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Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration of Lymph Nodes in the Radiologically Normal Mediastinum

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Conflict of Interest Statement

The prototype endobronchial ultrasound probe was loaned to the authors by Olympus Ltd., Tokyo, Japan for the duration of this study. None of the authors has any financial stake in Olympus Ltd., of Tokyo, Japan.

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ABSTRACT

Rationale: Endobronchial ultrasound-guided, transbronchial-needle aspiration (EBUS-TBNA) can sample enlarged mediastinal lymph nodes in patients with non-small cell lung cancer (NSCLC). To date, EBUS-TBNA has been used to sample only nodes visible on computed tomography (CT).

Objectives: To determine the accuracy of EBUS-TBNA in sampling nodes less or equal to 1 cm in diameter.

Methods: NSCLC patients with CT scans showing no enlarged lymph nodes (no node > 1 cm) in the mediastinum underwent EBUS-TBNA.

Measurements: Identifiable lymph nodes at locations 2r, 2l, 4r, 4l, 7, 10r, 10l, 11r and 11l were aspirated. All patients underwent subsequent surgical staging. Diagnoses based on aspiration results were compared to those based on surgical results.

Main Results: Among 100 patients (mean age 58.9 y; 68 men), 119 lymph nodes with a size between 5 up to 10 mm were detected and sampled. Malignancy was detected in 19 patients but missed in 2 others; all diagnoses were confirmed by surgical findings. The mean (SD) diameter of the punctured lymph nodes was 8.1 mm. The sensitivity of EBUS-TBNA for detecting malignancy was 92.3 %; the specificity was 100%; and the negative predictive value was 96.3 %. No complications occurred.

Conclusion: EBUS-TBNA can accurately sample even small mediastinal nodes, therefore avoiding unnecessary surgical exploration in 1 of 6 patients who have no CT evidence of mediastinal disease. Potentially operable patients with no signs of

mediastinal involvement on CT may benefit from presurgical EBUS-TBNA aspiration and staging.

[[Word count = 239]]

Keywords: lung cancer, transbronchial needle aspiration, endobronchial ultrasound, mediastinal lymphadenopathy

INTRODUCTION

The staging of lung cancer [1, 2] not only provides important information with regard to survival but also guides treatment.

For patients whose disease has metastasised to mediastinal lymph nodes (stage III) or with tumours that have invaded mediastinal structures, the benefit of surgery as primary therapy is questionable. Combined chemoradiotherapy is most appropriate, although chemoradiotherapy followed by surgery may be considered [2]. Mediastinal lymph node involvement is found in 26% of newly diagnosed lung cancer patients, and extrathoracic metastases are found in 49% [2]. Thus, reliable staging of mediastinal lymph nodes and the mediastinum is essential for choosing appropriate therapy.

In most centres, computed tomography (CT) is the initial method for staging mediastinal nodes. Nodes detectable by CT that are considered abnormal, generally have a short-axis diameter greater than 1 cm. Smaller lymph nodes can harbour metastatic foci, and enlarged nodes may be benign, especially when central tumours are accompanied by inflammation. Therefore, the accuracy of CT for diagnosing mediastinal disease is low. In a recent meta-analysis of 20 studies and 3,829 patients [3], the pooled sensitivity was 57%; the pooled specificity was 82%; and the pooled negative predictive value was 82% (range, 63% to 85%). Therefore, surgical mediastinal staging is commonly performed in patients with a radiologically normal mediastinum before a planned cancer resection, to rule out unexpected N2 or N3 disease. Approximately 18% (range, 15% to 37%) of patients with a negative CT scan who undergo surgical mediastinal staging are found to have metastatic disease.

Mediastinoscopy remains the reference standard for evaluating nodal disease. It has a sensitivity of 90% to 95% [4]. However, only certain mediastinal lymph node stations are accessible (levels 2, 4, and anterior level 7). For sampling levels 5 and 6, thoracoscopy, anterior mediastinotomy (the Chamberlain procedure), or extended

mediastinoscopy can be performed. The inferior mediastinum may be evaluated by thoracoscopy. However, all these more aggressive staging procedures require general anaesthesia, surgical incision, and therefore are associated with considerable costs [5, 6]. Positron emission tomography (PET) was expected to increase the accuracy of mediastinal staging in NSCLC, and indeed, a meta-analysis has confirmed its superiority [7] However, more recent reports have tempered enthusiasm for using PET as the sole tool for evaluating the mediastinum [8].

