left shows pattern 3, hard area ≥ 45%. B-mode sonographic image on right shows score 7, metastatic. Final diagnosis by histopathology was metastatic lymph node.

Fig. 6—Longitudinal sonogram of level 5 lymph node in 52-year-old man with nasopharyngeal carcinoma. Elastography image on left shows pattern 4, peripheral hard and central soft areas. B-mode sonographic image on right shows score 7, metastatic. Final diagnosis by CT was metastatic lymph node.
uation in the differentiation of reactive and metastatic lymph nodes are shown in Figure 8. The areas under the curves for B-mode sonography, elastography, and the combined evaluation were 0.901, 0.873, and 0.970, respectively.

Discussion
To our knowledge, this is the first English-language study documenting the accuracy of color sonographic elastography individually and combined with B-mode sonography in the differential diagnosis of reactive versus metastatic cervical lymph nodes. Elastography provides high specificity; especially when combined with B-mode sonography, elastography increases the accuracy of sonography for enlarged cervical lymph nodes.

B-Mode Sonography
Several studies have been published on the diagnosis of metastatic cervical lymph node by B-mode sonography [12, 14–21]; however, specific criteria for distinguishing reactive from metastatic cervical lymph nodes are not yet clear. The cutoff short-axis diameter for level 2 lymph nodes was two times higher than that for level 3. This suggests that, for the evaluation of cervical lymph nodes, a common cutoff diameter should not be set for all levels. In a study by Lyshchik et al. [6] using the fixed cutoff diameter of 8 mm, the accuracy of the short-axis diameter was 65%, whereas in our study it was 84%. With respect to shape, our calculation gave the best accuracy at S/L axis ratio \( \leq 0.6 \) for reactive and \( > 0.6 \) for metastatic nodes, which supports the findings of round shape for metastatic nodes in previous studies [6, 14, 15]. Very few studies have evaluated lymph node borders. Ying et al. [16], Ahuja and Ying [17], and Ying et al. [21] evaluated lymph node borders as sharp and unsharp. In this study, we evaluated regular and irregular lymph node borders as a criterion of reactive and metastatic lymph nodes, respectively, that showed 67% accuracy. The presence or absence of a hilum has been reported to be an important criterion for lymph node diagnosis [6, 18]. In our study also, this showed the best accuracy (86%).

Table 2: Results According to Criteria for Reactive and Metastatic Lymph Nodes

<table>
<thead>
<tr>
<th>Sonography Criteria</th>
<th>Reactive</th>
<th>Metastatic</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-mode</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size of short-axis diameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \leq ) Cutoff value</td>
<td>29 (88)</td>
<td>10 (19)</td>
<td>84</td>
</tr>
<tr>
<td>( &gt; ) Cutoff value</td>
<td>4 (12)</td>
<td>43 (81)</td>
<td></td>
</tr>
<tr>
<td>S/L axis ratio</td>
<td></td>
<td></td>
<td>56</td>
</tr>
<tr>
<td>( \leq 0.6 )</td>
<td>18 (56)</td>
<td>23 (43)</td>
<td></td>
</tr>
<tr>
<td>( &gt; 0.6 )</td>
<td>14 (44)</td>
<td>30 (57)</td>
<td></td>
</tr>
<tr>
<td>Border</td>
<td></td>
<td></td>
<td>67</td>
</tr>
<tr>
<td>Regular</td>
<td>24 (75)</td>
<td>20 (38)</td>
<td></td>
</tr>
<tr>
<td>Irregular</td>
<td>8 (25)</td>
<td>33 (62)</td>
<td></td>
</tr>
<tr>
<td>Hilum</td>
<td></td>
<td></td>
<td>86</td>
</tr>
<tr>
<td>Present</td>
<td>26 (81)</td>
<td>6 (11)</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>6 (19)</td>
<td>47 (89)</td>
<td></td>
</tr>
<tr>
<td>Echogenicity</td>
<td></td>
<td></td>
<td>78</td>
</tr>
<tr>
<td>Homogeneous</td>
<td>21 (66)</td>
<td>8 (15)</td>
<td></td>
</tr>
<tr>
<td>Inhomogeneous</td>
<td>11 (34)</td>
<td>45 (85)</td>
<td></td>
</tr>
<tr>
<td>Elastography pattern</td>
<td></td>
<td></td>
<td>89</td>
</tr>
<tr>
<td>1</td>
<td>19 (59)</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>13 (41)</td>
<td>7 (13)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>21 (40)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>13 (24)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>10 (19)</td>
<td></td>
</tr>
</tbody>
</table>

Note—Numbers in parentheses are percentages. S/L axis ratio = ratio of short-axis diameter to long-axis diameter.

