·*Technology and Method*·

Comparison of the autofluorescence bronchoscope and the white light bronchoscope in airway examination

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〔**Abstract**〕**Background and Objective:** The sensitivity and accuracy of white light bronchoscopy (WLB) in airway examination are low. Autofluorescence bronchoscope (AFB) can determine early lesions in bronchial mucosa more sensitively, but it has seldom performed in China. To assess the clinical value of the AFB in airway examination, we compared the sensitivity and specificity of the AFB and WLB in detecting cancer of the airway mucosa. **Methods:** Between September 2009 and May 2010, bronchoscope examinations using both the AFB and WLB were performed on 136 patients, 95 men and 41 women with a median age of 61.5 years (ranged from 25 to 84 years). There were 46 lesions located in the central airway, 84 in the peripheral lung parenchyma, and 6 in the mediastinal region. All patients received local and general anesthesia and were subsequently examined with the WLB and AFB in tandem. All procedures were completed safely. Abnormal visual findings were recorded, and biopsies of the affected regions were collected for pathologic examination. **Results:** Of 241 regions sampled for biopsy, 76 sites contained malignant lesions, whereas 165 sites contained benign lesions. The AFB detected 72 of the 76 malignant lesions, but the WLB detected only 50. The sensitivities of the AFB and WLB were 94.7% and 65.8%, respectively, and the specificities were 57.0% and 83.6%, respectively. The negative predictive values of the AFB and WLB were 95.9% and 84.1%, respectively. **Conclusions:** The AFB is more sensitive than the WLB in detecting cancerous lesions in the mucosa, and is an effective airway examination.

Key words: Autofluorescence bronchoscopy, white light bronchoscopy, airway examination, sensitivity, negative predictive value

Bronchial mucosa is naturally autofluorescent. When irradiated by blue laser light (442 nm in wavelength), fluorescent substances underneath the bronchial mucosa are stimulated and subsequently emit green fluorescence (520 nm in wavelength) and red fluorescence (630 nm in wavelength). Because the ratio of green to red fluorescence varies according to the phenotype of the examined tissues, observed images may display various colors. Thus, when the tissues change from normal mucosa to hypertrophy, carcinoma in situ, or even invasive carcinoma, the observed colors also change, yielding decreased green fluorescence and increased red fluorescence. Although tiny lesions are usually undetectable using standard light, they may be detected by a high-resolution imaging system that can distinguish subtle differences in autofluorescence. The autofluorescence bronchoscope (AFB) is a white light bronchoscope (WLB) updated with the addition of a blue laser. This new technology can detect tiny lesions in the bronchial mucosa by exploiting the autofluorescent nature of the tissue [1,2]. Autofluorescence bronchoscopy has already been reported in some developed countries [3], but never in China. Hence, this paper compares the values of the AFB and WLB based on the analysis of 136 cases examined in our hospital from September 2009 to May 2010.

Patients and Methods

Patients

From September of 2009 to May of 2010, 136 patients, including 95 males and 41 females with a median age of

61.5 years (ranged from 25 to 84 years), received both AFB and WLB examinations. Of the 136 patients, 125 received examinations for diagnosis and 11 received examinations for post-operative recheck. The number of central pulmonary lesions, peripheral pulmonary lesions, and mediastinal lesions were 46, 84, and 6, respectively.

Examination procedure

Facilities

The autofluorescence bronchoscope BF-F260 (OLYMPUS, Japan) has functions shared by both the AFB and WLB and can shift from one to the other freely. The xenon lamp CV260L was also from OLYMPUS (Japan).

Anesthesia

For painless bronchoscope examinations, patients received local anesthesia on the glottis and airway, as well as continuous venous anesthesia. For local anesthesia, 1% amethocaine was inhaled through ultrasonic nebulization for 15–30 min. Subsequently, sprays of 7% lidocaine were administered to the larynx 3 times at 5-minute intervals, with 2–3 pushes per time. Simultaneously, 1% lidocaine was also sprayed in the local mucosa. For venous anesthesia, patients received 2–3 mg midazolam, 3–6 mg propofolum, and 1 mg morphine. Autonomous respiration was reserved and mask ventilation was used.

Examination procedure

The bronchoscope was pushed into the airway through the mouth. First, in the WLB state, the glottis, trachea, carina, and bronchi (segments 0–V) were examined, and cartilage rings, mucosa, blood vessels, secretions, and neoplasms were observed. Suspicious lesions, such as hyperemia, edema, thickness, nodules, color changes and regression, or bucking of vessels, were recorded. Next, the bronchoscope was shifted to the AFB state, and all bronchi (segments 0–V), especially suspicious areas discovered by the WLB, were observed. All abnormalities detected by the AFB were also recorded. When observation was over, biopsies were collected from suspicious lesions for further pathological examination. Biopsies of normal mucosa were also randomly performed as controls.

