Endobronchial Ultrasound for Staging of Lung Cancer

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Abstract
Accurate preoperative staging in patients with non-small cell lung cancer is of paramount importance. It will guide choices of treatment and determine prognosis and outcome. Over the last years, different techniques have become available. For primary staging of the mediastinum and also in PET-positive mediastinal lesions, the findings should always be cyto- or histologically confirmed. Endobronchial ultrasound (EBUS) is a relatively new technique that provides a better view into the mediastinum. EBUS-guided transbronchial needle aspiration is an additional ultrasound technique, which allows a real-time ultrasound-controlled needle aspiration. Its specificity is high but the negative predictive value is limited. Because of this, if it yields negative results, an invasive surgical technique is indicated. However, if fine needle aspiration is positive, this may be valid as proof of N2 or N3 disease. For staging of early cancer lesions as carcinoma in situ and also for the differentiation of tumor ingrowths in central mediastinal structures, the radial EBUS system is an excellent technique to improve T staging.

The staging of lung cancer [1, 2] not only provides important prognostic information with regard to survival but also guides treatment. For patients whose disease has metastasized to mediastinal lymph nodes (stage III) or with tumors that have invaded mediastinal structures, the benefit of surgery as primary therapy is questionable. Combined chemoradiotherapy is most appropriate, although chemoradiotherapy followed by surgery may be considered [2]. Mediastinal lymph nodes are found in 26% of newly diagnosed lung cancer patients, and extrathoracic metastases are found in 49% [2]. Thus, reliable staging of mediastinal lymph nodes and the mediastinum is essential for choosing an appropriate therapy.

In most centers, computed tomography (CT) is the initial method for staging of mediastinal nodes. Nodes detectable by CT that are considered abnormal, generally have a short-axis diameter greater than 1 cm. Smaller lymph nodes can harbor metastatic foci and enlarged nodes may be benign, especially when central tumors are accompanied by inflammation. The accuracy of CT for diagnosing mediastinal disease is low. In a recent meta-analysis of 20 studies and 3,829 patients [3], the pooled sensitivity was 57%; the pooled specificity was 82%, and the pooled negative predictive value was 82% (range 63–85%). Therefore, surgical mediastinal staging is commonly performed in patients with a radiologically normal mediastinum before a planned cancer resection, to rule out unexpected N2 or N3 disease. However, approximately 18% (range 15–37%) of patients with a negative CT scan who undergo surgical mediastinal staging are found to have metastatic disease.

Mediastinoscopy remains the reference standard for evaluating nodal disease. It has a sensitivity of 90–95% [4]. However, only certain mediastinal lymph node stations are accessible (levels 2, 4 and anterior level 7). For sampling levels 5 and 6, thoracoscopy, anterior mediastinotomy (the Chamberlain procedure), or extended mediastinoscopy can be performed. The inferior mediastinum is evaluated by thoracoscopy. However, all these more aggressive staging procedures require general anesthesia, surgical incision, and therefore high costs [5, 6]. Positron emission tomography (PET) was expected to increase the accuracy of mediastinal staging in non-small cell lung cancer (NSCLC), and indeed, a meta-analysis confirmed its superiority [7]. However, more recent reports have tempered enthusiasm for using PET as the sole tool for evaluating the mediastinum [8].

Endobronchial ultrasound (EBUS) is especially useful in diagnosing mediastinal tumors involving the great vessels (e.g., aorta, vena cava, and main pulmonary arteries), the
central airways and the esophageal wall, which is frequently impossible with conventional radiology. Also for the local staging of esophageal cancer radial EBUS provides important information.

A further area where EBUS is helpful is the evaluation of early cancer lesions without nodal involvement. In small, radiologically invisible tumors, the decision to use local endoscopic therapeutic intervention depends on the intraluminal and intramural extent of the tumor within the different layers of the bronchial wall. In contrast to radiological imaging, radial EBUS allows even very small tumors of a few millimeters to be analyzed. As Kurimoto et al. [9] demonstrated EBUS is a very reliable tool for analyzing the extent of these small lesions. During preoperative staging, radial EBUS allows detailed analysis of intraluminal, submucosal, and intramural tumor spread, which can be essential for decisions on resection margins.

In the following sections the results of radial and linear EBUS will be described and the value for staging will be discussed.

**Mediastinal Lymph Node Staging**

Although a complete workup for metastases is important for staging, the presence of lymph node metastases remains one of the most adverse factors for prognosis in NSCLC. The presence of mediastinal lymph node involvement indicates the presence of stage IIIA or IIIB, which suggests inoperability and/or the need for treatment with chemotherapy and/or radiotherapy [10].

