Non Small Cell Lung Cancer Histopathology

ד"ר יהודית זנדבנק
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Lecture outlines

- WHO histological classification
- Macro/Micro assessment
- Early diagnosis
- Minimal pathology
- Main subtypes – SCC, AdCa, LCLC
  - Histology / Cytology
  - IHC
  - DD
  - Molecular genetics
  - Prognosis and histopathology
- Neuroendocrine tumor concept
- Targeted therapy
The most simple classification of lung cancer:

Small cell lung cancer (SCLC)

Non-small cell lung cancer (NSCLC)
WHO histological classification

- Squamous cell carcinoma
  - Papillary
  - Clear cell
  - Small cell
  - Basaloid
Adenocarcinoma
- Mixed subtype
- Acinar
- Papillary
- Bronchioloalveolar
  * Nonmucinous
  * Mucinous
  * Mixed
Solid adenocarcinoma with mucin production
* Fetal
* Mucinous (colloid)
* Mucinous cystadenocarcinoma
* Signet ring cell adenocarcinoma
* Clear cell adenocarcinoma
- Large cell carcinoma
  - Large cell neuroendocrine carcinoma
    *Combined large cell neuroendocrine ca.
  - Basaloid carcinoma
  - Lymphoepithelioma-like carcinoma
  - Clear cell carcinoma
  - Large cell carcinoma with rhabdoid phenotype
- Adenosquamous cell carcinoma
- Sarcomatoid carcinoma
  - Pleomorphic
  - Spindle cell
  - Giant cell
  - Carcinosarcoma
  - Pulmonary blastoma
- Salivary gland tumours
  - Mucoepidermoid
  - Adenoid cystic
  - Epithelial myoepithelial
Why classify?
Classification

- Prognosis
- Treatment
- Pathogenesis/biology
- Epidemiology
Macroscopic and Microscopic assessment of NSCLC

- Tumor size
- Tumor necrosis
- Pleural involvement
- Resection margin evaluation
- Assessment of sampled lymph nodes
- Search for intrapulmonary metastases
- Histological heterogeneity
- Grading
- Vascular, lymphatic involvement
Early lesions, Pulmonary epithelium

- Bronchial (ciliated, mucous, neuroendocrine, reserve, metaplastic)

- Bronchioles/alveoli (Clara cells, types I and II alveolar lining cells)
Early lesion, Bronchial:

- Squamous metaplasia
- Dysplasia
- Carcinoma in situ
- Invasive malignancy
Normal bronchial mucosa
Bronchial mucosa basal cell hyperplasia
Normal bronchial mucosa

Squamous metaplasia
Bronchial mucosa – Squamous cell carcinoma in situ (severe dysplasia)
Early lesion, bronchioles/alveoli

- Atypical Adenomatous Hyperplasia
- Spread of neoplastic cells along alveolar walls (bronchioaloalveolar carcinoma)
- True invasive adenocarcinoma
- THIS PATTERN IS BECOMING COMMONER
Atypical Adenomatous Hyperplasia (AAH)
Bronchiolalveolar carcinoma (BAC)
Minimal pathology

- Bronchoscopic biopsies
- Core needle biopsies
Minimal pathology (cont.)

- No tumor
- Minimal amount of tumor
- Morphology
- Immunohistochemistry
- Lung tumors - heterogeneous
Squamous cell carcinoma

- >90% smokers
- Central and peripheral in increase
- 44% in males
- 25% in females
- Macroscopy – large, grey, firm, cavitary, post obstructive pneumonia
- Tumor spread - locally aggressive
  - less locoregional metastases
  - common locoregional recurrence
Squamous cell carcinoma

Immunohistochemistry – HMW/CK, CK5/6, CEA – positive
TTF1, CK7, LMW/CK – rarely (+ve)
SCC – Differential diagnosis

- Large cell carcinoma
- Solid adenocarcinoma (focal mucin content – acceptable)
- Thymic carcinoma in case of massive mediastinal involvement
- SCC metastases
- Squamous metaplasia with atypia in reactive conditions, e.g., DAD
SCC – histological criteria for prognosis prediction

- Better prognosis than adenocarcinoma
- The more necrosis – the worse the prognosis
- Well differentiated SCC – more locoregional spread
- Poorly differentiated SCC – early metastases to distant sites
- Alveolar filling of peripheral SCC – more favorable prognosis
SCC – molecular genetics

- EGFR gene mutations – 84%
- K-RAS - rare
- Her2 – rare
- p53 gene function disruption – common
- Rb gene pathway disruption - common
Squamous Cell Carcinoma
Squamous cell carcinoma
Histology / Cytology
Squamous Cell Lung Cancer: FNA
Adenocarcinoma (AdCa)

- Surpassed SCC as most common lung cancer.
- Most in smokers
- But in women non smokers
  - Women – 42%
  - Men – 28%
- ~20% present with distant metastases
- Local recurrence not as common as SCC
Mixed subtypes – 80%
Mixed degree of differentiation
Therefore – ample sampling is necessary
When only bronchioloalveolar carcinoma seen – ample sampling to look for invasive component
AdCa - macroscopy

- Peripheral
- Central
- Diffuse pneumonia-like, BAC
- Diffuse bilateral disease – simulating interstitial pneumonia, BAC
- Growth along pleurae, simulating mesothelioma
- In background of underlying fibrosis
AdCa - immunohistochemistry