For patients who underwent surgery, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) or thoracotomy was performed to determine a pathological diagnosis. For peripheral lesions or extrabronchial lesions that could not be diagnosed by bronchoscope, EBUS-TBNA or thoracotomy was also performed for further pathological diagnosis. For patients with abnormal mucosal lesions, biopsies of affected areas were collected through thoracotomy for verification.

Classification of examination results

Classification standards in reference [4] were adopted in our study. Under the WLB state, lesions were classified into 3 grades: WLB-I, which included congenital anatomic abnormities, bronchial lesions resulting from neighboring pressure, or pure broadening of the bronchial uncus without mucosal color changes, hyperemia, or edema; WLB-II, which included hyperemia, edema, thickness, color changes, and regression or buckling of mucosal vessels; or WLB-III, which included granulation of the bronchial mucosa or visible neoplasm. WLB-II and WLB-III were considered abnormal findings. Under the AFB state, lesions were also classified into 3 grades: AFB-I, which included green anatomy abnormalities; AFB-II, which included pink or brown lesions; or AFB-III, which included classic magenta or amaranth lesions. AFB-II and AFB-III were considered abnormal findings.

Statistical analysis

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were used to evaluate the diagnostic power of the AFB and WLB. The aforementioned statistics were compared by McNemar test using SPSS13.0. The significance level was set to $\alpha = 0.05$.

Results

All examinations in our study were completed successfully without examination death or severe complications. In total, 138 examinations were completed with the intent of primary diagnosis or post-operative recheck. For primary diagnosis, 126 examinations were performed on 125 patients (one patient was examined before and after neo-adjuvant chemotherapy). For post-operative recheck, 12 examinations were performed on 11 patients diagnosed with adenocarcinoma (7 cases), squamous cell carcinoma (3 cases), or adenoid cystic carcinoma (1 case) and surgically treated with lobectomy (7 cases), trachea ring resection (2 cases), bronchus reconstruction (2 cases). The average examination time (including biopsy time) for all patients in our study was (22.5 ± 15.5) min (ranged from 5 to 80 min). Of 73 examinations during which visible lesions were discovered, 241 biopsies were obtained in total with an average of 3.4 ± 2.3 biopsies per examination (ranged from 1 to 9 biopsies per examination). Among them, there were 76 malignant biopsies (31.5% of 241, including 34 squamous cell carcinomas, 24 adenocarcinomas, 11 small cell lung cancers, 3 severe atypical hyperplasia, 2 adenoid cystic carcinomas, 1 adenosquamous carcinoma and 1 carcinoid) and 165 benign biopsies (68.5% of 241, including 124 slight-moderate chronic inflammations, 12 epithelial hypertrophy, 8 chronic inflammations with epithelial hypertrophy, 7 normal mucosa, 7 sub-mucosal

tuberculoses, 4 granulomas and 4 severe chronic inflammations).

Among 76 malignant biopsies, 72 were identified by the AFB and 50 by the WLB. In terms of malignant lesions, the sensitivities, specificities, and NPVs of the AFB and WLB were 97.4%, 57%, 95.9% and 65.8%, 83.6%, 84.1%, respectively. These measured differences between the AFB and WLB were all statistically significant ($P < 0.05$) (Table 1).

The AFB missed 1 squamous cell carcinoma, 1 adenocarcinoma, and 2 small cell lung cancers, each being a peripheral pulmonary lesion undetectable by bronchoscope. The WLB missed 10 squamous cell carcinomas, 10 adenocarcinomas, and 4 small cell lung cancers, including 15 central pulmonary lesions. All missed malignancies were identified by later biopsies. For either central or peripheral lesions, the accuracy of the AFB was significantly higher than the WLB (Tables 2 and 3).

Discussion

Since high-resolution CCD became an available imaging system, the definition and diagnostic power of bronchoscopes have improved remarkably. However, the most important tool for examining the bronchial mucosa, the commonly used WLB, is still plagued by limitations in diagnosing early-staged mucosal lesions. More specifically, the WLB is ineffective at detecting lesions smaller than 5 mm in diameter and at differentiating nonspecific mucosal changes caused by hypertrophy or carcinoma in situ[5]. The AFB is a new technology that exploits the autofluorescent nature of the bronchial mucosa to detect tiny and superficial lesions. The AFB can identify abnormal mucosa in different colors without the assistance of drugs. Therefore, compared to the WLB, the AFB can better identify early-staged mucosal lesions, thereby remarkably improving the bronchoscope's diagnostic efficiency for atypical hypertrophy and early-staged cancer of the mucosa[1,2].

