BDIAP Kristin Henry Lecture

Evolution of classifications in lung pathology

Nottingham Pathology 2016

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Nottingham, UK

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Deutsch G et al. AJRCCM 2007:176:1120-8

Classification of diffuse lung disease in infants: the reality of groups.

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...The ontological thesis I shall defend is that groups are material particulars. This ontological holism is a position motivated by...consideration of consistency in our taxonomic practices...
WHO Histologic Classification of Tumors of the CNS

1. Tumors of Neuroepithelial Tissue
2. Tumors of Cranial and Spinal Nerves
3. Tumors of the Meninges
4. Tumors of Uncertain Histogenesis
   a. Hemangioblastoma from primitive vascular structures
   b. Lymphomas and Hematopoietic Neoplasms
5. Germ Cell Tumor
   a. Ex: Germinoma - common in pineal gland area
   b. Cysts and Tumor-like lesions
5. Usually in the third ventricle
6. Tumors of the Sellar Regions
7. Local Extension from Regional Tumors
8. Metastatic Tumors

| Category | Definition (Involvement of):  
|----------|-------------------------------|
| T1       | Encapsulated or unencapsulated, with or without extension into mediastinal fat  
|          | a: Extension into mediastinal pleura                                      |
| T2       | Pericardium                                                                 |
| T3       | Lung, Brachiocephalic Vein, Superior Vena Cava, Chest Wall, or Phrenic Nerve |
| T4       | Aorta, Main Pulmonary Artery, Myocardium, Trachea, or Esophagus            |
AIMS OF PRESENTATION

- Review classifications in thoracic pathology and how they have changed in the past 20 years.
- Understand how and why classifications are formed and evolve.
- Consider requirements for future classifications.
- Update on thoracic pathology.
What is classification?

A systematic arrangement of similar entities on the basis of certain differing characteristics.

Entities are grouped into functionally (clinically) relevant groups.

Groupings may be based on a variety of characteristics dependent on the purpose of classification.
WHERE AND WHAT IS A WHO CLASSIFICATION?

A pathologic and genetic classification of human tumors designed to be accepted and used worldwide.

- Provides standard criteria for
  - Pathology diagnosis
  - Clinical practice
  - Cancer registration
  - Epidemiologic studies
  - Clinical trials
  - Cancer research

157 Authors from 29 countries

WHO classifications
1981
1999
2004
2015
REQUIREMENTS OF A CLASSIFICATION SYSTEM

March 30th 1998

- REPRODUCIBLE (strict and recognisable set of criteria)
- GLOBALLY APPLICABLE (that everyone can apply)
- THOROUGH (which can deal with atypical variants)
- DYNAMIC (adapts to recent advances)
- NOT EMBARRASSING
“~70% of non-small cell lung cancer presents in an advanced stage”

“No classification for biopsies”
Rationale For New ADC Classification
IASLC/ATS/ERS sponsored meeting(s)

Multidisciplinary criticisms in relation to 2004 classification...

- No classification for biopsies

- Bronchioloalveolar carcinoma (BAC) — confusing used many different ways despite 99/04 WHO; mucinous and non-mucinous

- Greater clinical relevance (too ſor pathologists by pathologistsœ듰 )

- Take into account rapid evolving molecular advances (EGFR)
BAC – BRONCHIOLOALVEOLAR CARCINOMA

RIP – REST IN PEACE

March 31, 2008
1-1: Introduction

1-1A Lung cancer staging and grading

1-1B Rationale for classification in small biopsies and cytology

1-1C Terminology and criteria in non-resection specimens

1-1D Molecular testing for treatment selection in lung cancer
### Specific Terminology and Criteria for Adenocarcinoma, Squamous Cell Carcinoma and Non-Small Cell Carcinoma-NOS in Small Biopsies and Cytology

