VIDEOBRONCHOSCOPY FOR BRONCHIAL PRE-NEOPLASIA AND EARLY CENTRAL AIRWAY CANCER: A PROSPECTIVE RANDOMIZED STUDY

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Key words:

Autofluorescence, videobronchoscopy, screening, early detection, lung cancer, bronchial pre-neoplasia

Word count: 2048

CONTRIBUTORSHIP STATEMENT

Pyng Lee has contributed to the data collection, analysis and writing of the manuscript

Ralf Eberhard has contributed to patient recruitment, procedure, data collection, analysis and writing of manuscript

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Felix Herth has contributed to patient recruitment, procedure, data collection, analysis and writing of manuscript

Conflict of interest: All authors have no conflict of interest to declare

No funding was received

ABSTRACT

Background: Autofluorescence bronchoscopy (AF) is more sensitive than white light bronchoscopy (WL) for the detection of bronchial pre-neoplasia, but lacks specificity which necessitates extensive biopsy resulting in longer procedural time. These studies evaluated fiber-optic based systems, and white-light video-bronchoscopy (WLVB) has replaced fiber-optic bronchoscopy more than a decade ago. The advantage of videobronchoscopy lies in delivering clearer images due to incorporation of miniature charge couple device to its tip, however a change of bronchoscope is required if AF is performed after WLVB. Autofluorescence-reflectance imaging is a video-bronchoscope that allows AFVB and WLVB by means of a hand-switch. We compared WLVB against AFVB for the detection of early airway cancer and bronchial pre-neoplasia where the order of procedures and bronchoscopists was random.

Methods: WLVB and AFVB were performed on all high risk patients. Each site was graded as normal, abnormal or suspicious. All abnormal and suspicious areas were biopsied as well as normal appearing second-generation carina as controls.

Results: 570 patients were recruited and 674 airway sites with biopsies were evaluated. WLVB demonstrated 90% sensitivity and 99% specificity for intraepithelial neoplasia (moderate dysplasia or worse) against 97% sensitivity and 94% specificity using AFVB. WLVB was also 100% sensitive and 93% specific for high-grade dysplasia (severe dysplasia or worse) compared with 96% and 86% using AFVB. Kappa agreements between WLVB and AFVB visual grades with pathology were 0.91 ($p<0.001$) and 0.86 ($p<0.001$) respectively.

Conclusion: WLVB performed better than AFVB for high-grade dysplasia and discriminated bronchitis which would otherwise require biopsy with AFVB.

INTRODUCTION

Over 1 million new cases of lung cancer are diagnosed each year and is the leading cause of mortality with more deaths than prostate, breast and colon combined. Five year survival remains dismal at 15% despite strides in radiological imaging, surgical techniques, and chemo-radiotherapy since majority have lymph node or extrathoracic metastases at presentation.[1] Although the potential for lung cancer prevention exists, complete eradication of smoking is difficult and former smokers continue to be at high risk for lung cancer.[2]

Chest computed tomography (CT) screening trials have reported 10 year survival in excess of 80% for stage I tumors if surgically intervened.[3,4] The recent National Lung Screening Trial of more than 53,000 individuals at risk for lung cancer randomized to 3 annual screenings with low dose CT or CXR demonstrated 20% reduction in cancer mortality in favor of low dose CT primarily due to more early stage lung cancers detected.[5]. Chest CT is good for cancers arising from the peripheral airways and lung parenchyma but poor for those involving the central airways.[3,4] Detection of radiographically occult airway cancers represents another potential target since they are accessible to the bronchoscope, and local treatments with photodynamic therapy, high dose brachytherapy, electrocautery, cryotherapy and surgery have yielded favorable survival outcome.[6-10] As these pre-invasive lesions are small, superficial and measuring only few cells thick, they are not easily observed on white light bronchoscopy (WL).[11] The need to identify bronchial pre-neoplasia and carcinoma in-situ (CIS) is important as Bota et al reported that 37% severe dysplasia and 88% CIS progressed to invasive cancer.[12] Most CIS did not resolve spontaneously, and when allowed to progress to invasive cancer they became incurable by local treatments thereby favoring early intervention than expectant observation.[13]

