MEDIASTINAL ADENOPATHY: FINDING THE ANSWER WITH ENDOSCOPIC ULTRASOUND GUIDED FINE NEEDLE ASPIRATION BIOPSY

ABSTRACT

Background: Endoscopic ultrasound guided fine needle aspiration biopsy (EUS FNA) is a relatively new imaging modality that has been reported to be useful for mediastinal nodal staging of lung cancer and evaluation of mediastinal adenopathy of unknown cause. However, the technique is not commonly used in Australia.

Methods: A retrospective review of all patients who had mediastinal EUS FNA was undertaken. Of a total of 787 patients who had undergone endoscopic ultrasound (EUS) studies from November 1999 to March 2004, 27 patients were identified to have had mediastinal EUS FNA. Details were recorded including study indication, history of malignancy, source of referral, prior attempts for tissue diagnosis, EUS and EUS FNA findings, complications, surgical pathology if available and clinical outcome after diagnosis.

Results: Mediastinal EUS FNA was performed on an outpatient basis and no complications were recorded. Diagnostic material was obtained from all patients with a mean number of 3 passes. Nodal stations sampled included: left paratracheal, subcarinal, aortopulmonary window and inferior mediastinum. Indications for the studies included mediastinal adenopathy of uncertain cause (17), lung cancer staging (7) and GI cancer staging (3). EUS FNA confirmed malignancy in 16/27 patients, sarcoidosis in 3 patients,

tuberculosis in 1 patient and 7 patients were deemed to have reactive adenopathy. Primary cytopathological diagnosis of malignancy was determined by EUS FNA in 9 patients.

Conclusions: EUS FNA is a safe, efficient and effective modality for mediastinal staging of lung cancer and diagnosis of mediastinal adenopathy of uncertain origin. EUS FNA has the potential to significantly impact on patient management, avoiding more invasive procedures as well as unnecessary operations.

Keywords: Endoscopic ultrasound, fine needle aspiration, mediastinal adenopathy, lung cancer, metastases

INTRODUCTION

Evaluation of mediastinal adenopathy and mass lesions can be a challenging diagnostic problem. Options for tissue diagnoses include CT guided percutaneous biopsy, transbronchial fine needle aspiration, mediastinoscopy/mediastinotomy or thoracoscopy, albeit these investigations have limitations in terms of tissue yield, safety profile and cost.

Endoscopic ultrasound guided fine needle aspiration biopsy (EUS FNA) of mediastinal nodes and mass lesions is a relatively new technique of tissue acquisition which is under-utilised in Australia at present. Using a transducer mounted in the end of an endoscope which is placed in the oesophagus, EUS FNA allows access to the posterior mediastinum and tissue acquisition under

real time ultrasound guidance through the oesophageal wall. As such, EUS FNA is safe, can be done on an outpatient basis, is well tolerated and provides excellent diagnostic yield. Burgeoning clinical indications for EUS FNA include mediastinal staging of lung cancer, evaluation of mediastinal lesions and pleural fluid aspiration. We report the first series of mediastinal EUS FNA from a single centre in Australia.

METHODS

Between October 1999 and March 2004, 787 patients had undergone endoscopic ultrasound studies at our institution for a variety of clinical indications. Review of the database was undertaken to identify patients who underwent mediastinal EUS FNA.

Technique

EUS FNA was performed in an outpatient endoscopy suite. Informed consent was obtained from each patient. Conscious sedation using a combination of midazolam, propofol and fentanyl was administered by an anaesthetist. Antibiotic prophylaxis was not routinely given.

The radial scanning videoechoendoscope (Olympus GF-UM2000, Olympus Australia, Mt Waverley, VIC) is an oblique viewing instrument that provides 360 degree ultrasound imaging at a right angle to the shaft of the instrument and, when in the oesophagus, provides quality views of the posterior mediastinum. The linear scanning videoechoendoscope (Olympus GF-UC2000P, Olympus Australia, Mt Waverley, VIC) provides for imaging in the

plane of the shaft of the scope and allows for real time ultrasound guided biopsy. Generally, the radial videoechoendoscope was first used to image and characterise the mediastinal structures and then the linear scanning instrument was inserted to perform EUS FNA of the targeted lesion. On occasions, where a suspicious posterior mediastinal mass was well identified on prior CT scan, the linear scanning instrument only was used.

