Endoscopic Ultrasound with Fine Needle Aspiration and Biopsy in Lung Cancer and Isolated Mediastinal Lymphadenopathy

P Nadarajan, I Sulaman, B Kent, N Breslin, ED Moloney, SJ Lane
AMNCH, Tallaght, Dublin 24

Abstract
Endoscopic ultrasound with fine-needle aspiration and biopsy (EUS-FNAB) is well established in diagnosing and staging lung cancer in patients with mediastinal adenopathy. EUS-FNAB is highly sensitive, less invasive and has lower complication rates when compared to surgical staging of mediastinal nodes. In this study we describe our experience of EUS-FNAB in lung cancer and other causes of mediastinal lymphadenopathy. EUS-FNAB was performed for assessment of PET positive mediastinal lymph nodes between January 2007 and March 2009 in AMNCH. The endpoints of our study were sensitivity and specificity of EUS-FNAB, morbidity and length of hospital stay. Thirty four patients underwent EUS-FNAB during the study period for both diagnosis and staging. Thirty patients had positive lymph node invasion and 4 had no evidence of malignant invasion. In these 4 patients negative cytology was confirmed on mediastinoscopy giving EUS-FNAB a sensitivity and specificity of 100%. EUS-FNAB upstaged the disease in 12 patients. EUS-FNAB is a reliable tool for mediastinal staging in lung cancer, significantly reducing the need for surgical staging procedures in patients with suspected mediastinal involvement.

Introduction
Lung cancer is the second most common cause of cancer death in Ireland. Traditional staging system of lung cancer has emphasised the importance of nodal involvement. For example, in stage IA Non-small cell lung cancer (NSCLC), surgery has not been shown to be beneficial. Traditionally, invasive surgical mediastinoscopy has been used to stage the mediastinum in lung cancer but it has its limitations. It is an invasive procedure with higher rates of morbidity, mortality, prolonged hospital length of stay and limited accessibility to posterior and inferior mediastinal lymph node stations when compared to EUS-FNAB and this in turn limits its role in mediastinal lymph node staging in lung cancer. Furthermore, sensitivity for mediastinoscopy is only 80-90% and carries a false negative rate of 10-15%. EUS-FNAB now provides us with a safe and accurate means of accessing both the posterior and inferior (stations 4L, 5, 7, 8, 9) mediastinal lymph nodes for both diagnosis and staging lung cancer. It gives rise to an impressive NPV of 97% and 98% respectively.

The major limitation of EUS-FNAB in lung cancer staging is its inability to assess lymph nodes in the anterior mediastinum. This shortcoming however, can be overcome by the newer endobronchial ultrason with transbronchial needle aspiration (EBUS-TBNA), which is proven to be a useful modality for accessing anterior and superior mediastinal and hilar lymph nodes (stations 2, 3, 4, 10, 11). Sensitivity and diagnostic yield of EBUS-TBNA is comparable, if not better, to mediastinoscopy for these nodes (97%) compared with either method alone (95%)(3,4). The combination of EUS-FNAB and EBUS-TBNA has a higher estimated sensitivity (93%) and NPV (97%) compared with either method alone (95%)(3,4).

A prospective study of patients undergoing staging investigations for lung cancer in AMNCH was carried out over a 27-month period between January 2007 and March 2009. A total of 34 patients underwent EUS-FNAB for suspected metastatic nodal disease during this period. Patients were referred to the Respiratory service from the A&E department, outpatient referrals from other medical teams and self-referral. All patients had CT Thorax/Abdomen/Pelvis as well as bronchoscopy and/or CT/Guided biopsy of the primary lesion. In all patients underwent PET scanning as recommended in the National Institute of Clinical Excellence (NICE) guidelines for lung cancer with positive PET scans (PET+) on staging CT scan, which were PET positive, had EUS-FNAB performed after discussion at the weekly Lung Cancer Multi-Disciplinary Team (MDT) meeting. Patients were not referred for EUS-FNAB if they had a malignant pleural effusion (M1 disease), evidence of distant metastatic disease or if they were deemed medically unfit for the procedure.

The EUS procedure was performed by 2 different endoscopists from the gastroenterology service using a curved linear echo-scanendoscope Pentax EG-370UTQ for examination and FNAs under direct ultrasonic vision. The EUS-FNA was performed with Wilson-Cook 22 gauge FNA needles (Cook UK Ltd, Letchworth, UK). Biopsies were performed with Cook Quick-Core 19 gauge Trucut needle. Samples obtained were analysed in the pathology department. An average of four passes was made for FNA. Each procedure lasted between 15 and 30 minutes. No cytopathologist was present during the procedures for Rapid On-Site Evaluation (ROSE). Samples obtained were analysed in the pathology department.

