

# Newer Modalities of Bronchoscopy

Inderpaul Singh Sehgal  
DM Seminar

# Introduction

- Access to the airways in a living patient had been tried by Hippocrates (460–370 BC)
- Gustav Killian 1897, removed a foreign body from right main bronchus

# Introduction

- “On March 30th of this year I had the honor to assist my admired principal, Prof. Killian in extraction of a piece of bone from the right bronchus. This case is of such peculiarity with respect to its diagnostic and therapeutic importance that a more extensive description seems justified.”

# Introduction

- Ikeda in Tokyo, Japan pioneer of first flexible bronchoscope
- The Machida flexible bronchoscope became commercially available in 1968
- In 1970, the first Olympus model was commercialized with better handling and imaging properties
- Endobronchial ultrasound (EBUS) in 1999 by Becker

What s Next?

# Recent advances

- Navigation bronchoscopy
- Autofluorescence bronchoscopy
- Narrow band imaging
- Optical coherence tomography
- Confocal Fluorescence Microscopy

# NAVIGATIONAL BRONCHOSCOPY

- Relatively new technology
- The first animal study was performed by Becker *et al.* in 2003
- The same group published the first human study in 2006
- Navigational assistance to localize and sample PPLs
- > 20,000 procedures performed since 2005

Respiration 2003;70:516-22.

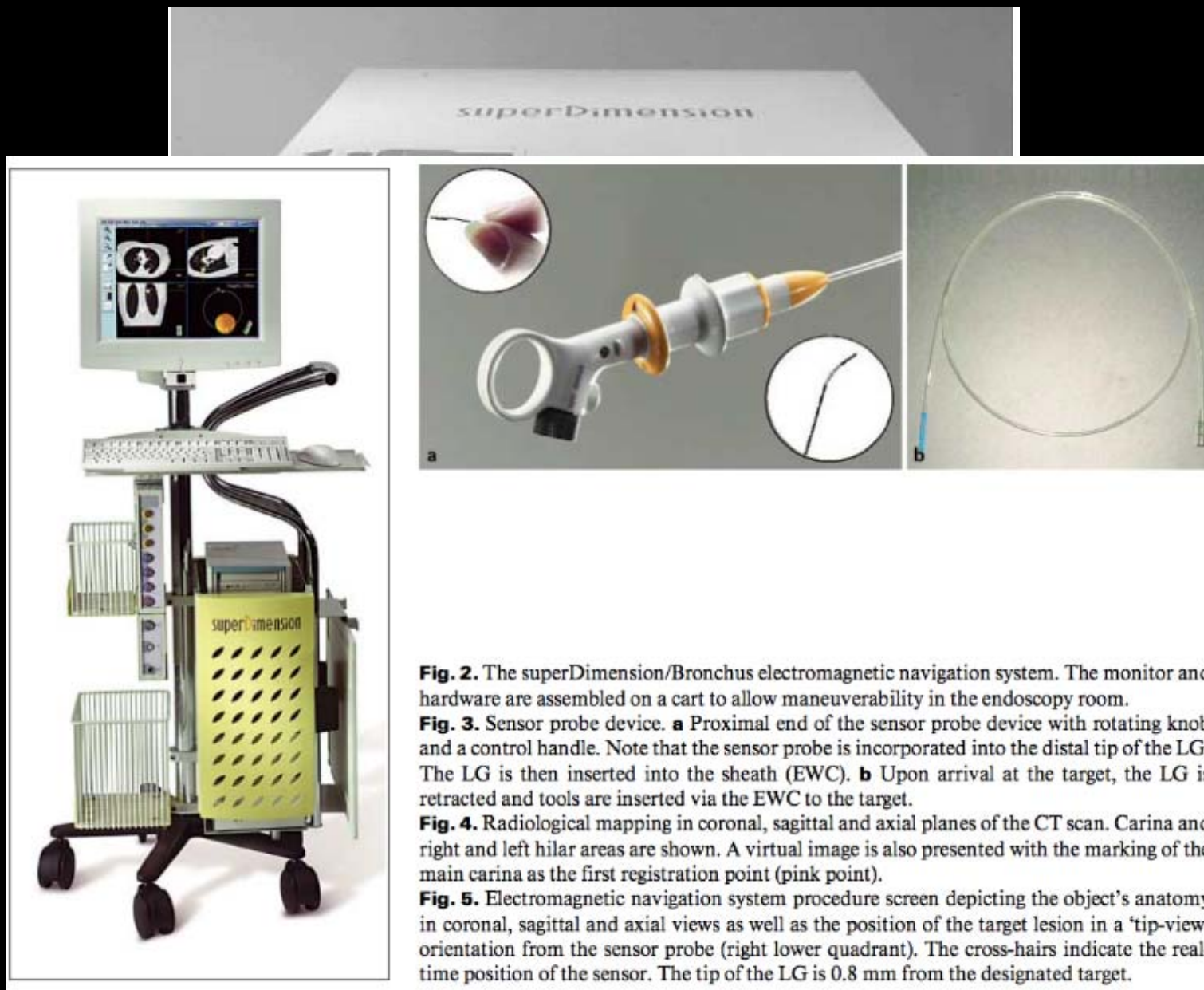
Chest 2006;129:988-94.

J Thorac Dis 2012;4(2):173-185

# Components of EMS

- Electromagnetic board
- Sensor probe mounted on the tip of a flexible metal cable
- Monitor with real time imaging
- The locatable guide (LG) with 360° maneuverability
- Probe with flexible catheter





**Fig. 2.** The superDimension/Bronchus electromagnetic navigation system. The monitor and hardware are assembled on a cart to allow maneuverability in the endoscopy room.

**Fig. 3.** Sensor probe device. **a** Proximal end of the sensor probe device with rotating knob and a control handle. Note that the sensor probe is incorporated into the distal tip of the LG. The LG is then inserted into the sheath (EWC). **b** Upon arrival at the target, the LG is retracted and tools are inserted via the EWC to the target.

**Fig. 4.** Radiological mapping in coronal, sagittal and axial planes of the CT scan. Carina and right and left hilar areas are shown. A virtual image is also presented with the marking of the main carina as the first registration point (pink point).

**Fig. 5.** Electromagnetic navigation system procedure screen depicting the object's anatomy in coronal, sagittal and axial views as well as the position of the target lesion in a 'tip-view' orientation from the sensor probe (right lower quadrant). The cross-hairs indicate the real-time position of the sensor. The tip of the LG is 0.8 mm from the designated target.

# Execution & Preparation

- Radiological mapping
  - CT thorax downloaded into the system
  - Reconstructed in axial,sagital,coronal views
- Endobronchial mapping
  - Flexible bronchoscope with LG inserted
  - Landmark on virtual images identified
- Real-time navigation

# Planning phase

- Four panels
- Registration points
- Breadcrumbs

Registration points



Target lesion

Navigation pathway

J Thorac Dis 2012;4(2):173-185

# Procedure - setting up the bronchoscopy suite and patient

- Avoid metal objects and/or mobile communications devices
- The location board : Magnetic field
- Three location pads : Precision
- General anaesthesia or conscious sedation

- Target Registration Error
  - distance between its position on the CT and its position after registration inside the actual body
- Fiducial Target Registration Error
  - defined to express both the registration quality and the stability of fiducial (registration)
  - calculated for every fiducial point by computing its target registration error
  - optimized (reduced) by repositioning the misplaced endobronchial landmark

- Registration accuracy (AFTRE)
  - Measured as the Average Fiducial Target Registration Error (AFTRE)
  - Radius of expected difference of the location of the tip of the steerable probe in the actual patient compared with where it is expected to be in the virtual patient
  - Should be  $<5$  mm
  - AFTRE  $>5$  mm signifies unacceptable divergence between the CT and patient anatomy
  - Registration should be repeated to reduce the disparity

- Majority of published literature describes case series of PPLs
- The diagnostic yield for ENB alone is highly variable (59% to 77.3%)



# Multimodality Bronchoscopic Diagnosis of Peripheral Lung Lesions

## A Randomized Controlled Trial

Am J Respir Crit Care Med Vol 176. pp 36–41, 2007

Ralf Eberhardt<sup>1</sup>, Devanand Anantham<sup>2</sup>, Armin Ernst<sup>2</sup>, David Feller-Kopman<sup>2</sup>, and Felix Herth<sup>1</sup>

<sup>1</sup>Department of Pneumology and Critical Care Medicine, Thoraxklinik, University of Heidelberg, Heidelberg, Germany; and <sup>2</sup>Interventional Pulmonology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

**Rationale:** Endobronchial ultrasound (EBUS) and electromagnetic navigation bronchoscopy (ENB) have increased the diagnostic yield of bronchoscopic diagnosis of peripheral lung lesions. However, the role of combining these modalities to overcome each individual technique's limitations and, consequently, to further increase the diagnostic yield remains untested.

**Objectives:** A prospective randomized controlled trial involving three diagnostic arms: EBUS only, ENB only, and a combined procedure.

**Methods:** All procedures were performed via flexible bronchoscopy and transbronchial forceps biopsies were obtained without fluoroscopic guidance. In the combined group, after electromagnetic navigation, the ultrasound probe was passed through an extended working channel to visualize the lesion. Biopsies were taken if ultrasound visualization showed that the extended working channel was within the target. Primary outcome was diagnostic yield. The reference "gold standard" was a surgical biopsy if bronchoscopic biopsy did not reveal a definite histological diagnosis compatible with the clinical presentation. Secondary outcomes were yields by size, lobar distribution, and lesion pathology. Complication rates were also documented.

**Measurements and Main Results:** Of the 120 patients recruited, 118 had a definitive histological diagnosis and were included in the final analysis. The diagnostic yield of the combined procedure (88%) was greater than EBUS (69%) or ENB alone (59%;  $p = 0.02$ ). The combined procedure's yield was independent of lesion size or lobar distribution. The pneumothorax rates ranged from 5 to 8%, with no significant differences between the groups.

**Conclusions:** Combined EBUS and ENB improves the diagnostic yield of flexible bronchoscopy in peripheral lung lesions without compromising safety.

### AT A GLANCE COMMENTARY

#### Scientific Knowledge on the Subject

Endobronchial ultrasound (EBUS) and electromagnetic navigation bronchoscopy (ENB) have increased the yield of flexible bronchoscopy in the diagnosis of peripheral lung lesions. Yet, direct comparisons and the role of combined diagnosis are unknown.

#### What This Study Adds to the Field

Combined EBUS and ENB improves the diagnostic yield of flexible bronchoscopy in peripheral lung lesions without compromising safety.

EBUS enables direct visualization of the target lesion before attempting biopsy. However, EBUS lacks a navigation system and requires the operator to maneuver the bronchoscope blindly to the lesion with the knowledge of prior radiological investigations like computed tomography (CT) scans. In previous studies, 11 to 24% of lesions could not be localized by EBUS (3, 5, 7, 9).

ENB consists of four components: an electromagnetic location board, a locatable sensor probe with an eight-way steering mechanism that is able to navigate the bronchial tree, an extending working channel (EWC) that can carry either the sensor probe or a flexible forceps, and computer software that converts

Table 1. Studies of ENB efficacy and safety.

