Clinical Impact of EUS-FNA of Mediastinal Lymph Nodes in Patients with Known or Suspected Lung Cancer or Mediastinal Lymph Nodes of Unknown Etiology

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Abstract

Introduction: Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) of mediastinal lymph nodes (LNs) has emerged as a valuable minimally invasive tool for staging. The objective of this study was to determine the accuracy of EUS-FNA of mediastinal LNs in patients with known or suspected non-small cell lung cancer (NSCLC) or with mediastinal LNs of unknown etiology and review its clinical impact.

Methods: A review was performed on 107 consecutive patients. If malignant cells were identified by EUS-FNA, the result was accepted as a true positive. When cytology was non-malignant, results were compared with the final surgical pathology.

Results: Of 79 patients with known or suspected lung cancer who had mediastinal LNs, 69 patients underwent EUS-FNA. Thirty-two received a definitive diagnosis with EUS-FNA and did not undergo further workup, while 37 patients had benign (33) or non-diagnostic FNAs (4); 26 patients further underwent surgical staging. Sensitivity, specificity, and accuracy for EUS-FNA of mediastinal LNs in patients with known or suspected lung cancer was 82.35%, 100%, and 90% respectively. The negative predictive value was 80% and the positive predictive value was 100%. There were 20 patients with suspicious mediastinal LNs of uncertain etiology, with a definitive diagnosis being made using EGD/EUS-FNA in 95%. Conclusion: Our data supports the use of EUS-FNA in the work-up of enlarged mediastinal LNs on cross sectional imaging, thus avoiding more invasive mediastinal sampling procedures and potentially futile surgery.

Key words


Introduction

Lung cancer continues to be the number one cause of cancer related death for both men and women in the United States, consequently causing a significant economic burden [1, 2]. Prognosis and management of non-small cell lung cancers (NSCLCs) are dependent on accurate staging, especially for metastatic lymph nodes (LNs). Mediastinal LNs are the primary site of metastasis in 75% of patients with NSCLC [3]. Mediastinal LNs metastasis is found in about 28% to 38% of NSCLCs at the time of diagnosis [4-6]. Routinely used mediastinal imaging studies like computed tomography (CT) scan and positron emission tomography (PET-CT) scan lack sensitivity and specificity to accurately predict mediastinal LNs metastasis and has false positive rate as high as 39% [7-14]. These non-invasive methods are not reliable in accurately diagnosing metastasis, and given the high false positive rates, pathologic confirmation of suspicious mediastinal LNs is required to select patients for surgery with curative intent or stage-specific treatments [15]. Traditionally used methods like CT guided percutaneous trans-thoracic needle biopsy and trans-bronchial needle aspiration lack good accuracy to diagnose mediastinal LNs metastasis and also has high rate of serious complications like pneumothorax [16, 17]. CT guided trans-thoracic needle aspiration carries a 30% risk of pneumothorax with 15% ultimately requiring chest tube placement [16]. Given the low accuracy and high complication rate of these methods, mediastinoscopy and/or thoracoscopy remain the gold standard for sampling the mediastinal LNs. However, mediastinoscopy is invasive, costly, requires general anesthesia with intubation, and has a reported complication rate of 1.6% [18]. Also, mediastinoscopy is limited by the fact that it can only evaluate the pretracheal, paratracheal,
and subcarinal areas [18]. The ipsilateral mediastinum can be visualized with thoracoscopy but this requires single lung ventilation, multiple incisions, and cannot access contralateral nodes.

In the last two decades, endoscopic ultrasound (EUS) with fine needle aspiration (FNA) and endobronchial ultrasound (EBUS) with FNA have emerged as valuable alternative to evaluate mediastinal LNs and tumor masses [19]. EUS-FNA is a minimally invasive procedure that can be performed safely in the outpatient setting. Several studies involving patients with lung cancer demonstrate a sensitivity and specificity of EUS- FNA in detecting metastases to the posterior mediastinal LNs of 88-96% and 80-100%, respectively [20-27]. In patients with enlarged mediastinal LNs on CT who would otherwise be candidates for mediastinoscopy or thoracoscopy, EUS-FNA was able to confirm advanced (stage III or IV) disease, thus avoiding surgical staging in up to 70% [21-24, 28-30].

