EUS-guided fine-needle aspiration in the mediastinum

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The evaluation and management of esophageal and mediastinal disease has changed considerably since the introduction of EUS. EUS provides precise imaging of the histologic layers of the esophageal wall and surrounding mediastinal structures. EUS is now a well-established modality for the staging of a variety of GI and pancreaticobiliary malignancies. Furthermore, it has been reported to play an important role in the evaluation of mediastinal lesions and in the detection of metastasis to lymph nodes.1-9

Traditionally, the mediastinum has been evaluated by radiographic imaging such as CT and by invasive studies like bronchoscopy and mediastinoscopy. Evaluation of the mediastinum using EUS has been reported to be useful for a number of indications. Most notable is the assessment of enlarged lymph nodes that are detected by other imaging modalities such as CT or magnetic resonance imaging. Probably the most important indication for mediastinal imaging is the detection and/or staging of lung cancer. Documentation of lymph node involvement with metastatic disease is crucial in the staging and management of non-small cell lung cancer (NSCLC).

The introduction of the curved linear array echoendoscope approximately 8 years ago led to the development of EUS-guided fine-needle aspiration (FNA), which is now becoming recognized as an integral part of endosonography. EUS-guided FNA has been reported to be a safe and effective approach for evaluation of lymph nodes and masses in the posterior mediastinum.10-13 Tissue diagnosis from these lesions has been difficult to obtain by conventional methods such as mediastinoscopy, which is an invasive and tedious procedure, or percutaneous CT-guided puncture, which has a low yield and increased risk, especially in the case of smaller lesions.14

The objectives of this article are twofold: to discuss the clinical utility of EUS and EUS-guided FNA biopsy for evaluating the mediastinum in benign and malignant disease processes including the detection of posterior mediastinal lymph node metastases in patients with NSCLC and to describe the technique for performing safe EUS-guided FNA biopsy in the mediastinum.

EVALUATION OF MEDIASTINAL LYMPH NODES WITH EUS

The esophagus provides an important window for the evaluation of mediastinal lymph nodes by means of EUS and EUS-guided FNA biopsy. Mediastinal lymph nodes are commonly present in patients with a suspected or known pulmonary malignancy, infections such as tuberculosis and histoplasmosis, or lymphoma. However, they can also be seen in normal healthy subjects.15 Several EUS features have been used to describe lymph nodes. Size is one such criteria, with lymph nodes more than 5 mm in the short axis considered suspicious, although lymph nodes ranging from 3 to 10 mm can also be seen in normal subjects. Other descriptive criteria include shape (round versus crescent or elongated), border demarcation (sharp versus indistinct), echo intensity (hypoechoic versus hyperechoic), and echo texture (homogenous versus heterogenous). All lymph nodes, when imaged, should be described using these EUS characteristics. Although attempts have been made in the past to differentiate benign from malignant nodes using these EUS criteria, it appears that EUS-guided FNA plays a more important role with respect to this.

BENIGN VERSUS MALIGNANT LYMPH NODES

Several studies have analyzed the previous variables and have compared EUS results with histologic findings.16,17 In general, round, sharply demarcated, homogenous, and hypoechoic lymph nodes are considered malignant, whereas elongated, heterogenous, and hyperechoic lymph nodes having indistinct borders are more likely to be benign or inflammatory in nature (Figure 1). Catalano et al.,16 using univariate analysis, demonstrated that the echo pattern was the single most sensitive parameter for discriminating benign from malignant lymph nodes. Malignant lymph nodes were found on histologic evaluation in 100% of the cases in which all
four ultrasonographic features were present. It is important to note that the previously mentioned endosonographic criteria may not be evident in cases of micrometastasis.

In addition, interobserver variability has been reported because evaluation of these features can be subjective and may vary between different observers and also for the same observer on different occasions.18 Direct tissue sampling of indeterminate lymph nodes is usually required to significantly improve the specificity and sensitivity of EUS for predicting lymph node involvement. With the development of the linear echoendoscope, EUS-guided FNA is now possible. The unique viewing angle of the linear array transducer allows for real-time observation of the needle as it exits the biopsy channel and enables the endoscopist to direct the needle tip into the target lesion.

