Histology – The Reclassification of Adenocarcinoma

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The Essentials of CT Screening for Lung Cancer
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Disclosures and Conflict of Interest

• None to declare for this presentation

Objectives

• Understand the changes in new lung adenocarcinoma classification providing better pathological-radiological and clinical correlations
• Learn how the new classification informs shared decision making for personalized patient management

History of Lung ADC Sub-Classification

According to the WHO

<table>
<thead>
<tr>
<th>Year</th>
<th>Terminology</th>
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<tbody>
<tr>
<td>1967</td>
<td>Bronchogenic, Acinar, Papillary, Bronchioloalveolar</td>
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<tr>
<td>1981</td>
<td>Acinar ADC, Papillary ADC, BAC solid carcinoma, BAC solid with mucin formation</td>
</tr>
<tr>
<td>1999</td>
<td>Acinar, Papillary, BAC, Mixed mucinous and nonmucinous, Solid ADC with mucin production</td>
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<tr>
<td>2004</td>
<td>ADC, mixed subtype, Acinar ADC, Papillary ADC, BAC</td>
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New 2011 International Lung Adenocarcinoma Classification

• Given advances in molecular sciences, overlap and confusion in pathology and imaging terminologies, a new International Lung Adenocarcinoma Classification was introduced in 2011
• New terminologies such as adenocarcinoma in-situ (AIS), minimally invasive adenocarcinoma (MIA) and lepidic predominant adenocarcinoma (LPADC) were introduced
• The new classification has implications for radiologists and the 7th edition of the TNM staging
• The clinical implication of single or multiple subsolid nodules needs to be factored in new TNM staging

Bronchioloalveolar Carcinoma (BAC, now AIS) (Defined in 1999: no stromal, vascular or pleural invasion)

*Travis et al. / J Clin Oncology 2005;23:3279-3287
BAC: The term has been used for a broad spectrum of radiological and clinical presentations, ranging from advanced multifocal invasive disease (a & b) with poor survival to a single noninvasive ground glass nodule (c) with excellent survival.

Pre-Invasive Lesions

- Atypical Adenomatous Hyperplasia (AAH)
- Adenocarcinoma in situ (AIS - formerly BAC)
- Non-mucinous
- Mucinous
- Minimally Invasive Adenocarcinoma (MIA)
  - Lepidic predominant tumor with ≤5 mm or <10% invasion
  - Definition currently being refined

Why the Change?

Current IASLC/ATS/ERS Adenocarcinoma Classification

- Invasive Adenocarcinoma
  - Lepidic pattern predominant (formerly non-mucinous BAC pattern)
  - Acinar pattern predominant
  - Papillary pattern predominant
  - Micropapillary pattern predominant
  - Solid pattern predominant
  - Recommend semiquantitative assessment of patterns in 5% increments
- Variants
  - Mucinous adenocarcinoma with lepidic pattern (formerly mucinous BAC pattern)
  - Mucinous cystadenocarcinoma
  - Colloid carcinoma
  - Fetal adenocarcinoma (low and high grade)
  - Enteric

Pre-Invasive Lesions

- Small, ground-glass or nonsolid nodules with overlapping features on CT
  - AAH nodules are often smaller with lower attenuation
  - Multiple nodules are reported in 15 to 30 % cases

Minimally Invasive Adenocarcinoma (MIA)

- This phenotype (mainly ground-glass, plus a small ≤5 mm central solid component) is a surrogate marker for MIA
- Also described as ≤2 cm and ≤0.25 cm solid portion
- Small (≤3 cm), usually solitary adenocarcinoma with a predominantly lepidic growth and ≤5 mm invasion, usually nonmucinous and rarely mucinous

Clinical Implications; pathology, resection

Invasive Adenocarcinoma

Reported as nonmucinous ADC mixed subtype with BAC and acinar components

New terminology: Acinar predominant ADC with lepidic components

Large, complex, mostly solid masses with spiculation, pleural tags, notching, and multiple other solid nodules in the right lung (often EGFR-positive). EGFR mutation and histologic subtypes
**Lepidic Predominant Adenocarcinoma (formerly nonmucinous BAC)**

- Invasive nonmucinous adenocarcinoma that has lepidic growth (ground glass pattern) as its predominant component. (EGFR exon 21 missense mutation and GGO vol percentage*)
- Multiple axial CT images demonstrate multilobar involvement with large areas of predominantly ground-glass opacities in the right upper and middle lobes

*Radiology 2013;268:254-264

**Adenocarcinoma Variant**

- Mucinous ADC: CK 20 + Lobulated hypodense mass with minimal spiculation in the right upper lobe. Strong correlations with KRAS and absent EGFR mutations

**Mucinous Adenocarcinoma with Lepidic Pattern (formerly mucinous BAC)**

- Coronal and axial CT images demonstrate multilobar involvement with left perihilar and lower lobe consolidation and multiple nodules in the right lung
- Strong correlations with KRAS and absent EGFR mutations

**Classification of Lung Adenocarcinomas Involving the Former Term BAC**

<table>
<thead>
<tr>
<th>Type</th>
<th>Pathology</th>
<th>Imaging</th>
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</thead>
<tbody>
<tr>
<td>AIS (adenocarcinoma in situ)</td>
<td>Pure lepidic</td>
<td>Usually part-solid, but may be solid</td>
</tr>
<tr>
<td>Minimally invasive adenocarcinoma</td>
<td>Pure lepidic</td>
<td>Usually part-solid, but may be solid</td>
</tr>
<tr>
<td>Lepidic predominant adenocarcinoma</td>
<td>Pure lepidic</td>
<td>Usually part-solid, but may be solid</td>
</tr>
<tr>
<td>Lymph node, metastatic or mixed-predominant adenocarcinoma</td>
<td>Mixed lepidic and solid</td>
<td>Usually solid, but may contain a small component</td>
</tr>
<tr>
<td>Mucinous adenocarcinoma</td>
<td>Mixed lepidic and solid</td>
<td>Mixed appearance from solid or mostly solid to part-solid or multinodular</td>
</tr>
</tbody>
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**Integration of Imaging, Histopathology, Molecular-Genomic and Clinical Data is Needed For Optimal Management of Persistent Subsolid Nodules**