After localisation of the lesion, Doppler was used to identify any adjacent or intervening vascular structures. The needle-catheter system (22FG) was then inserted through the working channel of the endoscope and the needle was advanced into the lesion under real time guidance, taking care not to pass through intervening vascular structures or primary mucosal tumour when sampling lymph nodes. Following removal of the stylet, a 20ml syringe was applied to the hub of the needle and suction applied as the needle was moved back and forth within the lesion for 30-60secs. Aspiration was terminated if blood became visible in the syringe. When aspiration was complete, suction was released, the needle withdrawn into the sheath, and the catheter system removed from the biopsy channel. The aspirated material was sprayed onto glass slides for cytopathology, or a core of tissue was placed in formalin for examination as a cell block and in some cases sent for flow cytometry.

All EUS FNA procedures were performed with a cytopathology technician in the endoscopy suite so as to verify adequacy of specimens and advise as to the need for additional passes.

The patients were observed in the recovery room for a minimum of 2 hrs before discharge. Post procedural laboratory or radiological data were not obtained unless a suspected complication arose. Patients were contacted by phone in the next 24 hrs to assess if complications had occurred.

Data analysis

Information about all patients undergoing EUS and EUS FNA had been entered into a database. Data recorded included patient demographics, referring doctor, indication, the location, size, type and sonographic features of the lesions sampled, the number of passes made and the type of needles used, sample adequacy, cytological results, final diagnosis, and procedure complications. Previous or subsequent investigations (including alternate methods of tissue acquisition and PET scan results) were also recorded. The EUS FNA diagnosis was compared with diagnosis made by surgical pathology (if resection performed) or clinical follow up. In this latter group, lesions were considered malignant if there was clinical progression of the disease or there was a response to chemoradiation. Benign lesions were characterised by resolution or lack of progression on serial imaging on follow up for at least six months in conjunction with continued patient well being. Where EUS FNA was the only method of tissue acquisition, referring doctors were contacted regarding clinical progress and/or mortality.

RESULTS

Twenty seven patients underwent mediastinal EUS FNA from May 2001 to March 2004. Indications for referral including suspicious mediastinal adenopathy identified on other imaging with no firm clinical diagnosis; mediastinal staging of known or suspected lung cancer with suspicious nodes on CT scan and/or positive PET scan; and EUS staging of gastrointestinal cancers, with an incidental finding of unrecognised mediastinal adenopathy (table 1). Only 8 of 27 patients had a history of histologically confirmed malignancy. Before EUS FNA 12 patients had other procedures in an effort to acquire histological diagnoses (including transbronchial biopsy, mediastinoscopy, pleurocentesis, CT guided biopsy). Referring doctors included thoracic physicians (11), gastroenterologists (7), cardiothoracic surgeons (6), oncologist (1), general surgeon (1) and gastrointestinal surgeon (1).

Nodes were considered suspicious for malignancy according to previously published criteria: round, discrete, homogeneous and size >10mm (1). However, nodes <10mm in diameter were sampled if other suspicious sonographic features were present. The mediastinal lymph nodes sampled were mainly from the subcarinal region (19 of 27 patients), with other nodal locations being left paratracheal (4), inferior mediastinum (7) and aortopulmonary window (2) (table 2). The mean size of the sampled lymph nodes was 19mm (range, 6-80). A mean number of 3 needle passes (range, 1-6) were made into each node before the attending cytopathology technician deemed adequate tissue sampling had taken place. Sufficient material was

obtained for cytology in all patients, and in 21 of 27 for cell block. There were no procedure related complications.

Mediastinal EUS FNA confirmed malignancy in 16 of 27 patients, 4 patients had granulomatous disease and 7 were determined to have reactive adenopathy (table 3).