<table>
<thead>
<tr>
<th>2015 WHO Classification in resection specimens</th>
<th>Morphology/Stains</th>
<th>New Small Biopsy/Cytology Terminology</th>
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<tbody>
<tr>
<td><strong>ADENOCARCINOMA</strong> (Predominant pattern)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acinar</td>
<td>Morphologic adenocarcinoma patterns clearly present</td>
<td>Adenocarcinoma (describe identifiable patterns present)</td>
</tr>
<tr>
<td>Papillary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micropapillary</td>
<td></td>
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</tr>
<tr>
<td><strong>Lepidic (nonmucinous)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Invasive mucinous adenocarcinoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Colloid adenocarcinoma</strong></td>
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<td><strong>Fetal adenocarcinoma</strong></td>
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<td><strong>Enteric adenocarcinoma</strong></td>
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<td><strong>SQUAMOUS CELL CARCINOMA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Morphologic squamous cell patterns clearly present</strong></td>
<td></td>
<td>Squamous cell carcinoma</td>
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**Adapted from**: Travis WD et al. IASLC/ATS/ERS classification of ADCs J Thor Oncol 2011;6:244-285
### SPECIFIC TERMINOLOGY AND CRITERIA FOR ADENOCARCINOMA, SQUAMOUS CELL CARCINOMA AND NON-SMALL CELL CARCINOMA-NOS IN SMALL BIOPSIES AND CYTOLOGY†

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<td></td>
<td>Adenocarcinoma with lepidic pattern (if pure, add note: an invasive component cannot be excluded)</td>
</tr>
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<td>Invasive mucinous adenocarcinoma</td>
<td></td>
<td>Invasive mucinous adenocarcinoma (describe patterns present; use term mucinous adenocarcinoma with lepidic pattern if pure lepidic pattern – see text)</td>
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DO NOT CLASSIFY BIOPSIES AS ADENOCARCINOMA IN SITU

Adenocarcinoma with a purely lepidic pattern in this sample

Biopsy here will show lepidic only

Biopsy here will show lepidic and other invasive patterns

Over 50% of pure GGO lesions >10mm had invasive areas

Lim HJ et al. Persistent pure ground-glass nodules>10mm at CT: histopathologic comparisons. Chest 2013;144
### CLASSIFICATION FOR SMALL BIOPSIES/CYTOLOGY COMPARING 2015 WHO TERMS WITH NEW TERMS FOR SMALL CELL CARCINOMA, LARGE CELL NEUROENDOCRINE CARCINOMA, ADENOSQUAMOUS CARCINOMA AND SARCOMATOID CARCINOMA †

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<tr>
<th>2015 WHO Classification</th>
<th>SMALL BIOPSY/CYTOLOGY: IASLC/ATS/ERS</th>
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<tbody>
<tr>
<td>SMALL CELL CARCINOMA</td>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td>LARGE CELL NEUROENDOCRINE CARCINOMA (LCNEC)</td>
<td>Non-small cell carcinoma with neuroendocrine (NE) morphology and positive NE markers, possible LCNEC</td>
</tr>
<tr>
<td>ADENOSQUAMOUS CARCINOMA</td>
<td>Morphologic squamous cell and adenocarcinoma patterns present: Non-small cell carcinoma, NOS, (comment that adenocarcinoma and squamous components are present and this could represent adenosquamous carcinoma).</td>
</tr>
<tr>
<td>No counterpart in 2015 WHO classification</td>
<td>Morphologic squamous cell or adenocarcinoma patterns not present but immunostains favor separate glandular and adenocarcinoma components Non-small cell carcinoma, NOS, (specify the results of the immunohistochemical stains and the interpretation) Comment: this could represent adenosquamous carcinoma.</td>
</tr>
<tr>
<td>Pleomorphic, spindle and/or giant cell carcinoma</td>
<td>NSCC with spindle and/or giant cell carcinoma (mention if adenocarcinoma or squamous carcinoma are present)</td>
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Programmed death-1 Ligand 1 (PD-L1) and 2 are highly expressed in pleomorphic carcinomas of the lung: Comparison of sarcomatous and carcinomatous areas. Kim S et al. Eur J Cancer. 2015;51:2698-707

High co-expression of PD-L1 and HIF-1α correlates with tumour necrosis in pulmonary pleomorphic carcinoma. Chang YL et al. Eur J Cancer. 2016 epub
### USE OF IMMUNOHISTOCHEMISTRY WHEN A TUMOUR SHOWS NON-SMALL CELL CARCINOMA-NOT OTHERWISE SPECIFIED (NOS) IN SMALL BIOPSIES AND CYTOLOGY

**SPECIFIC TERMINOLOGY AND CRITERIA FOR ADENOCARCINOMA, SQUAMOUS CELL CARCINOMA AND NON-SMALL CELL CARCINOMA-NOS IN SMALL BIOPSIES AND CYTOLOGY**