- Pan CK
- LMW/CK
- CK7
- EMA
- CEA
- TTF1
- SPB1
AdCa – differential diagnosis

- Atypical Alveolar Hyperplasia v` BAC (>5mm)
- Prominent bronchiolar metaplasia in fibrotic lesions, e.g. interstitial pneumonia
- Metastatic adenocarcinoma
- Mesothelioma, epithelial
AdCa - histogenesis

- Central - bronchial epithelium
  - bronchial glands
- Periphery - type II pneumocytes
  - clara cells
AdCa – prognostic histological factors

- Poor differentiation - increased local recurrence - increased lymph node metastases
- Grading – insignificant in peripheral T1 AdCas but...
- High grade histology, vascular invasion, mf, few intra-tumoral lymphocytes, extensive necrosis are unfavorable prognosticators
- Unfavorable – papillary and micropapillary patterns
AdCa – molecular genetics

- EGFR gene mutations
- K-RAS - ~30%
- P53
- P16ink4

K-RAS mutations contraindicate therapy with EGFR tyrosine kinase inhibitors
Adenocarcinoma
Adenocarcinoma
Adenocarcinoma: FNA
Adenocarcinoma: mucin stain
Adenocarcinoma with lepidic features

- Restricted to cases without pleural, vascular or stromal invasion
- ~20%
- 5 yr survival of localized, resected BAC is 100%
- Recent studies - AdCa with predominant BAC and small (<0.5cm) central scarring in tumor of ≤3cm have a similar favorable prognosis (~30%)
  - AdCa <2cm with BAC, without central desmoplastic reaction, 100% survival at 10 yrs
Bronchioloalveolar carcinoma macroscopy
Mucinous carcinoma

Non mucinous carcinoma
Mucinous Bronchioloalveolar carcinoma cytology/cell block

CK20

TTF1

CK7

BAC cell block
Large cell lung cancer (LCLC)

- Most peripheral
- 9%
- Locoregional invasion common to pleura, chest wall
- Metastases
- Poorly differentiated neoplasms
- Originate from a common pluripotent progenitor cell
LCLC – differential diagnosis

- Poorly differentiated SCC
- Poorly differentiated ADC/solid
- LCNEC

No precursor lesions
Non-small Cell Lung Cancer: NOS
Large cell carcinoma
Non-small Cell Lung Cancer: NOS
The concept of Neuroendocrine tumors

- Carcinoid
- Atypical carcinoid (AC)
- Large cell neuroendocrine tumor (LCNEC)
- Small cell lung cancer (SCLC)

- All in different categories in the WHO classification.
- WHO nomenclature to be used.
Low grade neuroendocrine tumors
Carcinoid v` Atypical carcinoid

- 2-10 mitotic figures/10 high power fields
- Necrosis – small foci
- Cytologic atypia – non significant

Thus – small biopsies may be non diagnostic between the two diagnoses.

**Both:**

- 20-40% are not smoking related
- May occur in patients with MEN
- May be associated with NE cell hyperplasia +/- tumorlets
High grade neuroendocrine tumors

- LCNEC - >11mf/10hpf
- Most LCNEC and SCLC – 70-80mf/10hpf
- Typical morphology for each tumor
- Histological heterogeneity, common
- Most are smoking related
- To be differentiated from NSCLC with NE differentiation
Treatment Selection in Advanced NSCLC

The OLD Way
- Empiric
  - Comparison of RR, PFS, and OS only in randomized, controlled trials
  - Best numbers = Standard of care

The NEW Way
- Rational
  - Emphasis on “targeted therapy”
  - Molecular targets
  - Histology guides therapeutic options
Conclusions

- Targeted therapies have demonstrated a survival benefit in selected patients with NSCLC
- Treatment of NSCLC should be individualized
  - Histology
  - Molecular markers
Targeted Therapies

- Erlotinib
- Bevacizumab
- Sunitinib
- Sorafenib
- Chemotherapy

Inhibition of programmed cell death (apoptosis)

Tumor cell proliferation

Tumor cell invasion/metastasis

Development of tumor vasculature (angiogenesis)
KRAS and EGFR

- EGFR and KRAS mutations in NSCLC are mutually exclusive
- KRAS is downstream in the EGFR pathway
- KRAS mutations are seen in a subset of patients with NSCLC
  - More common in smokers than non-smokers
  - More common in adenocarcinomas
- NSCLC patients with KRAS mutations may be less likely to respond to EGFR-TKIs
Tyrosine kinase inhibitors (ATP-binding cleft)

Ligand-binding domain

EGFR

Ligand

Receptor antibodies

PI3K

PTEN

Akt

mTOR

STAT 3/5

Survival

Proliferation

Markers of Interest for EGFR tyrosine kinase inhibitors: EGFR

- EGFR expression by IHC
  - Least helpful

- EGFR gene copy number by FISH

- EGFR mutations
  - Sensitizing: exons 19, 21, and others
  - Predictive of resistance: exon 20, T790
Squamous Cell Carcinoma:
EGFR Positive
EGFR
Gene copy number/
FISH assay
Molecular genetic abnormalities (potential therapeutic targets):

<table>
<thead>
<tr>
<th>Oncogenes, Tumor suppressor genes</th>
<th>SCLC</th>
<th>NSCLC</th>
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<tbody>
<tr>
<td>Myc, p53, Rb, p3, 1q3p, 9p, 11p, Rb, Her2</td>
<td>Myc</td>
<td>Myc, K-ras, Her2</td>
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Pathology/Early microscope

Molecular biology