Autofluorescence bronchoscopy (AF) is developed to address this limitation of WL and works on the principle that bronchial epithelium emits intense green autofluorescence when illuminated by blue light.[14] As the epithelium transforms from dysplasia, CIS to invasive cancer a progressive decline in green fluorescence occurs due to increased thickness and neovascularisation. AF has demonstrated superiority over WL for airway dysplasia but lacks specificity since a third of lesions with abnormal

fluorescence represent false-positives on histology.[14-18] Lacking in specificity is problematic as it necessitates extensive biopsy resulting in greater cost, longer procedural time, increased risk of bronchospasm, bleeding from multiple endobronchial biopsies, and more sedation that may compromise patient safety. However these studies evaluated fiber-optic based WL and AF systems,[14-18] and video-bronchoscopy has replaced fiber-optic bronchoscopy more than a decade ago.

The advantage of video-bronchoscopy lies in delivering clearer images due to incorporation of miniature charge couple device (CCD) to its tip. Autofluorescence-reflectance imaging (AFI) is a video-bronchoscope that allows autofluorescence (AFVB) and white-light videobronchoscopy (WLVB) examination by means of a hand-switch. We compared WLVB against AFVB for the detection of early airway cancer and bronchial pre-neoplasia where the order of procedures and bronchoscopists were randomly assigned. Part of the results have been reported in the form of an abstract.[19]

Materials and Methods

The protocol was approved by the institutional review board of Thoraxklinik Heidelberg (reference number 12-2004), and written informed consent was obtained from all patients.

Study Subjects

Included in the prospective randomized study were; (1) current or former smokers suspected of lung cancer scheduled for bronchoscopy; (2) surveillance after curative surgery for stage I and II non-small cell lung cancers (NSCLC), (3) those with previous head and neck cancers as well as (5) high-risk individuals with atypia on sputum cytology but normal CT. Excluded were patients who received photosensitising agents or chemopreventive drugs such as retinoids within 3 months, radiotherapy to chest or cytotoxic chemotherapy within 6 months of bronchoscopic procedure; pneumonia; acute bronchitis; unstable angina; bleeding disorders; pregnancy; and adverse reactions to topical lignocaine.

Methods

AFI (EVIS LUCERA BF –F260, Olympus, Japan) is a video-bronchoscope with a high resolution imaging CCD chip at the distal end which allows the bronchoscopist to change between WLVB and AFVB by means of a hand-switch. The AFVB image is a

composite of 3 signals; autofluorescence (460-690 nm) with blue excitation light (395-445nm); green and red light signals from respective green (550nm) and red (610nm) wavelengths. Hemoglobin in the blood vessels absorbs green light, and dysplasia would appear magenta, bronchitis blue and mucosal bleeding dark blue.

Each patient underwent both WLVB and AFVB. The order and bronchoscopists were randomized using random number generator in Microsoft Excel (Microsoft Corp, Redland, WA) such that 1 bronchoscopist was assigned only 1 procedure per patient. The bronchoscopists (RE, FH) performed airway examinations independently and recorded areas of visual abnormalities according to Table 1 in digital and video formats. After both examinations, biopsy was performed for areas recorded as abnormal and suspicious jointly by the bronchoscopists in addition to one control biopsy over the second generation carina. In those with normal WLVB and AFVB, 1 control biopsy was obtained from second-generation carina per patient. All biopsy specimens were evaluable as there was sufficient bronchial epithelium and interpreted by a dedicated lung pathologist who was blinded to the bronchoscopic findings in accordance to the International Histological Classification of Tumors [20] as (1) normal; (2) inflammation/bronchitis; (3) hyperplasia; (4) squamous metaplasia; (5) mild dysplasia; (6) moderate dysplasia; (7) severe dysplasia; (8) carcinoma in situ (CIS); or (9) carcinoma.

Statistics

For the purpose of statistical analysis, physicians' 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 “mild dysplasia and below” became ‘‘negative’’ and “moderate dysplasia and worse” became ‘‘positive’’. Sensitivity, specificity, positive predictive and negative predictive values of WLVB and AFVB were calculated. Correlation of the visual grade with pathology was determined by Spearman rho test, values were expressed as median and inter quartile range, and $p < 0.05$ was considered statistically significant.

Results

The study included 329 males and 241 females of which 162 were current or former smokers suspected of lung cancer; 312 for surveillance after curative surgery for

stage I and II NSCLC; 54 with previous head and neck cancers and 42 with suspicious sputum cytology. The median age was 55 years (range, 48-63) and 40 pack years' of smoking (range, 38-44). Six hundred and seventy-four airway sites and biopsies were evaluated (Table 2).

