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%

<u>the majority of the lung cancers</u>

<u>are diagnosed at late stages</u>

the treatment outcome is suboptimal.

1. *American Cancer Society Guidelines for the Early Detection of Cancer, 2009*
2. *A. McWilliams, B. Lam and T. Sutedja, Early proximal lung cancer diagnosis and treatment, Eur Respir J 2009; 33: 656–665*

Diagnosis and resection of lung cancer

early stage

dramatically improved survival rates

for resected patients

compared with patients with no surgery

Field JK, Brambilla C, Hirsch FR, Hittelman W, Hogan M, Marshall D, Mulshine JL, Rabbitts P, Sutedja T, Watson A, Weiss S. Molecular Biomarkers Workshop. A European strategy for developing lung cancer molecular diagnostics in high risk populations. Lung Cancer 2001;31:339–345.

Suzana Bota, Jean-Bernard Auliac, Christophe Paris, Josette Métayer, Richard Sesboüé, Georges Nouvet, and Luc Thiberville, Follow-up of Bronchial Precancerous Lesions and Carcinoma in Situ Using Fluorescence Endoscopy, American Journal Of Respiratory And Critical Care Medicine Vol 164, 2001, p 1688-1693

Advances in endoscopic technology

improved the detection

of precancerous bronchial lesions

associated

with the occurence of

proximal squamous cell lung cancer (SCC)

in high-risk individuals

Suzana Bota, Jean-Bernard Auliac, Christophe Paris, Josette Métayer, Richard Sesboüé, Georges Nouvet, and Luc Thiberville, Follow-up of Bronchial Precancerous Lesions and Carcinoma in Situ Using Fluorescence Endoscopy, American Journal Of Respiratory And Critical Care Medicine Vol 164, 2001, p 1688-1693

Distribution and Outcome of Preneoplastic Lesions in Bronchial Epithelium

<u>Related or unrelated</u> to various risk factors such as:

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

1. *Suzana Bota, Jean-Bernard Auliac, Christophe Paris, Josette Métayer, Richard Sesboüé, Georges Nouvet, and Luc Thiberville, Follow-up of Bronchial Precancerous Lesions and Carcinoma in Situ Using Fluorescence Endoscopy, American Journal Of Respiratory And Critical Care Medicine Vol 164, 2001, p 1688-1693*
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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)

1. *Suzana Bota, Jean-Bernard Auliac, Christophe Paris, Josette Métayer, Richard Sesboüé, Georges Nouvet, and Luc Thiberville, Follow-up of Bronchial Precancerous Lesions and Carcinoma in Situ Using Fluorescence Endoscopy, American Journal Of Respiratory And Critical Care Medicine Vol 164, 2001, p 1688-1693*
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3. *American Cancer Society Guidelines for the Early Detection of Cancer, 2009*
4. *A. McWilliams, B. Lam and T. Sutedja, Early proximal lung cancer diagnosis and treatment, Eur Respir J 2009; 33: 656–665*

“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.”

Breuer R, Pasic A, Smit E, Esther van Vliet, Vonk A Noordegraaf, Elle J. Risse, Pieter E. Postmus, and Thomas G. Sutedja1 The Natural Course of Preneoplastic Lesions in Bronchial Epithelium Clinical Cancer Research Vol. 11, 537–543,2005

The Natural Course of Preneoplastic Lesions in Bronchial Epithelium

Carcinoma *in situ* appeared more frequent in patients with a prior history or concomitant cancer

1. *Suzana Bota, Jean-Bernard Auliac, Christophe Paris, Josette Métayer, Richard Sesboüé, Georges Nouvet, and Luc Thiberville, Follow-up of Bronchial Precancerous Lesions and Carcinoma in Situ Using Fluorescence Endoscopy, American Journal Of Respiratory And Critical Care Medicine Vol 164, 2001, p 1688-1693*
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3. *American Cancer Society Guidelines for the Early Detection of Cancer, 2009*
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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

1. *Suzana Bota, Jean-Bernard Auliac, Christophe Paris, Josette Métayer, Richard Sesboüé, Georges Nouvet, and Luc Thiberville, Follow-up of Bronchial Precancerous Lesions and Carcinoma in Situ Using Fluorescence Endoscopy, American Journal Of Respiratory And Critical Care Medicine Vol 164, 2001, p 1688-1693*

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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**

1. *Suzana Bota, Jean-Bernard Auliac, Christophe Paris, Josette Métayer, Richard Sesboüé, Georges Nouvet, and Luc Thiberville, Follow-up of Bronchial Precancerous Lesions and Carcinoma in Situ Using Fluorescence Endoscopy, American Journal Of Respiratory And Critical Care Medicine Vol 164, 2001, p 1688-1693*

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The Natural Course of Preneoplastic Lesions in Bronchial Epithelium

- **that low-grade epithelial lesions could be safely <u>followed-up at 1- 2 years</u>**

- **severe dysplasia should be treated if they persist at <u>3 month</u>**

- **<u>Immediate treatment</u> of carcinoma *in situ***

1. *Suzana Bota, Jean-Bernard Auliac, Christophe Paris, Josette Métayer, Richard Sesboüé, Georges Nouvet, and Luc Thiberville, Follow-up of Bronchial Precancerous Lesions and Carcinoma in Situ Using Fluorescence Endoscopy, American Journal Of Respiratory And Critical Care Medicine Vol 164, 2001, p 1688-1693*
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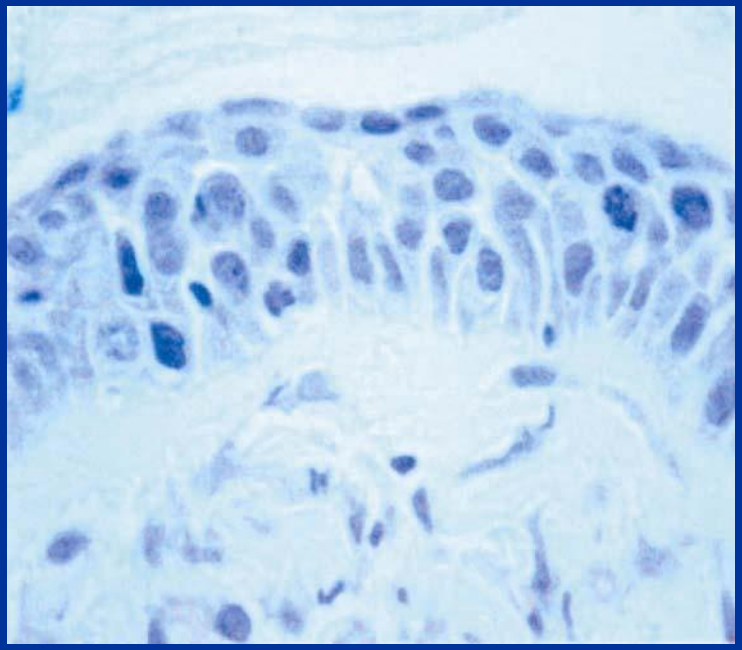
3. *American Cancer Society Guidelines for the Early Detection of Cancer, 2009*

