Endobronchial Ultrasound Elastography in the Diagnosis of Mediastinal and Hilar Lymph Nodes

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Objective: Endobronchial ultrasound elastography is a new technique for describing the stiffness of tissue during endobronchial ultrasound-guided transbronchial needle aspiration. The aims of this study were to evaluate the utility of endobronchial ultrasound elastography for mediastinal and hilar lymph nodes, and to compare the elastographic patterns of lymph nodes with results from endobronchial ultrasound-guided transbronchial needle aspiration.

Methods: Seventy-five lymph nodes were evaluated. A convex probe endobronchial ultrasound was used with a new endoscopic ultrasound processor to assess elastographic patterns that were classified based on color distribution as follows: Type 1, predominantly non-blue (green, yellow and red); Type 2, part blue, part non-blue (green, yellow and red); Type 3, predominantly blue. The elastographic patterns were compared with the final pathologic results from endobronchial ultrasound-guided transbronchial needle aspiration.

Results: On pathological evaluation of the lymph nodes, 33 were benign and 42 were malignant. The lymph nodes that were classified as Type 1 on endobronchial ultrasound elastography were benign in 24/24 (100%); for Type 2 lymph nodes, 6/14 (46.9%) were benign and 8/14 (57.1%) were malignant; Type 3 lymph nodes were benign in 2/37 (5.4%) and malignant in 35/37 (94.6%). In classifying Type 1 as ‘benign’ and Type 3 as ‘malignant,’ the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy rates were 100, 92.3, 94.6, 100 and 96.7%, respectively.

Conclusions: Endobronchial ultrasound elastography of mediastinal and hilar lymph nodes is a noninvasive technique that can be performed reliably and may be helpful in the prediction of nodal metastasis during endobronchial ultrasound-guided transbronchial needle aspiration.

Key words: bronchoscopy — EBUS-TBNA — elastography — lung cancer staging — nodal metastasis

INTRODUCTION

The appropriate treatment and outcome of lung cancer depends on proper staging and diagnosis (1). Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is a widely used minimally invasive procedure that has been shown to have a high sensitivity and diagnostic yield for detecting metastasis to hilar and mediastinal lymph nodes (LNs) (2).

The differentiation between malignant and benign LNs by ultrasound (US), computed tomography (CT) and magnetic resonance imaging traditionally relied on size and topographic distribution (3). In the evaluation of nodal metastasis in head and neck cancers, breast cancers and thoracic malignancies, sonographic features have been reported to be useful (4,5). A previous report on EBUS indicated that conventional B-mode features of mediastinal and hilar LNs, such as, size, shape, echogenicity and distinct border, were useful for the prediction of malignant metastasis (6). Other authors suggested that vascular pattern on power Doppler mode during EBUS can also predict nodal metastasis in patients with lung cancer (7).
While the prediction of a malignant process within a LN can possibly reduce unnecessary biopsies during mediastinal staging by EBUS-TBNA, these classifications using B-mode and power Doppler features may be difficult to discern in some cases like, avascular LNs or those with equivocal B-mode features.

Recently, elastography, a new ultrasonography-associated technology that measures tissue compressibility, was introduced. In principle, pathophysiological processes, such as malignancy, make tissues less deformable or stiff. Compression of surrounding structures produces a deformity or strain effect that is inversely related to the hardness of the pathologic tissue; harder tissues are less deformable than softer tissues. First applied in the field of breast US, elastography has also been used to measure tissue elasticity in thyroid and liver disease (8–13).

Recently, there have been several reports suggesting that endoscopic ultrasound (EUS) elastography had a high sensitivity and specificity for detecting malignant involvement of pancreatic lesions and LNs (14–16). Subsequently, elastography has become available for use during EBUS (17). As of yet, evidence is needed to assess whether elastography can be a valuable tool in the noninvasive discrimination between benign and malignant thoracic LNs during EBUS-TBNA.

The purpose of this study was to investigate the utility of elastography for hilar and mediastinal LNs during EBUS-TBNA and to explore the elastography patterns of benign and malignant lesions based on results of EBUS-TBNA.

