Ultrasound Elastography: Its Potential Role in Assessment of Cervical Lymphadenopathy

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Rationale and Objectives: The aims of this study were to investigate the value of ultrasound elastography (UE) in the diagnosis of lymphadenopathy and to explore whether UE could improve the differentiation between benign and malignant cervical lymph nodes (LNs).

Materials and Methods: B-mode ultrasound, power Doppler imaging, and UE were performed in 107 consecutive patients with 128 cervical LNs. Only LNs that unequivocally matched between sonography and pathology were analyzed. The results of B-mode ultrasound, power Doppler imaging, and UE were interpreted separately to assess cervical LNs, using histopathologic analysis as the reference standard.

Results: A marked difference ($P = .000$) was found in the strain ratio between 70 malignant LNs (median, 2.71; range, 1.36–36.09) and 58 benign LNs (median, 1.44; range, 0.62–3.90). Receiver-operating characteristic curves showed that a strain ratio > 1.5 had high utility in enlarged cervical LN classification, with 92.5% sensitivity, 53.4% specificity, and a Youden’s index of 0.463. These results were significantly better than those obtained using the best grayscale criterion, a ratio of long-axis to short-axis diameter > 2, which yielded 58.6% sensitivity, 70% specificity, and a Youden’s index of 0.286. The $k$ values for interobserver agreement were highest using UE, at 0.881 (observer 1 vs observer 2), 0.828 (observer 1 vs observer 3), and 0.946 (observer 2 vs observer 3).

Conclusions: UE as an adjunct ultrasound modality holds some promise in screening and monitoring lymphadenopathy.

Key Words: Ultrasound elastography; cervical lymphadenopathy; power Doppler imaging; B-mode ultrasound.

To date, open cervical lymph node (LN) biopsy combined with pathologic examination remains the gold standard to determine whether LNs metastasize (1). However, the procedure can alter patterns of lymphatic drainage for up to 1 year following surgery and may portend a poor prognosis, especially for patients to present late to the hospital (2). Fine-needle aspiration cytology has proven to be an efficient tool for diagnosis, but it is an invasive approach and is subject to sampling and analytic uncertainty. Thus, improved and more reliable criteria for determining which nodules should be followed up and which should be aspirated are needed (3). In response, significant research efforts have been directed toward identification using noninvasive methods for diagnosing enlarged LNs. This technique must be safe, accurate, and accessible, like many standard medical screening tests.

Ultrasonography, compared to computed tomography and magnetic resonance imaging, has proven to be a valuable tool for the detection of LNs, but making a clear differentiation between benign nodal diseases and malignant lymphadenopathy remains difficult. Recently, ultrasound elastography (UE) has been presented as a novel technique to aid cancer research. It can be superimposed during B-mode ultrasound (B-US) examination to assess and measure tissue elasticity.

The principle of UE is applying a mechanical force (compression or vibration) to soft tissue to measure the degree of stiffness, and the tissue elasticity resulting from the compression is displayed as an image called an elastogram, on which hard areas appear blue and soft areas appear red. Knowing that malignant tissue is generally harder than normal surrounding tissue, elastography might provide interesting clinical information to help observe rather than palpate the stiffness of tissue.

In addition to this qualitative information, using a quantitative phantom and an automatic compressor, Waki et al (4) found that an important index called the strain ratio can reflect tissue elasticity quantitatively. Thus, tissue firmness can be calculated objectively using UE.

Although the technique is not yet used in routine clinical practice, it has shown some promising results in the differential diagnosis of thyroid (5), breast (6), prostate (7), and pancreatic diseases (8) as well as in the assessment of the histologic stage of liver fibrosis (9). Neck LNs are well positioned for examination using UE. They are accessible and can be efficiently compressed against cervical anatomic structures with an ultrasound probe.