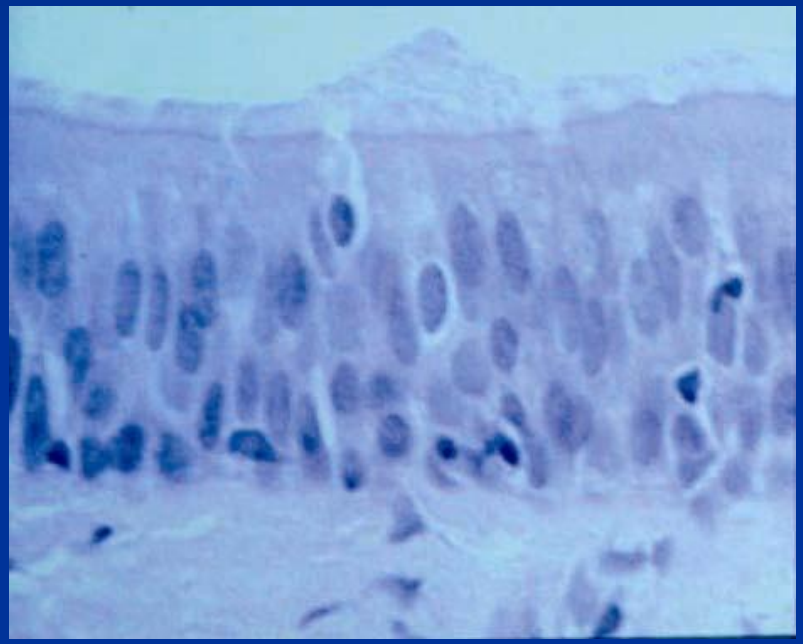
Severe dysplasia

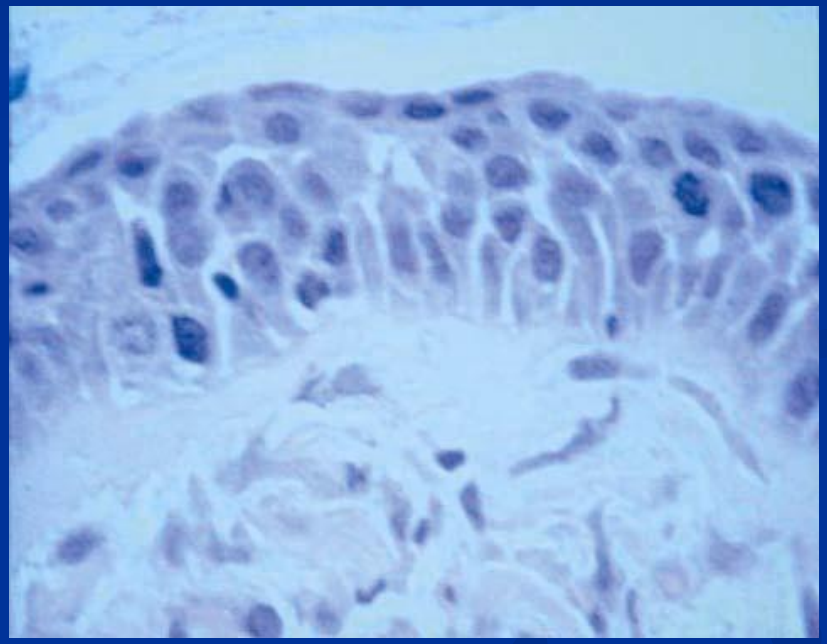


- nuclear enlargement
- hyperchromatism
- pleomorphism
- mitoses at all levels
- dyskeratosis
- sharp basal border
- loose stroma

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

Severe dysplasia

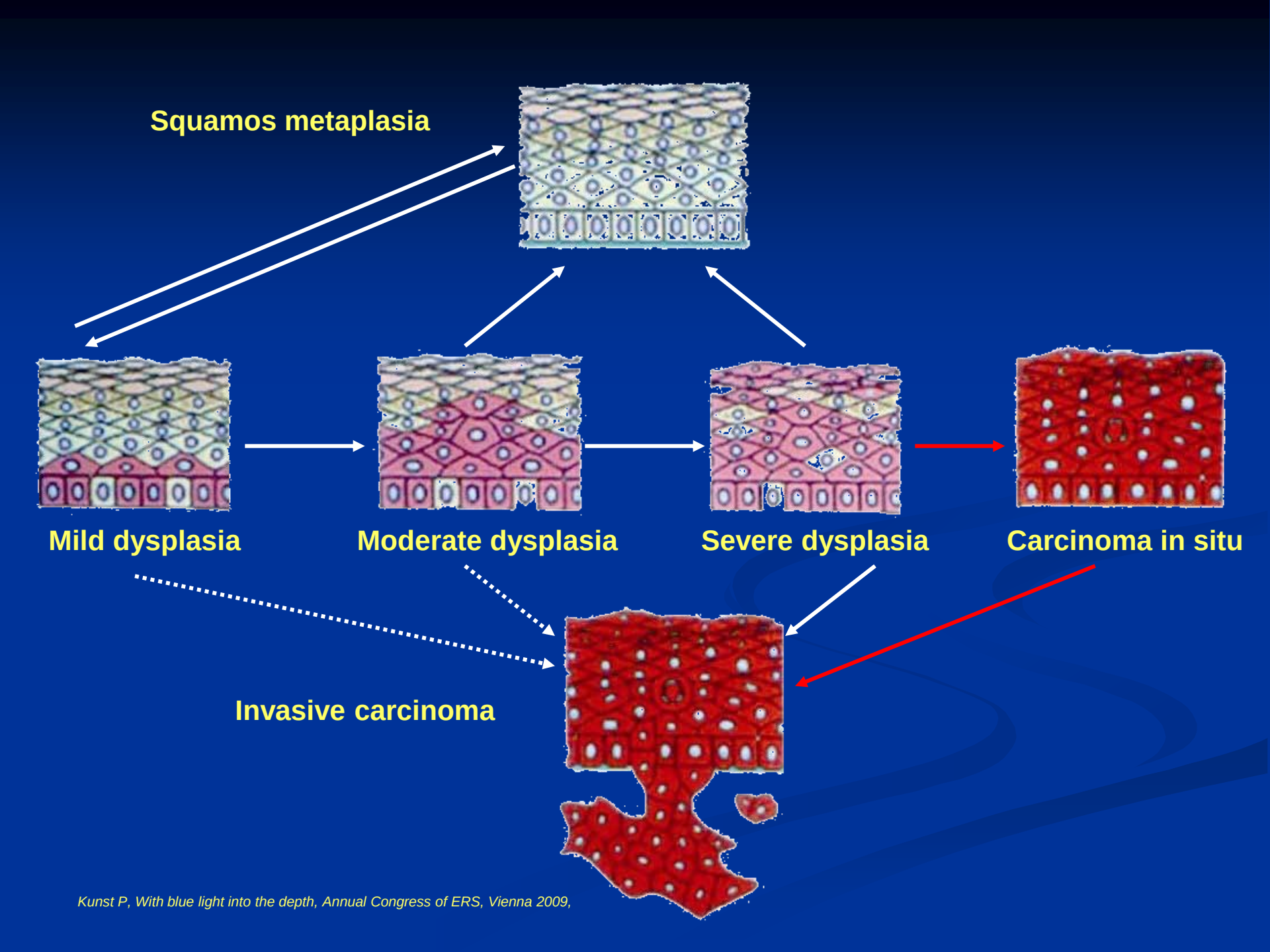




normal mucosa

severe dysplasia

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



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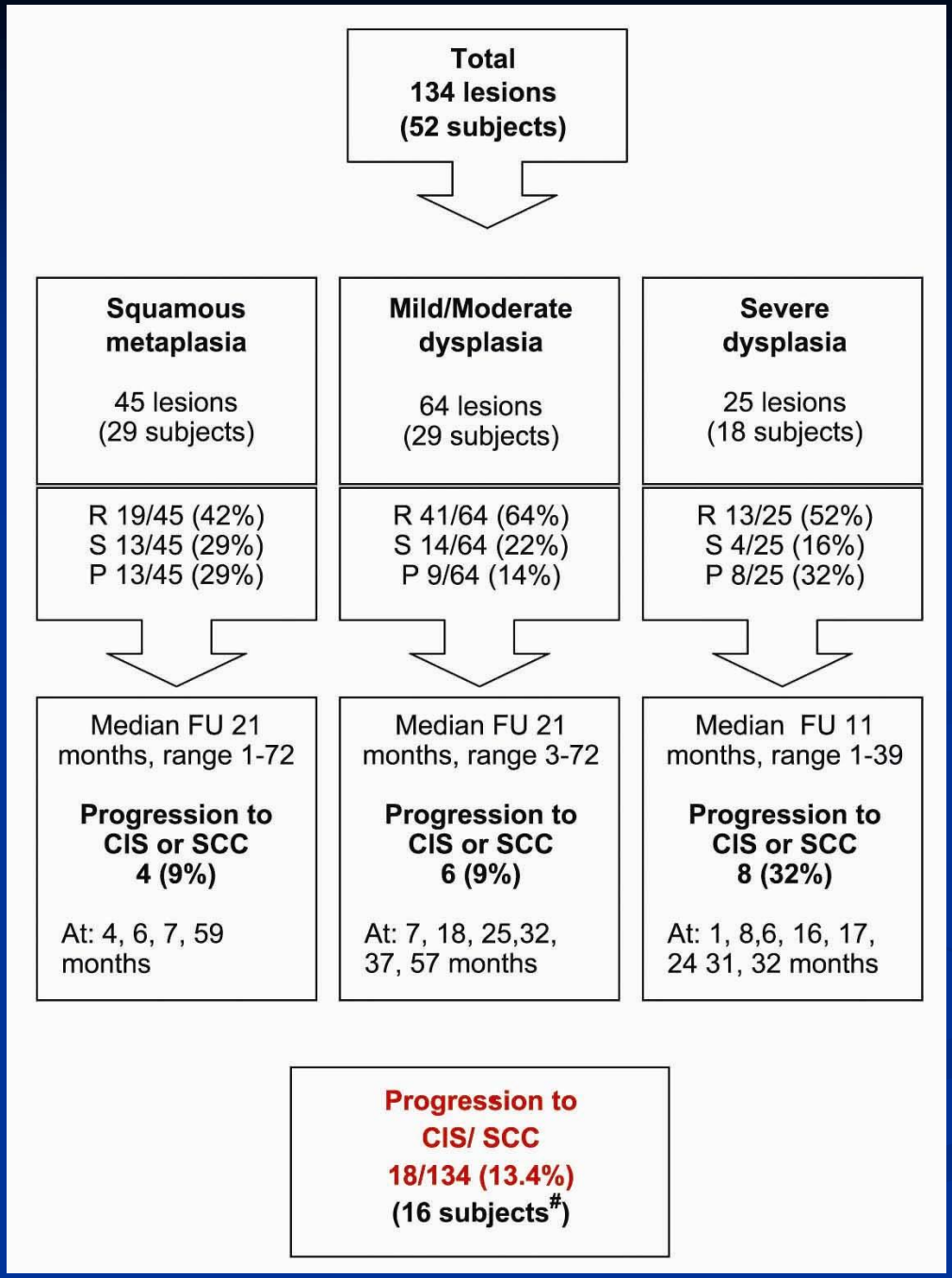

