Isolated mediastinal lymphadenopathy – performance of EBUS-TBNA in clinical practice

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Abstract

Background Isolated mediastinal lymphadenopathy is an increasingly common finding as a result of the increasing use of cross-sectional thoracic imaging. We investigated the performance of endobronchial ultrasound-guided transbronchial needle-aspiration (EBUS-TBNA) in establishing a pathological diagnosis in patients with isolated mediastinal lymphadenopathy.

Methods We retrospectively analysed all consecutive EBUS-TBNA examinations performed over a 4-year period at a single tertiary referral centre. Final diagnoses were made using pathology reports, correlated with clinical features and the results of any other investigations.

Results In total, 126 EBUS-TBNA examinations were performed to investigate isolated mediastinal lymphadenopathy. A positive pathological diagnosis was made following EBUS-TBNA in 54 cases (43%). When the results of further investigations and variable radiological follow up were included, the final sensitivity of EBUS-TBNA for making a diagnosis in isolated mediastinal lymphadenopathy was 80% (95% CI 69%–89%).

Conclusions This study confirms that EBUS-TBNA has acceptable sensitivity for detecting both benign and malignant pathologies underlying isolated mediastinal lymphadenopathy.

Keywords endobronchial ultrasound, lung cancer, mediastinal lymphadenopathy, sarcoidosis

Declaration of interests No conflicts of interest declared

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Introduction

Isolated mediastinal lymphadenopathy (IML) is an increasingly common finding as thoracic cross-sectional imaging is used with increasing frequency. IML comprises a heterogenous group of conditions with varying aetiology including occult metastatic malignancy, benign granulomatous disorders, lymphoproliferative disorders and reactive lymphadenopathy that may relate to underlying conditions such as interstitial lung disease or rheumatological disorders.[1] Patients identified as having IML on imaging will have a provisional diagnosis formulated upon clinical and radiological features; however, there is often a need to establish a tissue diagnosis before proceeding with management. These patients are commonly referred to respiratory services for further investigation.

Surgical mediastinoscopy has previously been regarded as the 'gold standard' for obtaining tissue to make a pathological diagnosis in mediastinal adenopathy. However, this technique does not allow access to all lymph node stations and is associated with significant morbidity as it is performed under general anaesthesia.[2] The utility of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) as an alternative to conventional mediastinoscopy for the diagnosis and staging of patients with suspected lung cancer has been firmly established.[3,4] EBUS-TBNA is a technique that utilises endoluminal ultrasound technology during bronchoscopy to identify lymph nodes that are amenable to sampling using transbronchial needle aspiration. Patient selection for this procedure is similar to that for conventional bronchoscopy (FEV1 > 1.0 L, oxygen saturations > 90% on room air and no coagulopathy or other contraindications to needle sampling) and the procedure can be performed under sedation as opposed to general anaesthesia. Recent studies have demonstrated superior sensitivity, cost savings and shorter time to treatment that may translate to a survival benefit when EBUS-TBNA is pursued as a first-line investigation for the investigation of non-small cell lung cancer.[5]

There is limited evidence on the performance of EBUS-TBNA in the investigation of IML in routine clinical practice.

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Figure 1. Aspirates obtained following EBUS-TBNA

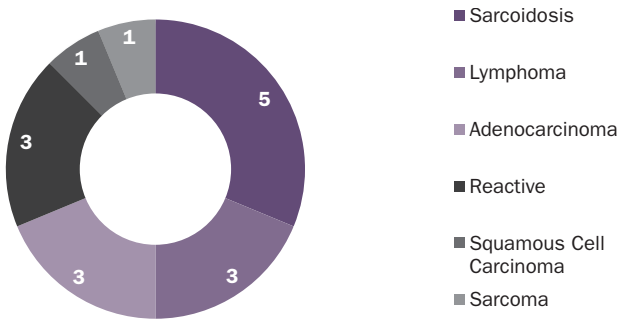


Figure 2. Malignant diagnoses identified with EBUS-TBNA aspirates. NSCLC, Non-small cell lung cancer