**PATIENTS AND METHODS**

**PATIENT ENROLLMENT**

This was a retrospective review of consecutive patients who underwent elastography during EBUS-TBNA at our institution between 1 February 2014 and 31 May 2014. Prior to each procedure, 5 mm-slice chest CT scan was done on all patients. Indications for EBUS-TBNA were mediastinal and hilar lymphadenopathy, defined as an enlargement (≥10 mm in short-axis diameter) on chest CT, or an increased 18 [F]-fluorodeoxyglucose (FDG) uptake (standardized uptake value (SUV) max ≥2.5) on positron emission tomography (PET)-CT. EBUS-TBNA was performed for clinical reasons independent of the purposes of the study.

![Figure 1.](image-url) Representative lymph nodes on EBUS elastography (this figure appears in colour in the online version). The image on the left displays EBUS scanning on B-mode. On the right is a superimposed elastographic image with color scale based on tissue elasticity (the hardest tissues appear as blue and the softest tissues appear as red). (A) Predominantly non-blue (green, yellow and red) (Type 1). (B) Part blue, part non-blue (green, yellow and red) (Type 2). (C) Predominantly blue (Type 3). EBUS, endobronchial ultrasound.
All patients gave written informed consent before the procedure. Institutional review board approval was granted for this retrospective review.

**DETERMINATION OF TARGET AREA BY EBUS**

All examinations were performed by the same bronchoscopist (T.I.). After local anesthesia to the pharynx with 4% lidocaine spray (10 ml), each patient was placed under moderate sedation with intravenous midazolam. The convex probe EBUS (CP-EBUS; BF-UC260FW, Olympus, Tokyo, Japan) was inserted through the oral route, with intermittent instillation of 2 ml aliquot doses of 2% lidocaine. Scanning was done on a 7.5 MHz frequency US and images were generated using a new dedicated US processor (EU-ME2 PREMIER PLUS, Olympus).

Based on previous reports, lymph nodes that had the following sonographic characteristics on B-mode and vascular pattern on power Doppler were deemed as probably malignant: short-axis size > 1 cm, round shape, distinct margin, heterogeneous echogenicity and abundant blood flow with varying vessel diameters and tortuosity (6,7). The presence of at least one or a combination of these features in a LN was designated as the target area for EBUS-TBNA. When multiple LNs were detected in the same station, the biggest LN with suggestive malignant features was chosen.

**EBUS-TBNA WITH ELASTOGRAPHY PROCEDURE**

Elastography was performed on all LNs that were candidates for EBUS-TBNA. The elasticity of tissue within the scanned area was reconstructed by comparing it with the surrounding tissue, and translated this into a color signal that overlaid the B-mode image. The colors associated with hard, intermediate and soft tissues were blue, green and yellow/red, respectively. The complete spectrum from blue to red encoding was applied to each elastographic record and indicated the calibration of relative elasticity of the scanned area. Elastographic and B-mode images were simultaneously displayed on the monitor side by side. The quality of the elastographic signal within the image was indicated by a numeric scale of 1–3. Maximal sensitivity for the elastographic recording was used. The scanned area, with a maximal depth of ~4.0 cm, was adjusted to include the pre-determined target area of the LN and variable portions of the surrounding tissue.

After elastography evaluation, TBNA with negative pressure was done for 10–20 times, under real-time EBUS guidance. Histology and cytology specimens were collected accordingly. Rapid on-site cytology evaluation (ROSE) was performed for every case. The final diagnosis was confirmed from independent pathological examination of EBUS-TBNA specimens by pathologists who did not know the results of EBUS elastography.

Immediately after every EBUS-TBNA procedure, the digital video recording and JPEG images of the sampled LNs were analyzed; subsequently, the EBUS elastography classification of LNs was performed. Elastographic patterns were described according to the dominant colors and their distribution within the target LN. This description formed the basis for the following classification of elastographic types:

- Type 1 (Fig. 1A): predominantly non-blue (green, yellow and red).
- Type 2 (Fig. 1B): part blue, part non-blue (green, yellow and red).
- Type 3 (Fig. 1C): predominantly blue.

Only LNs with adequate lymphocytes or those with a definitive diagnosis were included for data analysis.

