

# Lung adenocarcinoma: a new histological classification

## Algorithm for the subtyping of NSCLC

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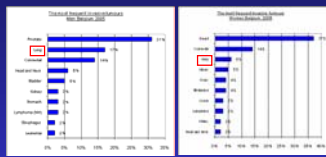
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# Introduction

- More and more Patient and Tumour-tailored treatments :
  - ◆ Need for biological markers
    - EGFR
    - KRAS
    - ERCC1 and RRM1
    - ...
  - ◆ Need for accurate diagnosis for specific treatments
    - SCLC vs NSCLC
    - NSCLC: SCC vs ADC

# Introduction

- Lung cancer
  - ◆ Frequent



- ◆ Adenocarcinoma is the most frequent subtype, representing 35 to 40% of all lung cancers
- ◆ Differential diagnosis may be difficult especially on cytological material and on small biopsy fragments, representing 85% of the received diagnostic material

# NSCLC

WHO histological classification of tumours of the lung 2004

<b>Malignant epithelial tumours</b>	8100	<b>Metastatic tumours</b>	8150
<b>Squamous cell carcinoma</b>	8101	<b>Metastatic squamous cell carcinoma</b>	8151
Papillary	81011	Papillary	81511
Clear cell	81012	Clear cell	81512
Small cell	81013	Small cell	81513
Basoid	81014	Basoid	81514
<b>Small cell carcinoma</b>	8102	<b>Small cell carcinoma</b>	8152
Combined small cell carcinoma	81021	Combined small cell carcinoma	81521
<b>Adenocarcinoma</b>	8103	<b>Adenocarcinoma</b>	8153
Adenocarcinoma, mixed subtype	81031	Adenocarcinoma, mixed subtype	81531
Acinar adenocarcinoma	81032	Acinar adenocarcinoma	81532
Papillary adenocarcinoma	81033	Papillary adenocarcinoma	81533
Bronchioloalveolar carcinoma	81034	Bronchioloalveolar carcinoma	81534
Bromchioloalveolar carcinoma	81035	Bromchioloalveolar carcinoma	81535
Mucinous	81036	Mucinous	81536
Mixed nonmucinous and mucinous or indeterminate	81037	Mixed nonmucinous and mucinous or indeterminate	81537
Solid adenocarcinoma with mucin production	81038	Solid adenocarcinoma with mucin production	81538
Fetal adenocarcinoma	81039	Fetal adenocarcinoma	81539
Mucinous ("colloid") carcinoma	81040	Mucinous ("colloid") carcinoma	81540
Mucinous cystadenocarcinoma	81041	Mucinous cystadenocarcinoma	81541
Signet ring adenocarcinoma	81042	Signet ring adenocarcinoma	81542
Clear cell adenocarcinoma	81043	Clear cell adenocarcinoma	81543
<b>Large cell carcinoma</b>	8104	<b>Large cell carcinoma</b>	8154
Large cell neuroendocrine carcinoma	81041	Large cell neuroendocrine carcinoma	81541
Combined large cell neuroendocrine carcinoma	81042	Combined large cell neuroendocrine carcinoma	81542
Basoid carcinoma	81043	Basoid carcinoma	81543
Lymphoepithelioma-like carcinoma	81044	Lymphoepithelioma-like carcinoma	81544
Clear cell carcinoma	81045	Clear cell carcinoma	81545
Large cell carcinoma with hybrid phenotype	81046	Large cell carcinoma with hybrid phenotype	81546
<b>Adenosquamous carcinoma</b>	8105	<b>Adenosquamous carcinoma</b>	8155
Squamous carcinoma	81051	Squamous carcinoma	81551
Pneumocystic carcinoma	81052	Pneumocystic carcinoma	81552
Basoid cell carcinoma	81053	Basoid cell carcinoma	81553
Signet ring carcinoma	81054	Signet ring carcinoma	81554
Carcinosarcoma	81055	Carcinosarcoma	81555
Pulmonary blastoma	81056	Pulmonary blastoma	81556
<b>Carcinoid tumour</b>	8106	<b>Carcinoid tumour</b>	8156
Typical carcinoid	81061	Typical carcinoid	81561
Atypical carcinoid	81062	Atypical carcinoid	81562
<b>Salivary gland tumours</b>	8107	<b>Salivary gland tumours</b>	8157
Mucoepithelial carcinoma	81071	Mucoepithelial carcinoma	81571
Adenoid cystic carcinoma	81072	Adenoid cystic carcinoma	81572
Epithelial myoepithelial carcinoma	81073	Epithelial myoepithelial carcinoma	81573

