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Review

Respiratory Review of 2012: Bronchoscopic Innovations and Advances

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Recent advances in bronchoscopy have led to changes in clinical diagnostics and therapeutics in pulmonary medicine. In diagnostic bronchoscopy, there have also been new developments in endobronchial ultrasound technology which may be incorporated into clinical practice in the near future. Functional bronchoscopy, which evaluates information such as airway pressure, airflow, or gas exchange, suggests promising clinical advances in the near future. In therapeutic bronchoscopy, bronchoscopic volume reduction is a novel approach for the treatment of severe emphysema. In this review, seven recently published articles representing current advances in bronchoscopy are summarized and discussed.

Key Words: Bronchoscopy; Ultrasonography; Bronchoscopy; Pulmonary Surgical Procedures

Introduction

Bronchoscopy is used in the diagnosis and therapy of pulmonary diseases. Recent advances, including various new methods, have broad implications for clinical practice. Linear endobronchial ultrasound has greatly contributed to recent advances in diagnostic bronchoscopy. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), which enables real-time sampling of peribronchial lesions, is useful for lung cancer diagnosis and tissue acquisition[1] and is likely to become a standard procedure in mediastinal staging of lung cancer[2,3]. Radial EBUS is used for localizing peripheral tumors, and navigation systems that facilitate bronchoscopic access to peripheral tumors are used in combination with radial EBUS[4,5]. Functional bronchoscopy, a part of diagnostic bronchoscopy, evaluates functional aspects of the respiratory system (endobronchial pressure, air flow, gas exchange, etc.) during bronchoscopic procedures[6].

New methods in the field of therapeutic bronchoscopy include bronchoscopic lung volume reduction for emphysema and bronchial thermoplasty for bronchial asthma[7-12]. An advantage of bronchoscopic lung volume reduction is that it is less invasive than surgical methods of lung volume reduction. Considering the medical burden of emphysema, the clinical impact of bronchoscopic volume reduction would be huge if its usefulness can be fully established. The effect, safety, and patient response subsequent to bronchoscopic lung volume reduction have been investigated but more studies are needed[7-11].

In this review, seven articles representing recent advances of bronchoscopy are summarized and briefly discussed. Articles published (in print or online) between April 2011 and March 2012 in major journals in respiratory medicine, thoracic surgery, or internal medicine were selected for review.

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Diagnostic Bronchoscopy

1. EBUS-TBNA in lung cancer staging

1) A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration com-

pared with mediastinoscopy for mediastinal lymph node staging of lung cancer. Yasufuku et al.[3] J Thorac Cardiovasc Surg 2011;142:1393-400

Can EBUS-TBNA replace mediastinoscopy in lung cancer staging? This study was well-designed, prospective, and undertaken to answer the question above. In this study, EBUS-TBNA was compared with standard cervical mediastinoscopy in operable non-small cell lung cancer patients. All patients underwent EBUS-TBNA followed by mediastinoscopy. If both methods provided negative results for mediastinal metastasis, surgical resection and mediastinal lymph node dissection were performed. One hundred fifty-three patients were eligible for final analysis. The prevalence of N2 or N3 stage disease was 35% (53/153). The sensitivity, negative predictive value, and diagnostic accuracy of EBUS-TBNA in detecting mediastinal metastasis were 81%, 91%, and 93%, respectively. The sensitivity, negative predictive value, and diagnostic accuracy for mediastinoscopy were 79%, 90%, and 93%, respectively. There were no statistical differences in diagnostic values between EBUS-TBNA and mediastinoscopy (McNemar's test, p=0.78). Following EBUS-TBNA, mediastinoscopy detected six additional cases with mediastinal metastasis and the negative predictive value was increased by 5% (from 91% to 96%). Four of these six had micrometastases. There were no complications related to the EBUS-TBNA procedure; however, four complications (hematoma, n=2; laryngeal nerve injury, n=1; and wound infection, n=1) from mediastinoscopy were observed. This study showed that EBUS-TBNA and mediastinoscopy gave similar results and that EBUS-TBNA could replace mediastinoscopy in patients with potentially resectable non-small cell lung cancer.