**STUDY VARIABLES AND STATISTICAL ANALYSIS**

Descriptive statistics was presented as frequency, percentage and median (range). The sensitivity, specificity, positive

**Table 1.** Baseline characteristics of the lymph nodes

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. or median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size, short axis</td>
<td>Median, mm (range)</td>
</tr>
<tr>
<td>Lymph node station</td>
<td></td>
</tr>
<tr>
<td>Upper paratracheal (2R)</td>
<td>2</td>
</tr>
<tr>
<td>Retrotracheal (3p)</td>
<td>1</td>
</tr>
<tr>
<td>Lower paratracheal (4R, 4L)</td>
<td>30</td>
</tr>
<tr>
<td>Subcarinal (7)</td>
<td>21</td>
</tr>
<tr>
<td>Hilar (10R, 10L)</td>
<td>4</td>
</tr>
<tr>
<td>Interlobar (11s, 11i, 11L)</td>
<td>17</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>22</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>5</td>
</tr>
<tr>
<td>Small cell carcinoma</td>
<td>4</td>
</tr>
<tr>
<td>Non-small cell carcinoma</td>
<td>3</td>
</tr>
<tr>
<td>Non-pulmonary malignancies</td>
<td>8</td>
</tr>
<tr>
<td>Benign</td>
<td>33</td>
</tr>
</tbody>
</table>

Data are presented as number or median (range).

**Table 2.** EBUS elastography classification of lymph nodes

<table>
<thead>
<tr>
<th>Elastography type</th>
<th>Number of benign LNs/total number (%)</th>
<th>Number of malignant LNs/total number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 (n = 24)</td>
<td>24/24 (100)</td>
<td>0/24 (0)</td>
</tr>
<tr>
<td>Type 2 (n = 14)</td>
<td>6/14 (42.9)</td>
<td>8/14 (57.1)</td>
</tr>
<tr>
<td>Type 3 (n = 37)</td>
<td>2/37 (5.4)</td>
<td>35/37 (94.6)</td>
</tr>
</tbody>
</table>

EBUS, endobronchial ultrasound; LNs, lymph nodes.
predictive value, negative predictive value and diagnostic accuracy were calculated. Spearman rank coefficient was used to test correlation between the results of EBUS elastography types and FDG-PET SUVmax.

Statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University; http://www.jichi.ac.jp/saitama-setc/SaitamaHP.files/statmed.html; Kanda), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, Ver. 2. 13.0) and a modified version of R commander (Ver. 1.8–4).

RESULTS

The baseline characteristics of all the LNs evaluated in this study were summarized in Table 1. There were 30 patients (17 males, 13 females; mean age 67.1 ± 15.5 years) who underwent elastography with EBUS-TBNA of 75 hilar and mediastinal LNs. A total of 75 hilar and mediastinal LNs were identified for sampling based on the presence of the following features on EBUS: size >1 cm in 50/75 (66.7%), round shape in 16/75 (21.3%), distinct margin in 45/75 (60.0%), round shape in 16/75 (21.3%), distinct margin in 45/75 (60.0%),

<table>
<thead>
<tr>
<th>Elastography Type</th>
<th>Short axis &gt; 1 cm</th>
<th>Round shape</th>
<th>Distinct margin</th>
<th>Heterogeneous echogenicity</th>
<th>Blood flow with varying vessel diameters and tortuosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 (n = 24)</td>
<td>10/24 (41.7)</td>
<td>6/24 (25.0)</td>
<td>16/24 (66.7)</td>
<td>14/24 (58.3)</td>
<td>7/24 (29.2)</td>
</tr>
<tr>
<td>Type 2 (n = 14)</td>
<td>11/14 (78.6)</td>
<td>1/14 (7.1)</td>
<td>9/14 (64.3)</td>
<td>9/14 (64.3)</td>
<td>9/14 (64.3)</td>
</tr>
<tr>
<td>Type 3 (n = 37)</td>
<td>29/37 (78.4)</td>
<td>10/37 (27.2)</td>
<td>20/37 (54.1)</td>
<td>34/37 (91.9)</td>
<td>18/37 (48.6)</td>
</tr>
</tbody>
</table>

Data are presented as the number of LNs/total number of LNs and percentage (%).
heterogenous echogenicity in 57/75 (76.0%) and abundant blood flow with varying vessel diameters and tortuosity in 34/75 (45.4%). Histological examination of the EBUS-TBNA specimens revealed 42 malignant LNs and 33 benign LNs. Among the benign LNs, diagnoses were normal lymphatic tissue ($n = 26$), sarcoidosis ($n = 5$) and anthracosis ($n = 2$).

