Longkankerscreening: is er een rol voor bronchoscopie?

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

Decrease in autofluorescence of "pre" and "early" malignant lesions:
- Epithelial thickening
- Tumor hyperemia
- Redox changes in the tumor matrix
- Reduced fluorophore concentration

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
- Excitation Light
- Processor
- Mucosa
- Light Source
- 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>Ref.</th>
<th>No. Biopsies</th>
<th>Sensitivity %</th>
<th>Relative sensitivity, AFB/WLB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lam 1998</td>
<td>700</td>
<td>25</td>
<td>NR</td>
</tr>
<tr>
<td>Kurie</td>
<td>234</td>
<td>NR</td>
<td>36</td>
</tr>
<tr>
<td>Vennmans 1999</td>
<td>139</td>
<td>78</td>
<td>89</td>
</tr>
<tr>
<td>J. 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>Haßlinger 2005</td>
<td>1521 (AFB) 1376 (WLB)</td>
<td>58</td>
<td>83</td>
</tr>
</tbody>
</table>

WLB: white light bronchoscopy; NR: not reported

**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

**Meta-analysis AFB moderate DYS or worse**

Lung cancer screening

14 detected cancers/561 volunteers

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>Diagnostic AFB</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>1</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

AFB in patients with sputum cytology suspicious or positive for malignancy

<table>
<thead>
<tr>
<th>AFB group</th>
<th>Control group (WLB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>64 patients preinvasive lesions –45</td>
<td>48 patients preinvasive lesions –7</td>
</tr>
<tr>
<td>–40.6% of the patients</td>
<td>–12.5% of the patients</td>
</tr>
</tbody>
</table>

Shibuya. Lung Cancer 2001;32:19-25
19. 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


20. Distribution of abnormal epithelia in the 50 patients

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

21. 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%)

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

22. 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


23. 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%


24. 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, IA

Nuclear Image analysis

- Stochiometrical staining of nuclei (Feulgen reaction) followed by image acquisition and digitisation of the chromatin pattern with determination of Malignant Associations
- 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>
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</table>

AFB after automated quantitative image cytometry

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<td>Diagnostic AFB</td>
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Sputum AQC improves the detection rate from 1.8 to 3.1%

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>Subjects</td>
<td>309</td>
<td>69</td>
</tr>
<tr>
<td>Mild DYS</td>
<td>41%</td>
<td>30%</td>
</tr>
<tr>
<td>Moderate DYS</td>
<td>5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Severe DYS</td>
<td>0.7%</td>
<td>0%</td>
</tr>
<tr>
<td>CIS</td>
<td>1.3%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

Known/previous lung cancer (synchronous/metachronous)

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%)

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

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td>Cortese 1983</td>
<td>54</td>
<td>7</td>
</tr>
<tr>
<td>Woolner 1984</td>
<td>54</td>
<td>7</td>
</tr>
<tr>
<td>Saito 1992</td>
<td>94</td>
<td>7</td>
</tr>
<tr>
<td>Usuda 1993</td>
<td>98</td>
<td>7</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)
28 lesions in 26 patients

- 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

AFB compared with WLB

<table>
<thead>
<tr>
<th>Risk group*</th>
<th>Arm</th>
<th>% (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>5</td>
<td>6.5 (5.2)</td>
<td>0.16 (0.1 to 0.36)</td>
</tr>
<tr>
<td>I</td>
<td>5</td>
<td>7.1 (5.2)</td>
<td>0.16 (0.1 to 0.36)</td>
</tr>
<tr>
<td>II</td>
<td>5</td>
<td>4.5 (3.6)</td>
<td>0.16 (0.1 to 0.36)</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>2.9 (2.0)</td>
<td>0.16 (0.1 to 0.36)</td>
</tr>
</tbody>
</table>

*Current smoking, relative risk adjusted for risk group, smoker- vs non-smoker

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

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)


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

<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
  - 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 CT 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%)
  - 46% 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


Metachronous cancers detected by AFB

- After lung cancer resection : 3/51 patients (6%) at a median of 13 months after surgery


Metachronous

- AFB compared with WLB
- Occupational and non occupational factors associated with high-grade preinvasive lesions detected during AFB
- AFB in 244 symptomatic smokers or patients treated for lung or HN cancers
- AFB for lung cancer surveillance
- Metachronous cancers detected by AFB
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

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 occurrence 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

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


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)


WLB followed by NBI-AFI

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

**NBI: conclusions**

- ???

**Other techniques**

- Confocal fluorescence microscopy
  - Enhances resolution, cellular structure by fluorescence
  - Will be used to target suspicious areas
    - Optical biopsy
    - Improve specificity, reduce number of control biopsies

- Optical coherence tomography
  - Offers visualizing of cellular structures by reflectance of infrared light

**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