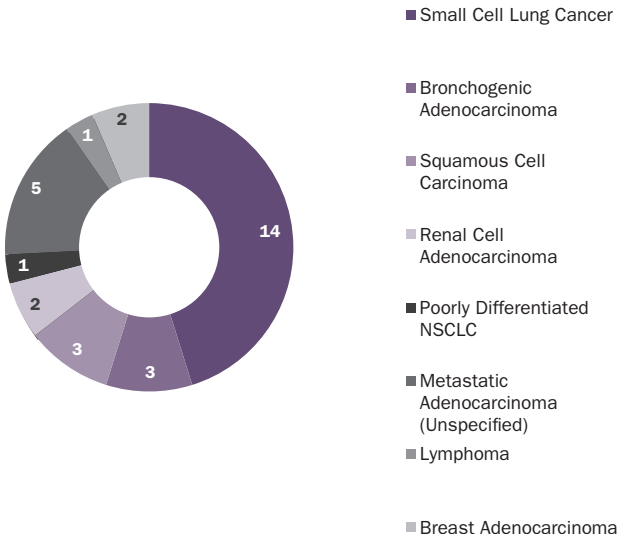
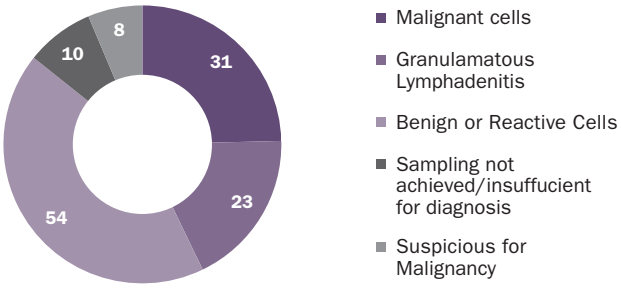


Figure 3. Diagnoses following further investigations in causes with non-diagnostic EBUS-TBNA



Some evidence supports the utility of EBUS-TBNA in investigating IML with reported sensitivities of EBUS-TBNA ranging from 82.7%–92%.[1,6] Individual studies have reported variable sensitivity of EBUS-TBNA according to the aetiology of IML, including 83–85% in sarcoidosis and 38% in lymphoproliferative disorders.[7–9] Our aim was to assess the diagnostic yield of EBUS-TBNA for IML in a consecutive patient series. We report the requirement for subsequent investigations (including mediastinoscopy) and follow-up strategies in cases where EBUS-TBNA yielded non-diagnostic samples.

Table 1. Patient demographics (n = 126)

Median age (years) (IQR)	60 (41–70)
Male sex (%)	87 (69)
Smoking status	
Non-smokers (%)	52 (41)
< 10 pack year exposure (%)	19 (15)
> 10 pack year exposure (%)	40 (32)
Not available (%)	15 (12)
Ethnicity	
White (%)	115 (91%)
Black African (%)	2 (2%)
South Asian (%)	8 (6%)
Other (%)	1 (1%)

Methods

Sequential EBUS examinations performed over a 4-year period from January 2011 to December 2014 at the Royal Infirmary of Edinburgh – a tertiary referral centre – were retrospectively reviewed. Referrals for EBUS examinations were accepted from a range of specialties. Procedures performed for the staging of lung cancer or for the investigation of a known/suspected primary malignancy (identified on prior cross-sectional imaging) with associated mediastinal lymphadenopathy were excluded from analysis. Patients were defined as having IML if they had mediastinal or hilar lymph node enlargement (either in single or multiple lymph node stations), without the presence of an obvious associated malignancy or alternative causation at the time of investigation.

All patients had a pre-sampling CT scan of the thorax. Mediastinal lymph nodes were classified according to the International Staging System. All cases that proceeded to EBUS-TBNA had a minimum lymph node diameter of > 10 mm. All procedures were performed or supervised by one of two lead lung cancer physicians. Intubation was performed via the oral route and sedation was achieved with intravenous midazolam and alfentanil. EBUS was performed with an Olympus BFUS 260 endoscope and 22-gauge cytology needle. Images were achieved with an Olympus Prosound 10 ultrasound machine. Sonographic nodal characteristics and number of passes were not recorded. Nodal samples were transferred into 'Cytolyt' fixative and processed, utilising a 'thin layer' technique and subsequent cell blocks as previously described.[10] Further sections from cell blocks were stained histochemically or immunohistochemically as indicated by the features identified.

A final diagnosis was made using a combination of cytopathology from EBUS-TBNA, imaging findings and the clinical picture at presentation and follow-up. In cases where a pathological diagnosis was not obtained following EBUS-TBNA, the decision to organise further investigations was made by the referring teams. Referring teams made a final diagnosis based on any additional pathology, clinical features and multidisciplinary team decision. Information on further

Table 2. Summary of further investigations and final diagnosis according to initial cytology following EBUS-TBNA

