Lung Carcinomas
New 2015 WHO Classification
WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart

Fourth Edition
WHO Classification of Tumours, Volume 7

***EXPECTED SPRING 2015***

“This authoritative, concise reference book provides an international standard for oncologists and pathologists and will serve as an indispensable guide for use in the design of studies monitoring response to therapy and clinical outcome.”
WHO Classifications

1967  HE
1981  HE & Mucin
1999  HE, Mucin & IHC
2004  HE, Mucin, IHC & Genetics
2015  HE, Mucin, **IHC, Genetics** & Radiology

- for resections
- includes small specimens
Review all available tumor material
Small Samples: NSCLC Subtyping

- Established morphological criteria present:
  
  Glandular differentiation and/or mucin → ADC
  Intercellular bridges and/or keratinization → SCC
Small Samples: NSCLC Subtyping

• Established morphological criteria present:
  Glandular differentiation and/or mucin → ADC
  Intercellular bridges and/or keratinization → SCC

• Established morphological criteria absent – do IHC
Small Samples: NSCLC Subtyping

• **ADC**: **TTF1**, Napsin
  – Expression may be focal
  – Coexpression with squamous markers possible

• **SCC**: **p40**, **p63**, **CK 5/6**
  – Expression diffuse
  – TTF1 expression not allowed

• **NSCLC, NOS** note: possibly **ADSC**
  – TTF1 and p40 expression in diff. cell populations
Small Samples: NSCLC Subtyping

• Established morphological criteria present:
  
  Glandular differentiation and/or mucin $\rightarrow$ ADC
  Intercellular bridges and/or keratinization $\rightarrow$ SCC

• Established morphological criteria absent – do IHC:
  
  TTF1+ $\rightarrow$ NSCLC, favor ADC
  p40+ $\rightarrow$ NSCLC, favor SCC
  Inconclusieve $\rightarrow$ NSCLC, NOS
Clinical Suspicion of Cancer

Up-front:
- HE
- alcian blue-PAS
- Unstained sections:
  - IHC (cocktails)
  - DNA extraction
  - FISH

- 10% neutral buffered formalin
- Fixation time: 6 - 48 hours
Squamous cell carcinoma

Adenocarcinoma
Large cell carcinoma
Sarcomatoid carcinomas

Biopsy/Cytology

NSCLC-NOS

ADC profile, NSCLC-NOS
TTF1+, TTF1-, p40-

SCC phenotype
p40+, TTF1-

Stage IV

EGFR / KRAS / BRAF / HER2neu
Gene sequencing

ALK IHC

ROS1 IHC

DNA
Sanger: ≈ 5 ng
NGS: ≈ 10 ng

SLPG 2014
Biopsy/Cytology

Squamous cell carcinoma

Adenocarcinaoma
Large cell carcinoma
Sarcomatoid carcinomas

NSCLC-NOS

ADC profile, NSCLC-NOS
TTF1+, TTF1-, p40-

Stage IV

EGFR / KRAS / BRAF / HER2
Gene sequencing

ALK
IHC

ROS1
IHC

Negative
91%

SLPG 2014
ALK, ROS1 FISH negative 57% negative

Squamous cell carcinoma

Adenocarcinoma
Large cell carcinoma
Sarcomatoid carcinomas

Biopsy/Cytology

NSCLC-NOS

ADC profile, NSCLC-NOS

TTF1+, TTF1-, p40-

Stage IV

EGFR / KRAS / BRAF / HER2neu
Gene sequencing

ALK IHC
ROS1 IHC

negative

RET, MET FISH

EGFR / KRAS / BRAF / HER2neu
Gene sequencing

negative

SLPG 2014
Squamous cell carcinoma
Adenocarcinoma
  Large cell carcinoma
  Sarcomatoid carcinomas
NSCLC-NOS
Biopsy/Cytology

ADC profile, NSCLC-NOS
  TTF1+, TTF1-, p40-

SCC phenotype
  p40+, TTF1-

Stage IV

EGFR / KRAS / BRAF / HER2neu
Gene sequencing

ALK IHC
ROS1 IHC

negative

positive

43%
Squamous cell carcinoma

Adenocarcinoma
  Large cell carcinoma
  Sarcomatoid carcinomas

NSCLC-NOS

Biopsy/Cytology

ADC profile, NSCLC-NOS
  TTF1+, TTF1-, p40+

SCC phenotype
  p40+, TTF1-

Stage IV

EGFR / KRAS / BRAF / HER2neu
  Gene sequencing

ALK
  IHC

ROS1
  IHC

FISH
  positive
  9%

SLPG 2014
Squamous cell carcinoma
Adenocarcinoma
Large cell carcinoma
Sarcomatoid carcinomas
NSCLC-NOS

