Endobronchial Ultrasound With Transbronchial Needle Aspiration for Restaging the Mediastinum in Lung Cancer

Felix J.F. Herth, Jouke T. Annema, Ralf Eberhardt, Kazuhiro Yasufuku, Armin Ernst, Mark Krasnik, and Robert C. Rintoul

ABSTRACT

Purpose
To investigate the sensitivity and accuracy of endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA) for restaging the mediastinum after induction chemotherapy in patients with non–small-cell lung cancer (NSCLC).

Patients and Methods
One hundred twenty-four consecutive patients with tissue-proven stage IIIA-N2 disease who were treated with induction chemotherapy and who had undergone mediastinal restaging by EBUS-TBNA were reviewed. On the basis of computed tomography, 58 patients were classified as having stable disease and 66 were judged to have had a partial response. All patients subsequently underwent thoracotomy with attempted curative resection and a lymph node dissection regardless of EBUS-TBNA findings.

Results
Persistent nodal metastases were detected by using EBUS-TBNA in 89 patients (72%). Of the 35 patients in whom no metastases were assessed by EBUS-TBNA, 28 were found to have residual stage IIIA-N2 disease at thoracotomy. The majority (91%) of these false negative results were due to nodal sampling error rather than detection error. Overall sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of EBUS-TBNA for mediastinal restaging after induction chemotherapy were 76%, 100%, 100%, 20%, and 77%, respectively.

Conclusion
EBUS-TBNA is a sensitive, specific, accurate, and minimally invasive test for mediastinal restaging of patients with NSCLC. However, because of the low negative predictive value, tumor-negative findings should be confirmed by surgical staging before thoracotomy.

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INTRODUCTION

At present, the optimal treatment for stage IIIA-N2 non–small–cell lung cancer (NSCLC) is being evaluated. There may be a role for surgical resection in patients who have been successfully downstaged with induction chemotherapy or chemoradiotherapy.1-3 Accurate restaging of the mediastinum in these patients will be of increasing importance in order to identify those patients who have been successfully downstaged and who may benefit from subsequent surgical resection. The most effective approach to restaging is controversial and is currently the subject of much debate.4 Until now, surgical approaches, such as cervical mediastinoscopy and anterior mediastinotomy, have been used for restaging.5-7 However, mediastinoscopy is recognized as technically more difficult to perform because of adhesions and fibrotic change induced by the initial procedure and the induction treatment.8,9 As a result, the reported sensitivity and accuracy of repeat procedures is lower10,11 than that of the initial procedure.11 Data from studies that examined the role of imaging techniques, such as computed tomography (CT) and positron emission tomography (PET), for restaging have produced conflicting results.12-16 The low sensitivity and specificity of imaging techniques for mediastinal restaging necessitates tissue sampling for the accurate determination of mediastinal lymph node status.

Recently, there has been increasing interest in the role of endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA) and transesophageal ultrasound–guided fine needle aspiration (EUS-FNA) for the sampling of mediastinal lymph nodes by using minimally invasive approaches. In the initial staging of lung cancer, EBUS-TBNA has been shown to have an accuracy of greater than 90%,17,18 To date, the accuracy of
EBUS-TBNA for mediastinal restaging has not been reported.

Therefore, the aim of this study was to assess the sensitivity and accuracy of EBUS-TBNA for restaging mediastinal lymph nodes after induction chemotherapy for NSCLC.

PATIENTS AND METHODS

Study Cohort

Between February 2003 and March 2006, all consecutive patients with stage IIIA-N2 NSCLC who had undergone EBUS for mediastinal restaging after neoadjuvant chemotherapy and who met the inclusion criteria below were reviewed, and their data was extracted. At initial staging, all patients had pathologically proven single- or dual-station ipsilateral or subcarinal lymph node metastases (stage IIIA-N2) and subsequently received two or three cycles of a platinum-based chemotherapy regimen. The exact chemotherapy regimen administered varied between centers, but all were platinum-based. After completion of chemotherapy, all patients were re-evaluated with a contrast-enhanced CT scan of the chest and abdomen within 2 to 3 weeks after the last cycle. Those patients who had either radiologically stable disease or a response as defined by Response Evaluation Criteria in Solid Tumors Group criteria19 underwent EBUS-TBNA within 1 to 2 weeks of the CT. PET was not utilized in this study, as it was not part of the standard clinical protocols in place at the study centers at that time. After EBUS, all patients-regardless of outcome—underwent thoracotomy with resection and systematic lymph node dissection with curative intent. In the majority of patients, the interval between EBUS and surgery was 1 to 2 weeks. Data collection and analysis were performed retrospectively.

