New Applications of Bronchoscopic Techniques

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Dual digital video-autofluorescence imaging for detection of pre-neoplastic lesions

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Summary
Aim: The incorporation of autofluorescence (AF) to white light bronchoscopy has led to improved sensitivity for the detection of pre-neoplastic lesions in the airways. However, AF has difficulty distinguishing benign epithelial changes such as bronchitis, previous biopsy, and airway fibrosis from pre-invasive lesions, which necessitates extensive biopsy. This frequently results in longer procedural time and need for additional sedation that may compromise patient safety, increase the risk of bronchospasm, and bleeding from multiple endobronchial biopsies. We postulate that dual imaging with simultaneous video and AF bronchoscopy of the tracheobronchial tree could improve the low specificity observed with AF in the detection of pre-invasive lesions, leading to targeted biopsy, good correlation with pathological diagnosis and shorter procedural time.
Methods: Forty-eight patients with known or suspected of lung cancer underwent video and AF bronchoscopy, which were provided as real-time dual images with SAFE 3000 (Pentax, Tokyo) between March and August 2006. Biopsy specimens were taken from all suspicious areas with two random specimens from normal areas. Values were expressed as median and range, and $p < 0.05$ was considered statistically significant.
Results: Twenty-five suspicious sites were detected by dual imaging bronchoscopy, and 126 endobronchial biopsies were evaluated, of which 22 (17.5%) were graded as moderate dysplasia and worse. Sensitivity and specificity of dual imaging for the detection of high-grade dysplasia were 86% and 94%, respectively, with good correlation between bronchoscopic assessment and pathology ($r = 0.77$, $p < 0.0001$). However, there were three random biopsy specimens obtained from normal or abnormal sites that showed severe dysplasia in two and moderate dysplasia in one. Median time taken for airway examination was 4 min (range, 4—4.8), and 5 min (range, 4—5) for biopsy, giving a total procedural time of 9 min (range, 8—10). There were no procedure-related complications noted.

Abbreviations: WLB, white light bronchoscopy; CIS, carcinoma *in situ*; LIFE, laser induced fluorescence endoscopy; AF, autofluorescence

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Conclusion: Dual imaging that allows simultaneous real-time assessment of the lesion with video and AF bronchoscopy not only achieves satisfactory sensitivity for the detection of pre-neoplastic lesions, importantly it improves specificity by allowing targeted biopsy, which has led to a marked decrease in procedural time and better patient safety.

1. Introduction

Lung cancer at the beginning of the twentieth century was rare. Since then the rates of lung cancer in men and women have increased 10-fold, making it the second most common cancer and the leading cause of cancer deaths in the United States. Today, lung cancer accounts for more deaths than breast, prostate and colon cancers combined [1]. Prognosis and survival depend on the stage of disease, and since more than two thirds of patients with lung cancer have mediastinal lymph node or distant metastases at presentation, it is not surprising that cure rate remains dismal at 15% [2]. Experience with cervical, oesophageal and colon cancers has demonstrated that if neoplastic lesions can be detected and treated in the intra-epithelial stage, significant improvement in cure rates translating to survival benefit can be achieved [3—5].

White light bronchoscopy (WLB) is reflectance imaging that exploits three optical properties of reflection, scattering and absorption when bronchial tissue is illuminated by light. This technology has led to the detection of early hilar lung cancer [6], and endoscopic features of dysplasia and carcinoma *in situ* (CIS) with WLB have been described [7]. However, Woolner have shown that only a third of patients with CIS could be identified with this modality [8].

Laser induced fluorescence endoscopy (LIFE; Xilix Technologies Corp., Richmond, Canada) is a device that has facilitated the detection of pre-neoplastic lesions by capturing the differences in fluorescence emitted by normal, pre-neoplastic or early malignant tissue when excited by monochromatic blue light (442 nm) delivered by a helium cadium laser. Subsequent clinical studies with LIFE have shown marked increase in sensitivity for the localization of lesions with moderate dysplasia and worse [9—14].