Study	Year	Number of lesions	Mean Lesion Size (mm)	Upper lobe lesions (%)	Anaesthesia	Navigational Success (%)	Samples taken	Diagnostic Yield (%)	Procedure time (mean mins)	Complications
Becker (47)	2005	30	39.81	66	GA	83.3%	Forceps, brush, curette	69	Additional 9.3 minutes (total procedure time not stated)	1 Ptx 3 self limited bleeding
Hautmann (48)	2005	16 (8 infiltration, 8 SPN or mass)	22	56	iv Midazolam, propofol	Ns	Forceps, TBNA	60	Additional 8 minutes (total procedure time not stated)	Nil
Schwarz (16)	2006	13	33.5	54	iv midazolam or propofol	Ns	Forceps, brush	69	46	Nil
Gidea (49)	2006	54 peripheral	22.8 peripheral	62.5	iv midazolam and morphine	100%	Brush 2-3 passes, TBNA 2-4 passes TBBx 4 samples, (peripheral) TBBx 8.5 (mean)	74%	51	2 (3.6%) Ptx
Makris (33)	2007	40	23.5	66.5	GA	18 cases $\leq 8$ mm from target (mean $8.7 \pm 0.8$ mm from target centre)	6.7 specimens obtained	62.5	Ns	3 (7.5%) Ptx
Eberhardt (21)	2007	39	28	56	Moderate sedation or GA	Ns	TBBx 4.1 (only forceps taken)	59	Ns	2 (5%) Ptx
Eberhardt (50)	2007	92	24	56.5	GA 55 patients iv midazolam/fent 34 patients	Mean error $9 \pm 6$ mm	Needle, brush, forceps (mean 5.1), or combination	67	26.9	2 (2%) Ptx 1 (1%) Perforated EWC 1 (1%) resp failure secondary to sedation
Wilson (24)	2007	279	21	50	iv midazolam, fentanyl and propofol	95.3% mean $8 \pm 5$ mm from tip to target centre	TBNA and forceps biopsy (3-4 samples)	65	Ns	3 (1%) Ptx 3 (1%) mod bleeding 1 (0.3%) hematomas 1 (0.3%) pneumonia
Eberhardt (32)	2010	55	23.3	60	Ns	$9 \pm 5$ mm	Catheter aspiration $\times 2$ Forceps biopsy $\times 5$	75.5	25.7	1 (1.9%) Ptx
Lamprecht (51)	2009	13	30	61.5	GA	Ns	Forceps, needle brush (median 3 biopsies - none had $> 5$ )	76.9	60	Nil
Bersolotti (30)	2009	53	31.2	Ns	NO/O <sub>2</sub> mix	$10 \pm 5.9$ tip to target centre	Forceps (planned 5 biopsies - actual not stated), brush	77.3	29.5	2 (4%) Ptx
Seijo (20)	2010	51	25	61	Midazolam 5 mg, fent 75 mcg (both mean)	8 mm (range, 4-9 mm) (minimum median distance from tip to target centre)	Needle, Forceps biopsy	67	56	4 (8%) mild hypoxemia

GA=general anaesthetic; Ptx=pneumothorax; Ns=not stated; NO=nitrous oxide; iv=intravenous; TBBx=transbronchial biopsy; TBNA=transbronchial needle aspiration.

# Factors affecting success

- Bronchus sign : bronchus leading directly to a peripheral pulmonary lesion
- For TBLB<sub>x</sub>
  - diagnostic yield of 60% V/S 30% in PPL<sup>^</sup>

<sup>^</sup>Chest 1988;93:595-8.

J Thorac Dis 2012;4(2):173-185



# Diagnostic Yield of Electromagnetic Navigation Bronchoscopy Is Highly Dependent on the Presence of a Bronchus Sign on CT Imaging

## Results From a Prospective Study

*Luis M. Seijo, MD; Juan P. de Torres, MD; María D. Lozano, MD; Gorka Bastarrika, MD; Ana B. Alcaide, MD; Maria M. Lacunza, RN; and Javier J. Zulueta, MD*

**Background:** Electromagnetic navigation bronchoscopy (ENB) has been developed as a novel ancillary tool for the bronchoscopic diagnosis of pulmonary nodules. Despite successful navigation in 90% of patients, ENB diagnostic yield does not generally exceed 70%. We sought to determine whether the presence of a bronchus sign on CT imaging conditions diagnostic yield of ENB and might account for the discrepancy between successful navigation and diagnostic yield.

**Methods:** We conducted a prospective, single-center study of ENB in 51 consecutive patients with pulmonary nodules. ENB was chosen as the least invasive diagnostic technique in patients with a high surgical risk, suspected metastatic disease, or advanced-stage disease, or in those who demanded a preoperative diagnosis prior to undergoing curative resection. We studied patient and technical variables that might condition diagnostic yield, including size, cause, location, distance to the pleural surface, and fluorodeoxyglucose uptake of a given nodule; the presence of a bronchus sign on CT imaging; registration point divergence; and the minimum distance from the tip of the locatable guide to the nodule measured during the procedure.

**Results:** The diagnostic yield of ENB was 67% (34/51). The sensitivity and specificity of ENB for malignancy in this study were 71% and 100%, respectively. ENB was diagnostic in 79% (30/38) patients with a bronchus sign on CT imaging but only in 4/13 (31%) with no discernible bronchus sign. Univariate analysis identified the bronchus sign ( $P = .005$ ) and nodule size ( $P = .04$ ) as statistically significant variables conditioning yield, but on multivariate analysis, only the bronchus sign remained significant (OR, 7.6; 95% CI, 1.8-31.7). No procedure-related complications were observed.

**Conclusions:** ENB diagnostic yield is highly dependent on the presence of a bronchus sign on CT imaging.

*CHEST 2010; 138(6):1316-1321*

# Factors affecting success

- Lower yields from lower lobes
- No difference b/w GA or conscious sedation
- Needle brush : cytology brush with a needle tip has higher diagnostic yield

Am J Respir Crit Care Med Vol 176. pp 36–41, 2007  
*Journal of Thoracic Disease, Vol 4, No2 April 2012*

# Navigation V/S TTNA

- Better safety profile
  - Lower rates of pneumothorax (0-10%)
  - Minor bleeding, hypoxia
  - No deaths

Eur Respir J 2007;29:1187-92

J Bronchology 2011;18:133-7

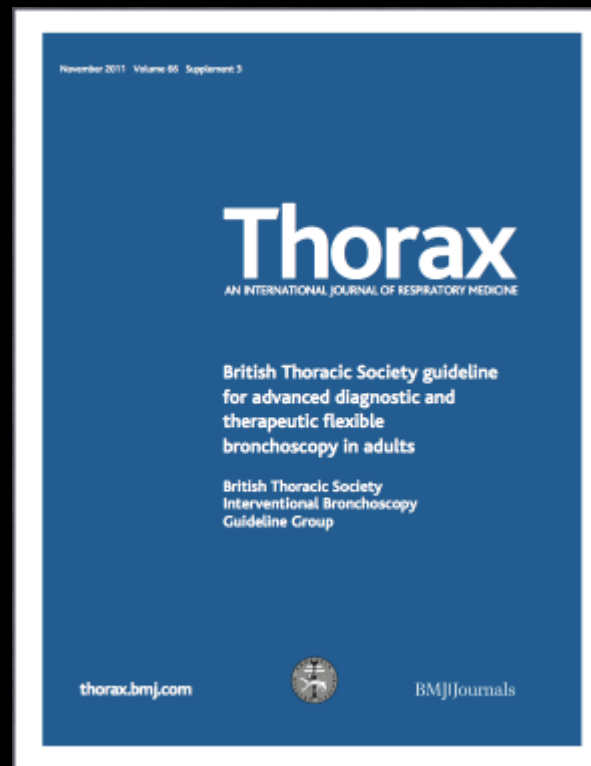
Journal of Thoracic Disease 2012;4(2):



# Other uses

- Targeted biopsy in patients with diffuse lung disease
- Mediastinal lymph node sampling
- Insertion of fiducial markers for radiotherapy
- Implantation of brachytherapy seeds or catheters
- Dye marker placement for surgical resection of peripheral mass

- Electromagnetic bronchoscopy may be considered for the biopsy of peripheral lesions or to guide TBNA for sampling mediastinal lymph nodes. (Grade D)





# Conclusion

- Seems promising
- Cost
- Proper training
- Lack of randomized trials
- Insufficient data for patient selection

# Autofluorescence bronchoscopy

- Profio et al used Red green ratio to detect preinvasive lung ca.
- Hung J et al studied the autofluorescence spectra of normal and malignant bronchial tissue
- Subsequently Stephen Lam et al in 1998 used autofluorescence to study 173 patients with Ca.lung

Med Phys 1984; 11:516-520

**Lasers in Surgery and Medicine 1991;11:99-105**

CHEST1998;113:696-702

## Autofluorescence of Normal and Malignant Bronchial Tissue

Jaclyn Hung MSc, Stephen Lam, MD, Jean C. LeRiche, MBChB,  
and Branko Palcic, PhD

*Cancer Imaging Section, Physics Division (J.H., S.L., B.P.), and  
Department of Pathology, British Columbia Cancer Agency (J.C.L.), Vancouver,  
British Columbia, Canada V5Z 4E6*

In vivo autofluorescence spectra were obtained in 5 patients with carcinoma in situ, 26 patients with invasive tumors, and 1 patient with severe dysplasia. Significant spectral differences were observed between pre-cancerous, cancerous, and normal bronchial tissues. This difference may afford a method to image and/or detect early lung cancer by using tissue autofluorescence alone.

**Key words:** in vivo autofluorescence, bronchial tissue, carcinoma in situ, severe dysplasia, lasers

### INTRODUCTION

Early lung cancers (carcinoma in situ or mi-

frin result in skin photosensitivity which lasts for several weeks, making these drugs unsuitable for diagnostic purposes. Recently, using ratio fluo-

# Localization of Bronchial Intraepithelial Neoplastic Lesions by Fluorescence Bronchoscopy\*

Stephen Lam, MD, FCCP; Timothy Kennedy, MD, FCCP;  
Michael Unger, MD, FCCP; York E. Miller, MD; David Gelmont, MD, FCCP;  
Valerie Rusch, MD, FCCP; Bruce Gipe, MD, FCCP; David Howard, MD;<sup>†</sup>  
Jean C. LeRiche, MB; Andrew Coldman, PhD; and Adi F. Gazdar, MB

**Background:** In the treatment of lung cancer, the best outcome is achieved when the lesion is discovered in the intraepithelial (preinvasive) stage. However, intraepithelial neoplastic lesions are difficult to localize by conventional white-light bronchoscopy (WLB).

**Objective:** To determine if autofluorescence bronchoscopy, when used as an adjunct to WLB, could improve the bronchoscopist's ability to locate and remove biopsy specimens from areas suspicious of intraepithelial neoplasia as compared with WLB alone.

**Method:** A multicenter clinical trial was conducted in seven institutions in the United States and Canada. WLB followed by fluorescence examination with the light-induced fluorescence endoscopy (LIFE) device was performed in 173 subjects known or suspected to have lung cancer. Biopsy specimens were taken from all areas suspicious of moderate dysplasia or worse on WLB and/or LIFE examination. In addition, random biopsy specimens were also taken from other parts of the bronchial tree.

**Results:** The relative sensitivity of WLB+LIFE vs WLB alone was 6.3 for intraepithelial neoplastic lesions and 2.71 when invasive carcinomas were also included. The positive predictive value was 0.33 and 0.39 and the negative predictive value was 0.89 and 0.83, respectively, for WLB+LIFE and WLB alone.

**Conclusion:** Autofluorescence bronchoscopy, when used as an adjunct to standard WLB, enhances the bronchoscopist's ability to localize small neoplastic lesions, especially intraepithelial lesions that may have significant implication in the management of lung cancer in the future.