Intra-epithelial neoplasia defined as moderate dysplasia or worse was identified in 143 biopsies (21%): 23% from current or former smokers suspected of lung cancer; 57% from surgically resected lung cancer subjects on surveillance; 12% from head and neck cancer patients; and 8% with sputum atypia. Sensitivity and specificity for its detection using WLVB and AFVB were 90%, 99%, and 97%, 94% respectively. Positive and negative predictive values with WLVB and AFVB were 96%, 97%, and 82%, 99%.

High-grade dysplasia defined as severe dysplasia or worse was found in 90 biopsies (13%): 22% from former and current smokers suspected of lung cancer; 56% from surgically resected lung cancer patients; 15% from head and neck cancer subjects; and 7% with sputum atypia. Sensitivity and specificity for its detection using WLVB and AFVB were 100%, 93% and 96%, 86% respectively. Positive and negative predictive values with WLVB and AFVB were 67%, 100% and 51%, 99% (Table 2). Sixty-eight airway sites (10%) graded suspicious by WLVB and AFVB had biopsies confirming carcinoma and CIS that were CT occult: 22% in current and former smokers; 56% in surgically resected lung cancer patients; 15% in head and neck cancer subjects; and 7% with sputum atypia.(figure 1,2)

Relative sensitivity of AFVB over WLVB was 1.07 for the detection of early airway cancer and bronchial pre-neoplasia. The physicians' visual classification by WLVB and AFVB correlated well with pathology: WLVB $r=0.91$, $p<0.001$ and AFVB $r=0.86$, $p<0.0001$. WLVB and AFVB graded all CIS and carcinomas suspicious. For severe dysplasia lesions, all 22 were graded suspicious by WLVB compared to 18 by AFVB. AFVB scored all 53 lesions with moderate dysplasia suspicious compared to 40 by WVB (Tables 3,4).

Value of AFVB when WLVB normal

Of the 423 sites that were graded normal by WLVB, 29 were graded abnormal (pathology: 16 normal, 13 squamous metaplasia) and 18 suspicious (pathology: 5 mild dysplasia and 13 moderate dysplasia) by AFVB. Addition of AFVB to normal WLVB led

to increased detection of moderate dysplasia, mild dysplasia and squamous metaplasia (figure 3,4).

Value of AFVB when WLVB abnormal

Two hundred and fifty one sites were graded abnormal and suspicious by WLVB. All 40 moderate dysplasia lesions appeared suspicious with AFVB compared to 39 with WLVB. WLVB graded all 90 sites of severe dysplasia, CIS and carcinoma suspicious compared with 86 suspicious sites by AFVB. Twenty-one out of 45 sites showing inflammation were graded suspicious with AFVB and abnormal due to bronchitis by WLVB. The addition of AFVB to abnormal WLVB identified 1 more site of moderate dysplasia but more inflammatory lesions that necessitated biopsy (Table 5).

Discussion

A multimodality approach that incorporates chest CT and bronchoscopy is necessary to assure a successful early lung cancer detection program. Early central lung cancers can be invisible, hypertrophic, nodular, polypoid or mixed. The hypertrophic lesion is the dominant type and may pose a challenge for WL since it only shows subtle mucosal changes and measures less than 1.5 mm thick.[21] It is a good target for AF as increased mucosal thickness and vascularity lead to reduced fluorescence in the background of normal green fluorescence. Previous studies with lung imaging fluorescence endoscopy (LIFE), D-Light and SAFE 1000 have reported relative sensitivities of 2 to 6.4 over WL for intra-epithelial neoplasia.[14-18,22] However the lower WL sensitivity is attributed to inferior fiber-optic based systems used in the studies, and videobronchoscopy has replaced fiber-optic bronchoscopy more than a decade ago. Chhajed et al demonstrated improved sensitivity for airway dysplasia using the videobronchoscope (sensitivity 72%, specificity 53%), but a change of scope was required which caused patient discomfort and inconvenience to the bronchoscopist.[23] Low specificity associated with AF was problematic particularly in distinguishing pre-neoplastic lesions from bronchitis, which could lead to unnecessary biopsy, longer procedural time, increased risk of bronchospasm, bleeding from multiple endobronchial biopsies and need for additional sedation that may compromise patient safety. Lee et al reported 86% sensitivity and 94% specificity with SAFE 3000 (Pentax, Japan) that displayed real-time video and AF images of the lesion side by side. Dual imaging

provided anatomic and functional information of the area of interest and was useful in diagnosing bronchitis, previous biopsy site and fibrosis following endobronchial therapy.[24]

