EBUS-TBNA for the diagnosis of central parenchymal lung lesions not visible at routine bronchoscopy

Kurt G. Tournoya, Robert C. Rintoulb, Jan P. van Meerbeecka, Nicholas R. Carrollb, Marleen Praeta, Robert C. Butteryb, Klaas W. van Kralingenc, Klaus F. Rabec, Jouke T. Annemac

a Department of Respiratory Medicine and Lung Oncologic Network, Ghent University Hospital, Ghent, Belgium
b Department of Thoracic Oncology, Papworth Hospital, Cambridge, United Kingdom
c Department of Respiratory Medicine, Leiden University Medical Center, Leiden, The Netherlands

ABSTRACT

Background: Obtaining a tissue diagnosis of malignancy is challenging in patients with suspected lung cancer presenting with centrally located intrapulmonary masses.

Objective: (1) To evaluate the yield of endobronchial ultrasound with real-time guided transbronchial needle aspiration (EBUS-TBNA) for diagnosing centrally located lesions after a non-diagnostic conventional bronchoscopy. (2) To assess the impact of EBUS-TBNA on patient management for this indication.

Study design and patients: A retrospective analysis of a series of patients with a central parenchymal lung lesion suspected to be lung cancer who had been referred to three university hospitals for EBUS-TBNA to obtain a tissue diagnosis was undertaken. If EBUS-TBNA did not result in a formal pathological diagnosis of malignancy, patients were subsequently referred for a transthoracic needle aspiration biopsy or a surgical diagnostic procedure.

Results: Sixty patients were investigated with EBUS-TBNA. The majority (82%) had a prior (non-diagnostic) flexible bronchoscopy. EBUS-TBNA was performed in an out-patient setting in 97%. With ultrasound, the primary lung lesion was observed in all cases. EBUS-TBNA confirmed lung cancer in 46 (77%). A final reference pathology diagnosis was available in 59 (98%) cases. The sensitivity of EBUS-TBNA for diagnosing lung cancer was 82% (95% confidence intervals (CI) 69–91%) with a negative predictive value of 23% (95%CI 5–53%). Based on the EBUS-TBNA findings, transthoracic needle aspiration biopsy or a surgical diagnostic procedure was cancelled in 47% and 30% of patients, respectively. No serious procedure-related complications were reported.

Conclusion: EBUS-TBNA is a sensitive tool for the diagnosis of centrally located primary lung cancer not visible at conventional bronchoscopy. Therefore, EBUS-TBNA can impact on patient management in this setting. However, the low negative predictive value indicates that a negative EBUS-TBNA result should be confirmed by other methods.

Implication: EBUS-TBNA can be considered as a diagnostic test in patients with a centrally located lung lesion after a previous non-diagnostic conventional bronchoscopy.

© 2008 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Lung cancer is the leading cause of cancer death with a 5-year survival rate of only 16% [1]. Lung cancer may be suspected in patients presenting with either an abnormal chest radiograph or with symptoms resulting from local or systemic tumour effects. If lung cancer is suspected, a histological diagnosis, in conjunction with accurate staging, should be obtained whenever possible in order to guide therapy and prognosis [2,3].

Flexible fibreoptic or video-bronchoscopy with its associated procedures (endobronchial biopsy, brushing and washing) is valuable in patients with suspected lung cancer, especially if there is endobronchial tumour visible. However, many central tumours are not visible at bronchoscopy due to their submucosal or parabronchial position and in these situations diagnostic yield by standard bronchoscopic techniques is much lower [4–6]. The addition of transbronchial needle aspiration (TBNA) may increase diagnostic rates [7] but this technique is not widely practiced and the yield is heavily operator-dependent. Although CT-guided

A R T I C L E   I N F O

Article history:
Received 4 December 2007
Received in revised form 21 February 2008
Accepted 9 April 2008

Keywords:
Lung cancer
Endobronchial ultrasound
Transbronchial needle aspiration
EBUS-TBNA
Bronchoscopy
Transthoracic needle biopsy

0169-5002/$ – see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.lungcan.2008.04.004

Lung Cancer 63 (2009) 45–49
Contents lists available at ScienceDirect
Lung Cancer
journal homepage: www.elsevier.com/locate/lungcan

EBUS-TBNA for the diagnosis of central parenchymal lung lesions not visible at routine bronchoscopy

Kurt G. Tournoya, Robert C. Rintoul, Jan P. van Meerbeeck, Nicholas R. Carroll, Marleen Praet, Robert C. Buttery, Klaas W. van Kralingec, Klaus F. Rabec, Jouke T. Annemac

a Department of Respiratory Medicine and Lung Oncologic Network, Ghent University Hospital, Ghent, Belgium
b Department of Thoracic Oncology, Papworth Hospital, Cambridge, United Kingdom
c Department of Respiratory Medicine, Leiden University Medical Center, Leiden, The Netherlands
trathoracic needle aspirations for centrally located parabronchial lesions can be undertaken, there is a high risk of pneumothorax and hemoptysis [8]. In addition, the diagnostic yield is lower than for peripheral lesions [8].

