Endoscopic Staging

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Felix J.F. Herth

Introduction

Lung cancer is still the leading cause of cancer mortality worldwide, with an overall poor survival rate. Mediastinal lymph node sampling in lung cancer is important for adequate staging to determine the appropriate treatment as well to predict outcome. Adequate staging of lung cancer also is important to improve research into lung cancer, for accurate comparison of data, and for quality control.

Mediastinal lymph node staging may be performed preoperatively by examining radiologic imaging, endoscopically, or surgically. CT scanning, MRI, positron emission tomography (PET), and PET-CT are useful noninvasive imaging techniques for lung cancer staging; however, they are not sufficiently sensitive or specific to determine mediastinal lymph node involvement. CT scanning is usually the initial method for staging of the mediastinal nodes. According to national and international guidelines, only lymph nodes with a short-axis diameter greater than 1 cm (e.g. ± positivity in PET scanning if performed as PET-CT) are usually considered suspicious for malignant involvement on radiologic criteria. However, given a high false-positive rate in CT and PET-CT and the fact that these tests do not provide a tissue diagnosis, it is important to obtain lymph node tissue to determine operability (Erasmus et al. 2008).

Mediastinoscopy, the gold standard for mediastinal staging for many years, has a sensitivity of 90–95 %. Only certain lymph node stations are accessible (2, 4, and anterior 7), whereas access to the posterior and inferior mediastinum is limited and requires extended cervical mediastinoscopy or thoracoscopy. However, it is an invasive procedure requiring general anesthesia and clinical admission. Endoscopic techniques provide a minimally invasive alternative to surgery; because they are less invasive, an increasing number of techniques, such as endobronchial and endoesophageal ultrasound, have been developed over the past few years (Silvestri et al. 2007).

Transbronchial needle aspiration. Merely a curiosity at its inception, flexible bronchoscopy has emerged as an essential diagnostic and therapeutic modality for a variety of lung diseases. The addition of transbronchial needle aspiration (TBNA) not only improved bronchoscopy's diagnostic yield, it further extended the role of bronchoscopy in the evaluation of mediastinal pathology and in the diagnosis and staging of bronchogenic carcinoma. The first description of mediastinal lymph node sampling through the tracheal carina using a rigid bronchoscope was by Schieppati. In 1978, Wang et al. demonstrated that it was feasible to sample paratracheal nodes using TBNA. Subsequent publications highlighted the use of this technique in diagnosing endobronchial and peripheral lesions and the ability of TBNA to provide a diagnosis even in the absence of endobronchial disease. The diagnostic yield of TBNA in assessing hilar–mediastinal lymph node involvement in lung cancer varies greatly in the published literature, from 15 to 85 %. Recently, a meta-analysis of TBNA for the mediastinal staging of non–small cell lung cancer (NSCLC) demonstrated that TBNA is highly specific for identifying mediastinal metastases, whereas the sensitivity depends heavily on the study population under investigation. In studies including patients with a 34 % prevalence of mediastinal metastases, the sensitivity was only 39 %, whereas in a population with an 81 % prevalence, it was 78 %. Today, TBNA is increasingly combined with rapid onsite cytopathologic examination of the smears, as several papers demonstrated. Despite the impact of TBNA on patient management, surveys demonstrate that only 10–30 % of pulmonologists regularly use this technique. The main reasons for its limited use are a lack of needle monitoring, difficulties in performing the procedure, and a belief, despite the evidence in the literature, that TBNA is not useful (Wang et al. 1978).

Endobronchial ultrasound. The integration of ultrasound technology and flexible fiber bronchoscopy enables the

F.J.F. Herth, MD, PhD, DCCP
Department of Pneumology and Critical Care Medicine,
Thoraxklinik, University of Heidelberg,
Amalienstraße 5, 69126 Heidelberg, Germany
e-mail: felix.herth@thoraxklinik-heidelberg.de

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imaging of lymph nodes, lesions, and vessels located beyond the tracheobronchial mucosa. Developed in 2002, the endobronchial ultrasound (EBUS) bronchoscope (Olympus BF-UC160F-OL8 or BF-UC260F-OL; Olympus America, Center Valley, PA) looks like a normal broncho-videoscope but is 6.9 mm wide and has a 2-mm instrument channel and a 30° side viewing optic. Furthermore, a curved linear array ultrasonic transducer sits on the distal end and may be used either with direct contact to the mucosal surface or via an inflatable balloon, which may be attached at the tip. This allows a conventional endoscopic picture side by side with the ultrasonic view. Ultrasonic scanning is performed at a frequency of 7.5–12 MHz with tissue penetration of 20–50 mm. An ultrasound processor processes the ultrasonic image. EBUS allows the bronchoscopist to visualize airway structures as well as surrounding processes. It is very valuable for staging advanced cancer with regard to intramural or nodal spread. EBUS can identify N1, N2, and N3 nodes without surgical intervention, reducing the need for expensive surgery (Herth et al. 2006a)