Although LIFE is highly sensitive, difficulties in distinguishing benign epithelial changes such as bronchitis from pre-invasive lesions as well as in the accurate prediction of pathological diagnosis based on the grade of tissue fluorescence have necessitated extensive biopsy with consequent greater health costs, longer procedural time and higher incidence of procedure related bronchitis which may require hospitalization for treatment. In fact, studies have demonstrated that as high as one third of these areas detected with abnormal fluorescence by LIFE represented false positives when correlated with pathology [10,15,16]. Of particular clinical relevance would be in chemoprevention trials and surveillance following endobronchial treatment of CIS where previous biopsy sites and consequent airway fibrosis may result in abnormal fluorescence that could persist for months to years, making interpretation a challenge.

This study was therefore undertaken to determine if real-time dual video and autofluorescence (AF) bronchoscopic images could improve specificity without compromising sensitivity for the detection of pre-neoplastic lesions to allow targeted biopsy, shorten procedural time and good pathological correlation.

2. Material and methods

The protocol was approved by the institutional review board of Vrije University (Amsterdam), and written informed consent was obtained from all patients.

2.1. Study population

Inclusion criteria for the study include: (1) current or former smokers with hemoptysis; (2) patients with known or suspected lung cancer scheduled for bronchoscopy; (3) those with abnormal sputum cytology and normal radiograph; (4) for follow up after curative surgery for stage I lung cancer. Patients who had received photosensitising agents or chemopreventive drugs such as retinoids within 3 months, radiotherapy to chest or cytotoxic chemotherapy within 6 months of bronchoscopic procedure were excluded. Other exclusion criteria were pneumonia, acute bronchitis, poorly controlled hypertension, unstable angina, bleeding disorders, pregnancy and adverse reactions to topical lignocaine.

2.2. Equipment and procedure

SAFE 3000 (Pentax, Tokyo, Japan) is a videobronchoscope that uses xenon lamp for white light bronchoscopy and allows real-time colour image transmission using the miniature charge couple device that is built into its tip. The AF mode utilizes a diode laser that delivers excitation light to the target from the tip of the scope, and fluorescence from the target is then captured by filtering out the wavelength of excitation light with the objective lens. As both light sources are available, it also allows for dual real-time imaging where both video and AF bronchoscopic images of the target are displayed simultaneously.

The procedure was performed in the bronchoscopy suite with local anaesthesia where only topical lignocaine spray was administered to the naso—oropharynx. Each site was visually classified by videobronchoscopy as normal, abnormal or suspicious and by autofluorescence as positive when there is definite decrease in fluorescence with distinct margin (Table 1). Biopsy was performed for all areas graded as class 3 by dual imaging. Endobronchial biopsies were obtained using fenestrated cup forceps (Pentax KW2415R) and carried out under the AF mode to ensure accurate acquisition of tissue especially from small suspicious areas. Two additional specimens were taken from sites identified as class 1 and/or 2. In patients with normal video and AF bronchoscopy, biopsy specimens were obtained from second-generation carina.

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Table 1 Visual classification of bronchoscopic findings with SAFE 3000

Class	Description of bronchoscopy	Autofluorescence
1/Normal	No visual abnormality	Negative (green)
2/Abnormal	Erythema, swelling or thickening of bronchial mucosa, airway inflammation and fibrosis	Negative (slight decrease in fluorescence with ill defined margin)
3/Suspicious	Nodular, polypoid lesions, irregular bronchial mucosa, focal thickening of the subcarina	Positive (definite decrease in fluorescence with defined margin)

Biopsy specimens were then graded in accordance with the International Histological Classification of Tumours published by the World Heath Organization [17] by expert pulmonary pathologists as either (1) normal; (2) inflammation/bronchitis; (3) hyperplasia; (4) squamous metaplasia; (5) mild dysplasia; (6) moderate dysplasia; (7) severe dysplasia; (8) carcinoma *in situ*; or (9) carcinoma.

2.3. Statistics

For the purpose of statistical analysis, physician's visual classification was converted to a two-point scale where classes 1 and 2 became ''negative'' and class 3 became ''positive''. Final pathological diagnosis was also converted to a two-point scale where codes 1—5 were labelled as ''negative'' and codes 6—8 as ''positive''. All biopsy specimens had to have sufficient bronchial epithelium for evaluation. Sensitivity and specificity conferred by dual imaging were calculated, and correlation between visual classification and final pathological diagnosis was determined by Spearman rho test. Values were expressed as median and range, and $p < 0.05$ was considered statistically significant.

