Communication from the ASGE Standards of Practice Committee

GUIDELINE

Role of EUS for the evaluation of mediastinal adenopathy

This is one of a series of statements discussing the use of GI endoscopy in common clinical situations. The Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy prepared this text. In preparing this guideline, a search of the medical literature was performed using PubMed. Additional references were obtained from the bibliographies of the identified articles and from recommendations of expert consultants. When few or no data exist from well-designed prospective trials, emphasis is placed on results from large series and reports from recognized experts. Guidelines for appropriate use of endoscopy are based on a critical review of the available data and expert consensus at the time that the guidelines are drafted. Further controlled clinical studies may be needed to clarify aspects of this guideline. This guideline may be revised as necessary to account for changes in technology, new data, or other aspects of clinical practice. The recommendations were based on reviewed studies and were graded on the strength of the supporting evidence (Table 1).[1] The strength of individual recommendations is based on both the aggregate evidence quality and an assessment of the anticipated benefits and harms. Weaker recommendations are indicated by phrases such as "we suggest," whereas stronger recommendations are typically stated as "we recommend."

This guideline is intended to be an educational device to provide information that may assist endoscopists in providing care to patients. This guideline is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment. Clinical decisions in any particular case involve a complex analysis of the patient's condition and available courses of action. Therefore, clinical considerations may lead an endoscopist to take a course of action that varies from these guidelines.

Mediastinal lymphadenopathy may be detected by radiographic imaging (eg, chest radiograph, CT, or positron emission tomography [PET]) or by the presence of extrinsic compression of the esophagus detected during upper endoscopy (EGD). Malignant (eg, metastatic cancer, lymphoma), infectious (eg, tuberculosis, histoplasmosis), and systemic processes (eg, sarcoidosis) can cause mediastinal adenopathy. EUS can both identify and guide FNA of nodes. In the posterior and inferior mediastinum, EUS visualizes and directs transesophageal FNA of adenopathy. In the anterior mediastinum, endobronchial US (EBUS) visualizes and directs transbronchial FNA of mediastinal adenopathy. This guideline is an update of a previous ASGE document[2] and discusses the role of EUS and EBUS in the evaluation of mediastinal adenopathy. The role of EUS in the evaluation of esophageal cancer is discussed in a separate guideline.[3]

IMAGING OF MEDIASTINAL ADENOPATHY BY EUS AND EBUS

EUS

Radial EUS performed within the esophagus provides an image of the mediastinum similar to an axial view on a CT scan. FNA cannot be performed with the radial EUS endoscope. The linear EUS endoscope produces an approximately 180-degree image relative to the endoscope tip and allows FNA. EUS can identify lymph nodes in the posterior and inferior mediastinum. Stations 8 and 9 are accessible, as are posterior nodes at station 7 (Fig. 1). If enlarged, station 5 nodes may be accessible.[4-7] Nodes within the anterior upper mediastinum are inaccessible to EUS because air within the trachea interferes with US imaging.[8] Paratracheal nodes at station 4L are closer to the esophagus and accessible, but 4R nodes are usually not, unless enlarged.[8] Intrapulmonary nodes lie within the visceral pleura and are inaccessible by EUS.

EBUS

EBUS can identify lymph nodes in the anterior and superior mediastinum (stations 1, 2, 4, and anterior nodes of station 7) as well as intrapulmonary nodes (stations 10, 11, and 12).[9] Inferior mediastinal nodes are not in close proximity to the trachea or bronchi and are inaccessible by EBUS.

OBTAINING TISSUE FROM MEDIASTINAL ADENOPATHY

CT and PET scans can detect abnormal mediastinal lymphadenopathy, but are usually inadequate for diagnosis and locoregional staging of malignancy.[10-16] Thus, tissue sampling is often required.[13] Mediastinal tissue can be obtained by needle techniques or surgical biopsy. Needle techniques include transthoracic needle aspirate (TTNA), transbronchial needle aspirate (TBNA), EBUS-FNA , EUS-

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TABLE 1. GRADE system for rating the quality of evidence for guidelines

Quality of evidence	Definition	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate of effect.	⊕⊕⊕⊕
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	⊕⊕⊕◯
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	⊕⊕◯◯
Very low quality	Any estimate of effect is very uncertain.	⊕◯◯◯

Adapted from Guyatt et al.[1]

FNA, and EUS needle core biopsy. Surgical biopsy techniques include cervical mediastinoscopy, extended cervical mediastinoscopy, anterior mediastinoscopy, and video-assisted thoracoscopy (VATS).

