Commentary

Innovations in bronchoscopic techniques will go a long way for diagnosis of early-stage lung cancers

Kangni Chen, Guangqiao Zeng

State Key Laboratory of Respiratory Disease, National Clinical Center for Respiratory Diseases, Guangzhou Institute of Respiratory Diseases, First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510120, China

Correspondence to: Guangqiao Zeng. State Key Laboratory of Respiratory Disease, National Clinical Center for Respiratory Diseases, Guangzhou Institute of Respiratory Diseases, First Affiliated Hospital of Guangzhou Medical University, 151 Yanjiang Rd, Guangzhou 510120, China. Email: zgqiao@vip.163.com.

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Introduction

Lung cancer is one of the most common malignancies and a leading cause of cancer-related death worldwide (1). In China, the morbidity and mortality rates of lung cancer have been increasing over the past decades along with the worsening environment (2) and concerning situation of tobacco use (3). Imaging studies and sputum cytology as the conventional diagnostic approaches for lung cancer, are in fact very limited for detecting the early-stage lesions, and therefore do not help reduce the death toll. A number of clinical practice guidelines have recommended bronchoscopy as an important common tool for diagnosis of primary lung cancers (PLCs) (4). The direct vision of bronchoscopy enables brush and puncture biopsies, and performing bronchoalveolar lavage for cytological and histological diagnosis, which contributes to significant improvement in detection rate, and ultimately, to early identification, early diagnosis and early treatment of lung cancers. With the advance and refinement in molecular biology, endoscopic and imaging techniques, current practice with bronchoscopic examination has been recognized to remarkably enhance clinical diagnosis of lung cancer, and have an extraordinary role in improving the prognosis and survival rate of patients. This article reviews the use of several diagnostic modalities related to bronchoscopic techniques in individuals with high risk for lung cancers.

Endobronchial ultrasound (EBUS)

EBUS is a relatively new technique and procedure that uses ultrasound probe along with bronchoscope to visualize the inner surface of airway and adjacent architecture in real time. Unlike the conventional bronchoscopy that can only determine with low diagnostic yield the changes inside the airway but not in bronchial walls or adjacent tissues, the high-resolution (≤4 cm) EBUS presentation improves the blurred imaging of tracheobronchial wall, the surrounding structures, and the mediastinum. Currently, recommended indications for EBUS include: hilar and mediastinal masses or lymphadenectasis to be diagnosed or lung cancer for staging; external compression to the airway; airway submucosal lesions; intratracheal lesions; peripheral pulmonary nodule or mass. Coupled with transbronchial needle aspiration (TBNA), EBUS-TBNA demonstrates high sensitivity, specificity, and accuracy in many studies (5-10), and has been widely used for diagnosis and staging of lung cancer. However, EBUS-TBNA is more complicated,

less well-tolerated by patients under local anesthesia, and more costly than conventional TBNA (11). Since the manipulation of the EBUS vision can be difficult, a successful and safe EBUS-TBNA usually requires longer curve of learning and skillful expertise. Innovative efforts have been attempted to develop more efficient devices. In a study, Xiang *et al*. tested a new Fuji EBUS scope, which has a 10 degrees forward oblique view and smaller external diameter, eliminating the need of a second scope and making the TBNA with or without EBUS simpler to do and easier to learn (12). Although not recommended as routine screening methods, EBUS-TBNA is helpful to accurate pathological diagnosis of N1 and N2 PLCs in a safe manner, which is encouraged to be used in well-equipped hospitals to facilitate diagnosis when applicable (4).

