Adenocarcinoma classification should be easy

Los Angeles Society Of Pathologists
January 25, 2014

Sanja Dacic, MD, PhD
University of Pittsburgh Medical Center
OUTLINE

- IASLC/ATS/ERS classification of lung adenocarcinomas
- Practical issues
  - Invasion
  - Histological subtyping
- Subtyping on cytology specimens
WHO 2004 classification of lung adenocarcinomas

- Mixed subtype
- Bronchioloalveolar carcinomas (in situ)
- Acinar
- Papillary
- Solid
- Fetal
- Mucinous (colloid)
- Mucinous cystadenocarcinoma
- Signet ring
- Clear cell
IASLC/ATS/ERS classification of lung adenocarcinoma

- **Obsolete terms**
  - Bronchioloalveolar carcinoma (BAC)
  - terms AIS (adenocarcinoma in situ) and minimally invasive adenocarcinoma (MIS) introduced
- **Mixed subtype adenocarcinoma**
  - comprehensive histologic subtyping and classification by the predominant subtype

- Provides **guidelines** for resection and small biopsies/cytology specimens
IASLC/ATS/ERS classification of lung adenocarcinoma for resection specimens

- **PREINVASIVE LESIONS**
  - Atypical adenomatous hyperplasia
  - Adenocarcinoma in situ (AIS) (formerly BAC)
    - Non-mucinous; mucinous

- **MINIMALLY INVASIVE ADENOCARCINOMA (MIA)**
  - A lepidic predominant tumor with ≤ 5 mm invasion
    - Non-mucinous; mucinous

- **INVASIVE ADENOCARCINOMA**

*Travis WD et al. JTO 2011; 6(2):244-285.*
PROBLEM 1

How to separate AIS from minimally invasive adenocarcinoma (MIA)?
Adenocarcinoma in situ (AIS)  
(formerly known as BAC)

Definition:

- A localized small (≤ 3.0 cm) adenocarcinoma with growth restricted to neoplastic cells along pre-existing alveolar structures (lepidic growth) lacking stromal, vascular or pleural invasion
- 100% disease-free specific survival if completely resected

Travis WD et al. JTO 2011; 6(2):244-285.
Minimally invasive adenocarcinoma (MIA)

Definition

- Solitary and discrete, ≤ 3.0 cm with a predominantly lepidic pattern and ≤ 5 mm invasion in any one focus

- 100% disease-free specific survival if completely resected

*Travis WD et al. JTO 2011; 6(2):244-285.*
DEFINITION OF INVASIVE COMPONENT

- Histologic subtypes other than a lepidic pattern
- Desmoplastic reaction
- MIA is excluded if the tumor shows
  - AL invasion
  - Pleural invasion
  - Tumor necrosis
HISTOLOGIC SUBTYPES SUPPORTING INVASION

ACINAR

PAPILLARY

MICROPAPILLARY

SOLID
DESMOPLASTIC REACTION
DESMOPLASTIC REACTION
Invasion vs. stromal collapse/central sclerosis
Basement membrane stains

COLLAPSE

INVASION
How to separate AIS from MIA?

- The diagnosis of AIS cannot be established with certainty on cytology or small biopsy specimens.

- Small tumors (3 cm or less) and tumors with a dominant lepidic growth should be entirely submitted.

- More aggressive search for stromal, vascular and pleural invasion (e.g. ancillary studies as a routine work up).
PROBLEM 2

What is the reproducibility of invasion criteria?
Typical (easy) cases
UNANIMOUS NON-INVASIVE

IASLC Pathology Committee, October 2010; Thunissen E. et al. Mod Pathol 2012; 25:1574-83.
UNANIMOUS NON-INVASIVE
UNANIMOUS INVASION

IASLC Pathology Committee, October 2010

Thunissen E. et al. Mod Pathol 2012; 25:1574-83.
UNANIMOUS INVASION

IASLC Pathology Committee, October 2010

Thunissen E. et al. Mod Pathol 2012; 25:1574-83.
• Difficult cases
≥10 for invasion and ≥ 10 for non-invasion
≥10 for invasion and ≥ 10 for non-invasion
Stroma can be an issue...
Pre-existing lung architectural changes

