ADENOCARCINOMA: WHAT ARE THE ISSUES?
New 2015 WHO Classification: Putting it into practice

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EUROPEAN LUNG CANCER CONFERENCE
GENEVA, SWITZERLAND
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Disclosure slide

- Board Member of IASLC
WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart

Edited by
William D. Travis, Elisabeth Brambilla, Allen P. Burke, Alexander Marx, Andrew G. Nicholson
WHAT ARE THE QUESTIONS?

- What happened to BAC?
- Do AIS and MIA have a 100% DFS?
- Does predominant subtyping have prognostic significance?
- What is the reproducibility?
- Are there any new concepts?
- Does it help comparing multiple tumors?
- What is impact on TNM?
2011 IASLC/ATS/ERS ADC CLASSIFICATION – DISCONTINUE BAC CONCEPT
FIVE PLACES IN NEW CLASSIFICATION

1. Adenocarcinoma in situ (AIS) which can be non-mucinous and rarely mucinous
2. Minimally invasive adenocarcinoma
3. Invasive adenocarcinoma with predominant nonmucinous lepidic pattern
4. Invasive adenocarcinoma with less than predominant nonmucinous lepidic pattern (probably most formerly clinically advanced adenocarcinomas with BAC pattern)
5. Invasive mucinous adenocarcinoma
Driver Mutations found in 65% of Adenocarcinoma Specimens

- KRAS 32%
- EGFR 23%
- No mutation 36%
- Co-mutation 1%
- AKT 0%
- MEK1 0%
- PIK3CA 1%
- BRAF 1%
- HER2 3%
- ALK 3%

--Courtesy of Mark Kris
2015 WHO (IASLC/ATS/ERS) ADENOCARCINOMA CLASSIFICATION

- **PREINVASIVE LESIONS**
  - ATYPICAL ADENOMATOUS HYPERPLASIA
  - ADENOCARCINOMA IN SITU (≤3 cm, formerly BAC pattern) †
    - non-mucinues
    - mucinous
- **MINIMALLY INVASIVE ADENOCARCINOMA** (≤3 cm, a lepidic predominant tumor with ≤5mm invasion)

- **INVASIVE ADENOCARCINOMA**

† Size should be specified. AIS and MIA should be completely sampled histologically
ADENOCARCINOMA IN SITU NONMUCINOUS
ADENOCARCINOMA IN SITU NONMUCINOUS
MINIMALLY INVASIVE ADENOMA
NONMUCINOUS
MINIMALLY INVASIVE ADENOCARCINOMA NONMUCINOUS
2015 WHO (IASLC/ATS/ERS) ADENOCARCINOMA CLASSIFICATION

INVASIVE ADENOCARCINOMA

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

*(Comprehensive histologic subtyping: semiquantitative assessment of patterns in 5-10% increments)*
LEPIDIC
SOLID WITH MUCIN  

DPAS STAIN
STAGE I ADENOCARCINOMA (N=514)  
RECURRENCE-FREE SURVIVAL (RFS) BY IASLC HISTOLOGIC TYPE  

Yoshizawa, A et al; Modern Pathology 24: 653-664, 2011

<table>
<thead>
<tr>
<th>Histologic Type</th>
<th>5 Year RFS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIS (1)</td>
<td>100</td>
</tr>
<tr>
<td>MIA (8)</td>
<td>100</td>
</tr>
<tr>
<td>Lepidic NM (29)</td>
<td>90</td>
</tr>
<tr>
<td>Papillary (143)</td>
<td>83</td>
</tr>
<tr>
<td>Acinar (232)</td>
<td>85</td>
</tr>
<tr>
<td>Inv Mucinous Ad (13)</td>
<td>76</td>
</tr>
<tr>
<td>Solid (67)</td>
<td>71</td>
</tr>
<tr>
<td>Micropapillary (12)</td>
<td>64</td>
</tr>
<tr>
<td>Colloid (9)</td>
<td>71</td>
</tr>
</tbody>
</table>

P=0.003
The Novel Histologic International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society Classification System of Lung Adenocarcinoma Is a Stage-Independent Predictor of Survival

Arne Warth, Thomas Muley, Michael Meister, Albrecht Stenzinger, Michael Thomas, Peter Schirmacher, Philipp A. Schnabel, Jan Budczies, Hans Hoffmann, and Wilko Weichert

Does Lung Adenocarcinoma Subtype Predict Patient Survival?