The findings of this study have major implications for patients undergoing preoperative staging for lung cancer. It seems that EBUS-TBNA is the first method that should be considered for mediastinal staging. The results suggest that EBUS-TBNA can replace mediastinoscopy, the current gold standard procedure for mediastinal staging. Is there a role for mediastinoscopy subsequent to EBUS-TBNA? This study suggests that such a role for mediastinoscopy would be small after EBUS-TBNA. The clinical usefulness of mediastinoscopy in finding a small number of cases with micrometastasis missed by EBUS-TBNA seems minimal. This trial was performed by one expert group of EBUS-TBNA. More studies are needed to establish EBUS-TBNA as the standard procedure in lung cancer staging.

2. EBUS-TBNA in biomarker studies of lung cancer

1) Multigene mutation analysis of metastatic lymph nodes in non-small cell lung cancer diagnosed by endobronchial ultrasound-guided transbronchial needle aspiration. Nakajima et al.[13] Chest 2011;140:1319-24

EBUS-TBNA is an important procedure for lung cancer diagnosis as well as for lung cancer staging. Samples obtained by EBUS-TBNA can be used for biomarker studies. In this study, the authors performed multigene mutation analysis on samples obtained by EBUS-TBNA from metastatic mediastinal or hilar lymph nodes in non-small cell lung cancer patients. Epidermal growth factor receptor (EGFR) was analyzed in 156 patients using the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method. V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (K-ras; exons 2～3) and tumor protein 53 (p53; exons 4～8) were analyzed by direct sequencing in 113 patients. *EGFR* gene mutations were detected in 42 cases (26.9%). *K-ras* gene mutations were detected in four cases (3.5%), and *p53* gene mutations were detected in 47 cases (41.6%). Among patients with *EGFR* mutation, 23 received gefitinib and partial response was observed in 54.5% of these. Fifty-two patients received conventional chemotherapy: patients with *p53* gene mutations showed chemoresistance (disease progression in 42.9% of patients, p=0.0339). The authors concluded that EBUS-TBNA allows genetic evaluation of tumor cells within the metastatic node, which might let physicians better select treatments, particularly EGFR tyrosine kinase inhibitors.

The utility of EBUS-TBNA for lung cancer tissue ac-

quisition is increasing. EBUS-TBNA aspirates are small samples obtained by 21G or 22G needles; however, we can perform multiple aspirations to obtain sufficient samples to use for various molecular studies. In patients with emphysema or poor pulmonary function, lymph node sampling can be a safer method than transthoracic needle aspiration (TTNA) of primary tumors. When mediastinal or hilar lymph nodes have a great likelihood for metastasis and the lesions are accessible by EBUS-TBNA, EBUS-TBNA can be an excellent method for tissue acquisition and molecular studies, as shown in this study.

3. EBUS-TBNA in the diagnosis of intrathoracic tuberculous lymphadenopathy

1) Utility of endobronchial ultrasound-guided transbronchial needle aspiration in patients with tuberculous intrathoracic lymphadenopathy: a multicentre study. Navani et al.[14] Thorax 2011;66:889-93

The usefulness of EBUS-TBNA in diagnosing intrathoracic tuberculosis lymphadenitis has not been established. This multicenter retrospective study evaluated 156 patients who were diagnosed as having intrathoracic tuberculous lymphadenopathy. EBUS-TBNA, performed in all patients, diagnosed tuberculosis in 146 patients and the diagnostic yield was 94% (confidence interval, 88～97%). Pathologic findings were consistent with tuberculosis in 134 patients (86%). In 74 of the 156 patients diagnosed (47%), *Mycobacterium tuberculosis* (MTB) was cultured and eight cases (5%) had drug-resistant MTB. Among 10 patients (6%) who were not diagnosed positive by EBUS-TBNA, four were diagnosed positive by mediastinoscopy and six were diagnosed positive by clinical response to anti-tuberculous medication. In one patient, serious complication (sepsis) occurred as a result of the EBUS-TBNA procedure. The conclusion of this study was that EBUS-TBNA is an effective first diagnostic method in patients with tuberculous intrathoracic lymphadenopathy.

