LUNG CANCER PATHOLOGY: UPDATE ON LUNG ADENOCARCINOMAS

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ATYPICAL ADENOMATOUS HYPERPLASIA
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- Incidental finding in 9-16% of lung CA pts
- Most often associated with ADCA
- Multiple in 5-7% of lung CA pts
- Accepted as preinvasive lesion for ADCA
- May explain relatively high incidence of multicentric synchronous and metachronous lung CA
LUNG ADENOCARCINOMA

- Most common type (30-70%) of lung cancer
- Very heterogeneous (path, rad, clinical, molecular)
- Literature confusing:
  - Divergent use of term BAC
  - Multiple different classifications - increasing
- Major Molecular pathways:
  - EGFR (10-40%): nonsmokers, women, East Asians, adenocarcinoma, BAC, response to TKIs
  - KRAS (15-20%): worse prognosis, lack of response to chemotherapy/TKI’s
  - Unknown major pathway in 30-70% cases
ADENOCARCINOMA
WHO CLASSIFICATION

1967 WHO
1. Bronchogenic
   a. acinar
   b. papillary

2. Bronchiolo-alveolar

With or without mucin formation

1981 WHO
Acinar
Papillary
Bronchioloalveolar carcinoma
Solid adenocarcinoma
Small Adenocarcinoma 2cm or <
Noguchi M. et al; Cancer 75:2844, 1995
1. EPITHELIAL TUMORS
1.3 Invasive Malignant - 1999

1.3.3 Adenocarcinoma
  1.3.3.1 Acinar
  1.3.3.2 Papillary
  1.3.3.3 Bronchioloalveolar carcinoma
  1.3.3.4 Solid adenocarcinoma with mucin formation
  1.3.3.5 Mixed
  1.3.3.6 Variants

–WHO/IASLC CLASSIFICATION OF LUNG AND PLEURAL TUMORS
Adenocarcinoma
Mixed subtype
Acinar
Papillary
Bronchioloalveolar carcinoma
Solid adenocarcinoma with mucin formation

Variants

--WHO/IASLC CLASSIFICATION OF LUNG AND PLEURAL TUMORS
LUNG ADENOCARCINOMA CLASSIFICATION - 2009

- Ladanyi M and Pao W; Mod Pathol: Suppl 2:S16-22
ADENOCARCINOMA MIXED SUBTYPE
ADENOCARCINOMA
ACINAR
ADENOCARCINOMA
PAPILLARY
WHO LUNG TUMORS - 2004
Bronchioloalveolar Carcinoma

Non-mucinous
Mucinous
Mixed mucinous and non-mucinous
BRONCHIOLOALVEOLAR CARCINOMA, NONMUCINOUS
BAC, NON-MUCINOUS WITH NOGUCHI B/“COLLAPSE” VS INVASION
BRONCHOLOALVEOLAR CARCINOMA, MUCINOUS COMPARED TO NONMUCINOUS BAC

- More often Kras mutations
- More often multicentric
- Overall worse outcome
TERMINOLOGY PROBLEM: CLINICAL CONCEPT OF ADVANCED BAC: POOR SURVIVAL


3 YR SURVIVAL
20-30%
TERMINOLOGY PROBLEM: CLINICAL CONCEPT OF ADVANCED BAC: POOR SURVIVAL

Major confusion with use of term BAC:

Clinical – advanced disease with poor survival

Pathologic – solitary small nodule – 100% 5-yr survival

MICROPAPILLARY ADENOCARCINOMA
MICROPAPILLARY ADENOCARCINOMA

TTF1

PE10
MICROPAPILLARY ADENOCARCINOMA

MICROPAPILLARY (MP) ADENOCARCINOMA

- Amin M et al: AJSP 26:358, 2002: 35 MP CA; 21% = focal <5%, 58% = moderate 5-30% and 21% = extensive >30% 
  • 94% metastasized to LN (74%), lung (49%), brain (26%), bone (26%)
- Miyoshi T, et al: AJSP 26:358, 2003: 40% of 344 adenocarcinomas had a MP pattern. More frequent LN mets (p<0.001), pleural invasion (p=0.02) intrapulmonary metastases (p<0.001), non-smoking status (p=0.002).
  • None; 1-5% - focal; 6-50% moderate; 51-100% extensive
  • Survival Stage I: 79% MPP pos (>5%) vs 93% MPP neg (p=0.004)
NCI DIRECTOR’S CHALLENGE