Thunissen E. et al. Mod Pathol 2012; 25:1574-83.
REPRODUCIBILITY OF INVASION

- “typical” cases
  - $\kappa = 0.55 \pm 0.06$

- “difficult” cases
  - $\kappa = 0.08 \pm 0.02$

Thunissen E. et al. Mod Pathol 2012; 25:1574-83.
PATHOLOGISTS CAN BE DIVIDED....

Group A  “invasion”

Group B  “no-invasion”

P=0.02

Thunissen E. et al. Mod Pathol 2012; 25:1574-83.
INVASIVE ADENOCARCINOMA

- The term “predominant” is appended to all categories of invasive adenocarcinoma

- Recording the percentages of the various histologic types in 5% increments (not just the most predominant type)

- No established histologic or cytologic grading criteria exists for lung adenocarcinoma
IASLC/ATS/ERS classification of lung adenocarcinoma

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

- **VARIANTS**
  - Mucinous adenocarcinoma (formerly mucinous BAC)
  - Colloid
  - Fetal (low and high grade)
  - Enteric
IASLC/ATS/ERS classification and survival

<table>
<thead>
<tr>
<th>IASLC/ATS/ERS Classification subtypes</th>
<th>Number (%)</th>
<th>Disease-free survival at 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma in situ</td>
<td>1 (0.2%)</td>
<td>100%</td>
</tr>
<tr>
<td>Minimally invasive</td>
<td>7 (1%)</td>
<td>100%</td>
</tr>
<tr>
<td>adenocarcinoma, non-mucinous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimally invasive</td>
<td>1 (0.2%)</td>
<td>100%</td>
</tr>
<tr>
<td>adenocarcinoma, mixed mucinous and non-mucinous</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate Grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lepidic predominant</td>
<td>29 (6%)</td>
<td>90%</td>
</tr>
<tr>
<td>Acinar predominant</td>
<td>232 (45%)</td>
<td>84%</td>
</tr>
<tr>
<td>Papillary predominant</td>
<td>143 (28%)</td>
<td>83%</td>
</tr>
<tr>
<td><strong>High Grade</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micropapillary predominant</td>
<td>12 (2%)</td>
<td>67%</td>
</tr>
<tr>
<td>Solid predominant</td>
<td>67 (13%)</td>
<td>70%</td>
</tr>
<tr>
<td>Colloid predominant</td>
<td>9 (2%)</td>
<td>71%</td>
</tr>
<tr>
<td>Invasive mucinous</td>
<td>13 (3%)</td>
<td>76%</td>
</tr>
<tr>
<td>adenocarcinoma, mixed mucinous/non-mucinous</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PROBLEM 3

What is the reproducibility of histological subtyping of lung adenocarcinoma?
## Reproducibility of Histological Subtyping

<table>
<thead>
<tr>
<th>Submitted pattern</th>
<th>Single pattern (%)</th>
<th>Predominant pattern (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinar (n=20)</td>
<td>17/26 (65)</td>
<td>25/26 (96)</td>
</tr>
<tr>
<td>Lepidic (n=19)</td>
<td>11/26 (42)</td>
<td>24/26 (92)</td>
</tr>
<tr>
<td>Micropapillary (n=16)</td>
<td>3/26 (12)</td>
<td>16/26 (62)</td>
</tr>
<tr>
<td>Papillary (n=19)</td>
<td>5/26 (19)</td>
<td>25/26 (96)</td>
</tr>
<tr>
<td>Solid (n=20)</td>
<td>17/26 (65)</td>
<td>26/26 (100)</td>
</tr>
</tbody>
</table>

“typical” cases $\kappa = 0.77 \pm 0.06$

“difficult” cases $\kappa = 0.38 \pm 0.14$
MICROPAPILLARY vs. PAPILLARY
LEPIDIC VS. PAPILLARY
PROBLEM 4

