Endobronchial Ultrasound for Diagnosis and Staging of Lung Cancer

Summary

Endobronchial ultrasound (EBUS) is a technique that enhances standard flexible bronchoscopy by providing an ultrasound-generated image of the lungs beyond the airway walls, extending to peribronchial structures and distal peripheral lung lesions. The purpose of EBUS is to allow navigation to distal regions of the lungs and facilitate biopsy of suspected cancerous lesions, especially for peripheral pulmonary nodules. Another intended use of EBUS is to examine and biopsy the mediastinal lymph node regions as part of staging for non-small cell lung cancer. Both techniques use transbronchial needle aspiration (TBNA) of lesions to obtain tissue samples.

The evidence for EBUS-guided TBNA (EBUS-TBNA) for diagnosis in individuals with peripheral pulmonary lesions and suspected lung cancer includes a recent systematic review and meta-analysis and 2 small randomized trials. Relevant outcomes are test accuracy, test validity, and morbid events. The body of evidence supports a conclusion that EBUS-TBNA has diagnostic performance characteristics for solitary pulmonary lesions similar to those of traditional flexible bronchoscopy with transthoracic needle aspiration. The evidence also indicates that the safety profile of EBUS-TBNA may be better than with other techniques, as reflected by pneumothorax and chest tube insertion rates. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for EBUS-TBNA for staging individuals with lung cancer and mediastinal lymph nodes seen on imaging includes multiple systematic reviews and meta-analyses. Relevant outcomes are test accuracy, test validity, and morbid events. Evidence supports a conclusion that EBUS-TBNA exhibits test performance characteristics similar to other needle-based methods used to stage the mediastinum in patients diagnosed with lung cancer. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.
### Policy

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.*

Endobronchial ultrasound guidance with transbronchial needle biopsy may be considered **medically necessary** for the evaluation of peripheral pulmonary lesions in patients with suspected lung cancer when the following criteria are met:

- Tissue biopsy of the peripheral pulmonary lesion is required for diagnosis (see Policy Guidelines)
- The peripheral pulmonary lesion is not accessible using standard bronchoscopic techniques

Endobronchial ultrasound guidance with transbronchial needle biopsy is considered **medically necessary** for mediastinal staging in patients with diagnosed lung cancer when the following criteria are met:

- The patient is suitable and willing to undergo specific treatment for lung cancer, with either curative or palliative intent (see Policy Guidelines)
- Tissue biopsy of abnormal mediastinal lymph nodes seen on imaging is required for staging and specific treatment planning (see Policy Guidelines)
- Abnormal lymph nodes seen on imaging are accessible by EBUS-TBNA biopsy

Endobronchial ultrasound is considered **not medically necessary** for diagnosis and staging of lung cancer when the above criteria are not met.

Endobronchial ultrasound is considered **investigational** for all other indications.

### Policy Guidelines

#### Diagnosis and Staging Guidelines

The American College of Chest Physicians (ACCP) have published comprehensive evidence-based clinical practice guidelines for the diagnosis¹ and staging² of lung cancer. Key elements of those guidelines relevant to this Policy are outlined below.

The general approach to patients who are suspected of having lung cancer begins with a comprehensive history and physical examination. Imaging studies will include a CT scan of the chest and a whole-body PET or PET-CT study to seek extrathoracic lesions. A patient’s suitability and desire for curative treatment of a proven lung cancer is the chief consideration in choosing among subsequent management options. These factors in turn will guide the approach to establishing a diagnosis and staging the disease, as follow:
1. Some individuals may prefer no treatment, particularly those with life-limiting comorbid conditions. In such individuals, neither surgical biopsy nor staging is justified. Aggressive surveillance using serial computed tomography (CT) may be used to monitor symptoms for palliation.

2. Two categories of patients, who could potentially benefit from curative surgical resection based on the presence of a solitary, locally confined pulmonary lesion and documented absence of extrathoracic metastatic disease, will not proceed to surgery for completely different reasons.
   a. One group would be considered ineligible for surgery due to sufficiently impaired cardiopulmonary function or other comorbidity that precludes general anesthesia.
   b. A second group of individuals would otherwise be eligible for curative surgery but for personal reasons refuse surgical resection.

For either category of patients listed above, surgical diagnostic and staging procedures are contraindicated. Their options include functional imaging (PET, PET-CT, magnetic resonance imaging [MRI]), CT scan surveillance, and needle-based nonsurgical biopsy, including guided bronchoscopic procedures such as EBUS.