The accuracy of conventional EBUS features in predicting malignant nodal metastasis were 70.0% (35/50) for size, 50.0% (8/16) for shape, 53.3% (24/45) for margin, 66.0% (37/57) for echogenicity and 67.6% (23/34) for vascular pattern.

**TABLE 2** shows the distribution of LNs according to EBUS elastography type. All Type 1 LNs (Fig. 1A) were diagnosed as benign; Type 2 LNs (Fig. 1B) were benign in 42.9% and malignant 57.1%; majority of Type 3 LNs (Fig. 1C) were malignant (94.6%). In the classifying Type 1 as ‘benign’ and Type 3 as ‘malignant’ the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy rates were 100, 92.3, 94.6, 100 and 96.7%, respectively.

The median values of FDG-PET SUVmax were 2.49 for elastography Type 1, 4.95 for Type 2 and 8.50 for Type 3. The computed Spearman rank coefficient ($r$) was 0.54 ($P < 0.0001$).

**Table 3** shows the correlation between EBUS elastography types, B-mode features and vascular patterns of lymph nodes. Representative cases of each EBUS elastography type are shown in Figs 2–4.

**DISCUSSION**

EBUS-TBNA is an established minimally invasive procedure for proper staging and diagnosis of lung cancer. Conventionally, B-mode and power Doppler features have been employed to predict the probability of a malignant process during EBUS scanning. Elastography, on the other hand, is a new non-invasive EBUS modality that is
hypothesized to predict mediastinal and hilar nodal metastasis based on hardness of tissue.

To our knowledge, only one preliminary feasibility letter on elastography histogram during EBUS has been published (17). Our data confirmed that real-time elastography during EBUS can be technically applicable for mediastinal and hilar LNs, and can produce plausible results. We deduce that the internal compression brought about by pulsations of the aorta and the heart induces deformations of mediastinal and hilar LNs thus, allowing quantification and discrimination of their stiffness.

This present study highlighted the efficiency and utility of elastography during EBUS-TBNA. Based on our results, we propose a simple EBUS elastography classification that could predict with 96.7% accuracy the presence or absence of mediastinal and hilar nodal metastasis. Type 1 (predominantly non-blue) indicates a benign pathology; Type 2 (part blue, part non-blue) is equivocal; and Type 3 (predominantly blue) indicates malignancy. For Type 1 elastography LNs, the high negative predictive value could minimize unnecessary punctures or prevent repeated biopsies when ROSE shows adequate TBNA specimen and benign lymphocytes. For Type 3 elastography LNs, the high positive predictive value could help in promptly deciding a target area to sample during EBUS-TBNA.

Nevertheless, we underscore the need for collecting tissue for definitive diagnosis, despite the high diagnostic efficacy of elastography. Studies that compare EUS morphology to EUS-FNA have shown that EUS-FNA is superior to imaging by EUS alone (18–21). Similarly, TBNA should always be performed on LNs that are suspicious for metastasis on EBUS. In one study, it was recommended that when at least one suspicious malignant feature is observed during the EBUS, subsequent needle aspiration must be performed (6).

In our methods, the diagnostic assignment to benign or malignant conditions is based on the results of EBUS-TBNA as gold standard. This design guarantees that the area that was examined histologically corresponds to the same area that was examined by elastography. In the detection of nodal metastasis by EBUS-TBNA, a few false positive and false negative results may have been reported (22), but even so, a diagnostic accuracy exceeding 90% for mediastinal and hilar LNs cannot be disregarded (23). Therefore, the design chosen seems to be adequate for the present investigation.
This study is limited by its retrospective, single-institution nature. Prospective, randomized, multi-center trials are needed in the future to confirm the utility of elastography images during EBUS-TBNA.

CONCLUSIONS

EBUS elastography is a useful tool with very high sensitivity, specificity and accuracy for differential diagnosis of mediastinal and hilar LNs. Aside from providing complementary information to conventional EBUS imaging, it may potentially increase the diagnostic yield of EBUS-TBNA and reduce the number of unnecessary biopsies.

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Conflict of interest statement

None declared.

References