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Pathology of preneoplasia and common lung cancers

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Lung Cancer Classification revised in 1999 (WHO)

- 17 years elapsed since the 1981 WHO classification
- Progress in understanding genetic and molecular basis of carcinogenesis
- Foundation for tumor diagnosis and patient therapy
- Cornerstone of comparative studies: clinical, epidemiologic and biological
- Complemented with clinical and genetic features of entities: Pathology and geneties (WHO 2004)

- Squamous Cell Carcinoma
- Small Cell Carcinoma
- Adenocarcinoma
- Large Cell Carcinoma
- Adeno Squamous Carcinoma
- Sarcomatoid carcinoma
- Carcinoid tumors
- Salivary gland tumors
- Preinvasive lesions
Preinvasive lesions

- Squamous dysplasia
  - mild
  - moderate
  - severe
- Carcinoma in situ
- Atypical adenomatous hyperplasia (AAH)
- Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
Normal bronchial epithelium
Bronchial epithelium: hyperplasia
Squamous metaplasia
Mild dysplasia
Moderate dysplasia
Severe dysplasia
Carcinoma in situ
Invasive carcinoma: T1
Pre- and neoplastic bronchial lesions

Hyperplasia
↓ ↓ ?

Metaplasia
↓ ↓ ?

Dysplasia
↓ ↓ ↓ ?

In situ carcinoma
↓ ↓ ↓ ↓ ?

Invasive carcinoma

Molecular Identity

- Cell cycle regulation
- Apoptosis / Senescence
- Angiogenesis / Migration
Atypical Alveolar Hyperplasia (AAH)

- A preinvasive lesion for Bronchiolo Alveolar Carcinoma (BAC)
- Focal lesion (1-10 mm) most often less than 3mm
- Slightly atypical epithelial cells covering alveoli and respiratory bronchioles

Differential diagnosis with BAC
  - size ≥ 5mm
  - no gaps between cells
  - more severe atypia
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

- A proliferation of neuroendocrine cells confined to the bronchiolar epithelium
- Scattered single cells, small nodules or linear proliferations
- Often associated with tumourlets
Neuroendocrine hyperplasia
Neuroendocrine hyperplasia
Tumourlet: less than 5mm  > 5mm: carcinoid
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

• Idiopathic: not a simple reaction to lung inflammation of fibrosis

• A preneoplastic lesions: some patients develop one or more carcinoid tumors

• A subset of patients have obstructive airway disease
Squamous cell carcinoma

A malignant epithelial tumour showing keratinization and/or intercellular bridges

**Variants:**
- Papillary
- Clear cell
- Small cell
- Basaloid
Squamous cell carcinoma
Squamous cell carcinoma
Squamous cell carcinoma: papillary variant
Squamous cell carcinoma: basaloid variant
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Small Cell Carcinoma</td>
<td>Small Cell Carcinoma</td>
</tr>
<tr>
<td>Variant</td>
<td>Oat cell</td>
</tr>
<tr>
<td>• Combined Small Cell Carcinoma</td>
<td>Intermediate Combined</td>
</tr>
</tbody>
</table>
SCLC: NCAM
SCLC: Chromogranin
SCLC: TTF1
SCLC combined
Adenocarcinoma

- Adenocarcinoma mixed subtype
  - Acinar adenocarcinoma
  - Papillary adenocarcinoma
- Bronchioloalveolar carcinoma
  - Non-mucinous
  - Mucinous
  - Mixed mucinous - non mucinous
- Solid adenocarcinoma with mucin

Variants:

WHO 1999 - 2004

WHO 1981

Adenocarcinoma

- a. Acinar
- b. Papillary
- c. Bronchioloalveolar carcinoma
- d. Solid adenocarcinoma with mucus formation
Adenocarcinoma

- 85% display mixed histology
  - Adenocarcinoma mixed type: more than one subtype

- Bronchioloalveolar carcinoma
  restrictive definition: a non invasive tumor
Adenocarcinoma: acinar
Adenocarcinoma: papillary
Bronchioloalveolar carcinoma (BAC)
BAC : Clara Cell Type
Bronchioloalveolar carcinoma (BAC)

- Pure “lepidic” growth pattern along respected alveolar walls
- No invasion (stromal, vascular, pleural)
- No central scar, no desmoplastic stromal reaction
- No papillary structures in alveolar lumens

→ Most previously reported BAC are now adenocarcinoma mixed sub type
→ The diagnosis of BAC cannot be achieved on small biopsies
Bronchioloalveolar carcinoma (non invasive)

Significant association with

- pathological stage I
  \[ p < 0.001 \]

- absence of lymph node metastasis
  \[ p < 0.001 \]

- 5 years patient survival among stage I cases
  \[ p < 0.005 \]

Noguchi M. (type AB-BAC < 2cm) Cancer 1995
Yokose et al Lung Cancer 2000
BAC: mucinous type
Mucinous BAC: satellite lesion
2cm Adenocarcinoma
Central scar: Acinous adenocarcinoma
Graph showing the survival rates of Type A and B, Type C, and Type D over 1000 days. The y-axis represents percentage survival, ranging from 0% to 100%, and the x-axis represents time in days, ranging from 0 to 1000 days. The graph indicates that Type A and B have a higher survival rate compared to Type C and Type D.
Bronchioloalveolar carcinoma: clinical significance