UE can also be used to differentiate between benign and metastatic LNs. Lyshchik et al (10) reported that a strain ratio > 1.5 had high utility in metastatic LN classification, with
98% specificity, 85% sensitivity, and 92% overall accuracy. These results were significantly better than those obtained using the best grayscale criterion, a ratio of long-axis to short-axis diameter (L/T) > 0.5, which had 81% specificity, 75% sensitivity, and 79% overall accuracy. However, primary malignance and tuberculosis, the two important lymphadenopathies, were not included in similar research.

The present study was the continuation of previous research to validate the potential role of UE in cervical lymphadenopathy differentiation and to compare the results with a classification based on B-US and power Doppler imaging (PDI) with the final diagnosis obtained by open biopsy.

**MATERIALS AND METHODS**

**Patients, Procedure, and Examination Technique**

This study was conducted at Xiangya Hospital, Central South University. From August to December 2009, 112 outpatients with suspected enlarged cervical LNs were examined with B-US, PDI, and UE before surgery dissection. Two patients with histories of chemotherapy or radiation therapy and three patients who were lost to further follow-up were dismissed from the research. The remaining 107 patients (57 male, 50 female; age range, 7–77 years; mean age, 41 years) were recruited in the study, and their final diagnoses were obtained by means of histologic examination of biopsy specimens (obtained with operative excision). The study was approved by the ethics committee of the hospital, and informed consent for diagnostic procedures was obtained from each patient.

During the whole ultrasound examination, patients maintained a supine position and bent their necks backward. The scanning process was carried out by the same sonographer using an HV-900 ultrasound scanner (Hitachi Medical Corporation, Tokyo, Japan) equipped with a 6.5-MHz to 13.0-MHz linear-array transducer. For each LN, the images from B-US and PDI were obtained first, and the scanning protocol included transverse and longitudinal real-time imaging of target nodes, hilar status, and the distribution of vascularization. It should be noted that a single imaging mode was used for B-US and PDI, but split-screen mode was used for UE to obtain identical images.

Focusing depth was set between 1 and 3 cm, the depth at which the target LNs were usually present. The method for appropriated gain optimization was in accordance with criteria described by Furukawa et al (12). Every LN of interest was scanned slowly in the horizontal and then longitudinal axes. In addition, when using UE to screen LNs, additional aspects require attention. First, the same depths of focus positions and gain settings were used as for B-US images; moreover, the area of the target LN occupied in the region of interest on the elastogram should be less than one third. To compare the elasticity of the target LN with that of normal surrounding tissues (neck muscles), both tissue types should be present in the region of interest (13). Second, the direction of the compression was perpendicular to the region of interest, and the probe was moved slightly upward and downward to obtain a stable image. There is a pressure indicator when UE modality is in use, and the freehand compression should be gauged to keep the pressure scale between 3 and 4; if the pressure scale is >4 or <3, pressure is too high or too low, respectively, which can cause nonlinear properties of tissue elasticity and lead to misdiagnosis. Finally, the elastogram was obtained and the strain ratio of muscle to LN was calculated accordingly. The sonographer selected representative transverse and longitudinal images of target LNs and saved them in a picture archiving and communication system as bitmap files on a hard disk so that reviewers could look at them individually for later blinded review. Three reviewers with ≥5 years of experience in sonographic diagnosis gave their impressions individually, without any clinical data.

**Ultrasound, PDI, and UE Evaluation**

The sonomorphologic features of ultrasound, PDI, and UE are shown schematically in Figure 1. As Vassallo et al (14) reported, the three B-US features were described as follows: LN shape, central echogenic hilum, and peripheral hypoechoic...
cortex. LN shape was assessed by measuring the largest and smallest diameters on the same scan and by calculating L/T. LNs were separated into two classes: L/T ≥ 2 and L/T < 2.

The central hilum was also assessed, and the nodes were separated into three hilar classes: wide, narrow, and absent. When the hilum appeared elliptic in the longitudinal nodal plane, generally conforming with the shape of the whole node, it was classified as wide. A flat, slitlike hilum was considered narrowed. Those nodes that showed no central zone of hyperechogenicity were classified as having no hilum or absent.

