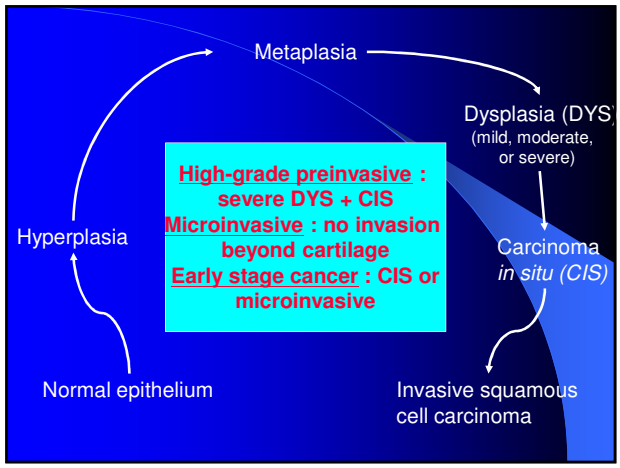
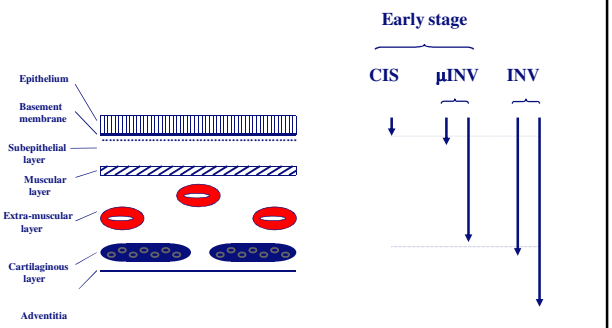
Longkankerscreening : is er een rol voor bronchoscopie?

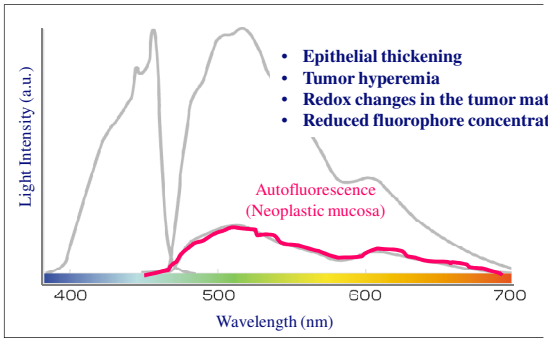
Vincent Ninane
Chest Service, Saint-Pierre Hospital, Brussels



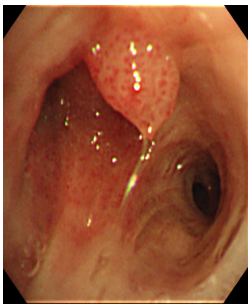
Indication : detection of "pre" or "early" malignant lesions



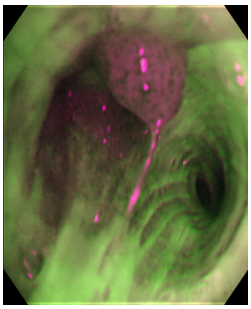
Decrease in autofluorescence of « pre » and « early » malignant lesio



