Endobronchial Ultrasonography for Mediastinal and Hilar Lymph Node Metastases of Lung Cancer*

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Study objectives: Conventional radiologic procedures are frequently unreliable in the diagnosis of mediastinal and hilar lymph node metastases of lung cancer. In order to improve diagnostic accuracy, we performed endobronchial ultrasonography (EBUS) during bronchofiberscopic examinations of patients with lung cancer.

Methods and patients: To evaluate mediastinal and hilar lymph node metastases, EBUS was performed prospectively using a radial scanning probe of 20 MHz through a bronchofiberscope.

Results: We observed hilar lymph nodes (10R, 11R superior, 11R inferior, 12R, 10L, 11L, 12L) in 20 of 37 patients who underwent EBUS, and we could clearly identify whether direct invasion of the pulmonary artery by a lymph node had occurred. Of the 27 patients who showed no hilar lymph nodes on chest CT scan, lymph node swellings < 10 mm or ≥ 10 mm in diameter were identified by EBUS in 9 patients and 2 patients, respectively. Interestingly, EBUS also revealed that the pulmonary artery was directly invaded by an interlobar lymph node < 10 mm in diameter in one patient. In most patients, lymph node 7 was easily identified and was clearly differentiated from the surrounding esophagus, vessels, and mediastinal fat tissue by EBUS. However, fused lymph nodes or lymph nodes with low central density when visualized by chest CT scan were occasionally observed as independent lymph nodes by EBUS. When compared with the pathologic diagnosis of lymph node metastasis in 16 patients who underwent surgery, the most specific and sensitive method for identifying lymph node metastases were EBUS alone (92%) and EBUS in combination with CT scan (100%), respectively. The overall accuracy of EBUS was 94% for the diagnosis of direct invasion of the pulmonary arteries by a hilar lymph node.

Conclusions: EBUS in combination with conventional radiologic tools may contribute to improved staging, especially in surgical cases with hilar lymph node metastases.

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Key words: endobronchial ultrasonography; lung cancer; lymph node metastasis

Abbreviation: EBUS = endobronchial ultrasonography

Conventional radiologic tools such as chest CT scan and chest tomography are frequently unreliable in the diagnosis of mediastinal and hilar lymph node metastases of lung cancer. The diagnosis of mediastinal lymph node metastasis by CT scan is based solely on size criteria, and diagnostic accuracy is approximately 60%.1 Because the hilar lymph nodes are adjacent to the pulmonary artery or vein, and movement and partial volume effects of these vessels occur, it is occasionally difficult to differentiate hilar lymph nodes from vascular structures with conventional radiologic tools. Therefore, the diagnosis of lymph node metastasis by CT scan and chest tomography is usually less reliable in the hilum than in the mediastinum.

The technique of endobronchial ultrasonography (EBUS) with a balloon has improved significantly in the last 5 years. However, it has been used mainly to determine the depth of tracheobronchial invasion,2,3

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and very few studies using EBUS in the evaluation of mediastinal and hilar lymph node metastases have been reported. EBUS may be superior to conventional radiologic tools in differentiating hilar lymph nodes from vascular structures. Clinically, it is very important to know whether hilar lymph node metastases are present, or whether direct invasion of the pulmonary arteries by the hilar lymph nodes has occurred prior to surgery. In order to improve the accuracy of diagnosis of lymph node metastases, EBUS was performed prospectively during bronchofiberscopic examinations of lung cancer patients.

**MATERIALS AND METHODS**

Although no definitive eligibility criteria were set for the EBUS study, suspicious surgical cases with primary lung cancer were preferentially entered into the study, because pathologic confirmation could be obtained. The patient accrual rate was 1 or 2 patients per month, which resulted in the EBUS assessment of 37 patients with lung cancer from July 1996 to April 2000. In all cases, conventional nonhelical contrast-enhanced CT scanning of the chest was performed, and lung cancer was histologically or cytologically confirmed by bronchofiberscopy. Chest CT scanning was performed (model TCT900S; Toshiba; Tokyo, Japan). Contiguous 10-mm-thick sections were acquired from the lung apices to the diaphragm in all cases. Findings were reviewed by at least two doctors (both authors of this article). Lymph node mapping was based on the classification by Naruke and colleagues.

