EUS in lung cancer

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The role of GI endosonographers has undergone a major shift in the development of accurate and safe methods for mediastinal lymph node staging in patients with cancer of the lung. Although GI endosonographers are traditionally outside the field of pulmonary disease, the ease, safety, clinical impact on management, and large volume of cases (greater than esophagus, stomach, pancreas, bile duct, and rectal combined) place EUS in a central role in this disease. The following paragraphs will summarize the role of staging, accuracy, safety, and clinical implications of EUS in lung cancer.

Carcinoma of the lung is the most common cause of cancer-related mortality in the United States with an annual incidence of 170,000 cases and 154,000 deaths. Treatment strategies are largely based on histology (small cell versus non-small cell) and the presence of mediastinal or distant spread of the tumor. Accurate staging also guides prognosis and is a prerequisite for comparing therapies in clinical trials. A classification for lung cancer staging has been adopted by the American Joint Committee on Cancer. Patients without mediastinal involvement (stages I and II) are potential candidates for surgical resection. Unfortunately, nearly 50% of patients with lung cancer harbor mediastinal disease at presentation. Direct mediastinal invasion (T4) or metastasis to contralateral mediastinal nodes (N3) is classified as stage IIIB disease. Five-year survival is less than 5% and patients are generally offered chemoradiotherapy without surgery. Metastases to ipsilateral and subcarinal nodes (N2) are classified as stage IIIA disease. Management of IIIA disease is more controversial, but many centers treat with chemoradiotherapy, unless surgery is added under investigational protocols.

STAGING MODALITIES

There are multiple modalities available for the staging of lung cancer (Fig. 1). CT is noninvasive and used almost universally, but is only able to characterize the size and location of lymph nodes, resulting in a sensitivity and specificity of around 70%. CT-guided fine-needle aspiration (FNA) of the mediastinum is limited by surrounding bony and cardiovascular structures. Positron emission tomography with fluorodeoxyglucose (FDG-PET) uses differing rates of glucose metabolism to distinguish benign from malignant nodes. PET is noninvasive and has an accuracy of 85%. However, it is limited by false-negative results in tumors with low metabolic activity or in nodes less than 1 cm in size and below the resolution of the PET camera. False-positive studies occur in benign lesions with high
metabolic activity such as granulomatous disease and pneumonia.

Noninvasive staging is limited by the inability to provide a pathologic diagnosis, which is critical for making decisions regarding therapy. However, noninvasive modalities may be used to guide lymph node sampling.

Bronchoscopy with transbronchial FNA of the subcarina and hilum is a safe, well-tolerated procedure, with a sensitivity of approximately 53% to 70%. However, it is not capable of accessing the aortopulmonary window (level 5) or inferior mediastinal nodes (level 8). The prior localizing of nodes with bronchoscopic US has not been shown to increase the sensitivity of this technique. Mediastinoscopy and thoracoscopy are highly accurate methods of mediastinal staging but are costly and invasive, requiring general anesthesia. One study on mediastinoscopy for staging lung cancer reported a morbidity of 16% and one death. Mediastinoscopy is also unable to access levels 5 and 8, and it may be necessary to schedule mediastinoscopy and thoracoscopy together.

**ENDOSCOPIC ULTRASOUND**

EUS was originally developed for the local staging of GI cancers but also provides excellent access to the posterior mediastinum through the esophageal wall. Early studies described the morphology of benign and malignant lymph nodes in terms of size, shape, echogenicity, and edge characteristics. The addition of the technique of EUS-guided FNA significantly improved both sensitivity and specificity in the detection of malignant lymph nodes by EUS. Initial studies in patients with lung cancer with posterior mediastinal adenopathy by CT demonstrated the superiority of EUS-FNA over CT in the detection of malignancy with a sensitivity and specificity of 90% and 100%. In the largest reported series to date, EUS-FNA identified advanced mediastinal disease in 75 of 97 patients (77%) with carcinoma of the lung and enlarged mediastinal nodes by CT, thus avoiding further invasive staging. EUS-FNA also detected mediastinal disease in 10 of 24 patients (42%) without mediastinal adenopathy by CT. EUS-FNA also identified T4 disease in 12 patients. This study reported an overall sensitivity of 87% and specificity of 100% for EUS-FNA for mediastinal lymph nodes.

This group of patients who are “CT negative” is interesting given the ability of EUS-FNA to sample nodes as small as 3 mm and given the high incidence of metastases found in normal-sized lymph nodes in lung cancer. Surgical studies have suggested the location of the tumor may predict the presence of mediastinal lymph node metastases at certain levels. Lymphatic pathways favor spread to aortopulmonary window nodes from left upper lobe tumors and subcarinal nodes from left and right lower lobe lesions.