3. Results

Forty-eight patients (43 males, 5 females) with median age 66 years (range, 62—72) underwent dual imaging bronchoscopy from March to August 2006 for indications as shown in Table 2. All were current and former smokers of 40 pack years (range, 36—48).

A total of 126 biopsy specimens were taken with median 3 (range, 2—4) biopsies per patient. All specimens showed adequate bronchial epithelium for evaluation by the pathologist, and 22 (17.5%) were classified as moderate dysplasia and worse (high grade dysplasia). Bronchoscopic and pathological characteristics of each biopsy site and specimen are shown in Table 3.

Dual imaging bronchoscopy identified 25 suspicious sites, of which 19 were positive for high grade dysplasia: moderate dysplasia in four, severe dysplasia in 11 and CIS in 4. Three random biopsy sites that were visually identified as abnormal (Class 2) were positive for moderate dysplasia in one and severe dysplasia in two. Calculated sensitivity and specificity of dual imaging bronchoscopy for the detection of high grade dysplasia were 0.86 (19/22) and 0.94 (98/104), respectively, and visual classification determined by simultaneous dual video and AF images also correlated well with pathology ($r = 0.77$, $p < 0.0001$).

Table 2 Patient demographics and procedure

Variables	Values
Patient, No.	48
Age, years	66 (range, 62—72)
Gender	
Male	43
Female	5
Smoking history, pack years	40 (range, 36—48)
Smoking status	
Current smoker	24 (50%)
Former smoker	24 (50%)
Indication for bronchoscopy	
Hemoptysis	4 (8%)
Suspicious sputum cytology	3 (6%)
Known or suspected lung cancer for bronchoscopy	2 (4%)
Surveillance of patients after surgery for stage I lung cancer	21 (44%)
Surveillance of CIS after endobronchial therapy	18 (38%)
Procedure	
Time taken for examination (min)	4 (range, 4—4.8)
Time taken for biopsy	5 (range, 4—5)
Total procedural time	9 (range, 8—10)
Complications	0

Time required perform a complete airway examination was 4 min (range, 4—4.8), and time taken to obtain specimens from suspicious sites as well as random biopsies of normal areas was 5 min (range, 4—5), giving a total procedural time of 9 min (range, 8—10). No additional sedation was required other than local anaesthesia, and no complications were observed.

4. Discussion

Clinical studies have shown that AF improves the detection of high grade dysplasia of the bronchial epithelium (moderate dysplasia and worse) by 1.3 to 6.4 times over WLB [9—11,13,14]. However, these earlier studies were carried out the fiberoptic bronchoscopes. With the advent of the videobronchoscope that has a miniature charge couple device built in its tip which delivers clearer images, sensitivity for the detection of premalignant lesions has

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Table 3 Visual classification and pathology characteristics of biopsy sites

Pathology	Sites	Dual image		
		Normal	Abnormal	Suspicious
Normal	78	45	30 (7 areas likely fibrosis; 6 previous biopsy sites)	3
Inflammation	10	2	6 (4 likely bronchitis)	2
Squamous metaplasia	10	2	7	1
Mild dysplasia	6	1	5	0
Moderate dysplasia	5	0	1	4
Severe dysplasia	13	0	2	11
Carcinoma *in situ*	4	0	0	4

Table 4 Comparison of sensitivity and specificity values for different imaging modalities in the detection of pre-neoplastic lesions

Authors (reference no.)	Equipment	Sensitivity sequential procedure	Specificity sequential procedure
Haussinger et al. [9]	BF, D-light	0.82 (WLB + D-light)	0.58 (WLB + D-light)
Hirsch et al. [10]	BF, LIFE	0.79 (WLB + LIFE)	0.29 (LIFE + WLB)
Lam et al. [11]	BF, LIFE	0.56 (WLB + LIFE)	0.66 (LIFE + WLB)
Venmans et al. [13]	BF, LIFE	1.0 (WLB + LIFE)	0.60 (LIFE + WLB)
Chhajed et al. [18]	VE, LIFE	0.72 VE/0.96 LIFE	0.53 VE/0.23 LIFE
Chiyo et al. [19]	VE, LIFE	0.56 VE/0.97 LIFE	0.5 VE/0.36 LIFE
Ikeda et al. [20]	VE, SAFE	0.65 VE/0.90 SAFE	0.49 VE/0.47 SAFE
Lee et al.[a]	VE, SAFE	0.86 dual image	0.94 dual image