# Adenocarcinoma

1999 World Health Organization/International Association for the Study of Lung Cancer: Histological Classification of Lung and Pleural Tumours :

2004 World Health Organization/International Association for the Study of Lung Cancer: Histological Classification of Lung and Pleural Tumours :

- 1.3.3. Adenocarcinoma
  - 1.3.3.1. Acinar
  - 1.3.3.2. Papillary
  - 1.3.3.3. Bronchioloalveolar carcinoma
    - 1.3.3.3.1. Non-mucinous
    - 1.3.3.3.2. Mucinous
    - 1.3.3.3.3. Mixed mucinous and non-mucinous or intermediate cell type
  - 1.3.3.4. Solid adenocarcinoma with mucin
    - 1.3.3.4.1. Fetal adenocarcinoma
    - 1.3.3.4.2. Mucinous ("colloid") carcinoma
    - 1.3.3.4.3. Signet-ring adenocarcinoma
    - 1.3.3.4.4. Clear cell adenocarcinoma
  - 1.3.3.5. Variants
    - 1.3.3.5.1. Well-differentiated fetal adenocarcinoma
    - 1.3.3.5.2. Mucinous ("colloid") adenocarcinoma
    - 1.3.3.5.3. Mucinous cystadenocarcinoma
    - 1.3.3.5.4. Signet-ring adenocarcinoma
    - 1.3.3.5.5. Clear cell adenocarcinoma

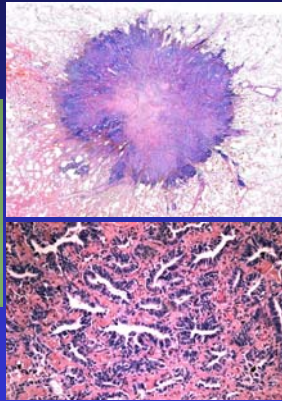
Adenocarcinoma	8140/3
Adenocarcinoma, mixed subtype	8250/3
Acinar adenocarcinoma	8550/3
Papillary adenocarcinoma	8260/3
Bronchioloalveolar carcinoma	8250/3
Nonmucinous	8250/3
Mucinous	8250/3
Mixed nonmucinous and mucinous or indeterminate	8254/3
Solid adenocarcinoma with mucin production	8220/3
Fetal adenocarcinoma	8332/3
Mucinous ("colloid") carcinoma	8400/3
Mucinous cystadenocarcinoma	8470/3
Signet ring adenocarcinoma	8490/3
Clear cell adenocarcinoma	8310/3

+ Atypical adenomatous hyperplasia

# Lung adenocarcinoma

- Definition :
  - ◆ Malignant epithelial tumour characterized by glandular differentiation or signs of mucin production
  - ◆ Heterogeneous group of histologically very different tumours
  - ◆ The mixed variant is the most frequent subtype, representing 80 to 90% of all adenocarcinomas

## Adenocarcinoma



## Proposal of a new classification for adenocarcinomas

- Preinvasive lesions
  - ◆ Atypical adenomatous hyperplasia
  - ◆ In situ adenocarcinoma (BAC pattern)
    - Non-mucinous
    - Mucinous
- Adenocarcinoma with minimal invasion (lepidic growth pattern with an invasive foci  $\leq 5\text{mm}$  or  $<10\%$  of invasion)
- Invasive adenocarcinoma
  - ◆ Classical forms (lepidic pattern, acinar, papillary, micropapillary and solid)
  - ◆ Variants (mucinous or colloid, cystadenocarcinoma and fetal adenocarcinoma)