Endoscopic ultrasound (EUS) guided fine needle aspiration has been reported as an endoscopic option to evaluate the mediastinum [9, 10, 11, 12]. Unfortunately, it does not allow for airway inspection during the procedure. Different authors [13, 14, 15] have reported that a real-time procedure, endobronchial ultrasound with transbronchial-needle aspiration (EBUS-TBNA) is a highly accurate and safe method for sampling enlarged mediastinal lymph nodes. However, EBUS-TBNA has not been applied to patients with CT-negative scans. The aim of this study was to determine the accuracy of EBUS-TBNA for mediastinal lymph nodes from NSCLC patients without enlarged mediastinal lymph nodes on chest CT- scans.

MATERIALS AND METHODS

The protocol of this multicenter study was approved by the Institutional Review Boards. All patients provided written informed consent.

Between January 2003 and March 2005, consecutive patients with an indication for bronchoscopy were screened for the study. A chest radiograph and CT scan of the chest (plain and contrast-enhanced) were performed in all patients. Only patients without CT evidence of enlarged mediastinal lymph nodes were included in this study.

Standard, conventional flexible bronchoscopy (model BF-T160 bronchoscope; Olympus, Tokyo, Japan) was first performed to examine the tracheobronchial tree,

followed by EBUS-TBNA using the ultrasound bronchoscope (model XBF-UC160F-OL8; Olympus, Tokyo, Japan). Both bronchoscopy procedures were performed with the patient under local anaesthesia and sedation (midazolam) or under general anaesthesia**.** All patients underwent surgical staging within 10 days after the EBUS-TBNA.

Noninvasive Imaging

Multislice computed tomography was performed in all patients, and TNM staging, including identification of distant metastases, was recorded by two thoracic CT radiologists. On-site CT examinations were performed with a Siemens helical scanner, using a single breath-hold technique. Off-site CT scans were evaluated by the same radiologists and were included if their quality was similar to the on-site CT studies. If the quality of an off-site CT was inadequate, an on-site CT was performed. Lymph nodes were considered enlarged if the short-axis diameter was greater than 1 cm.

Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration

Endobronchial ultrasound was performed using a linear array ultrasonic bronchoscope (XBF-UC 160F-OL8, Olympus Ltd., Tokyo Japan; Figure 1). The instrument is similar to a standard bronchoscope, with an outer diameter of 6.9 mm, a 2.0-mm instrument channel, and 30-degree 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. The angle of view is 90°, and the direction of view is 30° forward oblique. Image processing was performed by an Olympus ultrasound processor (EU-C60).

A 22-gauge needle (NA-202C Olympus Ltd.) was used to perform transbronchial aspiration. The needle exits the outer covering of the insertion tube at 20°. The needle can be visualised through the optics and on the ultrasound image.

The endoscope was passed through the mouth and vocal cords to the main

carina, the balloon, if used, was partially inflated (0.3 to 0.5 mL water), and the regional lymph node stations of the mediastinum and hilar regions (stations 2,, 4, 7, 10, and 11) [16] were systematically imaged and measured (short-axis diameter) during slow withdrawal and rotation of the transducer.

All visualised nodes with a size of between 5 and 10 mm were punctured. According to the size of normal lymph nodes, nodes smaller then 5mm were not punctured (17, 18, 19). Transbronchial needle aspiration was performed under real-time ultrasound control. Needle punctures were performed using the 'jabbing' method [20]. Integrated colour power Doppler ultrasound was used to avoid intervening vessels immediately before needle puncture (Figures 2 and 3). Every node was punctured twice.

The aspirate was placed onto glass slides, air-dried, stained, and classified. Papanicolaou staining [21, 22, 23] and light microscopy was performed by a cytopathologist who was blinded to the details of the patients. No rapid on-site cytology was performed.

Diagnoses based on the aspirates were confirmed by open thoracotomy, thoracoscopy, or mediastinoscopy in all patients.

Statistical Methods

Demographic and proportional data were tabulated using Microsoft Access and Excel (Microsoft Co., Redmond, WA). The chi quadrate test where appropriate, was used to compare proportional data. The type I error was set at 0.05 for all analyses. Confidence intervals were calculated to 95% using standard formulas. The sensitivity, specificity, and accuracy were calculated using the standard definitions.

RESULTS

We evaluated 983 patients for lung cancer until we identified 100 (mean age 58.9 y; 68 men), with CT evidence suggesting a tumour originating from the lung (T1 to 4)

without enlarged mediastinal lymph nodes and a suspicion of or known diagnosis of non-small cell lung cancer.