White Light Image



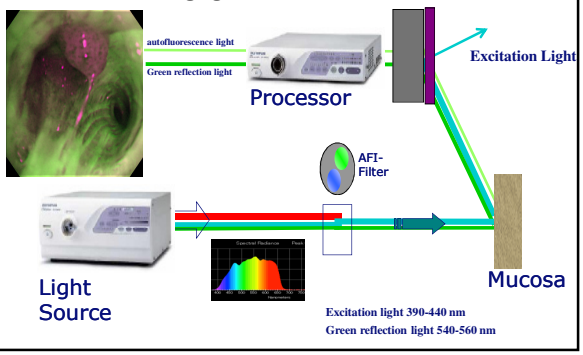
Autofluorescence Image



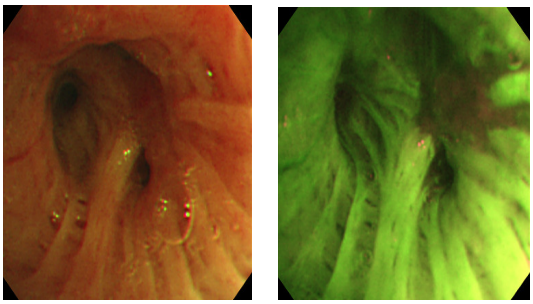
Bronchoscopic devices

- **Light Induced Fluorescence Endoscopy** (LIFE, Xillix Technologies Corp., Vancouver, BC)
  - 2 light sources including a low-energy helium-cadmium laser
  - **Onco-LIFE** (1 mercury arc lamp)
- **System D-Light AF** (Storz, Tuttlingen, Germany)
  - 1 xenon light source
- **DAFE system** (Wolf, Knittlingen, Germany)
  - 1 xenon light source
- **Safe 1000 System** (Pentax, Tokyo, Japan)
  - 1 xenon light source ⟹ **Safe 3000**

Autofluorescence Imaging

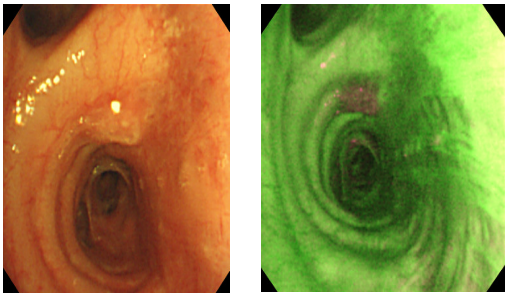


Hypertrophic "early" malignant lesion : white-light and AFI



CIS at the level of the right upper lobe

Hypertrophic "early" malignant lesion : white-light and AFI



Invasive SCC at the level of right intermediate bronchus

Autofluorescence bronchoscopy (AFB) detection of moderate DYS or worse

	No. Biopsies	Sensitivity %			Relative sensitivity, AFB+WLB /WLB
		WLB	AFB	WLB +AFB	
Lam 1998	700	25	NR	67	2.68
Kurie 1998	234	NR	38	NR	NR
Venmans 1998	139	78	89	100	1.28
Vermylen 1999	172	25	NR	93	3.75
Shibuya 2001	212	69	91	NR	NR
Hirsch 2001	391	18	73	79	4.4
Haüβinger 2005	1531 (AFB) /1376 (WLB)	58		83	1.42

WLB : white light bronchoscopy; NR : not reported

Meta-analysis AFB moderate DYS or worse

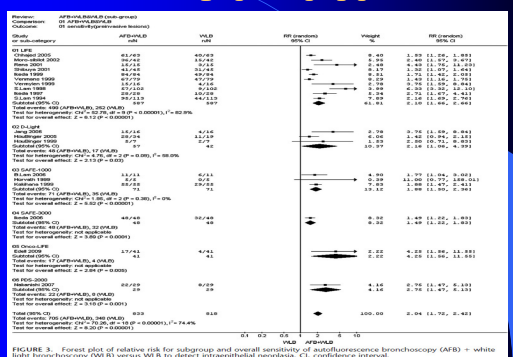


FIGURE 3. Forest plot of relative risk for subgroup and overall sensitivity of autofluorescence bronchoscopy (AFB) + white light bronchoscopy (WLB) versus WLB to detect intraepithelial neoplasia. CI, confidence interval.

Sun J et al. J Thorac Oncol. 2011;6: 1336–1344

Limitations

- low specificity and positive predictive value (13 to 76%)
- sensitivity of AFB compared to WLB is "relative" (gold standard?)
- Improvement of sensitivity by AFB
  - low for high grade dysplasia and CIS

Lung cancer screening

14 detected cancers/561 volunteers

AFB after automated quantitative image cytometry in 378 smokers (≥ 50 yrs, ≥ 30 pack/years)

	Sputum atypia	Normal sputum	Total
Diagnostic CT scan	9	1	10
Diagnostic AFB	4	0	4
Total	13	1	14

Sputum AQC improves the detection rate from 1.8 to 3.1%

McWilliams et al. AJRCCM 2003;168:1167

Screening using AFB : no place

- Prevalence of „isolated“ pre-/early malignant lesions is low
- Clinical relevance of pre-/early malignant lesions is not always clear
- Reduction of mortality?
- Cost effectiveness