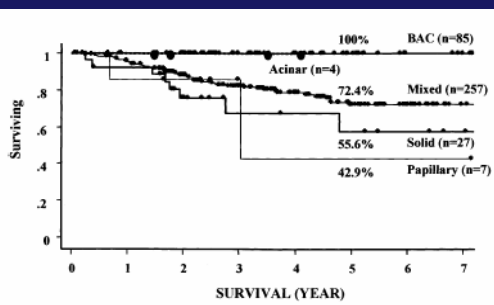
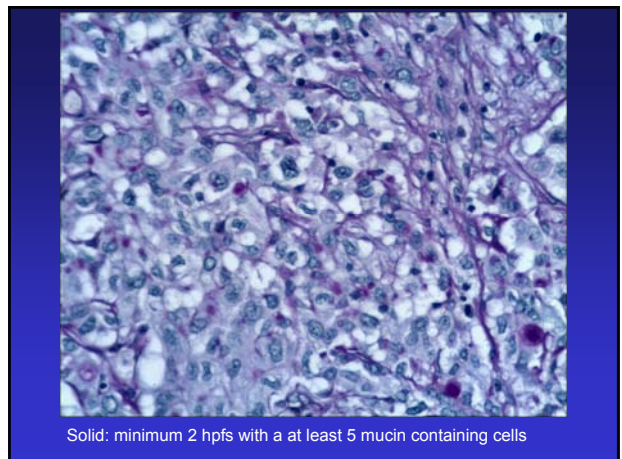
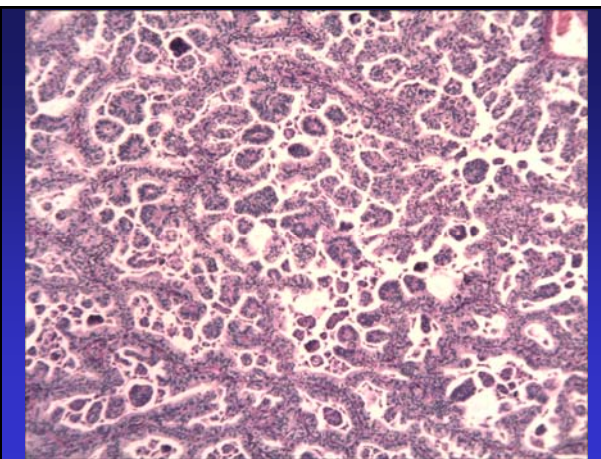
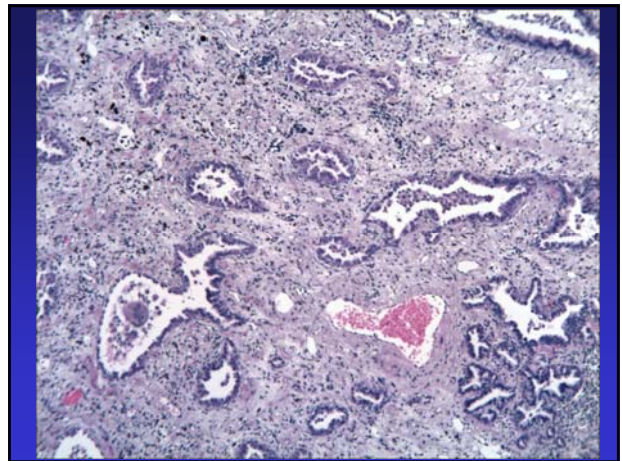


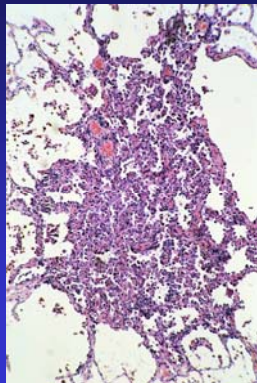
FIGURE 7. Survival curves according to the WHO classification. The 5-year disease-free survival rates are 100% (BAC), 72.4% (mixed subtypes), 55.6% (solid), and 42.9% (papillary), respectively.



Solid: minimum 2 hpf with a at least 5 mucin containing cells

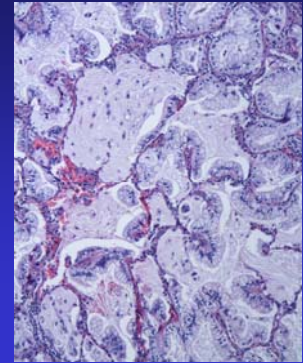
## Preinvasive lesions

- Atypical adenomatous hyperplasia (AAH)
  - ◆ Precursor of ADC
  - ◆ <5 mm
  - ◆ In the vicinity of ADC



## BAC

- Defined as growth of tumour cells along preexisting alveolar walls (lepidic growth pattern) without invasion of stroma, vessels or pleura and absence of metastases
- => by definition: diagnosis is not possible on small biopsies or cytology