Other staging procedures included chest radiography, CT scanning of the brain, CT or ultrasonography of the abdomen, and isotope bone scanning. All patients gave their written informed consent to the combined endoscopic-sonographic examination. Standard bronchofiberscopes (Models BF 1T10 and BF 1T20; Olympus; Tokyo, Japan) were used in this study. The working channel of the bronchofiberscopes must be ≥ 2.8 mm in diameter to accommodate the EBUS probe. EBUS was performed using the Olympus UM3R or XUM-B20R-26 radial scanning probe (Olympus) of 20 MHz through a bronchofiberscope to evaluate mediastinal and hilar lymph node metastases. The distal end of the EBUS probe was connected to an ultrasound unit (EU-M 30 Endoscopic Ultrasound Center; Olympus), and the ultrasonograms were recorded with a printer (Sony Color Video Printer; Mavigraph; Tokyo, Japan). The motor of the EBUS unit continuously rotated the transducer 360° to produce a real-time, cross-sectional image.

After insertion of the probe through a working channel of the bronchofiberscope, the balloon was inflated with sterile water to allow the entire circumference to be visualized undisturbed by air. The maximum diameter of the inflated balloon was approximately 20 mm. Using this method, the normal-sized main, truncus intermedius, and lobar bronchi were fully obstructed by the inflated balloon, and a 360° cross-sectional image could be clearly obtained. However, the trachea was not fully obstructed; thus, the ultrasonogram was obtained only for the mucosal surface at the points of contact between the balloon and tracheal lumen. EBUS was performed after routine observation with the bronchofiberscope but before biopsy. Mediastinal and ipsilateral hilar lymph nodes of patients with primary lung cancer were routinely observed. If a primary tumor existed on the right lung, EBUS was performed for the mediastinal and right hilar lymph nodes. Therefore, site selection was based on CT findings before EBUS. Lymph node size ≥ 10 mm in short-axis diameter was defined as a significant swelling on both EBUS and chest CT scan. Blood vessels were recognized as echo-free or relatively hypoechoic structures. Arteries were identified from their vigorous pulsations with real-time ultrasonography. However, veins were free of pulsations (unless pulsations were transmitted from adjacent vascular or cardiac structures). Lymph nodes were characterized as well-marginated hypoechoic structures with discrete borders. They were sometimes round, but usually ovoid or elliptical in shape. A hyperechogenic center was sometimes present, probably because of the reflective fatty hilum of the node.

Diagnostic ability was expressed as follows: detection rate = number of patients in whom a lymph node was detected/number of patients in whom a lymph node was examined; positive rate = number of patients with lymph node swelling ≥ 10 mm in diameter/number of patients in whom a lymph node was examined. Direct invasion of the pulmonary arteries by a hilar lymph node was defined as observation of either an extensive contact or an irregular margin between the lymph node and pulmonary artery. Sensitivity, specificity, and overall accuracy of the diagnosis of lymph node metastasis by chest CT scan, EBUS, or both in surgical cases were compared using χ² tests.