Despite the advancement in the latest imaging techniques, while noninvasive tests can identify nodes suspicious for malignancy, they do not provide definitive tissue diagnosis. Cytological or histological confirmation of suspected metastases is required. Possible endoscopic techniques are needle biopsy techniques which include transbronchial needle aspiration (TBNA), endoesophageal ultrasound-guided fine needle aspiration (EUS-FNA) and, most recently, EBUS-guided TBNA (EBUS-TBNA) [11, 12] (fig. 1).

TBNA for mediastinal staging is performed through the bronchoscope under local anesthesia. It can be performed as an outpatient procedure with no significant morbidity [12–14]. TBNA can be readily performed on the hilar and mediastinal lymph nodes adjacent to the tracheobronchial wall. Rapid on-site cytological evaluation of the aspirates improves the yield, is cost-effective and eliminates unnecessary passes during the procedure [15, 16]. However, conventional TBNA is a blind procedure preventing target visualization and therefore the yield for TBNA varies widely (14–91%) [12]. A meta-analysis of 12 studies in 910 evaluable patients showed a sensitivity of 76% [17].

EBUS-TBNA has access to all the mediastinal lymph node stations accessible by mediastinoscopy as well as N1 nodes. Lymph node stations accessible are the highest mediastinal (station 1), the upper paratracheal (station 2R, 2L), the lower paratracheal (station 4R, 4L), the subcarinal (station 7), as well the hilar (station 10), the interlobar (station 11) and the lobar (station 12) lymph nodes (fig. 2, 3) [18]. The convex probe EBUS was first reported to be useful in the visualization and TBNA of hilar lymph nodes in surgically resected lung cancer specimens before its clinical use [19]. After 4 years of clinical use, a growing number of studies have shown its usefulness and accuracy for mediastinal lymph node sampling [20–22].

More recently, a multicenter study of a larger number of patients showed the effectiveness and accuracy of EBUS-TBNA for the evaluation of mediastinal lymph nodes [23]. In 502 patients, 572 lymph nodes were punctured using EBUS-TBNA, resulting in a successful diagnoses in 535 lymph nodes (94%). The sensitivity was 94% and the specificity was 100%.

Although recent advances in imaging, such as PET with 18F-fluorodeoxyglucose, have been shown to be more accurate for the evaluation of the mediastinum compared with
CT, tissue confirmation of PET-positive lesions is recommended to prove that the lesions are truly malignant [24]. A more recent study comparing EBUS-TBNA, CT and PET for lymph node staging of lung cancer showed a higher yield in favor of EBUS-TBNA [25]. A total of 102 potentially operable patients with lung cancer were included. The sensitivities of CT, PET and EBUS-TBNA for the correct diagnosis of mediastinal and hilar lymph node staging were 76.9, 80.0 and 92.3%, respectively. The specificities were 55.3, 70.1 and 100%. The diagnostic accuracies were 60.8, 72.5 and 98.0%. EBUS-TBNA was proven to have a higher sensitivity as well as specificity compared with CT or PET for mediastinal staging.

Linear EBUS also allows for guidance of biopsies of lymph nodes in regions inaccessible to mediastinoscopy, such as posterior subcarinal and hilar nodes [17] (fig. 4). Though prospective data examining the influence of EBUS on clinical outcomes such as the need for surgery are not available at this time, it is expected that the impact could be significant. Current data suggest that almost 30% of patients undergoing TBNA biopsy of mediastinal and hilar lymph nodes for the staging of bronchogenic carcinoma are found to have unresectable disease [10].

Another study examined the accuracy of EBUS-TBNA in sampling nodes <1 cm in diameter [26]. Of 100 patients, 119 lymph nodes between 4 and 10 mm were detected and sampled. Malignancy was detected in 19 patients but missed in 2 others; all diagnoses were confirmed by surgical biopsy or exploration. The mean (SD) diameter of the sampled lymph nodes was 8.1 mm. The sensitivity of EBUS-TBNA for detecting malignancy was 92.3%; the specificity was 100%, and the negative predictive value was 96.3%.

Even in a completely negative mediastinum assessed by imaging techniques EBUS-TBNA increases the quality of staging. Herth et al. [27] published their experience of EBUS-TBNA in sampling mediastinal lymph nodes in patients with lung cancer and a radiographically normal mediastinum and no PET activity. Patients in whom NSCLC was highly suspected on the basis of CT scans showing no enlarged lymph nodes (no node >1 cm) and a negative PET of the mediastinum underwent EBUS-TBNA.