Review Article

The role of endobronchial ultrasound versus mediastinoscopy for non-small cell lung cancer

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: PubMed; (IV) Collection and assembly of data: K Czarnecka-Kujawa; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: This review provides an update on the current role of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and mediastinoscopy (Med) in assessment of patients with non-small cell lung cancer (NSCLC). Invasive mediastinal lymph node (LN) staging is the major application for both of these techniques. Up until recently, Med was the gold standard for invasive mediastinal LN staging in NSCLC. However, EBUS-TBNA has shown to be equivalent, and in some studies better than Med for invasive staging of lung cancer. EBUS-TBNA offers access to N1 LNs and development of the thin convex probe EBUS (TCP-EBUS) will expand EBUS-TBNA access from the paratracheal region and central airways to more distal parabronchial regions allowing for more extensive N1 LN assessment and sampling more distal lung tumors. EBUS-TBNA is more cost-effective than Med and it is currently recommended as the test of first choice for invasive mediastinal LN staging in lung cancer. Confirmatory Med should be performed selectively in patients with high pretest probability of metastatic disease. Addition of esophageal ultrasound fine needle aspiration (EUS-FNA) may increase diagnostic yield of EBUS-TBNA mediastinal staging. Both Med and EBUS-TBNA can be used in primary lung cancer diagnosis, restaging of the mediastinum following neoadjuvant therapy and in diagnosis of lung cancer recurrence. In the future, a combination of EBUS-TBNA with or without EUS-FNA and Med is most likely going to provide the most optimal invasive assessment of the mediastinum in patients with lung cancer. The decision on test choice and sequence should be made on a case-by-case basis and factoring in local resources and expertise.

Keywords: Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA); mediastinoscopy (Med); lung cancer

Submitted Nov 07, 2016. Accepted for publication Jan 02, 2017.
doi: 10.21037/jtd.2017.03.102
View this article at: http://dx.doi.org/10.21037/jtd.2017.03.102

Introduction

Lung cancer is the leading cause of cancer mortality worldwide (1). Despite evolving knowledge of lung cancer, its molecular genetics and improved ways of detection, the overall 5-year survival is still poor at approximately 18% (1). Accurate staging of patients with lung cancer is important as it determines the treatment and affects the outcome. Assessment of patients with non-small cell lung cancer (NSCLC) includes non-invasive staging [i.e., computed tomography (CT) of the chest, PET-CT, MRI of the brain] and invasive staging [mediastinal lymph node (LN) sampling].

In lung cancer patients, the role of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and mediastinoscopy (Med) centers on invasive evaluation, specifically diagnosis and staging. The techniques also have a role in lung cancer restaging

following neoadjuvant therapy in patients with N2 disease considered for a definitive surgical management, and detection of lung cancer recurrence.

In this article, we discuss the current role of EBUS-TBNA and Med in assessment of patients with NSCLC.

EBUS-TBNA and Med—role in lung cancer staging

Mediastinal staging in patients with NSCLC is a crucial step, offering prognostic information and guiding management. Detection of mediastinal nodal metastases can prevent futile surgeries. The non-invasive staging improves detection of intra- and extra-thoracic metastases, however, it cannot provide a definitive tissue diagnosis and is associated with relatively low sensitivity, specificity and high false positive and negative rates (2-8). Thus, CT chest and PET-CT "positive" results should be confirmed pathologically by invasive pre-operative staging (2,9). In addition, invasive mediastinal LN staging is indicated in patients with: (I) tumors >3 cm in size; (II) central tumors (central third of the hemithorax); (III) distinct enlargement or FDG avid N1 LN (2,9,10). Invasive mediastinal staging is also important in non-surgical candidates with clinical Stage IA disease considered for stereotactic body radiotherapy (SBRT) or ablative therapy [i.e., radiofrequency ablation (RFA)] in order to rule out N1 disease which would prelude use of these therapies (2).

Until just over two decades ago, mediastinal LN staging was performed with the use of bronchoscopic technique of a blind conventional TBNA and surgical invasive techniques including: Med, specifically cervical Med and less commonly, left anterior mediastinotomy (a.k.a. Chamberlain procedure). In addition, extended cervical Med, and more recently, video assisted thoracoscopic surgery (VATS) and "supermediastinoscopies", including transcervical extended mediastinal lymphadenectomy (TEMLA) and video-assisted mediastinal lymphadenectomy (VAMLA) have become available (11,12). EBUS-TBNA has become available for mediastinal LN staging in the last 14 years. All surgical techniques require general anesthesia.

