What do we know about the natural history of precancerous bronchial lesions?
Lung cancer remains the largest cause of cancer deaths worldwide. The overall 5-year survival rate is only 15%.

The majority of the lung cancers are diagnosed at late stages. The treatment outcome is suboptimal.

Diagnosis and resection of lung cancer early stage dramatically improved survival rates for resected patients compared with patients with no surgery.
Advances in endoscopic technology improved the detection of precancerous bronchial lesions associated with the occurrence of proximal squamous cell lung cancer (SCC) in high-risk individuals.
Distribution and Outcome of Preneoplastic Lesions in Bronchial Epithelium

Related or unrelated to various risk factors such as:

- smoking history
- past history of cancer
- chronic obstructive pulmonary disease.

5. Kunst P, With blue light into the depth, Annual Congress of ERS, Vienna 2009, 
Squamous cell carcinomas - progression model

from premalignant lesions to invasive cancer

basal or reserve cell hyperplasia (RCH)

↓

squamous metaplasia

↓

mild, moderate, and severe dysplasia

↓

carcinoma in situ (CIS)


“The optimal approach for management and treatment of these intraepithelial bronchial lesions has not yet been established. “

A. McWilliams, B. Lam and T. Sutedja, Early proximal lung cancer diagnosis and treatment, Eur Respir J 2009; 33: 656–665
“Little is known about the natural history of precancerous bronchial lesions.”

Carcinoma in situ appeared more frequent in patients with a prior history or concomitant cancer
Progression to Carcinoma in situ/SCC

is significantly higher for severe dysplasia, than for preneoplastic lesions showing lower-grade dysplasia

- squamous metaplasia

- mild and moderate dysplasia


The Natural Course of Preneoplastic Lesions in Bronchial Epithelium

- The 54% regression rate of all preneoplastic lesions
- 19% to 46% progression rate to CIS/SCC of individuals with severe dysplasia


The Natural Course of Preneoplastic Lesions in Bronchial Epithelium

- That low-grade epithelial lesions could be safely followed-up at 1-2 years

- Severe dysplasia should be treated if they persist at 3 months

- Immediate treatment of carcinoma *in situ*

---

Severe dysplasia

- nuclear enlargement
- hyperchromatism
- pleomorphism
- mitoses at all levels
- dyskeratosis
- sharp basal border
- loose stroma

Kunst P, With blue light into the depth, Annual Congress of ERS, Vienna 2009,
Severe dysplasia

normal mucosa

severe dysplasia

Kunst P, With blue light into the depth, Annual Congress of ERS, Vienna 2009,
Squamos metaplasia

Mild dysplasia

Moderate dysplasia

Severe dysplasia

Carcinoma in situ

Invasive carcinoma

Kunst P, With blue light into the depth, Annual Congress of ERS, Vienna 2009,

The Natural Course of Preneoplastic Lesions in Bronchial Epithelium

Clinical Cancer Research Vol. 11, 537–543, 2005

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Total Lesions</th>
<th>Median FU (months)</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous metaplasia</td>
<td>45 (29 subjects)</td>
<td>21 (range 1-72)</td>
<td>4 (9%) At: 4, 6, 7, 59 months</td>
</tr>
<tr>
<td>Mild/Moderate dysplasia</td>
<td>64 (29 subjects)</td>
<td>21 (range 3-72)</td>
<td>6 (9%) At: 7, 18, 25, 32, 37, 57 months</td>
</tr>
<tr>
<td>Severe dysplasia</td>
<td>25 (18 subjects)</td>
<td>11 (range 1-39)</td>
<td>8 (32%) At: 1, 6, 16, 17, 24, 31, 32 months</td>
</tr>
</tbody>
</table>

Progression to CIS/SCC

18/134 (13.4%) (16 subjects)
### Natural course

#### Evolution of preinvasive lesions

<table>
<thead>
<tr>
<th></th>
<th>Regression (to Normal)</th>
<th>Stabilization</th>
<th>Intraepithelial Lesion (High Grade)</th>
<th>Invasive Lesion</th>
<th>High Grade or More (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n = 36)</td>
<td></td>
<td>30</td>
<td>6 (0)</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>RCH, metaplasia (n = 152)</td>
<td></td>
<td>(56)</td>
<td>48</td>
<td>47 (2)</td>
<td>1</td>
</tr>
<tr>
<td>LGD (n = 169)</td>
<td>101 (39)</td>
<td>62</td>
<td>6</td>
<td>0</td>
<td>3.5%*</td>
</tr>
<tr>
<td>Severe dysplasia (n = 27)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Changes at 3 mo</td>
<td></td>
<td></td>
<td>(8)†</td>
<td>0</td>
<td>37%†</td>
</tr>
<tr>
<td>Changes at 24 mo or more</td>
<td></td>
<td></td>
<td>(2)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIS (n = 32)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Changes at 3 mo</td>
<td></td>
<td></td>
<td>(25)‡</td>
<td>0</td>
<td>87%‡;§</td>
</tr>
<tr>
<td>Changes at 24 mo or more§</td>
<td></td>
<td></td>
<td>(2)‡</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Definition of abbreviations: CIS = carcinoma in situ; LGD = low-grade dysplasia; RCH = reserve cell hyperplasia.