As reported in the literature, the AFB detected tiny lesions that were only 1 mm in diameter or were several cellular layers in thickness. The AFB's sensitivity in detecting airway lesions was nearly 1.5- to 6.3-fold stronger than the WLB (Table 4) [2-4,6-9]. In the present study, the sensitivity of the AFB was significantly higher than the WLB (94.7% vs. 65.8%, 1.44:1), consistent with the literature. With central pulmonary lesions, the AFB's sensitivity was a remarkable 100% with no missed diagnoses, while the WLB's missed diagnosis rate was 23.4%. This data suggests that the AFB has a higher diagnostic power on early-staged cancer in the airway than the WLB.

Although the AFB could detect small changes in the bronchial mucosa with high sensitivity, it was unable to identify the pathology of any detected lesions. Indeed, the AFB distinguishes only the optical properties of tissues based on their thickness, blood supply, or extracellular matrix composition. In some lesions, such as inflammation, hyperemia, injury, and so on, mucosal thickness and blood supply increase, and the mucosa accordingly appears more red. It is difficult to distinguish those negative diseases from carcinoma. Therefore, the AFB's false negative rate for cancer is very high. The biggest limitations of the AFB were its low specificity and PPV. According to the literature, the

Table 1 Evaluation of the diagnostic capability of the AFB and the WLB

Exam	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
WLB	65.8	83.6	64.9	84.1
AFB	94.7	57.0	50.3	95.9
P	< 0.001	< 0.001	0.038	0.004

Table 2 Evaluation of the diagnostic capability of the AFB and the WLB in central-type lung cancer

Exam	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
WLB	76.6	86.3	79.0	84.5
AFB	100.0	60.0	62.7	100.0
P	<0.001	< 0.001	0.029	0.002

Table 3 Evaluation of diagnostic capability of the AFB and the WLB in different types of lung cancer

Pathology	Sensitivity of AFB (%)	Sensitivity of WLB (%)	Relative sensitivity of AFB	*P*
Squamous lung cancer	97.1	70.6	1.38	0.003
Adenocarcinoma	95.8	58.3	1.64	0.002
SCLC	81.8	63.6	1.29	0.635

Table 4 Reported sensitivity of the AFB and the WLB

Author	Time	Number of cases	Sensitivity (%)	
			WLB	AFB
Lam[2]	1994	223	73.1	91.4
Hirsch[6]	2001	55	21.9	68.8
Beamis[7]	2004	293	10.6	61.2
Häußinger[4]	2005	1173	57.9	82.3
Lam[8]	2006	62	58.3	91.7
Ikeda[3]	2006	154	65.0	90.0
Ueno[9]	2007	31	73.7	94.7

AFB had either a lower specificity or PPV than the WLB. Similarly, in our study, the AFB had a lower specificity for malignancy than the WLB (57.0% vs. 83.6%). This result may be due to the methodological limitations of the AFB, including its inability to make pathological diagnoses and its nonspecific response to other nonmalignant abnormalities in the bronchial mucosa. In addition, as a precaution for our inexperience at the onset of the study, we took biopsies for all areas that presented with abnormal colors to avoid missing diagnoses. Thus, our sampling approach might be another cause for the low specificity.

Low PPV and low specificity suggested more mucosal points for biopsy, leading to longer duration of mucosal injury, more fees, and longer examination time. Of the 136 cases analyzed, we found that the AFB had a significantly higher NPV (95.5%) than the WLB, consistent with the literature (Table 5)[4,7,10] that usually reports an NPV > 95% for the AFB. A high NPV means that unnecessary biopsies can be avoided. Therefore, in our opinion, increased experience with the AFB will improve our examination techniques, resulting in reduced iatrogenic injury on the mucosa, increased ability to differentiate between hypertrophies and cancer, and fewer unnecessary biopsies. These improvements will reduce overall suffering from examinations and decrease examination fees and time.

In our study, the AFB was significantly more sensitive than the WLB in detecting adenocarcinoma and squamous cell carcinoma, but no similar effect was observed for small cell lung cancer. This differential detection may be due to the AFB's ability to identify lesions by optical changes in the bronchial mucosa but not by their pathology. Thus, as the AFB can only detect malignancies from the mucosa, it cannot easily detect small cell lung cancer, which usually arises from submucosal tissues. Further, as the present study included only 5 patients with 11 biopsies, more data are needed before any conclusions may be drawn.