(CHEST 1998; 113:696-702)

**Key words:** autofluorescence; bronchoscopy; early detection; lung neoplasm

**Abbreviations:** CI=confidence interval; LIFE=light-induced fluorescence endoscopy; WLB=white-light bronchoscopy

# Light Induced Fluorescence Endoscopy (LIFE) device

- Designed by Lam *et al* in Vancouver
- Employs a helium-cadmium laser to illuminate the bronchial tree with 442 nm light
  - Brown area : Abnormal
  - Green area : Normal

# Other devices

- Storz and Pentax have independently developed systems which use conventional blue light (440–480 nm) emitted by a xenon arc lamp
- Storz system employs an optical filter incorporated within the eyepiece of the bronchoscope to transmit red and green wavelengths, together with a narrow band within the excitation wavelength which allows visualisation in conditions of low fluorescence

- Fluorescence images can be viewed directly through the eyepiece or displayed on a monitor, abnormal tissues appearing as red/brown areas against a normal grey/blue background
- The Pentax system measures the intensity of green fluorescence and displays areas of abnormally low green fluorescence on a monitor as “cold spots” on a green background

Diagn Ther Endosc 1999;5:71–75

Diagn Ther Endosc 1999;5:65–70

# Principle

- Different wavelengths of light can be used to highlight the distinction between tumorous lesions and normal tissues
- Using blue light at 442 nm from a laser light source, autofluorescence distinctions between malignant and normal mucosa were demonstrated and could be detected in real time using image-intensified cameras



- When a natural fluorophore is excited to a higher electronic state by absorption of a photon of an appropriate wavelength, the fluorophore may return to its ground electronic state by emission of a photon of a higher wavelength (fluorescence)

- Bronchial epithelial fluorescence is measured in red ( $>630$  nm) and green (520 nm)
- The fluorescence intensities are displayed on a video monitor in real time
- Normal bronchial mucosa appears green
- Premalignant or malignant tissue appears brown, or brown-red

# Review of Recent Advances in Fluorescence Bronchoscopy in Early Localization of Central Airway Lung Cancer

TIMOTHY C. KENNEDY,<sup>a</sup> STEPHEN LAM,<sup>b</sup> FRED R. HIRSCH<sup>c</sup>

<sup>a</sup>Division of Pulmonary and Critical Care, University of Colorado Health Science Center, Denver, Colorado, USA; <sup>b</sup>University of British Columbia and the British Columbia Cancer Agency, Vancouver, British Columbia, Canada; <sup>c</sup>University of Colorado Cancer Center, Denver, Colorado, USA and Department of Oncology, Finsen Center, National University Hospital, Copenhagen, Denmark

**Key Words.** *Fluorescence bronchoscopy · Early hilar lung cancer · Early detection of lung cancer*

---

## ABSTRACT

Centrally located lung cancers are radiologically occult until so far advanced as to have a low cure rate or require extensive resection for cure, but at a cost of high morbidity. These cancers represent about one-fifth of new lung cancers.

Autofluorescence bronchoscopy appears to be an important tool in localizing premalignant and early malignant lesions in the large central airways, particularly when applied to high-risk patients. Applications include studies of molecular biology of premalignancy and early malignancy, chemoprevention studies, endobronchial

therapy studies, localization of synchronous tumors, estimation of the extent of field cancerization, and better estimation of resection margins. Autofluorescence bronchoscopy appears to be significantly more sensitive than white light examination but has low specificity.

This technology is likely to gain widespread use when evaluation of sputum for malignant changes is both more sensitive and specific, and when its application is demonstrated to reduce mortality in this important subgroup of non-small cell lung cancer patients. *The Oncologist* 2001;6:257-262

# Problem of Specificity

- Resulted in more biopsies
- Increased the cost
- Higher number of false positives
- Inability to distinguish b/w preinvasive lesions & inflammatory conditions

Lung Cancer 2001;32:19—25  
Chest 1998;113:696—702



## Effective detection of bronchial preinvasive lesions by a new autofluorescence imaging bronchovideoscope system

Masako Chiyo<sup>a</sup>, Kiyoshi Shibuya<sup>a</sup>, Hidehisa Hoshino<sup>a</sup>, Kazuhiro Yasufuku<sup>a</sup>,  
Yasuo Sekine<sup>a</sup>, Toshihiko Iizasa<sup>a</sup>, Kenzo Hiroshima<sup>b</sup>, Takehiko Fujisawa<sup>a,\*</sup>

<sup>a</sup> Department of Thoracic Surgery, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan

<sup>b</sup> Department of Basic Pathology, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan

Received 12 May 2004; received in revised form 17 November 2004; accepted 23 November 2004

### KEYWORDS

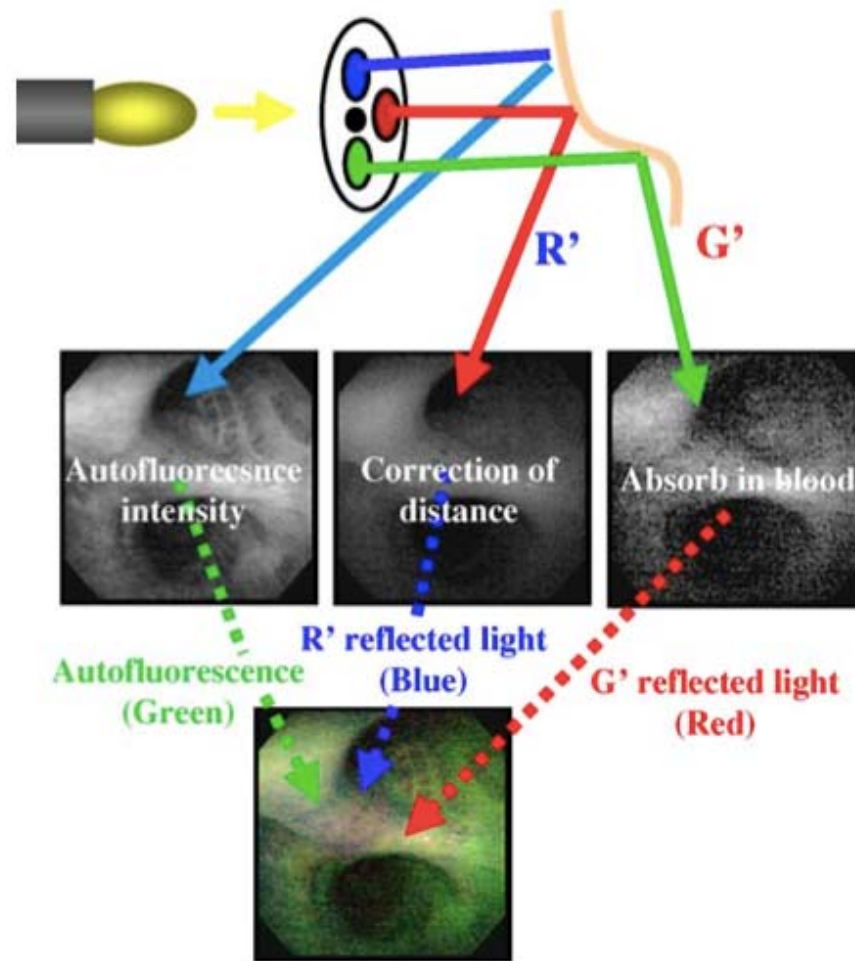
Autofluorescence;  
Bronchovideoscope;  
Reflected light;  
Detection;  
Preinvasive lesion;  
Magenta

**Summary** Autofluorescence bronchoscopy is an important tool for the early detection of preinvasive bronchial lesions. However, autofluorescence bronchoscopy has difficulty distinguishing between preinvasive lesions and other benign epithelial changes. A new autofluorescence imaging bronchovideoscope system (AFI) comprises three signals, including an autofluorescence (460–690 nm) on excitation blue light (395–445 nm) and two different bands of reflected light: G' (550 nm) and R' (610 nm). We hypothesized that color analyses of these three wave lengths would improve our ability to differentiate between inflammation and preinvasive lesions. In order to prove this hypothesis and to evaluate the efficacy of AFI for detecting preinvasive lesions, we conducted a prospective study. A total of 32 patients with suspected or known lung cancer were entered into this study. Conventional white light bronchovideoscopy (WLB) and light induced fluorescence endoscopy (LIFE) were performed prior to using AFI. WLB and LIFE detected 62 lesions, including lung cancers ( $n=2$ ), squamous dysplasias ( $n=30$ ), and bronchitis ( $n=30$ ). By utilizing AFI, 24 dysplasias and 2 cancer lesions were magenta in color, while 25 bronchitis lesions were blue. The sensitivities of detecting dysplasia by LIFE and AFI were 96.7% and 80%, respectively. The specificity of AFI (83.3%) was significantly higher than that of LIFE (36.6%) ( $p=0.0005$ ). We conclude that AFI appears to represent a significant

# Autofluorescence imaging videoscope system

- Displays a composite of 3 signals—  
auto fluorescence signal plus reflected green (G') and red(R')light signals

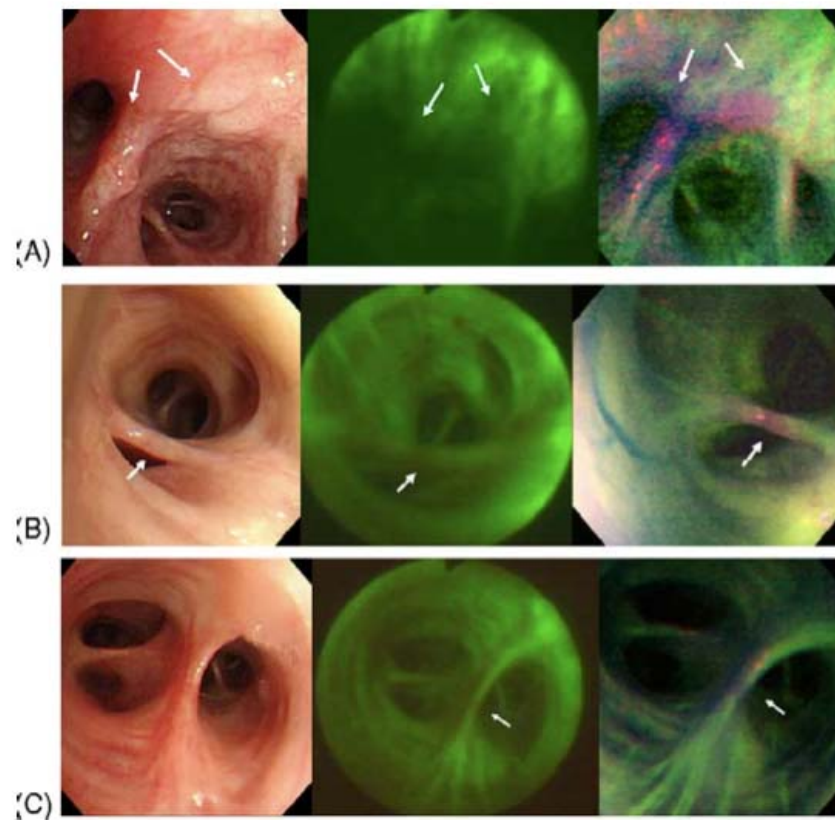




**Fig. 2** Illustration of AFI system. The autofluorescence signal (490–700 nm) and the G' and R' reflected signals are integrated by the video processor. The composite image displayed on the monitor is constructed from displaying the autofluorescence as green, G'-reflected light as red, and R'-reflected light as blue.

- 32 patients comprising 25 patients with suspicious or malignant sputum cytology and 7 patients with known lung cancer were entered into this study
- conventional white light bronchovideoscopy (WLB) using BF-240 (Olympus Optical Corporation, Tokyo, Japan), LIFE, and finally AFI





**Fig. 3** Images of WLB, LIFE, and AFI in patients with squamous cell carcinoma (A), squamous dysplasia (B), and bronchitis (C). AFI depicted squamous cell carcinoma and squamous dysplasia as magenta while depicting bronchitis as blue. Arrows indicate abnormal mucosal changes.

**Table 2** Diagnostic sensitivity and specificity of AFI and LIFE

	LIFE	AFI	<i>p</i> -Value
Sensitivity	96.7% (29/30)	80% (24/30)	0.1028
Specificity	36.6% (11/30)	83.3% (25/30)	0.0005

LIFE: laser-induced fluorescence endoscopy lung system; AFI: autofluorescence imaging bronchovideoscope system.

- AFI displays
  - Normal areas : green
  - Abundant blood flow and blood vessels : blue
  - Neoplastic lesions : magenta

# Conclusion

- AFI could accurately and objectively distinguish preinvasive and malignant lesions from bronchitis through color tone analysis.