Our prospective study is the largest with significant number of evaluable biopsies where the order of procedures (WLVB, AFBV) and bronchoscopists were randomized. We showed that WLVB was as good as AFVB for detection of early lung cancer and bronchial pre-neoplasia (relative sensitivity of AFVB over WLVB 1.07). WLVB was superior in discriminating bronchitis where AFVB led to increased biopsy. AFVB had a strong negative predictive value, and adding AFVB to WLVB enhanced the detection of moderate dysplasia, mild dysplasia and squamous metaplasia. Seven and 3 sites of squamous metaplasia were graded suspicious by WLVB and AFVB respectively. The significance of this finding is unclear at the time of writing since longitudinal follow up of these lesions is underway. Breuer and coworkers challenged the concept of squamous cell carcinogenesis by reporting rapid and non-stepwise progression in 3 (9%) squamous metaplasias with suspicious autofluorescence to CIS or invasive carcinomas within 4 to 7 months.[25] These lesions were subsequently discovered to possess DNA copy number alterations that were distinct from squamous metaplasia with normal autofluorescence and did not progress.[26]

Conclusion

Incorporating high definition color CCD chip to the bronchoscope tip provides WLVB images comparable to AFVB for the detection of bronchial pre-neoplasia and early central cancers, and better discriminated bronchitis which would otherwise require biopsy. AFVB where available improves identification of moderate dysplasia that carries 11% risk of progression to invasive carcinoma,[27] and may complement WLVB in the pre-surgical evaluation of patients with early lung cancers for synchronous CIS and intra-epithelial neoplasia as well as margin assessment of these cancers before resection.[28] Our study adds robust data in support of recent lung cancer guidelines recommendations for WLVB as the first modality in the evaluation of patients with sputum atypia, for surveillance of subjects harboring bronchial severe dysplasia or CIS as well as for synchronous lesions in those with early lung cancers undergoing surgery.[29]

Table 1: Visual Classificaton of Bronchoscopic findings with WLVB and AFVB

Class	WLVB	AFVB
1/ Normal	No visual abnormality	Negative (Green)
2/ Abnormal	Erythema, swelling or thickening of bronchial mucosa, airway inflammation and fibrosis	Negative (Blue)
3/ Suspicious	Nodular, polypoid lesions, irregular bronchial mucosa, focal thickening of the subcarina	Positive (Magenta)

Table 2: Clinical Demographics and Pathological Distribution of Airway lesions

	Suspected of lung cancer	Previous NSCLC	Previous head and neck cancer	Abnormal sputum
Patient (%)	162 (28)	312 (55)	54 (10)	42 (7)
Age, range (yrs)	55.5(48-63)	55.0(47-62)	55.5(51-64)	56.5(48-66)
Gender (M/F)	92/ 70	185/ 127	29/ 25	23/ 19
Smoking pack yrs (range)	41(40-42)	39(38-40)	40(39.5-41)	40(39-40.5)
Bx site (patient no)	1 (142) 2 (19) 3 (1)	1 (270) 2 (32) 3 (10)	1 (40) 2 (9) 3 (4) 4 (1)	1 (33) 2 (8) 4 (1)
Pathology				
Normal	116	211	38	27
Inflammation	12	22	6	5
Squamous Metaplasia	12	27	5	5
Mild Dysplasia	10	23	7	5
Moderate Dysplasia	13	31	4	5
Severe Dysplasia	5	12	4	1
CIS	0	2	2	1
Carcinoma (Adenoca) (NSCLC) (SCLC)	15 6 3 6	36 12 12 12	8 2 3 3	4 2 2 0

*Values are expressed as median
NSCLC: non small cell carcinoma
SCLC: squamous cell carcinoma

Table 3: WLVB Visual Classification and Pathology of Biopsy Sites

Pathology	Sites	Visual scoring with WLVB		
		Normal	Abnormal	Suspicious
Normal	392	392	0	0
Inflammation	45	0	45 (bronchitis)	0
Squamous Metaplasia	49	13	29	7
Mild Dysplasia	45	5	40	0
Moderate Dysplasia	53	13	1	39
Severe Dysplasia	22	0	0	22
Carcinoma in situ	5	0	0	5
Carcinoma	63	0	0	63

