Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration for Differentiating N0 Versus N1 Lung Cancer

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Background. The aim of this study was to assess the value of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for differentiating cN0 versus cN1 non-small cell lung cancer.

Methods. A retrospective review of EBUS-TBNA results in patients with potentially resectable clinical N0 or N1 non-small cell lung cancer based on computed tomography and positron emission tomography was performed. Systematic mediastinal and hilar lymph node sampling was performed by EBUS-TBNA. Lymph nodes larger than 5 mm in short axis or suspicious nodes were targeted. In the absence of N2 or N3 disease, patients underwent resection with lymph node dissection.

Results. A total of 981 patients underwent EBUS-TBNA during the study period, of which 163 patients met the study criteria. There were 94 cN0 and 69 cN1 patients. A total of 453 lymph nodes (338 mediastinal and 115 N1 lymph nodes, average 2.8 nodes/patient) were sampled. Endobronchial ultrasound upstaged 9 (5.5%) patients to N2 disease, but was falsely negative in the mediastinum in 7 (4.3%) patients. In cN0 patients, EBUS confirmed N0 in 87 (53.4%) and upstaged in 7 (4.3%, N1 in 1, N2 in 6). In cN1 patients, EBUS confirmed N1 in 19 (11.7%), downstaged in 47 (28.8%), and upstaged in 3 (1.8%). The sensitivity, specificity, diagnostic accuracy, and negative predictive value of EBUS-TBNA to accurately differentiate between N0 and N1 disease was 76.2%, 100%, 96.6%, and 96.2%, respectively. The accuracy of mediastinal staging was 95.7%.

Conclusions. Endobronchial ultrasound-guided transbronchial needle aspiration can accurately access the hilar and interlobar lymph nodes in patients with potentially resectable lung cancer. Accurate assessment of cN0 versus cN1 by EBUS-TBNA may be used to guide induction therapy before surgery.

During the staging process of non-small cell lung cancer (NSCLC), accurate mediastinal lymph node staging is a critical factor that affects patient outcome. Cervical mediastinoscopy has been considered the gold standard for invasive mediastinal staging in NSCLC [1]. Recently, there is increasing interest in minimally invasive endoscopic mediastinal staging techniques [2]. In particular, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has been shown to achieve similar results to mediastinoscopy for mediastinal staging in NSCLC [3–5]. Most recently, a head-to-head comparison of EBUS-TBNA and mediastinoscopy in patients with potentially resectable NSCLC showed that there were no differences in the diagnostic yield between the two modalities in a well-controlled setting [6].

One of the advantages of EBUS-TBNA includes the ability to access N1 lymph nodes [7]. This may become a big advantage in preoperative staging of NSCLC, as patients with N1 disease are an intermediate group of patients who have a variable prognosis [8]. Clinical N1 disease based on noninvasive staging alone may lead to both upstaging and downstaging [9]. Invasive staging of the hilar and interlobar lymph nodes has been performed through open thoracotomies and video-assisted thoracoscopic surgeries. Compared with surgical staging, EBUS-TBNA is a minimally invasive approach to N1 nodes that may be performed safely preoperatively to clarify the pathologic stage before surgery. There have been limited data on the role of EBUS-TBNA for differentiating N1 disease from N0 disease.

The aim of this study was to assess the diagnostic and staging value of EBUS-TBNA for differentiating N0 disease from N1 disease in patients with NSCLC.
Patients and Methods

The EBUS-TBNA database of the Department of Thoracic Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan, from April 2003 to June 2008 was reviewed, and the results of EBUS-TBNA in patients with potentially resectable clinical N0 or N1 NSCLC based on noninvasive staging modalities (computed tomography [CT] scan, positron emission tomography [PET] scan) were analyzed. The primary tumor and lymph node status was classified according to the international TNM staging system reported by Mountain and Dressler[10]. Patients who did not undergo surgical resection with lymph node dissection after confirming N0 or N1 disease on EBUS-TBNA were excluded from the study. Institutional review board approval was granted for this retrospective review (Graduate School of Medicine, Chiba University, No. 220).