# Narrow Band Imaging (NBI)

- NBI enhances vessels in the surface mucosa by using the light absorption characteristic of hemoglobin at a specific wavelength
- Uses narrow spectrum light (narrow band light) specifically suited to the optical characteristics of mucosal tissues and hemoglobin in blood

# Principle

- Takes advantage of altered blood vessel morphology of bronchial dysplasia

CHEST 2007; 131:1794–1799

## ORIGINAL ARTICLE

# Subepithelial vascular patterns in bronchial dysplasias using a high magnification bronchovideoscope

K Shibuya, H Hoshino, M Chiyo, K Yasufuku, T Iizasa, Y Saitoh, M Baba, K Hiroshima, H Ohwada, T Fujisawa

*Thorax* 2002;57:902-907

See end of article for authors' affiliations

Correspondence to:  
Dr T Fujisawa, Department  
of Thoracic Surgery,  
Graduate School of  
Medicine, Chiba  
University, 1-8-1 Inohana,  
Chuo-ku, Chiba 260-8670,  
Japan;  
fujisawa@  
med.m.chiba-u.ac.jp

Revised version received  
8 February 2002  
Accepted for publication  
25 May 2002

**Background:** We have developed a method of high magnification bronchovideoscopy that enables improved observation of subepithelial vascular patterns of the bronchial mucosa. A study was undertaken to investigate the value of high magnification bronchovideoscopy in the detailed examination of dysplasia in the bronchial mucosa of patients with abnormal mucosal fluorescence.

**Methods:** Thirty one patients with sputum cytology specimens suspicious or positive for malignancy were entered into the study. Conventional white light examination was first performed under local anaesthesia and fluorescence bronchoscopy was also carried out using a light induced fluorescence endoscopy (LIFE) lung system. A high magnification bronchovideoscope (XBF 200HM2) was then used to examine the microvascular network in the bronchial mucosa at sites of normal and abnormal fluorescence and the images obtained were compared with pathological diagnoses from bronchial biopsy specimens. Vascular area ratios were calculated using image analysing apparatus.

**Results:** Vascular networks with regular patterns were observed at 20 of 22 abnormal fluorescence sites in biopsy specimens from patients with bronchitis. However, vascular networks with increased vessel growth and complex networks of tortuous vessels of various sizes were observed in 15 of 21 abnormal fluorescence sites in dysplasia specimens. There was a significant difference between bronchitis and dysplasia specimens (OR=25, 95% CI 5.5 to 113,  $p<0.0001$ ). Mean vascular area ratios from 16 normal bronchial epithelium specimens with normal fluorescence, and 22 bronchitis and 21 dysplasia specimens with abnormal fluorescence were 0.054 (95% CI 0.039 to 0.07), 0.095 (95% CI 0.072 to 0.118), and 0.173 (95% CI 0.143 to 0.203), respectively. The results indicate a statistically significant increase in vascular area in the three groups ( $p<0.0001$ ).

**Conclusion:** Areas of increased vessel growth and complex networks of tortuous vessels in the bronchial mucosa detected using a high magnification bronchovideoscope at sites of abnormal fluorescence may enable discrimination between bronchitis and dysplasia.

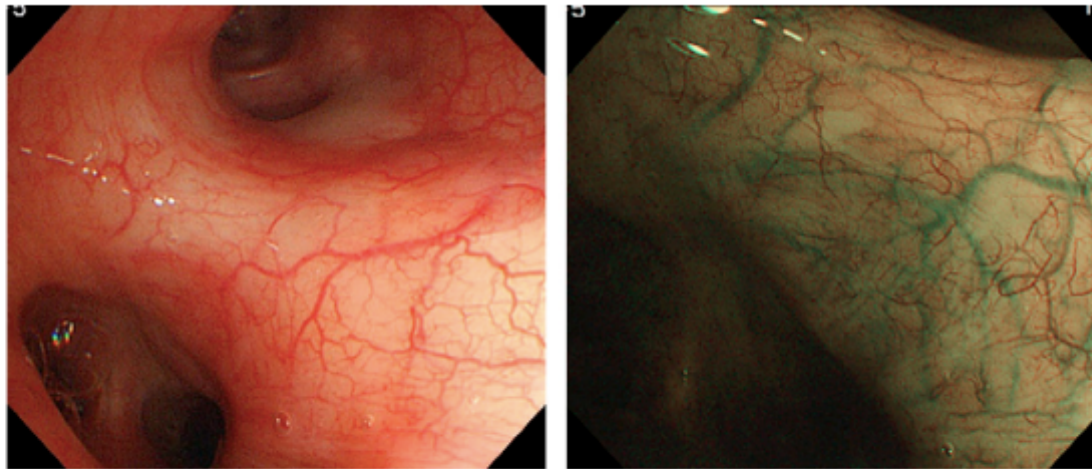
- NBI uses two bandwidths of light
  - 390 to 445 nm (blue) light that is absorbed by superficial capillaries
  - 530 to 550 nm (green) light that is absorbed by blood vessels below the mucosal capillaries
  - narrow bandwidths reduce the scattering of light
  - enable enhanced visualization of blood vessels



- Allows the visualization of abnormal distribution and dilatation of blood vessels
- The 415 nm blue light is absorbed by capillary vessels in the surface layer of the mucosa, whereas the 540 nm is strongly absorbed by blood vessels located below the capillary vessels in the surface layer of the mucosa

- Finer blood vessels near the surface are displayed in brown, whereas thicker vessels in deeper layers are shown in cyan
-

- Superficial thin vessels : Brown
- Deep thick vessels : Cyan



**Fig. 6.** Normal mucosa. Finer blood vessels near the surface are displayed in brown, whereas thicker vessels in deeper layers are displayed in cyan.

# Rationale

- Angiogenesis : dysplastic and neoplastic lesions,
- NBI may identify early dysplastic lesions better than WLB or AFB

## LUNG CANCER

# High magnification bronchovideoscopy combined with narrow band imaging could detect capillary loops of angiogenic squamous dysplasia in heavy smokers at high risk for lung cancer

K Shibuya, H Hoshino, M Chiyo, A Iyoda, S Yoshida, Y Sekine, T Iizasa, Y Saitoh, M Baba, K Hiroshima, H Ohwada, T Fujisawa

*Thorax* 2003;58:989-995

**Background:** We investigated the use of high magnification bronchovideoscopy combined with narrow band imaging (NBI) for the detailed examination of angiogenic squamous dysplasia (ASD). This was carried out in relation to bronchial vascular patterns with abnormal mucosal fluorescence in heavy smokers at high risk for lung cancer.

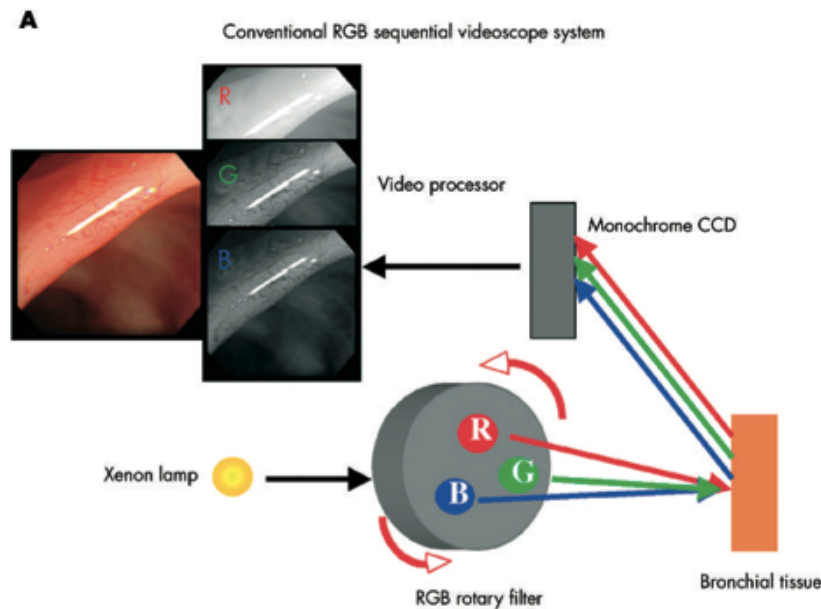
**Methods:** Forty eight patients with sputum cytology specimens suspicious or positive for malignancy were entered into the study. Conventional white light and fluorescence bronchoscopic examination was first performed. Observations by high magnification bronchovideoscopy with conventional white light were made primarily at sites of abnormal fluorescence, and then repeated with NBI light to examine microvascular networks in the bronchial mucosa. Spectral features on the RGB (Red/Green/Blue) sequential videoscope system were changed from the conventional RGB broadband filter to the new NBI filter. The wavelength ranges of the new NBI filter were B1: 400-430 nm, B2: 420-470 nm, and G: 560-590 nm. ASD tissues were also examined using a confocal laser scanning microscope equipped with argon-krypton (488 nm) and argon (514 nm) laser sources.

**Results:** The microvessels, vascular networks of various grades, and dotted vessels in ASD tissues were clearly observed in NBI-B1 images. Diameters of the dotted vessels visible on NBI-B1 images agreed with the diameters of ASD capillary blood vessels diagnosed by pathological examination. Capillary blood vessels were also clearly visualised by green fluorescence by confocal laser scanning microscopy. There was a significant association between the frequency of dotted vessels by NBI-B1 imaging and tissues confirmed as ASD pathologically ( $p=0.002$ ).

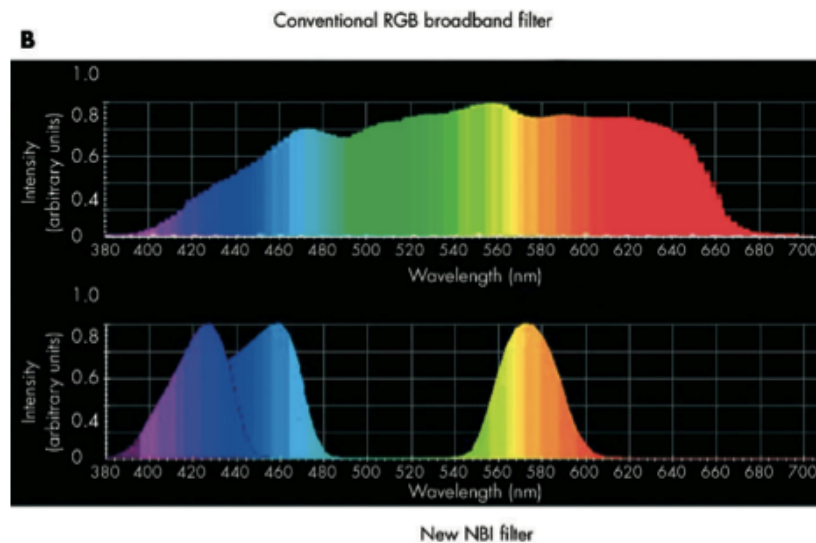
**Conclusions:** High magnification bronchovideoscopy combined with NBI was useful in the detection of capillary blood vessels in ASD lesions at sites of abnormal fluorescence. This may enable the discrimination between ASD and another pre-invasive bronchial lesion.

See end of article for authors' affiliations

Correspondence to:  
Dr T Fujisawa, Department  
of Thoracic Surgery,  
Graduate School of  
Medicine, Chiba  
University, 1-8-1 Inohana,  
Chuo-ku, Chiba 260-  
8670, Japan; fujisawa@  
med.m.chiba-u.ac.jp



**Figure 1** Conventional RGB system and the new NBI (narrow band imaging) system. The conventional RGB sequential videoscope system has a xenon lamp and rotation disk with 3 RGB optical filters. The rotation disk and monochrome CCD are synchronised and 3 band images are generated sequentially. Colour images can be synthesised using 3 band images by the video processor (fig 1A). Narrow band imaging (NBI) is a novel system that can be used to observe microvessel structure using a new narrow banding filter on an RGB sequential videoscope system instead of the conventional RGB broadband filter. Wavelength ranges of the new NBI filter were: B1 = 400–430 nm, B2 = 420–470 nm, and G = 560–590 nm. In contrast, the range of wavelengths in the conventional RGB broadband filter were: B = 400–500 nm, G = 500–600 nm, and R = 600–700 nm. X = Wavelength, Y = Light Intensity (fig 1B).