BF: bronchofiberscope; VE: videoendoscope.
[a] Present study.

correspondingly improved Table 4 [18—20]. Chhajed et al. showed that the addition of AF to videobronchoscopy could better target sites for biopsy as specimens taken from areas classified as normal by videobronchoscopy but showed suspicious fluorescence with LIFE, they were more likely to harbour dysplasia than random biopsies from areas that had normal fluorescence. The converse was also true for abnormal lesions detected by videobronchoscopy, that if the specimens were taken from lesions with abnormal fluorescence, they were more likely to reveal dysplasia than those obtained from areas with abnormal videobronchoscopy and normal fluorescence which accounted for only 1% of the total positive biopsies [18].

Our study has demonstrated that dual imaging with video and AF bronchoscopy is not only sensitive for the detection of pre-neoplastic lesions (0.86), it is highly specific (0.94) as display of video and AF images of the lesion side by side allows precise visual assessment analogous to PET/CT. By

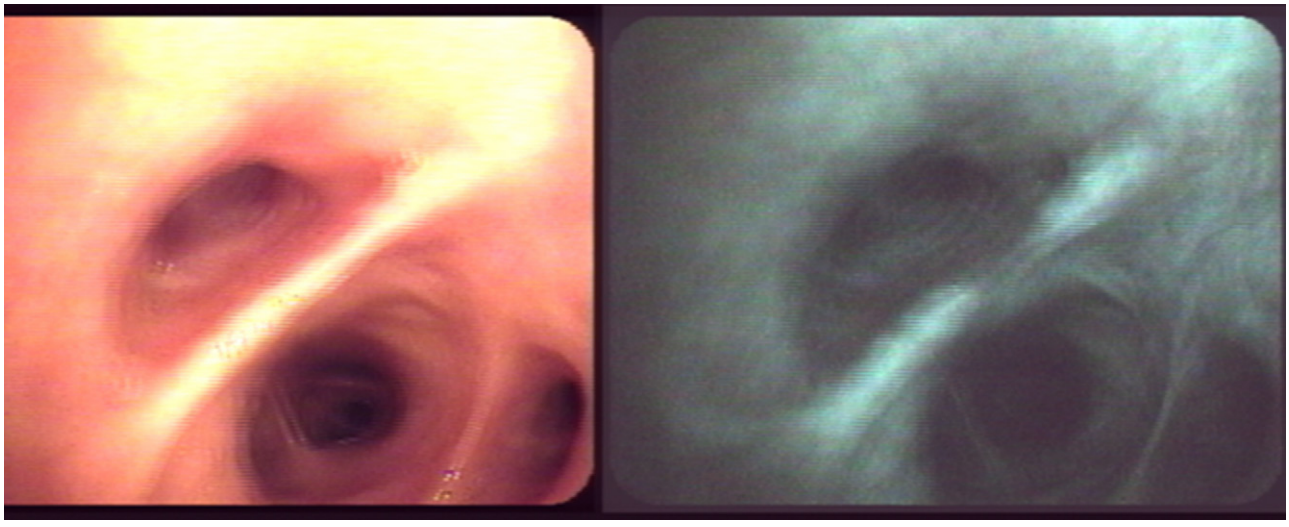

Fig. 1 Previous biopsy site visualized on videobronchoscopy but showed abnormal fluorescence. Biopsy was normal.