The utility of EBUS-TBNA has been studied in various diseases, including the staging and diagnosis of lung cancer[1,15]. Other conditions for which EBUS-TBNA has been used are mediastinal tumors (e.g., lymphoma), metastasis from extrathoracic malignancy, sarcoidosis, and other mediastinal lymphadenopathies[16-18]. This study demonstrated that EBUS-TBNA has great diagnostic value in intrathoracic tuberculous lymphadenopathy. High culture rate of MTB is impressive when using EBUS-TBNA. When mediastinal hilar nodes are suspicious for tuberculosis, culture for MTB should be performed. Even though this article's findings suffer from the limitations of being a retrospective study, the results are important because this is the first report to identify a useful role for EBUS-TBNA in tuberculous lymphadenopathy. Future prospective studies are, nonetheless, necessary to determine conclusively the utility of EBUS-TBNA in intrathoracic tuberculous lymphadenopathy.

4. Endobronchial ultrasound and navigation system in the diagnosis of peripheral tumors

1) Virtual bronchoscopic navigation combined with endobronchial ultrasound to diagnose small peripheral pulmonary lesions: a randomized trial. Ishida et al.[5] Thorax 2011;66:1072-7

A radial EBUS mini-probe is used to localize peripheral pulmonary nodules; however, sometimes it is difficult to find a bronchus closest to the peripheral lesion. Navigation systems such as virtual bronchoscopic navigation (VBN) or electromagnetic navigation can aid the process[4,19]. This randomized, controlled trial study showed the usefulness of VBN in radial EBUS-guided biopsy of peripheral tumors. This study enrolled 199 patients who had pulmonary peripheral lesions ≤3 cm. There were no statistical differences in lesion size, location, or proportions of malignant or benign diseases between the VBN-assisted group and the non-VBN-assisted group. The diagnostic yield in the VBN-group was greater than that in the non-VBN-assisted group (80.4% vs. 67.0%, p=0.032). Total examination time was shorter in the VBN group (median, 24.0 minutes; range, 8.7～47.0 minutes vs. median, 26.2 minutes;

range, 11.6～58.6 minutes) (p=0.016) and time elapsed until the start of sample collection was shorter in the VBN-assisted group (median, 8.1 minutes; range, 2.8～39.2 minutes vs. median, 9.8 minutes; range, 2.3～42.3 minutes) (p=0.045). The authors concluded that the diagnostic yield for small, peripheral pulmonary lesions is increased when VBN is combined with EBUS.

TTNA has great diagnostic value for identifying peripheral tumors; nonetheless, investigation of other bronchoscopic approaches is still important. TTNA has a high pneumothorax rate[20]. TTNA can be risky in patients with lower pulmonary functions and emphysema. Until now, the diagnostic value of than transbronchial lung biopsy (TBLB) has not approached that of TTNA[21]. Combinations of methods such as EBUS, advanced navigation system, and real-time sampling method may overcome limitations of current TBLB in the future. Localizing peripheral lesions with bronchoscopic techniques may be applied in therapeutic bronchoscopy. Fiducial marker placement has been accomplished by using endobronchial ultrasound and navigational bronchoscopy prior to stereotactic radiosurgery[22]. Investigations on bronchoscopic diagnostic methods will give us insights to future therapeutic interventions using bronchoscopy on peripheral tumors.