Needle techniques

TTNA. TTNA can be performed by guidance of a needle by CT scan or fluoroscopy and has a sensitivity of 90% for malignancy when performed in patients with extensive adenopathy.[13,17-22] With TTNA of the mediastinum, pneumothorax requiring treatment has been reported in 10% of patients.[13]

TBNA. TBNA of mediastinal adenopathy involves the passage of a needle transbronchially during bronchoscopy. Enlarged subcarinal lymph nodes (station 7) are readily sampled by TBNA. Paratracheal nodes can be sampled as well, with highest success when extensive mediastinal adenopathy is present.[13,23-27] With TBNA, pneumothorax has been reported in 0.4% to 5.5% of cases.[22,28,29]

EBUS with FNA. EBUS is capable of imaging anterior and superior mediastinal lymph nodes and directing real-time transbronchial needle aspiration of these nodes. Hilar nodes can also be sampled. EBUS can detect and guide needle aspiration of lymph nodes as small as 5 mm.[9] Systematic reviews of EBUS report major complication rates as high as 0.05%,[30,31] including pneumothorax and respiratory failure requiring ventilation.

EUS with FNA. Linear EUS is capable of imaging and directing real-time FNA of nodes as small as 5 mm.[32] EUS-FNA of lymph nodes in the mediastinum performed in patients with suspected lung cancer has a complication rate of 0.2%.[13]

Surgical techniques

Cervical mediastinoscopy. Cervical mediastinoscopy is a surgical approach for sampling of superior and anterior mediastinal adenopathy. With the patient under general anesthesia, biopsies of nodal stations 1, 2, 3, 4, and anterior nodes of 7 can be performed.[13] Complete lymph node excision can also be performed.[33] This typically outpatient surgical procedure[34-36] has a morbidity rate of 1% to 2% and a mortality rate of 0.05% to 0.08%.[13,37]

Anterior mediastinoscopy and extended cervical mediastinoscopy. Anterior mediastinoscopy is performed to obtain biopsy samples of enlarged station 5 nodes.[13] A complication rate of 6.8%, including transient ischemia, pneumothorax, bleeding, and nerve injury, has been reported.[38,39]

Extended cervical mediastinoscopy has been less commonly performed than anterior mediastinoscopy and is another means by which station 5 nodes can undergo biopsy.[13,40-42] Extended cervical mediastinoscopy has a complication rate of 2%,[43] including stroke and aortic injury.[13,43-45]

VATS. VATS is performed with the patient under general anesthesia to perform a biopsy of, and sometimes excise, lymph nodes. Collapse of 1 lung is usually necessary; therefore, the procedure typically evaluates either the right or left mediastinum. When the left mediastinum is studied, thoracoscopy can readily access nodal stations 5 and 6. VATS readily accesses the right paratracheal nodes (stations 2 and 4), subcarinal nodes (station 7), and inferior mediastinal nodes (stations 8 and 9).[13] The morbidity of VATS is approximately 2%.[13]

EUS FOR THE EVALUATION OF MALIGNANT ADENOPATHY

Lung cancer

Lung cancer is the most frequent cause of cancer death in the United States[46] and in the world.[47] Staging and treatment of lung cancer are determined by radiologic imaging and tissue diagnosis. The American Joint Committee on Cancer stages nodal metastases with lung cancer anatomically.[48]

A CT scan of the chest with imaging of the liver and adrenal glands should be performed in patients with suspected or known lung cancer who may undergo treatment.[12] Mediastinal lymph nodes with a short-axis diameter of 1 cm or larger are considered abnormal and should raise suspicion of nodal metastases.[13] A PET scan or a combined CT/PET scan may be helpful in detecting local or distant metastases.[12]

