What is new in the new WHO Classification of lung cancer

And the impact on small biopsy diagnosis

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Objectives

• Review the changes to lung cancer in the 2015 WHO classification
• Focus on the interpretation in small biopsies

2015 WHO Classification of Lung Cancer 4th Ed.

Adenocarcinoma

2004 WHO
• Variants
  • Mucinous (colloid)
  • Fetal
  • Signet ring
  • Clear cell

2015 WHO
• Variants
  • Mucinous
  • Colloid
  • Fetal
  • Enteric

Adenocarcinoma

2004 WHO
• Bronchioloalveolar cancer
  • Acinar
  • Papillary
  • Solid
  • Mixed

2015 WHO
• AIS
• MIA
• Lepidic predominant
• Acinar predominant
• Papillary predominant
• Solid predominant
• Micropapillary predominant

Adenocarcinoma, mucinous

• AD with goblet or columnar cells with abundant mucin
• All histologic patterns
  • Lepidic most common
• Immunostains
  • CK7+
  • CK20+
  • TTF1-
  • Napsin-
**Adenocarcinoma, enteric subtype**

- Resembles morphology of colorectal carcinomas
- Immunostains
  - Should retain CK7
  - CK20+
  - CDX2+
- Issues
  - Still could be 1ary GI, pancreaticobiliary

**2015 WHO recommendation**

- For non mucinous AD, assign most predominant growth pattern
- Grading scheme
  - Grade 1= lepidic
  - Grade 2= papillary and acinar
  - Grade 3= solid and micropapillary
- Prognostic value

**AIS/MIA**

- 3 cm and less
- No vascular, pleural invasion
- No airspace spread
- No necrosis
- Stromal invasion:
  - Absent in AIS
  - ≤ 5mm in MIA
- Predicts for 5-yr DFS of, or near 100%

**Lepidic predominant**

- 3 cm and less
  - >5mm of stromal invasion
- Pleural or vascular invasion
- Airspace spread
- Necrosis
- > 3cm
  - Even if ≤ 5mm or no invasion

**Reproducibility?**

- 534 cases – 2 observers
- Exact match 51.7%
- 27.3% in same prognostic score
- 21% with different prognostic score
LPA

Features of invasion

Papillary

Micropapillary

Active fibroblasts/ Desmoplasia = Invasion

Interobserver variation

<table>
<thead>
<tr>
<th>Rater 1</th>
<th>AIS</th>
<th>MIA</th>
<th>IA</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIS</td>
<td>11 (3.7%)</td>
<td>3 (1.0%)</td>
<td>0 (0.0%)</td>
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<tr>
<td>MIA</td>
<td>6 (2.0%)</td>
<td>71 (24.2%)</td>
<td>12 (4.1%)</td>
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<tr>
<td>IA</td>
<td>0 (0.0%)</td>
<td>36 (12.2%)</td>
<td>155 (52.7%)</td>
</tr>
</tbody>
</table>

Boland et al

More than one area of invasion

- Several recommendations
  - Measure the largest
  - In the WHO section on MIA and LPA
    - Estimate the % of invasive components
    - X by the overall tumor diameter
Squamous cell carcinoma

2004 WHO
- Squamous cell ca

2015 WHO
- Keratinizing
- Non-keratinizing
- Basaloid

Basaloid SQCC

- Nested architecture with palisading
- >50-100%
- Immunostains
  - p63 and p40+
  - CK5/6 +
  - TTF-1-
  - NE markers
  - <10% cases
  - Focal

Differential diagnosis
- LCNEC/SCLC
- NUT carcinoma
- Adenoid cystic ca

Adenosquamous cell carcinoma

2004 WHO
- Adenosquamous cell carcinoma

2015 WHO
- Adenosquamous cell carcinoma
  
  "...components of both SQCC and AD with each component constituting at least 10% of the tumor. Definitive diagnosis requires resection..."

Definitive diagnosis requires resection...

Adenosquamous cell carcinoma

AD component  SQC component

Immunostains

- TTF-1
  - 2 clones with different sensitivity and specificity
  - SPT24 is very sensitive not as specific
  - Can be + in SQCC
- p63
  - Up to 30% of AD + p40 more specific
- CK7
  - Up to 20% of SQCC +
  - Up to 10% of AD -

Immunostains in Adenosquamous cell ca

- Different tumor cells with different immunoprofile
- If the same tumor cells stain for TTF-1 and p63
  - It is NOT adenosquamous cell carcinoma
  - It is AD with p63 staining
Sarcomatoid carcinoma

2004 WHO
- Pleomorphic
- Spindle cell
- Giant cell
- Carcinosarcoma
- Pulmonary blastoma

2015 WHO
- Pleomorphic, spindle and giant cell
- Carcinosarcoma
- Pulmonary blastoma

Large cell carcinoma

2004 WHO
Large cell carcinoma
- Large cell NE carcinoma
- Basaloid
- Lymphoepithelioma-like
- Clear cell
- Rhabdoid

2015 WHO
Large cell carcinoma
- Undifferentiated NSCC
- Lacks cytological, architectural and immunohistochemical features of AD, SQCC, LCNEC and SCLC
- Requires resected tumor
**Neuroendocrine tumors**