The present study represents a descriptive analysis that investigates the clinical impact of EUS-FNA in the management of patients with mediastinal LNs and determines the nature and clinical consequences of false negative results.

**Study design**

**Objectives**

The primary objective of this study was to retrospectively determine the accuracy of EUS-FNA of mediastinal LNs in patients with known or suspected lung cancer, as well as mediastinal LNs of unknown etiology. The study reviewed clinical impact of EUS-FNA in a single multidisciplinary tertiary referral institution with a prospectively maintained EUS database. Secondary objectives included complication rate, feasibility of EUS-FNA in diagnosing non-malignant diseases, and diagnostic yield of EUS-FNA as a single test for the diagnosis and staging of lung cancer.

**Patients and methods**

The institutional review board at the University of Texas Medical Branch, Galveston, TX approved this protocol. All EUS and EUS-FNA procedures were performed by one expert endosonographer (MSB). Between October 19th, 2001 and November 29th, 2006, 1197 EUS procedures were performed for a variety of clinical indications. Patients were followed for a minimum of 6 months to confirm all data as final. A retrospective chart review of these reports was undertaken to identify patients with known or suspected lung cancer with mediastinal LNs, as well as mediastinal LNs of unknown etiology. Information about all eligible patients undergoing EUS and EUS-FNA was entered into a spreadsheet. Data recorded from the EUS report included patient demographics; referring physician; procedure indication; the location, size, shape and sonographic features of the lesions sampled; and the number of passes made. A chart review was performed to determine the adequacy of the sample, procedural complications, and final diagnosis of EUS-FNA cytopathology. Previous attempts or methods of tissue acquisition were also documented. The final diagnostic and therapeutic endpoints were also recorded.

**EUS-FNA method**

A LN was selected for FNA on the basis of its appearance and the feasibility in relation to surrounding vital structures. Traditional imaging features that are suggestive of metastasis (round shape, sharp distinct borders, homogeneous hypoechoic node, and nodes greater than 10 mm in short axis diameter) are useful, but imperfect [31]. In most cases, a linear array echoendoscope was directly inserted into the esophagus without previous radial EUS. On a few occasions, a radial echoendoscope was introduced first to identify any LNs amenable to FNA. The 22 gauge EUS FNA needle with stylet [Echotip ultrasound needle (Wilson-Cook, Winston-Salem, NC)] was introduced into the working channel of the echoendoscope. Doppler was used to identify any adjacent or intervening vascular structures. The needle was then introduced into the mediastinum, taking care not to pass through any intervening vascular structures. After slight retraction of the stylet, the lymph node was punctured (Fig. 1). The stylet was then completely removed, and suction was applied to the hub of the needle with a 10 cc syringe. The needle was moved back and forth within the lesion for 30 to 60 seconds while monitoring the needle movement on the ultrasonic screen. Aspiration was terminated if blood became visible in the syringe. When aspiration was completed, suction was released, and the needle was withdrawn back into the sheath, and the whole catheter system was removed from the biopsy channel. The aspirated material was sprayed onto glass slides and fixed in formalin for cytopathologic evaluation. Multiple passes were only made if the in-suite cytopathologist determined there was not acceptable cellularity for interpretation. If a new node was sampled, a different needle/catheter assembly unit was used.

![Fig 1. Using a linear scanning echoendoscope, a needle is passed into the targeted LN. Arrow points to tip of needle, LN is lymph node.](image)

**Data analysis**

Based on earlier studies demonstrating that a false positive EUS-FNA cytological result is extremely rare,
positive cytology obtained by EUS-FNA was taken as a true positive [24]. A benign EUS-FNA diagnosis was compared with the diagnosis made by surgical pathology (if resection was performed) or clinical follow-up. In the clinical follow-up group, lesions were considered malignant if there was progression of the disease or there was a response to chemoradiation. Benign lesions were confirmed by resolution or lack of progression on serial imaging for at least 6 months in conjunction with continued patient well-being as determined by chart review of clinic encounters. Where EUS-FNA was the only method of tissue acquisition, referring doctors were contacted regarding clinical progress and mortality.