* Comparison of progression/regression rate between LGD and RCH metaplasia lesions (NS).

† Comparison of progression/regression rate between severe dysplasia and CIS lesions (p = 0.0005, Chi-square test).

‡ Severe dysplasia and CIS lesions were defined as “progressive” if they remain high-grade lesions or more or relapsed after transient regression during follow-up.

§ One patient with CIS regressive at 3 and 12 mo died at 14 mo before the next endoscopic follow-up; rate of final progression was calculated on 31 lesions.
a. Wait and see

54% regression rate of all preneoplastic lesions

Progression of severe dysplasia to invasive cancer seen in 19-46%


Autofluorescence bronchoscopy (AFB)

Use of blue light for excitation of bronchial mucosa

! High prevalence of synchronous lesions in patients with:
- severe dysplasia
- carcinoma in situ (CIS)
- occult carcinoma

A. McWilliams, B. Lam and T. Sutedja, Early proximal lung cancer diagnosis and treatment, Eur Respir J 2009; 33: 656–665
Autofluorescence bronchoscopy (AFB)

premalignant and malignant bronchial epithelium fluoresces less than normal tissue

pre-invasive tumours carcinoma in situ, dysplasia

that may have a normal appearance during conventional white-light bronchoscopy

Autoﬂuorescence bronchoscopy (AFB)

Used:

• in conjunction with usual white light bronchoscopy

• blue light to induce tissue autoﬂuorescence

Airway trauma can also cause a different mucosal appearance!

5. Kunst P, With blue light into the depth, Annual Congress of ERS, Vienna 2009,
Autofluorescence bronchoscopy (AFB)

Normal and abnormal tissues appear different colors when viewed through a specialized bronchoscope

Diagram of tissue autofluorescence

Carcinoma in situ - Left Upper Lobe carina

a) White light imaging
b) Autofluorescence
c) Dual imaging

A. McWilliams, B. Lam and T. Sutedja, Early proximal lung cancer diagnosis and treatment, Eur Respir J 2009; 33: 656–665
Bronchus intermedius – middle lobe junction

Biopsy-SCC
Anterior tracheal wall – two cartilages

Biopsy-severe displasia
Right upper lobe carina bronchial biopsy 7 days ago
Trachea - Right Main Bronchus jonction
Right pneumonectomy ? NO !

R Ulmeanu, Institutul de Pneumofiziologie “Marius Nasta”, 2009
Optical coherence tomography

**Imaging method - micron scale resolution of the epithelium**

Radial scanning of airways

Small probe via a bronchoscope - infrared light to the endobronchial tissue

Optical coherence tomography

Kunst P, With blue light into the depth, Annual Congress of ERS, Vienna 2009,
Optical coherence tomography

Detects difference between:

dysplasia - metaplasia

invasive carcinoma - carcinoma *in situ*

useful for

relatively high false positive rate of autofluorescence

Narrow band imaging

-Detection of subtle mucosal abnormalities

-Utilizes the changes seen in the microvascular network

-Uses a special narrow band filter

Confocal imaging

Fibered confocal fluorescence microscopy (FCFM)

- Microscopic imaging of a living tissue
- Through a 1-mm fiberoptic probe that can be introduced into the working channel of the bronchoscope
- Analyze the microscopic autofluorescence structure of normal and pathologic bronchial mucosae
- 488 nm laser for excitation

A. McWilliams, B. Lam and T. Sutedja, Early proximal lung cancer diagnosis and treatment, Eur Respir J 2009; 33: 656–665
Confocal imaging

Fibered confocal fluorescence microscopy (FCFM)

Kunst P, With blue light into the depth, Annual Congress of ERS, Vienna 2009,
“There has been considerable controversy regarding the invasive potential of squamous cell carcinoma in situ and the need for curative treatment.”

“Most centres treat the lesions at the time of detection rather than await the development of invasion.”