3. Patients who are candidates for curative surgical resection by virtue of documented (PET, PET-CT) absence of distant metastatic lesions, locally confined single tumors, and otherwise sound physical condition are eligible for any type of diagnostic and staging procedure.

4. In patients suspected of having lung cancer based on radiographic imaging (CT), functional imaging (PET, PET-CT) and clinical findings (signs and symptoms of lung cancer), a presumptive diagnosis must be confirmed, preferably by the least invasive method, as dictated by the patient's presentation and desire for definitive treatment.

5. For patients with extensive mediastinal infiltration of tumor and no distant metastases, it is suggested that radiographic (CT) assessment of the mediastinal stage is usually sufficient without invasive confirmation.

6. In patients with discrete mediastinal lymph node enlargement (and no distant metastases) with or without PET uptake in mediastinal nodes, invasive staging of the mediastinum is recommended over staging by imaging alone.

Background

Individuals who are suspected of having lung cancer may present with widely differing signs and symptoms that are related to the type of cancer (e.g., non-small cell lung cancer [NSCLC] versus small-cell lung cancer [SCLC]), it’s location within the lung, and the stage of disease (i.e., localized, locoregionally advanced, metastatic). All three of the major parameters of type, location, and stage, will dictate subsequent management of the cancer, determining whether it is primarily surgical or requires systemic chemotherapy. Early diagnosis of lung cancer is essential because of the uniformly poor prognosis when cancer is diagnosed later in the disease course.

Approximately 75% to 80% of newly diagnosed lung cancers are NSCLC. The clinical presentation and findings on CT or fluoro\(^{18}\) -2-deoxyglucose (FDG) PET scan of the chest typically permit a presumptive diagnosis of lung cancer and differentiation between NSCLC and SCLC. If SCLC is suspected based on radiographic characteristics and other clinical findings, a diagnosis is made by whatever means is easiest (sputum cytology, thoracentesis if an accessible pleural effusion is present, fine-needle aspiration of a supraclavicular node, etc.).\(^1\) However, the diagnosis of suspected NSCLC is usually dictated by the stage of the disease. NSCLC can present with extensive infiltration of the
mediastinum, defined as a mass with no visible lymph nodes, or it may present as a solitary pulmonary nodule that may be bronchogenic or peripheral. In any patient with suspected NSCLC, the diagnosis should be established by the method that has the most favorable risk-benefit ratio.\(^1\)

### Diagnosis of Peripheral Pulmonary Nodules

Solitary pulmonary lesions are typically identified on plain chest radiographs or chest CT scans, often incidentally. Although most of these nodules will be benign, some will be cancerous. Peripheral lung lesions and solitary pulmonary nodules (most often defined as asymptomatic nodules <6 mm) are more difficult to evaluate than larger, centrally located lesions. There are several options for diagnosis, however none of the methods is ideal for safely and accurately diagnosing malignant disease in all patients.\(^3\) Sputum cytology is the least invasive approach.\(^1\) Reported sensitivity rates are relatively low and vary widely across studies, and sensitivity is even lower for peripheral lesions. Sputum cytology, however, has a high specificity; and a positive test may obviate the need for more invasive testing.

Flexible bronchoscopy, a minimally invasive procedure, is the most common approach to evaluating pulmonary nodules. The sensitivity of flexible bronchoscopy for diagnosing bronchogenic carcinoma has been estimated at 88% for central lesions and 78% for peripheral lesions.\(^3\) For small peripheral lesions, less than 1.5 cm in diameter, the sensitivity may be as low as 10% due to the inability to reach into smaller bronchioles.

Transthoracic (percutaneous) needle aspiration, using CT guidance, can be performed for peripheral nodules that are beyond the reach of traditional bronchoscopy. The diagnostic accuracy of transthoracic) needle aspiration (TNA) tends to be as high or higher than that of flexible bronchoscopy for peripheral lesions; the sensitivity and specificity are both > 90%.\(^3\) A disadvantage of TNA is that a pneumothorax may occur in as many as 15% of patients, although this number can range from 1% to 15%. About 1% to 7% will require insertion of a chest tube. Positron emission tomography scans are also highly sensitive for evaluating pulmonary nodules, yet may miss small lesions less than 1 cm in size. Surgical lung biopsy is the criterion standard for diagnosing pulmonary nodules but is an invasive procedure that is not indicated for all patients.