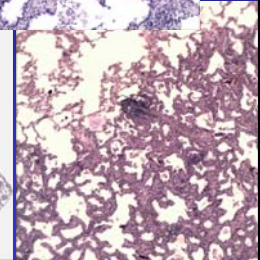
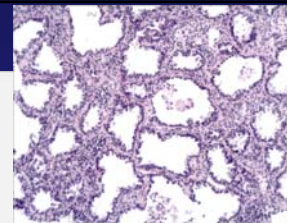
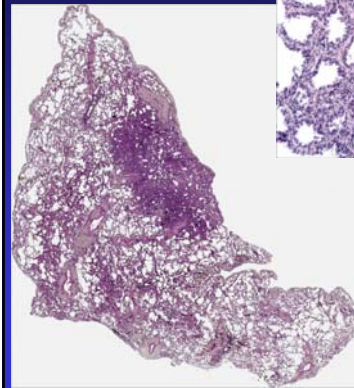


## BAC

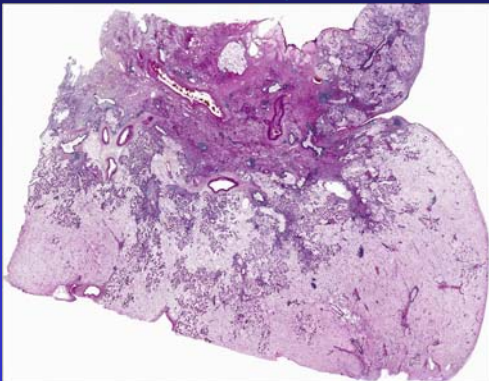
- Pure form:
  - < 2 cm
  - Rare : 3-4% of NSCLC
  - Pure ground glass aspect on CT
  - In situ adenocarcinoma with a 100% 5 year survival
- Minimally invasive :
  - < 2 cm
  - Invasive foci less than 5 mm
- BAC multifocal and bilateral :
  - Mostly mucinous forms
  - Often invasive component
- Mixed adenocarcinoma with a BAC component



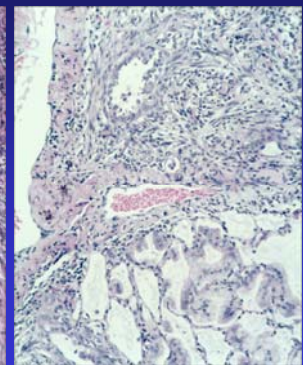
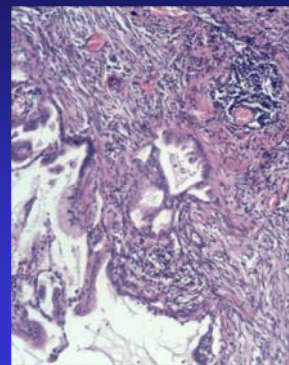
## Pure BAC