Surgical mediastinal LN staging

Med allows access to the upper paratracheal (stations 2R and 2L), lower paratracheal (stations 4R and 4L), anterior subcarinal (station 7) as well as hilar (stations 10R and 10L) LNs. Med cannot access the pulmonary ligament (station 9), paraesophageal (station 8), posterior subcarinal (station 7), and the aorto-pulmonary window (APW; stations 5 and 6) LNs. The video-assisted Med has now replaced the traditional Med in majority of thoracic surgery centers, increasing procedure safety and diagnostic performance in lung cancer staging (2). Anterior mediastinotomy (a.k.a Chamberlain procedure) allows access to station 5 and 6 LNs via the left second intercostal space (13). Reported sensitivity and negative predictive value (NPV) of anterior mediastinotomy in assessment of AP window LNs is 78% and 91% respectively (2). Extended cervical Med introduced by Kirschner in 1971, and popularized by Ginsburg, allows access to levels 5, 6, 2, 4 and 7 (14-16). Reported sensitivity of extended Med ranges from 71% to 81% while NPV is 91% (13). VAMLA allows access to bilateral paratracheal and subcarinal LNs (17). VAMLA sensitivity in lung cancer staging is: 0.96 (95% CI, 0.81–99.3); specificity, 1 (95% CI, 0.97–1.00); PPV 1 (95% CI, 0.87–1.00); NPV 0.99 (95% CI, 0.95–0.99); and diagnostic accuracy, 0.99 (95% CI, 0.96–0.99). TEMLA is an open technique, allowing access to stations 1, 2R, 2L, 3a, 4R, 4L, 5, 6, 7 and 8 LNs. Large number of nodes can be removed (mean 43; range, 26–85) (11,12). Reported sensitivity and NPV of TEMLA in detection of mediastinal LN metastases is 0.9 and 0.95, respectively. In contrast to other surgical mediastinal sampling methods, TEMLA and VAMLA offer complete lymphadenectomy (17). However, the high rate of complications (6.0–13.2%) make use of both VAMLA and TEMLA unpopular given development of endoscopic techniques with comparable diagnostic yield but much better safety profile and shorter procedure duration (11,12,17,18).

In this review, all Med data presented pertains to video assisted-cervical Med (the most commonly used surgical mediastinal assessment modality), unless specified otherwise.

In mediastinal LN staging of primary lung cancer, Med yield depends on LN location and operator skills (19,20). In a recent systematic review assessing Med performance in 995 patients with clinical N0 to N3 disease, Med sensitivity was 89% and NPV of 92% (2).

Med is an invasive procedure performed in an operating room. It requires general anesthesia. A transverse incision is made above the sternal notch to access the paratracheal fascia. Video mediastinoscope is then inserted into the mediastinum after blunt digital dissection and palpation of the mediastinal vessels with further blunt dissection to access the mediastinal LNs. Generally, Med is a safe procedure, performed in outpatient setting. Reported

complication rate is up to 2.5%, including a pneumothorax, infection and injury to the major mediastinal vessels (which can lead to a life threatening bleeding), peripheral nerves (which can result in vocal cord palsy), bronchi and the esophagus. Mortality has been reported at 0.08% in relation to vascular injury (21). The procedure is contraindicated in patients with tracheostomy, severe cervical spine arthritis or instability that prohibits neck extension. Mediastinal adhesions may make a repeat Med challenging (21-23).

Endoscopic mediastinal staging with EBUS-TBNA

Introduction of radial probe endobronchial ultrasound (RP-EBUS) in the early 1990's, has introduced the idea of less invasive mediastinal LN staging in lung cancer (24-27). Besides its role in diagnosis of peribronchial lesions (28,29) RP-EBUS has been used to guide TBNA in patients with mediastinal lymphadenopathy and in lung cancer mediastinal LN staging. Diagnostic yield of RP-EBUS guided TBNA of mediastinal LNs ranged between 72% and 80% [in a population with high prevalence of mediastinal nodal metastasis (86%)] (27,30). However, it wasn't until the early 2000's, and introduction of convex probe EBUS (CP-EBUS) that mediastinal LN staging in lung cancer has undergone a revolutionary change (31,32).

CP-EBUS is a flexible bronchoscope integrated with a convex transducer at the tip which scans parallel to the insertion direction of the bronchoscope. The outer and inner diameters of the insertion tube are 6.9mm and 6.2mm, respectively. Incorporation of EBUS at the tip of a flexible bronchoscope allows for real-time TBNA of the visualized structures (LNs, tumors). The ultrasound probe has B-mode and power color Doppler capabilities, allowing differentiation of LNs from vascular structures. In addition, the newer EU-ME2 processor (Olympus) is equipped with the elastography function. Elastography allows for real time assessment of LN deformability (which may be altered in a pathological LN) taking advantage of the tissue distortion caused by the compressions or vibrations generated by the heartbeat or vascular pulsations) (33). Elastography may offer a useful non-invasive adjunct to endosonographic LN assessment, pointing out the areas which are more likely to be involved with tumor, for a more directed TBNA (34).

Similar to Med, CP-EBUS can access station 2R, 2L, 4R, 4L and 7 LNs. Posteriorly and deep located station 7 LNs may not be readily accessible to Med, resulting in false negative results, but can be easily assessed with EBUS-TBNA (19,35). EBUS-TBNA can reach N1 LNs, including the hilar (station 10), interlobar (station 11) and some of the lobar LNs (station 12) which are not accessible by Med.

Neither EBUS-TBNA nor Med can access prevascular (3A), sub-aortic (station 5), para-aortic (station 6), para-esophageal (station 8) and pulmonary ligament (station 9) nodes.

EBUS-TBNA is a safe procedure, with an average complication rate of 1.23% (95% CI, 0.97-1.48%). Reported complications include: hemorrhage (0.68%), infection (0.19%) (mediastinitis, pneumonia, pericarditis, cyst infection, sepsis) pneumothorax (0.03%). EBUS-TBNA reported mortality is 0.01% (36,37). EBUS-TBNA is an out-patient procedure that can be performed safely in an endoscopy suite, under conscious sedation (38).

