Original Article

Detection of premalignant bronchial lesions can be significantly improved by combination of advanced bronchoscopic imaging techniques

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Abstract:

BACKGROUND: The search for the most efficient bronchoscopic imaging tool in detection of early lung cancer is still active. The major aim of this study was to determine sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each bronchoscopic technique and their combination in detection of premalignant bronchial lesions.

METHODS: This was a prospective trial that enrolled 96 patients with indication for bronchoscopy. Lesions were classified as visually positive if pathological fluorescence was observed under autofluorescence imaging (AFI) videobronchoscopy or dotted, tortuous, and abrupt-ending blood vessels were identified under narrow band imaging (NBI) videobronchoscopy. Squamous metaplasia, mild, moderate, or severe dysplasia, and carcinoma *in situ* (CIS) were regarded as histologically positive lesions.

RESULTS: Sensitivity, specificity, PPV, and NPV of white light videobronchoscopy (WLB) in detection of premalignant lesions were 26.5%, 63.9%, 34.4%, and 54.9%, respectively; the corresponding values for AFI were 52%, 79.6%, 64.6%, and 69.9% respectively, for NBI were 66%, 84.6%, 75.4%, 77.7%, respectively, while the values for combination of NBI and AFI were 86.1%, 86.6%, 84.6%, and 88%, respectively. Combination of NBI and AFI significantly improves sensitivity when compared to each individual technique ($P < 0.001$). When specificity is of concern, combination of techniques improves specificity of WLB ($P < 0.001$) and specificity of AFI ($P = 0.03$), but it does not have significant influence on specificity of NBI ($P = 0.53$).

CONCLUSION: Combination of NBI and AFI in detection of premalignant bronchial lesions increases both sensitivity and specificity of each technique. However, it seems that NBI is most sufficient and effective in detection of these lesions.

Key words:

Autofluorescence bronchoscopy, bronchoscopy, interventional pulmonology, lung cancer, narrow band imaging, premalignant lesions

Lung cancer remains one of the most lethal malignancies worldwide, among both men and women. Most important drawbacks in efficient treatment of lung cancer are delayed diagnosis and absence of effective screening. Detection and study of precancerous lesions of the bronchial mucosa might be one of the turning points in understanding of neoplastic transformation, and therefore creation of most effective treatment.[1-5] However, the use of white light videobronchoscopy (WLB) in detection of precancerous lesions yields low sensitivity and specificity. Introduction of narrow band imaging (NBI) and autofluorescence imaging (AFI) videobronchoscopy into diagnostic evaluation of lung cancer significantly improved sensitivity in detection of precancerous lesions. Improvement of specificity is questionable for AFI, but in case of NBI, specificity in detection of early lung cancer might be improved. Large number of clinical studies showed good potential of AFI and NBI in detection of precancerous bronchial lesions.[6-12] One of the most important clinical trials on autofluorescence bronchoscopy, Haussinger's study,[13] did not confirm the value of this technique in screening, but it did point out the value in detection of precancerous lesions in high-risk groups of patients. Both NBI and AFI are now widely used as scientific bronchoscopic tools in detection of early stage lung cancer. However, both are also efficient as tools for evaluation of endobronchially visible tumor, for detection of synchronous tumors, and for follow-up of surgically treated patients.[14-16]

Effective detection of precancerous lesions is one of the most important premises for their further investigations. Substantial number of clinical studies nowadays confirms the presence of important molecular changes in impaired bronchial epithelium that might be very important for further understanding of carcinogenesis. Evaluation and confirmation of

best bronchoscopic optical tools for detection of these changes might therefore be very important for continuation of research on precancerous bronchial lesions.[17-20]

AFI is one of the newest charged-couple device (CCD)-based videobronchoscopy systems. It is mainly constructed to detect weak autofluorescent signal from pathologically altered bronchial mucosa. The system successfully detects intraepithelial changes, and thus is successful in detection of squamous cell alterations. On the other hand, NBI is optical enhancement technology designed to detect subepithelial blood vessel grid. This enables NBI to detect all vascular abnormalities. These differences theoretically make the two techniques compatible; while AFI detects epithelial changes NBI captures abnormal subepithelial vascular patterns. That is why the combination of two techniques might be most efficient in detection of precancerous bronchial lesions.[7,8]

Primary aim of this clinical study was to determine sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each bronchoscopic technique, WLB, AFI, NBI, and their combination in detection of premalignant bronchial lesions. Secondary objectives were determination of sensitivity, specificity, PPV, and NPV of each bronchoscopic technique and their combination for each individual premalignant lesion and determination of the most efficient technique for detection of preinvasive lesions.