Of the group of patients with mediastinal adenopathy of uncertain origin, only 4 patients had a distant history of treated malignancy (melanoma, renal cell cancer, lymphoma, laryngeal cancer). EUS FNA confirmed recurrent disease in 3 of these patients, with confirmation of non-Hodgkin's lymphoma on both cytology and flow cytometry. In the patient with distant history of laryngeal cancer and emphysema, EUS FNA of subcarinal node was consistent with reactive adenopathy and on 23 month follow-up there was no progression of mediastinal nodal size on CT imaging. Of the remaining 13 patients in this group, EUS FNA identified malignant disease in 5, thereby providing the primary cytopathological diagnoses in this cohort and defining need for subsequent staging and treatment. Two of the abovementioned 5 patients had subsequent surgery (thoracotomy, laparotomy), with confirmation of EUS FNA diagnosis of invasive thymoma and metastatic gallbladder cancer respectively. Non caseating granulomata were found in 3 patients and diagnosis of sarcoidosis was afforded in conjunction with appropriate clinical histories and other investigations. In 1 patient with clinical suspicion of tuberculosis but non-diagnostic bronchoscopy, culture and PCR of aspirated

material from a calcified subcarinal node were positive for Mycobacterium tuberculosis. Of the remaining 4 patients determined to have reactive adenopathy, 1 patient was subsequently discovered to have poorly differentiated cancer in a supraclavicular node, suggesting that EUS FNA was likely to be a false negative result; another patient died unexpectedly 4 months after EUS FNA with no firm clinical diagnosis; and 2 patients remained well with no changes to mediastinal nodal features on follow-up of 6 and 7 months respectively.

In the group with known or suspected lung cancer, 6 of 7 patients were determined to have mediastinal nodal metastases and did not undergo further investigation. EUS FNA afforded a primary cytopathological diagnosis of cancer in 3 patients, whereby other investigations had not done so (including bronchoscopy, pleurocentesis and CT guided biopsy). The EUS FNA diagnosis of reactive adenopathy in the remaining patient was confirmed by subsequent thoracotomy and systematic nodal resection.

Three patients underwent routine EUS staging of gastrointestinal tumours (pancreas 2, oesophagus 1) and were noted to have mediastinal adenopathy that were not evident on CT scan. Both patients with pancreatic tumours did not have a histological diagnosis prior to the staging study. EUS FNA confirmed mediastinal nodal metastases in both patients with pancreatic tumours, such that these patients subsequently received palliative treatment only. The patient with mid oesophageal cancer was a smoker and EUS FNA of a 9mm left paratracheal node was consistent with a reactive node. The

patient subsequently received chemoradiation therapy and on follow-up of 6 months there has been no obvious mediastinal disease progression.

Only 7 patients underwent PET scanning. Of the 5 patients with positive scans, 2 were confirmed to have malignant disease by EUS FNA (SCC, renal cell cancer), 1 patient had reactive adenopathy at thoracotomy and the remaining 2 had reactive nodes by EUS FNA with no nodal changes on clinical follow-up of 6 and 23 months respectively. Of the 2 patients with negative PET scans, 1 patient proved to have metastatic small cell cancer on EUS FNA.

DISCUSSION

This study reinforces EUS and EUS FNA as an accurate and safe modality for the diagnosis of mediastinal adenopathy.

With the establishment of EUS as an integral diagnostic tool in gastrointestinal endoscopy there has been an expansion of clinical indications. Initially developed to image the pancreas it is now an important tool for staging of gastrointestinal cancers, evaluation of intestinal submucosal lesions and evaluation of the pancreatobiliary tree. The development of a linear scanning echoendoscope that allows real time ultrasound guided FNA biopsy has resulted in burgeoning of applications for EUS. An example of this is the role

of EUS FNA for mediastinal staging of lung cancer and in the diagnosis of mediastinal adenopathy of unknown origin.