Imaging Tests

Chest CT was performed with single-injection contrast and multidetector-row CT (Light Speed; GE Medical System, Milwaukee, WI). The slice thickness was 5 mm with a pitch of 1.6, and images were reconstructed at 5-mm intervals. Lymph nodes with the short axis larger than 1 cm were considered positive for malignancy.

Whole-body fluorodeoxyglucose-PET (GE PET Advance NXi; GE Medical System) was performed, followed by overnight fasting. The glucose levels of patients were within normal limits before examination. Sixty to 90 minutes after injection of 300 MBq of 18F-fluorodeoxyglucose, whole-body acquisition was performed. Images were reconstructed using the attenuation-weighted ordered-subset expectation maximization technique. Images were visually interpreted using a display of three orthogonal sections and maximal intensity projections. Standardized uptake values were calculated as the ratio of the regional radioactivity concentration divided by the injected amount of radioactivity normalized to body weight. Fluorodeoxyglucose-PET was considered positive for an N1, N2, or N3 lymph node if the PET report stated that there was hypermetabolic activity consistent with malignant disease (defined as standardized uptake value > 2.5) [11].

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

Endobronchial ultrasound-guided transbronchial needle aspiration was performed with the convex probe EBUS with a linear scanning transducer with a frequency of 7.5 MHz on the tip (XBF-UC260F-OL8; Olympus, Tokyo, Japan) connected to a dedicated ultrasound scanner (EU-C2000/EU-C60; Olympus) as previously reported [12]. All mediastinal and hilar lymph nodes were first systematically visualized and assessed. Briefly, the size, shape (oval or round), margin (indistinct or distinct), echogenicity (homogeneous or heterogeneous), presence or absence of central hilar structure, and presence or absence of coagulation necrosis sign were assessed for each lymph node visualized [13]. Any lymph nodes larger than 5 mm in short axis or suspicious nodes based on CT, PET scan, and ultrasound morphology were targeted and sampled. N3 lymph nodes were sampled first, followed by N2 and finally N1 nodes. Lymph node stations sampled included stations 2R, 4R, 2L, 4L, 7, 10R, 11R, 12R, 10L, and 11L. If multiple lymph nodes were present within the same lymph node station, the most suspicious lymph node was sampled. All procedures were performed under conscious sedation.

A dedicated 22-gauge TBNA needle (NA-201SX-4022; Olympus) was used for EBUS-TBNA. Specimens were processed by using the internal stylet to push out the histologic cores, which were fixed in formalin for histologic evaluation. The rest of the aspirated material was smeared onto glass slides for cytologic evaluation. Smears were air dried as well as fixed in 95% alcohol. Dried smears were stained by Diff-Quik staining and evaluated by an on-site cytopathologist to confirm adequate cell material. If adequate tissue was not identified by on-site cytology after five attempts, the procedure was terminated. Furthermore, Papanicolaou staining was carried out on permanent staining by a cytopathologist.

Pathologic Staging

After noninvasive and invasive staging, patients underwent thoracotomy or video-assisted thoracoscopic surgery for lung resection with systematic lymph node dissection if the absence of N2 or N3 disease was confirmed. Results of EBUS-TBNA were compared with surgical pathology staging. For N2 and N3 patients who did not undergo surgery, comparison was made according to clinical follow-up for at least 6 months.

Statistical Analysis

Patient demographics and disease characteristics were summarized using descriptive statistics. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated using the standard definitions. A true negative (N0 or N1) was defined as patients with no N2 or N3 lymph node metastases evaluated by EBUS-TBNA and confirmed by surgical-pathologic examination. Otherwise, the final pathology N stage was taken as the highest grade of EBUS-TBNA and surgical N stage.

Results

From April 2003 to June 2008, a total of 981 patients underwent EBUS-TBNA, of which 163 patients (mean age, 68 years; 120 male) met the study criteria and were included in the analysis. The final pathologic diagnosis of the primary tumor consisted of adenocarcinoma in 104, squamous cell carcinoma in 49, large cell neuroendocrine carcinoma in 8, and small cell carcinoma in 2. The clinical N staging based on imaging before EBUS-TBNA was cN0 in 94 patients and cN1 in 69 patients (Table 1). Of the 69 patients considered cN1, 22 patients had both PET-positive and enlarged lymph nodes on CT, 56 patients had PET-negative N1 nodes, and 35 patients had enlarged N1 lymph nodes on CT scan. A total of 453 lymph nodes (338 mediastinal and 115 N1 lymph nodes) were sampled.
using EBUS-TBNA, an average of 2.8 lymph node stations/patient (Table 2).