Methods

The study was a prospective, non-randomized trial, conducted at a dedicated respiratory endoscopy unit of a university teaching clinic at the Institute for Pulmonary Diseases of Vojvodina in Serbia in the period from June 2009 to December 2009. It was approved by the institutional review and ethics board. All the patients who decided to participate in the study were informed about the procedure, its potential benefits and the risks, and all of them had signed institutional informed consent form. All the patients screened for the enrollment were previously scheduled for routine bronchoscopy.

Inclusion criteria

Inclusion criteria for enrollment in the study were: age over 18 years, radiological suspicion for lung cancer, surveillance of patients after curative lung cancer surgery, evaluation of known malignancy, positive sputum cytology, and prolonged cough. Exclusion criteria were: patients who did not want to participate in the study, Eastern Cooperative Oncology Group (ECOG) ≥3, recent myocardial infarction, unresolved coagulopathies, unstable angina pectoris, chronic heart failure (New York Heart Association NYHA ≥ 3), uncontrolled arrhythmia or hypertension, and allergy to anesthetics. Prior to the enrollment in the study, all patients must have had chest X-ray, computed tomography (CT) scan of the thorax and abdomen, spirometry and body pletismography, blood gas analysis, complete blood count, and blood biochemistry. One hundred and nineteen patients were screened for the study; 96 of them met all the inclusion criteria and were not having any exclusion criterion.

Technique and design

Bronchoscopy was performed in a dedicated respiratory endoscopy unit by bronchoscopists experienced in the use of AFI and NBI. All procedures were performed in analgosedation. The routine vital parameters were monitored: noninvasive arterial blood pressure, oxygen saturation on pulse oximetry, and ECG for cardiac rhythm. Brochoscopic equipments used in the study were AF videobronchoscope BF-F260 and NBI videobronchoscope BF-1T180 and BF-1TQ180 (Olympus Corporation, Tokyo, Japan), and video processor unit EVIS LUCERA SPECTRUM (CV-260SL) (Olympus Corporation). Videobronchoscopy image was presented at a 19-inch LCD monitor OEV-191. The examination of the tracheobronchial tree started with WLB followed by NBI and AFI. All the suspected changes in bronchial mucosa were first examined with the WLB, followed by NBI and AFI modes. Once the pathologic sites were identified, we performed targeted biopsies in order to obtain material for pathological examination. A dedicated lung pathologist evaluated the biopsy specimens, blinded to bronchoscopic findings. In all patients, at least one but no more than three biopsies were taken from places identified as pathologic, either by WLB, AFI, NBI, or their combination. One to three random biopsies were taken from the places identified as normal.[6,14-16] Visually pathologic areas under AFI were defined as reddish-brown or magenta-colored area, while the healthy area was green. Visual scoring system for detection of pathologically altered mucosal areas under AFI is given in Table 1.

Visually pathologic areas under NBI were defined as dotted, tortuous, or abrupt-ending blood vessels. Dotted, abrupt-ending, and tortuous blood vessels as defined by Shibuya, and commonly known as Shibuya descriptors, were denominators for visual detection of pathological areas under NBI videobronchoscopic examination.[12] Visually positive areas in combined mode (NBI + AFI) were confirmed if the area of the mucosa was clearly pathological under both techniques.[6,14-16] Each targeted biopsy specimen was obtained by a separate dedicated forceps (usually FB-19C-1 or FB-15C-1). Biopsies were identified as positive if squamous metaplasia, dysplasia, or invasive carcinoma was identified in the tissue. If needed, for confirmation of the disease, additional transbronchial biopsies (TBB) were taken, these biopsies were not counted into consideration for the purposes of this study.

Biopsy-based specificity, sensitivity, PPV, and NPV for detection of each individual technique and their combination

Table 1: Visual appearance of normal and pathologically altered mucosa under autofluorescence videobronchoscopy

Visual appearance	AFI appearance
Normal mucosa	Green autofluorescence with normal endobronchial architectonics
Abnormal, not suspicious for malignancy (inflammation)	Discrete decrease in fluorescence with vaguely defined margins, dark green or light violet (light purple)
Suspicious for intraepithelial neoplasia	Definitive decrease in fluorescence, clearly defined margins, violet (or brownish) with clear distortion of endobronchial architectonics
Tumor	Visible tumor, reddish-brown (magenta) colored

AFI = Autofluorescence imaging

were calculated. Only the biopsies confirmed to be positive for premalignant or malignant lesions were taken into calculation of sensitivity and specificity.

