Abstract

Diagnosis of indeterminate mediastinal masses and staging of lung cancer poses a significant challenge. Transesophageal endoscopic ultrasound scanning (EUS) provides high resolution imaging of the mediastinum and offers the facility of fine needle aspiration or tru-cut biopsy under real-time ultrasound guidance. Accurate diagnosis of nodal involvement in lung cancer is pivotal to avoid unnecessary surgical exploration. The reported specificity of CT, MRI or PET is insufficient to exclude patients from curative management and mediastinoscopy or thoracoscopic sampling though specific requires general anaesthesia and hospital admission in addition to carrying 2-3% morbidity. EUS has a sensitivity of 60-90% and specificity of 70-100% in staging of lung cancer. For the staging of lung cancer, EUS has been found to be superior and specific as compared to CT, PET, mediastinoscopy as well as transbronchial aspiration. In other mediastinal lesions like tuberculosis or sarcoidosis, EUS is far more accurate in characterisation and obtaining tissue diagnosis than other contemporary modalities. EUS is thus emerging as the modality of choice in staging of lung cancer and diagnosis of mediastinal lesions.

Introduction

Evaluation of mediastinal adenopathy and mass lesions can be a challenging diagnostic problem. Options for tissue diagnoses include computed tomography (CT)-guided percutaneous biopsy, transbronchial fine-needle aspiration, mediastinoscopy/mediastinotomy or thoracoscopy, but 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 and minimal invasive method of tissue acquisition. EUS FNA allows access to the posterior mediastinum and tissue acquisition under real-time ultrasound guidance

Table 1: Established Indications of EUS-FNA in Pulmonary Medicine

<table>
<thead>
<tr>
<th>Indication</th>
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<tr>
<td>Suspected lung cancer, enlarged mediastinal lymph nodes (&gt;1 cm)</td>
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<td>Diagnosis of suspected lung cancer, primary tumor located adjacent to the</td>
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<td>esophagus</td>
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<td>Mediastinal staging of NSCLC in CT lymph node negative patients</td>
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<td>Mediastinal involvement suspected by PET</td>
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<td>Assessment of tumor invasion (T4) in centrally located tumours</td>
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<td>Mediastinal restaging after induction chemotherapy</td>
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<td>Diagnosis of sarcoidosis and TB</td>
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<td>Diagnosis of the unknown mediastinal lesion or lymph node</td>
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<td>Left adrenal mass in a lung cancer patient</td>
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Instruments and Procedure

A wide range of dedicated EUS endoscopes with linear transducers suitable for monitoring of a needle during biopsy is available (Figure 1). These EUS endoscopes use frequencies between 5 and 10 MHz with a penetration at 5 MHz of around 6-8 cm. EUS-guided biopsy is performed with a dedicated needle assembly which consists of a long steel needle, a sheath and a handle for manipulation of the needle, is attached to the working channel of the endoscope (Figure 2, 3). After the lesion has been outlined and the endoscope repositioned, the needle is advanced through the oesophageal wall. Indications of EUS-FNA in the mediastinum are shown in Table 1. The aim of the present article is to review the current status of transesophageal endoscopic ultrasound-guided biopsy in the mediastinum.

Fig. 1: The distal tip of a linear scanning echo-endoscope with a fine needle (Pentax/Hitachi EG 3830 U)
Indications of EUS-FNA in Lung Cancer

Treatment of lung cancer depends on the stage of the disease so preoperative staging of non-small-cell lung cancer (NSCLC) is one of the main indications of EUS. Non-small-cell lung cancer (NSCLC) accounts for 80% of lung cancers. NSCLC usually metastasizes first to hilar and mediastinal lymph nodes (Figure 6, 7). Up to 10% of operations for NSCLC result in explorative thoracotomies without tumor resection, and an additional 25-35% of the operations are unsuccessful because of postoperative recurrent disease. Therefore surgery may be regarded as futile or unnecessary in up to 45% of patients operated, apparently because the stage of the disease is more advanced than expected preoperatively by conventional methods.

Lymph Node Staging of Lung Cancer

Lymph nodes in the mediastinum are classified according to the Mountain/Dressler classification.1 Mediastinal lymph node staging can be divided into imaging and sampling.2,3 Computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) may be used to image mediastinal lymph nodes.3 Chest CT and MRI are not recognized as proof of advanced disease, because of inadequate accuracy of these examinations.2,4 PET has a high sensitivity in detecting advanced disease. However, its specificity is too low to finally exclude patients from surgery.6 Therefore, a pathological diagnosis of mediastinal tumor spread, obtained by an invasive staging method, is necessary to avoid unjustified rejection of patients from curative surgery. Pathologic sampling of suspicious lesions can be performed by thoracoscopy, trans-thoracic fine-needle aspiration, and “blind” transbronchial fine-needle aspiration (TBNA)2 but have variable sensitivities.