Can morphological subtyping be applied to small cytology/biopsy specimens?
MORPHOLOGIC ADENOCARCINOMA PATTERNS CLEARLY PRESENT

- Adenocarcinoma, describe identifiable patterns present
ADENOCARCINOMA, ACINAR PATTERN

Cytology images courtesy of Dr. Sara Monaco, UPMC
ADENOCARCINOMA, PAPILLARY PATTERN

Cytology images courtesy of Dr. Sara Monaco, UPMC
How accurate is subtyping on the cytology/small biopsy specimens?
WHAT DO YOU THINK?
WHAT DO YOU THINK?
ACINAR PATTERN
## Histologic-cytologic correlation

<table>
<thead>
<tr>
<th>Histologic pattern</th>
<th>Concordant (N=26)</th>
<th>Discordant (N=32)</th>
<th>Cytologic classification in discordant cases (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solid</td>
<td>6 (23%)</td>
<td>8 (25%)</td>
<td>Acinar (7); papillary (1)</td>
</tr>
<tr>
<td>Acinar</td>
<td>18 (69%)</td>
<td>6 (19%)</td>
<td>Solid (5); papillary (1)</td>
</tr>
<tr>
<td>Papillary</td>
<td>1 (4%)</td>
<td>6 (19%)</td>
<td>Acinar (5); mucinous (1)</td>
</tr>
<tr>
<td>Lepidic</td>
<td>0</td>
<td>7 (22%)</td>
<td>Acinar (5); solid (1); papillary (1)</td>
</tr>
<tr>
<td>Mucinous</td>
<td>1 (4%)</td>
<td>4 (12%)</td>
<td>Acinar (2); solid (1); lepidic (1)</td>
</tr>
<tr>
<td>Clear cell</td>
<td>0</td>
<td>1 (3%)</td>
<td>Acinar (1)</td>
</tr>
</tbody>
</table>
SPECIMEN CELLULARITY AND SUBTyPING

Cytology smears cellularity (%)

Number of tumor cells on cytology smears

- Concordant
- Discordant

<50  50-200  >200
NON-SMALL CELL CARCINOMA, FAVOR ADENOCARCINOMA

Cytology images courtesy of Dr. Sara Monaco, UPMC
ANCILLARY STUDIES

IHC
1 SQC/1 ADC and/or mucin

ADC
IHC + or mucin+
SQC
IHC -

SQC
IHC +
ADC
IHC - or mucin-

SQC
IHC +
ADC
IHC + or mucin+

NSCLC, favor ADC

NSCLC, favor SQC

NSCLC,NOS
possible adenosquamous

IHC-
mucin -

NSCLC,NOS
FREQUENCY OF ANCILLARY STUDIES

Ocque R. et al. AJCP 2011; 136 (1):81-7
Adenocarcinoma classification on cytology specimens

Ocque R. et al. AJCP 2011; 136 (1):81-7
Squamous cell carcinoma classification on cytology specimens

Ocque R. et al. AJCP 2011; 136 (1):81-7
TWO SCENARIOS WHEN COMMENT SHOULD BE MADE

Morphology
SQC and ADC present

IHC favor both ADC and SQC component

NSCLC, NOS
Comment: tumor may represent adenosquamous carcinoma
OTHER SUGGESTIONS FOR GOOD PRACTICE

- The term large cell carcinoma should not be used for diagnosis in small biopsy or cytology specimens.

- The term non-squamous cell carcinoma should not be used by pathologists in diagnostic reports.

- Tumors with sarcomatoid features should be regarded as ADC or SQC; or “poorly differentiated NSCLC with giant and/or spindle cell features.”

- NE markers should be used only if NE morphology is suspected.
SUMMARY

- Histological subtyping of invasive adenocarcinoma has prognostic significance

- Reproducibility of subtyping on resection and cytology/small specimens is poor

- IHC should be used only when morphological classification is difficult