Steering Committee

Paul A. Bunn, Jr., MD
Kavita Garg, MD
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Fred R. Hirsch, MD, PhD
Gregory Riely, MD, PhD
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William D. Travis, MD
Ming-Sound Tsao, MD, FRCPC
Ignacio I. Wistuba, MD
# Modules and Participating Faculty

## 1. Introducing The New IASLC/ATS/ERS Lung Adenocarcinoma Classification

<table>
<thead>
<tr>
<th>Faculty</th>
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<tbody>
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<td>William D. Travis, MD</td>
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## 2. Implications of the New IASLC/ATS/ERS Classification

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## 3. Highlights for the Pathologist

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<td>Ming S. Tsao, MD, FRCPC</td>
<td>Princess Margaret Hospital Toronto, Ontario, Canada</td>
</tr>
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<td>Ignacio I. Wistuba, MD</td>
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</tr>
<tr>
<td>Kim R. Geisinger, MD</td>
<td>Piedmont Pathology Associates Hickory, NC</td>
</tr>
</tbody>
</table>

The faculty wish to acknowledge Drs. Yasushi Yatabe (Aichi Cancer Center; Nagoya, Japan) and Andrew Nicholson (Royal Brompton Hospital; London, UK) as external reviewers for this module.

## 4. Highlights for the Radiologist

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The faculty wish to acknowledge Drs. Ryutaro Kakinuma (National Cancer Center Hospital; Tokyo, Japan) and Mathias Prokop (University Medical Center; Utrecht, Netherlands) as external reviewers for this module.

## 5. Case Studies for the Practicing Clinician

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Introducing The New IASLC/ATS/ERS Lung Adenocarcinoma Classification

Module 1
Introducing The New IASLC/ATS/ERS Lung Adenocarcinoma Classification
Rationale for New Adenocarcinoma Classification

- Lung cancer is the most common cancer, and is the most frequent cause of cancer mortality worldwide
- Adenocarcinoma is the most common histologic subtype
- Widely divergent clinical, radiologic, molecular and pathologic spectrum
- Evolving therapeutic landscape
  - Novel/molecular-targeted agents
  - Increased use of small biopsies vs surgical resections for tissue sampling

Rationale for New Adenocarcinoma Classification

- Shortcomings of 2004 WHO classification
  - e.g., “mixed subtype,” BAC

- Importance of distinguishing ADC from squamous cell carcinoma
  - Tumor biology and prognosis
  - Use of pemetrexed in adenocarcinoma or NSCLC-NOS only
  - Use of EGFR TKIs and crizotinib in EGFR-mutated or ALK-rearranged cancers
  - Safety risk for bevacizumab use in squamous

- New classification published in 2011:

ADC=Adenocarcinoma; BAC=Bronchioloalveolar Carcinoma; EGFR=Epidermal Growth Factor Receptor; TKI=Tyrosine Kinase Inhibitors; WHO=World Health Organization
Outline of this Module

• Objectives of new classification
• Brief summary of methodology
• Overview of the new IASLC/ATS/ERS classification
  – Comparison to the WHO 2004 classification
  – Explanation of key changes and additions (rationale and resolution)
    • Multidisciplinary approach
    • Classification for small biopsies and cytology
    • Classification for resection specimens

ATS=American Thoracic Society; ERS=European Respiratory Society; IASLC=International Association for the Study of Lung Cancer
Personalized Therapy for Lung Cancer Patients is Driven by Histology and Genetics

- Predictive of response
  - Adenocarcinoma or NSCLC-NOS
    - Pemetrexed
  - *EGFR* mutation (adenocarcinoma)
    - *EGFR* TKIs
  - *EML4-ALK* rearrangement or fusion (adenocarcinoma)
    - Crizotinib

- Predictive of toxicity
  - Bevacizumab
    - Contraindicated in squamous carcinoma (life-threatening bleeding)
Why Optimal Classification Matters

Results in *EGFR* Mutation Positive and Negative Patients
(All Asian, 94% Never Smokers)