Staging of lung cancer by EUS-FNA is not confined to the mediastinum. Excellent views are obtained of the left lobe of the liver and a substantial portion of the right lobe. The left, but not right, adrenal gland, a common site of distant metastases in lung cancer, can be identified in 97% of patients. EUS-FNA has also been shown to be of benefit in the initial diagnosis of lung cancer. Bronchoscopic methods fail to obtain a diagnosis in up to 30% of patients. CT-guided FNA is then most commonly used but has significant morbidity (bleeding and pneumothorax) and is often deemed too hazardous when the lesion lies close to mediastinal vessels. In one study, EUS-FNA of mediastinal nodes diagnosed lung cancer in 25 of 26 such patients.

EUS-FNA is performed with the patient under conscious sedation in an outpatient setting. Typical procedure time is approximately 30 minutes, with patients discharged after a short period in recovery. The procedure is safe when compared with other tissue-sampling modalities. Many studies have reported zero morbidity with EUS-guided FNA. By using a decision-analysis model, EUS-FNA has been shown to be a cost-effective technique compared to mediastinoscopy and mediastinotomy.

**TECHNIQUE**

After informed consent and sedation, the patient is intubated with the linear array echoendoscope. It is our practice to survey those areas first, in which...
metastatic disease would result in the highest disease staging. Accordingly the liver is inspected through the duodenal bulb and lesser curve of the stomach. The left adrenal gland can be identified by first finding the origin of the celiac artery, then turning the instrument 30 degrees to the right (clockwise), looking for the typical “seagull” morphology adjacent to the left kidney. The mediastinum is surveyed by first finding the descending aorta, then rotating 360 degrees through the mediastinum until the aorta again comes into view. The instrument is withdrawn 2 to 3 cm and the maneuver repeated until the entire mediastinum has been inspected. Specific lymph node stations such as the subcarinal nodes can be found quickly by withdrawing the instrument to approximately 27 cm with the endoscopist facing the patient. Subcarinal nodes are seen immediately under the endoscope, between the left atrium and right pulmonary artery. Aortopulmonary window nodes are found by following the descending aorta cephalad to just below the arch, then torquing 90 degrees to the right (clockwise) and tipping the up-down dial in the upward direction.

EUS-FNA is performed with a 22-gauge needle equipped with central stylet (to prevent contamination on traversing the wall of the GI tract). The node is punctured under real-time US guidance and the stylet withdrawn. The needle is then moved backward and forward within the node to acquire cellular material. The specimen is injected onto a slide for preparation and viewing. An on-site pathologist is helpful to review the specimens, avoiding additional unnecessary passes if a diagnosis is obtained. Three or 4 needle passes providing lymphocytes without malignant cells are deemed sufficient to exclude malignancy in a particular node.

**LIMITATIONS OF EUS-FNA**

The major limitation of EUS-FNA in lung cancer staging is the inability to assess nodes in the anterior mediastinum. US cannot penetrate through air-filled structures, so nodes immediately anterior to the trachea (levels 2 and 4) are not well visualized. This problem can be minimized by the practice of sampling all suspicious posterior mediastinal nodes, starting with the contralateral nodes that would, if positive, denote stage IIIB disease. The status of anterior mediastinal nodes would then be irrelevant. A second limitation is the imperfect sensitivity, with approximately 13% of mediastinal disease being missed by EUS-FNA. This may be due to micrometastatic nodal disease or selective involvement of different nodes in the same group. It should be remembered, however, that the primary purpose of lung cancer staging by EUS-FNA is to avoid expensive and invasive staging procedures in those with mediastinal disease. If EUS-FNA is negative, then patients should undergo further staging procedures such as mediastinoscopy because up to 30% of such patients will have malignant nodes at mediastinoscopy when clinical suspicion is high. Finally, the limited availability of linear EUS outside of tertiary referral centers and shortage of skilled endosonographers continue to restrict the adoption of this staging modality.

**FUTURE DEVELOPMENTS**

The 5-year survival rate of patients with disease confined to the lung and hilum (stage I and II disease) is 62% and 42%, respectively. These relatively poor figures are likely due to the failure in detecting micrometastases in mediastinal lymph nodes, resulting in a proportion of these patients being effectively misstaged. Molecular analysis with real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for quantitative measurement of altered gene expression associated with malignant transformation has been used successfully in the detection of nodal micrometastases in breast cancer. Studies are currently in progress to assess the impact of this technique in lung cancer, and these show promise in increasing the sensitivity of EUS-FNA.

The development of real-time bronchoscopic US-guided FNA (BUS-FNA) promises to have a major impact in assessment of the anterior mediastinum, just as EUS-FNA has changed evaluation of the posterior mediastinum. Development to date has been restricted by technical problems in the manufacture of a suitable instrument.

The obvious major advantage of BUS-FNA will be the ability to proceed with nodal staging immediately after diagnostic bronchoscopy.

**CONCLUSION**

EUS-FNA is an accurate, safe, and cost-effective means of screening patients with lung cancer for mediastinal metastases. In patients with suspected lung cancer it is useful in providing histologic confirmation of cancer where bronchoscopy has been nondiagnostic. Novel methods of molecular analysis for detecting micrometastases and the development of real-time BUS-FNA may further improve the sensitivity of this technique.

**REFERENCES**