The first study report of EBUS-TBNA in mediastinal LN staging in lung cancer showed sensitivity of 94.5%, specificity and PPV of 100%, NPV of 89.5% and diagnostic accuracy of 96.3% (31). The prevalence of mediastinal nodal metastasis was 63%. In 19% of patients, in addition to offering staging information, EBUS-TBNA provided diagnostic information, eliminating the need for further invasive tests. EBUS-TBNA staging, prevented 29 mediastinoscopy, eight thoracotomies, four thoracoscopy and nine percutaneous LN biopsies, streamlining the diagnostic work up (31). Another study of EBUS-TBNA staging in a population with high prevalence of mediastinal nodal metastasis (98.2%) and mediastinal lymphadenopathy confirmed high diagnostic performance of EBUS-TBNA with sensitivity, specificity, diagnostic yield and accuracy of 94%, 100%, 93% and 94%, respectively. However, NPV was only 11% suggesting that in a population of patients with high pretest probability of mediastinal nodal metastasis, confirmatory Med or other staging procedure should be performed to exclude false negatives (39).

Lung cancer management strategies have now been expanded to include non-surgical strategies like SBRT and RFA. In addition, tissue-sparing surgery (wedge, sublobar resection) have become more popular and may be the only treatment option for non-surgical candidates. Post-SBRT local failure can be as high as 15%. This may be due to undetected nodal metastasis in patients undergoing treatment under presumption that the clinical stage correlates with the pathological stage (2,40-48). In addition, lung cancer screening programs have proliferated since the recent lung cancer screening recommendations of the U.S. Preventative Services Task Force (49). These developments may expand the pool of patients with early disease who qualify for minimally invasive diagnosis and treatment.

Table 1 Performance characteristics of EBUS-TBNA and Med in mediastinal lymph node staging in patients with lung cancer

Study	Year	n	Prevalence of N2/N3 disease (%)	Sensitivity (%)		Negative predictive value (%)	
				EBUS	Med	EBUS	Med
Ernst *et al*. (20)	2008	66	89	87	68	78	59
Yasufuku *et al*. (35)	2011	153	32	81	79	91	90
Um *et al*. (19)	2015	127	59	88	81	85	79

Furthermore, given improved survival in patients with single versus multiple N1 LNs involvement, preoperative chemotherapy (not currently standard of care because of the lack of studies proving benefit) may become an option for patients with multiple N1 nodal disease. All of these recent developments stress the growing need for invasive nodal staging that extends beyond the mediastinum and into the hilar, interlobar, and perhaps even the lobar LNs (50). Performance of Med and EBUS-TBNA has been assessed in patients with clinical N0 disease.

A recent systematic review, showed that yield of video-assisted Med, unlike that of the traditional Med, is not affected by the prevalence of mediastinal nodal metastasis (sensitivity of 89% in cN0–3) (2). EBUS-TBNA has varying performance in patients with clinical N0 disease. Some studies report sensitivity and NPV ranging between 89–92.3% and 96.3–98.9%, respectively (44,45), while others show sensitivity and NPV ranging between 35–60% and 88.4–93.4% (41,43). There may be a variety of reasons for this discrepancy aside from clinical expertise of the operator: (I) presence of multiple LNs at a station, but only selective LN sampling; (II) LNs inaccessible to EBUS-TBNA sampling (i.e., vascular structures in the needle path); (III) micrometastases in LNs not sampled (i.e., in many studies the lower limit of LN size considered for TBNA was 5 mm, with LNs smaller than that not sampled); (IV) micrometastases in small LNs which may be more challenging to sample. Some authors reported higher percentage of non-diagnostic results from LNs smaller than 5 mm in size, suggesting that this may represent the lower limit of EBUS-TBNA accessibility beyond which, adequate tissue sampling may be challenging and negative results should be interpreted with caution (35). EBUS-TBNA can accurately distinguish between the pathological N0 and N1 disease with sensitivity, specificity, diagnostic accuracy and NPV of 73%, 100%, 96.6% and 96.2%, respectively (51). Overall, EBUS-TBNA can correctly identify mediastinal nodal metastasis in ~1 out of 3 patients with clinical N0 disease. Given EBUS-TBNA safety profile and the advantage of access to N1 LNs, staging with EBUS-TBNA may become an important step in work-up of patients with early lung cancer.

To date systematic reviews and four meta-analysis evaluated performance of EBUS-TBNA in lung cancer staging (2,52-55). Populations with different prevalence of mediastinal nodal metastasis were included (prevalence range 33.7% to 99.3%). Data from nearly 3,000 patients were analysed, 36 studies, spanning 12 years (from 2002 to 2012). Overall, EBUS-TBNA demonstrated excellent sensitivity and specificity of 0.88–0.93 (95% CI, 0.79–0.94) and 1.00 (95% CI, 0.92–1.00), respectively; NPV of 91% (range, 83–96%) (2,52-54).