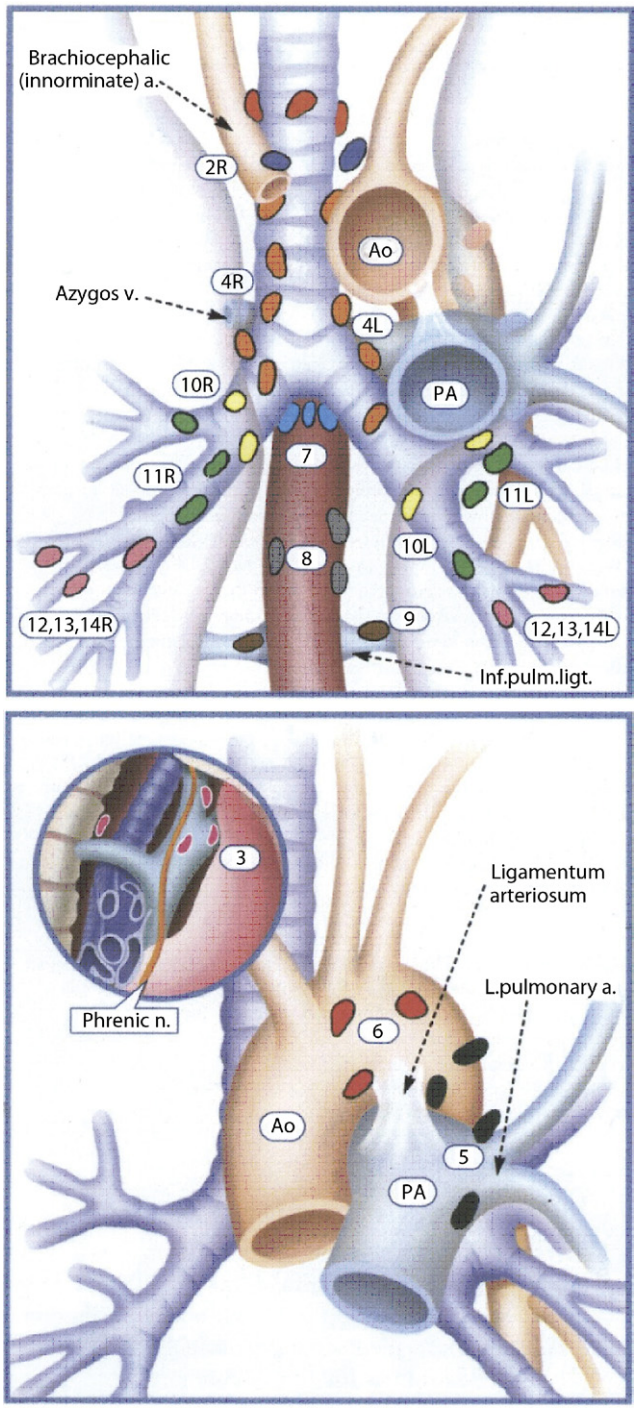

Figure 1. Mediastinal adenopathy. EUS-FNA can access stations 2, 4, 5,7, 8, and 9 (2, 4R, and 5 access is variable). EBUS-FNA can access stations 1, 2, 4, 7, 10, 11, and 12. Ao, aorta; PA, pulmonary artery. (Reprinted from Mountain and Dresler,[104] with permission.)

N1 disease is defined as tumor spread to peribronchial, hilar, and intrapulmonary nodes on the same side of the primary lesion. N2 disease involves ipsilateral mediastinal and/or subcarinal lymph nodes. N3 disease involves contralateral nodal spread. In general, patients with mediastinal nodal metastases (ie, N2 or N3) are unlikely to benefit from surgical resection.[49] However, neither CT nor PET scans are sensitive or specific enough for clinical staging of lung cancer, and diagnosis of tumor tissue or sampling of mediastinal nodes is frequently required to guide treatment.[13] Centrally located malignancies may involve the esophageal wall, which can be evaluated with EUS. A full discussion of the staging of lung cancer is beyond the scope of this document. However, EUS and EBUS have a role in assisting in the staging of patients with lung cancer.

EUS in the evaluation of lung cancer

EUS-FNA of adenopathy. In patients with lung cancer, mediastinal lymph nodes with a round shape, sharp margins, and a short axis greater than 8.3 mm are more likely to be malignant. When all 3 features are present, the probability of a malignant node is 63%.[50] However, because all features are present in only a minority of cases and image interpretation alone cannot distinguish benign from malignant nodes, FNA of nodes is recommended.[51]

When performing EUS-FNA of mediastinal adenopathy, tissue should be first obtained from sites that would provide the highest stage. Most studies of EUS-FNA of nodes in patients with suspected lung cancer were performed when imaging showed mediastinal nodes 1 cm or larger the in short-axis diameter at locations amenable to sampling by EUS.[5,8,13,52-59] In these studies, the sensitivity of EUS-FNA was approximately 90%.[13] Specificity in nearly all the studies was 100%, but these studies considered positive FNA an end point and did not verify the result. One study verified positive EUS-FNA by surgical excision of nodes. In this study, EUS-FNA had a false-positive rate of 2%.[53]