Statistical analysis

Statistical analysis was performed to assess the correlation between EUS-FNA and surgical pathology reports by calculating the sensitivity, specificity, and data accuracy. The negative predictive value, the false negative rate, and the positive predictive value were also calculated. Statistical analysis was performed with SPSS, version 12 (SPSS, SPSS Inc., Chicago, IL).

Results

A total of 107 patients underwent EUS evaluation for known or suspected NSCLC or mediastinal LNs of unknown etiology. The indications for referral included known NSCLC with mediastinal LNs on CT scan, lung mass of unknown pathology with mediastinal LNs on CT scan, or suspicious mediastinal LNs of unknown etiology. Of 107 patients, 8 patients did not undergo FNA during diagnostic EUS for the reasons listed in Fig. 2. Remaining 99 patients had EUS-FNA and qualified for the analysis; 79 patients had mediastinal LNs with known lung mass on cross sectional imaging, and 20 patients had suspicious mediastinal LNs of uncertain etiology.

There were 79 patients who had mediastinal LNs with known or suspected lung cancer (Fig. 3). Fifty two patients were already diagnosed with NSCLC and 27 patients had imaging suggestive of lung cancer. Thirty-eight of 79 patients (48%) underwent a non-diagnostic transbronchial needle aspiration prior to EUS. Of the 79 patients with mediastinal LNs with known or suspected lung cancer, 69 underwent FNA of suspicious nodes. A total of 71 nodes were sampled. The nodal station that was primarily sampled was the subcarinal region (41 nodes), followed by the subaortic region (AP window) in 27, and the para-aortic region (ascending aorta or phrenic) in 3. There were no life-threatening procedure-related complications. One patient did develop chest pain after the procedure and was admitted for observation. The patient’s chest pain was self-limited and resolved with no further episodes.

In these 69 patients with known or suspected NSCLC, 28 patients were determined to have mediastinal nodal metastases by FNA and did not undergo further investigations (Fig. 3). The malignant nodes were predominantly in the subcarinal nodal station (19 nodes), with 8 being in the aortopulmonary window and 1 in the parasaophaegal/paraortic location. One patient was found to have Mycobacterium tuberculosis, 1 patient had pulmonary Nocardia, and 2 patients were found to have reactive lymph nodes secondary to pulmonary infection. Therefore, 32 of 69 patients (46%) received a diagnosis with EUS-FNA that precluded the patient from undergoing any further diagnostic workup.

Of the remaining 37 patients, 33 patients had benign LNs, 2 patients had atypical cells, and 2 patients had an unsatisfactory specimen. From these, 11 did not undergo further surgical staging: 4 patients were found to have

![Flow diagram showing breakdown of total patients enrolled in study.](image-url)
metastatic disease elsewhere deeming surgery unnecessary, 5 patients were not surgical candidates secondary to poor lung function and patient functional status, and 2 patients (already had diagnosis of lung cancer and) refused further diagnostic workup for staging but received chemoradiation with improvement of mediastinal LNs on 6-month follow-up. Another 26 patients underwent surgical evaluation of mediastinal LNs: 19 patients were found to be true node negatives, 1 patient was found to have an infection, and 6 patients were found to have nodes positive on surgical resection (with 3 having nodal metastases outside the range of the echoendoscope - 2 patients with hilar nodes, 1 with peribronchial nodes). Sensitivity, specificity, and accuracy for EUS-FNA of mediastinal LNs in patients with known or suspected lung cancer was 82.35% (95% CI, 65%-93%), 100% (95% CI, 86%-100%), and 90%, respectively. The negative predictive value (NPV) was 80% (95% CI, 61%-92%), and the positive predictive value was 100% (95% CI, 87%-100%). The false negative rate was about 10%.