Detection using AFB

- Positive cytology
  - –Sputum, aspiration
- Detection of synchronous/metachronous lesions

Sputum cytology

AFB in patients with sputum cytology suspicious or positive for malignancy

AFB group

64 patients
preinvasive lesions
- –45
- –40.6% of the patients

Control group (WLB)

48 patients
preinvasive lesions
- –7
- –12.5% of the patients

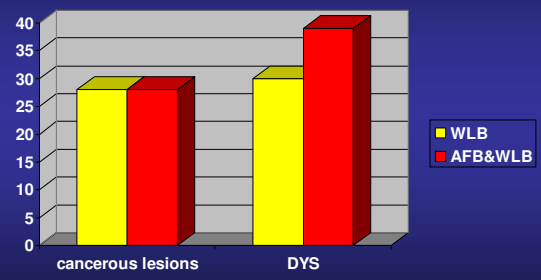
Shibuya. Lung Cancer 2001;32:19-25

AFB in patients with positive sputum cytology

- 50 patients in population-based lung cancer mass screening from 11/97 to 04/99
  - –17 suspected-positive sputum cytology
  - –33 positive cytology
- WLB followed by AFB
  - –123 biopsies including
    - **•28 cancerous lesions**
    - **•39 dysplasias**
  - –multiple lesions in 21 of the 50 patients

Sato et al. Lung Cancer 2001;32:247-253

Distribution of abnormal epithelia in the 50 patients



WLB vs WLB&AFB sensitivity: 85 vs 94% (p=0.078)

Sato et al. Lung Cancer 2001;32:247-253

AFB in patients with atypical or suspicious cells in sputum or bronchial aspirate

- **Atypical cells** (abnormal nuclear features but not suspected of being malignant) or **suspicious cells** (severe nuclear abnormalities but malignancy not ascertained)
- **Normal chest X-ray and WLB results**
- **62 patients (february 2002-october 2004) : 91 lesions in 45 patients; 8 patients with moderate DYS or worse**
- **AFB more sensitive than WLB (91 vs 58%)**

TABLE 2 Histopathological biopsy specimen results according to white-light (WLB) and autofluorescence bronchoscopic (AFB) appearance

	Normal	Metaplasia	Dysplasia			CIS	Invasive cancer	Other	Total
			Mild	Moderate	Severe				
AFB	25	6	5	2	3				41
WLB	14	3	2	1					20
AFB+WLB	10	3	3	2	1	2	1	1[#]	23
Total	49	12	10	5	4	2	1	1[#]	84

CIS: carcinoma *in situ*. [#]: endobronchial tuberculosis in this patient.

Lam et al. Eur Respir J 2006; 28:915

AFB in patients with moderate sputum atypia

- Current or former smokers ≥ 30 pack-years + airflow obstruction + moderate atypia sputum cytology + normal chest X-ray
- **79 subjects**
  - –5 : LC (3 invasive and 2 *CIS)*
  - –7 : severe DYS

Kennedy et al. Lung Cancer 2005;49:187-91

Video prior to AFB (LIFE) in patients with moderate dysplasia or worse on sputum

- 151 patients at high risk of LC + moderate dysplasia or worse on sputum cytology mass screening
- 83 out of 343 biopsies showed moderate DYS or worse
  - –Sensitivity of VB vs LIFE : 72 vs 96%
  - –Specificity of VB vs LIFE : 53 vs 23%

Chhajed et al. Eur Respir J 2005;25:951-5

Memorial SK and J Hopkins lung projects

- no control group (single vs dual screen group) ; no additional benefit from the addition of **sputum cytology** (every 4 months) to annual **chest X-ray**

ACCP 2007 : "We recommend against the use of single or serial sputum cytologic evaluation to screen for the presence of lung cancer" Grade of recommendation, 1A

Flehinger et al. Am Rev Respir Dis 1984;130:555, Frost et al. Am Rev Respir Dis 1984;130:549

Nuclear image analysis

- Stochiometrical staining of nuclei (Feulgen reaction) followed by image acquisition and digitisation of the chromatin pattern with determination of **M**alignant **A**ssociated **C**hanges
- *Marek et al. Eur Respir J 2001;18:942-950*
  - –radon- and uranium-exposed workers
  - –**Automated sputum cytometry** (ASC)
  - –correlations with conventional cytology and final diagnosis

