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.**

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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 paraesophageal 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