A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer

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Objective: The study objective was to compare endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) with mediastinoscopy for mediastinal lymph node staging of potentially resectable non–small cell lung cancer.

Methods: Patients with confirmed or suspected non–small cell lung cancer who required mediastinoscopy to determine suitability for lung cancer resection were entered into the trial. All patients underwent EBUS-TBNA followed by mediastinoscopy under general anesthesia. If both were negative for N2 or N3 disease, the patient underwent pulmonary resection and mediastinal lymphadenectomy.

Results: Between July 2006 and August 2010, 190 patients were registered in the study, 159 enrolled, and 153 were eligible for analysis. EBUS-TBNA and mediastinoscopy sampled an average of 3 and 4 lymph node stations per patient, respectively. The mean short axis of the lymph node biopsied by EBUS-TBNA was 6.9 ± 2.9 mm. The prevalence of N2/N3 disease was 35% (53/153). There was excellent agreement between EBUS-TBNA and mediastinoscopy for mediastinal staging in 136 patients (91%; Kappa, 0.8; 95% confidence interval, 0.7–0.9). Specificity and positive predictive value for both techniques were 100%. The sensitivity, negative predictive value, and diagnostic accuracy for mediastinal lymph node staging for EBUS-TBNA and mediastinoscopy were 81%, 91%, 93%, and 79%, 90%, 93%, respectively. No significant differences were found between EBUS-TBNA and mediastinoscopy in determining the true pathologic N stage (McNemar's test, $P = .78$). There were no complications from EBUS-TBNA. Minor complications from mediastinoscopy were observed in 4 patients (2.6%).

Conclusions: EBUS-TBNA and mediastinoscopy achieve similar results for the mediastinal staging of lung cancer. As performed in this study, EBUS-TBNA can replace mediastinoscopy in patients with potentially resectable non–small cell lung cancer. (J Thorac Cardiovasc Surg 2011;142:1393-400)

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Lung cancer remains the most commonly diagnosed cancer and the leading cause of cancer death worldwide despite advances in imaging, surgery, and multimodality treatment.[1] Accurate staging of the disease is mandatory to determine the prognosis and appropriate treatment. The most significant treatment decision lies in the distinction between those patients who can benefit from surgical resection and those who should receive chemotherapy and radiation therapy or both. The existence of metastatic contralateral adenopathy (N3) currently contraindicates surgery. Patients with ipsilateral lymph node metastasis (N2) may be considered for neoadjuvant therapy followed by surgery on the basis of studies reporting improved survival with this treatment approach.[2] Therefore, preoperative evaluation of mediastinal lymph nodes is important for selecting the optimal treatment.

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Abbreviations and Acronyms

CP-EBUS	= convex probe endobronchial ultrasound
CT	= computed tomography
EBUS-TBNA	= endobronchial ultrasound-guided transbronchial needle aspiration
EUS-FNA	= endoscopic ultrasound-guided fine-needle aspiration
NSCLC	= non–small cell lung cancer
PET	= positron emission tomography
ROSE	= rapid on-site evaluation
TBNA	= transbronchial needle aspiration

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At present, the best means to assess lymph node involvement is by direct sampling. The current gold standard method to obtain such direct sampling is by mediastinoscopy.[3] Mediastinoscopy has the ability to access samples of the paratracheal lymph node stations (levels 2R, 2L, 4R, 4L), the anterior subcarinal lymph node station (level 7), and the hilar lymph node station (level 10). Mediastinoscopy is performed under general anesthesia. Complications related to mediastinoscopy are extremely low when performed by experienced surgeons.[4] Given the invasive and costly nature of mediastinoscopy, there has been considerable interest recently in the development of techniques that allow minimally invasive sampling of mediastinal lymph nodes.

Minimally invasive techniques use needle biopsy to obtain tissue samples from mediastinal lymph nodes.[5,6] Needle biopsy techniques include transbronchial needle aspiration (TBNA), transthoracic needle aspiration, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), and, most recently, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).