EUS with FNA is not highly accurate for staging station 5 nodes,[59] with an accuracy of only 66% in 1 retrospective series.[4] EUS-FNA of station 6 has been described, but the approach requires transaortic passage of the needle, and further study of the safety of this approach is required.[60]

EUS-FNA of distant metastases. With lung cancer, the liver and adrenal glands are common sites of distant metastasis.[61] EUS-FNA can be performed for suspected metastases of the liver,[62] and occasionally EUS will detect metastases not identified by previous imaging.[63] EUS with FNA of the left and occasionally the right adrenal gland[64,65] can be performed when malignant metastasis is suspected. EUS-FNA of the left adrenal gland in a few small series was performed without complication,[66-68] although 1 episode of hemorrhage without serious complication was reported.[69]

EUS-FNA after neoadjuvant therapy. Neoadjuvant therapy followed by surgery in patients with confirmed N2 disease and stage III non-small cell lung cancer has not shown survival benefit.[49] EUS after neoadjuvant treatment in 1 small series had a negative predictive value of 67%,[70] whereas another small series had a negative predictive value of 91%.[71] In the studies, EUS-FNA was performed in all patients, regardless of whether imaging suggested response to treatment.

EBUS in the evaluation of lung cancer

EBUS-FNA of adenopathy. In patients with lung cancer, lymph nodes imaged by EBUS that have central necrosis, heterogeneous echogenicity, round shape with distinct margin, and a short-axis diameter greater than 1 cm are more likely to be malignant[72]; the presence of 1 or more of these features may guide FNA in the mediastinum. EBUS assesses and potentially samples the same nodal stations as cervical mediastinoscopy. Studies have reported wide-ranging sensitivity (79%-95%)[13] with specificity frequently reported as 100%, but the studies do not verify positive FNA results. However, the false-negative rate of EBUS is 24%, whereas mediastinoscopy has a false-negative rate of approximately 10%.[13] Therefore, it has been recommended that negative findings on EBUS should be followed with mediastinoscopy or other surgical evaluation of nodal stations before proceeding with resection of lung cancer.[13]

Combined EUS and EBUS of the mediastinum in patients with lung cancer

Combined EUS and EBUS have been performed to evaluate the entire mediastinum without a surgical procedure. In patients with known or suspected lung cancer and an enlarged mediastinal lymph node (≥1 cm) on CT, EUS and EBUS were performed with a sensitivity of 96% and negative predictive value of 96%.[73] In this study, the prevalence of malignant mediastinal metastases was 52%.

In patients who appear to have resectable lung cancer (ie, no mediastinal adenopathy) on CT and/or PET, the prevalence of mediastinal metastases is still 20% to 25%.[12] These patients may benefit from combined EUS and EBUS. In a study in which CT showed no evidence of enlarged mediastinal nodes in patients with suspected lung cancer, EUS followed by EBUS performed in 1 setting had a positive predictive value of 91% and a negative predictive value of 91%.[74] The prevalence of malignant mediastinal metastases in this study was 22%. Another study performed EUS and EBUS in patients with suspected lung cancer who underwent CT and PET.[75] In patients in whom CT and/or PET showed mediastinal nodes (≥1 cm), the negative predictive value of combined EUS and EBUS was 100%. When CT and PET showed no mediastinal adenopathy, combined EUS and EBUS had a negative predictive value of 94%. The prevalence of malignancy was 20% in the subgroup with negative findings on CT and PET, as determined by cytology diagnosis and surgical confirmation. Patients who were not surgical candidates were followed for at least 1 year.

Cost analyses of EUS-FNA and EBUS-FNA with lung cancer

Cost analyses compared EUS-FNA, EBUS-FNA, and combined EUS/EBUS-FNA with mediastinoscopy in the evaluation of mediastinal adenopathy with suspected lung cancer.[76-78] One study suggested that EUS-FNA is more cost-effective than mediastinoscopy, provided that the location of potential mediastinal metastases is in station 5, 6, or 7.[76] A second study determined that EUS-FNA was more cost-effective than mediastinoscopy, but assumes that EUS-FNA always successfully detects and samples the abnormal node on CT scan and that 50% of mediastinoscopies are performed on an inpatient basis.[77] A third study determined that EUS-FNA is most cost-effective if the probability of lymph node metastases is less than 32%; above this, combined EUS and EBUS are preferred.[78] However, the study also assumes that 50% of mediastinoscopies are performed on an inpatient basis.

