The Changing Spectrum of Lung Adenocarcinoma

An update on the 2015 WHO classification of lung tumors

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WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart

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New Classification: Rationale

“To address advances in oncology, molecular biology, pathology, radiology, and surgery of lung adenocarcinoma... a new adenocarcinoma classification is needed to:

1. Provide uniform terminology and diagnostic criteria, especially for broncholoalveolar carcinoma (BAC)
2. Provide guidelines to the overall approach to small nonresection cancer specimens (ie. FNAs and biopsies)
3. Give direction for multidisciplinary strategic management of tissue for molecular and immunohistochemical studies
Adenocarcinoma Classification: Timeline of Change

1. Pre-2004
   - No therapeutic implication of distinguishing histologic subtypes (adenoCA vs. SqCC)
   - Only significant distinction significance was SCC vs. NSCC

2. 2004 WHO Classification
   - BAC was recognized and all adeno CA’s were “mixed subtype”

3. Post-2004 therapeutic revolution
   - Pemetrexed and bevacizumab therapy differences in adenoCA vs. SqCC
   - Targeted therapy for EGFR gene mutation and ALK fusion in adenoCA

4. 2011 IASLC/ATS/ERS lung adenocarcinoma classification
   - Developed to respond to these therapeutic developments and address confusion and non-standardization in lung tumor classification and grading

5. 2015 WHO Classification
   - Uses 2011 IASLC/ATS/ERS system to provide classification system based on new understanding of histomorphology with incorporation of immunohistochemical characteristics
New Standardized Diagnostic Criteria and Terminology for Small Biopsies and Cytology

1. If NSCC has classic morphologic features of adenocarcinoma or squamous cell carcinoma, those terms may be used without further comment or work-up.

2. If NSCC does not show classic morphologic features, it is classified as NSCC-NOS:
   - Then do “limited” stain work-up
   - Tumors positive for adenoCA marker or mucin are classified as NSCC-favor adenocarcinoma
   - Tumors positive for squamous marker with negative adenoCA marker are classified as NSCC-favor SqCC

3. If tumor still cannot be classified after staining, it remains NSCC-NOS.
<table>
<thead>
<tr>
<th>2004 WHO Classification, Including Updated IASLC/ATS/ERS Terminology</th>
<th>Morphology/Stains</th>
<th>IASLC/ATS/ERS Terminology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adenocarcinoma</strong></td>
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<tr>
<td>Mixed subtype</td>
<td>Morphologic adenocarcinoma patterns clearly present</td>
<td>Adenocarcinoma (describe identifiable patterns present)</td>
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<tr>
<td>Acinar</td>
<td></td>
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<tr>
<td>Papillary</td>
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<tr>
<td>Solid</td>
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<tr>
<td>Micropapillary</td>
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<tr>
<td>Lepidic (nonmucinous)</td>
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<tr>
<td>Lepidic (mucinous)</td>
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</tr>
<tr>
<td>No 2004 WHO counterpart; most will be solid adenocarcinomas</td>
<td>Morphologic adenocarcinoma patterns not present (supported by special stains, ie, +TTF-1)</td>
<td>Non-small cell carcinoma, favor adenocarcinoma</td>
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<tr>
<td><strong>Squamous cell carcinoma</strong></td>
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<tr>
<td>No 2004 WHO counterpart</td>
<td>Morphologic squamous cell patterns clearly present</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td><strong>Large cell carcinoma</strong></td>
<td>Morphologic squamous cell patterns not present (supported by stains, ie, +p40)</td>
<td>NSCLC, favor squamous cell carcinoma</td>
</tr>
<tr>
<td>No clear adenocarcinoma, squamous or neuroendocrine morphology or staining pattern</td>
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</tbody>
</table>

Abbreviations: IASLC/ATS/ERS, International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society; NSCLC, non-small cell lung carcinoma; TTF-1, thyroid transcription factor-1; WHO, World Health Organization.


* NSCLC-NOS pattern can be seen not only in large cell carcinoma but also when the solid, poorly differentiated component of adenocarcinoma or squamous cell carcinoma is sampled but does not express immunohistochemical markers or mucin.
Classification in Resection Specimens: Key Changes

1. Discontinuation of the term “Bronchioloalveolar Carcinoma (BAC)”

2. New histomorphologic subclassification system for adenocarcinoma that has prognostic implications and may provide a substrate for a standardized grading system for lung adenocarcinoma
Bronchioloalveolar Carcinoma (BAC)

BAC was recognized to describe at least 5 separate entities with disparate clinical and molecular properties.

**TABLE 3. Categories of New Adenocarcinoma Classification Where Former BAC Concept was Used**

1. Adenocarcinoma in situ (AIS), which can be nonmucinous and rarely mucinous
2. Minimally invasive adenocarcinoma (MIA), which can be nonmucinous and rarely mucinous
3. Lepidic predominant adenocarcinoma (nonmucinous)
4. Adenocarcinoma, predominantly invasive with some nonmucinous lepidic component (includes some resected tumors, formerly classified as mixed subtype, and some clinically advanced adenocarcinomas formerly classified as nonmucinous BAC)
5. Invasive mucinous adenocarcinoma (formerly mucinous BAC)

BAC, bronchioloalveolar carcinoma.
To address two of these entities, the terms Adenocarcinoma in situ (AIS) and Minimally Invasive Adenocarcinoma (MIA) were proposed.