### Staging of lung cancer – Assessment of mediastinal involvement

The stage of a lung cancer – its extent through the body - at diagnosis will directly impact the management approach for each patient.\(^3,4\) The first step in staging is to identify whether the patient has distant metastatic disease (M stage) or the tumor is confined to the chest; this will determine if treatment should be aimed at palliation or at potential cure, respectively. If the primary tumor is confined (T stage), determining whether the mediastinal lymph nodes (N stage) are involved is a crucial factor in guiding therapy.
As for diagnostic procedures, there are a number of options for mediastinal staging. The choice of a noninvasive or invasive staging method is dictated by the patient’s condition, whether or not he or she can tolerate or will elect surgery. Thus, staging procedures may be based on noninvasive imaging (i.e., CT or positron emission tomography [PET], or combined PET-CT) methods, or be fully invasive such as mediastinoscopy, a surgical procedure that is performed under general anesthesia and is regarded as the reference standard for staging lung cancer.³

Recent advances in technology have led to enhancements that may increase the yield of established needle-based diagnostic methods that represent a third approach between noninvasive and surgical procedures.¹ CT scanning equipment can be used to guide flexible bronchoscopy and bronchoscopic transbronchial needle biopsy (TBN) but has the disadvantage of exposing the patient and staff to radiation.

**Endobronchial ultrasound with transthoracic needle aspiration (EBUS-TNA)**

Endobronchial ultrasound (EBUS) using ultrasound probes, previously used in the perioperative staging of lung cancer, can also be used to locate and guide sampling of peripheral lesions. With the use of an ultra-thin bronchoscope combined with a radial ultrasound probe (R-EBUS) through a guide sheath, a practitioner can reach and visualize the sixth- to eighth-generation bronchi, whereas a traditional bronchoscope can only reach the fourth-generation bronchi. The use of R-EBUS imaging allows the physician to verify visually that a lesion has been reached and to maintain position in the periphery to allow a needle biopsy to be performed for diagnosis.⁵ Curved probe linear array EBUS with TBNA also can be used for staging the mediastinal nodes.⁶ The curved linear probe technology allows real-time visualization and needle aspiration of a lesion. Because EBUS with TBNA of the mediastinal nodes may be performed under conscious sedation, it may be used in patients who are not surgical candidates but for whom accurate staging is needed to guide choice among systemic treatments, particularly targeted systemic agents such as tyrosine kinase inhibitors.⁷

Endobronchial ultrasound (EBUS) utilizes 2 distinct types of transducers that have specific uses:

1. radial transducer EBUS (R-EBUS), and
2. convex-probe curved linear array transducer EBUS

A radial EBUS probe comprises a 20 or 30 mega-hertz (MHz) rotating transducer to provide high-resolution 360 degree radial images. It is inserted into the airways via a standard therapeutic bronchoscope. Radial probes are used to assess the airway wall layers for tumor invasion, tracheal stenosis or tracheomalacia. These probes do not allow real-time imaging during biopsy. For biopsy or tissue sampling, the target area is located by R-EBUS; the radial probe is subsequently retracted and is replaced with a biopsy or sampling device.

A convex-probe curved linear array EBUS transducer is adjustable within a frequency range of 5-12 MHz. Such transducers are incorporated into the structure of a dedicated bronchoscope and provide real-time pie-slice sector views of 50-60 degrees parallel to the axis of the bronchoscope. Linear EBUS-transbronchial needle aspiration (EBUS-TBNA) is used to diagnose lung lesions and to stage the mediastinal and hilar node stations. In contrast to radial EBUS, the EBUS-TBNA bronchoscope allows for real-time imaging during biopsy because the needle is optically visualized.
Regulatory Status

A number of instruments are commercially available to perform EBUS-TBNA for diagnosis and staging of lung cancer. All have been cleared for marketing by FDA through the 510(k) process.

In December 2004, the Olympus Medical Systems EU-M60 EUS Exera Endoscopic Ultrasound Center and ATL HDI 5000 Ultrasound System were cleared to be used to acquire and to display high-resolution and high-penetration, real-time endoscopic ultrasound B-mode 2D and 3D images, including the upper airways and tracheobronchial tree.