Results
Of the 34 patients, 21 were male, age ranged between 55 and 82 years with a mean of 66 years (Table 1). All patients had enlarged mediastinal nodes (>10mm) on staging CT scan and PET positive (Standard Uptake Value, SUV)>2.5) mediastinal lymph nodes. 30 patients had malignant cytology following EUS-FNAB. Of these, 24 were EUS FNAB and NSCLC-2 small cell lung cancer i.e. Stage IIIB, 6 were small cell lung carcinoma (SCLC). Four of the 30 patients (13%) were diagnosed and staged in a single EUS procedure, further consolidating the value of EUS-FNAB in the diagnosis and staging of lung cancer. The remaining 26 patients underwent the EUS procedure for mediastinal staging purposes, as a histological diagnosis had been obtained via bronchoscopic biopsies (n=10) and CT-guided biopsies (n=16) prior to the EUS procedure. The 4 patients with EUS negative disease underwent surgical staging which confirmed the non-malignant cytology. These 4 cases had histology consistent with sarcoidosis. On retrospective review, the CT appearances of these 4 cases were compatible with sarcoidosis. Previous studies have shown that the morbidity from EUS-FNAB is no different from a standard gastroscopy and this in turn limits its role in mediastinal lymph node stations. This study focuses on our experience with EUS-FNAB in lung cancer and isolated mediastinal lymphadenopathy in the Adelaide and Meath Hospital, Dublin (AMNCH).

Discussion
Pathological evaluation of mediastinal lymph nodes in lung cancer is necessary to accurately stage patients and plan management. Conventional transbronchial needle aspiration (TBNA) is a limited procedure with blind needle punctures guided by stage and CT. It is highly operator dependent, and sensitivity varies between 20% and 89%. EUS-FNA is a safe, accurate and minimally invasive technique that improves the diagnostic accuracy in staging of patients with lung cancer. It is more accurate and has a higher predictive value than either the PET scan or CT scans for posterior inferior mediastinal lymph node stations. In patients undergoing thoracotomy with the intent to perform a curative resection, the addition of preoperative EUS is associated with a substantially lower rate of uncertain diagnosis (in the number of thoracotomies at which advanced inoperable disease is discovered) (4,12). A previous study found that approximately 16% of thoracotomies were avoided by the addition of EUS mediastinoscopy. When combined with EBUS-TBNA, it allows near complete access to all mediastinal lymph node stations and gives rise to an impressive NPV of 97% in approaching that of thoracotomy with mediastinal lymph node dissection.

This study shows EUS-FNAB to have a high diagnostic yield and a high level of accuracy as a primary test for the staging of lung cancer if patients with CT findings of a lung mass and mediastinal adenopathy. 88% (30/34) of cases in our study were correctly diagnosed and staged by EUS-FNAB, thus avoiding unnecessary and invasive surgical staging. The remaining 4 patients with EUS negative lymph nodes underwent surgical staging resulting in a diagnosis of sarcoidosis. This gives our study sensitivity and NPV of 100% for the study period, consistent with the general literature. It is also important to highlight the one-step approach to diagnosing and staging lung cancer that EUS-FNAB offers. Four patients in this study were diagnosed and staged in a single
EUS procedure. This would potentially minimise the number of procedures that a patient has to undergo whilst staging the posterior mediastinum to the highest level. It is also a particularly useful alternative to surgical diagnostic procedures for patients who are medically unfit. Additionally, given that EUS-FNAB is a safe procedure with minimal morbidity, 13 of these patients underwent the procedure as day case patients. This has significant impact on hospital admissions and bed occupancy.

Limitations of this study include the small sample size of 34 patients. It is possible a larger population size may have altered the sensitivity and specificity of this study. Moreover, as with any interventional procedure, EUS-FNAB has an element of operator dependency. In our study all the FNABs were performed by 2 Gastroenterologists and the anatomical site of lymph node sampling was poorly documented at the time of the procedure. A further limitation is the lack of availability of EBUS-TBNA in AMNCH. In summary, our study shows that EUS-FNAB is a safe, reliable and accurate diagnostic and staging tool in lung cancer with mediastinal adenopathy. It also highlights an additional role of EUS-FNAB in investigating isolated mediastinal lymphadenopathy. However, the possibility of false-negative cytology with FNAB remains, and it is recognised that some patients may still require a surgical staging procedure prior to definitive surgery.

Acknowledgements
We would like to acknowledge the very significant contributions of Dr Anthony O'Connor and Dr Barbara Ryan to this paper.

Correspondence: P Nadarajan
Centre for Respiratory Research, UCL, Rayne Building, 5 University St, London, WC1E 6JF, UK
Email: sanadarp2@yahoo.ie

References
11. The Diagnosis and Treatment of Lung Cancer: National Institute for Clinical Excellence: Clinical Guideline 24 February 2005