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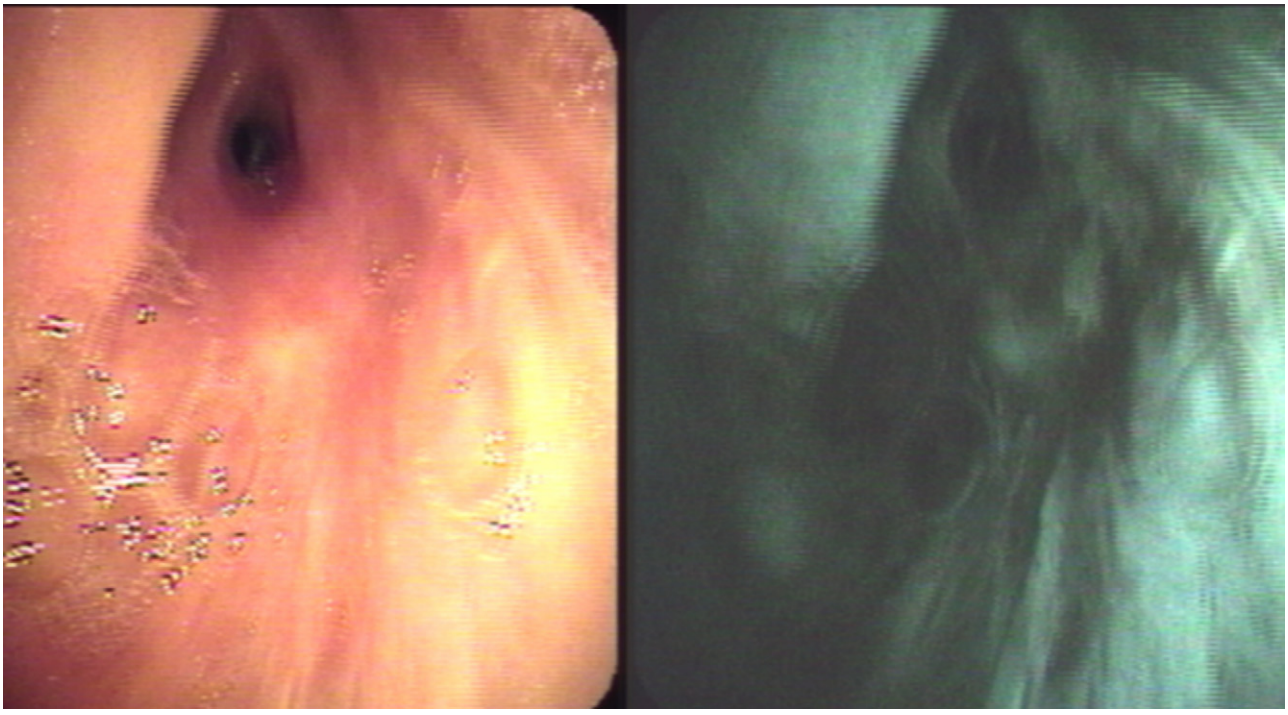

Fig. 2 Abnormal fluorescence involving left secondary carina was observed, however, videobronchoscopy suggested bronchitis. Biopsy of target confirmed inflammation.

providing functional and anatomic information at the same time, dual imaging aids the operator in targeting appropriate sites for biopsy which leads to shorter procedural time, better patient comfort and safety.

The time taken for complete airway examination and biopsy was 9 min, which was comparable to standard WLB, whilst in other clinical studies that included sequential WLB and AF, independent investigators had reported additional 5 to 13.8 min to standard procedural time [9,11,13,20]. Good correlation between visual classification and final pathology diagnosis was achieved by dual imaging ($r = 0.77$, $p < 0.0001$), particularly in distinguishing suspicious from non-suspicious areas which include abnormal lesions, and in identifying previous biopsy site (Fig. 1), bronchitis (Fig. 2), and airway fibrosis after endobronchial therapy, each case confirmed benign by pathology. These characteristic endoscopic findings could potentially obviate extensive biopsy although a larger sample size would be required to validate this observation.

Our study has several limitations. Firstly our sample size is relatively small and secondly it is not a comparative study where individual imaging modality namely video and AF bronchoscopy is assessed independently before dual imaging. However, our primary objective was to determine if this novel approach was feasible with good sensitivity and specificity for the detection of pre-neoplastic lesions compared against published data, notwithstanding that the sensitivity and specificity of LIFE derived from clinical studies were also biased as serial sections of the entire tracheobronchial tree could not be obtained for pathological examination after bronchoscopic procedures for the values to be verified.

5. Conclusion

Indeed our study with real-time dual display of video and AF images not only achieves good sensitivity and specificity for the detection of high grade dysplasia, it also facilitates targeted biopsy with good pathological correlation thereby translating to shorter procedural time, better patient comfort and safety. More research is required to validate its discriminatory value in distinguishing benign epithelial changes such as bronchitis, previous biopsy site and airway fibrosis from pre-invasive lesions.

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