In January 2006, the Olympus Medical Systems EVIS EXERA Bronchosfibervideoscope, Olympus BF type UC160F-OL8 bronchoscope and its diagnostic ultrasound transducer were cleared to be used to provide real-time endoscopic ultrasound imaging and ultrasound guided needle aspiration including the upper airways and tracheobronchial tree.

In July 2007, the Olympus Medical Systems XBF-UC180F-DT8 Ultrasonic Bronchosfibervideoscope and the ALOKA SSD-Alpha 5/10 Ultrasound System were cleared to be used to provide real-time endoscopic ultrasound imaging and ultrasound guided needle aspiration including the upper airways and tracheobronchial tree.

In April 2014, the PENTAX Medical Company PENTAX Ultrasound Video bronchoscope EB-1970UK + HI VISION Preirus endoscopic ultrasound and ultrasound bronchoscope and its ultrasound transducer were cleared to provide optical visualization of, ultrasonic visualization of, and therapeutic access to, the pulmonary track including but not restricted to the nasal passages, pharynx, larynx, trachea, bronchial tree (including access beyond the stem), and underlying areas.

In May 2009, the Medi-Globe SonoTip® II EBUS-TBNA Needle System was cleared to be used in conjunction with various legally marketed, FDA registered Ultrasound Endoscopes. The SonoTip II EBUS-TBNA Needle System is used for ultrasonically guided fine needle aspiration, (FNA) of submucosal and extra-luminal lesions of the tracheobronchial tree.

In January 2010, the Cook EchoTip® Ultra Endobronchial High Definition Ultrasound Needle was cleared to be used in conjunction with an endobronchial ultrasound (EBUS) endoscope to gain access to and sample submucosal and extramural lesions within or adjacent to the tracheobronchial tree through the accessory channel of an ultra sound endoscope for Fine Needle Aspiration (FNA).

In April 2014, the PENTAX Ultrasound Video Bronchoscope EB-1970UK + HI VISION Preirus endoscopic ultrasound and ultrasound bronchoscope and its ultrasound transducer (PENTAX Medical) were cleared by FDA to provide optical visualization of, ultrasonic visualization of, and therapeutic access to, the pulmonary tract including but not restricted to the nasal passages, pharynx, larynx, trachea, bronchial tree (including access beyond the stem), and underlying areas.

In May 2014, the Medi-Globe SonoTip® Pro and Pro Flex EBUS-TBNA Needle System was cleared to be used in conjunction with various legally marketed, FDA registered Ultrasound Endoscopes. The SonoTip Pro and Pro Flex EBUS-TBNA Needle System is used for ultrasonically guided fine needle
aspiration, (FNA) of submucosal and extra-luminal lesions of the tracheobronchial tree (e.g., lymph nodes, abnormal tissue in the mediastinum).

**Rationale**

**Diagnosis of Lung Cancer with EBUS Methods**

A substantial body of literature exists on the use of R-EBUS to diagnose lung cancer in individuals with solitary pulmonary nodules or lesions. The American College of Chest Physicians (ACCP) has published 2 reviews of evidence on R-EBUS and other technologies for diagnosis of lung cancer. The ACCP reviews state that in general, most of the evidence comes from small retrospective or prospective studies, plus 2 randomized controlled trials (RCTs).

A recent high-quality systematic review and meta-analysis prepared by Steinfort and colleagues evaluated R-EBUS diagnostic accuracy to determine point sensitivity and specificity, and construct a summary receiver-operating characteristic (SROC) curve. The bibliographic search for this review identified 968 papers, or which 24 were selected for full review. Among the latter, 8 were excluded, leaving 16 to form the basis for the MA. Inclusion criteria for the review were: 1) radial probe EBUS for diagnosis of peripheral pulmonary lesions (PPLs); 2) diagnoses were confirmed histologically or by close clinical follow-up for at least 6 months used as the reference standard; and, 3) enrolled at least 30 patients. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool was used to assess study quality. Two-by-two contingency tables were created for each study to categorize patients into one of 4 options: true positive, false positive, false negative and true negative. Meta-analysis was performed using Meta-DiSc (Version 1.4) using pooled weighted averages and a p-value < 0.05 considered statistically significant. Study heterogeneity was assessed by the I^2 index with a value > 50% indicative of significant interstudy heterogeneity.