Systemic and infectious diseases

Lymphoma. Lymphoma may present with diffuse mediastinal adenopathy. EUS-FNA or EBUS-FNA of mediastinal adenopathy may be helpful in diagnosing lymphoma, particularly in patients with a previous diagnosis in whom recurrence is suspected.[79-84] Tissue samples should be sent for immunophenotyping by flow cytometry, which requires special tissue media.

Although EUS-FNA and EBUS-FNA may be helpful in diagnosing mediastinal lymphoma, the sensitivity is reported at 73% to 80%.[80-82,85] Given the limited sensitivity of these modalities, excisional biopsy should be considered when FNA is negative.[84,86] In addition, prognostic information for certain subtypes of lymphoma requires tissue architecture, which cytology is unable to provide. For example, Hodgkin's lymphoma and T-cell lymphoma are difficult to diagnosis by cytology alone.[81,87] A 19-gauge needle designed to obtain core biopsy samples by EUS may provide a histologic tissue sample for pathology review.[81,88,89] Further study is necessary to determine the yield and the role of EUS-FNA and EBUS-FNA in the evaluation mediastinal adenopathy attributed to suspected lymphoma.

Sarcoidosis. Sarcoidosis is a systemic inflammatory process of unclear etiology that causes noncaseating granulomatous disease. Bihilar mediastinal adenopathy can be found incidentally with indolent disease, and active disease symptoms include coughing, shortness of breath, fever, weight loss, and fatigue. Sarcoidosis is a clinical diagnosis made with supporting radiologic, laboratory, and, sometimes, histopathologic studies. Because nodal tissue does not provide a specific diagnosis for sarcoidosis, the role of EUS and EBUS in the diagnosis of sarcoidosis is not defined. In many cases, EUS-FNA and EBUS-FNA are performed in cases of suspected sarcoidosis to exclude malignancy.[90-98] Noncaseating granulomas are difficult to identify from cytopathology taken by FNA, although multiple passes taken for cell block may be helpful.[91] EUS with a large-bore needle to obtain histology has been described.[99]

Infection. Tuberculosis and other infections can cause systemic illness with mediastinal adenopathy. Diagnosis of infection by EUS-FNA and EBUS-FNA has been described.[100-102] When systemic infection is a possible etiology of diffuse adenopathy, specimens obtained by EUS-

FNA or EBUS-FNA should be sent for acid-fast stain and culture as well as for fungal culture. The yield of these cultures from samples taken by EUS or EBUS has not been well studied. Needle core biopsy has been described as identifying granulomas from mediastinal tissue with tuberculosis.[89] Mediastinal-esophageal fistulae after EUS-FNA of tuberculosis of the mediastinum have been reported.[103]

RECOMMENDATIONS

1. In patients with known or suspected potentially resectable lung cancer whose imaging reveals mediastinal adenopathy, we suggest that EUS-FNA be performed in patients with paraesophageal, posterior, and inferior mediastinal adenopathy, if the expertise if available. ⊕⊕○○ Similarly, we suggest that EBUS-FNA be performed in patients with paratracheal mediastinal adenopathy if this information adds to the staging of the lung cancer. ⊕⊕○○ EUS-FNA and EBUS-FNA have been shown to be safe, and potentially cost-effective compared with mediastinoscopy, although individually each has a high false-negative rate that warrants surgical confirmation before proceeding with resection.
2. In patients with known or suspected potentially resectable lung cancer whose imaging shows no evidence of mediastinal adenopathy, we suggest combined EUS-FNA/EBUS-FNA for staging. ⊕⊕○○ Combined EUS-FNA/EBUS-FNA has been shown to have a negative predictive value comparable to that of mediastinoscopy. However, expertise in both modalities is not readily available at most institutions.
3. In patients who require evaluation of station 5 nodes, we suggest EUS-FNA as a safe and cost-effective first-line approach. ⊕⊕○○
4. When EUS-FNA is performed for suspected lymphoma, we suggest that specimens be sent for flow cytometry and, if technically possible, that EUS core biopsy specimens be obtained because immunophenotyping and histology are often required for diagnosis and subtyping of lymphoma. ⊕⊕○○
5. When EUS-FNA of mediastinal adenopathy is performed in patients with suspected infected nodes, we recommend that aspirate be sent for special stain and culture (eg, acid-fast stain, fungal culture). ⊕○○○

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