The peripheral cortex was then evaluated, and the nodes were separated into two cortical classes: concentric or eccentric. Those nodes that showed focal cortical widening (ie, the thickness of the cortex at one site was at least double that at its narrowest point) were classified as having eccentric cortices. Those without these characteristics were classified as having concentric cortices. Naturally, cortical width of a nodal hilum for which the reference structure was absent could not be assessed.

The five PDI patterns refer to criteria proposed by Wu et al (15) as follows: hilar type (pattern I), defined as centrifugal branches radially toward the periphery or only a simple hilar vessel signal; arboroid or spotted type (pattern II), defined as scattered spots or segments of vessel signals distributed chaotically within the LN; peripheral type (pattern III), defined as prominent peripheral vascularization; mixed type (pattern IV), defined as a mixture of more than one type of vascular distribution; and avascular type (pattern V), barely showing vascularization. The four scores of elastographic classification refer to Furukawa et al (15): a score of 1 indicates that ≥80% of the cross-sectional area of the LN is green or red, a score of 2 indicates that ≥50% and <80% is red or green, a score of 3 indicates that ≥50% and <80% is blue, and a score of 4 indicates that ≥80% or more of the cross-sectional area of the LN is blue.

Pathologic Examination

All patients underwent lymphadenectomy and surgical removal after a sonographer marked the position on the body. After being resected, the specimen was fixed in 10% formalin and embedded in paraffin. Then 6-μm sections were obtained at 20-μm to 30-μm intervals from either half of nodes or intact small nodes. Sections were then stained with standard hematoxylin and eosin.

During histologic examination, two or three histologic slices per LN were examined. The final diagnosis of malignant LN involvement was made by pathologists with ≥10 years of experience performing histologic cervical LN diagnosis. According to Loew (16) regarding the histologic classification of LN disease, the lymphadenopathies involved in this research were classified as follows: a total of 128 neck LNs (58 [45%] benign, 70 [55%] malignant) were examined. In the benign group, 37 benign nodes (29%) showed pathologic evidence of nonspecific lymphadenitis and 21 (20%) of tuberculosis. The former included one case each of plasmacytes involved in nodal hyperplasia, cat-scratch disease, granulomatous inflammation, and Castleman’s disease; two cases of dermatopathic lymphadenitis; three cases of histiocytic necrotizing lymphadenitis (Kikuchi’s disease); five cases of reactive follicular hyperplasia; and nine cases of sinus histiocytosis; and 14 cases of reactive paracortical lymphadenitis. In the malignant group, 23 (18%) had proved primary malignance, and 47 (37%) had metastases. Among these, there were 21 cases of non-Hodgkin’s lymphoma and one case each of leukemia and Hodgkin’s lymphoma. Nineteen cases of metastatic squamous cell carcinoma and two cases of metastatic melanoma belonged to the group of metastasis in addition to 26 cases of metastatic adenocarcinoma.

Statistical Analysis

SPSS for Windows version 13.0 (SPSS, Inc, Chicago, IL) was used for statistical analysis. The unit of analysis was each LN rather than each patient, and all data were registered separately and processed blindly. Differences in continuous measurements were checked using the Mann-Whitney U test. Qualitative variables were compared using the χ² test. Interpretation of the various diagnostic procedures was compared with regard to sensitivity, specificity, accuracy, positive and negative predictive values, and Youden’s index (17). Parameters with P values < .05 were considered statistically significant, and all tests were two tailed.

RESULTS

B-US

As Table 1 shows, of the 58 benign nodes, 70% of nonspecific lymphadenitis and 52% of tuberculosis showed L/T values ≥ 2, while 30% of the former and 48% of the latter had L/T values < 2. Of the 70 malignant nodes, 52% of primary nodal malignance and 79% of nodal metastasis showed L/T values < 2, while only 48% and 21% of primary and secondary malignance displayed L/T values ≥ 2. The difference in the distribution of malignant and benign nodes in two L/T classes was statistically significant (P = .000), but there was not much difference in the distribution between nonspecific lymphadenitis and tuberculosis (P = .256). It also found in the distribution between primary and secondary malignance (P > .05). Also, we can find out the contingency coefficient of 0.320, reflecting the agreement between benign and malignant LNs according to diameter ratio alone, was not very high in the table.