EBUS-TBNA vs. Med: a comparison of diagnostic performance in mediastinal LN staging

EBUS-TBNA performance in mediastinal LN staging in lung cancer has also been compared to that of Med, in prospective studies (19,20,35) (*Table 1*) and recently in a meta-analysis (56). Populations with moderate and high prevalence of mediastinal nodal metastasis were assessed (prevalence ranged from 32% to 89%). Yasufuku *et al*. performed a first heard-to-head comparison of EBUS-TBNA and Med staging in a cohort of 153 patients with potentially resectable lung cancer. Sensitivity, NPV, and diagnostic accuracy of EBUS-TBNA and Med were 81%, 91%, 93% and 79%, 90% and 93%, respectively. Specificity and the PPV for both staging procedures were 100%. This study demonstrated that in expert hands and controlled setting, EBUS-TBNA is equivalent to Med in mediastinal LN staging (35). Ernst *et al*. study showed similar results (20). Ninety three percent *vs*. 82% of patients with lung cancer evaluated by EBUS-TBNA and Med, respectively, had their pathological stage correctly identified (P=0.083). Overall, sensitivity and NPV of EBUS-TBNA and Med were 89% *vs*. 68% and 78% *vs*. 59%, respectively. However, per LN analysis showed that EBUS-TBNA had higher diagnostic accuracy (91%) than Med (78%, P=0.007).

There was a discrepancy in diagnostic yield at station 7 (79% for Med *vs.* 98% for EBUS-TBNA, P=0.007). Recently, Um *et al.* demonstrated that EBUS-TBNA can have a superior to Med performance in lung cancer staging in a cohort of patients with biopsy proven lung cancer (19). EBUS-TBNA and Med sensitivity and diagnostic accuracy were 88% *vs.* 81.3% and 92.9% *vs.* 89%, respectively (P=0.005). No difference was demonstrated between the procedures in specificity (100% for both), PPV (100% EBUS-TBNA *vs.* 89% Med) and NPV (EBUS-TBNA 85.2% *vs.* 78.8% Med). Similar to the Ernst *et al.* study, there was a discrepancy between the modalities in disease detection at station 7 LN, with a non-significant trend towards inferior yield with Med than EBUS-TBNA, 75% *vs.* 82% (P=0.0614). However, Med yield at station 4L was significantly lower than that of EBUS-TBNA (52.4% *vs.* 81%, P=0.0270).

Recently, a large meta-analysis was conducted comparing indirectly diagnostic yield of mediastinal staging with EBUS-TBNA to that of Med (56). Ten EBUS-TBNA and seven Med studies were included. Outcomes of nearly 1,000 patients staged were analysed and compared. Overall, sensitivity for detection of mediastinal metastasis was equivalent between EBUS-TBNA and Med at 0.84 (95% CI, 0.79–0.88) and 0.86 (95% CI, 0.82–0.90), respectively (P=0.6321). Med was associated with fewer false negatives, which in both staging modalities were attributed to metastasis in inaccessible LNs (station 5 and 6) and inadequate sampling at accessible LNs. Med, was associated with more complications (17 *vs.* 4). EBUS-TBNA related complications were minor and resolved without intervention.

These studies confirm that both techniques have similar performance in mediastinal LN staging in lung cancer, with EBUS-TBNA being less invasive, better tolerated and with fewer and only minor complications. These findings led to a recent recommendation by the American College of Chest Physicians (ACCP) and the European Society of Thoracic Surgeons (ESTS) that the endoscopic mediastinal staging with EBUS-TBNA or esophageal ultrasound fine needle aspiration (EUS-FNA) be the tests of first choice in invasive mediastinal LN staging, and that they be followed by Med in case of negative results if the index of suspicion for metastatic disease is high (2,9).

Combined ultrasonography

Given that neither Med nor EBUS-TBNA can access stations 5, 6, 8 and 9 nodes, some authors have advocated for a combined approach, and adding EUS-FNA to EBUS-TBNA [combined ultrasonography (CUS)] for mediastinal LN staging in lung cancer (57,58). EUS-FNA is complimentary to EBUS-TBNA and Med in terms of mediastinal LN access. It allows access to station 2R, 2L, 4L, 4R, 5, 7, 8 and 9 LNs. EUS-FNA can also access L adrenal, left lobe of the liver and celiac axis, some of which are common sites of metastasis from lung cancer. However, due to intervening airways, right sided upper paratracheal (2R, 2L) and lower paratracheal (4R) LNs may be more challenging to access. Detailed performance analysis of EUS-FNA in mediastinal LN staging in lung cancer is beyond the scope of this review, nonetheless, EUS-FNA sensitivity, specificity, PPV and NPV in mediastinal LN staging is equivalent to that of EBUS-TBNA at 89%, 100%, 100% and 86% respectively (2).

CUS has been shown to improve access to the mediastinum (59) and the extended LN sampling that occurs with both modalities combined may improve diagnostic yield as compared to EBUS-TBNA alone, thank to detection of additional metastatic foci (59-61). The concept of CUS was first presented by Vilmann *et al.* (60). Thirty one patients with suspected or proven lung cancer underwent CUS. A total of 119 lesions were sampled by EUS-FNA (n=59) and EBUS–TBNA (n=60). Cancer diagnosis was made in 26 EUS-FNA and 28 EBUS-TBNA sampled lesions, respectively. Eleven additional cancer diagnoses and three samples with suspicious cells were obtained by EBUS-TBNA that had not been obtained by the EUS-FNA. Conversely, 12 additional cancer diagnoses, one suspicious and one specific benign diagnosis (sarcoidosis) were found by EUS-FNA that had not been picked up by EBUS-TBNA. Mediastinal involvement was confirmed in 20 of the 28 patients in whom a final diagnosis was obtained. The accuracy of CUS, for diagnosis of mediastinal metastasis was 100% (95% CI, 83–100%).

