Histopathology of NSCLC, IHC markers and pTNM classification

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The management of patients with lung cancer is becoming ever more dependant on a knowledge of the pathology of each patient’s disease

‘Know your enemy’

Sun Tzu, The Art of War.
The management of patients with lung cancer is becoming ever more dependant on a knowledge of the pathology of each patient’s disease.

Lung cancer is

• NOT a single disease

• NOR is it just two diseases: Small Cell Carcinoma and Non-small Cell Carcinoma
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Lung cancer is

• NOT a single disease

• NOR is it just two diseases: Small Cell Carcinoma and Non-small Cell Carcinoma

Non-Small Cell Carcinoma is NOT a specific biological entity

• more a classification of convenience driven by a lack of therapeutic choice
2015 WHO Classification of Lung Tumours (part 1!!)

- **1-2: Adenocarcinoma**
  - 1-2A Invasive adenocarcinoma
  - 1-2B Variants of invasive adenocarcinoma
  - 1-2C Minimally invasive adenocarcinoma
  - 1-2D Preinvasive lesions
    - 1-2D-i: Atypical adenomatous hyperplasia
    - 1-2D-ii: Adenocarcinoma in situ

- **1-3: Squamous cell carcinoma**
  - 1-3A: Keratinizing and nonkeratinizing squamous cell carcinoma
  - 1-3B: Basaloid carcinoma
  - 1-3C: Preinvasive lesion: Squamous carcinoma

- **1-4: Neuroendocrine Tumours**
  - 1-4A: Small cell carcinoma
  - 1-4B: Large cell neuroendocrine carcinoma
  - 1-4C: Carcinoid tumors
  - 1-4D: Preinvasive lesion: DIPNECH

- **1-5: Large cell carcinoma**

- **1-6: Adenosquamous carcinoma**

- **1-7: Sarcomatoid carcinoma**
  - 1-7A: Pleomorphic, spindle cell and giant cell carcinoma
  - 1-7B: Carcinosarcoma
  - 1-7C: Pulmonary blastoma

- **1-8: Other carcinomas**
  - 1-8A: Lymphoepithelioma-like carcinoma
Small Cell Carcinoma of the Lung

- Nuclear features key to diagnosis
- Neuroendocrine markers and TTF1 IHC positive but not required for diagnosis
- Accurately diagnosed on cytology
- Aggressive disease, usually Stage 4 at presentation

- Therapeutic relevance
  - chemotherapy choice
  - radiotherapy strategy
  - prognosis
So all those other, biologically diverse malignant diseases are NOT small cell carcinomas – so we call them non-small cell carcinoma (NSCLC)

• Adenocarcinoma
• Squamous cell carcinoma
• Neuroendocrine tumours apart from SCLC
• Large Cell Carcinoma
• Adenosquamous Carcinoma
• Sarcomatoid Carcinomas
• Others
Atypical Adenomatous Hyperplasia (AAH) → Adenocarcinoma-in-situ → Invasive Adenocarcinoma

Two pathways (at least) of Lung Carcinogenesis:

- Bronchial Squamous Dysplasia → Squamous carcinoma-in-situ → Invasive Squamous Cell carcinoma
- Adenocarcinoma-in-situ → Invasive Adenocarcinoma
Central Bronchial Carcinogenesis?

- The progenitor cells express p63, p40, Cytokeratins 5&6

Peripheral airway Carcinogenesis?

- The progenitor cells Express TTF1
- The Terminal Respiratory Unit TRU
Adenocarcinoma

- Commonest subtype of lung cancer
- Associated with tobacco carcinogenesis
- Commonest subtype by far in never smokers
- Addictive oncogenic drivers are frequent in adenocarcinomas NOT associated with tobacco carcinogenesis

- Relatively inaccurately diagnosed by morphology alone
- ONLY 75-80% express TTF1

- Therapeutic relevance
  - Chemotherapy choice, Surgery choice
  - Anti-angiogenic agents for safety and efficacy
  - Testing for addictive oncogenic targets
  - Testing strategy for immuno-oncology therapy?
Five histological patterns of adenocarcinoma: Most cases are mixtures, Pure forms are rare

