Current advances of endobronchial ultrasonography in the diagnosis and staging of lung cancer

Chao-Chi Ho¹, Ching-Kai Lin², Ching-Yao Yang¹, Lih-Yu Chang², Shu-Yung Lin³, Chong-Jen Yu¹

¹Department of Internal Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan; ²Department of Internal Medicine, National Taiwan University Hospital, Hsin-Chu Branch, National Taiwan University College of Medicine, Hsin-Chu, Taiwan; ³Department of Internal Medicine, National Taiwan University Hospital, Jinshan Branch, National Taiwan University College of Medicine, New Taipei City, Taiwan

Contributions: (I) Conception and design: All authors; (II) Administrative support: CC Ho; (III) Provision of study materials or patients: CC Ho; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Chao-Chi Ho, MD, PhD. Division of Pulmonary Medicine, Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan. Email: ccho1203@ntu.edu.tw.

Abstract: The diagnosis and staging of patients with lung cancer has relied on tissue sampling. Endobronchial ultrasound (EBUS) is a minimally invasive procedure for the rapid and safe acquisition of tissue and can be done easily and repeatedly. EBUS transbronchial needle aspiration (TBNA) is now the standard for diagnosis of mediastinal and hilar lymphadenopathy and should be considered in patients who have a high probability of lymph node metastases without systemic involvement. EBUS also provides guidance for biopsy of peripheral lung lesions. Recent advances of EBUS with new techniques help to improve the diagnostic yield and decrease the complication rate and total procedure time.

Keywords: Endobronchial ultrasound (EBUS), lung cancer, diagnosis, staging

Submitted Jun 17, 2016. Accepted for publication Jun 23, 2016. doi: 10.21037/jtd.2016.08.21 View this article at: http://dx.doi.org/10.21037/jtd.2016.08.21

Introduction

Lung cancer is the leading cause of cancer related death (1). The prognosis for lung cancer is extremely poor and a five year survival rate remains less than 15% (2). Twothirds of patients had advanced disease when they were diagnosed (1,3). The factors that affect prognosis in patients with lung cancer are stage, histology, performance status, comorbidity, age and sex (4). Before the introduction of novel cytotoxic chemotherapy (pemetrexed) and biologic agents (bevacizumab), the main diagnostic modalities and focus on tissue acquisition were obtaining small samples for simple histopathological characterization: small cell lung cancer (SCLC) *vs.* non-small cell lung cancer (NSCLC) (5,6). Markers to differentiate between adenocarcinoma and squamous cell carcinoma are now necessary and are defined by the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) lung adenocarcinoma classification (7). Adenocarcinoma can also be classified according to the driver oncogene mutation that is present, which is usually mutually exclusive in the different subtypes (8). The current guidelines suggest molecular testing for EGFR and ALK after adenocarcinoma has been confirmed. Therefore, sufficient and high quality tissue for diagnosis, and molecular testing for treatment selection become important.

In the treatment of lung cancer, staging is a prognostic factor not only for determining whether there is surgically resectable disease but also for the treatment planning (9).

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How to improve techniques for tissue acquisition in diagnosis and staging becomes important for improving the prognosis.

Endobroncial ultrasound radial probe (EBUS RP)

EBUS has become an important tool in daily practice for diagnosis and staging of lung cancer in the last decade (10). There are two types of probes used in EBUS: the RP and the convex probe (CP), which have technical differences and distinct diagnostic abilities. EBUS RB as a guidance technique for peripheral pulmonary lesions (PPL) and for the evaluation of tumor involvement of the tracheobronchial wall is now used for the diagnosis of PPL (11). Before the EBUS RB as one of the tissue biopsy tools for PPL, transthoracic needle aspiration (TTNA), flexible bronchoscopy with traditional transbronchial biopsy (TBB) or even direct surgical excision were recommended (12). TTNA is currently preferred because it has a diagnostic yield of 90% but high pneumothorax rate (25%), of which at least 5% requires chest tube insertion (12,13). The sensitivity of flexible bronchoscopy biopsy ranges from 14% to 63%, depending on size and location (13,14). EBUS RP offers guidance during bronchoscopy to help reach the lesion. The diagnostic yield varied from 46% to 86.2% and pooled sensitivity was 73% for all lesions and even better in the diagnosis of lung cancer (15,16). There is no direct comparison between EBUS RB and fluoroscopy in lung cancer diagnosis (17), but combined these two modality increased the diagnostic yield (18). Guide sheath (GS) is designed to increase the reliability of collection from PPL. EBUS-GS can decrease the total procedure time and decreased the bleeding rate (19). However, a meta-analysis showed sensitivity increased 2% when compared with EBUS RP without GS (16). Efforts to increase the diagnostic accuracy of EBUS RP are still ongoing. The position of the probe (within or adjacent to the PPL) independently predicts the diagnostic yield, and all efforts to reach the small bronchus within the lesions should be done (19). Beyond the conventional diagnostic procedures (CDPs) including TBB, bronchial washing and brushing, there are several approaches to improve performance. EBUS RP with CDPs and combined with transbronchial needle aspiration (TBNA) can increase the diagnostic yield without additional risk (20). The diagnostic benefit of EBUS-GS for PPLs was minimal when the probe was adjacent to the lesion (19). TBNA (passing a needle through the bronchial wall) can be the better solution if the EBUS probe was adjacent to the lesions (20,21). Suction catheter-biopsy is one technique