**EGFR mutation-positive**

- Gefitinib CR/PR Rate 71%
- Carboplatin/paclitaxel CR/PR Rate 47%

**EGFR mutation-negative**

- Gefitinib CR/PR Rate 1%
- Carboplatin/paclitaxel CR/PR Rate 24%

**Why Optimal Classification Matters**

**First-Line EGFR TKI Therapy in EGFR-Mutated Advanced NSCLC**

EGFR TKIs are superior to chemotherapy in patients with *EGFR*-mutant tumors: evidence from randomized trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Treatment Comparison</th>
<th>PFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>WJTOG3405</td>
<td>177</td>
<td>Gefitinib vs. Cis/Docet</td>
<td>9 vs 6 mo</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR=0.49</td>
<td></td>
</tr>
<tr>
<td>NEJ002</td>
<td>230</td>
<td>Gefitinib vs. Carbo/Paclit</td>
<td>11 vs 5 mo</td>
<td>31 vs 24 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR=0.30</td>
<td></td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>165</td>
<td>Erlotinib vs. Carbo/Gem</td>
<td>14 vs 5 mo</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR=0.16</td>
<td></td>
</tr>
<tr>
<td>EURTAC</td>
<td>153</td>
<td>Erlotinib vs. Plat-based CT</td>
<td>10 vs 5 mo</td>
<td>23 vs 19 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR=0.42</td>
<td></td>
</tr>
</tbody>
</table>

All PFS differences were statistically significant (P < 0.0001)
OS differences were not statistically significant

ALK Inhibition in NSCLC: Crizotinib
Study A8081001

Best Response (N*=106)

- BOR
- PD
- SD
- PR
- CR

OS
- Median OS: NR (79% pts still in f/u)
- Survival probability
  - 6 months: 90.0%
  - 12 months: 80.5%

Retrospective comparison in ALK-positive patients
- Treated: from 1001 study
- Naïve: patient series from study sites

PFS
- Median PFS = 10.0 mo
Clinical Recommendation

• In patients with advanced ADC: test for \textit{EGFR} mutation and \textit{ALK} rearrangement (strong recommendation, moderate quality evidence)

• Similar recommendations proffered by ASCO and NCCN
Why Optimal Classification Matters
Pemetrexed is More Effective in ADC and LCC than in SQCC

Pemetrexed is not recommended for patients with SQCC (any line of treatment): evidence from randomized trials

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Population</th>
<th>N</th>
<th>Median OS (Pem vs control)</th>
<th>Treatment-by-Histology Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pem/Cis vs Gem/Cis</td>
<td>Squamous</td>
<td>473</td>
<td>9 vs 11 mo</td>
<td>$P = 0.002$</td>
</tr>
<tr>
<td></td>
<td>Non-squam</td>
<td>1252</td>
<td>11 vs 10 mo</td>
<td></td>
</tr>
<tr>
<td>Pem vs Docet</td>
<td>Squamous</td>
<td>172</td>
<td>6 vs 7 mo</td>
<td>$P = 0.001$</td>
</tr>
<tr>
<td></td>
<td>Non-squam</td>
<td>399</td>
<td>9 vs 8 mo</td>
<td></td>
</tr>
<tr>
<td>Pem vs Plbo</td>
<td>Squamous</td>
<td>182</td>
<td>10 vs 11 mo (NS)</td>
<td>$P = 0.033$</td>
</tr>
<tr>
<td></td>
<td>Non-squam</td>
<td>328</td>
<td>16 vs 10 mo</td>
<td></td>
</tr>
</tbody>
</table>

All OS differences were significantly different between treatment arms, except where noted (NS).
Treatment-by-histology interactions were also significant for PFS in all three trials (not shown).