Biopsy/Cytology

ADC profile, NSCLC-NOS
TTF1+, TTF1-, p40-

SCC phenotype
p40+, TTF1-

Stage IV

EGFR / KRAS / BRAF / HER2neu
Gene sequencing

ALK IHC
ROS1 IHC

FISH
positive 9%

negative

SLPG 2014
Resected Lung Carcinomas

• New classification of differentiated lung carcinomas
  – ADC
  – SCC

• New classification of undifferentiated lung carcinomas
  – LCC
Adenocarcinoma

2004 WHO

- Mixed subtype  >90%
- Acinar
- Papillary
- BAC
- Solid
- Variants

No established grading criteria
International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma

William D. Travis, MD, Elisabeth Brambilla, MD, Masayuki Noguchi, MD, Andrew G. Nicholson, MD, Kim R. Geisinger, MD, Yasushi Yatabe, MD, David G. Beer, PhD, Charles A. Powell, MD, Gregory J. Riely, MD, Paul E. Van Schil, MD, Kavita Garg, MD, John H. M. Austin, MD, Hisao Asamura, MD, Valerie W. Rusch, MD, Fred R. Hirsch, MD, Giorgio Scagliotti, MD, Tetsuya Mitsudomi, MD, Rudolf M. Huber, MD, Yuichi Ishikawa, MD, James Jett, MD, Montserrat Sanchez-Cespedes, PhD, Jean-Paul Sculier, MD, Takashi Takahashi, MD, Masahiro Tsuboi, MD, Johan Vansteenkiste, MD, Ignacio Wistuba, MD, Pan-Chyr Yang, MD, Denise Aberle, MD, Christian Brambilla, MD, Douglas Flieder, MD, Wilbur Franklin, MD, Adi Gazdar, MD, Michael Gould, MD, MS, Philip Hasleton, MD, Douglas Henderson, MD, Bruce Johnson, MD, David Johnson, MD, Keith Kerr, MD, Keiko Kuriyama, MD, Jin Soo Lee, MD, Vincent A. Miller, MD, Iver Petersen, MD, PhD, Victor Roggli, MD, Rafael Rosell, MD, Nagahiro Saijo, MD, Erik Thunnissen, MD, Ming Tsao, MD, and David Yankelewitz, MD
<table>
<thead>
<tr>
<th>2004 WHO</th>
<th>2015 WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mixed subtype</td>
<td>• Preinvasive lesions</td>
</tr>
<tr>
<td>• Acinar</td>
<td>– AAH</td>
</tr>
<tr>
<td>• Papillary</td>
<td>– AIS (≤ 3cm) (≈ 0.2%)</td>
</tr>
<tr>
<td>• BAC</td>
<td>• Minimally invasive ADC (MIA)</td>
</tr>
<tr>
<td>• Solid</td>
<td>– ≤ 3cm with ≤ 5mm invasion (≈ 3%)</td>
</tr>
<tr>
<td>• Variants</td>
<td>• Invasive ADC</td>
</tr>
<tr>
<td></td>
<td>– G1: Lepidic (≈ 10%)</td>
</tr>
<tr>
<td></td>
<td>– G2: Acinar, papillary</td>
</tr>
<tr>
<td></td>
<td>– G3: Micropapillary, solid</td>
</tr>
<tr>
<td></td>
<td>• Variants</td>
</tr>
</tbody>
</table>
Spread Through Alveolar Spaces (STAS)
Minimally invasive Adenocarcinoma

≤ 3cm
lepidic predominant

≤ 0.5cm invasion:
– invasive subtypes
– tumor cells infiltr. stroma

~ 100% disease-free survival

Travis WD et al., JTO 2011;6 (2)
Minimally invasive Adenocarcinoma

≤ 3cm
lepidic predominant

≤ 0.5 cm invasion:
- invasive subtypes
- tumor cells infiltr. stroma

no invasion of lymphatics, blood vessels or pleura, no tumor necrosis
Pleural invasion = Infiltration beyond elastic layer
Pleural invasion = Infiltration beyond elastic layer → Lepidic predominant invasive ADC
Invasive Adenocarcinoma

- Acinar predominant
- Papillary predominant
- Micropapillary predominant
- Solid predominant with mucin
Radiologic-pathologic correlation

In situ concept on CT measurement of tumor size: GGO vs Solid

Ground glass nodule (AIS, MIA)
→ watchful waiting
→ limited resection

Solid nodule
→ suspicious for invasive lung cancer

WCLC 2011, Kavita Garg
Travis WD et al., ECC 2014
Radiologic-pathologic correlation

In situ concept on CT measurement of tumor size: GGO vs Solid

Ground glass nodule (AIS, MIA)
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Solid nodule → suspicious for invasive lung cancer

WCLC 2011, Kavita Garg
Travis WD et al., ECC 2014
Implications for TNM Staging

- AIS would be classified as Tis
- MIA would be classified as Tmi
- T factor size - change to invasive size?
Large Cell Carcinoma

2004 WHO

- LCC
- LCNEC
- Basaloid carcinoma
- Lymphoepithel.-like CA
- Clear cell CA
- Rhabdoid phenotype
Large Cell Carcinoma