- Abnormal vessels
  - Tortuous
  - Dotted
  - Abrupt endings



## A Pilot Study of Narrow-Band Imaging Compared to White Light Bronchoscopy for Evaluation of Normal Airways and Premalignant and Malignant Airways Disease\*

Brad D. Vincent, MD; Mostafa Fraig, MD; and Gerard A. Silvestri, MD, FCCP

**Background:** The objectives of this study were to characterize the appearance of normal, dysplastic, and frankly malignant airway lesion appearance under narrow-band imaging (NBI), and to determine if NBI, when used in conjunction with white light (WL) bronchoscopy, could improve detection of dysplasia and malignancy.

**Patients and methods:** This was a prospective, partially blinded study at a university teaching hospital. Bronchoscopy was performed on 22 patients with known or suspected bronchial dysplasia or malignancy. Full airway examination was performed first under WL bronchoscopy and then under NBI. Directed endobronchial biopsies of likely dysplastic, malignant, and normal (control) areas were then performed and sent for examination by a pathologist blinded to the gross description of the lesion. Pathology interpretations were then compared to the corresponding WL and NBI images.

**Results:** There were one malignant and four dysplastic lesions in 22 patients detected by NBI when findings by WL imaging were considered normal. In cases when the WL appearance was abnormal, NBI did not improve the diagnostic yield. The increased rate of detection of dysplasia and malignancy by NBI was statistically significant ( $p = 0.005$ ).

**Conclusion:** NBI identified dysplasia or malignancy that was not detected by WL inspection in 23% of subjects. Further studies are needed to determine the efficacy of NBI in detection of premalignant airways lesions in an at-risk population. (CHEST 2007; 131:1794-1799)

**Key words:** bronchial dysplasia; carcinoma *in situ*; interventional bronchoscopy; lung cancer; malignancy; narrow-band imaging; white-light bronchoscopy

**Abbreviations:** AF = autofluorescence; CI = confidence interval; CIS = carcinoma *in situ*; NBI = narrow band imaging; WL = white light

## Narrow-Band Imaging Bronchoscopy Increases the Specificity of Bronchoscopic Early Lung Cancer Detection

Felix J. F. Herth, MD,\* Ralf Eberhardt, MD,\* Devanand Anantham, MRCP,†  
Daniela Gompelmann, MD,\* Mohamed Wafaa Zakaria, MD,‡ and Armin Ernst, MD\*§

**Background:** Detection of nonsmall cell lung cancer at the intraepithelial stage is believed to improve cure rates. New bronchoscopic technologies, including white light videobronchoscopy (WLB), autofluorescence imaging (AFI), and narrow band imaging (NBI), are aiming to diagnose airway neoplasia at a preinvasive stage.

**Objectives:** To evaluate the diagnostic yields of NBI individually and in combination with WLB and AFI.

**Methods:** A 10-month review of patients who were referred for airway screening or surveillance. Patients were randomized as to the order of AFI and NBI examinations. The airway mucosa was graded endoscopically as "normal," "abnormal," "suspicious," or "tumor." All areas that were not normal were biopsied. Biopsies with a histologic grading of moderate to severe dysplasia or carcinoma in situ were considered positive for intraepithelial neoplasia.

**Results:** Sixty-two patients with a mean age of  $56.2 \pm 9.8$  years were studied. Five patients had invasive cancers and were excluded from the analysis. The remaining 57 cases had a 30% prevalence of intraepithelial neoplasia. The sensitivity of WLB was 0.18 and the specificity was 0.88. The relative sensitivities (compared with WLB) of AFI and NBI were 3.7 ( $p = 0.005$ ) and 3.0 ( $p = 0.03$ ), respectively. The relative specificities of AFI and NBI were 0.5 ( $p < 0.001$ ) and 1.0 ( $p = 0.72$ ), respectively. Combining AFI and NBI did not increase diagnostic yield significantly. The sequence of performing AFI and NBI did not impact findings.

**Conclusions:** NBI is an alternative to AFI in the detection of early lung cancers because it has a comparatively higher specificity without significantly compromising the sensitivity.

**Key Words:** Narrow band imaging, Autofluorescence imaging, White light bronchoscopy, Early lung cancer.

(*J Thorac Oncol.* 2009;4: 1060–1065)

The stepwise progression of carcinogenesis is believed to be a potential target for improving the survival of patients with nonsmall cell lung cancer. Data from other epithelial organs, such as the cervix, colon, and esophagus, have shown that the detection of neoplasm at the intraepithelial stage has resulted in an improved cure rate.<sup>1–5</sup> Epithelial changes, such as high-grade dysplasia and carcinoma in situ (CIS), in the airways are regarded as squamous cell carcinoma presenting at an early stage.<sup>6–9</sup> These lesions bear the hallmarks of neoplasia, which are angiogenesis and structural changes of the mucosa.<sup>10</sup> New bronchoscopic technology has targeted these features of neoplasia to improve the detection of preinvasive lesions. Examples of this new technology include white light videobronchoscopy (WLB), autofluorescence imaging (AFI), and narrow band imaging (NBI).

WLB is reflectance imaging of bronchial tissue, which has been illuminated by white light. The image generated depends on the reflection, scattering, and absorption of light by the tissue that is being viewed.<sup>11</sup> Although the endoscopic features of intraepithelial neoplasia have been well described, the reported sensitivity of conventional bronchoscopy has been limited.<sup>10,12,13</sup> However, the quality of white light bronchoscopic images has improved with the advent of the videobronchoscope. These scopes have a color video chip built into the tip of the bronchoscope to deliver clearer images.<sup>14</sup>

Studies of AFI have shown improved sensitivity in the detection of preinvasive lesions in the airway when compared with WLB.<sup>1,15</sup> An image is generated when blue light (390–440 nm wavelengths) excites subepithelial cells into producing a fluorescence light signal that is visually enhanced by appropriate filtering. This autofluorescence signal is attenuated when blue light is absorbed by hemoglobin or when

**TABLE 1 Visual Classification of Endobronchial Findings**

Grade	WLB	AFI	NBI
Normal	No visual endobronchial abnormality	Green image with normal endobronchial architecture	Normal mucosal vascularity
Abnormal but not suspicious	Erythema, swelling/thickening of mucosa, airway inflammation, fibrosis, trauma, and granulation tissue	Slight decrease in fluorescence, with poorly defined margins; dark green or faint magenta image	Increased capillary density and less than 3 criteria present (see below)
Suspicious for intraepithelial neoplasia	Nodular, polypoid lesions; irregular mucosa; focal thickening of subcarina	Definite decrease in fluorescence, with clearly defined margins; magenta image; clear distortion of endobronchial architecture	More than or equal to three criteria present Capillary loops Dotted vessels Complex vascular networks of tortuous vessels Abrupt ending vessels
Tumor	Visible endobronchial tumor	Visible endobronchial tumor	Visible endobronchial tumor

WLB, white light videobronchoscopy; AFI, autofluorescence imaging; NBI, narrow band imaging.



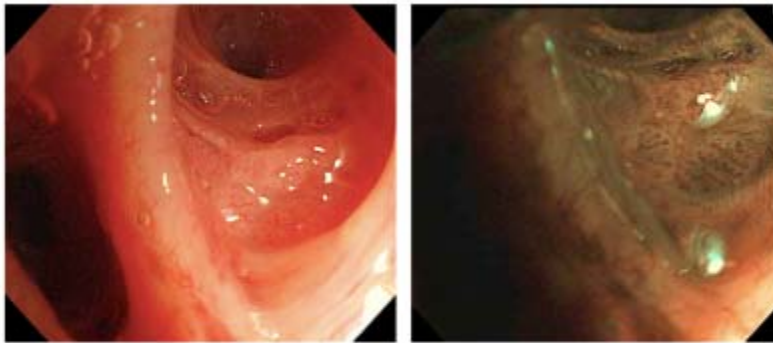
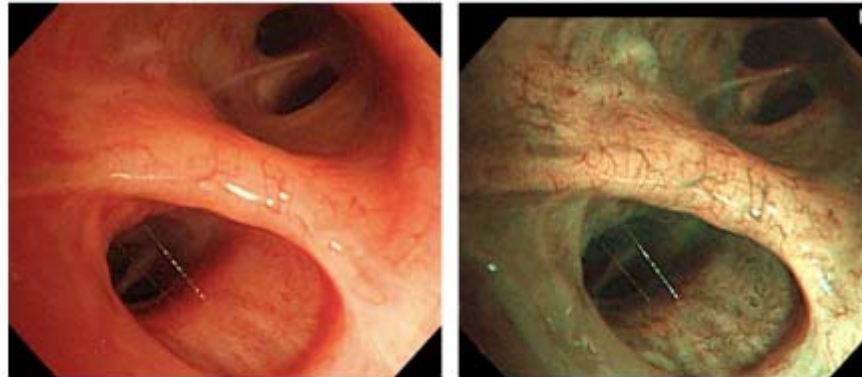


Fig. 8. CIS. Dotted vessels and tortuous vessels are clearly identified by NBI.



Squamous dysplasia. Complex networks of tortuous vessels are clearly identified by NBI.

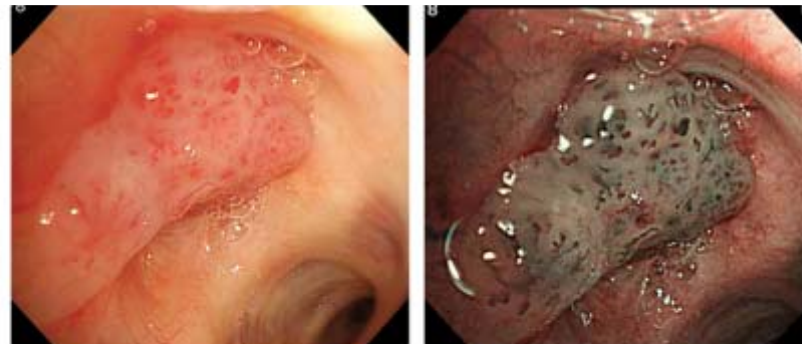


Fig. 9. Squamous cell carcinoma (invasive). Capillary loops of tortuous vessels of various sizes are identified by NBI.

# Combining Autofluorescence and Narrow Band Imaging With Image Analysis in the Evaluation of Preneoplastic Lesions in the Bronchus and Larynx

Phan Tien Nguyen, MBBS, FRACP,\*§ Olivier Salvado, PhD,†  
Ian Brent Masters, MBBS, FRACP, PhD,‡ Camile S. Farah, BDS, MSc, PhD, GCEd (HE),  
FRACDS (Oral Med), FIAAO, FICD,§ and David Fielding, MBBS, FRACP, MD (Lond.)\*

**Background and Objectives:** Autofluorescence (AF) techniques improve the diagnostic yield of white light inspection for preneoplastic lesions in the bronchus and head and neck region. Although highly sensitive, AF has poor specificity, particularly in situations where there have been earlier biopsies or treatments such as radiotherapy. Narrow band imaging (NBI) is a newer imaging technique that enhances the early abnormal angiogenesis seen in preneoplastic lesions. NBI has higher specificity when compared with AF. We aimed to combine these imaging modalities, using AF as an effective screening tool and NBI to confirm AF findings. We also used computer-assisted image analysis techniques to give objective confirmation to our visual inspection.

**Methods:** Three patients were selected for image analysis of their NBI images using the L\*a\*b\* color scale in manually drawn regions of interest of biopsy-confirmed areas. Each case compared pathology with a different benign condition: normal tissue, postbiopsy effect, and postradiation therapy change. Patients had white light followed by AF inspection. Abnormal areas of AF were cross-examined with NBI.