Endobronchial ultrasound (continued). The actual TBNA is performed by direct transducer contact with the wall of the trachea or bronchus. When a lesion is outlined, a 21-gauge needle (NA-201SX-4022; Olympus Corporation, Tokyo, Japan) may be advanced through the working channel and lymph nodes can be punctured under real-time ultrasound visualization. The needle has an internal sheath to prevent contamination during biopsy. At the same time, color Doppler may be used to identify surrounding vascular structures. Once the target lymph node or mass has been clearly identified with EBUS, the needle is inserted in the lesion under real-time ultrasound guidance. Suction is applied with a syringe, and the needle is moved back and forth inside the lesion. The stylet of the needle is left in place on the first puncture to minimize bronchial cell contamination; once the needle tip is inside the target tissue, the stylet is removed. We stab the target 10–15 times without suction and apply suction only for the last two or three stabbing motions. Prior to retracting the needle into the needle sheath, suction must be removed to minimize sample loss into the syringe. The specimen is then air-flushed on a slide, the needle is flushed with heparin–saline solution to avoid clotting, and the procedure is repeated three times at every lymph node station. Lymph node stations that can be reached via EBUS are the highest mediastinal (station 1), upper paratracheal (2L and 2R), lower paratracheal (4R and 4L), subcarinal (station 7), hilar (station 10), interlobar (station 11), and lobar nodes (station 12). The highest-staging node should be biopsied first; otherwise, the needle must be changed each time. Lymph nodes 5 mm and larger can be sampled successfully and, to date, have shown excellent diagnostic yield. The number of mediastinal lymph node stations to sample depends on the purpose of the examination. Clearly, NSCLC staging requires sampling of at least three stations (4R, 4L, and 7). Every

attempt should be made to sample nodes at these sites, even if size and ultrasonographic features are normal. At our institution, we routinely sample mediastinal lymph nodes that are 5 mm or larger in short-axis diameter. The learning curve for EBUS-TBNA has been evaluated and recorded from 10 procedures to achieve excellent sensitivity and diagnostic accuracy. In a recently published meta-analysis, EBUS-TBNA was shown to have a high-pooled sensitivity of 93 % and specificity of 100 %. Multiple publications have shown that even in patients with lymph nodes under 1 cm (which had been termed N0 by CT criteria), the use of EBUS-TBNA could still show a large percentage of patients with N2/N3 disease (some despite also being negative on PET-CT). Complications such as bleeding or infection are very rare and have been reported only as case reports (Adams et al. 2009).

Endoesophageal ultrasound. Endoesophageal ultrasound–guided fine-needle aspiration (EUS-FNA) has been shown to be useful in biopsying mediastinal lesions, even in patients with a previous nondiagnostic conventional technique, and may be more cost-effective than classical techniques as an initial staging procedure in NSCLC patients. The linear EUS scope (Olympus GF-UC160P-OL5/GF-UCT160-OL5 or Pentax EG-3830UT [Pentax Medical, Montvale, NJ]) has the same basic architecture as the EBUS scope and uses a scanner of between 5 and 10 MHz. The penetrating ultrasound depth may be up to 8 cm. Needles used for biopsy are 19 or 21 gauge, again equipped with a stylet. The procedure is usually performed on an outpatient basis and takes approx 30 min. As with EBUS, the puncture of lymph nodes is performed under real-time ultrasonic guidance. However, EUS-FNA has limited access, as only lymph node stations 2L, 4L, 7, 8, and 9 are accessible through a transesophageal approach. Lymph node station 5 is not routinely accessible via EUS, and may require transvascular FNA. EUS is especially useful in staging of the posterior mediastinum. The left adrenal can be reached and identified in 97 % of cases. It has a "seagull" shape on ultrasound and is particularly well-visualized in cases of metastatic enlargement. Furthermore, the left lobe of the liver also can be reached. The hilar and precarinal lymph nodes cannot be reached. This procedure carries only a very small risk of mediastinitis or bleeding. Unless cysts are punctured, antibiotics do not need to be administered routinely. Multiple publications and a meta-analysis of EUS-FNA have shown a high sensitivity and specificity. Even in patients without mediastinal lymph node enlargement on CT, EUS-FNA has been able to demonstrate metastases in 25 % of lung cancer patients. It is important to remember, however, that with EBUS and EUS, the negative predictive value is limited; therefore, samples that do not contain tumor cells require follow-up with a more definitive procedure, such as mediastinoscopy or video-assisted thorascopic surgery (Micames et al. 2007).