- 500 Lung adenocarcinomas: gene expression analysis using HG-U133A Affymetrix chip
- Four institutions: Memorial Sloan Kettering Cancer Center, Univ of Michigan, Univ of Toronto, Moffitt Cancer Center
- N. Motoi, et al peer reviewed the pathology in detail for all 500 cases
- 100 Cases from MSKCC – N. Motoi et al

MSKCC: 100 ADENOCARCINOMAS

## GENE EXPRESSION VS HISTOLOGIC SUBTYPE

<table>
<thead>
<tr>
<th>Gene expression profile</th>
<th>BAC vs Other</th>
<th>Papillary vs Other</th>
<th>Acinar vs Other</th>
<th>Solid Vs Other</th>
<th>All Histologic types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster 1 vs</td>
<td>0</td>
<td>16</td>
<td>11</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td>5</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Cluster 2 vs</td>
<td>77</td>
<td>27</td>
<td>66</td>
<td>88</td>
<td>55</td>
</tr>
<tr>
<td>Cluster 3 vs</td>
<td>00</td>
<td>40</td>
<td>99</td>
<td>31</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>99</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31</td>
<td>13</td>
</tr>
</tbody>
</table>

- **Cluster 1** - Papillary; EGFR mut; less smoking; >TTF-1
- **Cluster 2** - BAC
- **Cluster 3** - Solid; KRAS mut; more smoking; <TTF-1

N. Motoi et al; William Gerald – AJSP (in press)
### EGFR MUTATION VS PAPILLARY MSKCC: (P<0.001)

<table>
<thead>
<tr>
<th></th>
<th>Other Subtype</th>
<th>Papillary</th>
</tr>
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<tbody>
<tr>
<td>No EGFR mut</td>
<td>60 (95.2%) (71.4%)</td>
<td>24 (62.2%) (28.6%)</td>
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<tr>
<td>EGFR mut</td>
<td>3 (4.8%) (18.7%)</td>
<td>13 (37.8%) (81.3%)</td>
</tr>
<tr>
<td></td>
<td>63 (100%)</td>
<td>37 (100%)</td>
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</table>

## ADENOCARCINOMA SUBTYPES AND PERCENTAGES

<table>
<thead>
<tr>
<th>Histologic Subtype</th>
<th>Pure Histologic Subtype</th>
<th>Major Histologic Component</th>
<th>Any Amount</th>
<th>10% of Subtype present</th>
<th>30% of Subtype present</th>
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</thead>
<tbody>
<tr>
<td>Mixed subtype</td>
<td>94</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Acinar</td>
<td>1</td>
<td>30</td>
<td>88</td>
<td>88</td>
<td>43</td>
</tr>
<tr>
<td>Papillary</td>
<td>3</td>
<td>37</td>
<td>78</td>
<td>76</td>
<td>50</td>
</tr>
<tr>
<td>Micropapillary†</td>
<td>3</td>
<td>37</td>
<td>78</td>
<td>76</td>
<td>50</td>
</tr>
<tr>
<td>Bronchioloalveolar</td>
<td>0</td>
<td>7</td>
<td>51</td>
<td>33</td>
<td>10</td>
</tr>
<tr>
<td>Nonmucinous</td>
<td>3</td>
<td>4</td>
<td>33</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>Mucinous</td>
<td>3</td>
<td>4</td>
<td>10</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Mixed</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Solid with mucin</td>
<td>2</td>
<td>25</td>
<td>54</td>
<td>49</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>332</td>
<td>288</td>
<td>130</td>
</tr>
</tbody>
</table>