“Reported progression rates of carcinoma in situ to invasive cancer vary from 20% to 67% despite bronchoscopic therapy in some instances.”
Conclusion
The Natural Course of Preneoplastic Lesions in Bronchial Epithelium

- 54% regression rate of all preneoplastic lesions

- dysplasia 26-39% progression to carcinoma in situ

- carcinoma in situ 20 - 67% progression to invasive cancer

5. Kunst P, With blue light into the depth, Annual Congress of ERS, Vienna 2009,
Pre-invasive bronchial lesions

Treatment

Surgery

is still the gold standard

5. Kunst P, With blue light into the depth, Annual Congress of ERS, Vienna 2009,
Bronchoscopic treatment modalities

**Squamous cell carcinoma in situ**

**Microinvasive cancer of < 1 cm**

- with clearly visible distal tumour margins under AFB

- tumour invasion can be accurately excluded by EBUS

# Endobronchial treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Technique</th>
<th>Stage</th>
<th>Size cm</th>
<th>Lesions n</th>
<th>Complete response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tokyo Medical University [96, 99–102]</td>
<td>PDT (HpD/Photofrin)</td>
<td>Stage 0 (n=185) Stage 1 (n=79)</td>
<td>&lt;2</td>
<td>264</td>
<td>84.8% 93% ≤1 cm 45% &gt;1 cm</td>
</tr>
<tr>
<td>Sutedja [103]</td>
<td>PDT (Photofrin)</td>
<td>Stage 0 (n=17) Stage 1A/1B (n=22)</td>
<td>NA</td>
<td>39</td>
<td>72% Stage 0 100% Stage 1A/1B 50%</td>
</tr>
<tr>
<td>Cortese [104]</td>
<td>PDT (HpD)</td>
<td>Endobronchial</td>
<td>&lt;2</td>
<td>23</td>
<td>65% 88% ≤1 cm 33% &gt;1 cm</td>
</tr>
<tr>
<td>Kato [105]</td>
<td>PDT (NPe-6)</td>
<td>Stage 0 (n=23) Stage 1 (n=22)</td>
<td>&lt;2</td>
<td>45</td>
<td>84.6%</td>
</tr>
<tr>
<td>Usuda [106]</td>
<td>PDT (NPe-6)</td>
<td>Stage 0 (n=37) Stage 1A (n=1)</td>
<td>&lt;2</td>
<td>38</td>
<td>94% ≤1 cm 80% &gt;1 cm</td>
</tr>
<tr>
<td>Deygas [107]</td>
<td>Cryotherapy</td>
<td>Stage 0/1A</td>
<td>NA</td>
<td>41</td>
<td>91%</td>
</tr>
<tr>
<td>van Boxem [108]</td>
<td>EC</td>
<td>Stage 0 (n=2) Stage 1A (n=13)</td>
<td>≤1</td>
<td>15</td>
<td>80%</td>
</tr>
<tr>
<td>Vonk Noordegraaf [109]</td>
<td>EC/PDT/YAG laser</td>
<td>Stage 1A</td>
<td>≤1</td>
<td>32</td>
<td>97% 26 (EC) 5 (PDT) 1 (YAG)</td>
</tr>
<tr>
<td>Pérol [110]</td>
<td>HDR brachytherapy</td>
<td>Endobronchial</td>
<td>≤1</td>
<td>21</td>
<td>75%</td>
</tr>
<tr>
<td>MARSIGLIA [111]</td>
<td>HDR brachytherapy</td>
<td>Endobronchial</td>
<td>NA</td>
<td>34</td>
<td>85%</td>
</tr>
<tr>
<td>Cavaliere [112]</td>
<td>Nd:YAG laser</td>
<td>Stage 0</td>
<td>NA</td>
<td>38</td>
<td>63%</td>
</tr>
</tbody>
</table>

PDT: photodynamic therapy; HpD: hematoporphyrin derivative; NPe-6: N-aspartyl chlorin e6; EC: electrosurgery; YAG: yttrium-aluminium-garnet; HDR: high dose rate; NA: information not available. Photofrin is manufactured by Axcan Pharma, Mont-Saint-Hilaire, QC, Canada.
Endobronchial treatment

- electrocautery
- photodynamic therapy
- cryotherapy
- brachytherapy

is a good alternative especially for inoperable patients but might also be considered in operable patients

! Laser curative treatment is not recommended because of risk of perforation

Early proximal lung cancer
Algorithm – Diagnosis and treatment

Fluorescence brochoscopy (FUB)

Mild dysplasia
FU 1 Year

Moderate dysplasia
FU 6 months

Severe dysplasia
FU 3 months

Carcinoma in situ
Treatment

No dysplasia

Mild dysplasia
FU 1 year

Moderate dysplasia
FU 6 months

Severe dysplasia: Stabilisation / progression treatment