Figure 29.1

Classical TBNA of a lymphnode station 7. The needle pierce the bronchial wall

Figure 29.2

THe EBUS-TBNA scope from OLympus

Figure 29.1

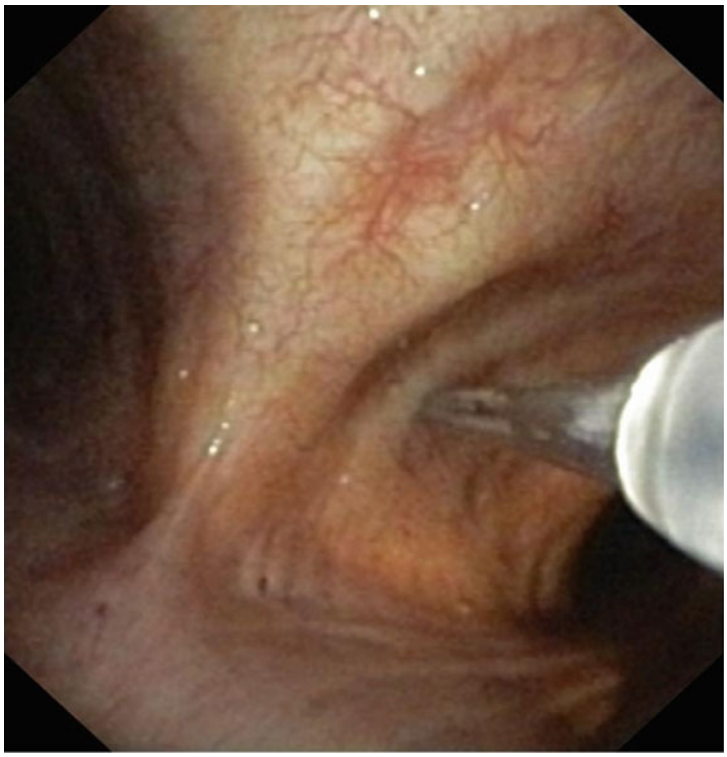
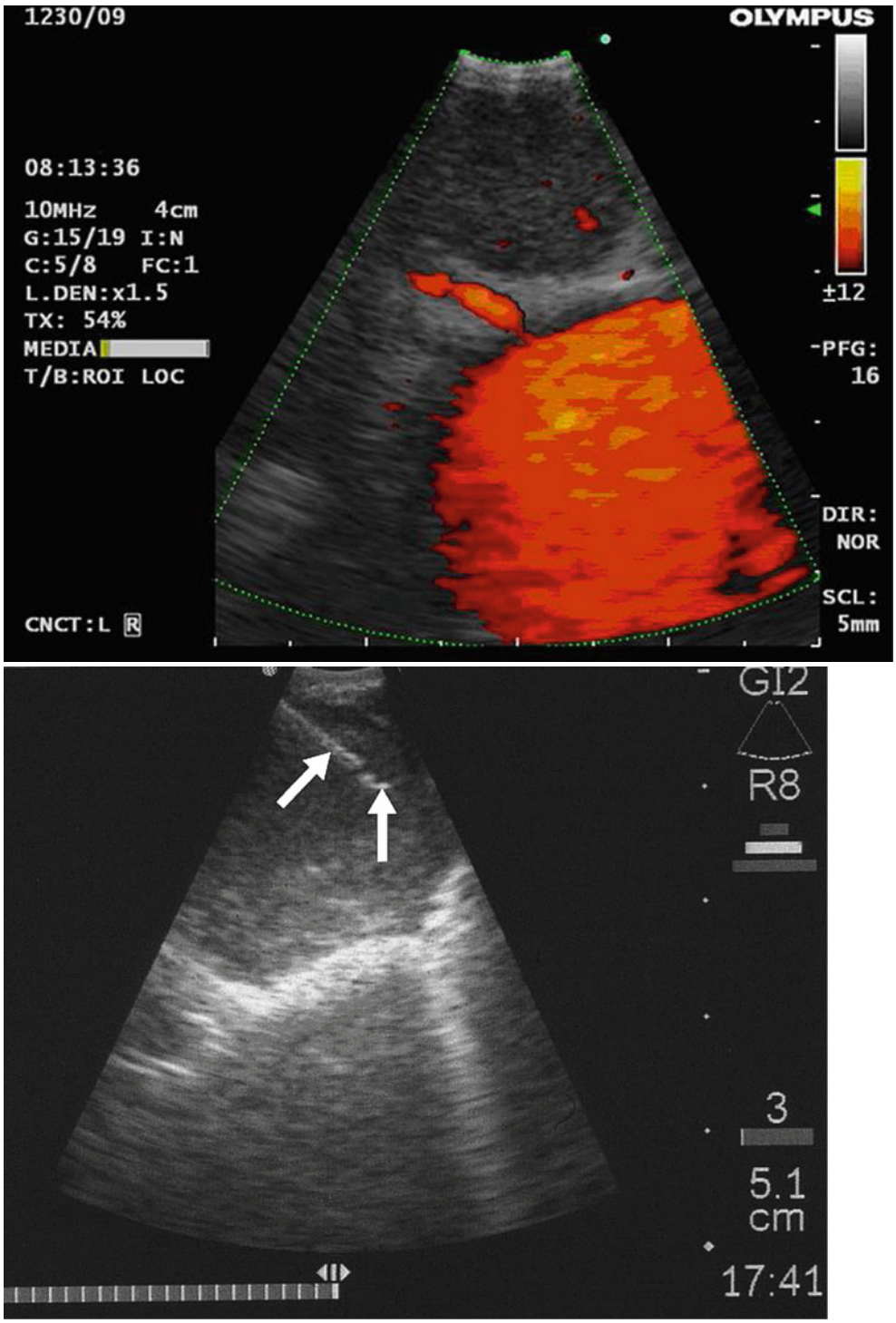