N. Motoi et al; William Gerald – AJSP (in press)
MAJOR HISTOLOGIC SUBTYPE

- Semiquantitative assessment of all histologic subtypes (10% increments) – avoid two equal major subtypes
- Assess – MAJOR subtype
- For Adenocarcinoma, mixed subtype, (further specify the major subtype)
- i.e.: Adenocarcinoma, mixed subtype with major papillary component

SURVIVAL BY SOLID, STAGE, GRADE

ADVANTAGES OF SEMIQUANTITATION

- EVERY MIXED SUBTYPE ADENOCA IS DIFFERENT – WAY TO DOCUMENT THIS
- PAPERS THAT FOCUS ON SINGLE SUBTYPE – DO NOT CONTROL FOR IMPACT OF OTHER SUBTYPES
- FORCES OBSERVER TO ADDRESS ALL TYPES: IF FOCUS ONLY ON BAC VS OTHER – DON’T REALLY ADDRESS ISSUES LIKE BAC VS PAPILLARY OR ACINAR
ADVANTAGES OF SEMIQUANTITATION

- REPRODUCIBILITY – NOT THAT BAD
- REALLY NOT TIME CONSUMING (LESS THAN LOOKING FOR VASCULAR INVASION)
- PROVIDES A QUANTITATIVE WAY TO COMPARE MULTIPLE TUMORS (SYNCHRONOUS, METACHRONOUS)
- RESEARCH: CAN ANALYZE DATA AS CONTINUOUS VARIABLE
PROGNOSTIC SIGNIFICANCE OF COMPREHENSIVE HISTOLOGIC SUBTYPING (CHS) AS BASIS FOR GRADING

- GRADE 1 – BAC
- GRADE 2 – Papillary and acinar
- GRADE 3 – Solid and micropapillary

PROGNOSTIC SIGNIFICANCE OF COMPREHENSIVE HISTOLOGIC SUBTYPING (CHS) AS BASIS FOR GRADING

- Example: adenocarcinoma with 40% acinar, 25% papillary, 15% micropapillary, 10% BAC, 10% solid.

- Predominant grades (two most abundant grades):
  - sum of two most abundant patterns – score 2+2 = 4.

- Worst grades (two highest grades):
  - sum of two highest grades - score 3+3 = 6

Stage IA Lung Adenocarcinoma, disease free interval

Predominant Histologies

Worst Grades

% disease free
days

P=0.001
P=0.04

<table>
<thead>
<tr>
<th>Score</th>
<th>Count (N)</th>
</tr>
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<tbody>
<tr>
<td>3</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>117</td>
</tr>
<tr>
<td>5</td>
<td>98</td>
</tr>
<tr>
<td>3 &amp; 4</td>
<td>127</td>
</tr>
<tr>
<td>5</td>
<td>154</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
</tr>
</tbody>
</table>
Genomic profiling: different profile = metastases

–Girard, N, Pao, W, Begg C et al
Genomic profiling: different profile = multiple primary

–Girard, N, Pao, W, Begg C et al
« Blinded » pathology review
DISTINGUISHING MULTIPLE PRIMARY LUNG TUMORS FROM METASTASES

- Genomic and mutational profiling were feasible to assess clonal relationships between multiple lung tumors
- Martini Melamed clinical criteria were inaccurate in 32% of cases
- Comprehensive histologic subtyping accuracy rate was
  - 91% on surgical pathology specimens
  - 64% on frozen specimens

—Girard, N, Pao, W, Begg C et al
ADENOCARCINOMA MSKCC
EXAMPLE OF DIAGNOSIS

- LUNG, LEFT LOWER LOBE, WEDGE RESECTION: ADENOCARCINOMA, MIXED SUBTYPE, WITH ACINAR (50%), PAPILLARY (30%) AND BRONCHIOLOALVEOLAR (20%) PATTERNS
THE QUEST FOR “MINIMALLY INVASIVE” BAC CRITERIA