Whether two dedicated scopes are used (a dedicated EBUS-TBNA scope and a dedicated EUS-FNA scope) or EBUS scope following the EBUS-TBNA is used to perform transesophageal needle aspiration (TENA), CUS sensitivity, NPV and diagnostic accuracy have been shown to remain high and perhaps higher than that of EBUS-TBNA alone (59,61,62). One study reported sensitivity and NPV of CUS of 96% *vs.* EBUS-TBNA alone of 92%, in lung cancer staging. However, no p value was provided for this difference. Another study showed, again, high EBUS-TBNA and CUS sensitivity, NPV and diagnostic accuracy of 84.4%, 93.3%, and 95.1% *vs.* 91.1%, 96.1% and 97.2%; P=0.332, P=0.37 9, and P=0.360, respectively

but with no statistically significant difference between the two approaches (59). The diagnostic yield was not affected regardless of whether one or two scopes were used for the CUS (59,61,63). However, one scope CUS significantly reduced procedure time as compared to the two scope approach (25±4.4 *vs.* 14.9±2.3 min, P=0.001) (63).

Based on these results, some authors argue for the use of CUS in mediastinal LN staging in patients with lung cancer and promote the use of EBUS-TENA over EBUS-TBNA for time-saving purposes (61,62,64,65). However, there are some important aspects of these studies that need to be taken into consideration before CUS can be recommended routinely. Herth *et al.* reported only three cases where positive results were obtained exclusively by EBUS-TENA from station 2L, 10L, and 7, all of which are accessible by EBUS-TBNA (61). In another study, three exclusively positive cases determined by EBUS-TENA (2.1% of patients) were from station 4L and 5 (frequently involved together with station 4L which is accessible to EBUS-TBNA). Stations 8 and 9 LNs did not contribute to increased diagnostic yield by EBUS-TENA in that study (59). Overall, prevalence of mediastinal LN metastasis in stations inaccessible to EBUS-TBNA is low, ranging between 0.19–1.2% for station 8, and 0.83–2.2% in stations 5 and 6 (35,58,62). The low prevalence of mediastinal metastasis in exclusively EUS-accessible LNs, limitations of EUS including underdiagnoses of N3 disease in left sided tumors, and N2 disease in right-sided tumors (due to decreased diagnostic yield resulting from higher rate of false negatives in the R sided LNs due to reduced LN visualization through the air-filled trachea) and given the equivalent to Med yield of EBUS-TBNA in hands of a skilled operator, may be the reasons behind the lack of statistically significant difference in diagnostic yield when adding EUS-FNA to EBUS-TBNA staging, while a statistically significant increase in diagnostic yield has been achieved by adding EBUS-TBNA to EUS-FNA (66).

The use of EBUS through the esophagus to increase the yield further or CUS using two scopes may not be justifiable form the health economics perspective and instead a selective use of CUS should be implemented if there is a high index of suspicion of metastasis in EBUS-TBNA inaccessible LNs. In 2005, Rintoul *et al.* selectively added EUS-FNA to EBUS-TBNA staging in 7 out of 20 patients subjected to endoscopic staging. Five of those patients had additional pathologic diagnosis detected by the EUS-FNA that wouldn't have been obtained with EBUS-TBNA alone. CUS sensitivity, specificity and accuracy were 85% (95% CI, 54.6–98.1%), 100% (95% CI, 47.8–100%) and 89% (95% CI, 65.3–98.6%), respectively (67).

A recent prospective study of mediastinal staging in patients with lung cancer, compared the yield of combined EBUS-EUS and Med with the results of surgical lymphadenectomy. CUS and Med approach diagnosed additional N2/N3 and M1 disease in 14% of study patients that had not been detected by the Med approach, preventing inappropriate surgical resections. CUS sensitivity, NPV and diagnostic accuracy was 91%, 100%, 96% and 97%, respectively. Interestingly, NPV and diagnostic accuracy of EBUS alone, CUS and Med compared with mediastinal lymphadenectomy at thoracotomy were quite similar (–90%, 95%CI, –0.84 to 0.95) (68).

Use of confirmatory Med after negative EBUS-TBNA

A positive result with mediastinal LN staging with EBUS-TBNA has a significant impact on patient management and may result in improved survival (2,24,69-71). However, if EBUS-TBNA staging is negative, the question remains whether there is a role for a confirmatory Med in this setting, and if so, which patients should it be offered to.