	ASC	ASC + Cytology
sensitivity (%)	75 (15/20)	80 (16/20)
specificity (%)	89.8 (520/579)	89.7 (523/581)

25

14 detected cancers/561 volunteers

AFB after automated quantitative image cytometry in 378 smokers (≥ 50 yrs, ≥ 30 pack/years)

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Sputum AQC improves the detection rate from 1.8 to 3.1%

McWilliams et al. AJRCCM 2003;168:1167

26

AFB results after automated quantitative image cytometry

	Sputum atypia	*Normal sputum*
Subjects	309	69
Mild DYS	41%	30%
Moderate DYS	5%	1.5%
Severe DYS	0.7%	0%
CIS	1.3%	0%

McWilliams et al. AJRCCM 2003;168:1167

27

known/previous lung cancer
(synchronous/metachronous)

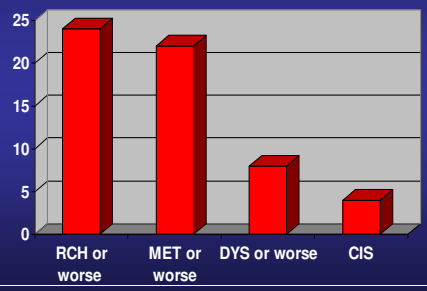
28

Synchronous
-Roentgenographically visible cancer before sugery
-Roentgenographically occult lung cancer

29

Before surgery : distribution of abnormal epithelia in 43 patients

Prospective evaluation of 43 consecutive patients (with 44 resectable LC) AFB before surgery in the same hospital; no abnormalities during initial diagnostic/staging white-light bronchoscopy



Pierard et al. Chest 2000;117:779-785

30

AFB before surgery

–3/34 patients (8.8%)

van Rens et al. Lung Cancer 2001;32:13

Roentgenographically occult lung cancer (ROLC)

- Positive sputum cytology but not detected by chest X-ray or CT scan
- Most often TIS or T1 and N0, usually **squamous cell carcinoma** in the proximal airways
- **20% (18/90) of cancers** diagnosed in the prevalence screen of the NCI-Mayo Lung Project
- **Improved outcome** : in a series of 51 patients, 86% were stage 0 or I and 5 years actuarial survival is 55% (10-15% for radiologically positive)
- **May fail to be detected** during conventional white-light bronchoscopy (subtle changes)
  - –70% of CIS *(Woolner et al. Mayo Clin Proc 1984)*
- Use of systematic brushings or washings in case of negative conventional bronchoscopy

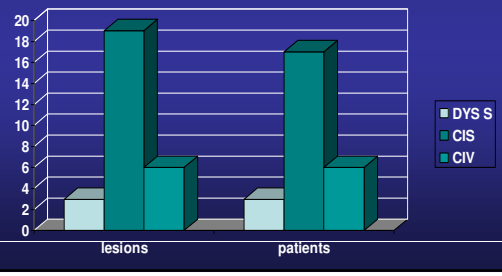
ROLC

	Nb of patients	Synchro-nicity (%)	Metachro-nicity (%/yr)
Martini 1980	47	14.9	
Cortese 1983	54	7	
Woolner 1984	54	7	5
Saito 1992	94	7	5
Usuda 1993	98	7	

Synchronous ROLC in patients with ROLC

01/1996 → 12/2001, 28 patients referred with ROLC (26 males, mean age 65 ± 11 y.
2 patients excluded because of metaplasia only)

28 lesions in 26 patients



Synchronous ROLC in patients with ROLC

- AFB in the 26 patients
  - –6 additional significant lesions in six patients
  - – **2 DYS S, 3 CIS, 1 CIV**
- 2 patients / 26 had 3 synchronous significant lesions (2 of them disclosed during previous WLB)
- **prevalence of synchronous lesions**
  - –initially : 7 % (2/26)
  - –**after AFB : 23 % (6/26)**