Eighty- seven patients did have a known diagnosis of NSCLC and 13 patients included in the population were highly suspicious for the disease (positive sputum cytology, increased tumour markers, CT criteria and tobacco abuse). All patients had at least one node identified by EBUS and a total of one hundred- nineteen lymph nodes with a size between 5 and 10 mm were detected and punctured by EBUS-TBNA (Table 1). The mean diameter of the punctured lymph nodes was 8.1 mm (SD± 0,7; R 4-10mm). Additionally we detected 89 nodes smaller than 5 mm, which were not punctured. Despite the negative CT scans, EBUS-TBNA of mediastinal lymph nodes were positive for metastases in 19 patients. The stage changed from N0 in 3 patients to stage N3 disease, in 13 to stage N2 disease and in 3 to stage N1 disease. All punctures were adequate, in every smear lymphocytes were visible. Seventy-eight patients were examined under general anaesthesia and 22 patients with moderate sedation and topical anaesthesia.

All 100 patients underwent mediastinoscopy (15%) or thoracotomy (85%) with mediastinal lymph node resection. Additional positive nodes were detected in 2 patients, 1 in the N1 and 1 in the N3 position. Overall, 17 patients had stage N2 or N3 disease, of which 16 were identified from EBUS-TBNA and 4 patients with stage N1 disease, of which 3 were identified by EBUS-TBNA. All samples obtained by EBUS-TBNA correctly identified all 79 patients without N1 or N2 disease. Of the 2 patients with lymph node metastases not identified by EBUS-TBNA, 1 had nodal involvement in position 10r and 1 in position 11 l, and both had undergone EBUS-TBNA puncture of lymph nodes in these regions. The smears showed lymphocytes, but no malignancy. The sensitivity of EBUS-TBNA for detecting malignancy was 92.3 %; the specificity was 100%; and the negative predictive value was 96.3 %.

COMMENT

We found that EBUS-TBNA identified malignant lymph nodes in patients with a normal CT of the mediastinum. The prevalence of mediastinal lymph node metastases in our series, 17%, is similar to that of surgical series, evaluating patients with negative mediastinal CT. These series describe metastatic lymph nodes to be present the time of surgery in 15% to 20% of CT-negative patients [4, 5, 6]

Compared to mediastinoscopy, EBUS-TBNA has the advantage that it is able to also routinely access posterior mediastinal (level 7) and hilar lymph nodes (levels 10 and 11) and that it can be performed using moderate sedation. Most of our patients were examined under general anaesthesia, as the examination was done immediately prior to the scheduled surgical procedure. As reported in prior studies, there is no difference in yield or patient tolerance if the procedure is performed under moderate sedation or general anaesthesia [24].

Similar approaches using esophageal ultrasound (EUS) guided FNA have been described with comparable results, albeit in smaller patient populations. Wallace et al. [25] published their experience in sixty-nine patients without enlarged mediastinal lymph nodes. Endoscopic ultrasound detected malignant mediastinal lymph nodes in 14 of 69 patients. The sensitivity of EUS for advanced mediastinal disease was 61% and the specificity was 98 %. Additionally they found advanced stage in 3 others (1 left adrenal metastasis and 2 patients with mediastinal invasion of tumor). LeBlanc et al. [26] examined seventy-six patients with NSCLC without mediastinal lymphadenopathy on CT. EUS-FNA was performed on sites that were suspicious for metastases. Of the 62 patients who underwent surgery, 23 (37%) patients had positive lymphnodes: 6 patients had peribronchial lymphnode (N1) involvement, whereas the remaining 17 patients had

ipsilateral or subcarinal lymphnode (N2) involvement. Aspirates of lymph nodes yielding lymphocytes only either by EUS FNA or EBUS TBNA do require follow-up with a more definitive procedure.

Depending on the Lypmh node localisation, EBUS-TBNA seems at least comparable to the established EUS guided FNA findings in the literature [15, 27, 28]. It is important to note that small lymph nodes are more difficult to identify with any imaging modality (including EBUS) and likely contain a small number of malignant cells, making a cytological diagnosis difficult. Nonetheless, in 100 patients, EBUS-TBNA identified almost all (19 of 21) patients with advanced disease. This study supports that ultrasound guided TBNA has excellent potential even in the patient with a normal mediastinum by CT scanning.