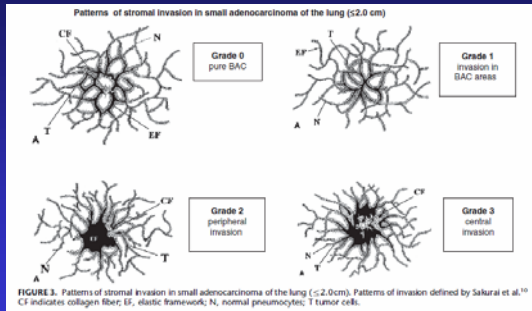
## BAC minimally invasive



## BAC minimally invasive

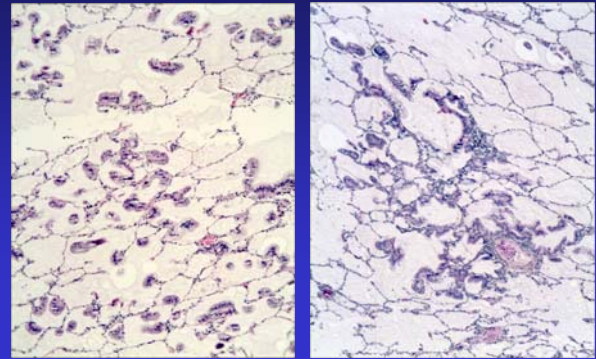


## Sakurai's classification

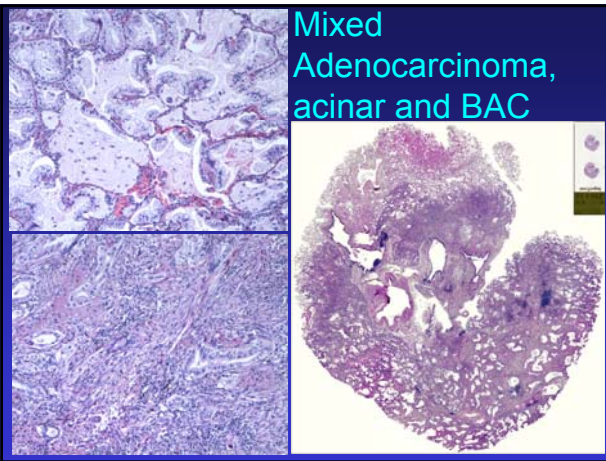


Sakurai et al. <sup>10</sup>	Invasion pattern	0	1	2	3	100
0	0	0	0	0	0	100
1	1	0	3	0	0	100
2	2	0	2	0	0	100
3	3	27	68	8	0	99

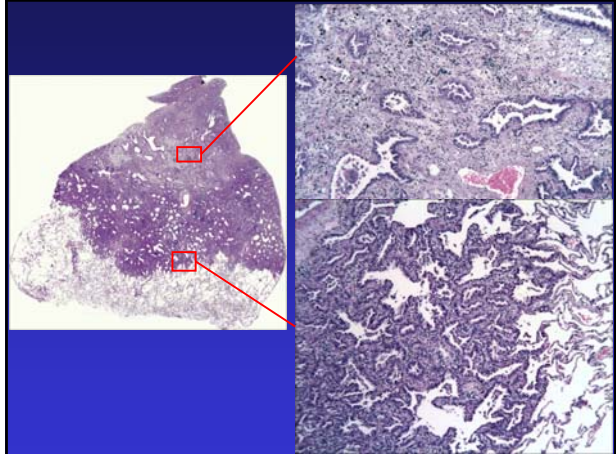
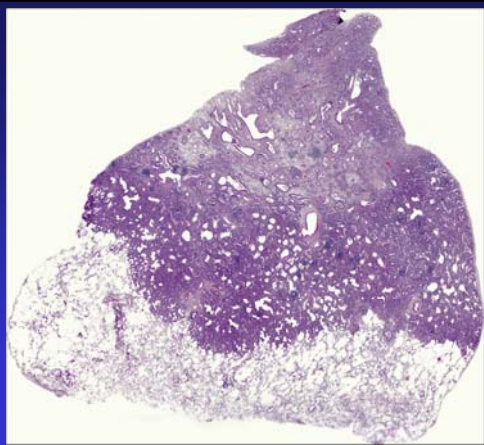
## BAC mucinous, multifocal



## Mixed Adenocarcinoma, acinar and BAC



Quiz

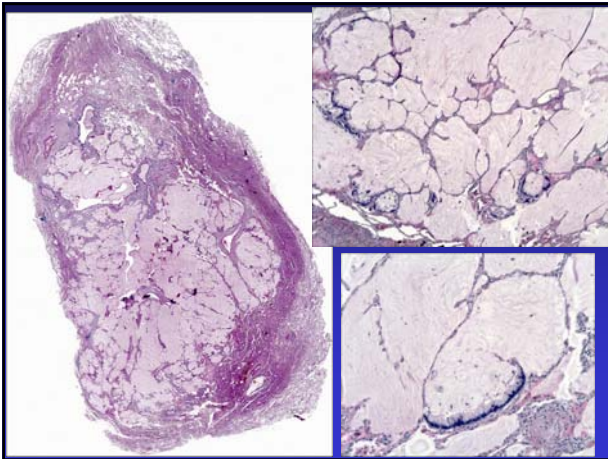
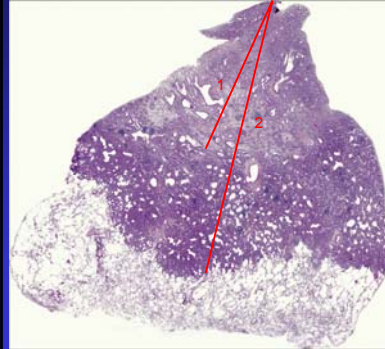


## What is your diagnosis?

### Peripheral lung adenocarcinoma

1. Adenocarcinoma NOS
2. Adenocarcinoma mixed subtype
3. Bronchioloalveolar carcinoma, Sakurai grade 3
4. Adenocarcinoma with minimal invasion

