The Efficacy of Restaging Endobronchial Ultrasound in Patients With Non-Small Cell Lung Cancer After Preoperative Therapy

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Background. Patient selection for surgery after neoadjuvant therapy for locally advanced non-small cell lung cancer depends on accurate restaging of mediastinal (N2) lymph nodes. Our objective is to assess the accuracy of endobronchial ultrasound (EBUS) for restaging N2 lymph nodes after neoadjuvant therapy.

Methods. This is a retrospective review of patients with non-small cell lung cancer who underwent staging with repeat computed tomography and positron emission tomography and had restaging EBUS for sampling of N2 lymph nodes. Endobronchial ultrasound was performed for suspicious nodes in stations 2R, 2L, 4R, 4L, and 7. Selected patients who were N2-negative underwent thoracotomy with complete thoracic lymphadenectomy.

Results. There were 32 patients with N2 disease who underwent preoperative chemotherapy or radiotherapy, or both, and subsequently had restaging EBUS. There were 3 patients who had recalcitrant N2 nodal disease detected by EBUS. There were 5 patients with pulmonary function or comorbidities that were prohibitive for surgery. Of the remaining 24 patients with negative EBUS, 3 underwent mediastinoscopy and 2 had recalcitrant N2 disease. The remaining 22 patients underwent thoracotomy. Recalcitrant N2 disease was noted in 1 patient at thoracotomy in the EBUS-assessable nodal stations. Thus EBUS was falsely negative in 3 patients. The sensitivity and negative predictive value of restaging EBUS were 50% and 88%, respectively.

Conclusions. Restaging EBUS is relatively accurate at predicting the absence of metastatic disease in N2 mediastinal lymph node in patients who underwent neoadjuvant therapy for non-small cell lung cancer.


The treatment of non-small cell lung cancer (NSCLC) includes surgery, chemotherapy, radiotherapy, or a combination of these modalities. The optimal therapy is based on biopsy-proven stage [1, 2]. In patients who undergo neoadjuvant chemotherapy or chemoradiation, the decision to proceed to surgical resection is often based on careful restaging of mediastinal (N2) lymph nodes. Surgery alone is usually not curative for most patients with N2 disease, and thus the decision to add surgery must be carefully considered [2–5]. There is general consensus that patients who have progression of disease after neoadjuvant treatment or those with residual (recalcitrant) N2 lymph node disease should not be offered surgical intervention [2, 4]. The goal of this study is to assess the accuracy of endobronchial ultrasound (EBUS) in restaging mediastinal lymph nodes in patients who have undergone preoperative chemotherapy or chemoradiation.

Material and Methods

This is a retrospective cohort study of patients abstracted from a database of all patients undergoing surgery at University of Alabama, Birmingham. Patients presented to 1 thoracic surgeon (R.J.C.) during a 5-year period after chemotherapy or chemoradiation before consideration of surgical resection for biopsy-proven NSCLC. All patients undergoing EBUS for invasive mediastinal staging were evaluated. Inclusion criteria mandated that all patients be 19 years or older, have biopsy-proven NSCLC, and have received chemotherapy or radiotherapy, or both, for curative or neoadjuvant intent. Importantly, not all patients had their pretreatment staging at the University of Alabama. Some were referred for surgical resection after initial staging and treatment with chemotherapy or chemoradiation at other institutions and may not have

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Abbreviations and Acronyms

- CT = computed tomography
- EBUS = endobronchial ultrasound
- maxSUV = maximum standardized uptake value
- NSCLC = non-small cell lung cancer
- PET = positron emission tomography

had biopsy-proven N2 disease. These patients were excluded from this study.

The University of Alabama at Birmingham’s Institutional Review Board approved the electronic prospective database used for this study and this trial (X030403013). Patient consent was obtained for entry into the prospective database. Approval was also obtained for this study (X100427006).

**Initial Staging**

Initial staging was performed as described at length by us previously [6]. All patients including those initially staged at home and those staged at the University of Alabama had computed tomographic (CT) scanning of the chest and upper abdomen with intravenous contrast and 5-mm cuts, and all had an integrated positron emission tomography/computed tomography (PET/CT) scan. The PET scans were performed from the skull base to mid-thigh level. Maximum standardized uptake value (maxSUV) of the primary and of each suspicious lymph node station was determined. Their tumor (T), node (N), and metastasis (M) stage was recorded. Any regions of suspicious extrathoracic metastases were confirmed by obtaining tissue for pathologic confirmation. With regard to the mediastinal assessment, invasive mediastinal staging with mediastinoscopy, EBUS, or endoscopic ultrasound were undertaken for suspicious lymph nodes on CT (greater than 1 cm in the short axis) or PET/CT (maxSUV > 2.5 or ratio of mediastinal lymph node to primary tumor > 0.5) using the appropriate test as we have previously reported for those patients staged at our institution [7]. Invasive mediastinal staging was also undertaken in patients with central tumor, those with clinical N1 disease, tumors greater than 4 cm and bilateral suspicious or biopsy-proven pulmonary nodules. Endobronchial ultrasound was used to assess lymph nodes in stations 2R, 2L, 4R, 4L, and 7. Mediastinoscopy was used selectively to confirm negative EBUS. Endoscopic ultrasound was used for stations 4L, 7, 8, and 9. Pulmonary function testing was performed in all patients, and cardiac clearance was performed in selected patients.