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<td><strong>Adenocarcinoma (solid pattern may be just one component of the tumor)</strong> ‡</td>
<td>Morphologic adenocarcinoma patterns not present, but supported by special stains, i.e. +TTF-1</td>
<td>Non-small cell carcinoma, favour adenocarcinoma using IHC</td>
</tr>
<tr>
<td><strong>Squamous cell carcinoma, (nonkeratinizing pattern may be just one component of the tumor)</strong> ‡</td>
<td>Morphologic squamous cell patterns not present, but supported by stains i.e. +p40</td>
<td>Non-small cell carcinoma, favour squamous cell carcinoma using IHC</td>
</tr>
<tr>
<td><strong>LARGE CELL CARCINOMA</strong></td>
<td>No clear adenocarcinoma, squamous or neuroendocrine morphology or staining pattern</td>
<td>Non-small cell carcinoma, not otherwise specified NSCLC-NOS using IHC</td>
</tr>
</tbody>
</table>

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GENERAL PRINCIPLES

- Cut tissue block as sparingly as possible
- Obtain unstained slides for molecular at time of cutting block for IHC
- Minimize stains to maximize tissue for molecular testing by using a limited panel of IHC (i.e. TTF-1 and P40)
- Further molecular testing, if clinically appropriate, can be performed on remaining tissue
LIGHT MICROSCOPY

SQUAMOUS CELL CARCINOMA
- 20-30%

NSCLC-NOS
- 20-40%

ADENO-CARCINOMA
- 40-50%

NEW CLASSIFICATION

TTF-1 and P40

GOAL = 5%
No clear ADC or SQCC morphology:

**NSCLC-NOS**

**Classic Morphology:**
- SQCC
- Keratinization, pearls, and/or intercellular bridges

**NE morphology, small cells, no nucleoli, NE IHC+, TTF-1 +/-, CK**

**Mucin**

**SCLC**

**Histology:** Lepidic, papillary, micropapillary and/or acinar architecture(s)
- Cytology: 3-D arrangements, delicate foamy/vacuolated (translucent) cytoplasm, Fine nuclear chromatin and often prominent nucleoli
- Nuclei are often eccentrically situated

**Classic morphology:**
- ADC

**STEP 1**
- POSITIVE BIOPSY (FOB, TBBx, Core, SLBx)
- NE morphology, large cells, NE IHC+

**STEP 2**
- POSITIVE CYTOLOGY (effusion, aspirate, washings, brushings)
- No clear ADC or SQCC morphology: NSCLC-NOS
- ADC marker and/or Mucin +ve; SQCC marker –ve (or weak in same cells)
- IHC –ve and Mucin –ve
- ADC marker or Mucin +ve; as well as SQCC marker +ve in different cells

**STEP 3**
- Molecular analysis: e.g. EGFR mutation, ALK rearrangement†
- NSCLC, favor ADC
- NSCLC, NOS, possible adenosquamous ca
- NSCLC, NOS, possible adenosquamous ca
- NSCLC, favor ADC
- NSCLC, favor SQCC

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Morgensztern, D-C et al. Journal of Thoracic Oncology. 10:S1-S63, January 2015

NEXT GENERATION SEQUENCING

IMMUNOMODULATORY THERAPY (e.g. PD-L1)
PUBCAN – ONLINE WHO BOOK COMING SOON – CAN BE UPDATED

www.pubcan.org
WHO Classification Of Adenocarcinoma 2004

Adenocarcinoma
- Mixed subtype
  - Acinar
  - Papillary
- Bronchioloalveolar carcinoma
  - Nonmucinous
  - Mucinous
  - Mixed mucinous and non-mucinous
- Solid adenocarcinoma with mucin formation

Variants
Preinvasive Lesions

- AAH
- ADC-in-situ (formerly pure BAC) *most non-mucinous (NM) (30mm or less)

Invasive

- Minimally invasive (< 5mm invasion) (30mm or less)
- Lepidic pattern predominant
- Acinar pattern predominant/pure
- Papillary pattern predominant/pure
- Micropapillary pattern predominant/pure
- Solid pattern predominant/pure
- Invasive mucinous adenocarcinoma

A multidisciplinary approach
- Respiratory Physician
- Imaging
- Surgery
- Oncology
- Pathology
- Molecular Biology
ADENOCARCINOMA-IN-SITU