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Natural course

Evolution of preinvasive lesions

	Regression (to Normal)	Stabilization	Progression to		
			Intraepithelial Lesion (High Grade)	Invasive Lesion	High Grade or More (%)
Normal (n = 36)	—	30	6 (0)	0	0%
RCH, metaplasia (n = 152)	(56)	48	47 (2)	1	2%*
LGD (n = 169)	101 (39)	62	(6)	0	3.5%*
Severe dysplasia (n = 27)					
Changes at 3 mo	19 (5)	—	(8)‡	0	37%†
Changes at 24 mo or more	17 (11)		(2)‡	0	
CIS (n = 32)					
Changes at 3 mo	7 (5)	—	(25)‡	0	
Changes at 24 mo or more§	4 (3)		(2)‡	0	87%†,§

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.

Bota et al, 2001

a. Wait and see

54% regression rate of all preneoplastic lesions

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

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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

1. *Suzana Bota, Jean-Bernard Auliac, Christophe Paris, Josette Métayer, Richard Sesboüé, Georges Nouvet, and Luc Thiberville, Follow-up of Bronchial Precancerous Lesions and Carcinoma in Situ Using Fluorescence Endoscopy, American Journal Of Respiratory And Critical Care Medicine Vol 164, 2001, p 1688-1693*
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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 !

1. *Suzana Bota, Jean-Bernard Auliac, Christophe Paris, Josette Métayer, Richard Sesboüé, Georges Nouvet, and Luc Thiberville, Follow-up of Bronchial Precancerous Lesions and Carcinoma in Situ Using Fluorescence Endoscopy, American Journal Of Respiratory And Critical Care Medicine Vol 164, 2001, p 1688-1693*
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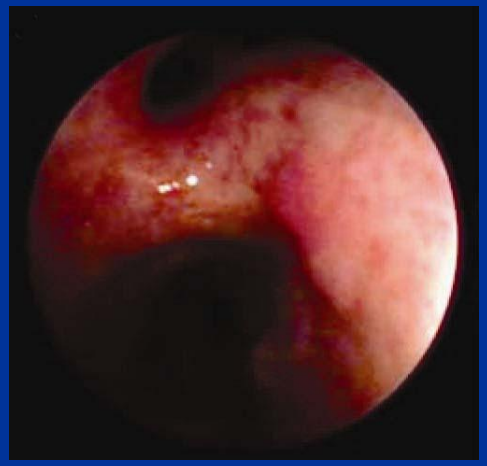
Autofluorescence bronchoscopy (AFB)

Normal and abnormal tissues appear

different colors when viewed through a

specialized bronchoscope



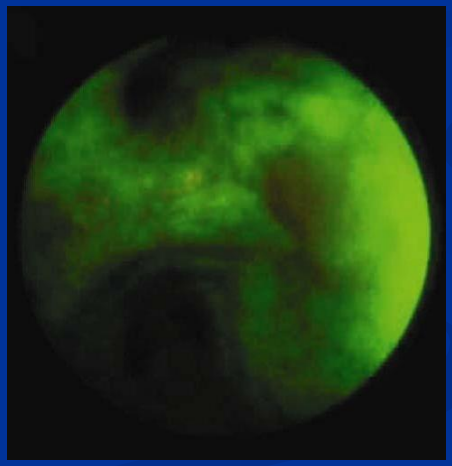


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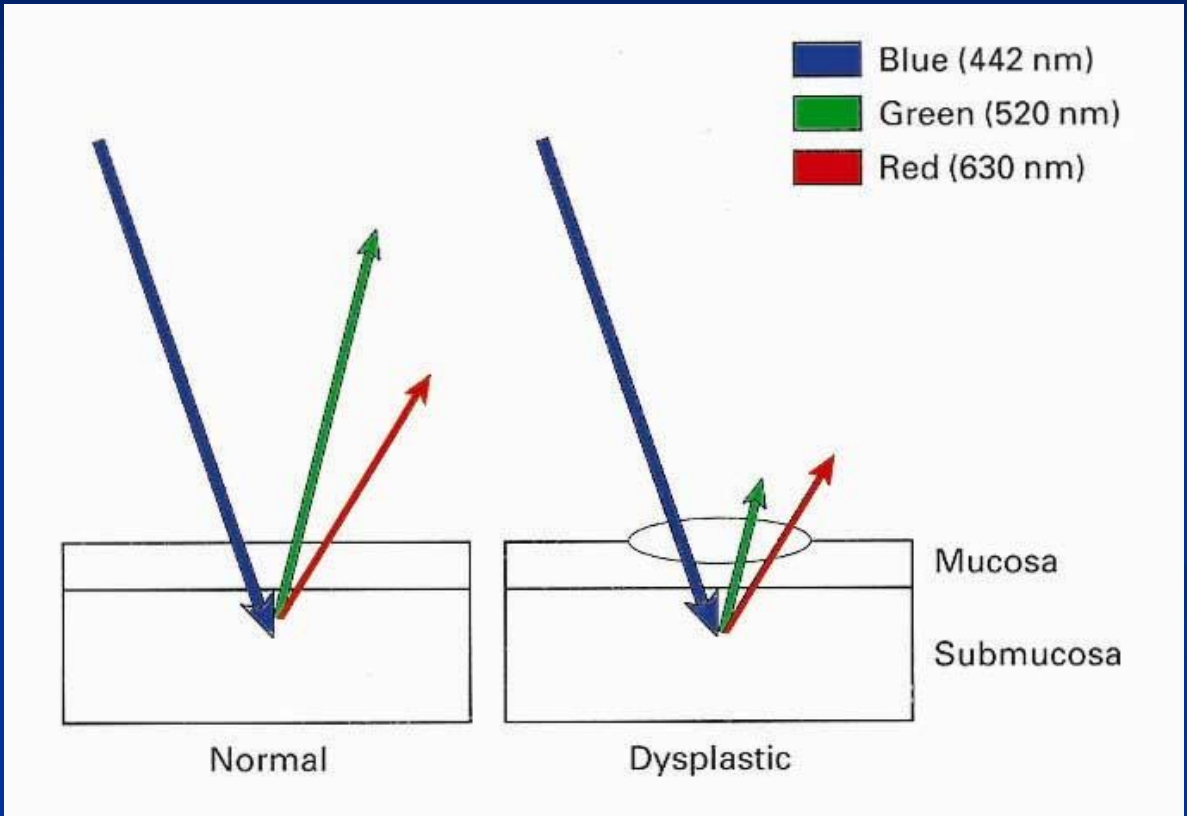
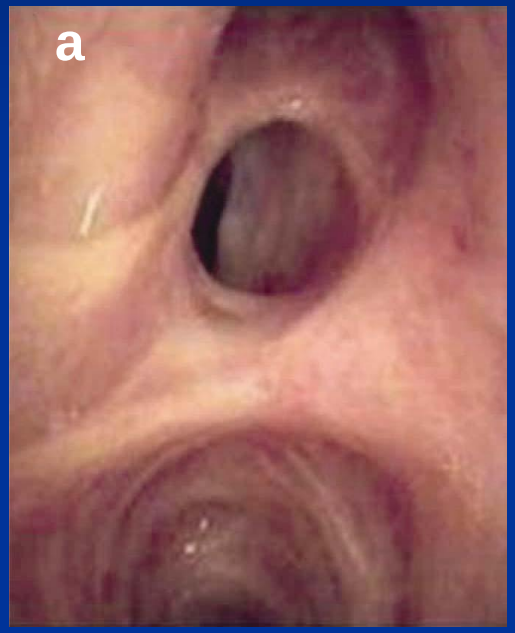
Diagram of tissue autofluorescence

