Role of EBUS TBNA in Staging of Lung Cancer: A Clinician’s Perspective

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Abstract

The treatment of non-small cell lung cancer (NSCLC) includes surgical resection with curative intent in early-stage disease and chemoradiation in the advanced stage disease. Therefore, an accurate preoperative mediastinal lymph node staging is required not only to offer the appropriate treatment but also to avoid unnecessary invasive procedures including thoracotomy. The mediastinal lymph nodes can be sampled using several techniques including mediastinoscopy, surgery (open or video-assisted thoracoscopic surgery), endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA), or endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA). Currently, EBUS-TBNA/EUS-FNA is the preferred modality for sampling mediastinal lymph nodes because of its minimally invasive nature and high diagnostic yield. In this review, we discuss the utility of endosonographic procedures in mediastinal lymph node staging of NSCLC.

Keywords: Endobronchial ultrasound, endoluminal ultrasound, transbronchial needle aspiration, transbronchial needle aspiration

In general, staging in lung cancer is indicated in those with potentially resectable NSCLC including the following: (i) those who have discrete enlarged mediastinal lymph nodes on computed tomography (CT) of the chest; (ii) those who have high standardized uptake value (SUV)-positive mediastinal lymph nodes on positron emission tomography (PET)-CT; (iii) in large (>3 cm) central airway tumors; and, (iv) in those with adenocarcinoma with high SUV uptake on PET-CT.[8,9]

Utility of EBUS-TBNA/EUS-FNA in Clinical Stage N0/N1 NSCLC

In subjects with NSCLC, the initial workup for staging is undertaken using radiological methods such as CT thorax and whole-body PET-CT. A radiologically normal mediastinum is defined when the size of lymph nodes on CT thorax is less than 10 mm and there is no uptake on PET-CT. In those with radiologically normal mediastinum or in those with lymph nodes limited to ipsilateral pulmonary and hilar region (N0/
N1), surgical resection is the treatment of choice.\textsuperscript{[5,8]} In clinical N0 disease, the current guidelines do not recommend mediastinal lymph node sampling. However, pathological upstaging (pN2) has been documented in up to 35% of clinical N0 status.\textsuperscript{[10,11]} The most common lymph node stations that were upstaged were 4R and 7,\textsuperscript{[10]} which are easily accessible by EBUS-TBNA. This sets up an argument for mediastinal staging in those with the clinical N0/N1 stage. In the preoperative staging of clinical N0/N1 lung cancer, a recent meta-analysis comprising nine studies demonstrated a pooled sensitivity and specificity of 49% [95% confidence interval (CI), 41%–57%] and 100% (95% CI, 99%–100%), respectively.\textsuperscript{[12]} The sensitivity improved to 55% on pooling studies that provided information for lymph nodes accessible for EBUS-TBNA. EBUS-TBNA detected radiologically occult N2/N3 disease in 7.7% (88/1146) of subjects.\textsuperscript{[12]} The number needed to perform EBUS-TBNA to upstage clinical N0/N1 disease was 14 (95% CI, 11–16). The combined use of EBUS-TBNA/EUS-FNA could further increase the sensitivity of endoluminal ultrasound-guided FNA to 73%. On combining EBUS-TBNA and EUS-FNA, the number of procedures (EBUS/EUS) needed to detect occult N2/N3 disease was 7, which underscores the need for mediastinal lymph node staging even in those with radiologically normal mediastinum.\textsuperscript{[12]}

Utility of EBUS-TBNA/EUS-FNA in clinical N2/N3 stage NSCLC

Compared with the clinical N0/N1 stage where surgical resection is the definitive form of therapy, the treatment in clinical N2/N3 stage lung cancer is either combination chemoradiotherapy or surgery in those with ipsilateral mediastinal lymph node metastases.\textsuperscript{[5,8]} In a meta-analysis of 11 studies with 1299 subjects who underwent EBUS-TBNA/EUS-FNA for staging before treatment, the pooled sensitivity and specificity of EBUS-TBNA/EUS-FNA to detect mediastinal lymph node metastasis were 93% (95% CI, 91%–94%) and 100% (95% CI, 99%–100%), respectively.\textsuperscript{[13]} The median prevalence of mediastinal metastases in the studies included in the meta-analysis was 68%.\textsuperscript{[13]} The pooled sensitivity was 94% in studies where EBUS-TBNA was performed in CT or PET-positive lymph nodes compared with a sensitivity of only 76% where CT or PET status was unknown.\textsuperscript{[13]} The complication rate of EBUS-TBNA was negligible (0.007%).\textsuperscript{[13]} However, this meta-analysis included studies with a retrospective study design, and only five studies used surgical specimen as the reference standard.\textsuperscript{[13]}

In another meta-analysis studying the role of EBUS-TBNA in pretreatment mediastinal staging, the combined sensitivity and specificity of EBUS-TBNA for mediastinal staging were 90% (95% CI, 84%–96%) and 99%, respectively.\textsuperscript{[14]} Only one complication of hypoxia was reported in one study. This meta-analysis included only studies that performed EBUS-TBNA and not EUS-FNA. Thus, in pretreatment mediastinal staging of NSCLC, endosonographic procedures are safe and have a high sensitivity and specificity.