- Less than 2 cm BAC can be curable by economic surgical resection: 100% - 5 year survival
  
  Noguchi et al. Cancer 1995

- **Size of central scar** in ADC with peripheral BAC less than 3cm
  
  - < 5mm      100% 5 year survival
  - 5-15mm     71% 5 year survival
  - ≥ 15mm     40% 5 year survival

  independent prognostic factor p = 0.01
  
Suzuki et al. 2000

- ≤ 5mm
- 5 - 15 mm
- > 15 mm

Days
1.3.4. Large cell carcinoma

Variants:

1.3.4.1. Large cell neuroendocrine carcinoma

Combined large cell neuroendocrine carcinoma

1.3.4.2. Basaloid carcinoma

1.3.4.3. Lymphoepithelioma-like carcinoma

1.3.4.4. Clear cell carcinoma

1.3.4.5. Large cell carcinoma with rhabdoid phenotype
Large cell carcinoma: NOS
Large Cell Neuroendocrine Carcinoma (LCNEC)
Large Cell NEuroendocrine Carcinoma (LCNEC)

- A variant of large cell carcinoma
- A high grade NE tumor
- Characteristic features
  - Neuroendocrine morphology (rosettes ...)
  - Non small cell cytology ($\neq$ SCLC)
  - High mitotic rate $\geq 11$ per $2\text{mm}^2$
    ($\neq$ Atypical carcinoid)
- 15 - 20% of LCNEC are Combined LCNEC
LCNEC: clinical features

- Heavy smokers. Mean age 62 years
- Poor prognosis: 27% - 5 y. survival, 9% - 10 y. survival
- Not significantly different from SCLC
- Surgical resection recommended
- Chemotherapy sensitivity?
  SCLC chemotherapy type?

Rossi et al JCO 2005
The spectrum of neuroendocrine (NE) proliferation and neoplasms

I - NE cell hyperplasia and tumorlets
   A. NE cell hyperplasia
   B. Tumorlets

II - Tumors with NE morphology
   A. Typical carcinoid
   B. Atypical carcinoid
   C. Large cell neuroendocrine carcinoma
   D. Small cell carcinoma

III - Non small cell carcinomas with NE differentiation
Lung neuroendocrine tumors

- Carcinoids: Typical carcinoid, Atypical carcinoid
  ➔ Sharp histopathological definition
  ➔ Significant prognostic differences
## Carcinoids: Typical versus Atypical

<table>
<thead>
<tr>
<th></th>
<th>Mitoses</th>
<th>Necrosis</th>
<th>5y. survival</th>
<th>10y. survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typical</strong> carcinoid</td>
<td>&lt; 2/ 2mm²</td>
<td>0</td>
<td>87%</td>
<td>87%</td>
</tr>
<tr>
<td><strong>Atypical</strong> carcinoid</td>
<td>2-10/ 2mm²</td>
<td>+/-</td>
<td>56%</td>
<td>35%</td>
</tr>
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</table>

PULMONARY NE TUMORS
KAPLAN MEIER SURVIVAL ESTIMATION

PERCENT LIVING

SURVIVAL (YEARS)

TC
AC
LCNEC
SCLC

AFIP/IASLC NE STUDY 8-97 (N=331; 78 TC, 81 AC, 78 LCNEC, 88 SCLC)
Large cell carcinoma

- **Large cell carcinoma**: no clinical significance
- Two variants with clinical significance
  - Large cell neuroendocrine carcinoma (5%)
  - Basaloid carcinoma (5%)
Basaloid carcinoma

- Proliferation of "reserve" stem cells
- No neuroendocrine markers
- High proliferative index
- Poor prognosis
Survival of stage I BC vs NSCLC

Survival

Time (months)

p : 0.0061

Basaloid Carcinoma

NSCLC
WHO 1999 - 2004

Sarcomatoid carcinomas

- Pleomorphic carcinoma
- Spindle cell carcinoma
- Giant cell carcinoma
- Carcinosarcoma
- Pulmonary blastoma
Sarcomatoid carcinoma

- Express the features of epithelial to mesenchymal transition
- Pleiomorphic carcinoma: 10% of giant or spindle cells
- Large peripheral tumors often invading chest and with endobronchial growth
- Differential diagnosis: sarcoma
Pleomorphic Carcinoma (Sarcomatoid carcinoma)

- Poor prognosis
  - median survival: 19 months
  - 47% - 5 year survival at stage I


→ Disease related survival significantly shorter than NSCLC stage I
Immuno histochemistry
Electron microscopy

Differential diagnosis

- Large cell Neuroendocrine Carcinoma / Basaloid Carcinoma
- Adenocarcinoma / Mesothelioma (calretinin, CK5-6, ACE…)
- Adenocarcinoma / Primitive / Metastatic (TTF1)
- Pleiomorphic carcinoma / Sarcoma (Ck)
- Sarcoma (desmin, E.M.)
- Melanoma (HMB45, S100)
World Health Organization Classification of Tumours

Pathology & Genetics

Tumours of the Lung, Pleura, Thymus and Heart

Edited by William D. Travis, Elizabeth Brambilla, Hans K. Muller-Hermelink & Curtis C. Harris

IARC