for obtaining tissue sample from PPLs. This approach is efficient, safe and is complementary to TTB (22). Another approach to increase the diagnostic yield is EBUS RP guided cryobiopsy, with which the diagnosis can be 61% by forceps and 74% by cryoprobe (23,24). The guidelines of the american college of chest physicians suggest the use of EBUS is recommended in patients with PPLs when tissue diagnosis is required due to uncertainty of diagnosis or poor surgical candidacy (25).

In the last decade, new techniques other than EBUS RP have emerged and helped to guide and biopsy PPLs through the tracheobronchial tree during bronchoscopy. Electromagnetic navigation bronchoscopy (ENB) and virtual bronchoscopy (VB) can create a virtual image for biopsy. ENB provides real-time directions for approach. The diagnostic yield is similar when ENB or VB is used for biopsy compared with EBUS RP guidance biopsy (16). But when combining two methods such as EBUS RP + ENB, or EBUS RP + VB, the diagnostic yield increases significantly (16,18,26-28). Ultrathin bronchoscopy is another tool to increase diagnostic accuracy. It has a diameter of 3.0 mm, incorporating a working channel with a different inner diameter, and can reach fourth-generation bronchi (29). The novel ultrathin bronchoscopy has a 1.7 mm working channel, which allows the use of a RP EBUS and 1.5 mm biopsy forceps (29). Combining ultrathin bronchoscopy with EBUS RP sans GS improved the diagnostic yield compared with thin bronchoscopy with EBUS GS (29).

Imaging from EBUS RP correlates well with the histopathologic findings of benign and malignant lesions (30,31), but final diagnosis needs to be made via tissue biopsy. During EBUS RP guidance PPL biopsy, rapid on site evaluation (ROSE) improved diagnosed yield (32). If ROSE is not available, at least 4–5 biopsies per lesion are necessary to get adequate sensitivity of diagnosis (33,34). The most frequent complications of EBUS RP guidance biopsy are bleeding and pneumothorax. But these complications are self-limited and seldom required intervention (15,35).

EBUS CP

Accurate staging is one of the important factors affecting patient management. Before the development of direct realtime EBUS-guided TBNA using a CP (36), mediastinoscopy remained the "gold standard" for mediastinal staging in lung cancer (37). Mediastinoscopy is invasive, requires general

anesthesia and cannot be performed repeatedly. Therefore, several minimally invasive methods have been used for tissue sampling including conventional bronchoscopy with TBNA guided by fluoroscopy or EBUS RP, but the yield varied widely (38-40). After one large randomized control trial compared surgical staging or combined EBUS-TBNA and transesophageal ultrasound fine needle aspiration (EUS-FNA) followed by surgical staging (41), EBUS CP guided TBNA (EBUS-TBNA) is now the first choice for mediastinal LN staging (9,42). Another single arm study also supports that EBUS TBNA is better than mediastinoscopy (43). EBUS TBNA is not only a minimally invasive procedure that can be performed repeatedly, but also has higher sensitivity and specificity in specific lymph node stations (9,44). Mediastinoscopy had lower diagnostic vield in lymph node station 7, which was easily approached by EBUS-TBNA with very high sensitivity (45).

In the previous guideline, lymph node staging by tissue sampling is usually suggested in lymph nodes with shortaxis diameter >1 cm on CT scan (46) or PET positive lymph nodes (47). But more than 10% of patients who had no lymph node metastasis by image criteria had lymph node metastasis confirmed by thoracotomy (48-50). Because EBUS TBNA can be performed in an outpatient setting, current guidelines suggest that with patients with clinical N1 disease (51), central tumor and tumor >3 cm, and mainly adenocarcinoma with high fluorodeoxyglucose (FDG)uptake (52,53) all lymph nodes >0.5 cm found in echosonography (9,42) should be sampled, precisely because all of these conditions are associated with a high probability of mediastinal lymph node metastases.