Statistical analysis

Descriptive statistics were generated for all study variables, including mean and standard deviation (SD) for continuous variables and relative frequencies for categorical variables. One sample Kolmogorov–Smirnov test was performed for testing the goodness of fit with the normal distribution. McNemar test was used to compare the diagnostic sensitivity and specificity, and statistically significant differences between categorical variables, sensitivity, specificity, PPV, and NPV of WLB, AFI, NBI, or NBI + AFI findings for detection of precancerous lesions were calculated. All probability values were calculated by assuming a two-tailed α value of 0.05 with confidence intervals at the 95% level. All statistical analyses were performed with SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

Ninety-six patients were included in the study, which comprised 72 (75%) males and 24 (25%) females. Average age of the patients was 56 ± 10 years (range 27-89 years). Majority of the patients were current smokers (67.7%); there were 26% of former smokers and only 6.3% of nonsmokers. Indications for bronchoscopy are given in Table 2. There were 32 (33.3%) patients with final diagnosis of squamous cell lung cancer and 12 (12.6%) with adenocarcinoma. In 9 (9.4%) patients, the final diagnosis was dysplasia grade I, 18 (18.8%) patients had dysplasia grade II, 20 (20.8%) patients had confirmed dysplasia grade III, 3 (3.1%) patients had squamous metaplasia only, and 2 (2%) patients were without pathological findings in biopsy. There were no patients with carcinoma *in situ* (CIS).

Average duration of WLB examination was 9 ± 3 min, while that of AFI and NBI was 10 ± 4 and 8 ± 2 min, respectively. Average duration of the entire examination was 18 ± 5 min. Sensitivity, specificity, PPV, and NPV of WLB were 26.5%, 63.9%, 34.4%, and 54.9%, respectively. Sensitivity of WLB in detection of squamous metaplasia was 27.3%. In detection of dysplasia grade I, II, and III, sensitivity of WLB was 39.5%, 17%, and 24.2%, respectively. AFI demonstrated sensitivity of 52%, specificity of 79.6%, PPV 64.6%, and NPV 69.9%. If analyzed by each type of lesion, sensitivity of AFI was 47.7% for squamous metaplasia, 58.1% for dysplasia grade I, 55.3% for dysplasia grade II, and 48.5% for dysplasia grade III. Sensitivity, specificity, PPV, and NPV of NBI were 66%, 84.6%, 75.4%, and 77.7%, respectively. When calculated by the type of the lesion, NBI showed a sensitivity of 65.9% in detection of squamous metaplasia, for detection of dysplasia grade I the sensitivity was 67.4%, for dysplasia grades II and III the sensitivity was 74.5% and 59.1%, respectively. Combination of techniques showed sensitivity, specificity, PPV, and NPV of 86.1%, 86.8%, 84.6%, and 88%, respectively. Sensitivity of combination in detection of squamous metaplasia was 72.7%. Sensitivity in detection of dysplasia grade I, II, and III was 83.7%, 85.1%, and 89.4%, respectively. Overall sensitivity, specificity, PPV, and NPV are highlighted in Table 3.

Combination of NBI and AFI significantly improves sensitivity when compared to each individual technique ($P < 0.001$). When specificity is of concern, combination of techniques improves specificity of WLB ($P < 0.001$) and specificity of AFI ($P = 0.03$), but it does not have significant influence on specificity of NBI ($P = 0.53$).

Table 2: Indications for bronchoscopy

Indication for bronchoscopy	Frequency	Percent
Radiological suspicion for lung cancer	43	44.8
Surveillance of patients after curative lung cancer surgery	18	18.8
Evaluation of known malignancy	22	22.8
Positive sputum cytology	4	4.2
Prolonged cough	9	9.4
Total	96	100

Table 3: Highlighted sensitivity, specificity, positive predictive value, and negative predictive value of each technique and their combination in detection of precancerous lesions

Technique	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
WLB	26.5	63.9	34.4	54.9
AFI	52	79.6	64.4	69.9
NBI	66	84.6	75.4	77.7
AFI+NBI	86.1	86.8	84.4	88

WLB = White light videobronchoscopy, AFI = Autofluorescence imaging videobronchoscopy, NBI = Narrow band imaging videobronchoscopy, PPV = Positive predictive value, NPV = Negative predictive value

Discussion

Data presented in this study show superiority of AFI and NBI videobronchoscopy over WLB in detection of precancerous lesions of bronchial mucosa. It is also observed from the data that specificity of AFI remains low and questionable, although one must have in mind that AFI performs better in indications outside of premalignant lesion detection. In pivotal studies, NBI showed superiority over WLB in detection of cancerous and precancerous bronchial lesions. It is also confirmed that NBI improves sensitivity and specificity of WLB along with sensitivity of AFI in detection of these lesions; however, the influence of NBI on specificity of AFI is still questionable. In our study, NBI improved specificity of AFI based on per-lesion and per-biopsy calculations, but larger number of patients would be required to calculate the per-patient efficacy. One of the drawbacks of our study lays in the fact that all examinations were performed by the bronchoscopists highly experienced in both techniques. The major aim of our study was determination of sensitivity, specificity, PPV, and NPV of each individual technique and their combination in order to select the best possible technique for detection of precancerous bronchial lesions. While combination of techniques yields highest sensitivities and specificities, NBI showed sufficient and superior detection of these lesions.