- Suzuki et al; ATS 69:893, 2000: Scar Size: 0-5mm, 5-15mm, >15mm. Less than 5mm has 100% survival
- Terasaki et al. AJSP 27: 937, 2003; Gr 1: pure BAC; 2a: <=5mm invasive area 2b >5mm. No survival data
- Sakurai et al. AJSP 28:198, 2004: Pattern invasion:
  - 0: none; 1 – invasion in BAC area; 2 - periphery of scar; 3 – within scar
  - 1 or 2 = excellent survival; 3: poor survival

Travis WD et al: JCO 23:3279, 2005
SMALL ADENOCARCINOMA 3 CM OR <
SURVIVAL BY SIZE OF SCAR

CASE FOR MINIMALLY INVASIVE LUNG ADENOCARCINOMA: N=141 Stage 1 or 2

- Group 1- BAC
- Group 2- mixed subtype with BAC and <5mm invasion
- Group 3- mixed subtype with BAC and >5 mm invasion
- Group 4- mixed subtype without BAC

CASE FOR MINIMALLY INVASIVE LUNG ADENOCARCINOMA: N=141 Stage 1 or 2

- Group 1- BAC
- Group 2- mixed subtype with BAC and < 5mm invasion
- Group 3- mixed subtype with >5 mm invasion
- Group 4- mixed subtype without BAC

INTERNATIONAL MULTIDISCIPLINARY LUNG ADENOCARCINOMA CLASSIFICATION

- **GOALS:**
  - Develop a multidisciplinary classification of lung adenocarcinoma
  - For this classification to become an international standard.

- **SPONSORED:** IASLC, ATS, ERS

- **CORE PANEL** – attend meetings, direct systematic review, write document

- **REVIEWER PANEL** – offer written comments, help with systematic review, edit/comment document
SQUAMOUS VS ADENOCARCINOMA/LARGE CELL THERAPY ISSUES

- Predictive of Toxicity:
  - Squamous cell carcinoma: Bevacizumab – contraindicated due to life threatening hemorrhage

- Predictive of Response:
  - Non-squamous histology: better survival with pemetrexed?
ADENOCARCINOMA CLASSIFICATION
(Biopsy and Cytology)

- Majority of lung cancers (about 70%) do not undergo resection – dx’d by biopsy/cytology
- Not covered in WHO/IASLC 1999 and 2004
- Requirement for more than just NSCLC vs SCLC
- This classification will address this topic for the first time – incorporating immunohistochemistry
PREINVASIVE LESIONS
  - ATYPICAL ADENOMATOUS HYPERPLASIA
  - ADENOCARCINOMA IN SITU (formerly BAC pattern) †
    - non-mucinous
    - mucinous

MINIMALLY INVASIVE ADENOCARCINOMA (a lepidic predominant tumor with \( \leq 5\text{mm} \) or \(<10\%\) invasion – definition being refined)

INVASIVE ADENOCARCINOMA

† Size should be specified. In well sampled tumors adenocarcinoma in situ is independent of size; extensive sampling is needed to exclude invasion, particularly in larger tumors
INVASIVE ADENOCARCINOMA

- Lepidic pattern predominant (formerly non-mucinous BAC pattern)
- Acinar pattern predominant
- Papillary pattern predominant
- Micropapillary pattern, predominant
- Solid pattern predominant

(In explanatory notes, recommend semiquantitative assessment of patterns in 5-10% increments)
VARIANTS

• Mucinous adenocarcinoma with lepidic pattern (formerly mucinous BAC pattern)
• Mucinous cystadenocarcinoma
• Colloid adenocarcinoma
• Fetal adenocarcinoma (low and high grade)
• Enteric adenocarcinoma