The ethical committees of each institution approved this study, and written informed consent was obtained from all patients in the study.

EBUS-TBNA

EBUS was performed by using a linear array ultrasonic bronchoscope (BF-UC260F-OL8; Olympus Ltd, Tokyo, Japan). The instrument is similar to a standard bronchoscope and has an outer diameter of 6.9 mm, a 2.0 mm instrument channel, and 30 degrees oblique forward-viewing optics. An electronic convex array ultrasound transducer is mounted at the distal tip and is covered by a water-inflatable balloon sheath. Scanning is performed at a frequency of 7.5 MHz, and image processing is performed by using an Olympus ultrasound processor (EU-C60; Olympus Medical, Tokyo, Japan). All examinations were performed in a standardized fashion under either moderate sedation (n = 71) or general anesthesia (n = 53). The probe was passed through the mouth and vocal cords to the main carina; the balloon, if used, was partially inflated (with 0.3 to 0.5 ml water), and the regional lymph node stations of the mediastinum (stations 2, 3, 4, and 7) were systematically imaged and measured (short axis diameter) during slow withdrawal and rotation of the transducer. All visualized nodes with a size greater than 5 mm were punctured. Fine needle aspiration was performed by passing a dedicated 22-gauge needle (XNA-202C; Olympus Ltd) through the airway wall and into lymph nodes under real-time ultrasound control. Needle punctures were performed by using the jabbing method.20 Once the needle was confirmed to be within the target lesion, the needle was moved back and forth while suction was applied. Before needle puncture, integrated color power Doppler ultrasound was used to exclude intervening vessels. Each node was punctured at least twice until a sufficient sample was obtained, as judged by the operator. On site cytologic evaluation was not available during the procedures.

Thoracotomy

At subsequent posterolateral thoracotomy, systematic hilar and mediastinal lymph node dissection was performed. All mediastinal nodes that could be reached were actively sought and were removed completely. Complete removal of all mediastinal fat was not performed.

In left-sided tumors, lymph node stations 2L, 3, and 4L, and 5 to 9 were dissected; in right-sided tumors, lymph node stations 2R, 3, 4R, and 7 to 9 were dissected. Lymph node downstaging was defined as the absence of viable tumor cells in the resected mediastinal lymph node specimen. Resection was defined as complete (R0) if the resection margins at the primary site were free of tumor microscopically and if the most proximal lymph node in the resected specimen was free of tumor. Resection was defined as incomplete when microscopic (R1) or macroscopic (R2) residual tumor was present at the end of the surgical procedure.

Statistics

The aim of this study was to assess the sensitivity and accuracy of EBUS-TBNA for mediastinal restaging after neoadjuvant chemotherapy. After EBUS-TBNA, all patients underwent thoracotomy with mediastinal lymph node dissection. Surgical pathologic staging was used as the reference standard. Diagnostic sensitivity [TP / (TP + FN)], specificity [TN / (TN + FP)], positive predictive value [TP / (TP + FP)], negative predictive value [TN / (TN + FN)], and accuracy [(TP + TN) / n] for EBUS-TBNA (where TP is true positive, TN is false negative, FP is true negative, and FN is false positive) were calculated with the software package SPSS v11.0 (SPSS Inc, Chicago, IL).

RESULTS

One hundred twenty-four patients (73 female, 51 male) were included in a 3-year period between February 2003 and March 2006 (Table 1). The mean age was 58 years (range, 19 to 82 years). Initial IIIA-N2 disease staging was confirmed by cervical mediastinoscopy (63 patients [51%]), by EUS-FNA (28 patients [22%]), or by EBUS-TBNA (33 patients [27%]). Single-station involvement was detected in 45 patients (36%), and dual-station involvement was in 79 patients (64%). Pathology showed squamous cell carcinoma in 24 patients, adenocarcinoma in 79 patients, mixed squamous and adenocarcinoma in 15 patients, and large-cell undifferentiated in six patients.

EBUS-TBNA

After chemotherapy, 58 patients (47%) were graded as having stable disease, and 66 patients (53%) had a partial response. All 124 patients underwent EBUS for restaging. A total of 203 lymph node stations were sampled (mean, 1.6/patient). Station 2L was sampled in 34 patients, 2R in 28, 4L in 33, 4R in 54, station 3 in 11 patients, and station 7 in 31 patients.