Chen and associates performed a meta-analysis in order to re-examine the diagnostic efficiency of AFB compared with WLB.[21] The included studies had to have conclusive histology as diagnostic standard for detection of lung cancer and premalignant lesions. Fourteen studies providing 15 sets of data were found to be suitable for analysis. Pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood

ratio for AFB were 0.90 (95% CI: 0.84-0.93), 0.56 (95% CI: 0.45-0.66), 2.0 (range 1.7-2.5), and 0.18 (range 0.13-0.26), respectively. Pooled diagnostic odds ratio was found to be 11. On the other hand, pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio for WLB were 0.66 (95% CI: 0.58-0.73), 0.69 (95% CI: 0.57-0.79), 2.1 (1.6-2.9), and 0.50 (0.43-0.58), respectively, while the diagnostic odds ratio was 4. Our study yielded comparable results. For AFI, specificity, sensitivity, PPV, and NPV were 79.6%, 52%, 64.6%, and 69.9%, respectively. Higher specificity obtained in our study could be attributed to high number of patients with invasive bronchial malignancy. Values of sensitivity, specificity, PPV, and NPV are also comparable. In our study, the corresponding values for WLB were 26.5%, 63.9%, 34.4%, and 54.9%, respectively. The authors of meta-analysis concluded that AFB was superior to conventional WLB in detecting lung cancer and preneoplastic lesions. In Sun's meta-analysis,[22] the main objective was comparison between accuracy of AFB combined with WLB versus WLB alone in the diagnosis of lung cancer. Twenty-one studies involving 3266 patients were ultimately analyzed in Sun's meta-analysis. The pool relative sensitivity on a per-lesion basis to detect intraepithelial neoplasia and invasive cancer was for AFB + WLB 2.04 (95% CI 1.72-2.42) and for WLB alone 1.15 (95% CI 1.05-1.26), and it was statistically significant (P = 0.003). The pool sensitivity on a per-lesion basis of AFB + WLB versus WLB to detect invasive cancer was 94.71% and 88.53%, respectively. The pool specificity on a per-lesion basis of AFB + WLB versus WLB alone was 60.94% and 79.7%, respectively. The main results of this meta-analysis showed that combination of AFB + WLB significantly improves sensitivity to detect intraepithelial neoplasia, even though this advantage seemed much less in detection of invasive lung cancer. Data from our study are consistent with the data presented in Sun's meta-analysis. It must be stated that sensitivity and specificity of AFB in detection of pre-malignant lesions could be highly dependent on several factors such as the type of AFB system, the grade of the lesion, and bronchoscopist's experience. Both sensitivity and specificity of autofluorescence videobronchoscopy show huge differences between the systems and authors. Huge variations in sensitivity and specificity of autofluorescence bronchoscopy are presented in Table 4.

Table 4: The sensitivities and specificities of autofluorescence videobronchoscopy in detection of precancerous lesions

Author	System	Sensitivity (%)	Specificity (%)
Chiyo[23]	AFI	80	83.3
Chiyo[23]	LIFE	96.7	36.6
Häuβinger[13]	D-light	82.3	58.4
Ueno[24]	AFI	94.7	71.1
Chhajed[25]	LIFE	96	23
Lam[26]	SAFE-1000	91.7	26.4
Stringer[27]	LIFE	84.4	60.7
Hanibuchi[28]	SAFE-1000	96.8	56.1
Beamis[29]	D-light	61.2	75.3
Ernst[30]	D-light	66	73
Herth[31]	AFI	65	40
Hirsch[32]	LIFE	73	46
Edell[33]	Onco-LIFE	44	75
Cetti[8,35]	AFI	93.3	81.8
Chen[21]	Meta-analysis	90	56
Sun[22]	Meta-analysis	94.7	60.9

