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

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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.
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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

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transthoracic 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 curvi-linear 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 the 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 OL8) 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 using a 22-gauge needle (NA-2015X-4022 Olympus Ltd). Patients were observed for 2 h post-procedure. A chest X-ray was performed if there were any symptoms or signs suggestive of a procedure-related complication. Smears of the aspirates obtained by EBUS-TBNA were air-dried and stained with Diff-Quik®. Specimens were categorized either positive (malignant cells present) or negative (no malignant cells) or not representative (inadequate material for diagnosis). If the pathology from the EBUS-TBNA samples resulted in a formal diagnosis of malignancy, this was judged to be a true positive finding. No further tissue confirmation was undertaken in these cases as it was judged unethical to confirm positive findings with additional (invasive) diagnostic tests. In cases where no malignancy was detected following EBUS-TBNA, patients were referred for further investigation including CT-guided transthoracic needle aspiration or surgical procedures such as thoracoscopy or thoracotomy to obtain a reference pathology result.

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) Fishers' Exact test.

Table 1
Characteristics of the study population

Number of patients, *n*	60
Median age, years (range)	65 (43–82)
Gender, *n* (%)	
Male	36 (60)
Female	24 (40)
Localisation of the lung lesion, *n* (%)[a]	
Left	12 (20)
Right	48 (80)
Abutting the mediastinum	24 (40)
PET-scan, *n* (%)	32 (53)
FDG uptake in lung lesion	30 (94)
Prior investigations to obtain diagnosis, *n* (%)	
Non-diagnostic Bronchoscopy	49 (82)
Endo- or transbronchial biopsy	21 (43)
Blind TBNA (negative)	6 (12)

[a] 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.

3. Results

In this international retrospective series, 60 patients (36 male) were referred between April 2006 and October 2007 to Ghent University Hospital, Belgium (*n* = 25), Papworth Hospital, Cambridge, UK (*n* = 10) or Leiden University Medical Center, The Netherlands (*n* = 25) for EBUS-TBNA to obtain a tissue diagnosis of lung lesion suspected to be malignant and with its medial margin within one-third of the hemithorax (Fig. 1).

Table 1 details patient characteristics. Forty-nine (82%) patients had a previous non-diagnostic bronchoscopy and in 27 (55%) cases a non-diagnostic endobronchial or transbronchial biopsy or blind transbronchial needle aspiration had been performed. In none of the patients was an endobronchial mass lesion visible at the time of the EBUS-TBNA examination. In 24 cases (40%) the target lesion abutted the mediastinum but did not lie within it. An FDG-PET-scan was available for 32 patients and showed FDG-uptake in 94% of cases.

Table 2 gives details of the procedures performed. EBUS-TBNA was performed as an out-patient procedure in the majority of cases. Local anaesthesia or moderate sedation was administered in 54

Table 2
EBUS-TBNA: procedural characteristics and yield

EBUS-TBNA outpatient, *n* (%)	
Yes	58 (97)
No	2 (3)
Anaesthesia, *n* (%)	
Moderate sedation (midazolam)	50 (83)
General anaesthesia	6 (10)
Local anaesthesia only	4 (7)
Scope time (min); median (range)	21 (10–60)
Primary lung lesion characteristics, *n* (%)	
Lesion observed	60 (100)
Lesion punctured	58 (97)
Pathology EBUS-TBNA sample, *n* (%)	
Malignant, non-small cell carcinoma	35 (58)
Malignant, small cell carcinoma	11 (18)
Suspicious for malignancy, but insufficient for diagnosis	4 (7)
Not representative; benign	8 (13)
No cytology obtained	2 (3)
Complications, *n* (%)	
None	57 (95)
Patient intolerance with procedure being abandoned	2 (3)
Self-limiting atrial fibrillation	1 (2)

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