Utility of EBUS-TBNA/EUS-FNA in mediastinal restaging after neoadjuvant therapy

In subjects with stage IIIa/N2 NSCLC, surgical resection with mediastinal lymph node dissection is a preferred modality after successful neoadjuvant therapy.\textsuperscript{[15]} However, a repeat staging of mediastinum is essential before surgery can be performed as the outcomes following surgery depend on the presence or absence of mediastinal lymph node involvement. Performing surgical restaging after neoadjuvant therapy is challenging as there may be mediastinal fibrosis and adhesions because of either a prior intervention or treatment. Endosonographic procedures could also be used to successfully restage the mediastinal lymph nodes. A recent meta-analysis (10 studies with 574 subjects undergoing mediastinal restaging with EBUS-TBNA/EUS-FNA) demonstrated a pooled sensitivity and specificity of 67% and 99%, respectively.\textsuperscript{[16]} This suggests that EBUS-TBNA combined with EUS/EUS-B-FNA can be reliably used to restage the mediastinum after neoadjuvant chemotherapy.

Utility of combining EBUS-TBNA and EUS/EUS-B-FNA

The specificity of EBUS and EUS in detecting mediastinal nodal metastases is high, but there remains a possibility of missing lymph nodes when either is performed alone. The combination of the two procedures provides a more comprehensive access to the mediastinum. While EBUS-TBNA provides an easy access to lymph nodes in the pretracheal and the paratracheal regions, EUS-FNA is useful for sampling the inferior mediastinum, the left paratracheal region, the left adrenal gland, and occasionally the aortopulmonary lymph node stations.\textsuperscript{[17,18]} Thus, combining both the procedures increases the domain of lymph node stations that can be sampled thereby enhancing the diagnostic yield. EBUS-TBNA and EUS-FNA are performed using a dedicated echobronchoscope and an echoendoscope, respectively. EBUS scope provides access to the mediastinum through the transtracheal route, whereas EUS is used through transesophageal route. Generally, EBUS is performed by a pulmonologist or a thoracic surgeon, whereas EUS is performed by a gastroenterologist. Transesophageal EUS-guided FNA can also be performed using EBUS scope (EUS-B) thus obviating the need for two different types of scopes and operators. A meta-analysis of studies describing the yield of combined EBUS-TBNA and EUS-B-FNA for mediastinal lymph node sampling identified four studies (465 subjects).\textsuperscript{[20]} The pooled sensitivity of EBUS-TBNA alone was 80% (95% CI, 74%–86%), whereas pooled sensitivity of the combined EBUS-TBNA and EUS-B-FNA was 91% (95% CI, 86%–95%).\textsuperscript{[20]} The pooled specificity of EBUS-TBNA and the combined procedure (EBUS-TBNA and EUS-B-FNA) was 100%.\textsuperscript{[20]} The number of combined procedure that needs to be performed to achieve one additional diagnosis was 10 (95% CI, 6–29).\textsuperscript{[20]} In another recent meta-analysis, 13 studies (n = 2395 subjects) were identified
What Is the Current Place of Mediastinoscopy?

Mediastinoscopy has been considered as the reference standard for mediastinal lymph node staging of NSCLC. However, with mediastinoscopy only lymph node stations 2L/2R and 4L/4R can be sampled, whereas stations 10L/10R, 8, and 9 cannot be sampled. Also, mediastinoscopy requires general anesthesia and is an invasive procedure. In a recent meta-analysis comprising studies that compared EBUS/EUS procedures head to head with mediastinoscopy, the pooled risk difference of the sensitivity of endosonography versus mediastinoscopy was 0.11 (95% CI, −0.03 to 0.25) suggesting equivalence of the two procedures. Moreover, the complication rate was significantly lower with endosonographic procedures compared with mediastinoscopy, making EBUS not only equally effective but also a safer method of mediastinal staging of NSCLC. In those with a negative EBUS-TBNA/EUS-FNA, the current practice is to perform staging mediastinoscopy to rule out false-negatives. However, a negative EBUS does not always result in a high unforeseen N2 disease at surgical resection. Furthermore, by omitting mediastinoscopy, there is a possibility to reduce extra waiting time, general anesthesia, and hospitalization. Thus, in patients with a negative EBUS-TBNA, a one approach is to perform surgery directly without waiting for confirmation with a second staging procedure.

In conclusion, endosonographic procedures are the preferred first-line modality for mediastinal lymph node staging in those with clinical stage N0/N1, clinical stage N2/N3, and for mediastinal restaging after neoadjuvant chemotherapy for NSCLC. The endosonography enabled procedures have high sensitivity and specificity both for diagnosing and staging NSCLC. The endosonographic procedures are safe and reproducible. For a complete mediastinal staging, EBUS-TBNA should be combined with EUS-B/EUS-FNA for optimal results.

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Conflicts of interest
There are no conflicts of interest.

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