**Example:** 61 year old female former smoker (>30 pack years) presented with SOB and cough in 2009, followed by yearly CT; >12 ground glass or part-solid nodules bilaterally; slow growth of nodules. Two nodules (LUL and RLL, blue arrows*) resected in 2014

<table>
<thead>
<tr>
<th>2009</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUL</td>
<td>AIS</td>
</tr>
<tr>
<td>RLL</td>
<td>AIS</td>
</tr>
</tbody>
</table>

- Conclusion: Synchronous primary AIS with similar histologies, separate genotypes
- Rx: Continued observation
Adenocarcinoma in situ (AIS): Defined in 1999: no stromal, vascular or pleural invasion
Bronchioloalveolar Carcinoma (BAC, now AIS): Small (<3 cm), usually solitary, pure lepidic growth, usually nonmucinous, rarely mucinous. This phenotype (small, ground-glass or nonsolid nodule) is a surrogate marker for AIS, with excellent prognosis.

Follow-up for persistent pure GGN or part-solid nodules with solid components ≤ 10 mm is evolving (with significantly longer volume and mass doubling times): surveillance noncontrast thin-section reduced-dose CT with intervals of 2 yrs (Sone et al Radiology 2014:273;276-284), can omit PET/CT

Minimally Invasive Adenocarcinoma (MIA): Small (<3 cm), usually solitary adenocarcinoma with a predominantly lepidic growth and ≤ 5 mm invasion, usually nonmucinous and rarely mucinous. FDG PET/CT may be helpful in staging if solid component ≤ 8 mm (ACR appropriateness criteria, J Am Coll Radiol 2014;11:849-856)

Implications of solid portion in a persistent part-solid nodule
- Typically it correlates with invasion
- Minimally invasive (<5mm solid portion) generally has same excellent clinical outcome as the GGN
- AAH, GGN and MIA can have overlapping CT findings and may be indistinguishable from each other. PET CT can be avoided for these phenotypes, whereas it can help in staging if solid component is larger than 8 mm

Examples
- The following slides present cases illustrating integrated personalized management decision making based on risk-stratification ranging from watchful waiting to surgical intervention

Shared Decision Making: Example
- 59 yr-old man former smoker with alpha-1 antitrypsin deficiency. Axial CT image (a) shows a 1.8 cm part-solid RUL nodule discovered as part of pre liver transplant workup. Percutaneous needle bx of the nodule attempted twice were nondiagnostic. Ultimately underwent liver transplant (MELD score 19) also underwent pre-op TACE for hepatoma seen on axial CT image (b). Plan is to resect once recovered from transplant

Shared Decision Making: Example
- 86 yr-old woman former smoker (30 pack-yr smoking quit in 1991) with dementia and CLL. Axial CT images (a & b) show a part-solid LUL lesion. There was minimal change since 2009, total 5 years. Bilateral axillary lymphadenopathy (arrows) is noted. Only watching given patient’s underlying dementia and family’s wish for non-invasive approach

Shared Decision Making: Example
- 68 yr-old man former smoker. No family history of cancer or asbestos exposure. Incidentally discovered part-solid nodule (CT axial images a & b), biopsied (at outside hospital, no molecular testing done) reported as adenomatous hyperplasia. PET (c) showed increased FDG uptake, SUV 4 in the solid component indicating invasive adenocarcinoma. However, being followed with serial imaging as has multiple other nonsolid nodules (arrows, d).
  - Issues: Sampling error, attempt should be made to sample the solid component. Variability in management. It is important not to overdiagnose or overtreat, however, such a lesion would probably be treated more aggressively in other hospitals with resection or radiation as follow-up and management should be determined by dominant lesion.
Surgery for part-solid lesions: Is sublobar resection adequate?

Initial axial CT images (a, b) show a part-solid 3 cm mass (EGFR mutant AD) in the right middle lobe which was hypometabolic on FDG-PET (not shown). Follow-up axial CT images (c, d) show a part-solid nodule around the suture at the resection site consistent with cut-end recurrence. Trials are ongoing to determine if limited resection is adequate for smaller, < 2cm subsolid nodules. It is suggested that limited resection should be offered in a trial setting and long-term follow-up of > 5 yrs should be done.

CALGB 140503-a RCT of lobectomy vs sublobar resection of small (<2 cm) peripheral NSCLC.
Clinicaltrials.gov NCT 00499330

90 yr-old man with prior right lung resection. New LUL lesion. Axial CT images show a tiny density in LUL (arrow, a) which increased in size on follow-up scan 15 months later (b, c). Given co-morbidities and age, patient opted for watchful waiting. Watchful waiting is usually for older patients or for those with significant comorbidities, where life expectancy is unlikely to be affected by the cancer.

Summary

- Better multidisciplinary correlation and stage discrimination with new classification. A variety of subsolid nodules can be seen especially on screening CT for lung cancer.
- Understanding the imaging findings and clinical implications per new classification is important for patient management.
- It is important to not over-treat the nonsolid or GGNs and also important to recognize suspicious changes to treat cancer in its early stage.
- Better understanding of behavior of subsolid nodules will improve risk-stratification and personalized follow-up and management.
- Future direction: Consideration of texture analyses, genetic profile (radiomics) and impact on clinical outcome.

References