Initial cytology	Diagnostic category; Number that underwent further investigations	Further investigation	Pathological diagnosis
Non-diagnostic	Suspicious for malignancy (8); five underwent further investigations	Surgical resection (1)	Sarcoma
		Core biopsy of peripheral lymph node (1)	Lymphoma
		Bone marrow biopsy (1)	Lymphoma
		Fibreoptic bronchiscopy at 3 months (1)	Squamous cell carcinoma
		EBUS-TBNA at 6 months (1)	Adenocarcinoma
	Ten underwent further investigations	Lymph node biopsy (1)	Lymphoma
		Mediastioscopy – non-diagnostic (1) followed by VATS biopsy	Reactive lymphadenopathy – inflammation and fibrosis with *Aspergillus* colonisation
		Mediastinoscopy (1)	Reactive lymphadenopathy - sinus histiocytosis
		Mediastinoscopy (2); 1 mediastinoscopy was non-diagnostic	Sarcoidosis
		VATS biopsy (1)	Lepidic adenocarcinoma
		EBUS (1)	Adenocarcinoma
		EUS (1)	Reactive
		EUS-B (1 – non-diagnostic)	Sarcoidosis (clinical diagnosis)
		Skin biopsy (1)	Sarcoidosis
Insufficient/No nodal sampling	Two underwent further investigations	Mediastinoscopy (1)	Sarcoidosis
		Skin biopsy (1)	Sarcoidosis

VATS, video-assisted thorascopic surgery; EUS, endoscopic ultrasound fine-needle aspiration; EUS-B, endoscopic ultrasound fine-needle aspiration with an endobronchoscope

investigations and radiological follow-up were obtained from a review of medical records. Statistical analyses were performed using GraphPad Prism software; 95% confidence intervals for sensitivity and specificity are 'exact' Clopper-Pearson confidence intervals.

Results

A total of 826 EBUS examinations were performed during the 4-year study period. Of these, 700 were excluded from this analysis following identification of radiologically evident primary malignancy. The remaining 126 patients were classified as having IML and were included in this analysis. Median age was 60 years and 87 patients (69%) were male. Patient characteristics are summarised in Table 1.

Results from EBUS-TBNA aspirates are summarised in Figure 1. A clear pathological diagnosis was achieved following EBUS-TBNA in 54 cases (43%). EBUS-TBNA aspirates yielded benign or reactive lymphoid cells, not confirming a pathological diagnosis, in 54 cases (43%) while nodal sampling was insufficient or not achieved in 10 cases (8%).

Malignant disease

A total of 41 patients (33%) had a final diagnosis of malignancy in our dataset (Figure 2). EBUS-TBNA yielded samples diagnostic of malignancy in 31 cases (25%). Features suggestive of, but not diagnostic for malignant disease were identified following EBUS-TBNA in 8 cases (6%) and further investigations were performed which confirmed the diagnosis of malignancy in 5 of these patients (two further patients received a consensus clinical diagnosis of malignant disease and one patient initially identified as having an EBUS-TBNA sample suspicious for malignancy was diagnosed with a viral myocarditis) (Table 2). Three further cases of malignancy were diagnosed following further investigations in patients where EBUS-TBNA yielded aspirates containing benign or reactive cells only.

A final diagnosis of lymphoma was made in four patients. EBUS-TBNA provided a pathological diagnosis of lymphoma in one case, suggested this diagnosis in two cases (who went on to have further investigations) but missed a diagnosis of lymphoma in one case.

Granulomatous lymphadenitis

Granulomatous lymphadenitis was identified in 23 cases (18%) following EBUS-TBNA. Sarcoidosis was the final diagnosis in 19 (83%) of these cases, with one patient having a confirmatory mediastinoscopy after EBUS-TBNA. The remainder of the diagnoses were mediastinal tuberculosis (negative tuberculosis culture, clinical diagnosis) and idiopathic interstitial pneumonia (sarcoidosis was the initial differential diagnosis considered but a consensus diagnosis of idiopathic interstitial pneumonia was made on review of imaging). One patient underwent radiological follow up and one patient was lost to follow up.

Samples where pathological diagnosis was not achieved

EBUS-TBNA did not yield a clear pathological diagnosis in 72 cases (57%). Further investigations to ascertain the diagnosis in these cases were performed in 16 cases, of which five were mediastinoscopies (Table 2). Further investigations in cases with non-diagnostic samples yielded a pathological diagnosis in 13/16 (81%) of these cases (Figure 3).

The remaining 59 cases (47%) were deemed to have reactive lymphadenopathy and underwent a combination of further investigations or radiological follow-up with CT chest or positron emission tomography. Of these patients, three underwent repeat fibreoptic bronchoscopy and one underwent EBUS but these procedures did not yield a clear diagnosis.

Performance

Ideally, the sensitivity of EBUS-TBNA would have been assessed against the accepted gold standard (mediastinoscopy) as a comparator. Given that not all patients in this cohort underwent further investigations, we adopted a pragmatic approach towards a sensitivity calculation.