WLVB: white light videobronchoscopy

Table 4: AFVB Visual Classification and Pathology of Biopsy Sites

Pathology	Sites	Visual scoring with AFVB		
		Normal	Abnormal	Suspicious
Normal	392	376	16	0
Inflammation	45	0	24	21
Squamous Metaplasia	49	0	46	3
Mild Dysplasia	45	0	39	6
Moderate Dysplasia	53	0	0	53
Severe Dysplasia	22	0	4	18
Carcinoma in situ	5	0	0	5
Carcinoma	63	0	0	63

AFVB: autofluorescence videobronchoscopy

Table 5: Histology of lesions with WLVB and AFVB

	AFVB		
	Normal	Abnormal	Suspicious
WLVB			
Normal (423) 392 normal 13 squamous metaplasia 5 mild dysplasia 13 moderate dysplasia	**376** normal	**29** 16 normal 13 squamous metaplasia	**18** 5 mild dysplasia 13 moderate dysplasia
Abnormal (115) 45 inflammation 29 squamous metaplasia 40 mild dysplasia 1 moderate dysplasia	**0**	**91** 24 inflammation 28 squamous metaplasia 39 mild dysplasia	**24** 21 inflammation 1 squamous metaplasia 1 mild dysplasia 1 moderate dysplasia
Suspicious (136) 7 squamous metaplasia 39 moderate dysplasia 22 severe dysplasia 5 CIS 63 carcinoma	**0**	**9** 5 squamous metaplasia 4 severe dysplasia	**127** 2 squamous metaplasia 39 moderate dysplasia 18 severe dysplasia 5 CIS 63 carcinoma

ABBREVIATIONS:

WL: white light

AF: autofluorescence

WLVB: white light videobronchoscopy

AFVB: autofluorescence videobronchoscopy

CCD: charge couple device

CT: computed tomography

NSCLC: non small cell lung cancer

CIS: carcinoma in-situ

LEGENDS

Figure 1(a) WLVB: irregular wall of anterior segment of right upper lobe bronchus

Figure 1(b) AFVB: irregular wall of right upper lobe lesions highlighted in magenta with clear margins

Figure 2: Histology of biopsy of right upper lobe. Squamous CIS with invasive squamous cell carcinoma (H&E x 20 magnification)

Figure 3(a) WLVB: abnormal lesion of posterior wall of trachea

Figure 3(b) AFVB: suspicious lesion of posterior wall trachea

Figure 4: Histology of biopsy posterior wall of trachea
Squamous metaplasia (H&E x 40 magnification)