Mediastinoscopy (MS) is considered as the “gold standard method” for invasive mediastinal staging, and recent guidelines recommend MS before all lung cancer resections with curative intention.5,7,8 MS is performed in the operating room under general anesthesia with a complication rate of 2-3 percent.2 In 10-15% of patients undergoing thoracotomy after a negative MS, N2-N3 disease is nevertheless ascertained.3,8 So there is a need for safer and accurate diagnostic procedure in patients suspected of mediastinal tumor growth.3 Trans-esophageal EUS gives an excellent overview of mediastinal structures5,9 and can assess mediastinal lymph nodes at most levels.
EUS-FNA and Conventional Transbronchial Needle Aspiration Biopsy

A single retrospective study in 14 patients showed that sensitivity, specificity and diagnostic accuracy of EUS in analyzing TBNA-negative lymph nodes was 100 percent.10

EUS-FNA and Mediastinoscopy

MS and EUS-FNA are often considered as complementary, MS covering the anterior- and EUS the posterior mediastinum.11 However, no studies have actually compared the two methods in a controlled and blinded design.

Larsen et al12 analysed a cohort of 60 patients with NSCLC considered for surgery that underwent both procedures. Mediastinoscopy and EUS-FNA was conclusive for para-tracheal or subcarinal mediastinal disease in 6 and 24 patients, respectively (sensitivity 24%/96%). These results suggest that mediastinoscopy is significantly inferior to EUS-FNA for staging of NSCLC patients.

EUS-FNA in CT-Negative Patients

EUS-FNA is able to demonstrate mediastinal lymph node metastases in a number of patients without enlarged mediastinal lymph nodes by CT. In 2 studies EUS-FNA demonstrated mediastinal malignancy in 10 of 24 (42%) and in four of 18 (22%) CT-negative patients respectively.13,14 These results suggest that EUS-FNA should be performed in all patients with lung cancer irrespective of the size of lymph nodes demonstrated by CT.

EUS-FNA and PET

Annema15 has evaluated EUS-FNA in 36 patients with NSCLC suspected of mediastinal involvement (N-2/N-3 disease) by PET. EUS-FNA confirmed mediastinal involvement in 25 (69%) of the patients. EUS-FNA correctly identified 25 (89%) of the 28 patients with clinically verified N2/N3 disease, EUS was suspicious in one and false-negative in two patients (sensitivity-93%). PET was false-positive in 8 (22%) of the 36 PET positive patients.

Clinical Impact Studies

A few clinical impact studies have been published. A study by Larsen et al17 including 84 patients selected for EUS-FNA by CT, evaluated the clinical impact of EUS-FNA. A board of thoracic specialists was asked to decide the further course of the patient if EUS-FNA had not been available, and this diagnostic strategy was compared with the actual clinical course after EUS-FNA. EUS-FNA demonstrated a sensitivity of 92%, specificity of 100%, PPV of 100%, NPP of 80%, and an accuracy of 94%, for cancer in mediastinum. In 18 (49%) of 37 patients a thoracotomy/-scopy was avoided as a result of EUS-FNA. In 28 (68%) of 41 patients a mediastinoscopy was avoided.

In a randomized study from Larsen et al18 with 104 patients, 53 patients were randomly assigned to routine EUS-FNA and 51 patients to a conventional strategy (CWU) including EUS-FNA if CT demonstrated enlarged lymph nodes in the mediastinum. In the routine EUS-FNA group five (9%) patients had a futile thoracotomy, compared with 13 (25%) in the CWU group, (p = 0.03), indicating that the routine use of EUS-FNA in LC staging significantly reduces the number of futile thoracotomies when compared to a conventional staging strategy.