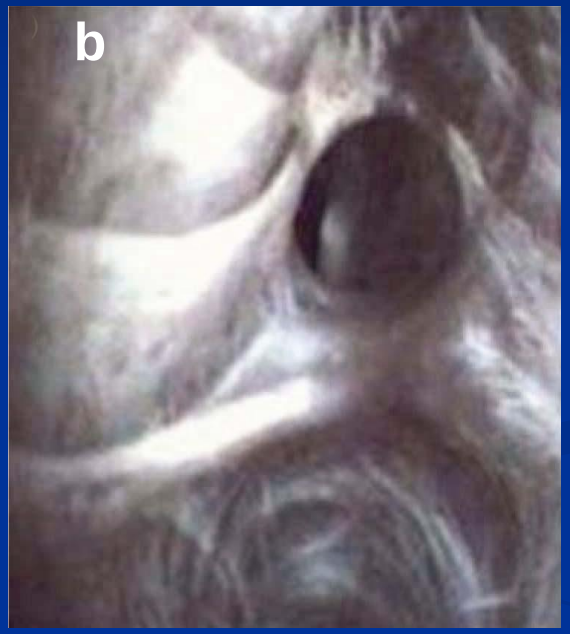


Nakhosteen J, Khanavkar B, Autoflurescence Bornchoscopy: The Laser Imaging Fluorescence Endoscope, in Bollinger CT, Mathur PN (eds): Interventional Bronchoscopy, Prog Respir Res. basel, Karger, 2000, vol 30, pp. 237

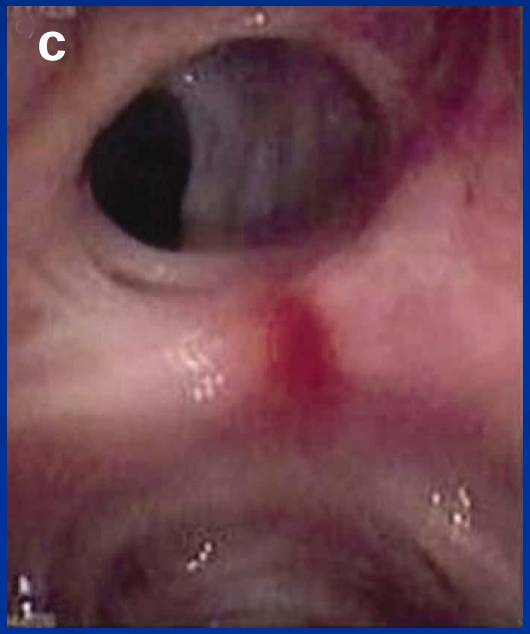
Carcinoma in situ - Left Upper Lobe carina



a) White light imaging



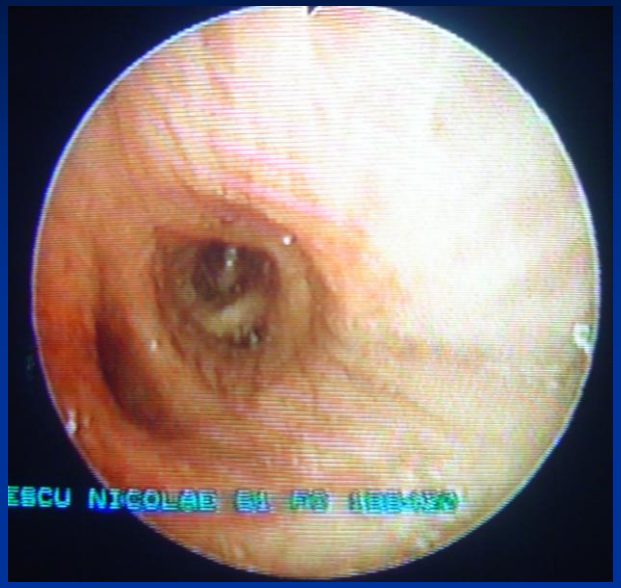
b) Autofluorescence

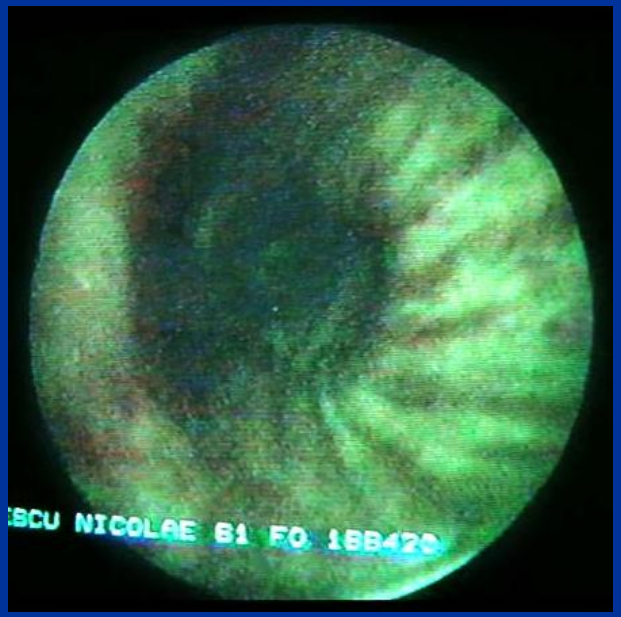


c) Dual imaging

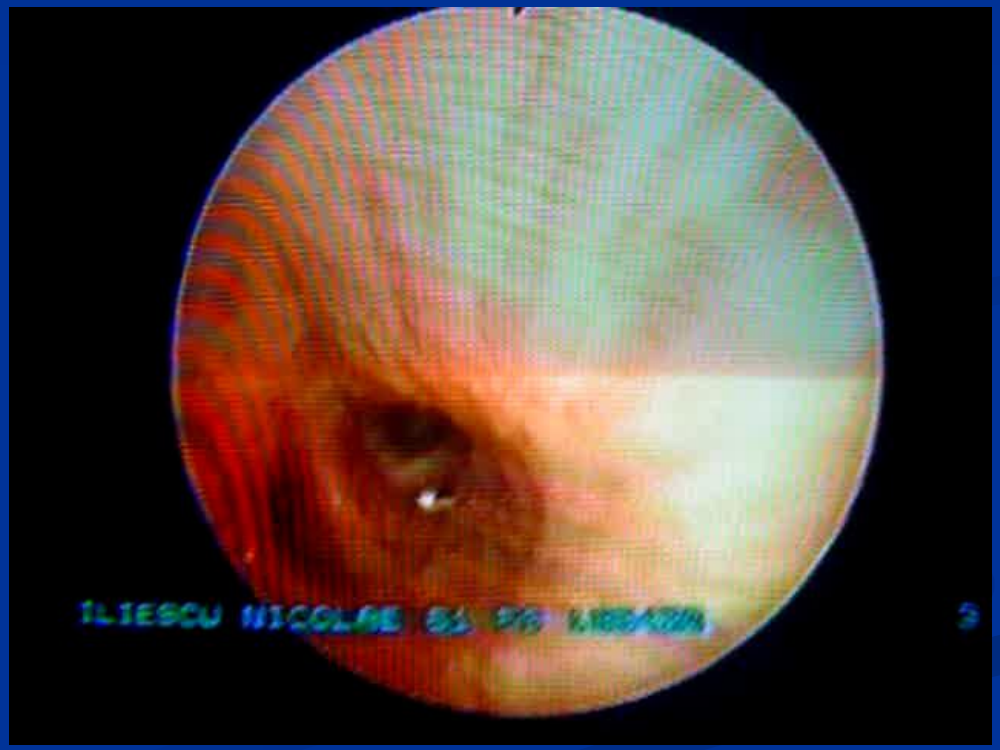
A. McWilliams, B. Lam and T. Sutedja, Early proximal lung cancer diagnosis and treatment, Eur Respir J 2009; 33: 656–665