**Results:** NBI clearly showed dysplasia and carcinoma in situ. It also confirmed abnormal fluorescence because of earlier biopsies and radiation therapy. Analysis of the L\*a\*b\* color space scale in each case showed segmentation between pathology and the benign tissue.

**Conclusions:** There may be additive and discriminatory benefits of NBI after AF inspection. Further study with computer-assisted color segmentation techniques and image analysis is required before optical diagnosis can become a reality in bronchoscopic techniques in the future.

**Key Words:** autofluorescence, narrow band imaging, optical diagnosis, optical biopsy, L\*a\*b\*, image analysis, endobronchial dysplasia

(*J Bronchol Intervent Pulmonol* 2010;17:109–116)

Autofluorescence (AF) techniques are used to improve detection of severe dysplasias and in situ carcinomas of the bronchus and the head and neck. This is because standard white light bronchoscopy (WLB) has limitations, potentially missing up to 29% of the endobronchial carcinoma in situ (CIS) lesions.<sup>1</sup> In high-risk groups, the detection of such lesions affords the possibility of early treatment with minimal adverse effects and excellent long-term outcomes. In situ carcinomas of the bronchus and persistent endobronchial severe dysplasias can be treated with modalities such as photodynamic therapy, cautery, argon plasma coagulation, or radiotherapy in which lesions are more extensive.

AF depends on the metabolic and biochemical changes occurring in cells. The fluorescence is because of the presence of chromophores in the airway mucosa, specifically, elastin, collagen, flavins, nicotinamide adenine dinucleotide (NAD), NADH (hydrogen), and porphyrins.<sup>2</sup> Normal respiratory epithelium will fluoresce green when exposed to light in the violet-blue spectrum (400–450 nm). There is progressive loss of the green signal from metaplasia to CIS leading to a red-brown or purple appearance depending on the AF system used. This is because of the reduction in chromophores, thickening of the epithelium, and increasing angiogenesis.<sup>3</sup>

AF bronchoscopy (AFB) more than doubles the yield of standard WLB for significant early endobronchial lesions,<sup>4</sup> with reported sensitivities of 94% to

# Conclusion

- Routine use not recommended
- Clinical trials
- Risk stratification
- Prognostication

# Conclusion

- Current clinical applications for AFB and NBI in the general pulmonary population do not exist, they may play an important role in future risk stratification, prognostication, and/or chemoprevention trials in high-risk patients

# OPTICAL COHERENCE TOMOGRAPHY

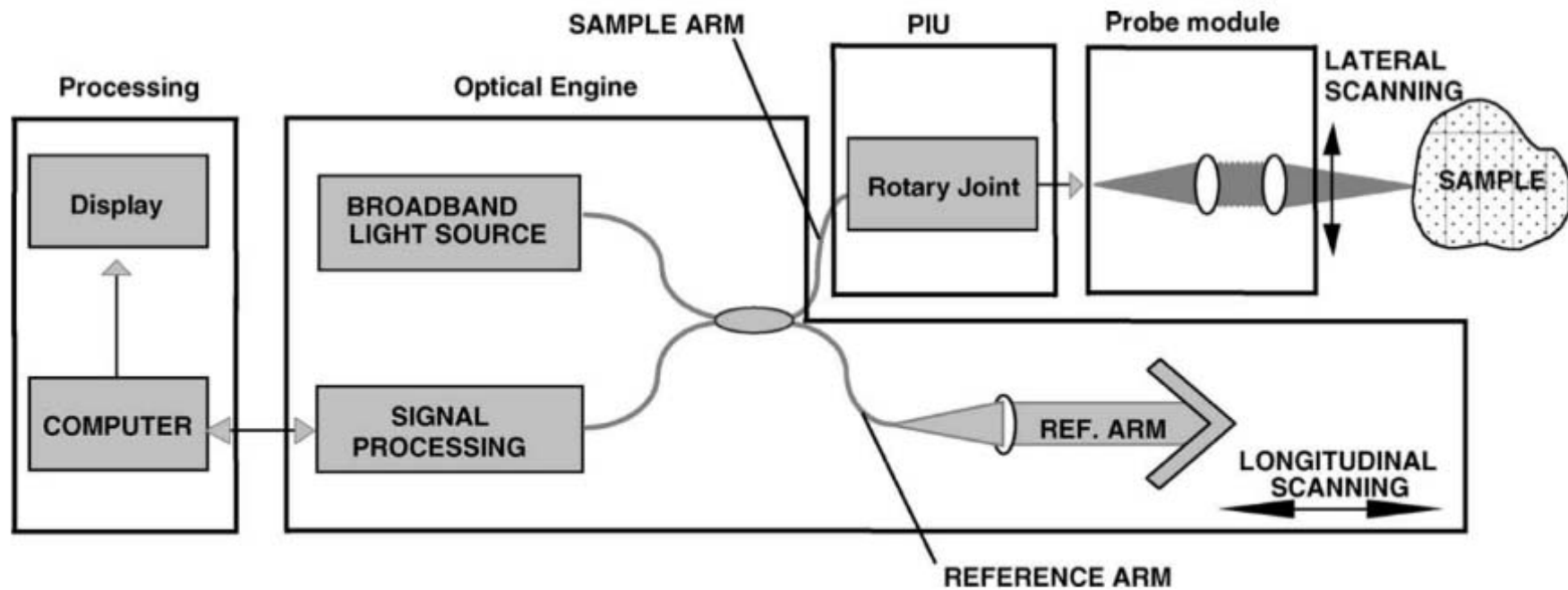
- Uses near-infrared light transit time and reflection to provide a macroscopic optical cross-sectional view of hollow organs
- OCT overcomes two major ultrasound limitations in the lung
  - inability to image through air
  - poor spacial resolution



- The physical principle of OCT is similar to that of B-mode ultrasound imaging
- OCT is capable of imaging the morphology of mucosal lesions
- OCT delivers near IR light waves to the imaged site through a single optical fiber
- Reflected light from internal microstructural layers within the scanned tissue, allows micron-scale resolution to pick-up normal anatomy and any in situ morphologic aberrations

# USG V/S OCT

- The velocity of the light is 200,000 times that of sound
- Hence reflected light cannot be analysed electronically
- OCT uses interferometry to measure the time delay of reflected light

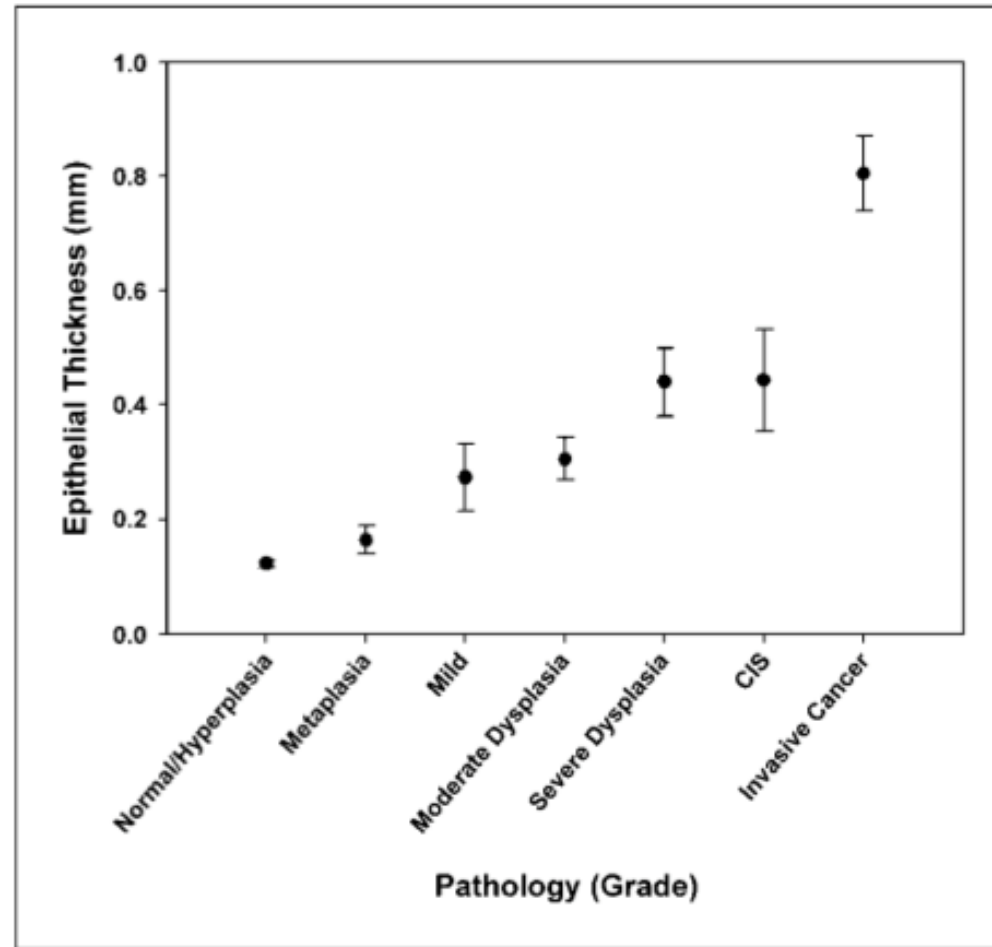


**Fig. 1** Shows a diagram of the OCT system (Light Lab Imaging, Boston, U.S.A., and Pentax, Tokyo, Japan) used in this study.

- Low coherence light or light containing many different wavelengths is generated from the source
- The light is split evenly, half toward the sample and half toward a moving mirror
- Light is then reflected, both from within the sample and from the mirror
- The propagation speeds for light and sound are enormously different

- The depth range of OCT is sufficient to penetrate through the upper layers of exposed tissues on airway surfaces (maximal depth average 2—3 mm)

- Interpretation of the OCT imaging is complex
- Differentiation between different premalignant stages can be quantified by measurement of the epithelial thickness
- The epithelial thickness is different between invasive cancer and CIS



**Fig. 4.** Quantitative measurements of the epithelium in the OCT images from different histologic grades. There is a progressive increase in the thickness due to a multilayer structure and larger nuclei as the epithelium changes from normal/hyperplasia to metaplasia, mild, moderate, or severe dysplasia, to CIS and invasive carcinoma.



## Optical coherence tomography in the diagnosis of bronchial lesions

Masahiro Tsuboi, Aeru Hayashi, Norihiko Ikeda, Hidetoshi Honda, Yasufumi Kato, Shuji Ichinose, Harubumi Kato\*

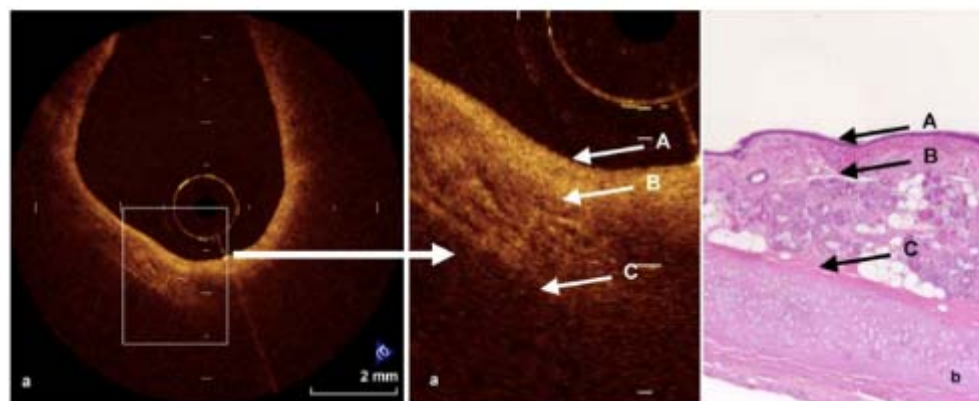
*Conclusions:* This study was the first report of the endobronchial OCT for lung cancer in clinical practice. Layers of the bronchial wall were distinctly observed in the normal bronchus on the OCT images, as opposed to bronchial tumors which lacked a layered structure. The ability of OCT to identify abnormal areas may well revise present methods for early diagnosis endoscopically.