With regard to nodal hilum, the lowest κ value suggested that it was not a good indicator either, although there were statistical differences between the two groups (P < .05), and the odds of having an abnormal lymph hilum with malignancy were 5.25 times higher than those of having a normal one. Of the 58 benign LNs, 38% showed concentric cortices,
including 7% with wide hilum, 41% with narrow hilum, and 53% with absent hilum. Of 70 malignant nodes, only 15% of primary malignant nodes exhibited concentric cortices. Sixty-five percent of primary malignancies and 100% of metastases displayed no hilum. The differences in the distribution between nonspecific lymphadenitis and tuberculosis in the three hilar classes were significant ($P = .001$). No significant difference was observed in the distribution between primary nodal malignancies and nodal metastasis according to appearance of the nodal hilum ($P > .05$).

**PDI**

In the benign group, 72.4% of LNs (42 of 58) showed pattern I, which included 28 nonspecific lymphadenitis and 14 tuberculosis, but no malignant LNs in the study showed this type, and 94.3% of LNs (66 of 70) displayed pattern II, III, or IV. Moreover, 87% of primary malignancies (20 of 23) showed pattern II. Only 14.2% of tuberculosis (3 of 21) and 8.5% of metastases (4 of 47) had showed pattern V. We thereby classified patterns I and V in the benign group and the other three types in the malignant group. Statistical analysis then proved that there were significant differences ($P = .000$) between benign and malignant groups (Table 2). Additionally, LNs with PDI patterns II, III, or IV were 57.115 times more likely to be malignant, and the connection between benign and malignant LNs according to the criterion was relatively high (contingency coefficient, 0.593).

**UE**

On UE, we found that 87.9% of benign LNs (51 of 58) scored 1 or 2, and 50% of malignant LNs (35 of 70) scored 3 or 4. Of 70 malignant LNs, 100% of primary malignant nodes (23 of 23) scored 2, and 74.5% of metastases (35 of 47) scored 3 or 4. We were therefore unable to classify these nodes according to the elastographic score alone. However, the concomitant quantitative analysis of tissue consistency among the four types of lymphadenopathies was relatively better, with a significant difference in the distribution of strain ratios between 70 malignant (median, 2.71; range, 1.36–7.43) and 58 benign (median, 1.44; range, 0.62–3.9) LNs ($P < .01$), as well as among groups of nonspecific lymphadenitis (median, 1.2; range, 0.62–2.55), tuberculosis (median, 2.3; range, 0.77–3.90), primary malignancy (median, 1.92; range, 1.36–4.50), and metastasis (median, 3.3; range, 1.44–36.09), except for the comparison between tuberculosis and primary malignancy ($P = .195$). The cutoff point of 1.5 was calculated using receiver-operating characteristic curve analysis.

With regard to sensitivity and negative predictive value, no significant differences among the three modalities were found. The specificity and accuracy of UE were significantly higher than those of B-US but lower than those of PDI ($P < .05$; Table 2). Moreover, though no obvious difference was found between UE and B-US, it seemed that PDI achieved the best results. PDI was much better than the other modalities in terms of positive predictive value and Youden's index ($P < .05$; Table 2).

An illustration of benign and malignant LNs detected by UE that had almost the same morphologic characteristics on sonography is shown in Figure 2.

**Interobserver Variability**

The three observers were independently asked to assess the sonographic features and to decide whether a particular node was benign or malignant. The observers had varying degrees of clinical experience in sonography, with 25 years (observer 1), 10 years (observer 2), and 5 years (observer 3) of experience interpreting sonographic images. The observers had no knowledge of the medical history or the findings from the other technique or interpretations of the other observers when they made diagnoses. By and large, interobserver agreement ($k$) was low when the determinations by the more
experienced observers were compared to those by the less experienced observers, and agreement was relatively high when comparisons were made among the equally experienced observers. Interobserver agreement was higher when we used UE alone: $\kappa = 0.881$ (observer 1 vs observer 2), $\kappa = 0.828$ (observer 1 vs observer 3), and $\kappa = 0.946$ (observer 2 vs observer 3); the corresponding $\kappa$ values for B-US and PDI were 0.603, 0.531, and 0.728 and 0.622, 0.467, and 0.602. It should be noted that in general, a $\kappa$ value < 0.40 indicates poor agreement, and a $\kappa$ value of 0.40 to 0.75 indicates moderate agreement.