## How should a BAC be measured ?



## What is your diagnosis?

### Bronchioloalveolar carcinoma

1. Yes
2. No



## For an accurate diagnosis

### ■ Histology first :

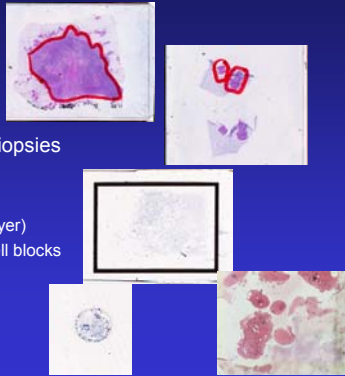
#### ◆ 4 main subtypes :

- SCC
  - ADK
  - LCLC
  - SCLC
- } NSCLC

### ■ If needed, IHC for DD SCLC vs NSCLC

## What type of specimen ?

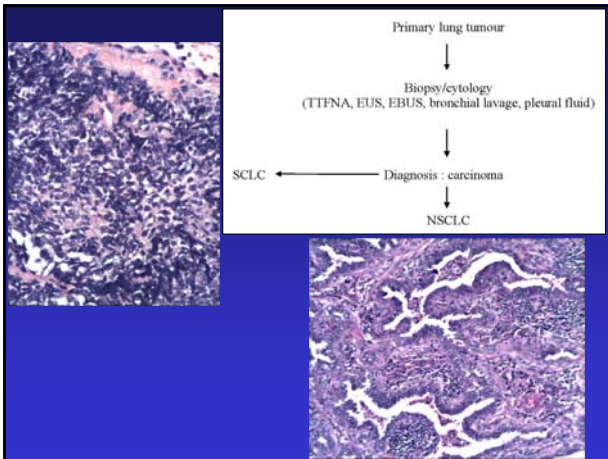
- ◆ Surgical resections
- ◆ Paraffin-embedded biopsies
- ◆ Cytology
  - Fresh (unfixed)
  - Alcohol-fixed (monolayer)
  - Paraffin-embedded cell blocks
- ◆ Frozen material



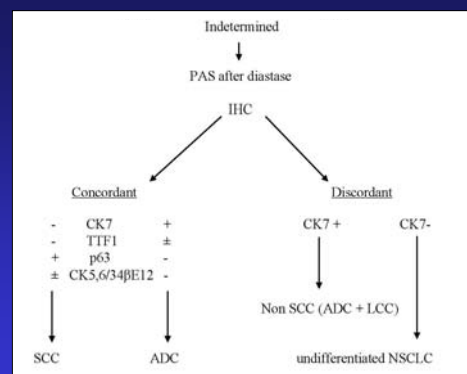
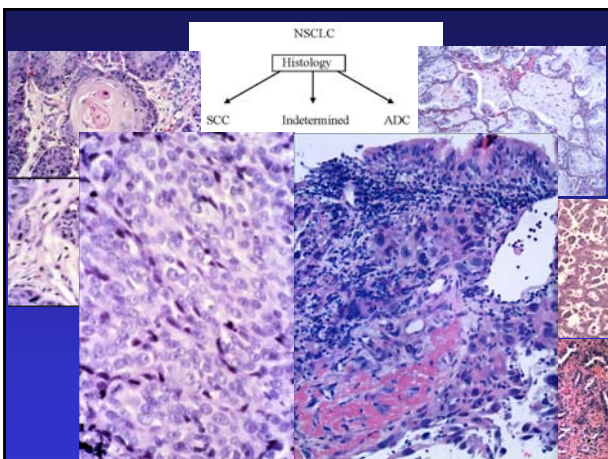
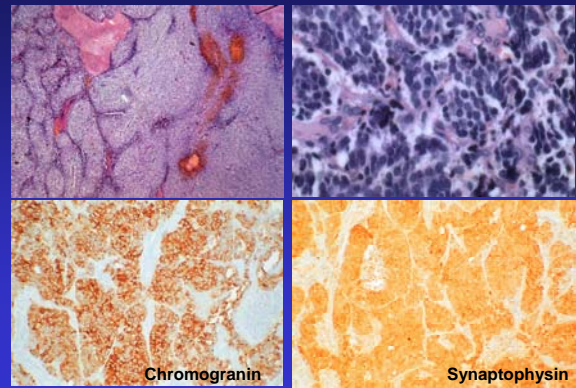
## Belgian algorithm proposed by the Belgian Mesothelioma Registry