Table 2 shows the breakdown of patients who were analyzed in our study. Based on the results of the final surgical pathology and clinical follow-up, the final pathologic N stage consisted of 126 pN0, 21 pN1, and 16 pN2 disease. An average of 4.1 ± 0.7 mediastinal lymph nodes (range, 3 to 7) and an average of 3.1 ± 0.9 N1 nodes (range, 2 to 7), accounting for a total of 7.2 ± 1.1 lymph nodes (range, 5 to 12), were assessed on resected specimens by the pathologist. There were no differences between the thoracotomy group (n = 70) and the video-assisted thoracoscopic surgery group (n = 93) in terms of the number of lymph nodes dissected. In patients who were judged to be cN0 based on noninvasive staging, EBUS confirmed N0 in 87 (53.4%) patients and upstaged 1 (0.6%) patient to N1 disease and 6 (3.7%) patients to N2 disease. Subsequent surgical pathology showed that EBUS was falsely negative in 8 (4.9%) patients (pN1 in 5, pN2 in 3). All N1-positive lymph nodes were stations not sampled by EBUS-TBNA. In patients judged to be cN1, EBUS confirmed N1 in 19 (11.7%) patients, downstaged to N0 disease in 47 (28.8%) patients, and upstaged to N2 disease in 3 (1.8%) patients. However, 4 patients actually had N2 disease on final pathology. In total, EBUS upstaged 9 (5.5%) patients to N2 disease, but was falsely negative in the mediastinum in 7 (4.3%) patients who were also CT and PET negative. The sensitivity, specificity, diagnostic accuracy, and negative predictive value of EBUS-TBNA to accurately differentiate between N0 and N1 disease was 76.2%, 100%, 96.6%, and 96.2%, respectively. The diagnostic accuracy of EBUS-TBNA for mediastinal staging in our study population with cN0 or cN1 disease based on noninvasive staging was 95.7%. The EBUS-TBNA procedure was uneventful, and there were no complications.

Comment

In the current study, we were able to demonstrate that EBUS-TBNA can accurately stage the hilar and interlobar lymph nodes to differentiate between N0 and N1 patients in potentially resectable lung cancer patients. Among the 163 patients who underwent EBUS-TBNA for lymph node staging, the majority of the patients (126 patients, 77.3%) had pathologic N0 disease without any evidence of lymph node metastases, and of note, all 163 patients had normal mediastinum based on CT and PET scans. Even in this carefully selected group of patients, the 95.7% diagnostic accuracy of EBUS-TBNA was similar to our previous report on the comparison of EBUS-TBNA and mediastinoscopy for mediastinal staging in potentially resectable lung cancer [6]. Strikingly, EBUS downstaged 47 patients from N1 to N0 disease in this series.

The focus of lymph node staging in NSCLC has been in the mediastinum because patients with metastases to the mediastinal lymph nodes (N2 or N3) are usually treated with chemotherapy or radiation, whereas those without involvement of the mediastinum (N0 or N1) are usually treated with surgical resection. One may ask, why bother sampling the N1 lymph nodes if you are going to do the resection anyway? In the study from the International Association for the Study of Lung Cancer looking at more than 67,000 patients with NSCLC, Rusch and colleagues [8] showed that in a subgroup analysis of patients with N1 disease, single N1 lymph node metastasis had significantly better survival compared with patients with multiple N1 lymph node involvement. Although there is no evidence to prove this, there may be a possibility of applying neoadjuvant treatment for patients with biopsy-proven N1 disease to improve the survival of these patient groups. Because EBUS-TBNA can assess the peribronchial, interlobar, and perihilar lymph nodes in a minimally invasive way, it would be an ideal modality for the assessment of N1 nodes for patients undergoing stereotactic body radiation therapy, as the existence of any lymph node metastasis would exclude them from treatment.