The identification of mediastinal nodal disease in patients with lung cancer has a significant impact on prognosis and treatment options (2). Patients with contralateral mediastinal nodal metastases (N3) have survival rates <5% and are generally not considered candidates for curative resection. Survival for patients with ipsilateral or subcarinal disease (N2) is better, albeit influenced by number of nodes, mediastinal levels involved and histology of the primary tumour (eg SCC have better outcome following resection than those with adenocarcinoma and large cell cancer). Whilst patients with N2 disease are considered candidates for resection, many centres would treat with chemoradiation alone or consider neoadjuvant therapy. Up to 37% of patients are found to have N2 disease at the time of surgery, despite conventional preoperative staging modalities (3).

Conventional mediastinal staging modalities have limitations in terms of accuracy, tissue acquisition, safety profile and cost (4). CT scan has sensitivity and specificity of only 70-75% for detection of mediastinal nodal metastases and generally only detects nodes >1cm in diameter. CT guided percutaneous needle biopsy caries a risk of pneumothorax and is unable to access the posterior mediastinum well. Transbronchial biopsy has a sensitivity of only 55-75% and is a blind procedure that cannot access the aortopulmonary window

and inferior mediastinal nodes. Mediastinoscopy and thoracoscopy are invasive, costly and generally require hospital stay.

EUS and EUS FNA is an accurate modality for mediastinal staging of lung cancer and potentially may represent its widest use. EUS alone can identify malignant nodes readily based on morphological features but the addition of EUS guided FNA biopsy improves both sensitivity and specificity for detection of malignant nodes. Multiple studies have confirmed its superiority to CT for mediastinal nodal staging (5-8). Compared to minimally invasive surgical approaches such as mediastinoscopy, EUS FNA requires only conscious sedation and can be routinely done on an outpatient basis. Whilst formal cost comparisons have not been performed, decision analysis models suggest that EUS FNA is cost effective as compared to other diagnostic approaches including PET, mediastinoscopy and transbronchial biopsy (9, 10).

Recent reports also attest to the accuracy of EUS FNA in the evaluation of mediastinal adenopathy of unknown origin, particularly in the diagnosis of malignant adenopathy. These reports confirm EUS FNA as having a significant impact on patient management with the avoidance of invasive and costly procedures. Catalano (11) followed 26 patients who had been referred for evaluation of a mediastinal mass without a diagnosis having been made. EUS gave a final diagnosis in 21 of 26 patients; 5 with infectious causes, benign/inflammatory in 9 and malignant in 12. EUS FNA had the lowest false

negative rate in malignant lesions (diagnosing 11 out of 12). EUS FNA also affected subsequent workup therapy in 73% of patients by avoiding invasive and expensive procedures. Larsen (12) looked at 84 patients referred with mediastinal lymphadenopathy demonstrated on CT. The patients had EUS FNA followed by thoracoscopy, mediastinoscopy or clinical follow up of at least 12 months. EUS FNA had sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 92%, 100%, 80% and 94% respectively for diagnosis of cancer involving the mediastinum. Eighteen of 20 malignant lesions were correctly diagnosed with no false positives for malignancy.

As with other series, mediastinal EUS FNA was done on an outpatient basis in our institution, and was well tolerated with no recorded complications. Overall, a positive diagnosis was afforded in 20 of 27 patients with confirmation of malignancy and granulomatous disease in 16 and 4 patients respectively. The smallest node sampled that yielded a diagnosis of cancer was only 6mm in longest axis. Importantly EUS FNA was able to provide a primary cytopathological diagnosis of malignancy in 9 patients, whereby prior investigations (eg transbronchial biopsy, pleurocentesis, CT guided percutaneous biopsy) in several patients had failed to elicit tissue diagnoses and, on occasion, resulted in procedural complications (eg pneumothorax). Therefore, if incorporated early into the diagnostic algorithm for mediastinal staging of lung cancer or evaluation of mediastinal adenopathy, EUS FNA has the potential to safely provide accurate tissue diagnosis and staging

information without resorting to more invasive diagnostic procedures, including mediastinoscopy.