**RESULTS**

**Patient Characteristics**

EBUS was performed on 37 patients with lung cancer between July 1996 and April 2000. In all

Table 1—Patient Characteristics*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>37</td>
</tr>
<tr>
<td>Surgical patients</td>
<td>16</td>
</tr>
<tr>
<td>Male/female gender</td>
<td>32/5</td>
</tr>
<tr>
<td>Median age (range), yr</td>
<td>68 (35-79)</td>
</tr>
<tr>
<td>Histology, Ad/Sq/Sm/other</td>
<td>23/10/3/1</td>
</tr>
<tr>
<td>Primary site, right/left</td>
<td>24/13</td>
</tr>
<tr>
<td>TNM</td>
<td></td>
</tr>
<tr>
<td>c-T 1/2/3/4</td>
<td>11/18/4/4</td>
</tr>
<tr>
<td>c-N 0/1/2/3</td>
<td>17/7/9/4</td>
</tr>
<tr>
<td>c-stage I/I/III/IV</td>
<td>12/5/7/13</td>
</tr>
<tr>
<td>p-N status in surgical patients</td>
<td></td>
</tr>
<tr>
<td>p-N 0/1/2/3</td>
<td>8/3/5</td>
</tr>
</tbody>
</table>

*Ad = adenocarcinoma; Sq = squamous cell carcinoma; Sm = small cell carcinoma; c = clinical; p = pathologic.

Table 2—EBUS vs Chest CT Scan in the Evaluation of Hilar Lymph Node Swellings (n = 37)*

<table>
<thead>
<tr>
<th>Findings</th>
<th>ND</th>
<th>&lt; 10 mm</th>
<th>≥ 10 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>ND</td>
<td>16 (43)</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>&lt; 10 mm</td>
<td>9 (24)</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>≥ 10 mm</td>
<td>2 (5)</td>
<td>0</td>
<td>8 (22)</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%). ND = not detected. Detection rate of EBUS, 54%; detection rate of CT, 27%. Positive rate of EBUS, 27%; positive rate of CT, 27%.
cases, EBUS added approximately 10 min to the duration of the bronchoscopic procedures. EBUS carried no particular risk and caused little discomfort. Patient characteristics are listed in Table 1. The patients included 5 women and 32 men, with a median age of 68 years (range, 35 to 79 years). Twenty-three patients (62%) had adenocarcinoma, and 16 patients (43%) underwent curative operations. Twenty patients had clinical stage III or IV lung cancer, and 17 patients had stage I or II lung cancer. Although bulky but not pathologically confirmed N2 disease and pathologically confirmed N2 disease were usually considered inoperable in our hospital, 5 of 16 surgical patients had N2 disease in the postoperative pathologic stage.

**Evaluation of Hilar Lymph Nodes**

The evaluations of hilar lymph node swellings by EBUS and chest CT are listed in Table 2. In 20 of 37 patients, hilar lymph nodes (10R, 11R superior, 11R inferior, 12R, 10L, 11L, and 12L) were observed. Of the 27 patients in whom no hilar lymph nodes were visible on chest CT scan, lymph node swellings < 10 mm or ≥ 10 mm in diameter were identified by EBUS in 9 patients and 2 patients, respectively. Although the positive rates were identical, the detection rate of EBUS was twice that of the CT scan. Using our conventional CT scanning technique, it is very difficult differentiate hilar lymph nodes from surrounding vascular structures unless lymph node size is > 10 mm in short-axis diameter. Therefore, no hilar lymph node metastasis was described as being < 1 cm in diameter on chest CT scans (Table 2).

Estimation of direct invasion of pulmonary arteries by hilar lymph nodes based on EBUS findings is listed in Table 3. In the 20 patients in whom hilar lymph nodes were observed, all were clearly identified regardless of whether there was direct invasion of pulmonary artery by the lymph node. Interestingly, EBUS also revealed direct invasion of the pulmonary artery by an interlobar lymph node < 10 mm in diameter in one patient (Fig 1).

<table>
<thead>
<tr>
<th>Lymph Node Size</th>
<th>n</th>
<th>With Invasion</th>
<th>Without Invasion</th>
<th>ND</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 mm</td>
<td>12</td>
<td>1</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>≥ 10 mm</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

*See Table 2 for expansion of abbreviation.