EUS AND EUS-GUIDED FNA IN THE EVALUATION OF MEDIASTINAL MASSES AND LYMPH NODES OF UNKNOWN CAUSE

It is not uncommon to detect lymph nodes in the mediastinum in patients with or without symptoms by means of routine chest x-ray evaluation or chest CT. Such lymph nodes can be either benign, caused by an underlying infection (i.e., tuberculosis, histoplasmosis) or idiopathic process (i.e., sarcoidosis), or malignant (i.e., metastatic cancer or lymphoma). EUS and EUS-guided FNA have been reported to be helpful in the evaluation of these lymph nodes. For example, Wiersema et al.19 evaluated three patients with dysphagia caused by esophageal compression from mediastinal masses. EUS was helpful in demonstrating these masses to be enlarged lymph nodes adjacent to the esophageal wall. These lymph nodes appeared hypoechoic compared with benign periesophageal lymph nodes found in individuals without symptoms.20 In addition, they contained anechoic areas that were thought to represent caseating necrosis. An EUS-guided FNA was performed in each case, and all were consistent with a reactive lymph node. The inability of FNA to diagnose histoplasmosis is not unexpected, because only 25% of resected mediastinal granulomas are found to have positive silver stains for histoplasmosis.21,22 However, the findings of reactive lymphocytes and necrosis are consistent with a granuloma. Savides et al.23 described 11 patients with dysphagia who were referred for EUS because endoscopy showed a midesophageal submucosal mass or stricture. All patients had similar EUS findings of a large mass of...
matted, posterior mediastinal lymph nodes that were adherent to a focally thickened esophageal wall. The cause was believed to be histoplasmosis, because 3 of the patients had positive complement fixation titers, and 1 had surgical resection showing caseating granuloma. The diagnosis was also supported by the EUS finding of lymph node calcification in 5 patients, and clinical improvement after oral antifungal drug therapy in 7 patients. Furthermore, none of these patients developed evidence of malignancy during a mean follow-up period of 20.5 months.

Both EUS and EUS–guided FNA have been reported to be accurate and simple diagnostic modalities for sarcoidosis. Mishra et al. described a series of 7 patients with mediastinal lymphadenopathy in whom EUS and EUS-FNA helped confirmed the diagnosis of sarcoidosis. The nodes seen were elongated, triangular, and draped around the esophagus. The long axis of the largest nodes ranged between 1.8 to 6 cm and the short axis between 1 to 4 cm. The mean number of lymph nodes detected was 2 (range 2 to 4). The nodes had discrete, well-demarcated margins. In 4 patients linear, hyperechoic, central foci were also noted. All patients had subcarinal nodes, and 6 had nodes present in the aorta-pulmonary window. EUS-guided FNA was performed in 6 patients. The findings included epithelioid histiocytes, granuloma, and noncaseating granuloma, all of which are suggestive of sarcoidosis.

Most of the experience with EUS and EUS-guided FNA in patients with lymphoma has been in the setting of primary gastric lymphoma. However, some reports have described its use in the mediastinum as well. It is imperative that in cases where mediastinal lymph nodes are suspicious and when the diagnosis of lymphoma is being considered, the endosonographer must obtain ample EUS-FNA specimens and submit a separate container for flow cytometry and immunocytochemistry. This will improve the yield of EUS-FNA and may influence diagnostic workup and treatment decisions. We recently evaluated a patient with a history of pheochromocytoma. The patient had a chest CT that showed a mediastinal mass located at the azygoesophageal recess. EUS-guided FNA was performed. Special staining of the FNA specimen proved the mass to be a benign extra-adrenal paraganglioma, which has been reported to be associated with pheochromocytoma.