A Clinicopathologic Study Based on the New International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Lung Adenocarcinoma Classification

Prudence A. Russell, MBBS, FRCPA,* Zoe Wainer, BMBS;‡ Gavin M. Wright, MBBS, FRACS;‡§ Marianna Daniels, MBBS;§ Matthew Corren, MBBS, FRACP;∥ and Richard A. Williams, MBBS, FRCPA, PhD*

Adenocarcinomas With Prominent Lepidic Spread: Retrospective Review Applying New Classification of the American Thoracic Society

Lauren Xu, MD,* Fabio Tavora, MD,† Richard Battafarano, MD,‡ and Allen Burke, MD*

Validation of the IASLC/ATS/ERS Lung Adenocarcinoma Classification for Prognosis and Association with EGFR and KRAS Gene Mutations

Analysis of 440 Japanese Patients


Warth A, J Clin Oncol 2013; 30: 1438-46

Russell PA et al: J Thor Oncol 2011;6:1496-1504
INVASIVE MUCINOUS ADENOCARCINOMA
INVASIVE MUCINOUS ADENOCARCINOMA
Frequent *KRAS* mutations
HNF4-α AS A MARKER FOR INVASIVE MUCINOUS ADENOCARCINOMA

INVASIVE MUCINOUS ADENOCARCINOMA WITH CD74-NRG1 FUSION (Cancer Discov 2014;4:415-22)

Provided by Y. Yatabe
REPRODUCIBILITY

Reproducibility of histopathological subtypes and invasion in pulmonary adenocarcinoma. An international interobserver study

Erik Thunnissen¹, Mary Beth Beasley², Alain C Borczuk³, Elisabeth Brambilla⁴,

Interobserver variability in the application of the novel IASLC/ATS/ERS classification for pulmonary adenocarcinomas

Arne Warth*, Albrecht Stenzinger*, Ann-Christin von Brünneck⁹, Benjamin Goeppert*, Judith Cortis*, Iver Petersen¹, Hans Hoffmann¹, Philipp A. Schnabel* and Wilko Weichert*

Training increases concordance in classifying pulmonary adenocarcinomas according to the novel IASLC/ATS/ERS classification

Arne Warth • Judith Cortis • Ludger Fink • Annette Fisseler-Eckhoff • Helene Geddert • Thomas Hager • Klaus Junker • Gian Kayser • Julia Kitz • Florian Länger • Alicia Morresi-Hauf • German Ott • Iver Petersen • Albrecht Stenzinger • Alex Soltermann • Saskia Ting • Verena Tischler • Ekkehard Vollmer • Philipp A. Schnabel • Wilko Weichert • on behalf of the Pulmonary Pathology Working Group of the German Society of Pathology

–Mod Path 25:1574, 2012
Selected images: kappa
Typical patterns: 0.77
Difficult cases: 0.38
Invasion vs noninvasion
Typical: 0.55
Difficult: 0.08

Predominant pattern : Kappa
Lung Pathologists: substantial (0.44-.72)
Residents: fair (0.38-0.47)

–Virch Arch 461:185-93, 2012
Digital images:
Consensual votes: 59.6-75%
Disagreement decreased significantly after educational sessions (p<0.001)
Patients distribution by lepidic pattern and their recurrence-free probability (RFP)

- Lepidic pattern (patient, %)
  - AIS: n=2  
    - (0.2%)
  - MIA: n=34  
    - (3%)
  - Lepidic: n=103  
    - (10%)
  - Others: n=907  
    - (87%)

- AIS/MIA/Lepidic  
  - Totally n=138  
    - (13%)

- RFP by lepidic pattern

# Clinicopathologic characteristics of four recurrent cases in lepidic predominant ADC

<table>
<thead>
<tr>
<th>Case</th>
<th>surgical procedure</th>
<th>type of rec.</th>
<th>duration until rec.</th>
<th>staple margin</th>
<th>stage</th>
<th>Ly</th>
<th>V</th>
<th>PL</th>
<th>micropapillary</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>lobectomy</td>
<td>distant (bone)</td>
<td>1.4 yrs</td>
<td>NA</td>
<td>IA</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>wedge resection</td>
<td>local rec. (lung)</td>
<td>1.1 yrs</td>
<td>2 mm</td>
<td>IA</td>
<td>+</td>
<td>-</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>wedge resection</td>
<td>distant (chest wall)</td>
<td>3.3 yrs</td>
<td>5 mm</td>
<td>IA</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>lobectomy</td>
<td>local rec. (lung)</td>
<td>3.8 yrs</td>
<td>NA</td>
<td>IA</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- **Lepidic predominant ADC with no recurrence (n=99)**
  - lymphatic invasion: 6% (n=6)
  - vascular invasion: 4% (n=4)
  - micropapillary pattern: 2% (average)

CRIBRIFORM PATTERN
POOR SURVIVAL FOR CRIBRIFORM ADENOCARCINOMA

A

In all patients

B

In all patients

Recurrence-free probability

Recurrence-free probability

Cribiform pattern  N  5-yr RFP  p value

<table>
<thead>
<tr>
<th>Cribiform pattern</th>
<th>N</th>
<th>5-yr RFP</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10%</td>
<td>824</td>
<td>84%</td>
<td>0.010</td>
</tr>
<tr>
<td>10-39%</td>
<td>171</td>
<td>76%</td>
<td>0.096</td>
</tr>
<tr>
<td>≥40%</td>
<td>43</td>
<td>65%</td>
<td></td>
</tr>
</tbody>
</table>

Years since surgery

Years since surgery

Kadota K et al: Mod Pathol 2014; 27: 690-700
SHOULD CRIBRIFORM BE ADDED TO CLASSIFICATION?
NOT YET (high grade acinar)

INVASIVE ADENOCARCINOMA

• **Lepidic pattern predominant**  (formerly non-mucinous BAC pattern)
• Acinar pattern predominant
• Papillary pattern predominant
• **Micropapillary pattern, predominant**
• Solid pattern predominant
• ??? Cribiform predominant???

