Endoscopic mediastinal staging of lung cancer

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Summary
The advent of endoscopic ultrasound-guided sampling procedures such as endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) has lead to significant advances in the mediastinal diagnosis and staging of lung cancer. These endoscopic techniques can be performed in the outpatient setting under conscious sedation and local anesthesia, in contrast to the surgical standard, mediastinoscopy (MS), which requires operating theatre time and general anesthesia. Proponents of mediastinoscopy have always emphasized the advantages of mediastinoscopy, namely its sensitivity even with a low prevalence of mediastinal metastases and its low false negative rate. Newer endoscopic techniques such as EBUS-TBNA are showing sensitivities exceeding that of mediastinoscopy, even in the setting of an equally low prevalence of mediastinal metastases. However, endoscopic techniques have double the false negative rate of mediastinoscopy. As the tracheobronchial route and esophageal route provide almost complete access to mediastinal lymph nodes, these endoscopic techniques are complementary rather than competing. When used in combination, it is possible mediastinoscopy may be superseded. The challenge however, is how best to select the appropriate endoscopic procedures to accurately stage lung cancer in the most cost-effective manner.

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Lung cancer is the most commonly diagnosed cancer in the world and also the leading cause of cancer mortality. Surgery offers the best chance of cure for non-small cell lung cancer, which accounts for more than 80% of lung cancers. The 5-year survival rate is about 45% after surgical resection for clinically resectable disease. In the absence of extrathoracic metastases, mediastinal lymph nodes are the commonest site of metastases and this generally precludes surgical resection. With ipsilateral mediastinal lymph node metastases, the 5-year survival falls to a dismal 23%. Therefore, in the absence of distant metastases, mediastinal lymph node involvement is the most important prognostic factor that is critical to determining appropriate therapy.

Non-invasive mediastinal staging

The most commonly used modality for mediastinal staging is CT scanning of the chest and the criterion used is enlargement of the lymph node to \( \geq 1 \text{ cm} \) on its short axis. The major limitation of using the CT criteria is not only its poor sensitivity, but also its poor specificity. In a meta-analysis of 5111 patients, the pooled sensitivity and specificity were 51% and 85% respectively. In fact, in one of the included studies, up to 40% of lymph nodes deemed malignant by CT criteria were actually benign. Functional imaging with \( ^{18} \text{F-fluoro-2-deoxy-D-glucose} \) has a higher sensitivity than CT, but again, specificity remains poor. Thus, when there are abnormal findings with the non-invasive imaging modalities for mediastinal staging, tissue confirmation is usually recommended.

Surgical mediastinal staging

The diagnostic standard for tissue diagnosis in the mediastinal staging of lung cancer is mediastinoscopy, which involves passing a rigid mediastinoscope into the mediastinum. This surgical technique has a reported morbidity and mortality rate of 2% and 0.08% respectively. Excision biopsy of lymph nodes lateral to the trachea (station 2 and 4) and anterior subcardinal lymph nodes (station 7) can be performed with this technique through dissection via a supra-sternal incision while biopsy of subaortic (station 5) and para-aortic (station 6) lymph nodes usually requires another point of entry via a left anterior paraaortal mediastinotomy. Lymph nodes posterior to the carina and those in the inferior mediastinum are however, beyond access of the mediastinoscope. The availability of videomediastinoscopy (VMS) allows better visualization and more extensive lymph node sampling with a lower incidence of recurrent laryngeal nerve damage and post-operative bleeding. VMS also gives improved sensitivities (90%) and lower false negative rates (7%) as compared to conventional mediastinoscopy (80% and 10%), but both surgical procedures require operating theatre time and general anesthesia.

Endoscopic mediastinal staging

Transbronchial needle aspiration (TBNA)

Transbronchial needle aspiration on the other hand, allows sampling of mediastinal lymph nodes lying adjacent to the tracheobronchial tree during bronchoscopy, which may be done under local anesthesia as an outpatient procedure. TBNA does not require expensive specialized ultrasound equipment, is safe, and can be done as part of the initial diagnostic bronchoscopy. However, its diagnostic accuracy is highly variable as this is a blind technique that is operator dependent. The sensitivity depends critically on the prevalence of mediastinal lymph node metastases and varies from 39% with a prevalence of mediastinal metastases of 34%, to 78% with a prevalence of mediastinal metastases of 81%. It also has a high false negative rate that approaches 30%. Therefore, its limitations have precluded its use where accurate mediastinal staging is required.

