Longkankerscreening : is er een rol voor bronchoscopie?

Vincent Ninane
Chest Service, Saint-Pierre Hospital, Brussels
Hyperplasia → Normal epithelium → Metaplasia → Dysplasia (DYS) (mild, moderate, or severe) → Carcinoma in situ (CIS) → Invasive squamous cell carcinoma

- High-grade preinvasive: severe DYS + CIS
- Microinvasive: no invasion beyond cartilage
- Early stage cancer: CIS or microinvasive
Indication: detection of “pre” or “early” malignant lesions

Early stage

- CIS
- μINV
- INV

Layers:
- Epithelium
- Basement membrane
- Subepithelial layer
- Muscular layer
- Extra-muscular layer
- Cartilaginous layer
- Adventitia
Decrease in autofluorescence of «pre» and «early» malignant lesions:

- Epithelial thickening
- Tumor hyperemia
- Redox changes in the tumor matrix
- Reduced fluorophore concentration
Olympus booth lectures – ERS 2006, Munich

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

Monochromatic CCD + barrier filter

Processor

Light Source

Excitation Light

Mucosa

Excitation light 390-440 nm
Green reflection light 540-560 nm
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

<table>
<thead>
<tr>
<th></th>
<th>No. Biopsies</th>
<th>Sensitivity %</th>
<th>Relative sensitivity, AFB+WLB/WLB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WLB</td>
<td>AFB</td>
<td>WLB +AFB</td>
</tr>
<tr>
<td>Lam 1998</td>
<td>700</td>
<td>25</td>
<td>NR</td>
</tr>
<tr>
<td>Kurie 1998</td>
<td>234</td>
<td>NR</td>
<td>38</td>
</tr>
<tr>
<td>Venmans 1998</td>
<td>139</td>
<td>78</td>
<td>89</td>
</tr>
<tr>
<td>Vermylen 1999</td>
<td>172</td>
<td>25</td>
<td>NR</td>
</tr>
<tr>
<td>Shibuya 2001</td>
<td>212</td>
<td>69</td>
<td>91</td>
</tr>
<tr>
<td>Hirsch 2001</td>
<td>391</td>
<td>18</td>
<td>73</td>
</tr>
<tr>
<td>Haüßinger 2005</td>
<td>1531 (AFB)/1376 (WLB)</td>
<td>58</td>
<td>83</td>
</tr>
</tbody>
</table>

WLB: white light bronchoscopy; NR: not reported
Meta-analysis AFB moderate DYS or worse

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)

<table>
<thead>
<tr>
<th></th>
<th>Sputum atypia</th>
<th>Normal sputum</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic CT scan</td>
<td>9</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Diagnostic AFB</td>
<td>4</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>1</td>
<td>14</td>
</tr>
</tbody>
</table>

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
  - 45 patients
  - 40.6% of the patients

- **Control group (WLB)**
  - 48 patients
  - 7 patients
  - 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)

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

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Metaplasia</th>
<th>Dysplasia</th>
<th>CIS</th>
<th>Invasive cancer</th>
<th>Other</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFB</td>
<td>25</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td></td>
<td>41</td>
</tr>
<tr>
<td>WLB</td>
<td>14</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>AFB-WLB</td>
<td>10</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>49</td>
<td>12</td>
<td>10</td>
<td>5</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

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

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%

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

Nuclear image analysis

- Stochiometrical staining of nuclei (Feulgen reaction) followed by image acquisition and digitisation of the chromatin pattern with determination of Malignant Associated Changes

  - radon- and uranium-exposed workers
  - Automated sputum cytometry (ASC)
  - correlations with conventional cytology and final diagnosis

<table>
<thead>
<tr>
<th></th>
<th>ASC</th>
<th>ASC + Cytology</th>
</tr>
</thead>
<tbody>
<tr>
<td>sensitivity (%)</td>
<td>75 (15/20)</td>
<td>80 (16/20)</td>
</tr>
<tr>
<td>specificity (%)</td>
<td>89.8 (520/579)</td>
<td>89.7 (523/581)</td>
</tr>
</tbody>
</table>
14 detected cancers/561 volunteers

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

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</tr>
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<td>14</td>
</tr>
</tbody>
</table>

Sputum AQC improves the detection rate from 1.8 to 3.1%

*McWilliams et al. AJRCCM 2003;168:1167*
### AFB results after automated quantitative image cytometry

<table>
<thead>
<tr>
<th></th>
<th>Sputum atypia</th>
<th>Normal sputum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects</strong></td>
<td>309</td>
<td>69</td>
</tr>
<tr>
<td><strong>Mild DYS</strong></td>
<td>41%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Moderate DYS</strong></td>
<td>5%</td>
<td>1.5%</td>
</tr>
<tr>
<td><strong>Severe DYS</strong></td>
<td>0.7%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>CIS</strong></td>
<td>1.3%</td>
<td>0%</td>
</tr>
</tbody>
</table>

McWilliams et al. AJRCCM 2003;168:1167
known/previous lung cancer
(synchronous/metachronous)
Synchronous

- Roentgenographically visible cancer before surgery
- Roentgenographically occult lung cancer
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

AFB before surgery

- 3/34 patients (8.8%)
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
<table>
<thead>
<tr>
<th></th>
<th>Nb of patients</th>
<th>Synchronicity (%)</th>
<th>Metachronicity (%/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martini 1980</td>
<td>47</td>
<td>14.9</td>
<td></td>
</tr>
<tr>
<td>Cortese 1983</td>
<td>54</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Woolner 1984</td>
<td>54</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Saito 1992</td>
<td>94</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Usuda 1993</td>
<td>98</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>
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)

Synchronous/Metachronous
### Table 1: Overall prevalence of patients with preinvasive lesions and stratified into risk groups

<table>
<thead>
<tr>
<th>Risk groups*</th>
<th>Arm</th>
<th>% (n)</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>WLB+AFB (n = 589)</td>
<td>5.1% (30)</td>
<td>1.86* (1.03 to 3.38)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WLB (n = 584)</td>
<td>2.7% (16)</td>
<td>p = 0.037**</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>WLB+AFB (n = 178)</td>
<td>6.7% (12)</td>
<td>1.36 (0.59 to 3.14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WLB (n = 181)</td>
<td>5.0% (9)</td>
<td>p = 0.475</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>WLB+AFB (n = 328)</td>
<td>4.6% (15)</td>
<td>2.45 (0.96 to 6.25)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WLB (n = 322)</td>
<td>1.9% (6)</td>
<td>p = 0.051</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>WLB+AFB (n = 27)</td>
<td>11.1% (3)</td>
<td>2.78 (0.31 to 24.99)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WLB (n = 25)</td>
<td>4.0% (1)</td>
<td>p = 0.336</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>WLB+AFB (n = 56)</td>
<td>0% (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>WLB (n = 56)</td>
<td>0% (0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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...)

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

<table>
<thead>
<tr>
<th>Preneoplastic lesions</th>
<th>Invasive carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers with symptoms (n=136)</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Previous resected lung cancer (n=79; 9 to 39 months)</td>
<td>10 (13%)</td>
</tr>
<tr>
<td>Follow-up HN cancer (n=29)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

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)
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 disease, 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 in situ
  - Seven of 13 lung cancers (58%) were stage Ia or less, including three patients with squamous cell carcinoma

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)

ACCP recommendations 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)
- Recommendation against AFB use for surveillance after curative intent therapy
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 occurrence of tortuous vessels as early event during carcinogenesis
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

• 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)

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)

WLB followed by NBI-AFI

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

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

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

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