Bronchus intermedius – middle lobe jonction



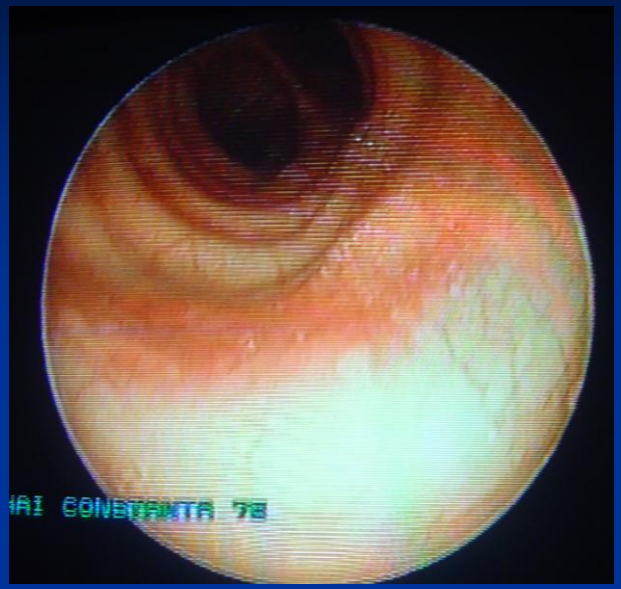


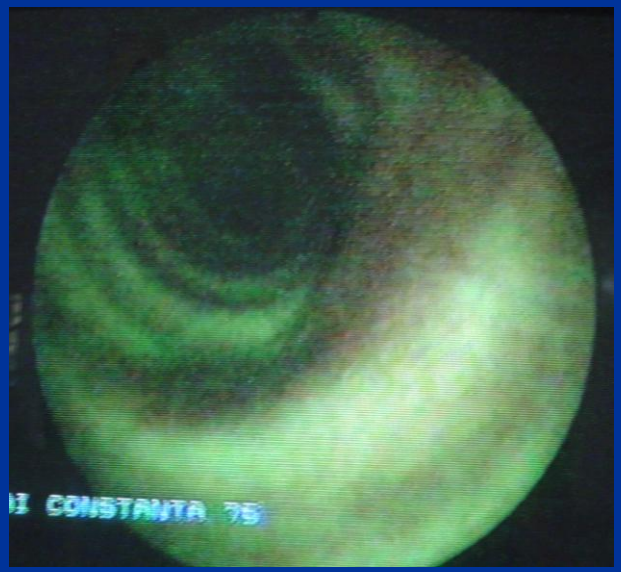
Biopsy-SCC



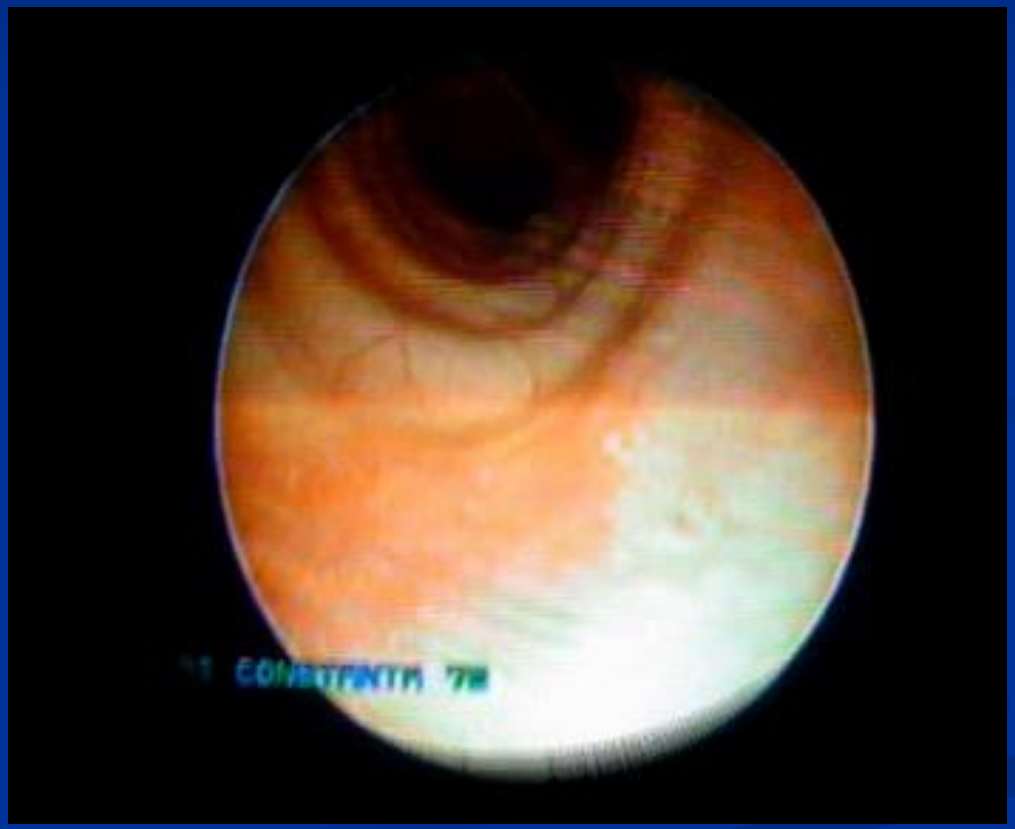
R Ulmeanu Institutul de Pnemoftiziologie "Marius Nasta", 2009