Whilst only a small number of patients, EUS FNA proved accurate in the mediastinal nodal staging of known or suspected lung cancer in that 6 of 7 patients proved to have metastatic disease and the 1 patient who underwent thoracotomy had confirmation of reactive adenopathy. Two patients who had no prior investigation other than CT scan underwent no further studies following EUS FNA confirmation of mediastinal disease, again highlighting the potential to avoid invasive procedures. The majority of the patients had mediastinal nodes seen on CT scan but 1 patient had confirmation of small cell cancer in a 10mm subcarinal node, not detected by CT or PET scan. The utility of EUS FNA in identifying nodal metastases has not been well defined in patients with node negative CT scans but is an area of interest with the potential of reducing the number of patients who have N2/N3 disease found only at surgery. A recent study reported that 14 of 69 (20%) patients without enlarged mediastinal nodes on CT scan had nodal metastases detected by EUS FNA (13). This would suggest that all patients with potentially operable non-small lung cancer may benefit from staging EUS FNA, regardless of whether mediastinal nodes are enlarged or not on CT scan.

Our series also confirms the ability of EUS FNA to identify lymphoma and granulomatous disease despite the use of small gauge needles. It has been reported that the technique is less sensitive for such diagnoses than for

malignant disease (14). However, the addition of flow cytometry can enhance the diagnosis of lymphoma and application of culture and PCR to aspirated material can confirm mycobacterial disease (15). In our cohort, the finding of granulomata on nodal aspirates in conjunction with appropriate clinical setting, afforded a confident diagnosis of sarcoidosis in 3 patients. Another patient with clinical suspicion of tuberculosis, proved to have positive cultures and PCR for mycobacterium tuberculosis from subcarinal nodal aspirates. As with other investigators, we believe it important that a cytopathologist/ technician be in attendance to verify specimen adequacy. For the future, the development and use of spring loaded core biopsy devices may provide larger tissue specimens that further enhance diagnosis.

From our small series it is difficult to draw any firm conclusions regarding comparative merits of PET and EUS FNA. Only 7 patients had PET scans and of the 5 patients with positive studies, 2 had cancer confirmed by EUS FNA and the remaining 3 were probably false positive results as determined by surgical resection (1) and clinical follow-up (2). One patient had a false negative study with cancer found in a small 10mm node. Nonetheless, PET scanning is increasingly used for cancer staging. Accuracy rates of 85% for detection of mediastinal nodal metastases in lung cancer have been reported for PET but is limited by false negative results in tumours with low metabolic activity or nodes <10mm in size, and by false positive results that can occur in reactive or inflammatory nodes (16). Ideally, pathologic confirmation is recommended with the finding of PET positive mediastinal nodes. In a recent

comparison of CT, PET and EUS+/- FNA for the detection of lymph node metastases, EUS FNA was found to be superior to the other two modalities in both sensitivity (94% v. 57% v. 73%) and specificity (100% v. 74% v. 83%) (17). Thus, EUS FNA has the potential advantage over PET in that the technique can identify and sample discrete nodes <10mm in size, and differentiate benign from malignant disease. Further studies are needed to better define the exact role of EUS FNA and PET scanning in this clinical setting.

Despite its advantages, EUS FNA has several limitations. The technique cannot access well the anterior/superior mediastinum nodal stations because of artefact from intervening trachea and great vessels. This can limit its utility for mediastinal staging of lung tumours that may drain preferentially to these nodal stations (eg right upper lobe lesions). Nodal micrometastases can also result in false negative cytology results particularly if using only fine guage needles, as was likely with our patient who later proved to have poorly differentiated cancer in another nodal site. However, in conjunction with improvements in needle design, future application of real time PCR techniques on EUS FNA nodal aspirates may enhance diagnoses in pathologically benign nodes (18). Perhaps more importantly, the technique is not widely utilised in Australia and there are still only a relatively small number of established EUS centres. Nonetheless, even when EUS FNA is available in centres where

thoracic oncologic surgery is performed, it is not often incorporated into staging or diagnostic protocols by thoracic physicians and surgeons. EUS and EUS FNA is also operator dependent, with a relatively steep learning curve and only limited local training opportunities. Nevertheless the technique of mediastinal EUS FNA is relatively straight forward and safe. Hopefully, with establishment of more EUS services and greater awareness of its potential, the technique can be utilized early in the diagnostic algorithm for patients with possible mediastinal disease.