Pierard et al. Lung Cancer 2004;46:341-7

Synchronous/Metachronous

AFB compared with WLB

Table 1 Overall prevalence of patients with preinvasive lesions and stratified into risk groups

Risk groups*	Arm	% (n)	RR (95% CI) p value
Overall	WLB+AFB (n = 589)	5.1% (30)	1.86* (1.03 to 3.38)
	WLB (n = 584)	2.7% (16)	p = 0.037**
I	WLB+AFB (n = 178)	6.7% (12)	1.36 (0.59 to 3.14)
	WLB (n = 181)	5.0% (9)	p = 0.473
II	WLB+AFB (n = 328)	4.6% (15)	2.45 (0.96 to 6.25)
	WLB (n = 322)	1.9% (6)	p = 0.051
III	WLB+AFB (n = 27)	11.1% (3)	2.78 (0.31 to 24.99)
	WLB (n = 25)	4.0% (1)	p = 0.336
IV	WLB+AFB (n = 56)	0% (0)	
	WLB (n = 56)	0% (0)	

Absolute (n) and relative frequencies (%), relative risks (RR), and 95% confidence intervals (95% CI) are given. *Common relative risk adjusted for risk groups, Breslow-Day test for homogeneity of the odds ratio, $\chi^2 = 0.99$; df = 2, p = 0.62. **Cochran-Mantel-Haenszel test statistic.

I : known bronchogenic carcinoma; F-up after surgical resection
III : abnormal cytological findings; normal radiograph

Häussinger et al. Thorax 2005; 60: 496-503

Occupational and non occupational factors associated with high-grade preinvasive lesions detected during AFB

- 241 subjects; prevalence severe dysplasia/CIS : **21/241 (9%)**
- significant and independent association between the presence of severe dysplasia/CIS and
  - **–current smoking, relative to former smokers**
  - **–synchronous invasive lung cancers (prevalence SD/CIS : 8/24, 33%) (cancer at the moment or in the previous year)**
  - **–duration of asbestos exposure**
  - **–exposure to other occupational carcinogens** (silica, polycyclic aromatic hydrocarbons, nickel and chrome salts…)

Paris et al. Eur Respir J 2003;21:332-341

Metachronous

AFB in 244 symptomatic smokers or patients treated for lung or HN cancers

- 92 low-grade lesions, 42 preneoplastic lesions (moderate dys to CIS) and 39 invasive carcinomas

	Preneoplastic lesions	Invasive carcinoma
Smokers with symptoms (n=136)	2 (1.5%)	20 (15%)
Previous resected lung cancer (n=79; 9 to 39 months)	10 (13%)	5 (6%)
Follow-up HN cancer (n=29)	0 (0%)	4 (14%)

- **Factors +**
  - –current smokers : number pack/years and duration former smokers : history of epidermoid carcinoma
  - –previous resected Squamous CC

  (No effect of age, gender, age at smoking initiation)

Moro-Sibilot D et al. Chest 2002;122:1902-8

AFB for lung cancer surveillance

- 402 patients registering at Roswell Park Cancer Institute
  - –207 eligible for the study
  - –at least **two** of the following risk factors: (1) >20 pack year history of tobacco use, (2) asbestos-related lung disease on the chest radiograph, (3) chronic obstructive pulmonary and (4) prior aerodigestive cancer, with no evidence of disease for 2 years
- AFB and low-dose SCT scan of the chest without contrast, and a sputum sample
- 186 have been enrolled with 169 (50 with prior cancers, 29%) completing the surveillance procedure
- Thirteen lung cancers (7%) were detected in the 169 subjects
  - **–AFB : 3 CIS + 2 cancers (3%)**
  - –66% of patients had squamous metaplasia or worse
  - –Conventional sputum cytology missed 100% of the dysplasias and 68% of the metaplasias detected by AFB, and failed to detect any cases of carcinoma or carcinoma-in-situ
  - –Seven of 13 lung cancers (58%) were stage Ia or less, including three patients with squamous cell carcinoma

Loewen et al. Thorax 2007;62:335–340

Metachronous cancers detected by AFB

–After lung cancer resection : 3/51 patients (6%) at a median of 13 months after surgery *(Weigel et al. Ann Thorac Surg 2001;71:967)*