AFI = Autofluorescence imaging

In a study performed by Beamis *et al*.[29] AFB (D-light Autofluorescence System, Karl Storz Endoscopy America; Culver City, CA, USA) was used in the detection of class III endobronchial neoplasia (severe dysplasia, CIS, and early invasive lung cancer). The sensitivity of AFB was 61.2% and the sensitivity of WLB was only 10.6% (P < 0.0001 by McNemar test). Specificity was 94.6% under WLB and 75.3% under AFB (P < 0.0001). PPV for AFB was 22.2% versus 18.4% for WLB (P = 0.49); NPV for AFB was 94.4% versus 90.2% for WLB (P < 0.01). This trial undoubtedly proved significant improvement in sensitivity of detecting class III bronchial lesions under AFB examination. One of the most favorable findings is high negative predictive value of AFB in detection of class III bronchial lesions. Similar results are shown in our study.

One of the most important studies about the use of NBI in respiratory endoscopy was published by Vincent *et al*. in 2009.[34] The authors investigated whether NBI in conjunction with WLB improves detection of dysplasia and malignancy. Results of the study showed that indication for enrollment in 50% of the patients was known lung cancer. In 32% of the patients, indication was radiological suspicion for lung cancer, undiagnosed parenchymal lung mass was underlying in 36%, while hemoptysis and mediastinal adenopathy were each present in 23% of the patients. There were 64 evaluable biopsies, 22 were control, and 42 were targeted to sites appearing pathological by NBI, WLB, or both. Of the 42 diagnostic biopsies 16 were confirmed to be normal and 26 abnormal. Four biopsies confirmed squamous dysplasia, 9 (41%) were carcinoma, 8 were inflammation, and 5 were non-malignant. This study showed that the NBI is significantly better for detection of dysplasia or cancer (P < 0.005); it detected five times more dysplasias and carcinomas than WLB. Relative sensitivity ratio for NBI + WLB over WLB alone was calculated to be 1.63, confirming significantly better detection with the addition of NBI. The specificity of NBI + WLB for dysplasia and cancer was 81% versus 64% for WLB alone. Specificity of NBI in our study was 84.6%, while the specificity of WLB was 63.9%, results which are completely comparable to Vincent *et al*. One of the most recent publications on NBI videobronchoscopy was published by Herth *et al*.[31] The authors evaluated the diagnostic yields of NBI individually and in combination with WLB and AFI. The primary aim was to determine the value of NBI over the AFI and WLB, and not to examine the value of bronchoscopy in early lung cancer detection. In Herth *et al*. study, sensitivity and specificity of WLB were 18% and 88%, respectively. Sensitivity of AFI, NBI, and combination of techniques was 65%, 53%, and 71%, respectively. Specificity of AFI, NBI, and combinations was 40%, 90%, and 40%, respectively. The results of our trial practically confirmed Herth *et al*. data.

One of the most valuable autofluorescence machines is SAFE-3000 (Pentax, Tokyo Japan). Several trials confirmed that dual imaging system achieves satisfactory sensitivity for the detection of preneoplastic lesions, and improves specificity by allowing targeted biopsy. In a study performed by Lee *et al*. in patients with known or suspected malignancy, sensitivity of

SAFE-3000 system was 86% while specificity reached 94%. The reason why the procedure was shorter in time than in our study could lay in one more additional procedure in our group.[32] In Divisi's trial,[33] SAFE-3000 bronchoscopy used "Twin Mode" and "Multiple Image Xposition (MIX)" technologies. The sensitivity of the Twin Mode and MIX techniques in the detection of premalignant and malignant lesions was 96% versus 100%. The specificity was 60% in both of these technologies. This trial confirmed high potential of autofluorescence videobronchoscopy in detection of precancerous lesions. Once again low specificity of autofluorescence, no matter which technique was used, is confirmed. The specificity of NBI alone or in combination with AFI determined in our trial could be the solution for overcoming the pitfall of low specificity of autofluorescence videobronchoscopy.

Large-scale multicenter prospective studies are necessary in order to determine the best bronchoscopic imaging technique for detection of premalignant bronchial epithelial lesions. While waiting for results of such trials, we must rely on available data, which are at least for now suggesting that NBI might be a preferable tool for detection of premalignant bronchial lesions.

Conclusions

Both techniques, AFI and NBI, show significantly higher sensitivity and specificity in detection of premalignant bronchial lesions, when compared to WLB alone. Combination of techniques is superior over WLB and AFI. However, combination did not demonstrate statistically significant improvement in sensitivity and specificity over NBI. The choice of the technique for improvement in detection of premalignant bronchial lesions mainly depends on availability of technology and experience of the bronchoscopists. If both techniques are available, priority should be given to NBI. If highest rate detection is needed for investigational purposes, techniques should be combined.[35]

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