AIS and MIA should define patients with 100% or near 100% 5-year disease survival if completely resected.
Preinvasive Lesions: Adenocarcinoma in situ and Atypical Adenomatous Hyperplasia

**Atypical Adenomatous Hyperplasia (AAH)**
- AAH is a localized, small ($\leq 0.5$ cm) proliferation of mild to moderately enlarged type II pneumocytes and or Clara cells lining alveolar walls and respiratory bronchioles
- Continuum of morphologic changes with AIS
- Counterpart to squamous dysplasia
- Grading not recommended
Adenocarcinoma in situ

- AIS is defined as a localized, small ($\leq 3$ cm) adenocarcinoma composed of neoplastic pneumocytes growing along pre-existing alveolar structures (lepidic growth)
- NO stromal, vascular, or pleural invasion
- NO invasive histological patterns such as acinar, papillary, micropapillary or any other intra-alveolar tumor cell growth
- Solitary and well-circumscribed
- Never diagnose on small biopsy (instead say “Adenocarcinoma with lepidic growth pattern, cannot exclude invasion”
Adenocarcinoma in situ (non-mucinous)
Adenocarcinoma in situ (non-mucinous)
Adenocarcinoma in situ (mucinous)

- Note: Pure mucinous AIS is very rare
- Most lesions formerly called “mucinous BAC” are actually Invasive Mucinous Adenocarcinoma, which is a new separate 2015 WHO category
- Often are negative for TTF-1 and Napsin A
- Often harbor KRAS mutations (90%)
What not to do

• What not to do is think that Adenocarcinoma in situ is just a new name for good old BAC
• Most of the tumors previously called BAC were actually invasive carcinomas, thus mixing together tumors with a wide range of aggressiveness and metastatic potential
• AIS has strict diagnostic criteria to assure lesions diagnosed as such will have 100% disease-free survival and in which surgery is curative
AIS: Staging

2015 WHO: “Although the current TNM classification does not address adenocarcinoma in situ in the lung, if the TNM staging principles for other tumors such as breast cancer were applied, adenocarcinoma in situ would be classified as Tis. Because carcinoma in situ can occur with both lung squamous cell carcinoma and adenocarcinoma in situ, these should be further classified as Tis (squamous) or Tis (adenocarcinoma).”
Minimally Invasive Adenocarcinoma

- Defined as a small, solitary adenocarcinoma (≤ 3 cm), with a predominantly lepidic pattern and ≤ 5 mm invasion in greatest dimension
- MIA is usually non-mucinous but may be mucinous
- Invasion = any subtype besides lepidic or tumor cells infiltrating myofibroblastic stroma
- Lesions that look like AIS/MIA but are larger than 3 cm = “Lepidic-predominant adenocarcinoma” with note saying AIS or MIA is suspected – this is because there is insufficient data to show that these patients have 100% 5-year disease free survival
Minimally Invasive Adenocarcinoma
Invasive Adenocarcinoma

- Invasive adenocarcinomas often demonstrate a heterogeneous mixture of histologic patterns
- THEN: Most adenocarcinoma were subclassified as “mixed-subtype”, if subclassified as all, usually with some comment on differentiation (grade)
- NOW: Classify adenocarcinoma per predominant subtype
  - Semiquantitative subtyping in 5-10% increments
  - “It is useful to record in the diagnosis each adenocarcinoma subtype that is present along with the percentages”
Invasive Adenocarcinoma Subtypes

- **Lepidic**
  - Mostly lepidic growth with at least one focus of invasion measuring over 5 mm or any invasion of lymphatics, pleura, or contains tumor necrosis
  - Early stage lepidic-predominant adenocarcinoma has 86-90% 5-year disease-free survival

- **Acinar** (gland forming)

- **Solid**

- **Papillary**

- **Micropapillary**

- **Other less common subtypes**: Mucinous, Colloid, Fetal, Enteric
Lepidic Pattern
Acinar Pattern
Papillary Pattern
Micropapillary Pattern
Solid Type
Invasive Mucinous Adenocarcinoma

- Strong correlation with KRAS mutation
- Tumor cells have goblet cell or columnar cell morphology with abundant intracytoplasmic mucin; areas of stromal invasion show less mucin and more atypia
- Strong tendency for multicentric, multilobular, bilateral lung involvement (?aerogenous spread)
**Last word: Lung cancer grading**

- Tumor grading: Division of a specific tumor group into two or more prognostically relevant grades based on morphologic appearance.
- Unlike other tumors with widely accepted grading systems, such as breast (Elston) and prostate (Gleason), such a system has not been accepted for lung cancer.
The new histologic classification system may provide the basis for a simple architectural grading system applicable to resection specimens. Predominant histologic subtypes have been shown to be associated with prognostic differences. These grades seem to correspond well to well-, moderately, and poorly differentiated tumors.

- Grade I: Lepidic
- Grade II: Acinar, Papillary
- Grade III: Micropapillary, Solid

Several more complicated systems have been proposed.
Thank you!