The mean number of patients per study included in the Steinfort MA was 89 (range 30-158). Lung cancer prevalence was reported in 13 studies, with a median of 68% (range 50-84%). In the analysis, only 13 studies presented data that were deemed sufficient for inclusion in the MA. The pooled analysis of those 13 studies included 1,090 patients, and demonstrated a point sensitivity of 0.73 (95% CI, 0.70, 0.76) and pooled specificity of 1.00 (95% CI, 0.99, 1.00). The area under the SROC curve was 0.9376 (standard error 0.049). The diagnostic odds ratio was 103.75 (95% CI, 46.4, 231.7), corresponding to a positive likelihood ratio of 26.84 (95% CI, 12.60, 57.20) and a negative likelihood ratio of 0.28 (95% CI, 0.23, 0.36). Subgroup analysis suggested significant interstudy sources of heterogeneity for sensitivity included prevalence of malignancy, lesion size and the reference standard that was used. Complication rates were not reported in 2 of 16 studies included in the review, with rates in the other 14 ranging from 0% to 7.4%. In this MA, the pneumothorax rate ranged from 0% to 5.1%, with a pooled rate across 14 studies of 1.0% (11 of 1,090 patients). The pooled rate of intercostal catheter drainage of pneumothorax was 0.4%. No procedure-related deaths were reported in any included study.

The Steinfort meta-analysis indicated very good diagnostic performance of EBUS-TBNA for evaluation of PPLs. The authors note significant variation in the technique of EBUS-TBNA between institutions, particularly with respect to additional guidance tools (e.g., fluoroscopy, guide sheath use, etc.). However, they did not identify any effect of such characteristics as an influence on sensitivity.
The performance of EBUS-TBNA (pooled sensitivity 73%, pooled specificity 100%) in the Steinfort MA appears superior to that of flexible bronchoscopy for peripheral nodules in an ACCP meta-analysis (diagnostic sensitivity of 33% for lesions < 2 cm, 62% for lesions > 2 cm, 57% for all peripheral lesions).\(^1\) In the same review, the pooled sensitivity of guided TBNA of peripheral nodules was 90% (95% CI, 88%, 91%), with individual study estimates from 62% to 99%. However, like EBUS-TBNA, the false negative rate is high (20% -30%), which means that non-diagnostic findings with either technique does not serve as sufficient reassurance of the absence of malignancy. Thus, a substantial proportion of surgical candidates would be considered for further investigation to rule out cancer. On the other hand, EBUS-TBNA has a significant advantage over guided percutaneous needle biopsy methods in its safety profile. The Steinfort MA demonstrated an overall pneumothorax rate of 1.0% and an overall intercostal chest tube insertion rate of 0.4%. By comparison, a cross-sectional analysis of nearly 16,000 cases in studies describing guided percutaneous biopsy report pneumothorax rates of 15% (95% CI, 14%,16%) with 7% (95% CI, 6%, 7.2%) of all biopsies requiring a chest tube.\(^1,9\)

Two small randomized trials compared EBUS-TBNA with conventional fluoroscopy-guided flexible bronchoscopy and transbronchial biopsy (TBB) were identified.\(^10,11\) In one prospective RCT, patients with identified peripheral lung lesions suspicious as malignancy who could undergo a complete clinical diagnostic follow-up (n = 293) were enrolled in the study and randomly assigned to EBUS-TBNA (N = 97) or TBB (N = 124).\(^10\) Patients in whom biopsies were not diagnostic underwent more invasive procedures to obtain a final diagnosis, and a complete follow-up was possible in 206 patients (87 EBUS-TBB and 119 TBB). Lung cancer was diagnosed in 61 patients in the EBUS-TBB group and in 83 patients in the TBB group. For patients with lung cancer, sensitivity was 0.79 in the EBUS group and 0.55 in the TBB group (p = 0.004), and accuracy was 0.85 and 0.69, respectively (p = 0.007). The analysis of a subset of patients with lesions > 3 cm showed no significant difference in diagnostic ability between the two procedures. A considerable decline in TBB sensitivity and accuracy (0.31 and 0.50) was observed in lesions < 3 cm, while EBUS-TBB maintained the diagnostic yield (0.75 and 0.83) [p = 0.0002 and p = 0.001, respectively]. A similar difference was observed when the sensitivity of the two procedures was compared in lesions < 2 cm (0.23 vs 0.71, p < 0.001).