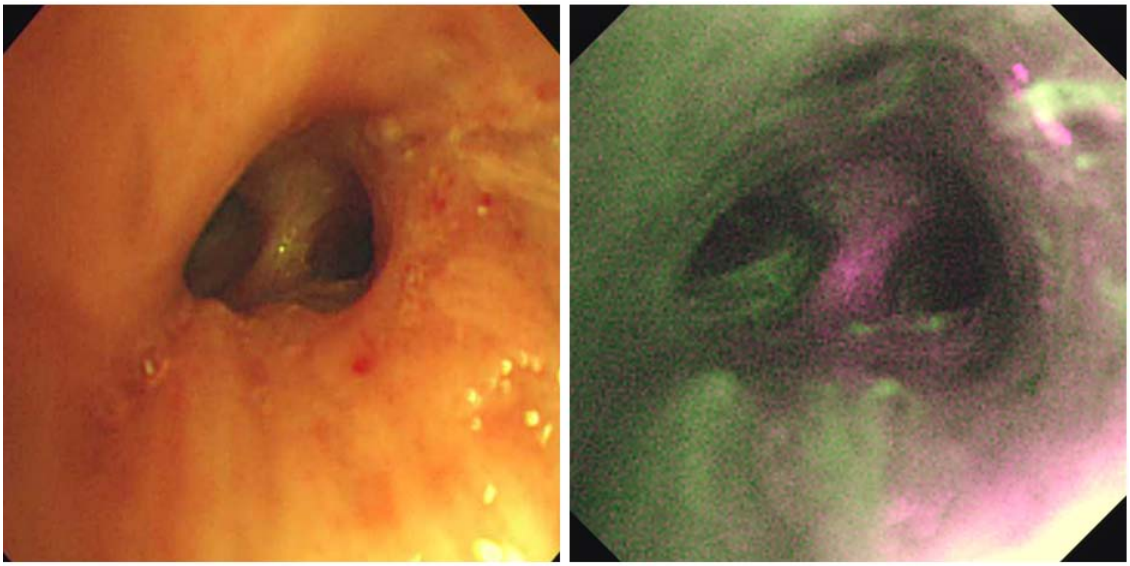


Figure 1(a) WVB: irregular wall of anterior segment of right upper lobe bronchus
Figure 1(b) AFI: irregular wall of anterior segment of right upper lobe bronchus highlighted in magenta with clear margins (histology CIS with microinvasive component)

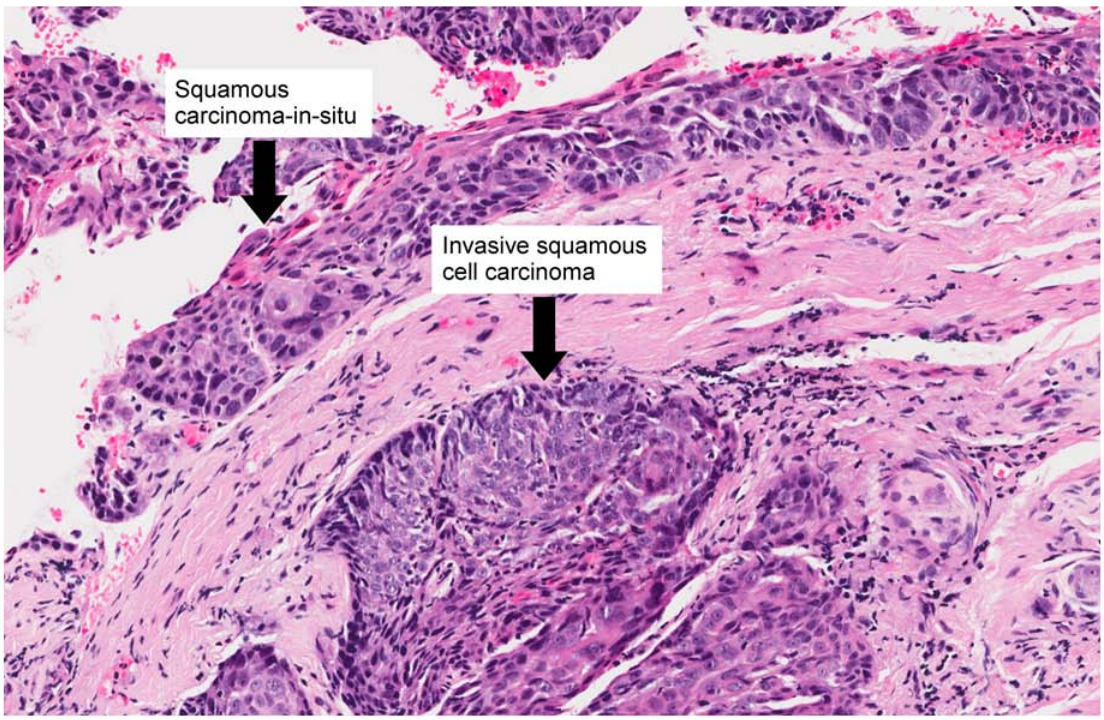
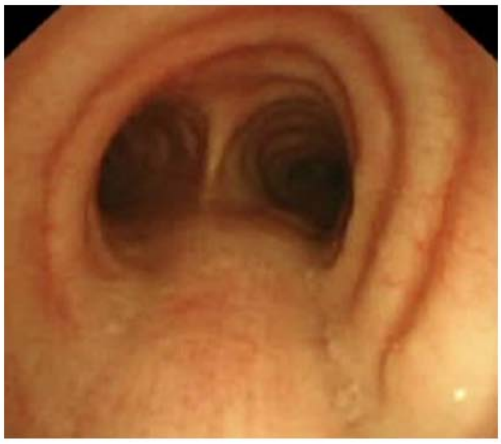
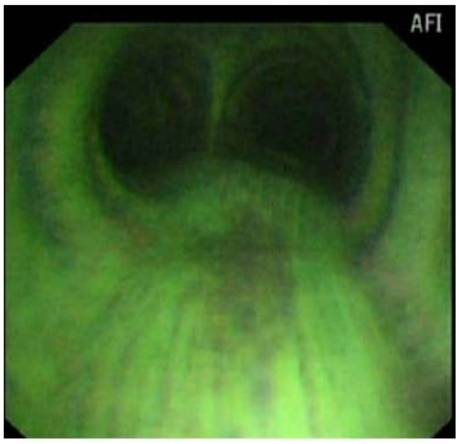