EUS-FNA in Non-Lung Cancer Disease

A number of studies have demonstrated that other diagnoses from mediastinal lesions can be obtained by EUS-FNA. The diagnoses obtained are TB, lymphoma, sarcoidosis, histoplasmosis, metastases from other primary tumors such as renal cancer, breast cancer, gynecological cancer, esophageal cancer, gastric cancer and pancreatic cancer.
In patients with suspected sarcoidosis a tissue diagnosis is strongly recommended to exclude malignant diseases or tuberculosis, especially when treatment is considered. Biopsy specimens should be obtained from the most readily accessible organ using the least invasive method. Bronchoscopy with transbronchial lung biopsy (TBLB) is the initial technique of choice and has a yield of 65% (range 40–90%) in demonstrating noncaseating granulomas. Mediastinoscopy is the next diagnostic step after a nondiagnostic bronchoscopy. Mediastinoscopy has high yields of 82–97% in demonstrating noncaseating granulomas. Endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) is an accurate technique for the analysis of mediastinal LNs.

Fritscher-Ravens found a sensitivity of 94% of EUS-FNA in 19 patients suspected of sarcoidosis.

Annema included 51 patients with suspected sarcoidosis stage I and II. Thirty-six patients (71%) previously underwent a nondiagnostic bronchoscopy. All patients were clinically followed (median 18 months) and surgical-pathological verification occurred in those patients with EUS aspirates that contained unrepresentative material. EUS-FNA demonstrated non-caseating granulomas without necrosis in 41 of 50 patients (82%) with the final diagnosis of sarcoidosis.

Wildi et al showed in 124 patients that the sensitivity and specificity for EUS-FNA were 89% (95% CI 82 to 94) and 96% (95% CI 91 to 98), respectively. Tubercular lymphadenitis accounts for 4% to 7% of all cases of tuberculosis and is most frequently cervical in location. Intrathoracic lymph nodes are involved in only 10% of these patients. Hilar and mediastinal tubercular lymphadenitis was diagnosed in 4.4% of all patients attending a tuberculosis clinic in India. However, no large series of EUS-FNA for diagnosis of TB is at present published but studies are ongoing. In the era of drug resistant tuberculosis and acquired immunodeficiency syndrome, the importance of correct diagnosis in such cases cannot be overemphasized.

Complications

EUS-FNA is generally considered to be a safe method. Most complications reported are case studies. Barawi prospectively studied the incidence of complications associated with EUS-FNA. In 842 mediastinal EUS-FNA procedures, 1-infection, 2-hemorrhages, and 1-inexplicable transient hypotension were reported. FNA of a cystic mediastinal lesion should be avoided, or when necessary be preceded by prophylactic antibiotics.

Conclusion

EUS gives an excellent overview of mediastinal structures and has been shown to yield a diagnosis even when other invasive modalities like CT-guided FNA, bronchoscopy and mediastinoscopy are negative or inconclusive. EUS FNA of mediastinal nodes can provide a specimen adequate for interpretation in over 95% of cases and with a low complication rate of less than one percent. The specificity of EUS FNA for malignancy is close to 100% and with a sensitivity ranging between 88% and 96 percent. The role of EUS in mediastinal adenopathy due to tuberculosis needs to be evaluated further. However, it seems logical to presume that EUS-FNA will become an important method for diagnosis of TB in endemic areas with a high prevalence of this disease. As EUS is superior, safe, and less costly than other modalities, it is expected that EUS-FNA will obtain an important role in the future in India also.

References


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**ANNOUNCEMENT**

**18th Annual Conference of Hypertension Society of India (HSICON - 2009)**

*Host*: API, Magadh Division, Gaya, Bihar  
*Dates*: 10th & 11th October, 2009  
*Venue*: Hotel Royal Residency, Bodhgaya, Bihar  
*Registration*: Please send your details (Name, Address, Phone No., Membership No. of HSI or API or CSI) with Delegate fee of Rs.1,000/- only (Accompanying Person free) by Demand Draft favouring HSICON 2009 payable at Gaya.  

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**ANNOUNCEMENT**

**BHARAT**

**BASICS IN HEALTH APPRAISAL, RESEARCH AND STATISTICS**

This course is designed for post graduates, clinicians and health service researchers who want a thorough grounding in research methods and to develop life-long skills in leadership and research. It enables clinical researchers to plan, carry out, and analyze health research and evaluate the quality of research studies.  

At the end of the course you would expect to:  
• Understand the basics of research: Planning, Methodology, implementation and publications.  
• Basics of statistical methods in workshop form.  
• Be able to launch a research project – clinical or basic  
• Appraise and critique a research paper.  
• Funding.  

The course will be arranged under the auspicious of National Allergy Asthma Bronchitis Institute (NAABI) on the 4th and 5th of July, 2009.  
Interested candidates may please contact:  
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