In a subset analysis of the 27 patients that had mediastinal LNs with lung mass on CT scan without a tissue diagnosis (Fig. 4), a diagnosis was made in 15 patients (11 patients with metastatic NSCLC, 1 patient with Mycobacterium Tuberculosis, 1 patient with pulmonary Nocardia, and 2 patients with pulmonary infection). Therefore, the diagnostic yield of EUS-FNA as primary evaluation of patients with lung mass and mediastinal LNs on CT scan was 56%.

For the subgroup of 20 patients with mediastinal LNs of uncertain etiology, (Fig. 5), the diagnostic yield of EGD/ EUS-FNA was 95% (19 of 20 patients). Five patients did not undergo EUS, as the initial EGD prior to EUS diagnosed laryngeal cancer; esophageal cancer; and gastric cancer, in 3 different patients. One patient did not have any suspicious node on diagnostic EUS and was followed clinically. One patient had small nodes proximal to the heart and FNA was not performed due to the risk of serious bleeding. Remaining 15 patients underwent successful EUS-FNA without any complication and were found to have wide variety of diagnoses as shown in Fig. 5.

**Discussion**

This study concludes that EUS-FNA of mediastinal LNs has a high diagnostic accuracy with a high NPV and low false negative rate. Our data supports the use of EUS-FNA early in the work-up of mediastinal LNs, thus avoiding more invasive mediastinal sampling procedures. Mediastinal EUS-FNA was performed predominantly as an outpatient procedure and was well tolerated with no significant complications. Compared to minimally invasive surgical
approaches, such as mediastinoscopy, EUS-FNA requires only moderate sedation and can be routinely performed on an outpatient basis. The sensitivity of EUS-FNA for mediastinal LN aspiration in this study was 82.35%, which is comparable with the approximately 90% (95% CI, 84% to 94%) reported on a recent meta-analysis of pooled data on NSCLC staging [32]. Moreover, in patients with mediastinal LNs with known or suspected lung cancer, 32 patients (46%) received a diagnosis with EUS-FNA, thus precluding further diagnostic studies.

Most patients with mediastinal LNs associated with a lung mass usually undergo bronchoscopy (with biopsy, washing, brushing, or trans-bronchial FNA) or CT-guided FNA of the primary lung mass to determine pathology and diagnosis before EUS-FNA is performed for staging. In our study, a subset analysis was performed on 27 patients that had mediastinal LNs with lung mass on CT scan with no tissue diagnosis before undergoing EUS. A definitive diagnosis was made with EUS-FNA in 15 patients (56%) in whom therapy was accordingly started. In the 11 patients that were
diagnosed with metastatic NSCLC, a primary diagnosis and staging was performed with a single procedure, thus reducing overall costs, implementing therapy in a quicker and more efficient way, and avoiding unnecessary tests with high complication rates. CT-FNA is an accurate method for tissue acquisition; however, it can carry a risk for pneumothorax with up to 15% of these patients requiring a chest tube [16], although more recent techniques designed to create FNA access windows and minimize the risk of pneumothorax have decreased the rate of pneumothorax [33-35].

EUS and EUS-FNA has been used in the diagnosis of patients with mediastinal LNs of unknown etiology. Catalano et al followed 26 patients referred for evaluation of a mediastinal mass without a diagnosis, reporting that EUS gave a final diagnosis in 21 of 26 patients, with final diagnosis consisting of infectious causes in 5, benign/inflammatory in 9, and malignancy in 12 patients [36]. EUS-FNA had the lowest false negative rate in diagnosing malignant lesions (11 out of 12) [36]. EUS-FNA also affected subsequent workup and treatment in 73% of patients by avoiding invasive and expensive procedures [36].

Larsen et al looked at 84 patients referred with suspicious mediastinal LNs identified on CT Scan [26]. The patients had EUS-FNA followed by thoracoscopy, mediastinoscopy, or clinical follow up of at least 12 months. EUS-FNA had excellent sensitivity (92%), specificity (100%), positive predictive value (100%), negative predictive value (80%), and accuracy (94%) for the diagnosis of cancer involving the mediastinum. Eighteen of 20 malignant lesions were correctly diagnosed with no false positives for malignancy [26]. In our study, we also found a high diagnostic yield of EUS-FNA in patients with mediastinal LNs of unknown etiology found on CT scan. We found that EUS/EUS-FNA delivered a diagnosis in 19 out of 20 patients (95%), and further diagnostic workup was unnecessary.