**DISCUSSION**

This preliminary clinical study tentatively confirms that UE, a new screening modality, is helpful in detecting and identifying cervical LNs, though it was not superior to PDI in terms of differential diagnosis and needs to be further refined. To our knowledge, there are mechanical characteristics of tissue that depend on several conditions, such as molecular building blocks (collagen, cells, fat, etc), microscopic and macroscopic structural organization, and metabolic activity. The use of different echoes (eg, hyperecho, isoecho, hypoecho) on B-US, different densities on computed tomography, and different signals on magnetic resonance imaging to delineate the biologic morphology of tissue is of long standing. Now, to display mechanical properties, compared to the palpation, the technique of elastography can lead to better understanding of viscoelastic properties (18). Because changes in tissue elasticity are usually related to an abnormal, pathologic process, UE may prove to be a more viable tool to efficiently aid in the characterization of different internal echoes. One node from a patient with tuberculosis showed hyperechoic area on sonography but green zones on elastography, suggesting necrosis with loss of the hilum; typical caseous necrosis was confirmed at subsequent pathologic examination (Fig 2). Moreover, the greatest advantage of this novel imaging method is that the strain ratio obtained can be used to quantitatively differentiate between malignant and benign nodes. The addition of elastic features into the diagnostic feature space can aid physicians in making more accurate diagnoses with consensus, given that the $\kappa$ values among three observers with different clinical experience were all >0.75. The cutoff point of 1.5 was effective in screening out 92.8% of histologically confirmed benign disease, and no significant differences were found in sensitivity between UE and PDI. Contrary to Chikui et al (19), who reported that the B-US criteria most predictive of metastatic cervical LNs were absent hilar echoes and that increases in short-axis length, as assessed by logistic regression analysis and color-flow criteria, had fewer predictive advantages, we found that those grayscale criteria were not superior. L/T is easily evaluated in all nodes, but the criterion of L/T > 2 yielded 58.6% sensitivity, 70% specificity, and a Youden’s index of 0.286. Abnormal hilum is not a good indicator to infer malignancy, because 53.4% (31 of 58) of benign LNs’ hilum was absent and 24.1% (14 of 58) was narrow or wide with eccentrically cortex. However, PDI as a diagnostic workup has more predictive advantages, and it had the highest accuracy, positive predictive value, and Youden’s index compared to the other two modalities. The reason may be that PDI is the image modality showing the inner vascular distribution of the tissue. Multiple studies have proven that vascularity increases in various tumors, either by histopathology or by imaging studies, including color Doppler ultrasound and angiography. The vascular pathology of malignant lymphadenopathy was found to be characterized by higher vascular density and aberrant vascular patterns by some researchers (14,19). The contours of vessels were clearly shown to mimic angiography somewhat on PDI, while B-US and UE represented the overall morphologic characteristics. We therefore can conclude that the PDI is a feasible LN flow-mapping technique with the advantage of less angle and velocity dependence. But the dynamic image tends to be more associated with the sensitivity of the instrument and the sonographer’s experience. This may also explain why the $\kappa$ value for PDI among three observers was inferior to that for UE. As Figure 2 shows, histopathology proved that the metastatic LNs stemmed from malignant melanoma. In fact, the patient whose node was excised had undergone arm amputation 3 months previously for the disease. Although we still confirm the value of UE in the differential diagnosis of lymphadenopathy, there was an overlap of elasticity between tuberculosis and primary malignant LNs. No significant difference ($P = .195$) was discovered in strain ratio between the two groups, which could have affected the overall