Efforts to improve the diagnostic yield are still ongoing, including large size needle (22 vs. 21 gauge needle) (54) and transbronchial needle forceps (55). None of the new techniques improved the diagnostic yield because EBUS TBNA with 22 gauge needle and ROSE had nearly 90% sensitivity and 100% specificity (9,44). However, the accuracy of EBUS-TBNA is quite dependent on experience (56). High-volume hospitals were associated with high diagnostic yields (56,57). How to acquire mastery during training is important in interventional bronchology (57).

There are several sonographic characteristics of malignant lymph nodes found by EBUS CP. These factors include large size, round shape, distinct margin, absent central hilum sign and distinct vascular pattern (58,59). A hard lymph node demonstrated by elastography of new CP is also a predictor of malignancy (60). But none of these factors had high sensitivity or specificity compared with direct sampling.

It is now suggested to assay all lymph nodes with size more than 0.5 cm, and at least 3-4 lymph node stations if possible (42). At least one tissue core is needed per lymph node to get adequate diagnosis. If tissue core is not available, three aspirations are advised (61). ROSE should always be considered because it can decrease the frequency of aspiration and total time of procedure. Higher N stage LNs should always be sampled first: N3 > N2 > N1, because the final stage only includes high N stages. Another reason is that if we use one needle for one patient, sampling lower N stage LNs before the high N stage may upgrade N stage through contamination. If possible, lymph node stations 4R, 4L and 7 should be evaluated in all patients who receive EBUS CP study (42). Because EBUS TBNA is the first choice for LN staging with high sensitivity and specificity, several studies suggest EBUS TBNA for lung cancer diagnosis and staging at the same time because it reduces the time to treatment decision compared with conventional diagnosis and staging techniques (62,63). The Complication rate for EBUS TBNA is low. In a national survey of complications associated with EBUS-TBNA by the Japan Society for Respiratory Endoscopy, the most frequent complications were hemorrhage and infection with only one mortality due to ischemic stroke after withdrawal of antiplatelet drugs (replaced by heparin) (64).

Conclusions

EBUS is a powerful tool for lung cancer diagnosis and staging (Table 1). EBUS CP guided TBNA (EBUS TBNA) is now the first choice for staging mediastinal LNs. Because of the high sensitivity (>90%) and specificity (almost 100%), little improvement could be made by new techniques. However, the sensitivity is mainly dependent on the operator. How to improve the diagnostic yield through training is still an issue. EBUS RP guided TBB has lower sensitivity compared with TTNA in tissue sampling. But the complication rate of EBUS TBB is significantly lower than that of TTNA. There are many new techniques that can be combined with EBUS TBB to increase the diagnostic yield. EBUS also helps these techniques in sampling of PPL and vice versa. It is suggested that for peripheral lesions, we could perform bronchoscopy for airway evaluation and EBUS TBB for tissue sampling at the same time before moving to more the invasive TTNA for diagnosis.

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Items	EBUS radial probe	EBUS convex probe
Target	Peripheral lung lesions via TBB	Mediastinal and hilar lymph node via TBNA
Approach	CT bronchogram (19), electromagnetic navigation bronchoscopy and virtual bronchoscopy (16,27)	N3 then N2 then N1* (42)
Number of biopsies (without ROSE)	More than 4–5 biopsies per lesion (33,34)	At least 3 aspirations per lymph node (61)
Sensitivity	~73% (15)	~88% (44)
Methods to increase sensitivity	Guide-sheath (19), ROSE (32)	Experience (56,57), ROSE (65), [large size needles (66) or forceps (55)?]
New techniques to increase sensitivity	Ultrathin bronchoscopy (29), electromagnetic navigation bronchoscopy (67)	Elastography (60)
Complications	Pneumothorax (35), bleeding (rare)	Infection, bleeding (rare) (64)

Table 1 Summary of EBUS in the diagnosis and staging of lung cancer

EBUS, endobronchial ultrasound; TBB, transbronchial biopsy; TBNA, transbronchial needle aspiration; ROSE, rapid on-site evaluation. *, N stage of 7th edition AJCC lung cancer staging.

Acknowledgements

None.

Footnote

Conflicts of Interest: CC Ho has received grants from AstraZeneca (#ISSIRES0105). The other authors have no conflicts of interest to declare.

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Cite this article as: Ho CC, Lin CK, Yang CY, Chang LY, Lin SY, Yu CJ. Current advances of endobronchial ultrasound in the diagnosis and staging of lung cancer. J Thorac Dis 2016;8(Suppl 9):S690-S696. doi: 10.21037/jtd.2016.08.21

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