Another prospective randomized study aimed to determine diagnostic rate, complications and patient tolerability of endobronchial ultrasound-guide sheath (EBUS-GS) and computed tomography (CT)-guided percutaneous core biopsy for peripheral lung lesions among patient who had visible lesions suspicious of malignancy.\(^12\) Lesions >1 cm diameter on CT were randomly assigned to either EBUS-GS biopsy or CT-guided PNB. Patients with severe chronic obstructive airway disease, lesions touching visceral pleura or hilum, and patients with symptoms needing bronchoscopic evaluation were excluded. Patients completed preprocedure and postprocedure questionnaires on tolerability. Among 64 participants (mean lesion size 29±16 mm), 57 completed the study. Diagnostic sensitivity was 67% for EBUS-TBNA and 78% for CT-guided biopsy (p = not significant). In those with negative results, nine patients in the EBUS group had a CT-guided biopsy as a cross-over, seven of which were diagnostic. In the CT group, four had cross-over EBUS-GS of which three were diagnostic. Sensitivity for malignancy was 17/23 for EBUS-GS (74%) and 23/26 (88%, p = not significant). For lesions <2 cm, CT-guided biopsy had a significantly better diagnostic yield (80% vs 50%, p = 0.05). In EBUS-TBNA cases, for lesions with an air bronchogram, sensitivity was 89%. Pneumothorax and intercostal catheter insertion was performed in three and two cases, respectively, for EBUS, and 10 and 3 cases for CT-guided biopsy (p = 0.02 for pneumothorax). Nine unexpected admissions occurred after CT-guided
biopsy compared with three after EBUS-GS. Overall, tolerability was high for both groups; however three patients had moderate-to-severe pain after CT-guided biopsy.

**Section Summary: Diagnosis of Lung Cancer With Endobronchial Ultrasound Methods**

Evidence compiled in the Steinfort MA and from 2 RCTs supports a conclusion that EBUS-guided TBNA has diagnostic performance characteristics for solitary pulmonary lesions similar to those of traditional flexible bronchoscopic techniques with transthoracic needle biopsy. The quality of the included studies, as measured by the QUADAS instrument, was the major limitation of their analysis. and it was unclear from individual study selection criteria whether the patient populations in individual studies were consistently similar and representative of patients who would undergo EBUS-TBNA in clinical practice. Other factors that may influence performance characteristics of EBUS-TBNA were not well described, such as bronchoscopist experience, the number of biopsies taken, the proximity of peripheral nodules to central airways and their radiological appearance (e.g., solid versus ground-glass opacity). However, the overall results of the studies were relatively consistent in reporting that EBUS-TBNA has a moderately high sensitivity, and very high specificity, for the patients studies. The evidence also indicates that the safety profile of EBUS-TBNA may be less risky than other techniques as reflected by pneumothorax and chest tube insertion rates. The Steinfort findings are supported by evidence from 2 individual RCTs, one of which was included in the MA, showing similar performance of EBUS-TBNA compared to CT-guided biopsy. The body of evidence thus supports use of EBUS-TBNA in patients with solitary pulmonary nodules or lesions when criteria are met.

This evidence does not establish that one technique is clearly better than the others. The choice of technique for biopsy depends on a number of factors, including the size and location of the lesion(s), in addition to the risks of the planned procedure. In general, the least invasive technique for biopsy should be used first, and if non-diagnostic, followed up by more invasive techniques until a definitive result is obtained.

**Staging of Lung Cancer with EBUS Methods**

A number of methods are used to determine the stage of lung cancer in patients who have been diagnosed with the disease.\(^2\,13\,14\) As outlined in the Background and Policy Guidelines here, clinical management of a lung cancer patient is dictated by the stage of disease at diagnosis as well as the patient’s underlying condition, primarily whether he or she is a candidate for curative surgical therapy or not. The ACCP has produced a systematic review with pooled analyses that provides a comprehensive resource for noninvasive and invasive methods, including EBUS-based techniques, to stage the mediastinum.\(^3\) In addition, at least 5 systematic reviews and meta-analyses are available that report pooled parameters of EBUS-TBNA diagnostic performance in staging lung cancer.\(^15\,-\,20\) The following table provides a summary of pooled test performance characteristics for a number of staging procedures drawn from the ACCP evidence review.\(^3\)
Table 1. Pooled Performance Characteristics of Techniques Used to Stage the Mediastinum in Patients With Lung Cancer\(^a\)\(^,\)\(^b\)