Figure 2: Histology of biopsy of right upper lobe. Squamous CIS with invasive squamous cell carcinoma (H&E X20 magnification)



3(a)



3(b)

Figure 3 (a) WVB: abnormal over posterior wall of trachea
Figure 3 (b) AFI: suspicious over posterior wall of trachea (histology squamous metaplasia)

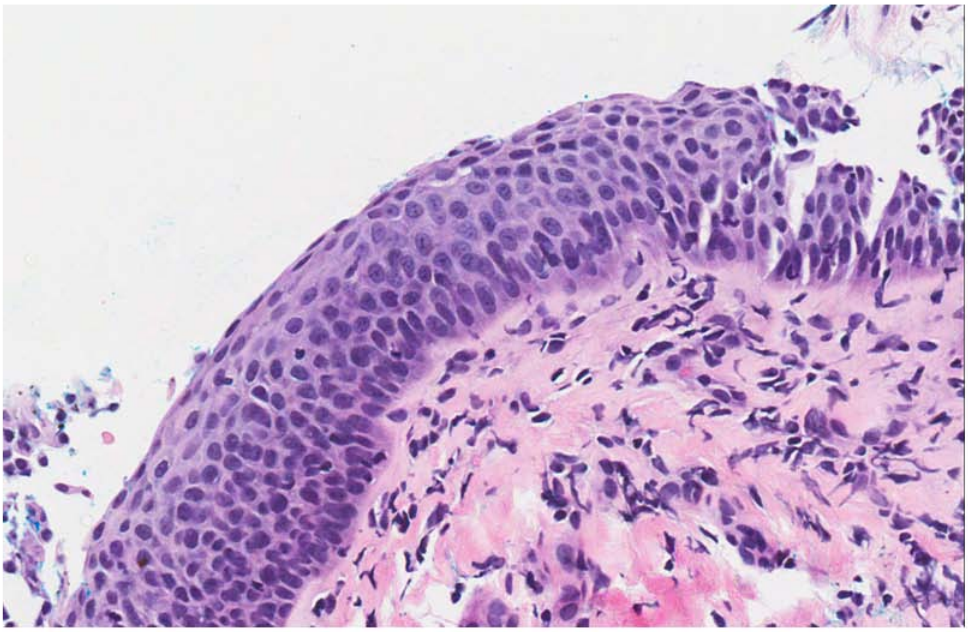


Figure 4: Histology of biopsy posterior wall of trachea. Squamous metaplasia (H&E x40 magnification)

REFERENCES

1. Jemal A, Siegel R, Xu J, et al. Cancer statistics, 2010. CA Cancer J Clin. 2010;60:277-300.
2. Tong L, Pitz MR, Fueger JJ, et al. Lung carcinoma in former smokers. Cancer 1996;78:1004-10.
3. Henschke CI. Medicine on lung cancer screening: a different paradigm. Am J Respir Crit Care Med 2003;168:1143-4.
4. International Early Lung Cancer Action Program Investigators, Henschke CI, Yankelevitz DF, Libby DM, et al. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006;355:1763-71.
5. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
6. Kato H, Usuda J, Okunaka T, et al. Basic and clinical research on photodynamic therapy at Tokyo Medical University Hospital. Lasers Surg Med 2006;38:371-5.
7. Hannequin C, Bleichner O, Tredaniel J, et al. Long-term results of endobronchial brachytherapy: a curative treatment? Int J Radiat Oncol Biol Phys 2007;67:425-30.
8. Van Boxem TJ, Venmans BJ, Schramel FM, et al. Radiographically occult lung cancer treated with fibreoptic bronchoscopic electrocautery: a pilot study of a simple and inexpensive technique. Eur Respir J 1998;11:169-172.
9. Deygas N, Froudarakis M, Ozenne G, Vergnon JM. Cryotherapy in early superficial bronchogenic carcinoma. Chest 2001;120:26-31.
10. Saito Y, Nagamoto N, Ota S, et al. Results of surgical treatment for roentgenographically occult bronchogenic squamous cell carcinoma. J Thorac Cardiovasc Surg 1992;104:401-7.
11. Woolner LB, Fontana RS, Cortese DA, et al. Roentgenographically occult lung cancer: pathologic findings and frequency of multicentricity during a 10-year period. Mayo Clin Proc 1984;59:453-66.