THE ROLE OF EUS AND EUS-GUIDED FNA IN THE DIAGNOSIS AND MANAGEMENT OF PATIENTS WITH NSCLC

Probably the biggest area affected by EUS is the evaluation of NSCLC. Mediastinal lymph node metastases are present in nearly one half of patients with NSCLC. The presence of metastases has a significant negative impact on prognosis and is probably the most frequent obstacle to a cure, despite a localized presentation. As a result of revisions to the staging system for lung cancer, ipsilateral mediastinal and subcarinal lymph node involvement is now classified as potentially resectable (N2 disease), whereas contralateral mediastinal lymph node involvement (N3 stage) precludes resection. Presently, CT of the chest is the standard method by which mediastinal lymphadenopathy is evaluated for NSCLC metastases. Several studies have reported an accuracy ranging from 52% to 88%. Recently, promising results have been shown for EUS in detecting posterior mediastinal lymph nodes in patients with NSCLC.

Table 1 summarizes some of the studies using the operating characteristics reported for EUS-FNA of mediastinal lymphadenopathy. These preliminary data have suggested a possible role for EUS in staging this disease. Hawes et al. reported the results of EUS staging in 17 patients with NSCLC. The overall accuracy for detecting mediastinal lymph node metastasis was 71% compared with 41% for CT (p = 0.032). In a larger single-center series, Gress studied 52 patients with NSCLC. EUS had an overall accuracy of 84% for predicting metastasis.

### Table 1. The results of published data for EUS-guided FNA of mediastinal lymphadenopathy

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<th>No.</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<td>Giovannini et al.</td>
<td>24 81 100 83</td>
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<td>Gress et al.</td>
<td>24 93 100 96</td>
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<td>Hunerbein et al.</td>
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<td>Silvestri et al.</td>
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<td>Wiersema et al.</td>
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<td>Williams et al.</td>
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G Barawi, F Gress EUS-guided fine-needle aspiration S14 GASTROINTESTINAL ENDOSCOPY VOLUME 52, NO. 6 (Suppl), 2000
to lymph nodes, whereas CT had an accuracy of 49% \( (p < 0.025) \). However, 24 of these patients also underwent EUS-guided FNA. The accuracy of EUS-FNA for diagnosing metastasis to lymph nodes was 96%, and furthermore, the results of this test prompted a change in the treatment of 95% of the patients who had the procedure. Recently, Savides reported, in abstract form, the effectiveness of EUS-FNA for diagnosing lung cancer in a managed care setting. Forty-four patients were studied. The sensitivity for EUS-guided FNA in diagnosing malignant lymph nodes was 96%, the specificity 100%, and the accuracy 98%. EUS-FNA was shown to be a safe, accurate, and minimally invasive method for diagnosing and staging this malignancy and resulted in patients undergoing fewer thoracic surgical procedures.

**TECHNIQUE FOR PERFORMING EUS-GUIDED FNA OF MEDIASTINAL LYMPH NODES AND MASSES**

The preparation of the patient for EUS-guided FNA of a suspicious mediastinal lesion is the same as that used for standard endoscopy. In general, prophylactic antibiotics are not given to patients undergoing EUS-guided FNA unless recommended by the American Heart Association and/or by the American Society for Gastrointestinal Endoscopy. We have also shown in a prospective study that EUS-guided FNA is not associated with significant bacteremia or infectious complications. After obtaining informed consent, we start conscious sedation by administering droperidol (5 mg) intravenously, which is based on our previous study supporting its use as an effective presedative medication. This is then followed by meperidine and midazolam, both titrated slowly to the patient's need and tolerance. After performing an upper endoscopy to evaluate the anatomy of the esophagus, we start the EUS examination with the radial scanning echoendoscope (GFUM-2O or GFUM 130, Olympus America Inc., Melville, N.Y.). The scope is advanced into the stomach and slowly withdrawn until the celiac axis is identified. The area is examined for the presence of celiac lymphadenopathy. The probe is then slowly withdrawn to the gastroesophageal junction and then cephalad at 1 cm intervals, keeping the aorta (the landmark) at the 6 o'clock position. Images are obtained with 7.5 MHz and 12 MHz frequencies at each 1 cm interval. All mediastinal lymph nodes seen are “mapped” by location according to the American Thoracic Society classification scheme (Fig. 2).