Lepidic

Papillary

Solid

Acinar

Micropapillary
Post operative survival vs predominant pattern in pulmonary adenocarcinoma

Yoshizawa A et al. Mod Pathol 2011; 24, 653-664   Stage 1 only
Russell PA et al. J Thorac Oncol 2011; 6,1496-1504 Stages 1-3
Warth A et al. J Clin Oncol 2012; Mar 5 epub     Stages 1-4
Squamous Cell Carcinoma

- Still common in populations who smoke
- Archetypal cancer of central, bronchial tobacco-driven carcinogenesis
- Rare in never smokers; rarely driven by addictive oncogene
- Relatively accurately diagnosed by morphology
- Most strongly express p63, p40, CK5/6

Therapeutic relevance
  - Chemotherapy choice
  - Toxicity and efficacy of anti-angiogeneics
  - Choice of molecular testing
  - Immunotherapy choice?
Neuroendocrine tumours other than SCLC

Large Cell Neuroendocrine Carcinoma (LCNEC)

- High grade neuroendocrine carcinoma
- Strongly associated with tobacco carcinogenesis
- Molecularly similar to SCLC
- Generally a diagnosis for surgically resected tumours only, however.........
- Requires immunohistochemistry

- Therapeutic relevance
  - Chemotherapy choice?
  - Uncertainty due to diagnostic problems in advanced disease
Neuroendocrine tumours other than SCLC

Typical Carcinoid
- Usually central bronchial tumour, Obstructive pneumonia
- Paradoxical lesion
  - Low grade, wrong location
- Metastatic disease rare
  - 10% regional nodes
  - Distant metastases very rare

Atypical Carcinoid
- Very rare, Relatively aggressive
- Mitoses & necrosis – area dependent: 2mm²

Diagnosis on small samples vs surgical material

Therapeutic relevance
- Context important
  - bronchial polyp or peripheral nodule
- Confusion with SCLC in biopsy or cytology
Large Cell Carcinoma

- ONLY diagnosed on surgical resection
- NEVER a diagnosis on small biopsy or cytology
- Most cases (66%) re-assigned as squamous or adenocarcinoma by IHC (WHO 2015)

Therapeutic relevance
- Relatively aggressive tumour
- KRAS mutation dominant
Adenosquamous Carcinoma

• Relatively rare tumour
• Relatively aggressive tumour
• Peripheral or central?
• Requires minority component to comprise at least 10% of the lesion
• A surgical resection diagnosis
  • Small biopsy or cytology suspicion only
  • Morphology vs IHC

• Therapeutic relevance
  • Manage like adenocarcinoma
Sarcomatoid Carcinoma

• Very rare lesions
• Pleomorphic carcinoma if >10% of lesion shows pleomorphic, spindle or giant cells
• Usually combined with squamous cell or adenocarcinoma
• Surgical resection for definitive diagnosis
• Therapeutic relevance
  • Chemoresistant
  • KRAS mutations relatively frequent
  • Found in TKI-recurrent disease
  • MET exon14 skipping mutations?
The subtyping accuracy of NSCLCs in small biopsy and cytology was inaccurate by morphology alone

- Previous WHO classifications not designed for small samples
- This drove the adoption of the NSCLC-NOS diagnosis
- Which became a problem when therapy diversified by histology

- Most NSCLC-NOS diagnosis came from differentiated tumours
  - 67% were adenocarcinoma when resected Edwards S et al 2000

- Immunohistochemistry has transformed this diagnostic landscape
  - NSCLC-NOS rates should be <10% cases
Bronchial Basal cells express p63, p40 and CK5/6

TRU epithelium expresses TTF1

Normal

Dysplasia

Squamous CIS

Normal

AAH

AIS

Invasive Adenocarcinoma (75-80% express TTF1)

Invasive Squamous Cell Carcinoma (~100% express these markers)
NSCLC – probably adenocarcinoma

TTF1 positive in tumour cell nuclei

Tumour cells express Nuclear p63

NSCLC – probably squamous cell
Subtyping NSCLC: How good?