Convex curvilinear endobronchial ultrasound with real-time guided transbronchial needle aspiration (EBUS-TBNA) is a useful technique for mediastinal lymph node staging of non-small cell lung cancer [9–12]. In this paper, we have evaluated the yield and clinical impact of using EBUS-TBNA for diagnosing centrally located parenchymal lung lesions which are not visible by conventional bronchoscopy and which are hardly amenable to CT-guided needle biopsy.

2. Subjects and methods

2.1. Study design and patients

We retrospectively reviewed the diagnostic performance of EBUS-TBNA in patients with a high clinical suspicion of a centrally located primary lung cancer. These patients were referred to three expert institutions to obtain a tissue diagnosis of the primary lung lesion by EBUS-TBNA. The centrally located lung lesions were defined as an intrapulmonary mass with the medial margin located within the inner third of the hemithorax based on chest CT-scan imaging. Patients with primary mediastinal masses were not eligible for the study.

2.2. EBUS-TBNA procedure

EBUS-TBNA was performed by trained operators using a curvilinear scanning ultrasound bronchoscope (Olympus, BF UC160F OLR) connected to an ultrasound unit (EU-C60 Olympus Ltd.). The procedures were performed under local anaesthesia and moderate sedation (Midazolam) or general anaesthesia according to investigators' preference. If general anaesthesia was chosen, EBUS-scope introduction was made possible by using high-frequency jet ventilation. For paratracheal masses, the scope was positioned endotracheally. For masses in the respective hilar regions, upper or lower lobes or middle lobe, the scope was positioned in the respective main stem bronchi, upper or lower or middle lobar bronchus in order to visualise the lung lesion. TBNA was performed as an out-patient procedure in the majority of cases.

2.3. Statistical analysis

Analysis of test performance of EBUS-TBNA for patients in whom a reference pathology was available was performed using SPSS 15.0 (SPSS Inc., Chicago, IL). Comparison between patients with small lesions (<25 mm short axis) and large lesions (≥25 mm short axis) was performed using the (two-sided) Fisher’s Exact test.

### Table 1

**Characteristics of the study population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n</td>
<td>60 (100)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>65 (43–82)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36 (60)</td>
</tr>
<tr>
<td>Female</td>
<td>24 (40)</td>
</tr>
<tr>
<td>Localisation of the lung lesion, n (%)</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>12 (20)</td>
</tr>
<tr>
<td>Right</td>
<td>48 (80)</td>
</tr>
<tr>
<td>Abutting the mediastinum</td>
<td>24 (40)</td>
</tr>
<tr>
<td>PET-scan uptake in lung lesion, n (%)</td>
<td>32 (53)</td>
</tr>
<tr>
<td>Prior investigations to obtain diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>Non-diagnostic Bronchoscopy</td>
<td>49 (82)</td>
</tr>
<tr>
<td>Endo– or transbronchial biopsy</td>
<td>21 (43)</td>
</tr>
<tr>
<td>Blind TBNA (negative)</td>
<td>6 (12)</td>
</tr>
</tbody>
</table>

* For left sided lesions, there were six in the upper lobe, two in the lower lobe and four in the left central hilar region. For the right-sided lesions, there were 24 in the upper lobe, 12 in the lower/middle lobe and 12 in the right central hilar region.

### Table 2

**EBUS-TBNA: procedural characteristics and yield**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBUS-TBNA outpatient, n (%)</td>
<td>58 (97)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Anaesthesia, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate sedation (midazolam)</td>
<td>50 (83)</td>
<td></td>
</tr>
<tr>
<td>General anaesthesia</td>
<td>6 (10)</td>
<td></td>
</tr>
<tr>
<td>Local anaesthesia only</td>
<td>4 (7)</td>
<td></td>
</tr>
<tr>
<td>Scope time (min); median (range)</td>
<td>21 (10–60)</td>
<td></td>
</tr>
<tr>
<td>Primary lung lesion characteristics, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion observed</td>
<td>60 (100)</td>
<td></td>
</tr>
<tr>
<td>Lesion punctured</td>
<td>58 (97)</td>
<td></td>
</tr>
<tr>
<td>Pathology EBUS-TBNA sample, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant, non-small cell carcinoma</td>
<td>35 (58)</td>
<td></td>
</tr>
<tr>
<td>Malignant, small cell carcinoma</td>
<td>11 (18)</td>
<td></td>
</tr>
<tr>
<td>Suspicious for malignancy, but insufficient for diagnosis</td>
<td>4 (7)</td>
<td></td>
</tr>
<tr>
<td>Not representative; benign</td>
<td>8 (13)</td>
<td></td>
</tr>
<tr>
<td>No cytology obtained</td>
<td>2 (3)</td>
<td></td>
</tr>
</tbody>
</table>