Performance of EBUS-TBNA depends on the operator's skill and prevalence of mediastinal metastasis in the studied population. In skilled hands, performance of EBUS-TBNA has been shown to be equivalent or better than that of Med (19,35). In a population with intermediate prevalence of mediastinal metastasis (35%), Yasufuku *et al.* showed sensitivity and NPV of EBUS-TBNA of 81% and 91%, respectively (35). Combined EBUS-TBNA and Med improved sensitivity to 91% and NPV to 96%. This represents an overall 5% increase in NPV and number needed to treat of 9. In other words, in a population with intermediate prevalence of nodal metastasis, both procedures would have to be performed in nine patients to detect one patient with metastatic disease. In a patient population with clinical N0 disease, surgical staging may not contribute significantly to improving diagnostic yield. Szlubowski *et al.* demonstrated CUS sensitivity, specificity, diagnostic accuracy, PPV and NPV of 68% (95% CI, 48–84%), 98% (95% CI, 92–100%), 91% (95% CI, 86–96%), 91% (95% CI, 70–99%) and 91% (95% CI, 83–96%). TEMLA was performed in 99 patients whose CUS was negative detecting 9 additional cases of mediastinal metastatic disease (8%) (72).

Therefore, in a patient population with clinical N0 disease and low prevalence of mediastinal nodal metastasis, confirmatory Med following negative EBUS-TBNA

staging, may not be justifiable. Annema *et al.* compared the yield of CUS and Med combined to that of Med in a population of patients with high prevalence of mediastinal nodal metastasis (49%) (58). Sensitivity for detecting N2 and N3 disease was 79% (95% CI, 66–88%) in Med arm, 85% (95% CI, 74–92%) in CUS arm (P=0.47) and 94% (62/66; 95% CI, 85–98%) for the CUS strategy followed by Med (P=0.02). Evaluating sonography (CUS) and surgical components (Med) separately, showed sensitivity and NPV of 85% and 85% for CUS and 79% and 86% for Med. This demonstrated that Med and CUS staging may be equivalent but that CUS approach followed by Med in CUS negative cases in a patient population with high prevalence of mediastinal nodal metastasis has higher than Med alone sensitivity and results in fewer unnecessary surgeries (7% in CUS and Med arm *vs.* 18% in the Med alone arm, P=0.02). Adding Med to CUS increased sensitivity and NPV of staging by 9% (94%) and 11% (93%), respectively indicating that with rising prevalence of mediastinal nodal metastasis, confirmatory Med may be of value and that the decision about confirmatory testing should be made on a case by case basis. (Post hoc analysis of survival data from this trial has recently been reported, showing no survival advantage in the CUS and Med arm as compared with the Med alone arm. This may be explained by insufficient powering of the study to detect survival difference) (73).

Cost-effectiveness of EBUS-TBNA and Med in mediastinal LN staging in primary lung cancer

Multiple studies explored costs, cost-benefit and cost-effectiveness of EBUS-TBNA and Med in lung cancer staging (74-79). In 2006, Meyers *et al.* evaluated cost effectiveness of mediastinal LN staging with Med in patients with clinical Stage I disease (by PET and CT). Prevalence of N2 disease was 5.6% (74). The results showed that routine Med in this patient population is not cost-effective. If neoadjuvant therapy in N2 disease is assumed to convey a survival benefit over adjuvant chemotherapy (suggested by some studies) (69-71), then invasive staging may be cost-effective in this patient population (80). Routine Med is, however, cost-effective once the prevalence of mediastinal nodal metastasis exceeds 10% (74). Five years following Meyers *et al.* study, Steinfort *et al.* performed a decision analysis comparing costs of mediastinal LN staging in lung cancer, in which they incorporated EBUS-TBNA into the model. Other strategies included: Med, EBUS-TBNA followed by Med (if endoscopic staging was negative) and conventional TBNA (75). In a population with high prevalence of mediastinal nodal metastasis EBUS-TBNA followed by Med was the least costly strategy, suggesting a clear role for confirmatory Med in some patients, while advocating for EBUS-TBNA as the test of first choice in invasive staging. All studies demonstrate that EBUS-TBNA sensitivity and prevalence of mediastinal nodal metastasis are important factors in deciding on the most cost-effective staging modality. Recent study showed that if the EBUS-TBNA sensitivity of at least 25% cannot be achieved, Med should be the preferred staging strategy. Cost comparison between Med and EBUS-TBNA showed that the needle based technique is less expensive than Med if the staging procedure is performed in the endoscopy suite while it is more expensive than Med if performed in the operating room, however, it generates less waste than Med (75,81).

EBUS-TBNA and Med—role in lung cancer diagnosis

EBUS-TBNA has also been shown to be a useful modality in diagnosis of primary lung cancer (82-85). Peribronchial lesions adjacent to large central or segmental airways of the lower lobes can be accessed with EBUS-TBNA with sensitivity and diagnostic accuracy ranging between 82% and 97.2% (82-85). NPV is quite low at 23% (95%CI, 5–53%), indicating that negative results in patients with high pretest probability of lung cancer, should be evaluated with other modalities (83). Only minor complications have been reported including self-limited atrial fibrillation (83). Importantly, no pneumothoraces or bleeding were reported.

Endobronchial biopsy and percutaneous lung biopsy are two commonly utilized modalities for diagnosis of lung lesions suspicious for cancer. Beside exposure to radiation, percutaneous, CT-guided lung biopsy, carries a risk of pneumothorax and or hemoptysis of 30–40% (86,87). Percutaneous lung biopsy in centrally located lesions is more expensive and with lower yield than transbronchial biopsy (87,88). Flexible bronchoscopy may be a useful diagnostic modality if the lesion has an endobronchial component, but without it, diagnostic yield has been reported at 0% (83).