Functional Bronchoscopy

1. Measurement of airway pressure in tracheal stenosis

1) Assessing the site of maximal obstruction in the trachea using lateral pressure measurement during bronchoscopy. Nishine et al.[6] Am J Respir Crit Care Med 2012;185:24-33

This article is the first prospective investigation demonstrating the usefulness of lateral pressure differences on each side of a tracheal stenosis during interventional bronchoscopy. The authors showed that the degree of obstruction correlated positively with functional impairment. They used a dedicated double lumen catheter to measure airway lateral pressure of the proximal site and the distal site (the carina) of tracheal obstruction. Pressures at the two points were plotted on a pressure-pressure (P-P) curve (X-axis as pressure at carina; Y-axis as pressure at proximal site) during tidal respirations, and the slope angle of the P-P curve was measured. The authors enrolled 15 normal volunteers and 30 patients with tracheal obstructions. In normal subjects, there were no pressure differences between the carina and the proximal site-the angle of P-P curve was close to 45°. In patients with tracheal stenosis, however, pressure difference and the angle of P-P curve changed significantly when obstruction was greater than 50% ($p<0.0001$). Dyspnea score was also increased in patients with tracheal narrowing more than 50% ($p<0.0001$). The degree of tracheal obstruction was significantly correlated with the pressure difference ($r=0.83$, $p<0.0001$) and the angle of P-P curve ($r=-0.84$, $p<0.0001$). The cross-sectional area, dyspnea scale, pulmonary function tests, pressure difference, and the curve angle significantly improved after interventional procedures such as stenting ($p<0.0001$). The conclusion of this study was that the degree of stenosis can be determined by measuring airway lateral pressure on each side of the stenosis. The results suggest that the pressure difference and the angle of the P-P curve maybe used to estimate the outcome of interventional bronchoscopy.

The future of functional bronchoscopy is promising. A good example of functional bronchoscopy is the Chartis pulmonary assessment system, which is used to evaluate collateral ventilation when deciding on an endobronchial valve (EBV) procedure[23]. The system can assess airflow and pressure generated from the distal part of an occluded bronchus, which is related to the presence of collateral ventilation. Diagnostically, bronchoscopy has been used for visual interpretation of lesions and for sample collection. Additional functional information, such as pressure, air flow and gas exchange profile, would aid precise diagnosis and inform therapeutic intervention.

Therapeutic Bronchoscopy

1. Bronchoscopic lung volume reduction

1) Bronchoscopic lung-volume reduction with Exhale airway stents for emphysema (EASE trial): randomised, sham-controlled, multicentre trial. Shah et al.[9] Lancet 2011;378:997-1005

An airway bypass is used to reduce lung volume in severe homogeneous emphysema. A paclitaxel-coated stent is inserted to create an artificial bypass between lung parenchyma and segmental bronchus. A doppler probe is used to identify a blood vessel-free location. This study was a randomized, double-blind, sham-controlled, multicenter trial that was performed to evaluate the safety and efficacy of airway bypass in patients with severe homogeneous emphysema. Participants were randomly allocated (in a 2:1 ratio) to either airway bypass (n=208) or sham control (n=107). The 6-month co-primary efficacy endpoint required a 12% or greater improvement in forced vital capacity and a one point or greater decrease in the modified Medical Research Council (MMRC) dyspnea score from baseline. The composite primary safety endpoint incorporated five severe adverse events. At 6 months, no statistical differences were found between the airway bypass group and the control group (30/208 for airway bypass vs. 12/107 for sham control; posterior probability=0.749, below the Bayesian success threshold of 0.965). The 6-month composite primary safety endpoint was 14.4% (30 of 208) for airway bypass vs. 11.2% (12 of 107) for sham control (judged non-inferior, with a posterior probability of 1.00 [Bayesian success threshold＞0.95]). Initial benefit was observed in the airway bypass group, but the benefit was not maintained to 6 months. Stent closure seemed to be a cause of the loss of initial benefit. On day 1, 66% (n=421) of stents were graded as completely unblocked, which fell to only 21% (n=124) by 6 months. In lobes with unblocked stents, reduction of residual volume was preserved till 6 months. The authors concluded that no sustainable benefit was observed with airway bypass in patients with severe homogeneous emphysema.