During the past 10 years, lung cancer screening studies using CT in high-risk lung cancer populations have shown that CT is more sensitive than chest radiographs for detecting small lung cancers [14, 15]. A recent
multicenter, randomized, controlled lung cancer screening trial in current and former heavy smokers showed that there were 20% fewer lung cancer deaths seen among those who were screened with low-dose CT than with chest x-ray [16]. As smaller lung cancers will be discovered as part of the lung cancer CT screening programs, the optimal surgical treatment needs to be determined by thoracic surgeons, particularly for lesions less than 20 mm or lesions that have at least 50% ground-glass opacification. Studies have shown that sublobar resection can generally be considered acceptable for less than 20-mm ground-glass opacification lesions or adenocarcinoma with minimal invasion [17]. However, the necessity of hilar and mediastinal lymph node dissection exists because of the fact that nearly 20% of pulmonary adenocarcinoma less than 20 mm and 5% of cases less than 10 mm are reported to have nodal metastases [18]. This raises the importance of evaluation of N1 nodes before consideration of sublobar resection. If the results of two randomized trials comparing lobectomy with sublobar resection for NSCLC of 20 mm or less favor lobectomy in Japan Clinical Oncology Group JCOG 0802 and West Japan Oncology Group WJOG 3406L in Japan; Cancer and Leukemia Group B, CALGB 140503 in North America), a detailed preoperative assessment of N1 nodes will be mandatory. We believe that EBUS-TBNA will be an ideal modality for a complete systematic evaluation of the mediastinum as well as the hilum.

There are several limitations to our current study. First, this study was a retrospective analysis of an experienced center in EBUS-TBNA. Most of the procedures were performed by two well-experienced bronchoscopists (KY and TN). Further studies with more operators and centers will be necessary to establish the usefulness of EBUS-TBNA in routine practice. Second, rapid on-site cytology was available for all cases. Not all centers have rapid on-site cytology available during EBUS-TBNA, and the results of our current study may not be applicable to all settings. Lastly, because of the size of the convex probe EBUS, not all N1 nodes were accessible by EBUS-TBNA. The rigid part on the tip as well as the outer diameter of the convex probe EBUS prevents visualization of lobar lymph nodes in the upper lobes and the middle lobe (station 12). This contributes to the distribution of the N1 nodes sampled in this study. In fact, all 5 patients with false-negative EBUS had metastases in N1 nodes not assessed by EBUS-TBNA.

The development of a smaller convex probe EBUS with the ability to sample lobar and segmental lymph nodes will be the only solution to this issue. In conclusion, EBUS-TBNA can accurately access the hilar and interlobar lymph nodes in addition to the mediastinal lymph nodes in patients with potentially resectable lung cancer. Accurate assessment of N1 nodes by EBUS-TBNA may open up possibilities of new neoadjuvant clinical trials for stage II NSCLC. In addition, preoperative differentiation of N0 disease versus N1 disease will allow surgeons to consider selective mediastinal lymphadenectomy or selective limited resection for NSCLC.

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References

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INVITED COMMENTARY

Traditionally, invasive assessment of N1 nodes during the pretreatment evaluation of lung cancer has received little attention. Biopsy of N1 nodes before resection has not provided strong justification for sampling N1 nodes by EBUS. Thus, at least with the current technology, in compromised cN0 patients considered for localized therapy, EBUS is unlikely to have a major impact in the assessment of N1 nodes (but may still be important for N2 nodes). Highly localized treatment is considered selectively in noncompromised patients primarily for ground glass opacities or very small tumors. EBUS in such patients appears even more unlikely to find N1 involvement.

However, the finding is important that 68% of cN1 patients actually had N0 disease by final pathologic analysis and that this could be confirmed reliably by EBUS. It seems likely that the performance of EBUS demonstrated in this study would apply to these patients. Given the safety of EBUS in general, it seems that even compromised patients with severe chronic obstructive pulmonary disease would probably be able to tolerate EBUS assessment of N1 (and N2) nodes if they are candidates for treatment at all. Such patients may benefit the most: EBUS may allow many of these compromised cN1 patients to be treated, whereas by imaging alone they might be considered not candidates for any treatment. It remains to be seen whether the results demonstrated by this excellent team can be duplicated more broadly.

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Reference