**Restaging and Surgical Therapy**

Patients were then carefully restaged clinically and pathologically after completion of the preoperative treatment as we have previously described using the T, N, and M classification system [8]. All patients underwent repeat PET/CT at approximately 1.5 months after the last radiation treatment. If the maxSUV of a biopsy-proven benign area decreased on the repeat PET, no further biopsies were performed after restaging. However, all biopsy-proven malignant N2 mediastinal lymph nodes were rebiopsied after neoadjuvant therapy irrespective of their size on repeat CT or their maxSUV on repeat PET/CT scan, and any new area of suspicious N2 disease was also biopsied. Patients with new suspected M1 disease in the liver, adrenal gland, or contralateral lung underwent definitive biopsy to prove or disprove M1 cancer. If the brain was suspected to harbor metastases, magnetic resonance imaging was considered the standard reference. If M1 or N3 disease developed after neoadjuvant therapy, surgery was not performed.

All patients underwent invasive mediastinal restaging before resection. The lymph node station that was initially positive was rebiopsied after the completion of the neoadjuvant therapy using repeat EBUS transbronchial needle aspiration or endoscopic ultrasound–guided fine-needle aspiration for paratracheal and paraeosophageal lymph nodes. Video-assisted thoracoscopy was used for stations 5 and 6. Occasionally, a combination of the three modalities may be undertaken as previously described [8]. In cases that were highly suspicious despite negative preoperative biopsies, a lymph node dissection using a robotic approach, or even thoracotomy and frozen section before proceeding to resection, was performed. Mediastinoscopy was chosen if the 2R, 2L, 4R, 4L, or 7L lymph node was suspicious and the patient did not have a previous mediastinoscopy.

**Endobronchial Ultrasound Technique**

Endobronchial ultrasound was performed under conscious sedation. The convex probe EBUS was used to perform EBUS transbronchial needle aspiration (BF-UC160F-OL8; Olympus, Tokyo, Japan). The scope is integrated with a 7.5-MHz transducer that scans parallel to the long axis of the bronchoscope. The ultrasound image is processed in a dedicated ultrasound scanner (EU-C60; Olympus). Selective nodes that were suspicious on preoperative imaging or nodes greater than 5 mm at the time of EBUS or had significant heterogeneous echogenicity were biopsied. A dedicated 22-gauge needle (NA-201SX-4022; Olympus) was used to perform all needle aspiration procedures. For initially positive N2 nodes, a needle biopsy was performed in all patients at that same nodal station. Smears were air dried and fixed. The air-dried smears were stained with a modified Field’s stain and evaluated by an on-site cytopathologist to confirm “adequate” cell material. Adequate cell material was defined as sufficient material for a specific diagnosis or the presence of lymphocytes on the specimen. Four passes were made at the initially positive lymph node. If the pathologic examination was initially positive for metastatic disease and then it became pathologically negative, we defined this as being “downstaged.” If these patients were then found to be medically fit for surgery and a complete resection could be offered without the need for pneumonectomy, patients were offered thoracotomy or, more recently, a robotic approach and pulmonary resection with complete thoracic lymphadenectomy. Complete thoracic lymphadenectomy is defined...
as complete removal (not biopsy) of all visible nodes in the chest; in the right chest, these are lymph node stations 2R, 4R, 7, 8, and 9, and the appropriate N1 nodes. On the left side, this would be complete removal of all lymph nodes in stations 5, 6, 7, 8, and 9, and appropriate N1 nodes.

Operations were performed within 40 days after the repeat staging studies. Pathologic review was performed with standard techniques, and immunohistochemical staining was used in selected cases at the pathologist’s discretion.

**Definitions and Statistical Methods**

A negative result was defined as a lymph node labeled as benign by EBUS either by sonographic criteria or by needle aspiration that identified lymphocytes and absence of tumor cells. For initially positive N2 nodes, a needle biopsy was performed. Absence of lymphocytes indicated a nondiagnostic study. A false-negative result was defined as the presence of disease within a lymph node by mediastinoscopy or at the time of resection that was labeled as benign by EBUS. False-negative results include nondiagnostic samples but did not include lymph nodes outside the scope of EBUS (for example level 5, 6, 8, and 9 lymph nodes). Data were stored using an Excel database (Microsoft Corp, Redmond, WA). The efficacy (accuracy, sensitivity, negative predictive value) of these tests was computed using standard definitions.