<table>
<thead>
<tr>
<th>Technique</th>
<th>Total No. of Patients</th>
<th>Cancer Prevalence in Study, %</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Positive Predictive Value, %</th>
<th>Negative Predictive Value, %</th>
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<tbody>
<tr>
<td>CT with contrast enhancement</td>
<td>7368</td>
<td>30</td>
<td>55</td>
<td>81</td>
<td>58</td>
<td>83</td>
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<td>PET alone</td>
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<td>28</td>
<td>80</td>
<td>88</td>
<td>75</td>
<td>91</td>
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<tr>
<td>PET-CT</td>
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<td>22</td>
<td>62</td>
<td>90</td>
<td>63</td>
<td>90</td>
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<tr>
<td>Traditional mediastinoscopy</td>
<td>9267</td>
<td>33</td>
<td>78</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
</tr>
<tr>
<td>Video-assisted mediastinoscopy</td>
<td>995</td>
<td>31</td>
<td>89</td>
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<td>(100%)</td>
<td>92</td>
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<tr>
<td>Mediastinal lymphadenectomy</td>
<td>386</td>
<td>34</td>
<td>81</td>
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<td>(100%)</td>
<td>91</td>
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<tr>
<td>Video-assisted thoracic surgery</td>
<td>246</td>
<td>63</td>
<td>99</td>
<td>(100%)</td>
<td>(100%)</td>
<td>96</td>
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<tr>
<td>Transthoracic needle aspiration (percutaneous)</td>
<td>215</td>
<td>84</td>
<td>94</td>
<td>(100%)</td>
<td>(100%)</td>
<td>Not reported (all patients had mediastinal disease)</td>
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<tr>
<td>Transbronchial needle aspiration</td>
<td>2408</td>
<td>81</td>
<td>78</td>
<td>(100%)</td>
<td>(100%)</td>
<td>77</td>
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<tr>
<td>Esophageal endoscopic ultrasound-guided needle aspiration</td>
<td>2443</td>
<td>58</td>
<td>89</td>
<td>(100%)</td>
<td>(100%)</td>
<td>86</td>
</tr>
<tr>
<td>Real-time EBUS-TBNA</td>
<td>2756</td>
<td>58</td>
<td>89</td>
<td>(100%)</td>
<td>(100%)</td>
<td>91</td>
</tr>
</tbody>
</table>

CT: computed tomography; EBUS-TBNA: endobronchial ultrasound‒guided transbronchial needle aspiration; PET: positron emission tomography.

\(^a\) Technically, the specificity and positive predictive value cannot be assessed in those studies reporting 100% values because a positive result was not followed by an additional criterion standard test.

It is apparent that the grouping of imaging techniques as a whole does not perform as well as the invasive techniques overall. Within the invasive grouping, there seems to be little apparent difference in terms of performance characteristics. Traditional surgical mediastinoscopy has long been considered to be the gold standard for staging the mediastinum in patients with a diagnosis of lung cancer; variants of it are used in specific cases when the cervical approach does not provide information specific to certain node stations. Mediastinoscopy is indicated mainly for patients who would be candidates for curative surgical resection.

The less-invasive guided needle-based methods are suitable for non-surgical candidates or those who refuse surgery, yet require staging to plan specific systemic therapy or radiotherapy. They appear to have very similar performance characteristics based on the ACCP analyses, including EBUS-TBNA. This agrees with results from the 5 independent meta-analyses mentioned above, which showed pooled sensitivities that ranged from 0.88-0.93 and pooled specificities of 0.99-1.00. However, this would be expected given that the ACCP analysis contains generally the same body of evidence.

The choice of a needle-based technique thus would be based on factors other than test performance criteria, as outlined in the Policy Guidelines. As shown above in this Policy, EBUS-TBNA appears to be as safe if not safer than other needle-based biopsy techniques, based on differences in the reported rates of pneumothorax and post-procedure necessity for chest tube placement. Other factors that could
influence choice would include the availability of different procedures. All invasive tests require specialized skills and experience that are gained through performance, regardless of whether it is a surgical or needle-based technique.