12. Bota S, Auliac JB, Paris C, et al. Follow-up of bronchial precancerous lesions and carcinoma in situ using fluorescence endoscopy. Am J Respir Crit Care Med 2001:1;164:1688-93.
13. George PJ, Banerjee AK, Read CA, et al. Surveillance for the detection of early lung cancer in patients with bronchial dysplasia. Thorax 2007;62:43-50.
14. Lam S, Kennedy T, Unger M, et al. Localization of bronchial intraepithelial neoplastic lesions by fluorescence bronchoscopy. Chest 1998;113:696-702.
15. Hirsch FR, Prindiville SA, Miller YE, et al. Fluorescence versus white-light bronchoscopy for detection of preneoplastic lesions: a randomized study. J Natl Cancer Inst 2001;93:1385-91.
16. Haussinger K, Becker H, Stanzel F, et al. Autofluorescence bronchoscopy with white light bronchoscopy compared with white light bronchoscopy alone for the detection of precancerous lesions: a European randomised controlled multicentre trial. Thorax 2005;60:496-503.
17. Edell E, Lam S, Pass H, et al. Detection and localization of intraepithelial neoplasia and invasive carcinoma using fluorescence-reflectance bronchoscopy. J Thorac Oncol 2009;4:49-54.
18. Sato M, Sakurada A, Sagawa M, et al. Diagnostic results before and after introduction of autofluorescence bronchoscpy in patients suspected of having lung cancer detected by sputum cutology in lung cancer mass screening. Lung Cancer 2001;32:247-53.
19. Lee P, Eberhardt R, Herth F. Improved accuracy for bronchial pre-neoplasia with videobronchoscopy. Proffered oral presentation at World Congress of Lung Cancer 2009.
20. World Health Organization. Histological typing of lung and pleural tumors. 3rd ed. Springer-Verlag, Berlin 1999.
21. Akaogi E, Ogawa I, Mitsui K, et al. Endoscopic criteria of early squamous cell carcinoma of the bronchus. Cancer 1994;74:3113-7.
22. Sun J, Garfield DH, Lam B, et al. The value of autofluorescence bronchoscopy combined with white light bronchoscopy compared with white

light alone in the diagnosis of intraepithelial neoplasia and invasive lung cancer: a meta-analysis. J Thorac Oncol 2011;6:1336-44.

23. Chhajed P, Shibuya K, Hoshino H, et al. A comparison of video and autofluorescence bronchoscopy in patients at high risk of lung cancer, Eur Respir J 2005;25:951-5.
24. Lee P, Brokx HAP, Postmus PE, Sutedja TG. Dual digital video-autofluorescence imaging for detection of pre-neoplastic lesions. Lung Cancer 2007;58:44-9.
25. Breuer RH, Pasic A, Smit EF, et al. The natural course of preneoplastic lesions in bronchial epithelium. Clin Cancer Res 2005;11:537-43.
26. van Boerdonk RA, Sutedja TG, Snijders PJ, et al. DNA copy number alterations in endobronchial squamous metaplastic lesions predict lung cancer. Am J Respir Crit Care Med 2011;184:948-56.
27. Frost JK, Ball WC, Levin ML, et al. Sputum cytopathology: use and potential in monitoring the workplace environment by screening for biological effects of exposure. J Occup Med 1986;28:692-703.
28. Pierard P, Faber J, Hutsebaut J, et al. Synchronous lesions detected by autofluorescence bronchoscopy in patients with high-grade preinvasive lesions and occult invasive squamous cell carcinoma of the proximal airways. Lung Cancer 2004;46:341-7.
29. Wisnivesky JP, Yung RC, Mathur PN, Zulueta JJ. Diagnosis and treatment of bronchial intraepithelial neoplasia and early lung cancer of the central airways: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e263S-77S.