**TABLE 2. Comparison of Sensitivity, Specificity, Accuracy for B- US, PDI, and UE**

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>PPV</th>
<th>NPV</th>
<th>Youden’s Index (Sensitivity – [1 – Specificity])</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-US</td>
<td>88.6% (62/70)</td>
<td>46.6% (27/58)</td>
<td>69.5% (89/128)</td>
<td>66.7% (62/93)</td>
<td>77.1% (27/35)</td>
<td>35.2%</td>
</tr>
<tr>
<td>PDI</td>
<td>94.3% (66/70)</td>
<td>77.6% (45/58)</td>
<td>86.7% (111/128)</td>
<td>95.5% (66/70)</td>
<td>98.8% (45/49)</td>
<td>75.3%</td>
</tr>
<tr>
<td>UE</td>
<td>92.8% (65/70)</td>
<td>53.4% (31/58)</td>
<td>75% (96/128)</td>
<td>70.7% (65/92)</td>
<td>86.1% (31/36)</td>
<td>46.3%</td>
</tr>
</tbody>
</table>

B-US, B-mode ultrasound; NPV, negative predictive value; PDI, power Doppler imaging; PPV, positive predictive value; UE, ultrasound elastography.

* $P < .05$ versus PDI.

$^1P < .05$ versus PDI.
value of UE diagnosis on benign and malignant lymphadenopathy. However, marked differences were found between benign and metastatic cervical LNs in patients suspected of having thyroid or hypopharyngeal cancer, and accuracy has been reported to reach 92% (10). Some investigators (20) obtained high sensitivity of 92%, specificity of 94%, and accuracy of 93% using a 10-point elastographic scoring method combined with B-US examination. The combination of highly specific elastography with highly sensitive B-US has the potential to further improve the diagnosis of metastatic

Figure 2. Tuberculosis lymphadenitis. (a, b) Sonograms obtained from a 32-year-old woman with symptoms of dry cough and weight loss. (c, d) In this lymph node (LN), which was $18 \times 12 \times 7$ mm, a hyperechoic area of $5 \times 3$ mm was seen on power Doppler imaging (PDI). Gross pathology and histologic samples proved that the area was typical caseous necrosis of tuberculosis. (e–g) In a negative LN, hyperechoic area corresponding to the hilum was observed, and blood flow distributing evenly from the hilum was seen on PDI. The node also appeared as a soft mass on elastography, in which $\approx80\%$ of the node was green or red. Finally, the soft, uniform, pale to creamy tan nodal parenchyma and distinct hilum were proved by pathology. (h–j) In a positive LN, no hyperechoic area corresponding to the hilum was noted, and random blood flow was observed in its capsule and interior. The node was entirely blue or mixed with small areas of green. Open biopsy validated the inner bleeding of the resected LN.
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enlarged cervical LNs. Also, it is a simple, convenient, and easily grasped method for clinical use. After obtaining the strain image, it takes only 1 minute to acquire the strain ratio. Thus, we have full reason to believe that with the development of this technique, ultrasonography could be a more objective predictor in the future.

There exists some technique limitations of UE. First, some strain images of large LNs were suboptimal, because probe contact over large lesions was not very good, and motion of surrounding tissues and vessels during compression scanning can cause some artifacts. In addition, the regions of interest in large LNs included only the nodes themselves, leaving out the surrounding tissue, which affected the strain presentation of both normal and abnormal structures. Second, a simultaneous display of both grayscale images and elastograms could influence the interpretation of the findings, although we attempted to assess both UE images and B-US independently. However, the acquisition method and dual imaging display likely led to some biases. Last but not least, because some cervical LNs are close to great vessels, the pulse of the vessels can affect the operation of the sonographer.

In conclusion, UE is superior to B-US and better than or equal to PDI in differentiating between benign and malignant lymphadenopathies. By combining these three modalities, detection accuracy can be improved greatly, and the combination potentially can reduce unnecessary biopsy. UE is a promising technique for the differentiation of cervical lymphadenopathy. Compared with palpation, we have full reason to believe that UE has a bright future.

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