In summary our series confirms EUS FNA as a safe, efficient and effective modality for mediastinal staging of lung cancer and diagnosis of mediastinal adenopathy of uncertain origin. The technique is readily able to confirm carcinoma but can also identify lymphoma and granulomatous disease. As such EUS FNA has the potential to significantly impact on patient management, avoiding more invasive diagnostic procedures as well as unnecessary operations. Whilst it is complementary to other staging and diagnostic modalities such as PET and mediastinoscopy, we believe that EUS FNA should be considered as a first line investigation for evaluating mediastinal nodal disease particularly if the posterior mediastinal and/or subcarinal nodal stations are involved.

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Table 1: Indications for Mediastinal EUS FNA

	Adenopathy of uncertain origin	Lung cancer staging	Incidental adenopathy at staging of GI cancer	Total
Number patients	17	7	3	27
Age yrs (range)	68 (33-89)	66 (58-72)	73 (68-78)	69 (33-89)
History of confirmed malignancy	4	3	1	8
Attempts at tissue diagnosis before EUS (pts)*	7	5	0	12
PET positive	3	2	0	5
PET negative	0	1	1	2

*methods included bronchoscopy and/or biopsy (10), CT guided percutaneous biopsy (3), pleurocenteses (3), mediastinoscopy (1)

Table 2: Nodal Groups sampled by Mediastinal EUS FNA

Lymph Node Location	Patient numbers	Mean Nodal Size mm (range)	Mean no. passes (range)
Left paratracheal	4	14 (9-20)	3 (1-4)
Inferior mediastinum	4	20 (6-40)	4 (2-4)
Subcarinal (alone)	14	29 (9-80)	3 (1-6)
Subcarinal + inferior mediastinum	3	8 (6-10)	4 (3-4)
Subcarinal +aortopulmonary window	2	10 (7-13)	2 (1-3)

Table 3: Mediastinal EUS FNA cytology results

Indication	Findings
Mediastinal adenopathy of uncertain origin (17)	Cancer (8): small cell (1), large cell (1), SCC (1), renal cell (1), melanoma (1), invasive thymoma (1), gallbladder (1), Non Hodgkin's Lymphoma (1) Sarcoidosis (3), Tuberculosis (1), Reactive (5)
Lung cancer staging (7)	Nodal metastases (6): small cell (3), large cell (2), SCC (1) Reactive (1)*
Incidental finding on staging of GI cancer (3)	Metastatic disease (2), Reactive (1)

* reactive nodes confirmed by surgical pathology

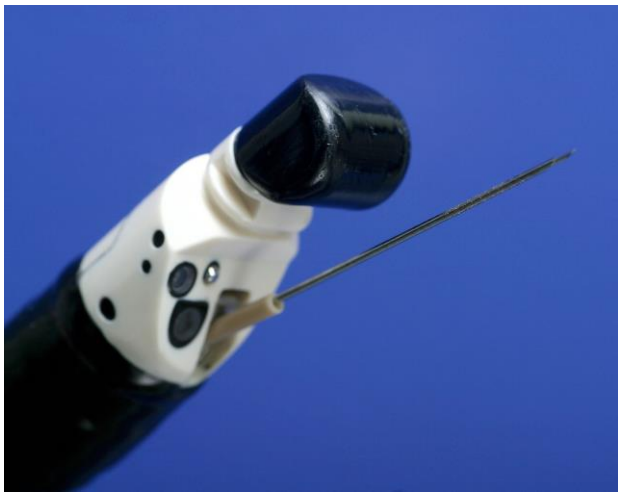

Figure 1. Linear scanning echoendoscope (Olympus GF-UC2000P) with aspiration needle extending from the working channel.