- Predictive IHC has ‘levelled the playing field’
- Better diagnosis possible on poorer specimens

Bar chart showing:
- Cytology plus IHC: 6% Specific subtype, 40% NSCLC-NOS
- Cytology Morphology: 25% Specific subtype, 75% NSCLC-NOS
- Topsy Morphology: 0% Specific subtype, 100% NSCLC-NOS
Lung Cancer Classification and sample type

WHO 2004 (et prev): intended for, and only applicable to, resected cases
- Small Cell Carcinoma
- Squamous Cell Carcinoma
- Adenocarcinoma
- Large cell carcinomas
- Sarcomatoid carcinomas
- Adenosquamous carcinomas
- Carcinoid tumours
- Salivary-type carcinomas

WHO 2015: a simplified classification intended for small sample diagnosis
- Small Cell Carcinoma
- Squamous Cell Carcinoma
  - Probable Squamous Cell Carcinoma
- Adenocarcinoma
  - Probable Adenocarcinoma
- NSCLC-NOS
  - NSCLC-NOS (null IHC)
- Carcinoid tumour
- Salivary-type (occasionally)
pTNM classification (7th edition: adopted by UICC and AJCC)

- Tumour Nodes Metastases
- pTNM based upon pathological examination
Carcinoma in situ: pTis

Squamous Carcinoma In situ

Adencarcinoma In situ - AIS
pT1a
≤ 2cm

The lesion MUST NOT Involve a main bronchus

Unless...........

pT1b
>2cm but ≤ 3cm
The lesion involving the main bronchus is a superficial spreading lesion with invasion limited to the bronchial wall – pT1a
pT2a: >3 cm ≤ 5 cm

pT2b: >5 cm ≤ 7 cm
Pleural invasion upstages a tumour to pT2
Regardless of size, this tumour is associated with atelectasis of a whole lobe. Obstuctive pneumonitis extending to the hilar region but not involving the whole lung.
Small tumour but it involves main bronchus

T2
Chest wall

pT3

Invasion of Mediastinal pleura

Chest wall

Superior sulcus

Phrenic nerve

Diaphragm

Parietal pericardium

Main bronchus within 2cm of carina

Chest wall
pT3

Atelectasis or Obstructive Pneumonitis of the entire lung
pT3

'Same lobe'

Intrapulmonary metastases
Satellite nodules may be histological findings but there is no definition of a ‘nodule’
pT4 Invasion of
Mediastinum
Heart
Great vessels
Trachea
Recurrent laryngeal nerve
Oesophagus
Vertebral body
Carina

SVC Obstruction
pT4

‘Different lobe’
Intrapulmonary metastases

Left upper lobe
Primary tumour

Oblique fissure

Left lower lobe
metastasis

Issues with Pulmonary Metastases versus synchronous Primary tumours
Which part or element of adenocarcinoma should be measured to determine T status?

- Lepidic growth
- Invasive tumour

Lepidic growth is often measured to determine T status in adenocarcinoma.
pN disease identified by pathological examination
Histology can define node positive disease

N1  Stations 10 - 14
N2  Subcarinal Station 7
N3  Contralateral mediastinal or hilar nodes
    Scalene or supraclavicular nodes
The presence of isolated tumor cells and micrometastases in the intrathoracic lymph nodes of patients with lung cancer is not associated with decreased survival

Alberto M. Marchevsky MD,*, Ruta Gupta MD, Donato Kusuanco BS, James Mirocha MS, Robert J. McKenna Jr MD

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<th>p-Value</th>
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<td>Hashimoto</td>
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**Molecular**

NS p = 0.138

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**IHC**

NS p = 0.462
M1a

Contralateral lung metastases
Pleural nodules
Malignant pleural or pericardial effusion

M1b

Distant Metastases
- Liver, Adrenals, Bone, Brain, Skin, etc etc
- Cervical nodes above scalene are also M1

M1a or M1b defines Stage 4 disease
TNM defines Stage – Stage defines prognosis
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