Anterior tracheal wall – two cartilages



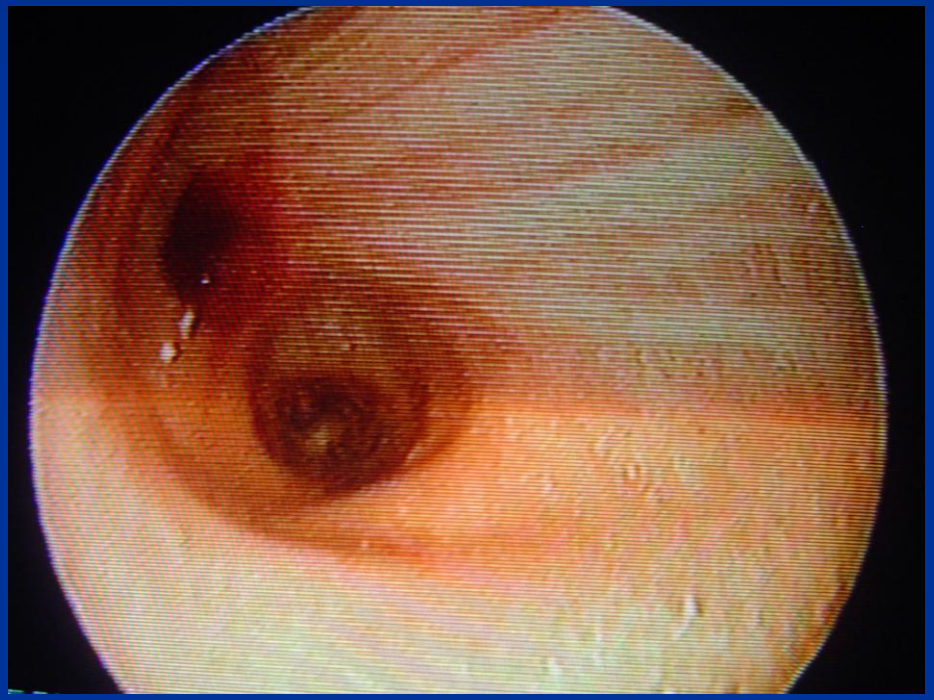


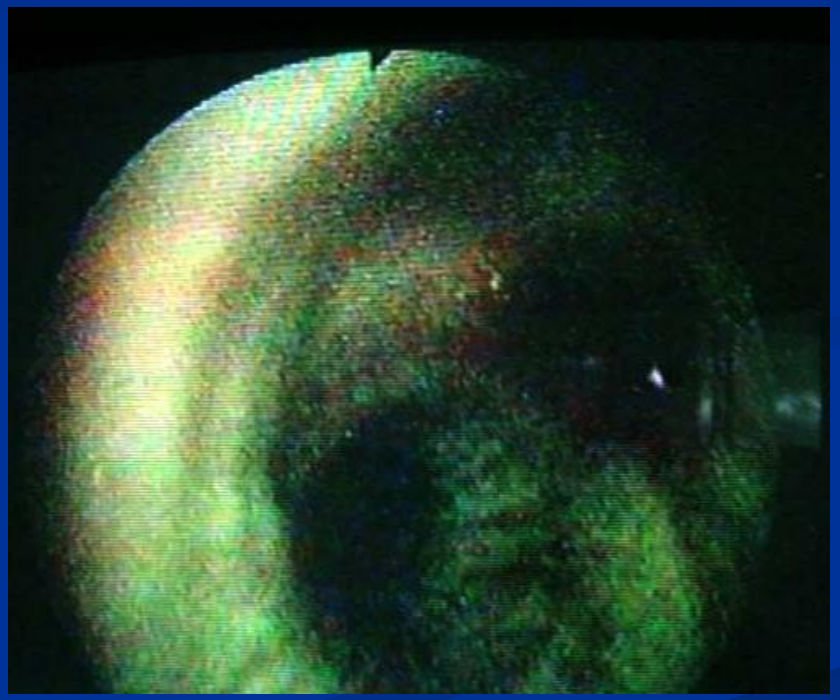
Biopsy-severe displasia



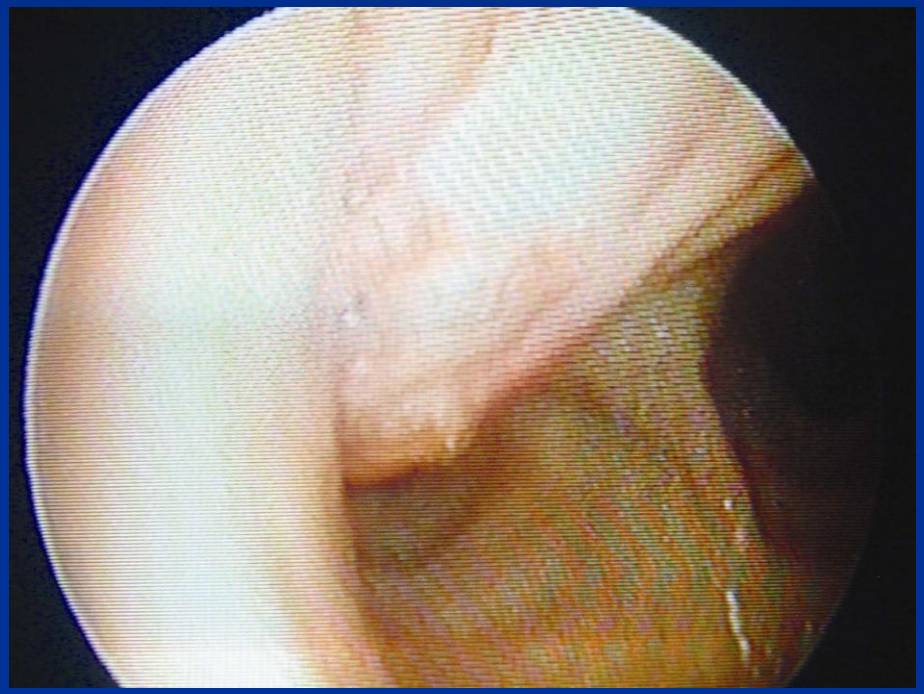
R Ulmeanu, Institutul de Pnemoftiziologie "Marius Nasta", 2009

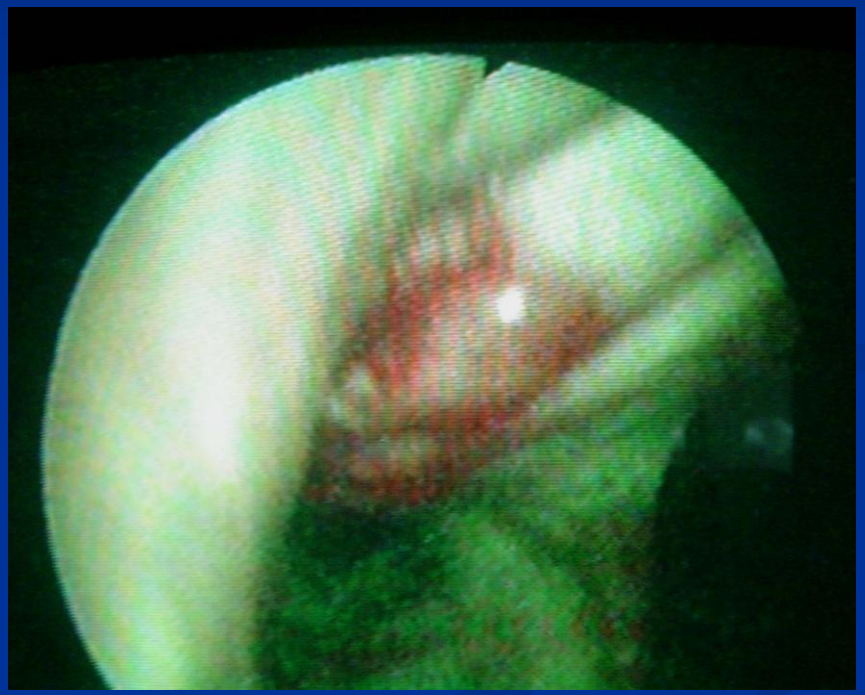
Right upper lobe carina
bronchial biopsy
7 days ago





Trachea - Right Main Bronchus jonction
Right pneumonectomy ? NO !