Electromagnetic navigation bronchoscopy (ENB)

ENB is gaining increasing acceptance as a diagnostic modality (13). According to ENB working principle, the complete CT digital images of the lungs and bronchi are obtained for three-dimensional reconstruction of a virtual bronchial tree. In the examination, the positioning probe is controlled by computer and guided to the CT determined lesion site for final examination by biopsy needle. The ENB system consists of four parts: a computer-connected electromagnetic "location board"; an eight-way steerable sensing probe; an extended working channel that is connected with the probe, brush and biopsy needle; and bronchoscopy planning software, which reconstructs the acquired image into virtual three-dimensional simulated image. The position of the probe in bronchial tree can be reflected in the computer software by electromagnetic "location board". Then, the probe can be guided to the site of lesion. Therefore, ENB makes possible the biopsy of invisible bronchoscopic or fluoroscopic lesions at the pulmonary periphery or mediastinum, and guides the TBNA. Eberhardt *et al*. found that the diagnostic yield of ENB in peripheral lung lesions was 67%, which was independent of lesion size (14). A higher ENB yield of 88% was found in diagnosing lesions in the right middle lobe. There were two incidences of pneumothorax for which no intervention was required among 89 subjects. It has been shown that ENB does not increase the morbidity caused by operation, or the risk of pneumothorax (15-17). Instead, using the ENB alone in early peripheral lung cancer shows a higher positive rate, reduced duration of radiation exposure in patients, compared with the conventional bronchoscopy. In addition, procedures with ENB are safe, well-tolerated, and without serious complications.

Autofluorescence bronchoscopy (AFB)

AFB was developed by using cell autofluorescence to detect preinvasive lesions. Identification and treatment of such lesions are expected to improve the outcomes of airway squamous cell carcinoma (18,19). As AFB provides more information for potential submucosal invasion or minimal mucosal change (20), it can improve the sensitivity of bronchoscopy for early identification of lung cancers and pre-cancerous lesions. The so-called "fluorescence" is a special type of physical phenomenon that radiates luminescence. In other words, when certain objects emit longer wavelength of light than usual under the irradiation with a specific wave length, the emitted longer wave length of light become the fluorescence. Many studies have confirmed higher sensitivity for detection of precancerous bronchial lesions by using AFB, when compared to the conventional white-light bronchoscopy (WLB) alone (21). AFB can diagnose carcinoma in situ in 1.6% of cases deemed high risk, and moderate and severe dysplasia in 19% of current heavy or former smokers with sputum atypia (22). In a multicenter clinical trial, Edell *et al*. found that the relative sensitivity on a per-lesion basis of WLB + AFB versus WLB was 1.50 [95% confidence interval (CI), 1.26–1.89] (23). The relative sensitivity to detect intraepithelial neoplasia (moderate/severe dysplasia or CIS) was 4.29 (95% CI, 2.00–16.00) and 3.50 (95% CI, 1.63–12.00) on a per-lesion and per-patient basis, respectively; moreover, using AFB as an adjunct to WLB with the Onco-LIFE system improved the detection and localization of intraepithelial neoplasia and invasive carcinoma compared with WLB alone. Currently, suitable candidates for AFB examination include (24): patients with moderate to severe atypical hyperplasia found by sputum cytology, or patients without lesion on chest X-ray but with suspected canceration in 6 months; in census of high-risk populations of lung cancer; patients with persistent cough, hemoptysis and chest pain (smokers aged <20 years, daily smoking >20 cigarettes, years of smoking >20 years); patients with highly suspected lung cancer; patients with suspected recurrence after surgery of early-stage lung cancer (phases I and II); patients with intracavitary tumor underwent the positioning therapy to monitor the effect of the treatment on intratracheal tumors. In Chinese patients, AFB has been confirmed to improve the diagnostic yield for early-stage lung cancer (25,26).

Compared with conventional fiberoptic bronchoscopy, AFB is not associated with an increase in complications, except for a modestly longer duration of the procedure.

In summary, lung cancer is becoming one of leading causes of cancer death, whereas the prognosis and treatment outcomes in patients with lung cancer are influenced by the accurate staging of lung cancer. The need to improve the diagnostic rate of early-stage lung cancer, thereby increasing the survival rate, is urgent for all chest physicians. Advances in new screening and testing methods have greatly added to the armamentarium of diagnostics for lung cancers, in a sharp contrast to the past 30 years when chest X-ray represented the only criteria to determine the diagnosis of lung cancer. Novel, emerging technologies have been increasingly minimized the limitations of conventional bronchoscopy. The resultant output of these innovations, such as EBUS, ENB and AFB, is in widespread use in clinics. A future with more effective screening, earlier detection and staging of lung cancer, and improved survival and recovery rates in patients, can be foreseen.

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