Section Summary: Staging of Lung Cancer With EBUS Methods

The evidence underlying the pooled accuracy for mediastinal staging is less than optimal. The literature review for staging did not identify any RCT evidence to compare EBUS guidance with any other needle-based technique. There are differences among the patient populations, the use of reference standard confirmation of node positivity, and where reported, very low quality among the studies assessed using the QUADAS tool.15,16

Evidence summarized in this Policy support a conclusion that EBUS-TBNA exhibits test performance characteristics similar to other needle-based methods used to stage the mediastinum in patients diagnosed with lung cancer. Although it could be used in patients who are surgical candidates and plan to undergo surgery, it also may be suitable for those who are not eligible for curative resection or refuse to undertake major surgery but still require staging for planning systemic or radiotherapy. A major advantage of EBUS-based methods is that it can be performed on an outpatient basis under limited sedation if necessary, and thus is less invasive and risky than traditional mediastinoscopy. Therefore, EBUS-TBNA is a reasonable alternative to traditional mediastinoscopy when criteria are met.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT00832715</td>
<td>Diagnostic Utility of Endobronchial Ultrasound Guided Mediastinal Lymph Node Sampling in Clinical Stage I and II Non Small Cell Lung Cancer</td>
<td>120</td>
<td>Apr 2017</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

Summary of Evidence

The evidence for endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA) for diagnosis in individuals with peripheral pulmonary lesions and suspected lung cancer includes a recent systematic review and meta-analysis and 2 small randomized trials. Relevant outcomes are test accuracy, test validity, and morbid events. The body of evidence supports a conclusion that EBUS-TBNA has diagnostic performance characteristics for solitary pulmonary lesions similar to those of traditional flexible bronchoscopy with transthoracic needle aspiration. The evidence also indicates that the safety profile of EBUS-TBNA may be better than with other techniques, as reflected by pneumothorax and chest tube insertion rates. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.
The evidence for EBUS-TBNA for staging individuals with lung cancer and mediastinal lymph nodes seen on imaging includes multiple systematic reviews and meta-analyses. Relevant outcomes are test accuracy, test validity, and morbid events. Evidence supports a conclusion that EBUS-TBNA exhibits test performance characteristics similar to other needle-based methods used to stage the mediastinum in patients diagnosed with lung cancer. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

American College of Chest Physicians
The American College of Chest Physicians (ACCP) offers a number of evidence-based guidelines for the use of EBUS-guided needle aspiration of pulmonary lesions for diagnosis of lung cancer and mediastinal staging of patients diagnosed with lung cancer. A separate guideline and expert panel report addresses technical aspects of EBUS-TBNA and addresses use outside the setting of lung cancer.

Diagnosis of Peripheral Pulmonary Nodules

ACCP 2.3.2. In patients suspected of having lung cancer, who have extensive infiltration of the mediastinum based on radiographic studies and no evidence of extrathoracic metastatic disease (negative PET scan), it is recommended that the diagnosis of lung cancer be established by the least invasive and safest method (bronchoscopy with TBNA, EBUS-NA, EUS-NA, TTNA, or mediastinoscopy).

ACCP 3.3.2.1. In patients suspected of having lung cancer, who have a peripheral lung nodule, and a tissue diagnosis is required due to uncertainty of diagnosis or poor surgical candidacy, radial EBUS is recommended as an adjunct imaging modality.

Staging of the Mediastinum in Patients Diagnosed with Lung Cancer

ACCP 4.4.4.3. In patients with high suspicion of N2,3 involvement, either by discrete mediastinal lymph node enlargement or PET uptake (and no distant metastases), a needle technique (EBUS-NA, EUS-NA, or combined EBUS-EUS-NA) is recommended over surgical staging as a best first test.

In cases where the clinical suspicion of mediastinal node involvement remains high after a negative result using a needle technique, surgical staging should be performed.

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for endobronchial ultrasound have been identified.
**Section:** Radiology  
**Effective Date:** July 15, 2016  
**Subsection:**  
**Original Policy Date:** March 20, 2015  
**Subject:** Endobronchial Ultrasound for Diagnosing and Staging of Lung Cancer  
**Page:** 13 of 14

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**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**References**


Policy History

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<th>Action</th>
<th>Reason</th>
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<tbody>
<tr>
<td>March 2015</td>
<td>New Policy</td>
<td>Policy created with literature review through October 6, 2014. Endobronchial ultrasound is medically necessary for diagnosis and staging of lung cancer when criteria are met</td>
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This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 24, 2016 and is effective July 15, 2016.

Deborah M. Smith, MD, MPH