Figure 29.2

Figures 29.3 and 29.4

An EBUS image from an enlarged lymphnode. in orange the flow in the pulmonary artery (doppler-flow). An EBUS-TBNA of an enlarged lymph node. The needle is mark by *arrows*

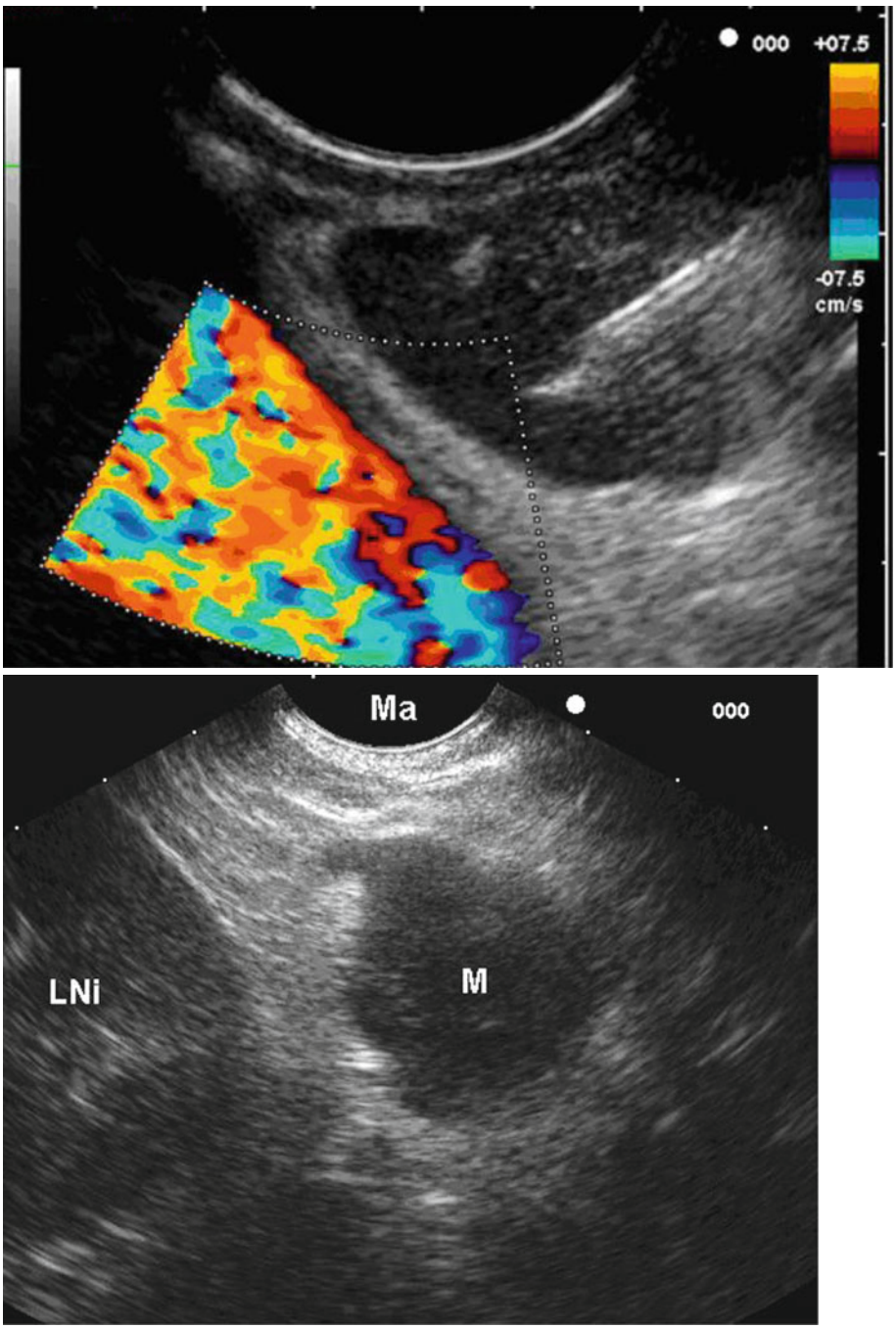
Figures 29.3 and 29.4



Figures 29.5 and 29.6

An EUS FNA procedure from a lymphnode in position 7, the descending aorta is shown by a doppler flow examination. THe needle reflex is seen in the node. An EUS image of an enlarged left adrenal (*LNi* left kidney, *M* adrenal, *MA* stomach)

Figures 29.5 and 29.6



Combining EBUS and EUS

As shown earlier, EUS and EBUS provide access to different areas of the mediastinum. In combining both techniques, most lymph node stations, as well as the left adrenal gland, can be reached (apart from stations 5 and 6). In six recent series, the accuracy of EUS-FNA and EBUS-TBNA used in combination for diagnosing mediastinal cancer was 95 %. With use of the EBUS scope for both endobronchial and endoesophageal sampling, the sensitivity for cancer detection might be as high as 96 % (EUS 89 %, EBUS 91 %), the specificity 100 %, and the negative predictive value 96 % (EUS 82 %, EBUS 92 %) (Herth et al. 2006b, 2010).

Restaging Patients with Lung Cancer After Chemotherapy

Patients with N2 disease (stage IIIA) considered unresectable at diagnosis may become candidates for surgical resection if chemotherapy or chemoradiation can lead to successful downstaging. Documentation of downstaging (complete pathologic response in N2 lymph nodes) is essential for such potentially curative resection. EUS-FNA, EBUS-TBNA, or both may be performed, depending on the location of the lymph nodes initially involved. Usually, the mediastinal N2 lymph node initially proven to be positive should be rebiopsied using the same technique(s). All