### Complications, n (%)

- None                                           | 57 (95)  |
- Patient intolerance with procedure being abandoned | 2 (3)   |
- Self-limiting atrial fibrillation                | 1 (2)   |
(90%) cases while general anaesthesia was administered in 6 (10%) patients. The scope time did not differ with the type of anaesthesia applied. In all cases the primary lung lesion was visualised with EBUS. TBNA was performed in 58 (97%) of cases. In two cases vessel interposition prevented TBNA from being undertaken safely. In 46 patients (77%), EBUS-TBNA provided a formal diagnosis of lung cancer. This was non-small cell cancer in 35 (58%) and small cell lung cancer in 11 (18%). In 12 (20%) patients, the TBNA samples were insufficient to make a definitive diagnosis. In four cases (7%) malignancy was suspected but could not be confirmed and in eight (13%) EBUS-TBNA showed respiratory epithelial cells or lymphoid cells only. There were no serious procedure-related complications.

![Fig. 1.](image1.png)

**Fig. 1.** The upper panel shows the CT-scan (left) and integrated FDG-PET/CT scan images of a patient in whom lung cancer was suspected. The inner margin of the lesion was judged to be within the inner one-third of the hemithorax. There were no endobronchial abnormalities upon conventional videobronchoscopy. With EBUS-TBNA, the lung lesion was visualised (left lower panel) and punctured with the 22-G needle yielding a cyto-aspirate with non-small cell carcinoma cell groups besides the red blood cells and respiratory epithelial cells.

![Fig. 2.](image2.png)

**Fig. 2.** Patient flow chart. Only those patients in whom EBUS-TBNA did not provide a classifying diagnosis were referred for a confirmatory procedure. This was either a surgical procedure or a CT-guided transthoracic needle aspiration.
In two patients EBUS-TBNA was stopped early because of patient intolerance and in one case there was an episode of self-limiting atrial fibrillation.

Fig. 2 shows the patient flow chart according to the final reference pathology. In one patient, no tissue confirmation was obtained following a negative EBUS-TBNA and therefore a formal reference pathology was available for 59 (98%) of patients. Lung cancer was the final diagnosis in 56 patients (95%), while another diagnosis was obtained in three. These were lymphoma, hamartoma and atypical carcinoid, respectively. In the patients in whom a definitive reference pathology was available, the sensitivity to diagnose lung cancer using EBUS-TBNA was 82% (95% confidence intervals (95%CI) 69–91%) with a negative predictive value of 23% (95%CI 5–53%). The median size of the lung lesions was 25 mm (range 10–70 mm; short axis). An exploratory analysis showed that the sensitivity was comparable for small versus large lesions when a short-axis cut-off was arbitrarily set at 25 mm (78% (95%CI 57–91%) vs. 86% (95%CI 68–96%)) respectively, P = 0.50. A scheduled transthoracic CT-guided biopsy or other (mainly surgical) diagnostic procedure was cancelled in 28 (47%) and 18 (30%) of patients, respectively. As such, EBUS-TBNA had an impact on the diagnostic management of 46 of the patients (77%).

4. Discussion

In this study, EBUS-TBNA provided a diagnosis of malignancy in 77% of patients with a centrally sited lung lesion that was not visible at routine bronchoscopy. The sensitivity to diagnose lung cancer was 82%. In addition, in this setting EBUS-TBNA was shown to be both safe and have a high impact on patient management.