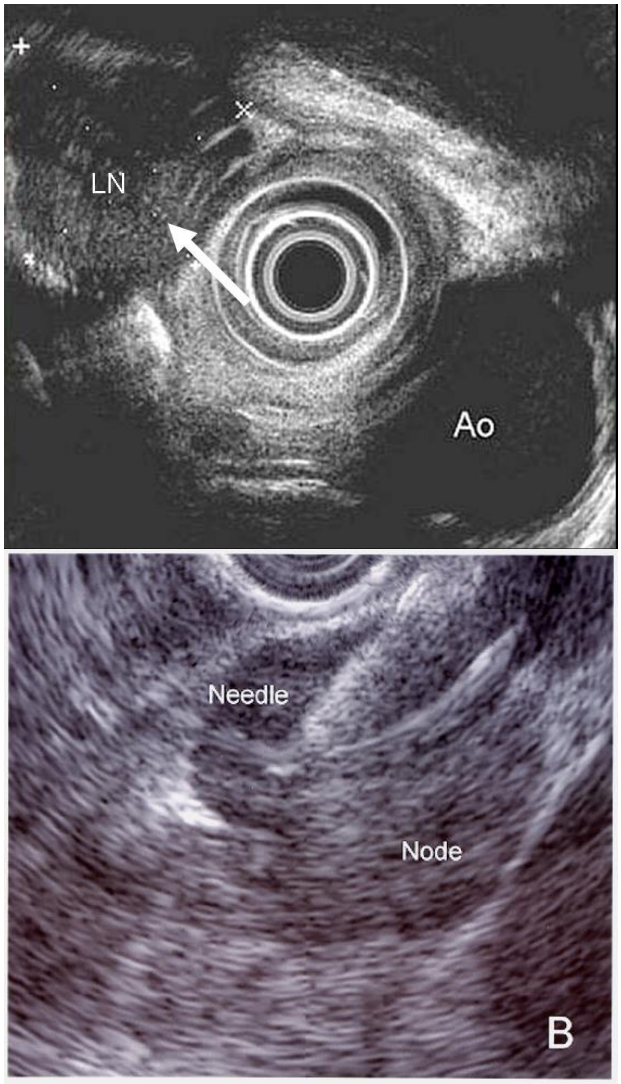

Figure 2. A. Radial image of a malignant appearing subcarinal lymph node. B. Using the linear scanning instrument a needle is passed into the targeted node.

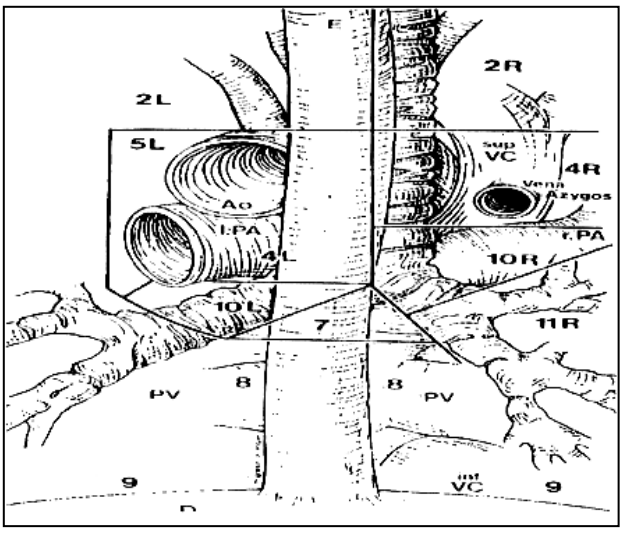

Figure 3. Posterior view of the mediastinal nodal stations as defined by the American Thoracic Society. Lymph nodes that can be sampled by EUS FNA include: subaortic (station 5), subcarinal (station 7), paraoesophageal (station 8), inferior pulmonary ligament (station 9) and left paratracheal (stations 2, 4).