Table 3: Diagnostic Performance of Elastography, B-Mode Sonography, and Combined Evaluation

<table>
<thead>
<tr>
<th>Performance Measure</th>
<th>B-Mode Sonography</th>
<th>Elastography</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity (%)</td>
<td>98 (94–100)</td>
<td>83 (73–93)</td>
<td>92 (85–100)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>59 (42–76)</td>
<td>100 (100–100)</td>
<td>94 (85–100)</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>84 (76–91)</td>
<td>89 (83–96)</td>
<td>93 (88–98)</td>
</tr>
<tr>
<td>Positive predictive value (%)</td>
<td>80 (70–89)</td>
<td>100 (100–100)</td>
<td>96 (91–100)</td>
</tr>
<tr>
<td>Negative predictive value (%)</td>
<td>95 (85–100)</td>
<td>78 (65–91)</td>
<td>88 (77–99)</td>
</tr>
</tbody>
</table>

Note—Values in parentheses are 95% CIs (in percentages).
Sonographic Elastography of Cervical Lymph Nodes

Elastography

Stiffness of cervical lymph nodes was independently assessed both quantitatively and qualitatively by Lyshchik et al. [6] using external sonographic gray-scale elastography. Those authors assessed the diagnostic potential of qualitative criteria—lymph node visibility, relative brightness, margin regularity, and margin definition—as well as the quantitative criterion strain index, which was obtained by comparing the absolute values of lymph node strain with the absolute values of surrounding muscle strain. Among those criteria, strain index greater than 1.5 was the most useful in metastatic lymph node classification, having 98% specificity, 85% sensitivity, and 92% accuracy. We obtained a similar level of results (100% specificity, 83% sensitivity, and 89% accuracy) using the combination of both qualitative and quantitative criteria. However, we propose the combined criteria, for the following reasons: The presence of a central green area in pattern 4 was considered to be central necrosis. Our study showed 12 of the 13 pattern 4 lymph nodes had primary SCC supports this consideration. Furthermore, we considered a large blue area in a scattered distribution to suggest the manifestation of focal cortical metastatic invasion and therefore categorized this appearance as pattern 3. This criterion did not show any false-positive results.

In endoscopic sonographic elastography of lymph nodes, Giovannini et al. [23] reported 100% sensitivity and 50% specificity without using any qualitative pattern analysis, whereas Saffioti et al. [24] reported 91.7% sensitivity and 94.4% specificity using a pattern analysis. These facts also indicate the importance of qualitative pattern analysis. However, another pattern of elastographic lymph node analysis has been reported in which only the percentage of blue area was used as a criterion [25].

The greatest advantage of elastography is its high specificity, which has been found not only in our study but also in other studies [6, 24]. Because of this, elastography may reduce unnecessary invasive procedures for the diagnosis of cervical lymph node metastasis.

Combined Evaluation

Accuracy and area under the ROC curve showed that the diagnostic power of the combined evaluation was higher than that of the individual evaluations. This suggests that the examination can be best performed when B-mode sonography, with its high sensitivity, and elastography, with its high specificity, are complementary. The scope of our study was to test the performance of elastography and the combined test compared with B-mode sonography alone. In clinical practice, however, sonography practitioners should use both methods in real time.

Gray-Scale and Color Elastography

In the gray-scale elastography study by Lyshchik et al. [6], postprocessing of radio-frequency images was done on an off-line computer. In our color elastogram study, postprocessing was done in real time, which made the process quicker. Although our study was performed on an off-line computer, in clinical practice real-time color elastography seems to have an advantage over gray-scale. Real-time diagnosis needs further investigation.

Limitations

This study had some limitations. First, our data sample was small; we used the lymph node as our unit, not the patient. Second, we included only enlarged lymph nodes, whereas elastographic findings of normal-sized lymph nodes should also be explored. Most metastatic lymph nodes in our study were in patients who had either primary SCC or thyroid cancer. Lymph nodes with primary malignancy or metastases from other primary malignancies such as melanoma or breast cancer were not included. Third, the final diagnosis of almost all reactive lymph nodes was done based on follow-up findings instead of histopathologic findings. Fourth, evaluation was done on an off-line computer from single images, which would not be practical for real-time evaluation.

Although elastography is a good improvement in the field of sonography, we still need to address one limitation for the future. Our evaluation had to be done in only one section of the lymph node. Assessment of the stiffness of the whole lymph node, by volumetric measurement, may increase the diagnostic performance of elastography.

In conclusion, elastography, with its high specificity, can improve the performance of sonography for the diagnosis of enlarged metastatic cervical lymph nodes. The combined evaluation of elastography and B-mode sonography offers the strongest diagnostic power, and we recommend it in clinical practice.

Acknowledgments

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References