–After lung cancer resection versus after radiotherapy (± chemotherapy), free of cancer after 2 years : 0/13 patients treated with surgery versus 1 CIS/13 pateints treated with radiotherapy (Means-Markwell et al. Clin Cancer Res 2003;9:5915-21)

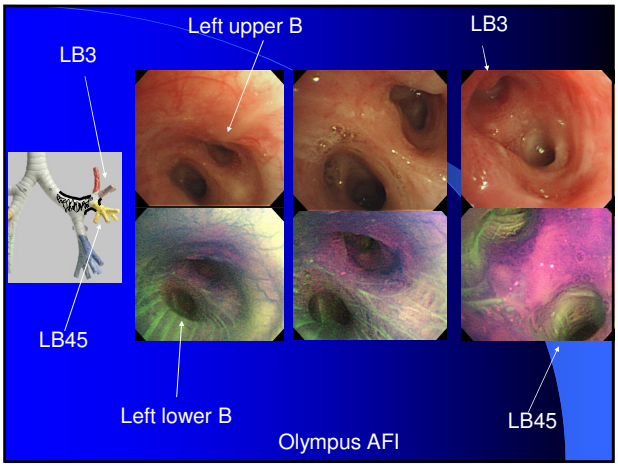
ACCP recommandations for AFB use

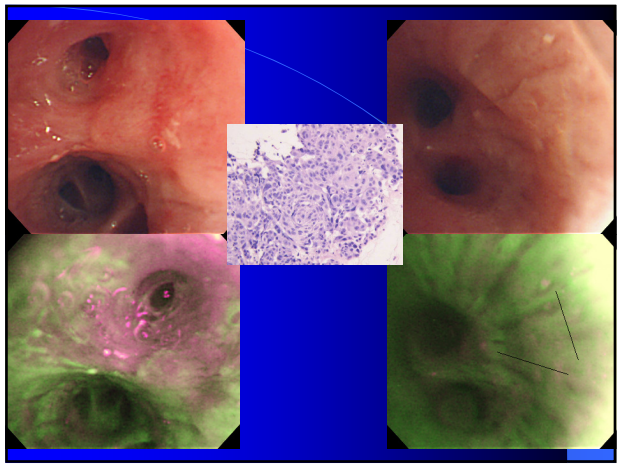
- Positive sputum cytology, negative chest imaging (grade 1B)
- Guidance to treat CIS in curative aim (grade 2C)
- Follow up known dysplasia and CIS (grade 2C)
- Recommandation against AFB use for surveillance after curative intent therapy

ROLC staging with AFB

- Better assessment of **tumor dimension** with impact on therapeutic strategy

Sutedja et al. Chest 2001;120:1327





AFB : my view

- AFB should be used in patients with positive /suspicious sputum cytology
- AFB should be used in pretreatment evaluation of ROLC (synchronous lesions/surgery vs localized therapeutical modality) and follow-up (recurrence/metachronous lesions)
- AFB should be used in all patients at risk who undergo a bronchoscopy
  - Additional lesions
  - Should be incorporated in all routine bronchoscopes

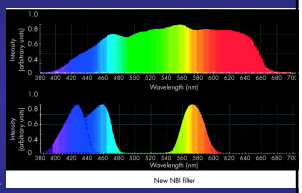
Narrow band imaging

- enables visualization of vascular networks
- increased vessel growth and occurence of tortuous vessels as early event during carcinogenesis

Narrow Band Imaging

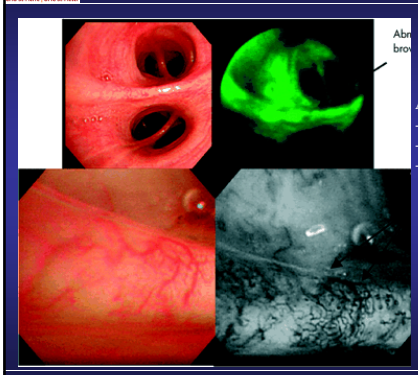
Conventional filter with large band

Filters with narrow bands
390-445 nm : blue light; absorbed by superficial capillaries
530-550 nm : green light, absorbed by blood vessels below the mucosal capillaries