*(Comprehensive histologic subtyping: semiquantitative assessment of patterns in 5-10% increments)*
A grading system combining architectural features and mitotic count predicts recurrence in stage I lung adenocarcinoma

Kyuichi Kadota¹,², Kei Suzuki¹, Stefan S Kachala¹, Emily C Zabor³, Camelia S Sima³, Andre L Moreira⁴, Akihiko Yoshizawa⁴,⁵, Gregory J Riely⁶, Valerie W Rusch¹, Prasad S Adusumilli¹,⁷ and William D Travis⁴

SPREAD THROUGH AIR SPACES (STAS) IS AN IMPORTANT PATTERN OF INVASION IN LUNG ADENOCARCINOMA
MICROPAPILLARY ADCA IS AN INDEPENDENT PREDICTOR OF RECURRENCE IN LIMITED RESECTIONS (≤2CM)

Multivariate analysis, presence of tumor STAS remained independently associated with the risk of recurrence (hazard ratio, 3.08; \( P=0.014 \)).

*Kadota K et al; JTO 2015; epub ahead*
Spread Through Air Spaces (STAS)

- Is true invasion, not an artifact
- Introduced into the definition of invasion in lung adenocarcinoma
- Should not be included in tumor size
- Should not be included in subtyping
- Should be searched for in staple line margins
IMPLICATIONS OF NEW CLASSIFICATION FOR TNM STAGING OF ADENOCARCINOMAS

- Multiple tumors: Metastasis vs synchronous/metachronous primaries
- Terminology: implication of AIS and MIA
- Tumor size
DISEASE FREE SURVIVAL COMPARING MARTINI MELAMED VS MOLECULAR VS SURGICAL PATHOLOGY

Martini Melamed: P=0.052
Molecular: P=0.013
Surgical Pathology: P=0.001

IMPLICATIONS OF NEW CLASSIFICATION FOR TNM STAGING OF ADENOCARCINOMAS

- Multiple tumors: Metastasis vs synchronous/metachronous primaries
- Tumor size (use only invasive size)
- Terminology: implication of AIS and MIA
IMPLICATIONS OF IN SITU CONCEPT ON CT MEASUREMENT OF TUMOR SIZE: GGO VS SOLID

POTENTIAL NEW APPROACH TO TUMOR SIZE MEASUREMENT

- GROUND GLASS OPACITY
- PART SOLID

Contributed by C. Henschke & colleagues
When size is a criterion for the T/pT category, it is a measurement of the invasive component. If in the breast, for example, there is a large in situ component (e.g. 4 cm) and a small invasive component (e.g. 0.5 cm), the tumor is coded for the invasive component only, i.e. pT1a.
STAGE 1 ADENOCARCINOMA
Standard Gross Size
T1a <= 2 cm vs. T1b >2-3 cm

Yoshizawa, A et al; Modern Pathology 24: 653-664, 2011
STAGE 1 ADENOCARCINOMA
Size adjusted by % invasion (not in situ)
T1a <= 2 cm vs. T1b >2-3cm

P<0.001

Yoshizawa, A et al; Modern Pathology 24: 653-664, 2011
## 514 Stage I Adenocarcinomas Multivariate Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IASLC/ATS/ERS classification (High vs. Intermediate/Low Grade)</td>
<td>1.7 (1.0 – 2.8)</td>
<td>0.038</td>
</tr>
<tr>
<td>Gender (Male vs Female)</td>
<td>1.8 (1.2 – 2.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>Stage (IB vs IA)</td>
<td>1.4 (0.8 – 2.3)</td>
<td>0.19</td>
</tr>
<tr>
<td>Invasive Tumor size*</td>
<td>1.3 (1.0 – 1.6)</td>
<td>0.026</td>
</tr>
<tr>
<td>2004 WHO Histologic grade (Poor vs Moderate/Well)</td>
<td>1.1 (0.6 – 1.8)</td>
<td>0.86</td>
</tr>
<tr>
<td>Necrosis (Yes vs. No)</td>
<td>2.1 (1.3 – 3.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Vascular invasion (Yes vs No)</td>
<td>1.5 (0.9 – 2.3)</td>
<td>0.085</td>
</tr>
</tbody>
</table>

Yoshizawa, A et al; Modern Pathology 24: 653-664, 2011

* Tumor size adjusted by subtracting percentage of lepidic growth
IMPLICATIONS FOR TNM STAGING

- AIS would be classified as Tis
  - Tis (squamous CIS)
  - Tis (AIS)
- Similar to breast cancer
  - Tis (DCIS)
  - Tis (LCIS)
- MIA would be classified as Tmi
- T factor size - change to invasive size?
WHAT ARE THE QUESTIONS?

- What happened to BAC?
- Do AIS and MIA have a 100% DFS?
- Does predominant subtyping have prognostic significance?
- What is the reproducibility?
- Are there any new concepts?
- Does it help comparing multiple tumors?
- What is impact on TNM?