© 2005 Elsevier Ireland Ltd. All rights reserved.

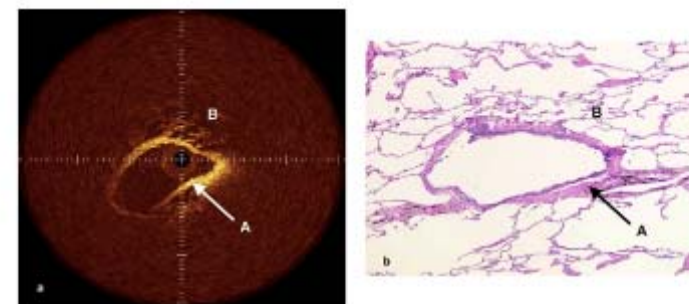


**Table 1** OCT findings of resected lung

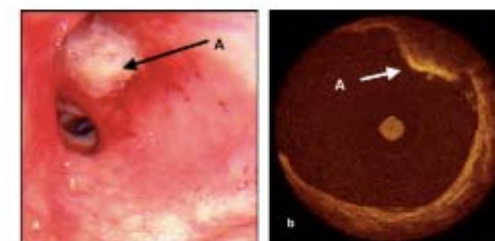
	Findings	Seen in
Normal bronchus	Layered structure	7/7
Alveoli	Honeycomb structure	7/7
Tumor	Loss of layered structure	2/2



**Fig. 2** Shows the OCT image (a), and histological finding (b), of normal bronchus. The bronchial mucosal and submucosal layer (A) appear homogenous in OCT image. The submucosal layer is relatively reflective due to the presence of extracellular matrix. A gap can be seen between the submucosa (A), and smooth muscle layer (B), and cartilage layer shows mach scattering (C). Epithelium, mucosa, and cartilage are clearly differentiated, as well as a number of glandular tissues and micro vessels by both OCT and histology. (a) OCT images, (b) histological finding, (A) mucosal and submucosal layer, (B) smooth muscle layer, (C) cartilage.



**Fig. 3** Shows the OCT image (a), and histological findings (b), of normal peripheral bronchus and alveoli. The uniform bronchial wall (A), and the structure of alveoli (B), containing air can be observed. (a) OCT Images, (b) histological finding, (A) peripheral bronchus, (B) alveoli.



**Fig. 4** Preliminary case: bronchoscopically nodular-infiltrative type squamous cell carcinoma is observed in left B1+2 (a). The tumor, A, is depicted by unevenly distributed high backscattering area and resultant loss of layer structure in the OCT image (b). (a) bronchoscopic findings, (b) OCT image, (A) tumor.

## Optical Coherence Tomography: Real-time Imaging of Bronchial Airways Microstructure and Detection of Inflammatory/Neoplastic Morphologic Changes

Suzanne C. Whiteman, Ying Yang, Daniel Gey van Pittius, et al.

*Clin Cancer Res* 2006;12:813-818. Published online February 7, 2006.

**Abstract** **Purpose:** Current diagnostic imaging modalities for human bronchial airways do not possess sufficient resolution and tissue penetration depth to detect early morphologic changes and to differentiate in real-time neoplastic pathology from nonspecific aberrations. Optical coherence tomography (OCT) possesses the requisite high spatial resolution for reproducible delineation of endobronchial wall profiling.

**Experimental Design:** To establish whether OCT could differentiate between the composite microstructural layers of the human airways and simultaneously determine *in situ* morphologic changes, using a bench-top OCT system, we obtained cross-sectional images of bronchi from 15 patients undergoing lung resections for cancer. All scanned sections underwent subsequent detailed histologic analysis, allowing direct comparisons to be made.

**Results:** OCT imaging enables characterization of the multilayered microstructural anatomy of the airways, with a maximum penetration depth up to 2 to 3 mm and 10- $\mu$ m spatial resolution. The epithelium, subepithelial components, and cartilage are individually defined. The acquired OCT images closely match histologically defined patterns in terms of structural profiles. Furthermore, OCT identifies *in situ* morphologic changes associated with inflammatory infiltrates, squamous metaplasia, and tumor presence.

**Conclusions:** Our results confirm that OCT is a highly feasible optical tool for real-time near-histologic imaging of endobronchial pathology, with potential for lung cancer surveillance applications in diagnosis and treatment.





## Optical Coherence Tomography as an Adjunct to Flexible Bronchoscopy in the Diagnosis of Lung Cancer

### A Pilot Study

Ross G. Michel, MD; Gary T. Kinsewitz, MD, FCCP;  
Kar-Ming Fung, MD, PhD; and Jean I. Keddissi, MD, FCCP

Lung cancer is the leading cause of cancer-related deaths in the United States and the second most common type of cancer in both men and women. Optical coherence tomography (OCT) scanning can generate high-resolution cross-sectional images of complex, living tissues in real time. The objectives of this study were to determine the feasibility of using OCT imaging during flexible bronchoscopy and to preliminarily assess the ability of OCT imaging to distinguish an endobronchial malignancy from normal endobronchial mucosa. A Niris OCT probe was introduced into the airways of patients with an endobronchial mass during flexible bronchoscopy. An investigational device exemption was approved by the US Food and Drug Administration for the use of the OCT system in this study. Conventional OCT scans of an endobronchial mass and a control area of normal bronchial mucosa were performed to generate real-time images in each patient. Following OCT imaging, the same sites were biopsied for pathologic correlation. We report on the first five patients enrolled. A total of 60 OCT images with corresponding endobronchial biopsy specimens were obtained. The average procedure time was 29 min. The histopathologic diagnoses of the endobronchial masses included two small cell carcinomas, one squamous cell carcinoma, one adenocarcinoma,

and one endobronchial schwannoma. Microstructures of normal bronchial mucosa, including epithelium and lamina propria, were identified with OCT imaging. OCT scan features of malignancy included loss of normal, identifiable microstructures and subepithelial "optical fracture" of tissues. All patients tolerated the endobronchial imaging well without complications.

Preliminary results suggest that OCT imaging is a technically feasible adjunct to flexible bronchoscopy in the diagnosis of lung cancer. This is the first reported use of OCT to generate images of endobronchial neoplasms during flexible bronchoscopy in the United States. This technology may in the future provide a noninvasive "optical biopsy," which could potentially guide the bronchoscopist to areas for biopsy or even obviate the need for conventional lung biopsies.

**Trial Registration:** clinicaltrials.gov; Identifier: NCT01039311 **CHEST** 2010; 138(4):984-988

**Abbreviations:** FDA = US Food and Drug Administration; OCT = optical coherence tomography

Lung cancer is the leading cause of cancer-related deaths in the United States and the second most common type of cancer in both men and women.<sup>1</sup> More than 85% of lung tumors originate in the bronchial epithelium with multistage cellular changes advancing over a relatively long period of time before the first presentation of invasive cancer.<sup>2</sup> Endobronchial samples are obtained when suspected mucosal abnormalities or visible endobronchial masses are identified, most commonly by chest radiograph, CT scan, and PET scan. Sometimes, it is difficult to identify subtle mucosal changes that may be a precursor or a harbor of a malignant process. Several endobronchial techniques, such as autofluorescence bronchoscopy and endobronchial ultrasound, have been investigated to better identify areas in need of biopsy. Autofluorescence bronchoscopy enhances identification of in situ mucosal abnormalities, but this method is limited by inadequate image resolution and tissue depth penetration.<sup>3</sup> High-frequency endobronchial ultrasonography achieves deeper penetration of airway tissue but offers insufficient spatial resolution for clear demarcation of the microstructural profile and morphologic changes.<sup>4,5</sup>

Manuscript received March 22, 2010; revision accepted April 9, 2010.

**Affiliations:** From the Division of Pulmonary/Critical Care Medicine (Drs Michel, Kinsewitz, and Keddissi), and the Department of Pathology (Dr Fung), Oklahoma City Veterans Affairs Medical Center, Oklahoma City, OK.

# Airway Wall Thickness Assessed Using Computed Tomography and Optical Coherence Tomography

Harvey O. Coxson<sup>1,2</sup>, Brendan Quiney<sup>1,2</sup>, Don D. Sin<sup>2,4</sup>, Li Xing<sup>2</sup>, Annette M. McWilliams<sup>3,4</sup>, John R. Mayo<sup>1</sup>, and Stephen Lam<sup>3,4</sup>

<sup>1</sup>Department of Radiology, Vancouver General Hospital, Vancouver, British Columbia, Canada; <sup>2</sup>The James Hogg iCAPTURE Centre for Cardiovascular and Pulmonary Research at the Heart and Lung Center of St. Paul's Hospital, Vancouver, British Columbia, Canada; <sup>3</sup>British Columbia Cancer Agency, Vancouver, British Columbia, Canada; and <sup>4</sup>Department of Medicine (Respiratory Division), The University of British Columbia, Vancouver, British Columbia, Canada

**Rationale:** Computed tomography (CT) has been shown to reliably measure the airway wall dimensions of medium to large airways. Optical coherence tomography (OCT) is a promising new micron-scale resolution imaging technique that can image small airways 2 mm in diameter or less.

**Objectives:** To correlate OCT measurements of airway dimensions with measurements assessed using CT scans and lung function.

**Methods:** Forty-four current and former smokers received spirometry, CT scans, and OCT imaging at the time of bronchoscopy. Specific bronchial segments were identified and measured using the OCT images and three-dimensional reconstructions of the bronchial tree using CT.

**Measurements and Main Results:** There was a strong correlation between CT and OCT measurements of lumen and wall area ( $r = 0.84$ ,  $P < 0.001$ , and  $r = 0.89$ ,  $P < 0.001$ , respectively). Compared with CT, OCT measurements were lower for both lumen and wall area by 31 and 66%, respectively. The correlation between FEV<sub>1</sub>% predicted and CT and OCT measured wall area (as percentage of the total area) of fifth-generation airways was very strong ( $r = -0.79$ ,  $r = -0.75$ ), but the slope of the relationship was much steeper using OCT than using CT ( $y = -0.33x + 82$ ,  $y = -0.1x + 78$ ), indicating greater sensitivity of OCT in detecting changes in wall measurements that relate to FEV<sub>1</sub>.

**Conclusions:** OCT can be used to measure airway wall dimensions. OCT may be more sensitive at detecting small airway wall changes that lead to FEV<sub>1</sub> changes in individuals with obstructive airway disease.

**Keywords:** chronic obstructive pulmonary disease

## AT A GLANCE COMMENTARY

### Scientific Knowledge on the Subject

Computed tomography is widely used to quantify airways in subjects with chronic obstructive pulmonary disease. Optical coherence tomography (OCT) is a new micron-scale resolution optical imaging method used in studies of the eye, gastrointestinal tract, and preneoplastic bronchial lesions.