other diagnostic techniques, including mediastinoscopy, show lower restaging sensitivity and accuracy than those achieved in pre-therapeutic staging. In a study of 124 patients with NSCLC who had undergone induction chemotherapy, restaging by EBUS-TBNA found persistent nodal metastases in 89 patients (72 %); however, 28 of the 35 patients with negative EBUS were found to have residual N2 disease at surgery (Adams et al. 2009).

Conclusion

Overall, TBNA, EBUS, and EUS are safe and effective techniques for staging of the mediastinum. The novel diagnostic methods of EBUS-TBNA and transesophageal ultrasound–guided FNA enable ultrasound-controlled mediastinal tissue sampling. They are minimally invasive and reduce the number of invasive staging procedures.

Currently, the main limitation for TBNA is underuse of the technique, and that of EBUS and EUS is that they are performed predominantly at centers of excellence and hence only on selected patients. Training of physicians and surgeons remains the issue, and performance of an adequate number of procedures per year is required to maintain competency. Reimbursement remains an issue in some countries, as does actual implementation into cancer guidelines within hospitals. Increasingly, both techniques are being used in hospitals across the world, improving the diagnostic yield. Combined EBUS and EUS should be regarded as the "first techniques into the mediastinum," called "complete endo–echo staging."

Beyond doubt, implementation of these techniques will alter lung cancer staging algorithms drastically in the near future. Thanks to its minimally invasive approach, safety record, accuracy, and diagnostic reach, complete ambulant endoscopic staging of lung cancer might be the future.

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