**Figure 1.** Lymph node 11 superior (11s) was located between the pulmonary artery (PA) and truncus intermedius. Although the lymph node was < 10 mm in diameter, extensive contact between the lymph node and the pulmonary artery indicated direct invasion of the pulmonary artery.
Figure 2. Lymph node 11 superior (11s) swelling $> 10$ mm in diameter was clearly observed by EBUS and did not invade the pulmonary artery (PA) [top]. However, it was unclear on the chest CT scan [bottom].
Figure 2, top, shows that lymph node 11 superior swelling 10 mm in diameter was clearly observed by EBUS and was not invading the pulmonary artery. However, the presence of lymph node 11 superior was unclear on the chest CT scan (bottom). Figure 3, top, shows that for the lymph node 11 superior, swelling < 10 mm in diameter was observed by EBUS, and there was no direct invasion of the pulmonary artery (PA) [top]. However, it was unclear on the chest CT scan (bottom).
Evaluation of Mediastinal Lymph Nodes

As shown in Table 4, the detection rates for lymph node 7 by EBUS and chest CT scan were 86% and 49%, respectively. However, the positive rates by EBUS and chest CT scan were 19% and 19%, respectively. Although the positive rates were identical, the detection rate of EBUS was twice that of the CT scan. In other words, the diagnostic ability of EBUS was superior to that of the CT scan in identifying lymph nodes <10 mm in diameter. In most patients, lymph node 7 was easily identified and was clearly differentiated from the surrounding esophagus, vessels, and mediastinal fat tissue by EBUS. However, fused lymph nodes or lymph nodes with low central density when visualized by CT scan were occasionally observed as independent lymph nodes by EBUS. However, when compared with the chest CT scan, there was no advantage in the evaluation of swelling in lymph nodes 2 to 4 by EBUS (Table 5). Both the detection and positive rates by these two methods were almost identical. The detection of lymph nodes 2 to 4 by UBUS was occasionally difficult because of the presence of thick cartilage in the trachea.

Pathologic Confirmation in Surgical Cases

The detection accuracy of lymph node metastases by chest CT scan and EBUS in surgical cases is listed in Table 6. When compared with the pathologic diagnosis of lymph node metastasis in 16 patients who underwent surgery, the most specific and sensitive methods for identifying lymph node metastases was EBUS alone (92%) and EBUS in combination
with CT scan (100%), respectively, although these differences were not statistically significant.

Of the five patients with N2 disease in the postoperative pathologic stage, three patients had a microscopic metastasis, one patient had lymph node 9 metastasis, and one had lymph node 7 metastasis that could also be identified by EBUS. The overall accuracy of EBUS was 94% (15 of 16 procedures) for

Figure 5. Lymph node 11 inferior (11i) demonstrated an irregular margin at the pulmonary artery (PA), indicating direct invasion of the pulmonary artery (top). However, the presence of lymph node 11 inferior (11i) was unclear on the chest CT scan (bottom).
the diagnosis of direct invasion of the pulmonary arteries by the hilar lymph nodes (Table 7).