Table 1. Characteristics of Patients in the Non–Small-Cell Lung Cancer Stage IIIA-N2 Study Cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Data Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>Mean 58 Range 19-82</td>
</tr>
<tr>
<td>Sex</td>
<td>Male 51 Female 73</td>
</tr>
<tr>
<td>Tumor location</td>
<td>Right 76 Left 48</td>
</tr>
<tr>
<td>Histology</td>
<td>Squamous 24 Adenocarcinoma 79 Mixed squamous and adenocarcinoma 15 Large cell 6 Prechemotherapy mediastinal nodal involvement Single station 45 Dual station 79</td>
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station 7 in 42 patients. The presence of lymphocytes in the sample was used to confirm that the sample had come from a lymph node. Samples from all except 10 patients contained lymphocytes. Lymph node size ranged from 8 to 25 mm in short-axis dimension and was a mean of 16 mm. Figure 1 shows the breakdown of EBUS-TBNA results as well as the final diagnosis for all patients. Malignant cells were identified in lymph node biopsies from 89 patients (72%), which confirmed the presence of persistent N2 disease. In 35 patients (28%), EBUS-TBNA did not show any evidence of N2 disease (Fig 2).

**Thoracotomy**

At thoracotomy, N2 metastases were present in 117 (94%) of 124 patients. EBUS-TBNA findings of persistent N2 disease were confirmed in all 89 patients. In addition, residual N2 disease was found in 28 of the 35 patients in which EBUS-TBNA had not detected malignancy. Analysis of the individual lymph nodes in the 28 false-negative EBUS-TBNA instances showed that 91% of metastatic lymph nodes had been located correctly by EBUS during the procedure but that failure to detect malignancy was due to sampling error. In the remaining 9%, EBUS had failed to identify malignant lymph nodes (ie, there was a detection error). In the instances that involved sampling error, lymphocytes were present in 86% of the aspirates, which indicated that the lymph node had been successfully biopsied but that no malignant cells were identified.

Consequently, the sensitivity of EBUS-TBNA for the detection of residual mediastinal N2 disease after induction chemotherapy was 76%, the specificity was 100%, and the accuracy was 77%. Negative and positive predictive values were 20% and 100%, respectively.

In a subgroup analysis, there was no significant difference in sensitivity or in accuracy of EBUS-TBNA for the detection of residual mediastinal N2 disease in patients who had a partial response after chemotherapy versus those who had stable disease (Table 2). Similarly, the sensitivity and accuracy of EBUS-TBNA for the detection of malignancy in this scenario were independent of lymph node size when a cutoff of 15 mm for the short axis was applied.

![Fig 1. Endobronchial ultrasound image of a 12-mm short-axis mediastinal lymph node that shows the needle lying within the node.](image)

**DISCUSSION**

Accurate evaluation of mediastinal lymph nodes after induction chemotherapy is essential to accurately restage patients and to determine which patients should be offered surgical resection. We have found that EBUS-TBNA is a highly specific (100%) and sensitive test (76%) for mediastinal restaging after neoadjuvant chemotherapy. To our knowledge, this is the first study in which EBUS-TBNA has been used as a restaging method. Importantly, all EBUS-TBNA outcomes, whether positive or negative, were confirmed by surgical and pathologic staging at thoracotomy. No false-positive EBUS findings were identified; therefore, the specificity of the test was confirmed as 100%.

The sensitivity of EBUS-TBNA in this restaging study is lower than the reported sensitivity and accuracy of EBUS-TBNA for the pretreatment diagnosis and staging of lung cancer.\(^{17,18}\) There are several reasons that may explain this. After chemotherapy, lymph nodes that originally contained tumor often begin to undergo necrosis and fibrosis. Lymph nodes that have become fibrotic may be more difficult to biopsy and may yield less cellular material for histologic analysis. This may explain in part why, in many of the EBUS-TBNA false-negative results, lymph node tissue was aspirated successfully but no malignant cells were seen. Malignant cells may be focal within the node and/or may be located within areas of dense extracellular matrix. Similarly, the presence of necrosis within the aspirated sample often makes pathologic interpretation more difficult. Rapid onsite evaluation was not used in

![Diagram](image)

| Table 2. Outcomes for Restaging EBUS-TBNA According to Tumor Response After Chemotherapy As Assessed by RECIST Criteria |
|---|---|---|
| **Criteria** | **Partial Response (n = 66)** | **Stable Disease (n = 58)** |
| Sensitivity | 77 | 75 |
| Specificity | 100 | 100 |
| PPV | 100 | 100 |
| NPV | 22 | 18 |
| Accuracy | 79 | 76 |

Abbreviations: EBUS-TBNA, endobronchial ultrasound–guided transbronchial needle aspiration; RECIST, Response Evaluation Criteria in Solid Tumors Group; PPV, positive predictive value; NPV, negative predictive value.
this study. However, in this setting, rapid onsite evaluation may further increase sensitivity for the detection of malignancy.