Shibuya et al. Thorax 2003;58,989-995

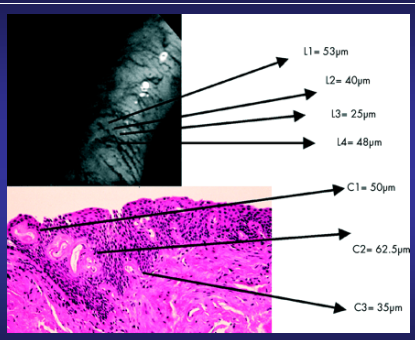
Narrow band imaging



Abnormal vessels
-Dotted
-Tortuous
-Abrupt-ending vessels with large caliber

Shibuya et al. Thorax 2003;58,989-995

Narrow band imaging



Shibuya et al. Thorax 2003;58,989-995

NBI vs WLB

- Pilot study
- Prospective
- 22 patients with known or suspected bronchial dysplasia or malignancy
- WLB followed by NBI
  - –Biopsies of all abnormal area (NBI : blood vessel concentration or appearance) + control area

Vincent et al. Chest 2007:131:1794-99

NBI vs WLB

- Results
  - –NBI abnormal with WLB normal : one malignant and four dysplastic lesion (23% of the subjects)
  - –WLB abnormal : NBI did not increase the yield
  - –Increased rate of detection of dysplasia and malignancies was significant (p=0.005)

Vincent et al. Chest 2007;131:1794-99

WLB followed by NBI-AFI

- Prospective study
- Primary aim : value of NBI to AFI and WLB
- Order of AFI vs NBI randomized
- 62 patients
  - –Airway screening or surveillance
- Grading of airway mucosa : normal, abnormal, suspicious, tumor
- Biopsies of all abnormal area (no control biopsy)

Herth et al. J Thoracic Oncol 2009;4:1060-1065

WLB followed by NBI-AFI

TABLE 1. Visual Classification of Endobronchial Findings[1,11,16,17]

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.

Herth et al. J Thoracic Oncol 2009;4:1060-1065

WLB followed by NBI-AFI

TABLE 3. Sensitivity, Relative Sensitivity, Specificity, and Relative Specificity of Detecting Lesions That Were Graded as Moderate to Severe Dysplasia and CIS (Per-Patient Analysis)

	WLB	AFI	WLB + AFI	NBI	WLB + NBI	AFI + NBI	WLB + NBI + AF
Number of patients with dysplasia (moderate to severe) and CIS identified as bronchoscopically positive (n = 17)	3	11	11	9	9	12	12
Sensitivity (CI)	0.18 (0–0.78)	0.65 (0.39–0.90)	0.65 (0.39–0.90)	0.53 (0.26–0.80)	0.53 (0.39–0.90)	0.71 (0.41–1.00)	0.71 (0.41–1.00)
Relative sensitivity	1.0	3.7	3.7	3.0	3.0	4.0	4.0
Number of patients with metaplasia and mild dysplasia identified as bronchoscopically negative (n = 40)	35	16	14	36	31	16	14
Specificity (CI)	0.88 (0.76–1.00)	0.4 (0.24–0.56)	0.35 (0.06–0.64)	0.90 (0.80–1.00)	0.78 (0.62–0.94)	0.40 (0.13–0.67)	0.35 (0.06–0.64)
Relative specificity	1.0	0.5	0.4	1.0	0.9	0.5	0.4

WLB, white light videobronchoscopy; AFI, autofluorescence imaging; NBI, narrow band imaging; CIS, carcinoma in situ; CI, confidence interval.

Herth et al. J Thoracic Oncol 2009;4:1060-1065

NBI : conclusions

- ???

Other techniques

- Confocal fluorescence microscopy
  - –Enhances resolution, cellular structure by fluorescence
- Optical coherence tomography
  - –Offers visualizing of cellular structures by reflectance of infrared light

will be used to target suspicious areas

→ optical biopsy

→ improve specificity, reduce number of control biopsies

Conclusions

- Lung cancer mass screening : no place for bronchoscopy
- AFB/NBI allow to detect abnormal airway lesions
- AFB : positive sputum cytology, staging and surveillance of high grade preneoplastic lesions and early stage cancers