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA)

With a curved linear array ultrasound transducer, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), permits real-time ultrasound-guided needle sampling of lymph node stations adjacent to the esophagus and therefore has a higher sensitivity and accuracy as compared to TBNA. The esophageal route allows access to left-sided mediastinal (station 4L and 5) and subcardinal (station 7) lymph nodes. It also allows access to lymph nodes in the inferior mediastinum such as the lower parasaophaegal (station 8) and the pulmonary ligament (station 9) lymph nodes that are beyond the reach of the mediastinoscope and tracheobronchial tree, but these lymph nodes are not commonly involved in lung cancer. Even the para-aortic lymph node (station 6) can be sampled through the intervening aorta via the esophagus. The pooled sensitivity is about 84% but the false negative rate is still high at 19%. However, its sensitivity drops to 24% for right paratracheal lymph nodes where an air-filled intervening trachea limits ultrasound access from the left-sided esophagus.

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)

Endobronchial ultrasound-guided transbronchial needle aspiration uses very similar equipment to EUS-FNA, with the
main difference being that it is smaller, allowing the tracheobronchial route to be employed for real-time ultrasound-guided sampling of lymph nodes adjacent to the trachea. These are the mediastinal lymph nodes that are commonly involved in lung cancer and include the para-tracheal (station 2 and 4) and the subcarinal (station 7) lymph nodes. A recent meta-analysis reported an impressive pooled sensitivity of 93%.15

The advantage of both the ultrasound-guided endoscopic procedures is that they can be performed safely in the outpatient setting under local anesthesia. When the sensitivities of TBNA, EUS-FNA, and EBUS-FNA are compared to mediastinoscopy in studies where the prevalence of mediastinal metastases is low, only the EBUS-TBNA sensitivity exceeded that of mediastinoscopy (Table 1). In a prospective study directly comparing EBUS-TBNA with mediastinoscopy, the diagnostic yield of EBUS-TBNA also surpassed that of mediastinoscopy.16

Limited accessibility of each endoscopic route and fine-needle sampling error however contribute to a false negative rate which is double that of mediastinoscopy (EBUS-TBNA and EUS-FNA has a false negative rate 20% and 19% respectively, while mediastinoscopy has a false negative rate of 10%).8 The deficiencies of the ultrasound-guided endoscopic techniques seem to be minimized when these procedures are used in combination. Wallace and colleagues have demonstrated in a landmark study that when EUS-FNA and EBUS-FNA were used in combination, the sensitivity was 93% in a population with a mediastinal lymph node prevalence of only 30.4%.17 More importantly, they also reported a high negative predictive value of 97% and suggested that this combination of ultrasound-guided endoscopic procedures might substitute mediastinoscopy. As the endobronchial and esophageal routes are complementary, virtually all lymph node stations within the mediastinum may be accessed via these endoscopic routes.

**Selecting a mediastinal staging method**

While the result of combining two ultrasound-guided endoscopic procedures may supercede that of the surgical standard, a single appropriately selected endoscopic procedure that is diagnostic for mediastinal metastases may well be all that is required.18 In the event that both endoscopic routes allow equal access to a suspicious lymph node station, the issue becomes that of selecting the procedure of choice. Though EUS-FNA may offer better patient tolerance with less coughing as compared to EBUS-TBNA, it has limited access to some of the lymph nodes that are commonly involved in lung cancer. Finally, targeting the mediastinum first in the setting of suspected lung cancer may lead to simultaneous diagnosis and mediastinal staging of non-small cell lung cancer with a single procedure.12,16,19 This may be more cost-effective than performing biopsy of the lung mass, followed by mediastinal staging in a sequential manner, especially when the likelihood of mediastinal metastases is high (See Fig. 1).

In conclusion, given the availability of an armamentarium of staging techniques for lung cancer, the challenge is to select the most cost-effective way to accurately stage the tumor. Due to the heterogeneity of patients and the availability of techniques at different institutions, the optimal approach to patient and procedure selection in diagnosing and staging lung cancer remains to be defined, but EBUS-TBNA is likely to be a key component.

**Conflict of interest**

No conflict of interest exists.

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