2004 WHO

- LCC
- LCNEC
- Basaloid carcinoma
- Lymphoepithel.-like CA
- Clear cell CA
- Rhabdoid phenotype
# Large Cell Carcinoma
Redefined by Immunohistochemistry and Genomics

<table>
<thead>
<tr>
<th>Reference</th>
<th># of cases</th>
<th>Immunohistochemistry panel</th>
<th>Other studies</th>
<th># reclassified as ADC</th>
<th># reclassified as SCC</th>
<th># unclassified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monica et al. [12]</td>
<td>54</td>
<td>DSC3, TTF-1</td>
<td>N/A</td>
<td>24 (44%)</td>
<td>26 (48%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Barbareschi et al. [51]</td>
<td>56</td>
<td>TTF-1, p63, CK5, CK7, Napsin A, p40, DSC3</td>
<td>miR205 and miR21 profiling</td>
<td>19 (34%) with IHC alone</td>
<td>14 (25%) with IHC alone</td>
<td>23 (41%) with IHC alone</td>
</tr>
<tr>
<td>Rekhtman et al. [11**]</td>
<td>102</td>
<td>TTF-1, p40</td>
<td>N/A</td>
<td>62 (61%)</td>
<td>20 (20%)</td>
<td>20 (20%)</td>
</tr>
<tr>
<td>Rossi et al. [52*]</td>
<td>74</td>
<td>TTF-1, p63, CK5/6, CK7, Napsin A, p40, DSC3, chromogranin, synaptophysin, CD56</td>
<td>N/A</td>
<td>40 (80%)</td>
<td>6 (12%)</td>
<td>4 (8%)</td>
</tr>
</tbody>
</table>

ADC: 55%  
SCC: 26%  
Null: 19%

Large Cell Carcinoma
Redefined by Immunohistochemistry and Genomics

Combined frequency of mutations characteristic of ADC (%)

- LCC-ADC: 50% (95% CI 38-62%, n=62)
- LCC-SQCC: 0% (95% CI 0-19%, n=20)
- LCC-null: 30% (95% CI 14-52%, n=20)

P-values:
- P = 0.131
- P < 0.001
- P = 0.02

Rekhtman N, Mod Pathol. 2013;26(4)
## Large Cell Carcinoma

<table>
<thead>
<tr>
<th>2004 WHO</th>
<th>2015 WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>• LCC</td>
<td>• LCC</td>
</tr>
<tr>
<td>• LCNEC</td>
<td>– Null-IHC features</td>
</tr>
<tr>
<td>• Basaloid carcinoma</td>
<td>– With no stains available</td>
</tr>
<tr>
<td>• Lymphoepithel.-like CA</td>
<td>• TTF1+ → solid ADC</td>
</tr>
<tr>
<td>• Clear cell CA</td>
<td>• P40 + → non-keratinizing SCC</td>
</tr>
<tr>
<td>• Rhabdoid phenotype</td>
<td></td>
</tr>
</tbody>
</table>
Large Cell Carcinoma

**2004 WHO**

- LCC
- LCNEC
- Basaloid carcinoma
- Lymphoepithel.-like CA
- Clear cell CA
- Rhabdoid phenotype

**2015 WHO**

- LCC (mucin -, null-IHC)
- NE Tumors
- SCC
- Other carcinomas
- Cytol. pattern, not subtype
- Cytol. pattern, not subtype
### Squamous Cell Carcinoma

<table>
<thead>
<tr>
<th>2004 WHO</th>
<th>2015 WHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SCC</td>
<td>• Keratinizing</td>
</tr>
<tr>
<td></td>
<td>• Non-keratinizing (p40+/TTF1-)</td>
</tr>
<tr>
<td></td>
<td>• Basaloid CA (p40+/TTF1-)</td>
</tr>
</tbody>
</table>
# Neuroendocrine Tumors

<table>
<thead>
<tr>
<th>2004 WHO</th>
<th>2015 WHO</th>
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</thead>
<tbody>
<tr>
<td>• Carcinoid tumors</td>
<td></td>
</tr>
<tr>
<td>– Typical Carcinoid</td>
<td></td>
</tr>
<tr>
<td>– Atypical Carcinoid</td>
<td></td>
</tr>
<tr>
<td>• Carcinoid tumors</td>
<td></td>
</tr>
<tr>
<td>– Typical Carcinoid</td>
<td></td>
</tr>
<tr>
<td>– Atypical Carcinoid</td>
<td></td>
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<tr>
<td>• SCLC</td>
<td></td>
</tr>
<tr>
<td>– Combined SCLC</td>
<td></td>
</tr>
<tr>
<td>• LCNEC</td>
<td></td>
</tr>
<tr>
<td>– Combined LCNEC</td>
<td></td>
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</tbody>
</table>
Summery

• Small samples
  – Safe tissue for predictive markers

• ADC
  – Defined by morphology or expression of pneumocytic markers

• SCC
  – Defined by morphology or expression of squamous markers

• LCC
  – Only on resections
  – No squamous, adeno- or neuroendocr. diff. by morphol. and IHC