Current CP-EBUS can only assess paratracheal and peribronchial areas located around the main and segmental airways of lower lobes. Majority of lung cancers occur in the right upper lobe and tumors of left upper lobe and lingula are not uncommon. Recently, Wada *et al.* reported

on performance of a prototype thin convex probe-EBUS (TCP-EBUS) in a porcine lung (89). The TCP-EBUS has a smaller external diameter of 5.9 mm and grater bending angle of 170° up than the current CP-EBUS (6.9 mm external diameter and 120° up angulation). Thanks to these characteristics, the TCP-EBUS on average has a 14.7 mm greater endoscopic visibility range and a 16.0 mm greater maximum reach than the current CP-EBUS. The TCP-EBUS visualized 1 to 3 distal bifurcations further than the current CP-EBUS, accessing the segmental airways of the left upper lobe and the tracheobronchus (intubation of which, requires significant scope angulation, not possible with the current CP-EBUS). Adequate nodal tissue was sampled from lobar and segmental LNs (89). Improved airway access and ability to sample upper and lower lobe peribronchial tissue and segmental LNs are expected in human lung, given larger than pig's airway diameter. Performance of the prototype TCP-EBUS offers a promising improvement to diagnosis of peribronchial tumors. In addition, it would improve the assessment of intrathoracic LNs, moving the lung cancer staging beyond the mediastinum and into the segmental and lobar regions and into the upper lobes. This could prove useful in planning treatment for ablative therapy and sublobar resection candidates. In addition, the ability to safely access, sample and accurately diagnose lung cancer in patients with centrally located lesions by EBUS-TBNA opens up a possibility of accomplishing both, obtaining tissue diagnosis from the primary tumor and mediastinal staging in a single procedure, reducing overall costs of the diagnostic work up and accelerating patient's access to appropriate definitive therapy.

In the era of personalized medicine, determining molecular signature of lung cancer has become the standard of care. EBUS-TBNA samples provide sufficient quantity and quality material for molecular testing. Reported adequacy of EBUS-TBNA samples for molecular diagnosis ranges from 77% to 98% (90,91). EBUS samples have one of the lowest insufficiency rates (4%) for EGFR and KRAS mutational analysis (compared with CT-FNA, 7.5%; ultrasound guided/superficial FNA, 10%) and can provide sufficient tissue quantity for multigene testing (i.e., p53 mutation, BRAF and PIK3CA) (90,92).

Med can also be used in assessment of primary lung lesions assessing for presence and the extent of mediastinal tumor invasion (T component). In mediastinal staging studies, Med has been shown to correctly identify mediastinal tumor invasion, preventing futile thoracotomies (58).

Med and EBUS-TBNA in lung cancer re-staging and recurrence

Neoadjuvant chemoradiation followed by surgery in lung cancer patients with N2 disease may offer survival advantage over definitive chemoradiation, if the mediastinum can be down-staged to N0/N1 preoperatively (93-95). Both Med and EBUS-TBNA have been used for mediastinal restaging (41,96-102). However, performance of both Med and EBUS-TBNA in restaging is worse than in original staging. This is due to LN and mediastinal scarring that results from neoadjuvant therapy and prior Med. In the past, the prevailing thought was that prior manipulation of the mediastinum may make a repeat Med impossible. However, multiple studies have reported feasibility of repeated Med for restaging with 98–100% planned procedures completed (97,100), low morbidity (1.9%) (100) but unfortunately also a death reported in one study due to perioperative bleeding (97). One of the largest series was reported by De Waele *et al.* (97), 104 patients were restaged with Med after neoadjuvant therapy. Med sensitivity, specificity, and diagnostic accuracy were 71%, 100% and 84%, respectively (97). Med prevented 20 futile thoracotomies by detection of persistent N2/3 disease. Patients without nodal metastasis proceeded to surgical resection with median survival of 28 months (95% CI, 15–41 months). Survival in patients with positive and false-negative Med was 14 months (95% CI, 8–20 months) and 24 months (95% CI, 3–45 months), respectively. This suggests that Med is also able to provide a prognostic information. Other studies reported similar performance characteristics for Med with sensitivity of 61–83%, diagnostic accuracy of 84–91% and NPV of 85% (96-98,100). One, study however, showed very low sensitivity and diagnostic accuracy of Med, 29% and 60%, respectively, which was presumed to be due to inadequate sampling of station 7 LN in majority of patients (99).

Sensitivity and NPV of EBUS-TBNA for mediastinal restaging has shown to be lower than in initial mediastinal staging, ranging between 50% and 77%. This is thought to be attributable to LN necrosis and fibrosis (101-104). However, the procedure is safe with no complications reported.