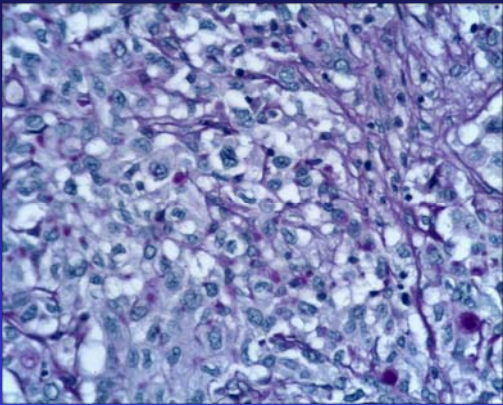


BJMO 2010;4:155-7

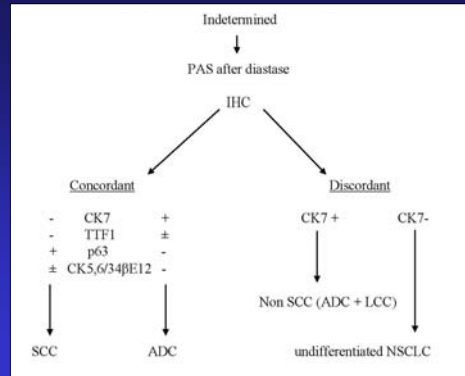


## SCLC



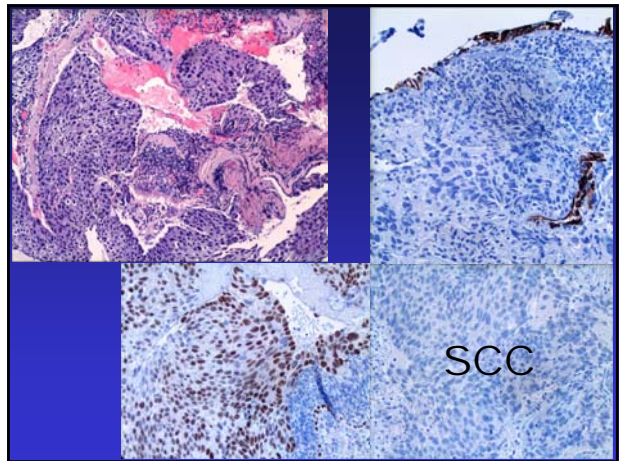


Solid form of adenocarcinoma : at least 5 mucin containing cells in minimum 2 HPF