LCC=Large-Cell Carcinoma; SQCC=Squamous-Cell Carcinoma
Why Optimal Classification Matters
Growth Pattern: Efficient Prognostic Factor

- Single institution study of patients with completely resected invasive ADC, N=487, stages IA through IV
- Patients with lepidic-predominant ADC have better survival than the other subtypes

Warth A. J Clin Oncol 2012; epub March 5
Lung Adenocarcinoma
Classification In Small Biopsy And Cytology Specimens

Because this was never addressed by WHO, by necessity other histologies needed to be addressed.
Paradigm Shift in Lung Cancer Pathology/Oncology


- Approximately 70% of lung cancer patients are diagnosed at the advanced stage by cytology or small biopsies.

- Based on current state-of-the-art, specific diagnoses of squamous carcinoma vs adenocarcinoma or NSCLC-NOS are critical.
Commentary

• Worse prognosis in NSCLC-NOS and cytologically diagnosed cases
  – Probably, advanced stage or comorbidities

• Use of NSCLC-NOS partly due to WHO recommendation
  – No encouragement for further classification

• This has now changed with the new 2011 IASLC/ATS/ERS classification of adenocarcinoma
NSCLC-NOS Diagnoses Cannot Inform Treatment Decisions

Proportion of NOS diagnoses in key histology-driven trials

<table>
<thead>
<tr>
<th>Trial and Treatment</th>
<th>Population</th>
<th>N</th>
<th>% NOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>JMDB trial: Pem/Cis vs Gem/Cis in 1st L</td>
<td>Non-squamous</td>
<td>1252</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>NSCLC-NOS</td>
<td>252</td>
<td></td>
</tr>
<tr>
<td>Pem vs Docet in 2nd L</td>
<td>Non-squamous</td>
<td>399</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td>NSCLC-NOS</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>JMEN trial: Pem vs Plbo in 1st L maintenance</td>
<td>Non-squamous</td>
<td>328</td>
<td>41%</td>
</tr>
<tr>
<td></td>
<td>NSCLC-NOS</td>
<td>133</td>
<td></td>
</tr>
</tbody>
</table>

- High percentage of NSCLC-NOS diagnoses noted in trials where histology was a determinant factor on outcomes
- In small biopsies and cytology, classify NSCLC into ADC or SQCC, as specifically as possible

Epithelial Tumors
Invasive Malignant - 2004

- Adenocarcinoma
  - Mixed subtype
  - Acinar
  - Papillary
  - Bronchioloalveolar carcinoma
  - Solid adenocarcinoma with mucin formation
  - Variants

Over 90% are mixed subtype - with very heterogeneous mixture of patterns

Diagnostic Algorithm for Small Biopsy and Cytology Specimens

Based on morphology and IHC markers

**STEP 1.**
Positive Biopsy (FOB, TBBx, Core, SLBx) or Positive Cytology (effusion, aspirate, washings, brushings)

- **NE morphology, NE IHC(+), large cells**
  - NSCLC (probably LCNEC)
- **NE morphology, NE IHC(+), small cells, no nucleoli, TTF-1(+/−), CK(+)**
  - SCLC
- **Keratinization, pearls and/or intercellular bridges**
  - Classic Morphology: SQCC
- **Histology: Lepidic, papillary, and/or acinar architecture(s)**
  - Classic Morphology: ADC
  - Molecular Analysis: e.g. EGFR mutation

No clear ADC or SQCC morphology: NSCLC-NOS
Further Classification of NSCLC-NOS
(when morphology is indefinite)

STEP 2.
Apply ancillary panel of one
SQCC and one ADC marker
+/OR Mucin

No clear ADC or SQCC
morphology:
NSCLC-NOS

IHC(-) and Mucin(-)

ADC-marker(+) or Mucin(+)
AND
SQCC-marker(+) in
different cells

ADC-marker(+) and/or
Mucin(+)
AND
SQCC-marker(-) (or weak in
same cells)

SQCC-marker(+)
AND
ADC-marker(-) or Mucin(-)

NSCLC NOS

NSCLC-NOS, possible
adenosquamous

NSCLC (favor ADC)

NSCLC (favor SQCC)