EBUS-TBNA has been evaluated in patients with new mediastinal lymphadenopathy following treatment of lung cancer (105). PET-CT is not highly reliable in assessment of patients suspected to have cancer recurrence. False positives are common and can be related to post inflammatory mediastinal changes due to surgery or

related to chronic bronchitis due to smoking (105,106). Pathological confirmation of positive imaging is, therefore, important. In one study, EBUS-TBNA mediastinal LN sampling was performed in patients with progressive mediastinal lymphadenopathy following initial treatment of NSCLC (105). Cancer recurrence and a new primary cancer were diagnosed in 64% and 25% of patients, respectively. Patients diagnosed with early new lung cancer, following EBUS-TBNA staging proving no mediastinal involvement, underwent surgery with curative intent. Patients with recurrence and new small cell lung cancer obtained appropriate therapy. A recent study reported a 100% sensitivity, specificity, PPV and NPV of EBUS-TBNA for assessment of mediastinal LN in patients following treatment of lung cancer (107). These results show that EBUS-TBNA can be used to obtain a definitive diagnosis of newly developed mediastinal and hilar abnormalities after primary therapy in patients with lung cancer. Diagnostic accuracy of EBUS-TBNA in such setting is 95.1%. Added benefit is that the procedure can be repeated safely without additional risk to the patient, even if the mediastinum had previously been assessed by Med.

Due to adhesions that occur following LN dissection during lung cancer resection, confirming cancer recurrence with Med meets the same challenges as using Med for restaging after neoadjuvant therapy (108,109).

At present there is insufficient evidence to clearly define the role of surgical and endoscopic modalities in patients with advanced lung cancer and considered for trimodality therapy and in setting of suspected recurrent lung cancer. Given better performance of Med when performed for the first time, and equivalent performance of Med and EBUS-TBNA in primary mediastinal staging, it appears that saving Med for re-staging after neoadjuvant therapy and staging initially with EBUS-TBNA might be the most cost-effective staging approach in lung cancer patients considered for a curative resection. However, if EBUS-TBNA is performed for restaging, a confirmatory Med should be performed in the event of negative EBUS-TBNA (9). Given excellent performance characteristic of EBUS-TBNA in diagnosis of lung cancer recurrence and the potential challenges of Med, EBUS-TBNA should be used for initial evaluation of new mediastinal lymphadenopathy in patients with prior lung cancer.

Conclusions and future directions

Lung cancer diagnosis and management have undergone significant changes over the past decade with introduction of the minimally invasive endoscopic techniques. EBUS-TBNA offers an accurate and cost-effective means of mediastinal evaluation at all stages of lung cancer, from the original mediastinal staging to detection of disease recurrence. Quality data on performance of EBUS-TBNA in mediastinal LN staging in lung cancer led to a recent recommendation from the ACCP and ESTS to use the needle based techniques for the initial mediastinal staging (2,9). Currently, endoscopic staging is recommended for patients with distinct mediastinal or N1 LN enlargement on CT chest, or FDG avidity on PET, in central tumors and all patients with T2 tumors (2). When combined with EUS-FNA, EBUS-TBNA offers nearly complete assessment of the mediastinum and may have higher diagnostic accuracy than the previous gold standard, Med in patients with metastatic disease in EBUS-TBNA-inaccessible LNs. When performed by a skilled bronchoscopist EBUS-TBNA can not only provide mediastinal LN staging but also, in some patients, offer diagnosis of the primary tumor including information on its molecular profile (110,111).

Practice of medicine has evolved in many specialities with focus on minimally invasive diagnosis and treatment as well as personalized treatments of disease. At present, lung cancer is being treated not only with surgery but also with therapies like RFA, SBRT. Sublobar resections may become standard of care for T1a tumors (112) and are the only surgical option for patients with significantly impaired lung function (40). In this setting, development of a TCP-EBUS scope opens up a possibility of not only reaching further into the airways and sampling the more distant and upper lobe N1 LNs, but also, personalized therapy where a tumor-specific treatment could be delivered to a metastatic LN or a primary lung tumor, using a real time ultrasound imaging (113,114).

Even though many centers globally have acquired endoscopic ultrasound technology, it is unlikely that Med will be eliminated from the armamentarium of invasive tests used in lung cancer patients. Instead, a combination of endoscopic and surgical assessments will become the standard of care, depending on the unique clinical scenario. This will allow highest diagnostic yield at all stages of the disease and as a result, most optimal patient management. For example, Med is recommended as a confirmatory test in patients with negative needle-based staging in patients with high pretest probability of mediastinal metastasis and it should be the test of first choice for mediastinal

restaging, following neoadjuvant therapy (especially if EBUS-TBNA was used to stage mediastinum initially). In addition, despite the recent change in the guidelines and a shift to the minimally invasive endosonography for staging, acquisition of this technology in many thoracic surgery and pulmonology centers is hindered by the lack of EBUS-TBNA expertise and limited resources. Therefore, Med is still the test of first choice in many thoracic surgery programs worldwide for mediastinal staging, restaging and diagnosis of disease recurrence. For these reasons, it important that thoracic surgeons get adequate training in both Med and the needle based techniques like EBUS-TBNA or EUS-FNA and that the focus of lung cancer diagnosis and treatment be on a multidisciplinary approach with a close collaboration of the radiologists, thoracic surgeons, pulmonologists, pathologists and oncologists to ensure the optimal patient management at all stages of the disease.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Czarnecka-Kujawa K, Yasufuku K. The role of endobronchial ultrasound versus mediastinoscopy for non-small cell lung cancer. J Thorac Dis 2017;9(Suppl 2):S83-S97. doi: 10.21037/jtd.2017.03.102