**Results**

Between January 2008 and December 2012, 309 patients underwent EBUS for staging of NSCLC. Of those, 32 patients met the inclusion criteria described above of having biopsy-proven NSCLC with biopsy-proven N2 disease and having undergone treatment with neoadjuvant chemotherapy or radiation, or both. The demographic data for these patients are shown in Table 1. All patients underwent CT and PET/CT scanning at initial staging. Biopsy-proven N2 disease was established by mediastinoscopy in 28 patients, thoracotomy in 1 patient, and EBUS in the remaining 3 patients. Preoperative chemotherapy was given in 1 patient, and the remaining 31 patients received preoperative concurrent chemoradiation.

Of the 32 patients who underwent EBUS after chemotherapy or radiotherapy for biopsy-proven NSCLC, 3 were found to have recalcitrant N2 disease, and were deemed nonoperative candidates. Of the remaining 29 patients, 5 patients were denied surgery owing to comorbidities. Of these remaining 24 patients, 3 patients underwent mediastinoscopy; 1 patient was found to be N2 negative and 2 were found to harbor recalcitrant N2 disease missed by EBUS. The patient who was negative at mediastinoscopy proceeded to thoracotomy.

Thus a total of 22 patients underwent thoracotomy with curative intent. Of those, 1 patient was found to have N2 disease in the level 4 and 7 lymph nodes, missed by both mediastinoscopy and EBUS. The remaining patients were N2 negative; however, not all underwent resection because 2 patients had other factors that prevented resection. The remaining 19 patients underwent complete resection. The flow of patients is summarized in Figure 1. Pathologic N stage was N0 in 20 patients and N1 in 1 patient. The total number of patients with recalcitrant N2 disease is 6 patients, indicating a prevalence of 18.8%. Of the patients undergoing resection, 7 patients were found to have a complete pathologic response.

For the purposes of calculation of accuracy data, the 5 patients who did not undergo resection or mediastinoscopy owing to comorbidities were excluded. All patients with positive EBUS results were deemed true positives. The number of patients with false-negative EBUS was 3, including 2 discovered at mediastinoscopy and 1 discovered at thoracotomy after a negative mediastinoscopy. All false-negative results were found in stations assessed by EBUS (2 at 4R at mediastinoscopy and 1 at stations 4R and 7 at thoracotomy). Based on these results, we calculated a sensitivity of 50%, negative predictive value of 88%, and an accuracy of 89% (Table 2).

**Comment**

The treatment of patients with stage IIIA lung cancer because of N2 mediastinal lymph node involvement is controversial. This is because of the mixed results seen in the literature with the addition of surgical therapy to chemotherapy and radiotherapy and because these patients are a heterogeneous group of patients with varied prognosis [1-5]. We have previously reported on the proportion of patients who undergo neoadjuvant chemoradiation with the intent of posttreatment surgery [9]. This previous study was a carefully selected group of

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**Table 1. Demographic Data of 32 Patients Who Underwent Endobronchial Ultrasound for Mediastinal Staging After CompletingPreoperative Induction Therapy With Chemotherapy or Radiation**

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>32</td>
</tr>
<tr>
<td>Age, y (median)</td>
<td>67</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22 (69%)</td>
</tr>
<tr>
<td>Female</td>
<td>10 (31%)</td>
</tr>
<tr>
<td>Location of lesion</td>
<td></td>
</tr>
<tr>
<td>Right upper lobe</td>
<td>17 (53%)</td>
</tr>
<tr>
<td>Right middle lobe</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Right lower lobe</td>
<td>4 (12.5%)</td>
</tr>
<tr>
<td>Left upper lobe</td>
<td>4 (12.5%)</td>
</tr>
<tr>
<td>Left lower lobe</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Hilair</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>23 (72%)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>9 (28%)</td>
</tr>
<tr>
<td>Neoadjuvant therapy</td>
<td></td>
</tr>
<tr>
<td>Chemoradiation</td>
<td>31 (97%)</td>
</tr>
<tr>
<td>Chemotherapy only</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>
patients with nonbulky, biopsy-proven N2 disease who underwent similar staging procedures, neoadjuvant therapy protocols, restaging, and surgical procedures. The study on 402 patients who underwent neoadjuvant chemoradiation showed that only 49% returned for surgical restaging and only 37% underwent surgical resection. The 5-year survival of the resected group was 47% versus 8% in the patients who did not undergo resection. The best survival was in patients who had a complete pathologic response, with a 5-year survival of 53%, and in those who were N2 negative.