According to the literature[11-13], applications for the AFB include (1) sputum examinations; (2) screening tests for populations at high-risk of developing lung cancer, including individuals with a cigarette smoking index ≥ 400 and symptoms like prolonged cough or hemoptysis; (3) localization studies to identify the exact position and region of suspected lung cancer lesions; (4) re-examinations for airway recurrence after surgery to treat early-staged lung cancer; and (5) studies to monitor therapeutic effects on tracheal tumors. Because the AFB is more sensitive than the WLB and can be used without any additional medicine, injury, examination time or fees, or special protective facilities, this new technology, in our opinion, should be suited to all cases receiving bronchoscopy. This is especially true for patients at high-risk for developing lung cancer, patients with central-type lung cancer, or patients receiving post-operative recheck.

The AFB has a higher sensitivity than the WLB. By identifying the location of tumors, existence of multiple lesions, and recurrence of airway lesions, it improves the diagnostic efficiency of the bronchoscope for tracheobronchial mucosal cancer. The clinical value of AFB is, therefore, higher than the WLB.

References

[1] Lam S, MacAulay C, Hung J, et al. Detection of dysplasia and carcinoma in situ by a lung imaging fluorescence endoscope (LIFE) device [J]. J Thorac Cardiovasc Surg, 1993,105 (6):1035–1040.

[2] Lam S, MacAulay C, Le Riche JC, et al. Early localization of bronchogenic carcinoma [J]. Diagn Ther Endosc, 1994,1(2):75–78.

[3] Ikeda N, Honda H, Hayashi A, et al. Early detection of bronchial lesions using newly developed videoendoscopy-based autofluorescence bronchoscopy [J]. Lung Cancer, 2006,52(1):21–27.

[4] Häußinger K, Becker H, Stanzel F. Autofluorescence bronchoscopy with white light bronchoscopy compared with white light bronchoscopy alone for the detection of precancerous lesions: a European randomised controlled multicentre trial [J]. Thorax, 2005,60(6):496–503.

Table 5 Negative predictive value of the AFB and the WL

Author	Time	Cases	Negative predictive value (%)
Beamis[7]	2004	293	94.9
H.äußinger[4]	2005	1173	99.1
Hanibuchi[10]	2007	123	96.8
Ours	2010	138	95.9

［5］ Woolner LB, Fontana RS, Cortese DA, et al. Roentgegraphically occult lung cancer: pathologic findings and frequency of multicentricity during a 10-year period [J]. Mayo Clin Proc, 1984, 59(7):453–466.

［6］ Hirsch FR, Prindiville S, Miller YE, et al. Fluorescence versus white-light bronchoscopy for detection of preneoplastic lesions: a randomized study [J]. J Natl Cancer Inst, 2001, 93 (18): 1385– 1391.

［7］ Beamis JF, Ernst A, Simoff M, et al. A Multicenter study comparing autofluorescence bronchoscopy to white light bronchoscopy using a non-laser light stimulation system [J]. Chest, 2004,125(5 Suppl): 148S–149S.

［8］ Lam B, Wong MP, Fung SL, et al. The clinical value of autofluorescence bronchoscopy for the diagnosis of lung cancer [J]. Eur Respir J, 2006,28(5): 915–919.

［9］ Ueno K, Kusunoki Y, Imamura F,et al. Clinical experience with autofluorescence imaging system in patients with lung cancers and precancerous lesions [J]. Respiration, 2007,74(3):304–308.

［10］ Hanibuchi M, Yano S, Nishioka Y, et al. Autofluorescence bronchoscopy, a novel modality for the early detection of bronchial premalignant and malignant lesions [J]. J Med Invest, 2007, 54(3–4):261–266.

［11］ Loewen G, Natarajan N, Tan DF, et al. Autofluorescence bronchoscopy for lung cancer surveillance based on risk assessment [J]. Thorax, 2007,62(4):335–340.

［12］ Sutedja TG, Codrington H, Risse EK, et al. Autofluorescence bronchoscopy improves staging of radiographically occult lung cancer and has an impact on therapeutic strategy [J]. Chest, 2001,120(4):1327–1332.

［13］ Weigel TL, Kosco PJ, Dacic S, et al. Postoperative fluorescence bronchoscopic surveillance in non-small cell lung cancer patients [J]. Ann Thorac Surg, 2001,71(3):967–970.