**Discussion**

The diagnosis of lymph node metastases by both CT and EBUS is based solely on size criteria. However, because a chest CT scan may be inferior to EBUS in differentiating hilar lymph nodes from vascular structures, chest CT scan is frequently unreliable in the diagnosis of hilar lymph node metastases of lung cancer. In fact, as shown in Table 2, although the positive rates for the evaluation of hilar lymph node swellings were identical, the detection rate of EBUS was twice that of the CT scan. In other words, the diagnostic ability of EBUS was superior to that of CT scanning in identifying hilar lymph nodes <10 mm in diameter. Clinically, it is very important to know whether hilar lymph node metastases are present, or whether direct invasion of pulmonary arteries by the hilar lymph nodes has occurred before surgery, because these factors influence the choice of surgical approach. As shown in Table 3, of the 20 patients in whom hilar lymph nodes were observed, all were clearly identified regardless of whether or not there was direct invasion of the pulmonary arteries by the lymph nodes. Furthermore, although there were relatively many true-negative patients, the overall accuracy of EBUS based on our criteria was 94% for the diagnosis of direct invasion of the pulmonary arteries by the hilar lymph nodes in 16 surgical patients (Table 7). These favorable results may have been due to the excellent visual power of EBUS, which can differentiate lymph nodes from vascular structures in the hilum. In contrast, additional benefits in evaluating mediastinal lymph nodes by EBUS seem to be relatively low when compared with the chest CT scan. As shown in Table 5, both the detection and positive rates by these methods were almost identical. One possible reason may be that the detection of lymph nodes 2 to 4 by EBUS was sometimes difficult because of the presence of thick cartilage in the trachea, so it was often necessary to position the probe in the space between the rings. Another reason may be that 360° cross-sectional images could not be obtained in the trachea using our local anesthesia. However, in most patients, lymph node 7 was easily identified and was clearly differentiated from the surrounding esophagus, vessel, and mediastinal fat tissue by EBUS. This fact represents a large advantage of the EBUS technique because it is frequently difficult to differentiate lymph node 7 from these structures by chest CT scan.

Kondo and coworkers reported that lymph nodes containing metastases could be differentiated from metastasis-free nodes by their clear contours, thickened images, and low echoing images of fusion or lobulation using transesophageal endoscopic ultrasound examination. This procedure had an excellent specificity of 98% in 101 surgical patients; however,
its sensitivity was 54%. Becker reported that lymph nodes could be discriminated to a diameter of 3 mm. However, no reliable sign for malignant infiltration could be established in 84 resected lymph nodes using the same EBUS technique as in our study. Although the diagnosis of lymph node metastases by both CT and EBUS was based solely on size criteria in our study, the best specificity and sensitivity in identifying lymph node metastases were obtained by EBUS alone (92%) and EBUS in combination with CT scan (100%), respectively (Table 6). In other words, a more accurate diagnosis could be achieved by using EBUS and chest CT scan together.

However, since only 16 of the 37 patients studied underwent surgery, only in these patients were the findings of EBUS and their interpretation evaluated against a standard. In all other cases, our new method was validated only using our own defined diagnostic criteria. Unfortunately, lymph nodes that were found to be enlarged on EBUS were not histologically evaluated in patients who did not undergo operation. Furthermore, the EBUS finding of arterial invasion based on extensive contact or irregular margins between the lymph node and the pulmonary artery could be validated in only one patient (Table 7). Although the presence of vascular invasion was not a factor in the decision to perform surgery, there were no false-positive results in 16 surgical cases by chance. Although the overall accuracy of EBUS was 94% for the diagnosis of arterial invasion, only 2 of 16 surgical cases had positive pathologic findings of arterial invasion. Therefore, the most critical shortcoming of this study was that diagnostic accuracy based on our criteria may be somewhat unreliable because of patient bias.

Although our method was useful in evaluating hilar lymph node metastases, another recently developed technique of transesophageal endoscopic ultrasound and transesophageal endoscopic ultrasound-guided fine-needle aspiration is also playing an important role in evaluating mediastinal lymph nodes adjacent to the esophagus for the diagnosis and staging of lung cancer. However, this method requires a gastroscope equipped with an ultrasonic transducer and cannot evaluate hilar lymph nodes apart from the esophagus. If an ultrasound transducer integrated into a bronchoscope with a separate working channel is developed, aspiration cytology of the lymph node through the bronchial wall would be possible by allowing direct visualization of needle placement and confirming placement of the needle within the region of interest.

Finally, fused lymph nodes or lymph nodes with low central density when visualized by CT scan occasionally appeared as independent lymph nodes by EBUS. In order to establish EBUS criteria for the diagnosis of lymph node metastases, further study analyzing a large number of surgical patients by EBUS is warranted. In conclusion, EBUS in combination with conventional radiologic tools may contribute to improved diagnosis and staging, especially in surgical cases with hilar lymph node metastases.

**References**