Limitations of the Study

A limitation of our study is the lack of routine PET scanning. Although PET has become increasingly available and is approved for lung cancer staging, it is still not routinely performed in practice. Recent guidelines for staging of NSCLC recommend PET staging [29], but the evidence supporting this recommendation is only moderate [7, 8] Furthermore, the limitations in accuracy discussed above make it unlikely that PET with its current resolution, even in combination with CT, will replace the need for tissue sampling.

Lymph nodes are often grouped in stations. A potential exists that the surgically sampled lymph nodes in the examined stations were not identical to the ones punctured during endoscopy. This appears unlikely, as in our routine all lymph nodes are dissected and the results of the endoscopically and surgically sampled lymph nodes are highly congruent.

Conclusions

Our findings suggest that EBUS-TBNA should be considered in the preoperative staging of all patients both with and without mediastinal lymph node enlargement on CT scan. Further studies are needed to compare the different invasive and non-invasive staging techniques (CT, PET, EBUS-TBNA, EUS-FNA, mediastinoscopy and thoracoscopy) in patients with non- small cell lung cancer. To establish a definitive way of staging the mediastinum in patients with NSCLC a comparison study of all imaging, minimal-invasive and also invasive techniques should be considered.

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Table 1. Results of Endobronchial Ultrasound-Guided, Transbronchial-Needle Aspiration (EBUS-TBNA) in Sampling and Staging 119 normal sized Mediastinal Lymph nodes in 100 Patients With Non-Small Cell Lung Cancer.

Location	Biopsied Nodes, n	Nodes Positive for Cancer, n (%)	Surgically Confirmed Diagnoses, n (%)
2r	13	5 (38)	6 (46)
2l	16	2 (13)	2 (13)
4r	17	2 (12)	2 (12)
4l	17	3 (18)	3 (18)
7	13	1 (8)	1 (8)
10r	12	3 (25)	3 (25)
10l	10	1 (10)	1 (10)
11r	10	1 (10)	2 (20)
11l	11	4 (36)	4 (36)
Total	**119**	**22 (19)**	**24 (20)**

Figures

Figure 1: Tip of the linear array ultrasonic bronchoscope (BF-UC40F-OL5, Olympus Ltd., Tokyo Japan). The needle is extended through the working channel and exits obliquely.

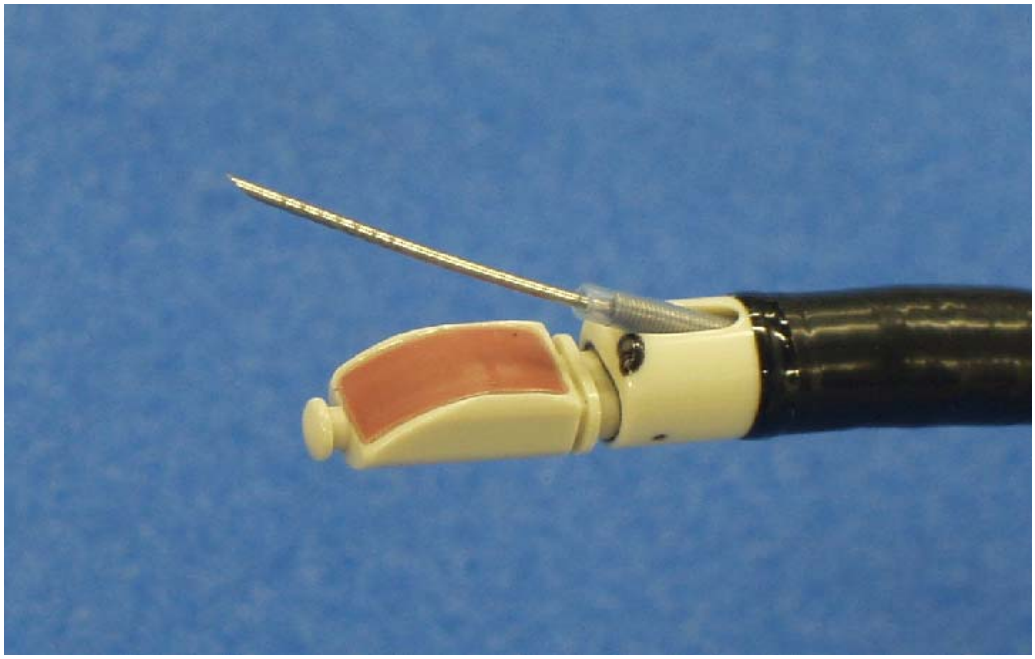

Figure 2: Puncture of a 8 mm lymph node in position 4r. The needle is visible (arrows) within the node.