A 'True Positive' was accepted as the ability of EBUS-TBNA to identify a pathological diagnosis when there was one apparent (e.g. malignant cells or granulomatous lymphadenitis in sarcoidosis). 'True Negatives' were deemed to be cases of reactive lymphadenopathy where EBUS-TBNA identified cytologically benign or reactive lymphoid cells only. The sensitivity of EBUS-TBNA for a diagnosis in our cohort was 80% (95% CI 69%–89%), including cases where nodal sampling was not achieved.

Discussion

Our study confirms that EBUS-TBNA has a good yield for both benign and malignant pathologies resulting in IML and should be considered as a non-invasive alternative to mediastinoscopy, particularly in cases where lymphoma is considered less likely. A significant proportion of patients in our cohort had a final diagnosis of malignant disease indicating that occult malignancy is an important cause of mediastinal lymphadenopathy. Malignant disease was identified in eight cases where EBUS-TBNA failed to achieve a pathological diagnosis (including three cases of lymphoma), highlighting the importance of further investigations to obtain a pathological diagnosis where malignancy is suspected even when fine needle aspiration cytology is negative.

A particular difficulty encountered with the use of EBUS-TBNA in the investigation of IML is the high prevalence of 'non-diagnostic' samples, where only benign or reactive cells are obtained following cytological examination. Reactive mediastinal lymphadenopathy is relatively common and samples obtained in these cases are difficult to differentiate from low-grade lymphoma. This presents a dilemma to clinicians and may necessitate further investigations in cases where samples from EBUS-TBNA are non-diagnostic. Strategies employed to overcome the problem of non-diagnostic samples following EBUS-TBNA in published studies range from mediastinoscopy in all patients (as a comparator or gold standard) to clinical and radiological surveillance.[1,6] These patients formed part of a 'trial population' and were able to undergo both EBUS-TBNA and/or mediastinoscopy as a comparator. However, this is not always the case in clinical practice due to patient fitness and preference. Seventeen of our patients underwent further investigations, five of which were mediastinoscopies. It can be assumed that diagnostic EBUS-TBNA helped avoid mediastinoscopy in a proportion of patients in our cohort. In our cohort, patients with non-diagnostic samples who did not undergo further investigations underwent radiological follow-up or were followed up by the referring clinical teams. There was variability in modality used (chest CT or PET-CT) and duration of follow-up.

In our unselected series, the overall sensitivity of EBUS-TBNA to yield a pathological diagnosis was 80%, comparable to the sensitivity reported by other studies: 92% by Navani et al,[6] and 83% by Evison et al.[1] The large number of negative examinations in our cohort could be attributed to the high proportion of patients with reactive lymphadenopathy; similar to the proportion reported by Evison et al. (48% of whom had reactive lymphadenopathy). The mean age of our study population was 60 years compared to 59 years in Evison et al., providing further evidence of an association between increasing age and reactive lymphadenopathy.[1]

The retrospective nature of our study limits our ability to correct for selection bias. Patient age was a likely determinant in the low threshold for referral for EBUS-TBNA compared to the threshold for referral for subsequent mediastinoscopy when pathology from EBUS-TBNA was non-diagnostic (only five in our cohort). The retrospective nature of our study also limited our ability to access information on the rationale behind follow-up strategies pursued by referring teams. Generally there was wide variability between the decision to pursue further investigations or pursue a surveillance strategy using cross-sectional imaging. We believe this is reflective of current clinical practice but would have preferred to have been able to report the rationale behind these decisions. The lack of a comparator such as mediastinoscopy in patients with non-diagnostic samples limits our interpretation of the performance of EBUS-TBNA, allowing us to report an

estimated sensitivity but not a specificity, negative or positive predictive values. Given the variability in the decision to pursue further investigations or surveillance, it is possible that some pathological diagnoses may have been missed and reactive lymphadenopathy may have been overdiagnosed.

The requirement for further investigation and/or surveillance following non-diagnostic cytology from EBUS-TBNA should be reviewed on a case-by-case basis in collaboration with referring teams in a multidisciplinary forum. When practical, tissue diagnosis should be pursued, particularly if there are concerns that the diagnosis could be malignancy. A more clearly defined surveillance strategy to standardise follow-up cases where a tissue diagnosis is not obtained is advisable. This could mirror the strategy used to follow up pulmonary nodules identified on cross-sectional imaging of the chest. Future work focusing on performance of surveillance strategies following non-diagnostic EBUS-TBNA would aid the development of a comprehensive and safe strategy for the investigation and management of IML.

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