Whether the improved survival in this group of patients was increased because of the addition of surgical therapy or other factors is unknown. There is a general consensus that patients with persistent N2 disease or progression of cancer after neoadjuvant therapy are not helped much by resection [2, 9–11]. These data provide the reason that we aggressively restage the mediastinum using repeat PET scan, repeat CT scans, and invasive mediastinal staging in patients without significant downstaging on PET. However, options for restaging include mediastinoscopy, repeat mediastinoscopy, EBUS, endoscopic ultrasound, thoracoscopy, and a robotic approach. Typically, many of these patients have undergone initial mediastinoscopy or even lymph node dissection by means of thoracotomy before. Although described, reoperative mediastinoscopy remains technically challenging, with an increased risk for complications and unreliable results and has not been adopted widely [12]. Furthermore, reports of its accuracy have not been consistent, and do not seem to be equivalent to mediastinoscopy in the pretreatment setting [13].

Thus, EBUS is the preferred route chosen by most and why this clinical study is relevant and clinically important. Its efficacy in this setting has not been well documented. We have demonstrated in this study that EBUS has a sensitivity of 50% and negative predictive value of 88% in a subset of the population in which the prevalence of recalcitrant N2 disease is 18.8%. The lower prevalence of disease in this study indicates a highly selected group of patients. In this setting, the performance of EBUS is satisfactory. The question of what to do with negative results and whether they need to be confirmed remains a challenge. As stated, a confirmatory mediastinoscopy would likely be a reoperative mediastinoscopy. Although mediastinoscopy did identify 2 patients with a false-negative EBUS and thus prevented a nontherapeutic thoracotomy, there is 1 patient with negative mediastinoscopy who had disease identified in level 4 and 7 lymph nodes at thoracotomy. Therefore, even mediastinoscopy has a false-negative result in this setting. Perhaps in the virgin mediastinum, a confirmatory

Table 2. Performance of Endobronchial Ultrasound as a Restaging Tool

<table>
<thead>
<tr>
<th>Results of EBUS</th>
<th>Results of Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>True positive</td>
</tr>
<tr>
<td>N = 3</td>
<td>False positive</td>
</tr>
<tr>
<td></td>
<td>N = 0</td>
</tr>
<tr>
<td>Negative</td>
<td>False negative</td>
</tr>
<tr>
<td>N = 3</td>
<td>True negative</td>
</tr>
<tr>
<td></td>
<td>N = 21</td>
</tr>
<tr>
<td>Sensitivity = 50%</td>
<td>Specificity = 100%</td>
</tr>
</tbody>
</table>

EBUS = endobronchial ultrasound.
mediastinoscopy may improve results; however, in the setting of operative mediastinoscopy, we believe that the risks outweigh the benefits. Thus, we still prefer EBUS for the restaging of 4R, 7, and 4L lymph nodes.

There have been several reports showing the accuracy of EBUS in the initial staging of patients with NSCLC [14, 15]. The data are scant on the accuracy of EBUS in restaging patients after neoadjuvant therapy. In a study by Szlubowski et al [16], 61 patients who underwent neoadjuvant therapy after confirmed stage IIIA-N2 disease documented by EBUS were included. These patients returned for restaging procedure, and EBUS documented disease in 18 patients. Transcervical extended mediastinal lymphadenectomy (a procedure we do not perform) identified an additional 9 patients with N2 disease. Of these, 7 patients had disease in lymph node stations accessed by EBUS (stations 2R, 4R, and 7). The sensitivity and negative predictive value of EBUS in their study were 67% and 78%, respectively. The conclusions from this study were that EBUS is an effective and safe technique for mediastinal restaging in NSCLC patients after neoadjuvant therapy and that after a negative result of EBUS, a surgical restaging of the mediastinum might not be mandatory.

There are several limitations of our study. First, it is a retrospective analysis that carries all the inherent flaws associated with retrospective data. The patients were highly selected. The prevalence of N2 disease in the patients studied was only 19%, and thus, the negative predictive value of any test on a group of patients with a low incidence of disease is likely to be good. Another limitation is we did not test for a false-positive EBUS because if it yielded a positive test that showed metastatic cancer in an N2 lymph node, that was considered a true positive.

In conclusion, a repeat EBUS for the restaging of N2 mediastinal paratracheal and subcarinal lymph nodes after preoperative neoadjuvant chemotherapy or chemoradiotherapy is a relatively reliable test. It provides a high accuracy of 89% and a negative predictive value of 88% with low morbidity. However, a negative result of a lymph node that initially harbored cancer still requires further investigation before pulmonary resection. For patients who have not had an initial mediastinoscopy, we prefer it before thoracotomy if the restaging EBUS is negative for N2 disease.

References