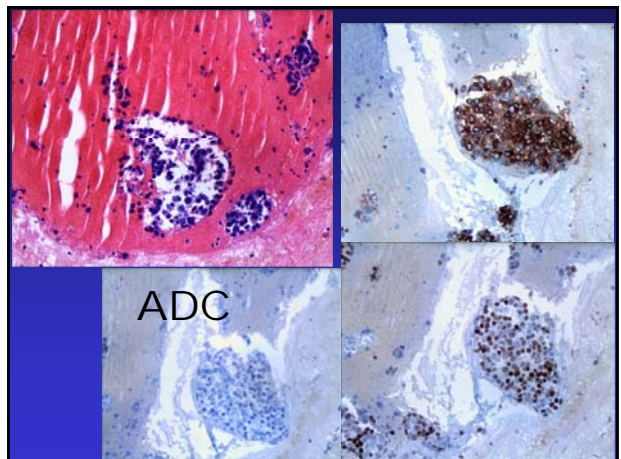
Concordant

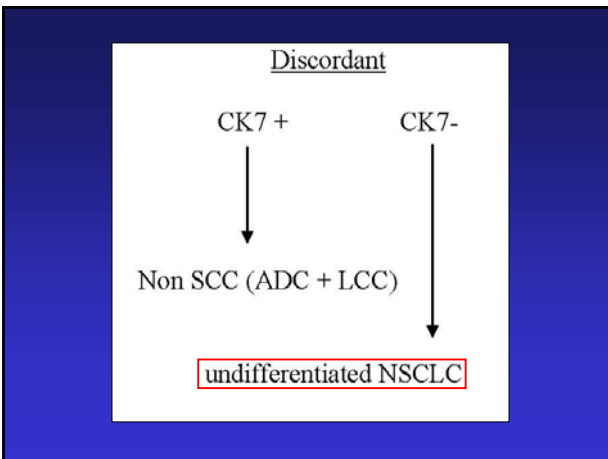
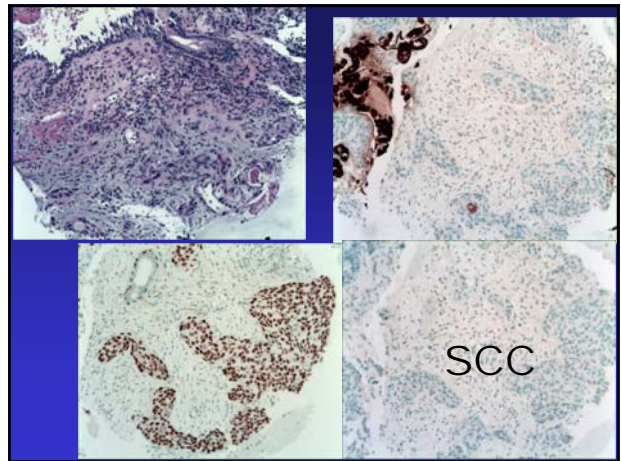
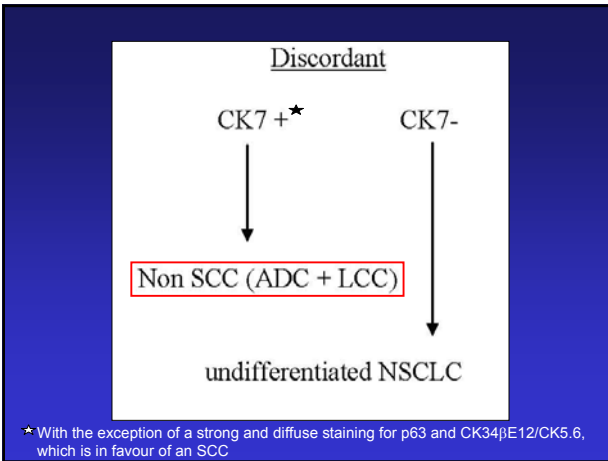
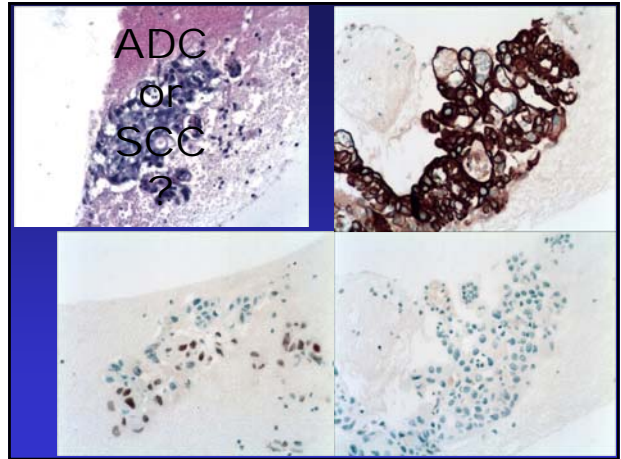
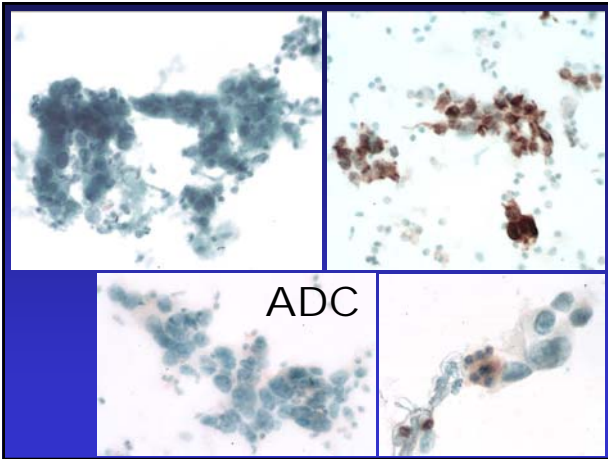
-	CK7	+
-	TTF1	±
+	p63	-
±	CK5,6/34βE12	-



Concordant

-	CK7	+
-	TTF1	±
+	p63	-
±	CK5,6/34βE12	-





- ## Conclusion
- Proposal of a new classification for lung adenocarcinomas based on survival curves
  - A diagnosis of BAC can not be done on cytology or small biopsies
  - Numerous subtypes of adenocarcinoma, the mixed subtype being the most frequent one
  - Proposal of a Belgian algorithm for the subtyping of NSCLC