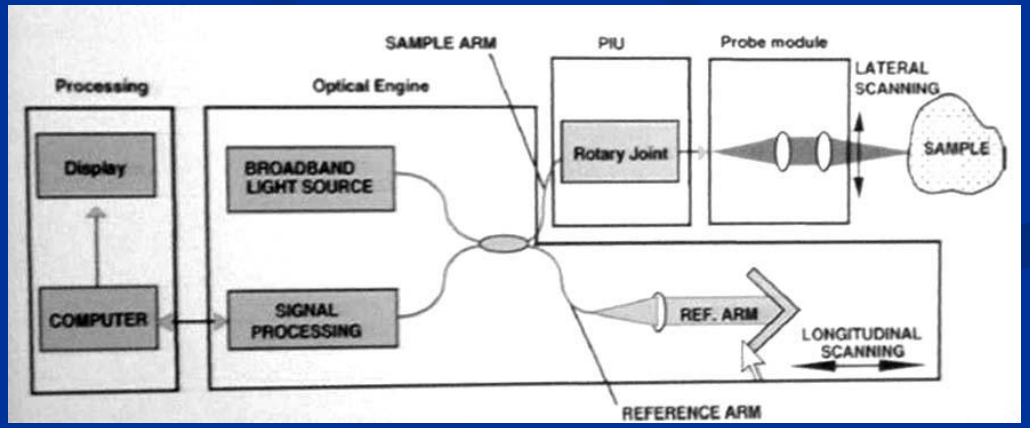


Optical coherence tomography

Imaging method - micron scale resolution of the epithelium

Radial scanning of airways

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



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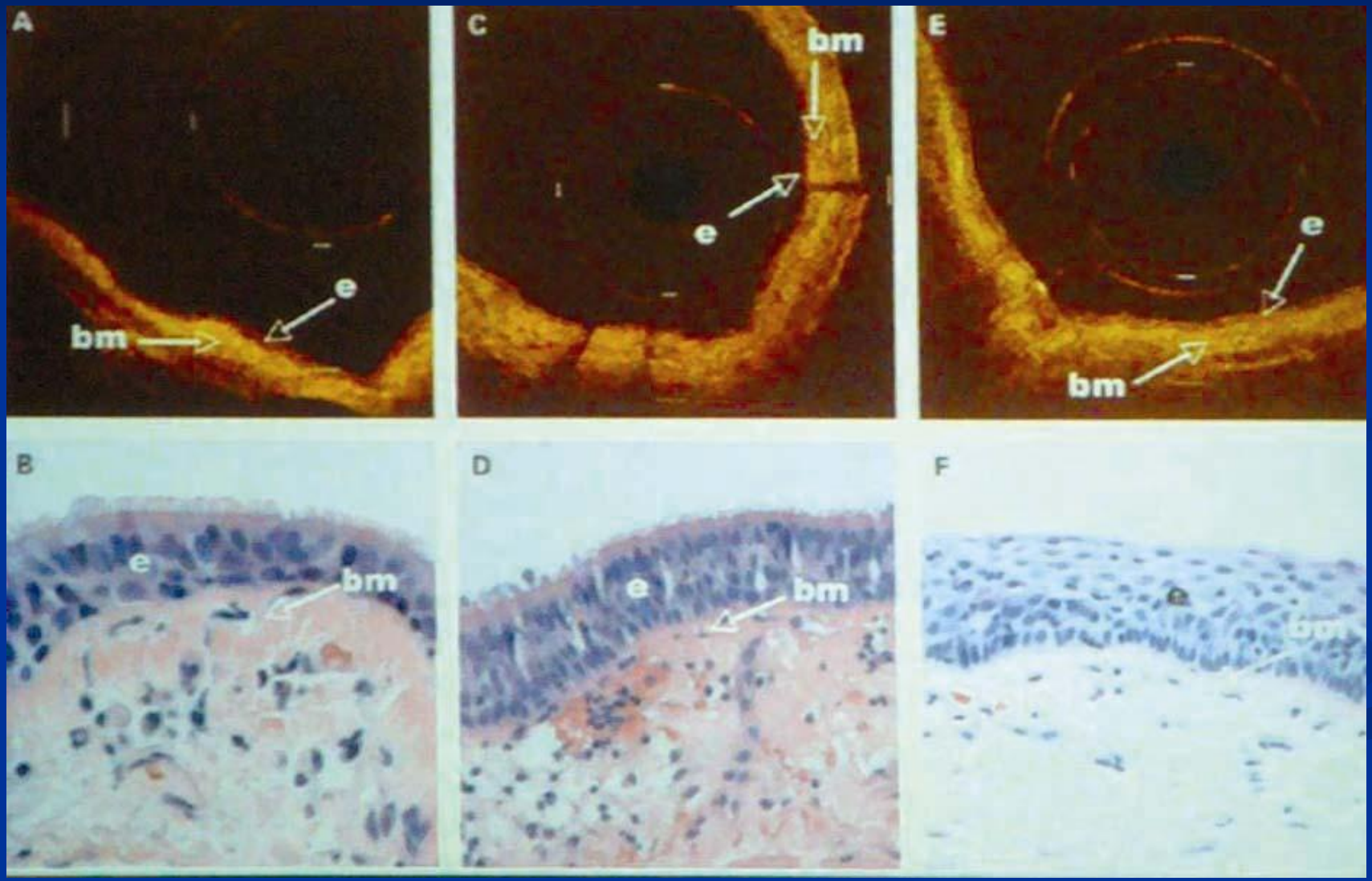
Optical coherence tomography



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

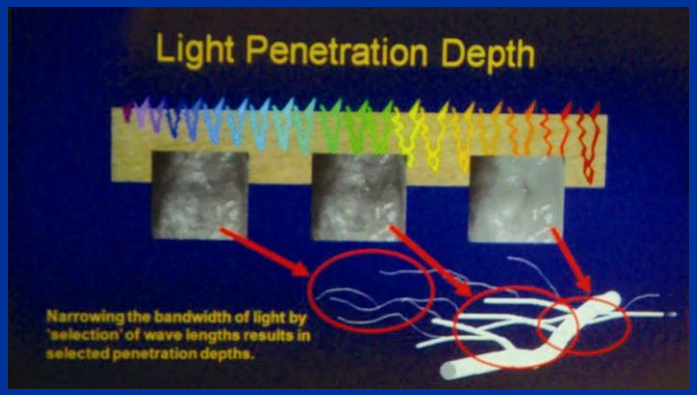
A. McWilliams, B. Lam and T. Sutedja, Early proximal lung cancer diagnosis and treatment, Eur Respir J 2009; 33: 656–665

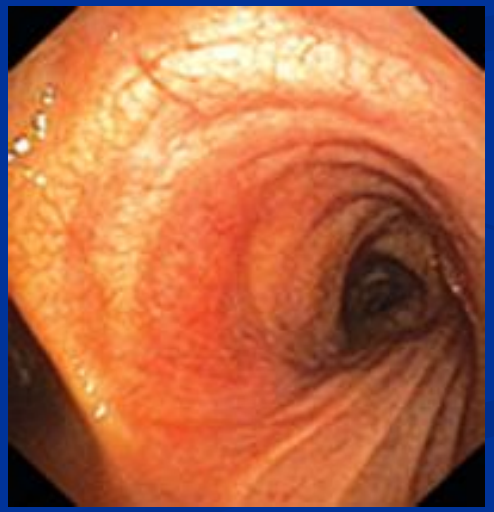
Narrow band imaging

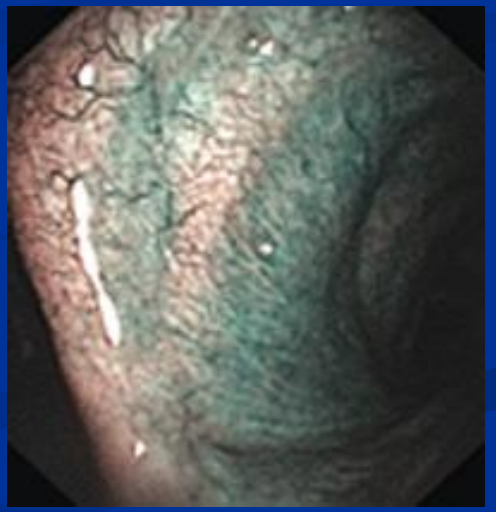
-Detection of subtle mucosal abnormalities

-Utilizes the changes seen in the microvascular network

- Uses a special narrow band filter







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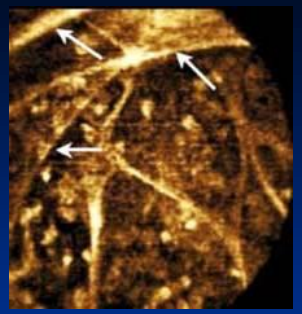


Confocal imaging

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

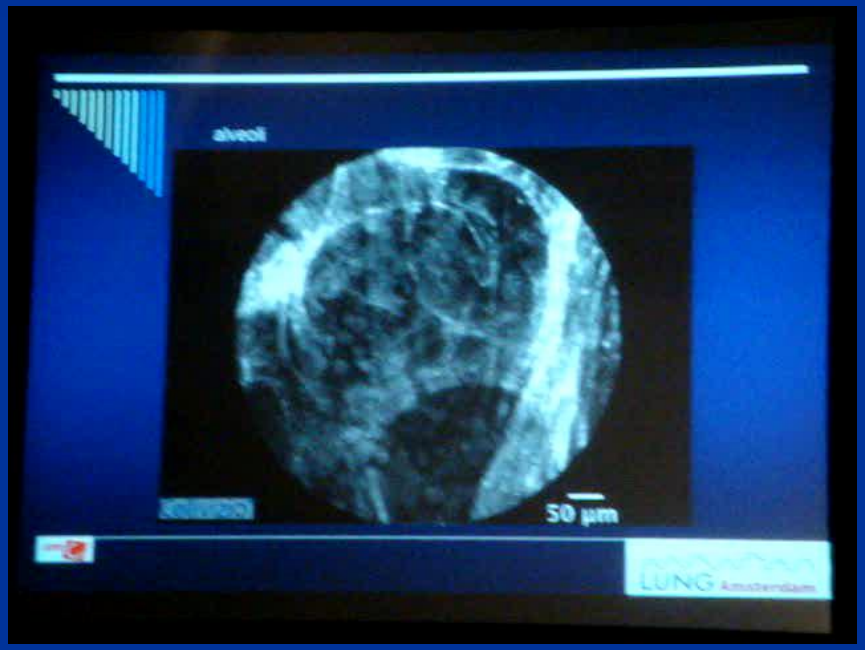
-analyze the microscopic autofluorescence structure of normal and pathologic bronchial mucosae

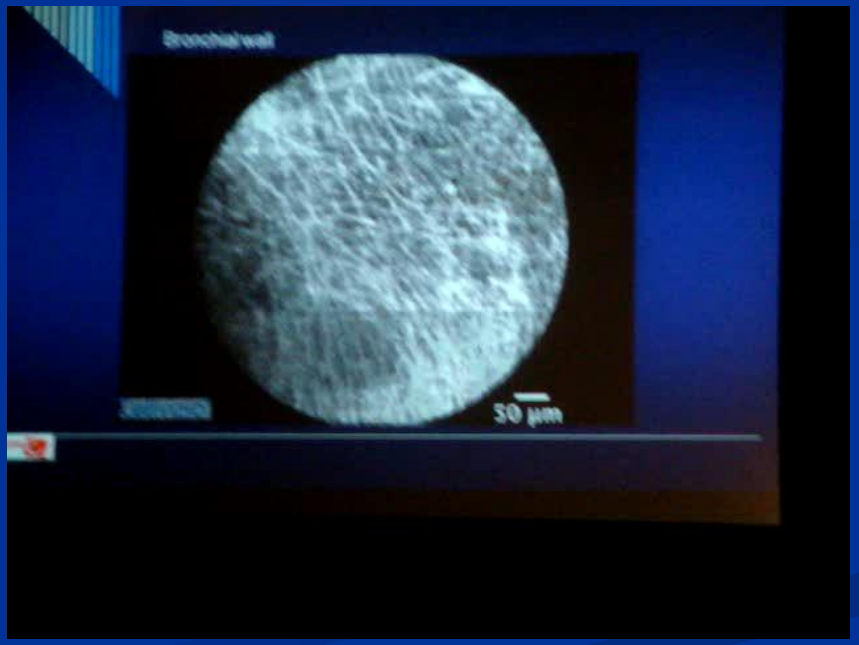
- 488 nm laser for excitation

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.”