If suspicious lymphadenopathy is seen, the radial echoendoscope is then withdrawn and the linear echoendoscope (FG36UX, Pentax Precision Instruments, Orangeburg, N.Y.) introduced. The target area is identified, the needle catheter device with the stylet in place is then advanced through the biopsy channel, and the handle mechanism is secured by the luer-lock to the accessory port. If the instrument has an elevator, the elevator should be fully released or in the down position to allow the passage of the needle without causing damage to the scope channel. The balloon is usually left inflated to some degree while the up-down control is kept in an upward position to displace the balloon behind the transducer. Suction should be applied to remove the air pocket that may interpose between the transducer and the bowel wall.

Doppler scanning can also be used as needed to identify surrounding vascular structures. When the target lesion is correctly positioned, the needle is slowly advanced 1 to 2 cm out of the catheter so that the reflection of the needle tip can be seen on the screen. The elevator can be used to gently direct the needle into the lesion. The stylet is withdrawn a few millimeters, and the needle with the stylet is pushed into the target lesion under EUS guidance. Once the needle has entered the lesion, the stylet is removed. At this time the endosonographer or his or her assistant applies suction to the catheter system using a 5 or 10 cc luer-lock syringe. Figure 3 depicts a mediastinal node during EUS-guided FNA using the linear array echoendoscope.

Typically, 5 to 10 gradual in and out movements of the needle are made within the lesion, making sure the needle is not pulled outside the lesion.
into the bowel lumen, because this will increase the risk of contamination of the aspirated specimen by luminal contents and/or epithelium. Before the needle is removed, the negative pressure is released slowly. Locking the needle will prevent accidental advancement and possible damage to the patient and/or scope. The needle is then unscrewed from the endoscope. Some have suggested using no suction when performing EUS FNA biopsy of a lymph node, because suction will result in a bloody sample that may be difficult to examine by the cytopathologist.43

We recommend having a cytopathologist present during the EUS-FNA portion of the procedure, because it can improve the efficiency of the technique. The FNA sample obtained is sprayed onto glass slides that have been labeled with the patient’s name and pass number. These slides are prepared with Diff-Quik stain (Harleco, Gibbstown, N.J.) or fixed with ethanol. In cases where lymphoma is suspected, additional material is collected in a preservative solution (Roswell Park Memorial Institute media, Buffalo, N.Y.) for flow cytometry. In addition, in patients in whom an infectious cause is suspected, a culture media can also be used. The biopsy procedure is repeated until sufficient material is aspirated.

CONCLUSIONS

EUS alone or with FNA biopsy is an accurate modality for evaluating the mediastinum and determining mediastinal lymph node metastasis in patients with NSCLC. Furthermore, EUS FNA has also been shown to be highly accurate at diagnosing unknown mediastinal masses. Numerous reports have demonstrated a role for EUS-guided FNA for diagnosing sarcoid, lymphoma, and histoplasmosis.

Based on our experience, EUS evaluation of the mediastinum and staging of mediastinal lymph nodes for NSCLC is best achieved by using radial scanning endosonography followed by EUS-guided FNA biopsy of any equivocal or suspicious lymph nodes that would affect the clinical management. Furthermore, EUS with FNA appears to provide an accurate, efficient, and less invasive method for the preoperative staging of patients with NSCLC.

We know that EUS provides accurate information about posterior mediastinal lymph nodes in patients with enlarged nodes or NSCLC. The addition of transesophageal EUS-guided FNA improves the overall accuracy of lymph node staging to 91%. It would seem that EUS with FNA is emerging as a useful modality for evaluating mediastinal lesions and for the preoperative staging of potentially resectable NSCLC where EUS appears to be capable of establishing the pathologic diagnosis of N2 and N3 disease. The ability of EUS to diagnose locally advanced disease appears to aid the clinical decisions regarding therapeutic options. It is hoped that outcome studies will solidify the clinical effectiveness of EUS and EUS FNA in the mediastinum.

REFERENCES

20. Wiersema MJ, Hassig WM, Hawes RH, Wonn MJ. Mediastinal...