Our study also confirms the ability of EUS-FNA to identify lymphoma and granulomatous disease despite previous reports that using a small gauge needle decreases the sensitivity of diagnosis [25]. The addition of flow cytometry enhances the diagnosis of lymphoma and the application of culture, and polymerase chain reaction (PCR) to aspirated material can confirm mycobacterial disease [37]. In our study, 3 patients with mediastinal LN of unknown etiology were found to have lymphoma. All three patients had confirmation of disease with additional samples obtained for flow cytometry. In the single patient with sarcoidosis, FNA aspirate showed non-caseating granulomatous disease. One patient with mediastinal LNs without known etiology had a diagnosis of Mycobacterium tuberculosis. This patient was started on multi drug therapy for tuberculosis after the suggested diagnosis by EUS-FNA aspirate and continued for long-term therapy after verification by cultures. We confirm that EUS-FNA should be incorporated early in the diagnostic workup of patients with mediastinal LNs of unknown etiology to preclude more invasive diagnostic approaches.

The recent availability of the linear array endobronchial ultrasound (EBUS) bronchoscope has further expanded the ability to obtain cytologic specimens from mediastinal LNs in a less invasive fashion than mediastinoscopy. Initial studies report that EBUS-TBNA is highly accurate for mediastinal staging of NSCLC [38, 39]. A recent systematic review, based on 11 separate reports, found EBUS-TBNA to have a pooled sensitivity of 93% (95% confidence interval 91% - 94%) [40]. Although EBUS-TBNA and EUS-FNA appear to be equally successful at sampling the subcarinal nodal station, nodes in the right paratracheal regions are more easily accessed by EBUS-TBNA, whereas nodes in the subaortic and left tracheobronchial angle are better sampled by EUS-FNA [40]. One advantage of EUS-FNA is the potential to biopsy nodes in the paraesophageal (level 8) and inferior pulmonary ligament (level 9) stations. Conversely, EBUS-TBNA has easy access to hilar and peribronchial nodes. For these reasons, EBUS-TBNA and EUS-FNA may complement each other and the combination may provide optimal mediastinal staging [19, 41]. Wallace et al showed that combined EUS-FNA plus EBUS-TBNA had sensitivity of 93% (95% CI, 81%-99%) and negative predictive value of 97% (95% CI, 91%-99%) [19]. Most recently Ohnishi et al showed that combined EUS-FNA and EBUS-TBNA had significantly higher diagnostic accuracy in mediastinal LNs staging of lung cancer compared to PET-CT scan (90.0% vs. 73.6%, p = 0.0001) [41].

Despite its advantages, EUS-FNA has several limitations. The technique cannot sample the anterior/superior mediastinal nodal stations given artifact from tracheal air and the limited avascular window overlying the great vessels. This can limit the staging of lung cancers that primarily drain into these nodal stations, such as the right upper lobe. Also, nodal micro-metastases may not be identified with routine cytopathologic evaluation. Future application of real time PCR techniques on EUS-FNA nodal aspirates is showing promise in diagnosing occult metastasis in mediastinal LNs [33].

**Conclusion**

Our study reveals that EUS-FNA is a safe, efficient, and effective modality for mediastinal staging in patients with known or suspected lung cancer and the diagnosis of mediastinal adenopathy of uncertain origin. EUS-FNA has the potential to significantly impact on patient management, avoiding more invasive diagnostic procedures as well as unnecessary operations. EUS-FNA could be considered as the first-line investigation for evaluating mediastinal nodal disease, particularly if the posterior mediastinal and/or subcarinal nodal stations are involved. The actual algorithm undertaken may be affected by the availability of EUS FNA, EBUS-TBNA or both at a particular institution. Future studies should help define the most cost effective sequence of these technologies.

**Conflicts of interests**

None to declare.
References