1. *Kennedy TC, McWilliams A, Edell E, et al. American College of Chest Physicians. Bronchial intraepithelial neoplasia/early central airways lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007; 132: Suppl. 3, 221S–233S.*
2. *Woolner L, Fontana R, Cortese D, et al. Roentgenographically occult lung cancer; pathologic findings and frequency of multicentricity during a 10-year period. Mayo Clin Proc 1984; 59: 453–466.*
3. *Vonk-Noordegraaf A, Postmus P, Sutedja T. Bronchoscopic treatment of patients with intraluminal microinvasive radiographically occult lung cancer not eligible for surgical resection: a follow-up study. Lung Cancer 2003; 39: 49–53.*

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

1. *Fujimura S, Sagawa M, Saito Y, et al. A therapeutic approach to roentgenographically occult squamous cell carcinoma of the lung. Cancer 2000; 89: Suppl. 11, 2445–2448.*
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3. *Kennedy TC, McWilliams A, Edell E, et al. American College of Chest Physicians. Bronchial intraepithelial neoplasia/early central airways lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007; 132: Suppl. 3, 221S–233S.*
4. *Woolner L, Fontana R, Cortese D, et al. Roentgenographically occult lung cancer; pathologic findings and frequency of multicentricity during a 10-year period. Mayo Clin Proc 1984; 59: 453–466.*
5. *Vonk-Noordegraaf A, Postmus P, Sutedja T. Bronchoscopic treatment of patients with intraluminal microinvasive radiographically occult lung cancer not eligible for surgical resection: a follow-up study. Lung Cancer 2003; 39:49–53.*

“Reported progression rates of carcinoma in situ to invasive cancer vary from 20% to 67% despite bronchoscopic therapy in some instances.”

1. *Venmans B, van Boxem T, Smit E, Postmus P, Sutedja T. Outcome of bronchial carcinoma in situ. Chest 2000; 117: 1572–1576.*
2. *Deygas N, Froudarakis M, Ozenne G, Vergnon JM. Cryotherapy in early superficial bronchogenic carcinoma. Chest 2001; 120: 26–31.*
3. *Bota S, Auliac J, Paris C, et al. Follow-up of bronchial precancerous lesions and carcinoma in situ using fluorescence endoscopy. Am J Respir Crit Care Med 2001; 164: 1688–1693.*
4. *Moro-Sibilot D, Fievet F, Jeanmart M, et al. Clinical prognostic indicators of high-grade pre-invasive bronchial lesions. Eur Respir J 2004; 24: 24–29.*

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

1. *Suzana Bota, Jean-Bernard Auliac, Christophe Paris, Josette Métayer, Richard Sesboüé, Georges Nouvet, and Luc Thiberville, Follow-up of Bronchial Precancerous Lesions and Carcinoma in Situ Using Fluorescence Endoscopy, American Journal Of Respiratory And Critical Care Medicine Vol 164, 2001, p 1688-1693*
2. *Breuer R, Pasic A, Smit E, Esther van Vliet, Vonk A Noordegraaf, Elle J. Risse, Pieter E. Postmus, and Thomas G. Sutedja1 The Natural Course of Preneoplastic Lesions in Bronchial Epithelium Clinical Cancer Research Vol. 11, 537–543,2005*
3. *American Cancer Society Guidelines for the Early Detection of Cancer, 2009*
4. *A. McWilliams, B. Lam and T. Sutedja, Early proximal lung cancer diagnosis and treatment, Eur Respir J 2009; 33: 656–665*
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

1. *Suzana Bota, Jean-Bernard Auliac, Christophe Paris, Josette Métayer, Richard Sesboüé, Georges Nouvet, and Luc Thiberville, Follow-up of Bronchial Precancerous Lesions and Carcinoma in Situ Using Fluorescence Endoscopy, American Journal Of Respiratory And Critical Care Medicine Vol 164, 2001, p 1688-1693*
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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

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Endobronchial treatment

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

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

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Endobronchial treatment

- electrocautery
- photodynamic therapy
- cryotherapy
- brachyterapy

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

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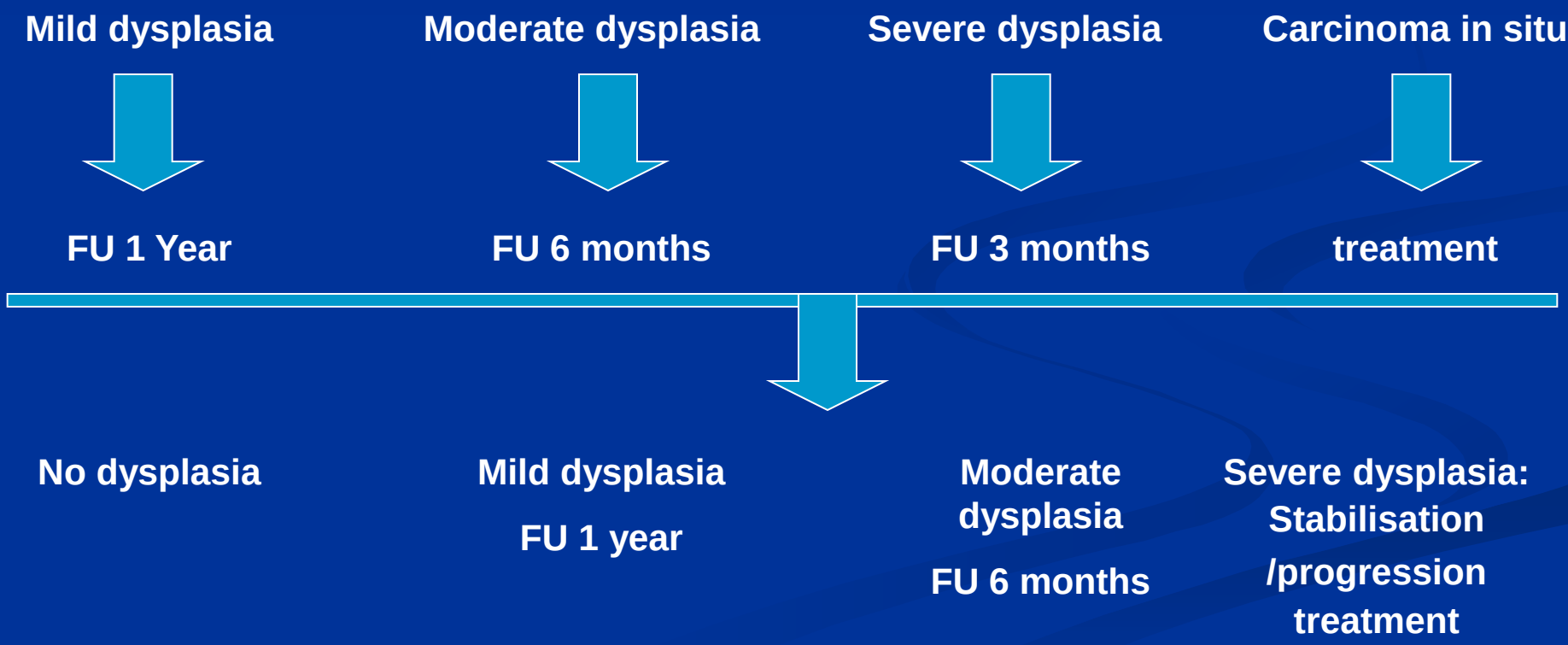
Early proximal lung cancer Algorithm – Diagnosis and treatment

Fluorescence brochoscopy (FUB)



Suzana Bota, Jean-Bernard Auliac, Christophe Paris, Josette Métayer, Richard Sesboüé, Georges Nouvet, and Luc Thiberville, Follow-up of Bronchial Precancerous Lesions and Carcinoma in Situ Using Fluorescence Endoscopy, American Journal Of Respiratory And Critical Care Medicine Vol 164, 2001, p 1688-1693