The negative predictive value of EBUS-TBNA in this setting was low. In our opinion, although EBUS-TBNA is an excellent method to demonstrate persistent mediastinal nodal metastatic involvement, surgical staging is required if the EBUS-TBNA findings are negative for malignancy. In other words, EBUS for mediastinal restaging is a good test to confirm, but not to exclude, mediastinal metastases.

Before the advent of minimally invasive techniques for sampling mediastinal lymph nodes, the standard approach had been surgical staging and restaging by means of a cervical mediastinoscopy. Several studies that examined the utility of mediastinoscopy for restaging have been reported. Mateu-Navarro et al reported a sensitivity of 70% in 24 patients, and Van Schil et al reported a sensitivity of 73% in 27 patients. In a larger study, Stamatis et al reported a sensitivity of 74% and an accuracy of 93% in 165 consecutive, repeat mediastinoscopies after chemoradiotherapy. Recently, De Leyn et al conducted a prospective study that compared the performance of PET-CT and mediastinoscopy for the evaluation of mediastinal lymph nodes after induction chemotherapy. Somewhat unexpectedly, the mediastinoscopy data revealed a sensitivity and accuracy of 29% and 60%, respectively. The lower figures in this study were attributed to increased adhesions and to fibrosis after a comprehensive initial mediastinoscopy, which made the repeat procedure technically more difficult and, consequently, less successful. Similar reasons were cited by Pitz et al to explain their low biopsy success rate. Because of these technical difficulties, surgical restaging of the mediastinum is not performed regularly in clinical practice. The accuracy of EBUS-TBNA, a minimally invasive test that can be performed in an outpatient setting, compares well with the best results obtained by surgical restaging.

Until now, the only other endoscopic approaches to restaging the mediastinum have utilized EUS-FNA. Annema et al reported a sensitivity of 75% and an accuracy of 83% in a series of 19 patients. More recently, Varadarajulu et al reported that EUS-FNA had an accuracy of 86% in restaging the mediastinum after induction chemotherapy in a study of 14 patients. These results reflect those presented in the current study. At present, they are the only published studies to use ultrasound localization of mediastinal lymph nodes to guide biopsy. However, it is important to appreciate the different lymph node territories that are routinely accessible by EUS and EBUS. EBUS permits access to the N2 paratracheal and subcarinal lymph node stations (stations 2, 3, 4, and 7) and to the N1 hilar stations (10 and 11). By using EUS, the posteroinferior N2 mediastinal lymph node stations are routinely accessible (stations 4L, 7, 8, and 9). Given the complementary areas of the mediastinum accessible by EBUS and EUS, it is possible that the two approaches in combination might improve sensitivity and diagnostic accuracy compared with EBUS or EUS alone. It has been demonstrated previously that sequential EBUS and EUS can be tolerated well by patients who are under conscious sedation.

Several limitations apply to this study. First, the analysis was performed retrospectively. To minimize potential selection bias, we carefully assessed all consecutive patients who were restaged by EBUS. Second, the prevalence of persistent lymph node metastases was high (94%), which potentially could introduce a bias in favor of an improved outcome for EBUS. In this study, only seven (5%) of 124 patients were downstaged successfully by chemotherapy. This is considerably lower than in previous studies and may reflect the relatively high proportion of patients (64%) who had dual-level lymph node involvement at initial staging. Of the patients who were successfully downstaged, all had single-station lymph node involvement at the time of initial staging. Third, all the EBUS operators in this study were experienced at performing the procedures, and it remains to be seen whether these findings are reproducible by less experienced operators.

In conclusion, we have shown that EBUS-TBNA is an accurate method for the restaging of mediastinal lymph nodes for patients with NSCLC after induction chemotherapy. The sensitivity and accuracy that were reported compare favorably with surgical data from mediastinoscopy and at the same time are achieved with considerably less invasive and resource-dependent methods than surgical approaches. On the basis of the data presented here, additional randomized, controlled studies that compare EBUS and EUS with surgical staging modalities, as well as with PET scanning, for restaging after chemotherapy are justified to clarify not only the role of these techniques in this setting but also their positions within the staging/restaging algorithm.

### Authors’ Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

### Author Contributions

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### References


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