EBUS-TBNA is a minimally invasive method of mediastinal biopsy performed under direct real-time endobronchial ultrasound guidance.[7-18] EBUS-TBNA allows access to the paratracheal lymph node stations (levels 2R, 2L, 4R, 4L), the subcarinal lymph node (level 7), and the hilar, interlobar, and lobar lymph nodes (levels 10, 11, and 12). Previous studies, including systematic reviews and meta-analyses, have demonstrated a major impact of EBUS-TBNA on management of patients with non–small cell lung cancer (NSCLC), with a diagnostic yield comparable to mediastinoscopy. However, there have been few comparative studies involving direct comparison of EBUS-TBNA and the gold standard mediastinoscopy.[11] The purpose of the current study was to compare EBUS-TBNA with mediastinoscopy for mediastinal lymph node staging of NSCLC.

MATERIALS AND METHODS

Study Design

This was a prospective, controlled trial performed in patients with confirmed or suspected NSCLC who required a mediastinoscopy as part of their staging investigations of the mediastinum to determine suitability for lung cancer resection. This study was approved by the University Health Network Institutional Research Ethics Board (University Health Network REB#06-0085-C). A written informed consent was obtained from all patients. All patients received chest and upper abdominal computed tomography (CT) with contrast injection. CT was used for assessment of resectability of the primary tumor, evaluation of mediastinal lymph nodes, and exclusion of distant metastases. Lymph nodes with the short axis larger than 1 cm on chest CT were classified as positive for malignancy by CT criteria. Positron emission tomography (PET) was available for patients who were eligible to undergo PET scan during our study period (n = 88). Between July 2006 and August 2010, 190 patients were registered and 153 were eligible for evaluation (Figure 1).

The inclusion and exclusion criteria for the study were as follows:

Inclusion criteria. (1) Patients aged 18 years or older and (2) patients with confirmed or suspected NSCLC who required a mediastinoscopy as part of their staging investigations of the mediastinum to determine suitability for lung cancer resection.

Exclusion criteria. (1) Patients who were deemed on clinical grounds to be medically unfit for a bronchoscopy or a mediastinoscopy, (2) patients who had verified stage IV disease or who were not appropriate for lung cancer resection by virtue of technical inoperability, (3) patients with known small cell lung cancer, (4) patients with a high clinical suspicion of lymphoma, and (5) patients unable to give informed consent.

After the administration of a general anesthetic, all patients underwent EBUS-TBNA as detailed below. All patients then underwent standard cervical mediastinoscopy in the same setting. Each patient served as his/her own control. The surgeon was blinded to the pathologic findings of EBUS-TBNA. The on-site cytopathologist reported the specimen as ''adequate'' or ''inadequate'' for diagnosis. Both EBUS-TBNA and mediastinoscopy were performed in all patients even if EBUS-TBNA result yielded N2 or N3 disease. If there was no evidence of N2 or N3 disease on EBUS-TBNA or mediastinoscopy samples, patients underwent thoracotomy, pulmonary resection, and mediastinal lymphadenectomy at the same setting or at a different time.

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

The convex probe endobronchial ultrasound (CP-EBUS) was used to perform EBUS-TBNA (BF-UC160F-OL8, Olympus, Tokyo, Japan). The CP-EBUS is integrated with a convex transducer (7.5 MHz) that scans parallel to the insertion direction of the bronchoscope. The ultrasound image is processed in a dedicated ultrasound scanner (EU-C60, Olympus). Static ultrasound images were obtained, and the size of lesions were measured in 2 dimensions. Doppler mode imaging was used selectively.

After the induction of general anesthesia, patients were intubated with an endotracheal tube size 8 or greater or a laryngeal mask airway. Conventional flexible bronchoscopy was first performed, followed by examination of the mediastinum using the CP-EBUS. The location and size of the lymph nodes (ipsilateral and contralateral) were characterized and classified as N1, N2, or N3. A dedicated 22-gauge needle (NA-201SX-4022, Olympus) was used to perform all EBUS-TBNA procedures as previously described.[7,8] In brief, a dedicated needle equipped with a protective sheath was first passed through the working channel of the bronchoscope. After visualizing the lymph node, the needle was passed out of the sheath, through the airway, and into the lymph node. After penetration into the lymph node, the internal stylet was used to clean out the internal lumen clogged with bronchial membrane or cartilage. The internal stylet was then removed, and negative pressure was applied with a syringe. The