Bronchoscopic lung volume reduction for emphysema is an important issue in therapeutic bronchoscopy. EBVs, airway bypass stents, lung volume reduction coils, bronchial thermal vapor ablation, and biological lung volume reduction are methods that have been studied for endobronchial lung volume reduction[7-11]. This study evaluated the role of airway bypass in homogenous emphysema and showed negative results; however, in lobes with patent stents, reduction of residual volume was maintained. Loss of the initial benefit is probably attributable to loss of stent patency. Even though this study demonstrated negative results, the study suggests that future use of airway bypass will require improved stent durability to preserve residual volume reduction.

2) Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. Herth et al.[8] Eur Respir J 2012;39:1334-42

EBV is a promising method for reducing endobronchial lung volume. Small one-way valves were implanted in segmental or sub-segmental bronchus to create lung volume reduction in heterogeneous emphysema. In this study, a European cohort of valve for emphysema palliation trial (VENT), patients with advanced emphysema were randomly assigned (2:1) to EBV treatment (n=111) or medical management (n=60). Unilateral EBV (Zephyr) procedure was performed on the EBV group. At 6 months, EBV patients demonstrated significant improvement compared to controls for average change in forced expiratory volume in 1 second (FEV1; 7±20% vs. 0.5±19%; p=0.067), cycle ergometry (2±14 W vs. −3±10 W; p=0.04), and Saint George's Respiratory Questionnaire (SGRQ; −5±14 points vs. 0.3±13 points; p=0.047). Complication rates did not differ significantly between the two groups. The EBV patients with computed tomography (CT) suggestive of complete fissure tended to have greater improvements in FEV1, SGRQ, and cycle ergometry workload than did the control group with complete fissure at 6 months.

This difference was not observed in patients with incomplete fissure. In patients with complete fissure, cases that showed lobar occlusion had better outcome than cases without lobar occlusion (FEV1 change, 26±24 vs. 6±12; p=0.004). This study has limitations because of its small sample size and absence of sham control. The conclusion of this study was that unilateral EBV treatment significantly improves clinical outcomes over medical management in severe heterogeneous emphysema. Unilateral EBV treatment was safe and superior clinical results correlated with CT suggestive of complete fissures and successful lobar occlusion.

The US cohort of VENT was published in the New England Journal of Medicine in 2010 and showed similar results with this study (of the European cohort)[7]. The US VENT trial enrolled 321 patients and showed that EBV treatment for advanced heterogeneous emphysema induced modest improvements in lung function, exercise tolerance, and symptoms. The complication rate, however, was higher in the EBV group (e.g., chronic obstructive pulmonary disease exacerbation, 7.9% vs. 1.1%; p=0.03). The European study showed similar complication rates between treatment and control groups, which may be related to small sample size. Considering complications and medical costs, the selection of candidates (good responder group) is the most important issue in EBV treatment, as evaluated in this study. More trials are needed to answer definitively this issue.

Summary

The seven articles summarized in this review describe recent efforts to find new roles for bronchoscopy in diagnosing lung cancer and other pulmonary diseases. Novel diagnostic technologies added to conventional methods have expanded the roles of diagnostic bronchoscopy. Linear EBUS attached to a flexible bronchoscope has broadened the area that can be accessed by bronchoscopy. Navigation systems combined with radial EBUS have increased the diagnostic yield of TBLB. Functional investigations performed during bronchoscopy now give us more physiologic knowledge of the respiratory system. Bronchoscopic lung volume reduction is a promising method for the treatment of severe emphysema. Various methods of bronchoscopic lung volume reduction are under investigation. Other new diagnostic technologies in bronchoscopy that were not mentioned in this review include optical coherence tomography, narrow band imaging, confocal fluorescence microscopy, endocytoscopy, and others[24-27]. Advances in new techniques and their combination will provide more precise diagnostic information and new insights with therapeutic implications.

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