Non-NE Markers:
ADC: TTF1, Napsin-A
SQCC: P63, CK5/6, p40

STEP 3. Molecular Analysis (e.g. EGFR mutation, ALK rearrangement). If tumor tissue is inadequate for molecular testing, discuss need for further sampling (Back to STEP 1)
### IASLC/ATS/ERS Terminology for Small Biopsies and Cytology

<table>
<thead>
<tr>
<th>2011 IASLC/ATS/ERS CLASSIFICATION</th>
<th>2004 WHO CLASSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphologic ADC patterns clearly present: ADC, describe identifiable patterns present</td>
<td>ADC Mixed subtype; Acinar; Papillary; Solid</td>
</tr>
<tr>
<td>Morphologic adenocarcinoma patterns not present, positive ADC marker (TTF-1), and negative squamous marker (p40): NSCLC, favor ADC</td>
<td>No 2004 WHO counterpart – most will be solid ADC</td>
</tr>
<tr>
<td>Morphologic squamous cell patterns clearly present: Squamous cell carcinoma</td>
<td>Squamous cell carcinoma Papillary; Clear cell; Small cell; Basaloid</td>
</tr>
<tr>
<td>Morphologic squamous cell patterns not present, positive squamous marker (p40), negative ADC marker (TTF-1): NSCLC, favor squamous cell carcinoma</td>
<td>No 2004 WHO counterpart</td>
</tr>
<tr>
<td>NSCLC with IHC markers negative for ADC and squamous markers: not otherwise specified (NOS)</td>
<td>Large cell carcinoma</td>
</tr>
</tbody>
</table>

Travis WD. J Thor Oncol 6:244-85, 2011
Rationale for Small Biopsy/Cytology Terms

- Clinical trial data – based on light microscopy
- Most of the 20-40% NSCLC formerly NOS cases will be reclassified
- **NSCLC, favor adenocarcinoma or squamous-cell**
  - Comment about IHC results can clarify which cases have been reclassified based only on IHC
- Clinicians want to know uncertainties in diagnosis
- Clinical trials, need to capture data to know for which cases diagnoses are changing
Diagnoses that Cannot be Made Based on Small Biopsies/Cytology

- Large Cell Carcinoma
- Adenosquamous Carcinoma
- Pleomorphic Carcinoma

- Difficult To Make:
  - Typical vs Atypical Carcinoid
  - Large Cell Neuroendocrine Carcinoma
Tissue Management

• Each multidisciplinary team must develop a tissue management strategy
  – Thoracic physicians: clinicians, radiologists, surgeons, pathologists, molecular pathologists

• Obtaining biopsies or cytology samples

• Optimal processing by laboratories/pathologists for diagnosis AND molecular studies

• Pathologists should lead tissue management
Key Principles

• Minimize diagnostic stains to maximize tissue for molecular studies
• Approach to workup needs to address possible diagnoses other than ADC or SQCC
  – Metastatic carcinomas or other tumors (lymphoma/melanoma)
• Immunostains are not needed to diagnose most adenocarcinomas or squamous cell carcinomas
Clinical: Key Messages
Good Clinical Practice

• If molecular testing is planned, biopsies should provide sufficient tissue for
  – Pathologic diagnosis
  – Molecular analyses

• Make cell block whenever possible from cytology specimens (i.e. pleural fluid)

• Multidisciplinary coordination necessary for rapid diagnosis and molecular testing
Terminology And Classification

• Avoid the following terms whenever possible:
  – NSCLC
  – Non-Squamous

• Specify the diagnosis:
  – Exact histology
  – Was it based on light microscopy alone?
  – Did it require IHC and/or mucin stains?
Conclusions

- NSCLC NOS is no longer sufficient. It is important to distinguish ADC from SQCC
- Molecular characterization (e.g. EGFR, ALK) is an important part of pathology evaluation of lung adenocarcinoma
- Material obtained at biopsy should be sufficient for all analyses, if possible (cell block from cytology specimens)
- Tissue obtained at biopsy must be managed to allow for all necessary analyses (IHC, molecular)
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• Check www.IASLC.org for upcoming program and event registration dates, and IASLC membership information