### What This Study Adds to the Field

OCT can be used to measure airway wall dimensions. OCT may be more sensitive at detecting small airway wall changes that lead to FEV<sub>1</sub> changes in individuals with obstructive airway disease.

that remodels the wall of the small airway, ultimately resulting in nonreversible airflow limitation (3, 4). Remodeling of the small airways is believed to occur early in the disease process and worsens with disease progression. The "gold standard" for assessing small airway disease is morphometry of resected lung tissue, but the invasiveness of this approach precludes its use in clinical studies. With the advent of high-resolution computed tomography (CT), and the development of multislice CT scanning techniques, CT has become a very popular technique for



Respirology (2011) 16, 34–43

## Phenotyping airway disease with optical coherence tomography

HARVEY O. COXSON,<sup>1,2</sup> PETER R. EASTWOOD,<sup>3,4</sup> JONATHAN P. WILLIAMSON<sup>3,4</sup> AND DON D. SIN<sup>1,5</sup>

<sup>1</sup>Providence Heart and Lung Institute and The UBC James Hogg Research Center, St. Paul's Hospital, and Departments of <sup>2</sup>Radiology and <sup>5</sup>Medicine (Pulmonary Division), University of British Columbia, Vancouver, British Columbia, Canada, and <sup>3</sup>Department of Pulmonary Physiology, Sir Charles Gairdner Hospital, and <sup>4</sup>School of Anatomy and Human Biology, University of Western Australia, Perth, Western Australia, Australia

### ABSTRACT

Airway diseases are a major concern around the world. However, the pace of new drug and biomarker discovery has lagged behind those of other common disorders such as cardiovascular diseases and diabetes. One major barrier in airway research has been the inability to accurately visualize large or small airway remodelling or dysplastic/neoplastic (either pre or early cancerous) changes using non- or minimally invasive instruments. The advent of optical coherence tomogra-

phy (OCT) has the potential to revolutionize airway research and management by allowing investigators and clinicians to visualize the airway with resolution approaching histology and without exposing patients to harmful effects of ionizing radiation. Thus, with the aid of OCT, we may be able to accurately determine and quantify the extent of airway remodelling in asthma and chronic obstructive pulmonary disease, detect early pre-cancerous lesions in smokers for chemoprevention, study the upper airway anatomy of patients with obstructive sleep apnea in real time while they are asleep and facilitate optimal selection of stents for those with tracheal obstruction. In this paper, we review the current state of knowledge of OCT and its possible application in airway diseases.

**Key words:** airway disease, Imaging, optical tomography.

### INTRODUCTION

Airway diseases (asthma, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA) and lung cancer) are worldwide epidemics that are associated with considerable morbidity and mortality. Unfortunately, the developments of novel therapies to treat and prevent these disorders lag behind

**The Authors:** Dr Coxson is an Associate Professor of Radiology specializing in quantitative imaging of the lung. His research interest includes CT and optical coherence tomography and how these techniques relate to lung structure–function relationships in health and disease. Dr Eastwood is a National Health and Medical Research Council (Australia) Senior Research Fellow and Professor at University of Western Australia with research interests in respiratory and sleep physiology. Dr Williamson is a Respiratory Physician with research interests including lower airway optical coherence tomography, airway mechanics and interventional bronchology. Dr Sin is a Professor of Medicine, who holds a Canada Research Chair in COPD and a senior scholarship with the Michael Smith Foundation for Health Research. His research interests are in identifying new biomarkers to improve the health outcomes of patients with chronic airway diseases.

- OCT holds promise
  - Avoid biopsies by giving real time images of submucosal structure
  - Phenotyping of airway disease
  - Assessment of small airways disease

# FIBERED CONFOCAL FLUORESCENCE MICROSCOPY

- Based on confocal microscopy
- Allows thin-section biological specimen imaging by replacing the microscope's objective with a flexible fiberoptic miniprobe that can be introduced through an FB
- Relies on cellular and tissue autofluorescence on laser excitation

- A flexible miniprobe with an outer diameter of 1 mm
- miniprobe has thousands of fiber cores which are scanned, one at a time, by a laser source, by the use of two rapidly moving mirrors
- Two different wave lengths are available
- Application of external dye like methylene blue enhances the image



# In Vivo Imaging of the Bronchial Wall Microstructure Using Fibered Confocal Fluorescence Microscopy

Luc Thiberville, Sophie Moreno-Swirc, Tom Vercauteren, Eric Peltier, Charlotte Cavé, and Genevieve Bourg Heckly

Am J Respir Crit Care Med Vol 175. pp 22–31, 2007

Clinique Pneumologique, and Pathology Department, Rouen University Hospital, Rouen; Mauna Kea Technologies; CNRS UMR7033, Université Pierre et Marie Curie, Paris; and INRIA Sophia Antipolis, Sophia Antipolis Cedex, France

**Rationale:** Fibered confocal fluorescence microscopy (FCFM) is a new technique that produces microscopic imaging of a living tissue through a 1-mm fiberoptic probe that can be introduced into the working channel of the bronchoscope.

**Objectives:** To analyze the microscopic autofluorescence structure of normal and pathologic bronchial mucosae using FCFM during bronchoscopy.

**Methods:** Bronchial FCFM and spectral analyses were performed at 488-nm excitation wavelength on two bronchial specimens *ex vivo* and in 29 individuals at high risk for lung cancer *in vivo*. Biopsies of *in vivo* FCFM-imaged areas were performed using autofluorescence bronchoscopy.

**Results:** *Ex vivo* and *in vivo* microscopic and spectral analyses showed that the FCFM signal mainly originates from the elastin component of the basement membrane zone. Five distinct reproducible microscopic patterns were recognized in the normal areas from the trachea down to the more distal respiratory bronchi. In areas of the proximal airways not previously biopsied, one of these patterns was found in 30 of 30 normal epithelia, whereas alterations of the autofluorescence microstructure were observed in 19 of 22 metaplastic or dysplastic samples, five of five carcinomas *in situ*, and two of two invasive lesions. Disorganization of the fibered network could be found on 9 of 27 preinvasive lesions, compatible with early disruptions of the basement membrane zone. FCFM alterations were also observed in a tracheobronchomegaly syndrome and in a sarcoidosis case.

**Conclusions:** Endoscopic FCFM represents a minimally invasive method to study specific basement membrane alterations associated with premalignant bronchial lesions *in vivo*. The technique may also be useful to study the bronchial wall remodeling in nonmalignant chronic bronchial diseases.

## AT A GLANCE COMMENTARY

### Scientific Knowledge on the Subject

Fibered confocal fluorescence microscopy is a new technique that can be used during a bronchoscopy to analyze the nature of the bronchial mucosa fluorescence microstructure.

### What This Study Adds to the Field

Alterations in the fluorescence structure of the bronchial basement membrane zone are frequently found in individuals at high risk for lung cancer.

cell hyperplasia to different grades of epithelial dysplasia and carcinoma *in situ* (CIS) (1), with evidence of cumulative molecular alterations from one stage to the other (2), and a variable spontaneous evolution over time (3). *In vitro* studies have shown that these preinvasive changes are associated with early modifications of the underlying matrix, both at the biochemical (4) and histopathologic (5) levels. The bronchial epithelium also appears to be an active participant in tissue remodeling of the reticular basement membrane, especially in different bronchial inflammatory conditions such as chronic obstructive pulmonary disease and asthma (6).

Until now, assessment of these early changes relied primarily

## A Pilot Study of the Feasibility of Confocal Endomicroscopy for Examination of the Human Airway

Ali I. Musani, MD,\* Michael Sims, MD,\* Candice Sareli, MBBCh,\*  
William Russell, RT,\* Wendy J. McLaren, PhD,† Peter M. Delaney, BSc(Hons),†  
Leslie A. Litzky, MD,‡ and Reynold A. Panettieri, Jr, MD\*

**Background:** Traditional methods of evaluating human airway histology, such as surgical biopsy or endobronchial biopsy, are limited by the risks associated with these tissue-sampling procedures.

**Objective:** The purpose of this study was to develop and evaluate the first confocal endomicroscope for real-time, in vivo imaging of human respiratory mucosa in a clinical setting.

**Methods:** A confocal endomicroscope prototype was designed using Pentax bronchoscope parts (EB1970K). Airways of adult patients ( $N = 5$ ) undergoing rigid bronchoscopy for various clinical indications were imaged with the confocal endomicroscope after intravenous administration of fluorescein sodium. The device was introduced into the airways through the rigid bronchoscope. Images were collected from the trachea, primary and secondary carinae, and any endobronchial mass. The images were compared with those obtained from histologic sections from conventional endobronchial biopsies.

**Results:** Confocal endomicroscopy provided real-time images of the cellular and subcellular structures of the respiratory mucosa and submucosa in vivo. The pseudo-stratified columnar epithelium (including columnar cells and goblet cells) could be visualized. Images obtained at increasing depth showed the lamina propria and micro-

vasculature. Longitudinal folds in the mucosa enabled imaging in cross-section, showing alignment of epithelial cells along the basement membrane and cilia on the surface of the cells. Below the epithelium, the smooth muscle could be identified. In images from a patient with an endobronchial adenocarcinoma, confocal imaging could distinguish between a normal airway epithelium and malignant tissue.

**Conclusions:** Confocal endomicroscopy is a feasible method for analyzing human airway wall architecture and endobronchial abnormalities in histologic detail in vivo.

**Key Words:** confocal endomicroscope, airway remodeling, endobronchial biopsy, rigid bronchoscopy, epithelium, goblet cells, microvasculature, adenocarcinoma

(*J Bronchol Intervent Pulmonol* 2010;17:126–130)

Currently, few techniques exist to study changes in tissue morphology in airway diseases such as asthma, chronic obstructive pulmonary disease, bronchiectasis, and endobronchial malignancy. Studies of airway remodeling in experimental animal models of asthma and chronic obstructive pulmonary disease<sup>1</sup> are often constrained by the need to kill the animals to obtain sufficient tissue for study. Studies of human airway tissue morphology are limited to surgical explants



# Bronchoscopic Fibered Confocal Fluorescence Microscopy Image Characteristics and Pathologic Correlations

Joshua J. Filner, MD, MPH,\* Eric J. Bonura, MD,† Stephanie T. Lau, MD,‡  
Khader K. Abounasr, MD,† David Naidich, MD,† Rodolfo C. Morice, MD,‡  
George A. Eapen, MD,‡ Carlos A. Jimenez, MD,‡ Roberto F. Casal, MD,‡  
and David Ost, MD, MPH‡

**Background:** Fibered confocal fluorescence microscopy (FCFM) is a new imaging modality in bronchoscopy. The purpose of this study was to assess FCFM reliability, interpretation, and to make image-pathologic correlations.

**Methods:** Twenty-six patients underwent FCFM. A validation set was used to determine image characteristics and interobserver reliability. Each patient underwent bronchoscopy using a standardized protocol. The images were evaluated by 4 observers based on brightness, fiber thickness, and alveolar cellularity. Image characteristics showing good interobserver agreement were tested to see if they were related to smoking status. Subsequently, 18 consecutive patients underwent FCFM and biopsy to correlate images with pathology. The blinded reviewers were asked to distinguish between controls and patients with pathologically proven disease.

**Results:** Interobserver agreement for image brightness, as measured by intraclass correlation coefficients (ICCs), ranged from 0.48 to 0.92 ( $P < 0.001$ ) and varied by location. ICCs for image brightness were high, ranging from 0.53 to 0.99 ( $P < 0.001$ ). Agreement for fiber thickness was poor for respiratory bronchioles (ICC 0.12,  $P < 0.05$ ) and fair for alveoli (ICC range, 0.37 to 0.42,  $P < 0.001$ ). The intraobserver (ICC range,

0.69 to 0.91,  $P < 0.001$ ) and inpatient (ICC 0.65 to 0.84,  $P < 0.001$ ) reliability were excellent. Computer image interpretation showed excellent agreement with humans (ICC 0.62 to 0.99,  $P < 0.001$ ). Smoking was inversely associated with respiratory bronchiole brightness ( $P < 0.001$ ). In FCFM-pathologic correlation, FCFM could distinguish normal from diseased tissue; however, specific diseases could not be distinguished from other diseases.

**Conclusion:** FCFM shows a high degree of image reliability and can detect changes in the respiratory bronchioles because of smoking and other diseases, but whether it can discriminate among diseases requires additional study.

**Key Words:** bronchoscopy, diagnostic imaging, image interpretation, computer assisted, microscopy, confocal, tomography, optical coherence

(*J Bronchol Intervent Pulmonol* 2011;18:23–30)

Fibered confocal fluorescence microscopy (FCFM) is a new technique, which can be used to image the microscopic structure of lung tissue in real time.<sup>1</sup> Fibered confocal microscopy provides a clear, in-focus image of a thin section within a biological sample. However, instead of using a microscope's objective lens, a flexible fiberoptic

Time for a change?

Which is better?

- "Even though the technologies are very attractive and pilot data are extremely encouraging, more studies establishing selection criteria and best utility are needed"

THANK YOU