**2004 WHO**
- Small cell carcinoma
- Carcinoid tumors
  - Typical
  - Atypical

**2015 WHO**
- Neuroendocrine tumors
- Small cell carcinoma
- Large cell NE carcinoma
- Carcinoid tumor
  - Typical
  - Atypical

**Small cell carcinoma**
- Still defined by H&E morphology
- About 10% of SCLC negative or focally weakly + for NE markers
- Up to 30% NSCLC + for NE markers
- IHC useful IF
  - SCLC vs SQCC
    - TTF-1+/p40-
    - NOT p63 (20% +)
  - SCLC vs carcinoid
    - Ki-67

**Large cell neuroendocrine carcinoma**
- Neuroendocrine morphology
  - Rosettes
  - Trabecula
  - Peripheral palisading
- Nucleoli prominent
- >10 mitosis/HPF
- AND expresses IHC markers

**Other unclassified**
- Lymphoepithelioma-like
- NUT carcinoma
  - EBV ISH
Interpretation on small biopsies
Recommendations of the 2015 WHO

GOAL
- To make a diagnosis on H&E or at least with the smallest number of immunostains
- Save tissue for molecular testing
  - Most cancers in advanced stage
  - If surgically resectable not as critical

Remember that...
- ...our diagnosis dictates mostly additional studies to be performed...
  - Everything but SQCC may be tested for EGFR, ALK, ROS etc
- ...eventually SQCC with own studies

Tissue Processing
- Do not decalcify
  - If can’t be avoided, consider making 2 blocks
    - 1 with the calcified tissue
    - 1 with softer tissue
- If more than 1 core or “abundant” aggregate of tissue
  - Consider making 2 paraffin blocks

Most useful stains in Lung 1ary
- TTF-1 and p40
- Could even argue p40 is sufficient
  - SQCC versus all others

A few things about IHC
- If not sure about tumor type
  - Carcinoma by far most common
  - Keratin stains with unstained slides
  - Keratin, CD45, S100 prot with unstained slides
  - Use morphology to guide stains
    - Best avoid many stains in 1st round
    - Avoid exhausting block
A few things about IHC

- If considering metastasis from another site
  - CDX2 can be + in Lung AD
  - ER can be + in Lung AD
  - STP24 clone of TTF-1 can be + in primaries from other sites

  *Use clinical/radiologic information, compare to prior specimens, use and interpret IHC cautiously*

A few things about IHC

- Neuroendocrine markers
  - Do *only* if tumor looks like a carcinoid (or LCNEC)
  - SCLC can be negative – H&E diagnosis
  - Many NSCLC that are not carcinoid or LCNEC can be focally +

Non small cell carcinoma

- 68 yo male
- Smoker
- Lung mass with mediastinal adenopathy

Diagnosis

Non-small cell carcinoma, NOS
Adenosquamous cell carcinoma?

• NO
  • Not 2 distinct cell morphology
  • Not 2 distinct cell population with different immunoprofile
  • The cells + for TTF-1 are also positive for p40
  • p40 trumps

Diagnosis
Non-small cell carcinoma, favor SQCC
Diagnosis

Non-small cell carcinoma, NOS

Comment: AD and SQC components present, could represent ADSQC carcinoma

Diagnosis

Non-small cell carcinoma with spindle cells

Comment: Could represent a pleomorphic, spindle cell and/or giant cell carcinoma i.e. sarcomatoid carcinoma
Benign versus Neoplastic

- If benign reactive pneumocyte hyperplasia, reactive to what?
- AAH?
  - Size ≤ 5mm
- Radiologic context is very helpful and knowing that the lesion has actually been sampled

Clinical and radiologic findings

- 65 yo woman
- Single GGO 2.5cm

Concluded that it is neoplastic

- Adenocarcinoma with pure lepidic growth, no stromal invasion....
- AIS? MIA? LPA?
Diagnosis?
Adenocarcinoma with lepidic pattern
Comment: Although no invasion identified, an invasive component which is unsampled cannot be excluded

How much is too little?
Amount of tissue needed for molecular testing

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<th>Test</th>
<th>Thickness</th>
<th># slides</th>
<th># tumor cells</th>
<th>% tumor cells</th>
<th>Amount of DNA</th>
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<td>5,000 3X6mm²</td>
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<td>5</td>
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<tr>
<td>50 gene panel</td>
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<td>Mayo Lung Cancer panel</td>
<td>5 μ</td>
<td>10</td>
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<td>10ng DNA, 10ng RNA</td>
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<tr>
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Questions & Discussion