Flexible bronchoscopy and CT/ultrasound guided transbronchoscopic needle aspiration are the most commonly used techniques to obtain a tissue diagnosis when lung cancer is suspected. Whereas the former has a good yield for diagnosing lung cancer presenting as an endobronchially visible exophytic mass, the latter is commonly used to biopsy peripheral lung lesions which are not visible at bronchoscopy. In the current series, no patient had endobronchially visible tumour and the majority of patients had had a prior bronchoscopy which was non-diagnostic. CT-guided transthoracic needle aspiration causes, besides the inherent radiation exposure, pneumothorax and/or hemoptysis in 30–40% of patients [8,13], especially when the lesions are centrally located. Yield is also lower for central rather than peripheral lesions [8]. Alternative approaches include radial endobronchial ultrasound and electromagnetic navigation systems [14–18]. The former has limitations in that real-time guided aspiration of lesions is not possible and the latter is still undergoing clinical evaluation. Both EBUS-TBNA and transoesophageal endoscopic ultrasound with fine needle aspiration (EUS-FNA), have been shown to have high sensitivity and accuracy for staging malignant mediastinal lymph node invasion in a minimally invasive way [19–23]. Furthermore, with EUS-FNA, tissue diagnosis can be obtained for intrapulmonary lesions situated close to the oesophagus [24].

To our knowledge, this is the first report to assess EBUS-TBNA for diagnosing centrally located parabronchial lung cancer. In a selected population of patients in whom lung cancer is suspected, EBUS-TBNA provides a diagnosis in a high percentage of patients. As a consequence, we suggest that when there is no endobronchial abnormality seen, EBUS-TBNA can be considered the procedure of choice for centrally located parabronchial lesions. Recently, a case report showed that EBUS-TBNA can also contribute to the diagnosis of intrapulmonary metastasis of a thyroid carcinoma [25]. In our experience the procedure is safe and no cases of pneumothorax were observed. Unlike CT-guided biopsy which invariably necessitates traversal of the pleura with risk of pneumothorax, transbronchial needle biopsy can often be performed without traversing the pleura.

In this series, the sensitivity of EBUS-TBNA for diagnosing primary tumour is slightly lower than that which has been reported for the diagnosis and staging of mediastinal lymph nodes [22]. There may be several reasons for this. First, we observed that sometimes primary lung lesions can have parenchymal consolidation and an associated inflammatory or fibrotic reaction around the main tumour that is not clearly distinguishable by ultrasound. This can lead to biopsy of peri-tumoural inflammatory tissue rather than the tumour itself. Secondly, anatomical factors such as the interposition of large vessels can impede safe puncture of a lung lesion. Thirdly, it may on occasion, be difficult to visualise the lung mass due to the interposition of aerated lung tissue through which ultrasound waves do not travel well. However, we did observe that by careful placement of the scope in lobar bronchi more peripheral lung masses can often be visualised and biopsied (Fig. 1). Biopsy of such lesions is aided by the design of the needle which can be extended up to 40 mm unlike a standard TBNA needle which extends approximately 13 mm. However, it is clear that the success of the technique critically depends on careful selection of the patient. The exact reach of the scope was not evaluated here, and although masses abutting the mediastinum or large airways can readily be approached, it can be expected that sublobar lesions or upper lobe lesions may be beyond the reach of the scope.

In four (7%) cases the pathologist observed that biopsies were suspicious but insufficient to provide a formal diagnosis of carcinoma. It is important that in such cases, further tissue diagnosis is pursued as we found subsequently a hamartoma, a lymphoma and an atypical carcinoid upon surgical intervention. The fourth patient had a mixed small/non-small cell carcinoma, a diagnosis that could not be made from the EBUS-TBNA samples.

It should be noted that several limitations apply to this case series. First, the retrospective character of the study means that there are no well-defined inclusion criteria. The localisation of the medial margin of the lesion within the inner one-third of the hemithorax fitted best with the consecutive patients we investigated with EBUS-TBNA. A prospective series with clear inclusion criteria, or even a randomized controlled trial could overcome this bias. Secondly, the prevalence of lung carcinoma was very high because the majority of patients included had a high suspicion for lung cancer initially and this results in an additional selection bias. As a result the value of EBUS-TBNA in the diagnosis of non-malignant lesions remains unanswered and the negative predictive value that we calculated is difficult to interpret. It is, however, clear that in cases where no malignancy is found, further tissue confirmation should be pursued. Thirdly, patients were selected on the basis of having parabronchial or centrally localised primary lung lesions thereby defining a population in whom CT-guided biopsy may be more difficult [8]. Therefore, although EBUS-TBNA provides an alternative to CT-guided transthoracic puncture, especially for more centrally located lesions, it should be appreciated that this study was not designed to compare the two modalities and that they should be regarded as complementary rather than exclusive.

In conclusion, we show that EBUS-TBNA is a useful and safe procedure for diagnosing primary centrally located lung cancers when there is no endobronchial abnormality.

Conflict of interest

None declared.

References


