Steering Committee

Paul A. Bunn, Jr., MD
Kavita Garg, MD
Kim Geisinger, MD
Fred R. Hirsch, MD, PhD
Gregory Riely, MD, PhD
Paul Van Schil, MD, PhD
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>William D. Travis, MD</th>
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<td>Aurora, CO</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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<tr>
<th>Ming S. Tsao, MD, FRCPC</th>
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<tr>
<td>Princess Margaret Hospital</td>
<td>The University of Texas M.D. Anderson Cancer Center</td>
<td>Piedmont Pathology Associates</td>
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<tr>
<td>Toronto, Ontario, Canada</td>
<td>Houston, TX</td>
<td>Hickory, NC</td>
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## 4. Highlights for the Radiologist

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## 5. Case Studies for the Practicing Clinician

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The New IASLC/ATS/ERS Lung Adenocarcinoma Classification

Module 5
Case Studies for the Practicing Clinician
Patient # 1 – Clinical History

- Patient is a 70-year-old man who presented with increased cough over 6 months, productive of grey sputum
- Past medical history: Cholecystectomy, 15 pack-year history of smoking (1ppd x 15 years, quit 40 years ago)
- Family history: No family history of cancer
CT Chest

Mass-like consolidated bilateral pulmonary opacities with satellite nodules
Initial Evaluation

- MRI brain – no evidence of metastases
- Bone Scan – no evidence of bone metastases
- Routine Labs – normal blood count and chemistries
- Bronchoscopy performed: brushings for cytology reported as non-small cell carcinoma
• For small biopsies/cytology, NSCLC should be further classified into more specific histologic types (e.g. adenocarcinoma, squamous-cell carcinoma), whenever possible

• The term NSCLC-NOS be used infrequently and only applied when a more specific diagnosis is NOT possible by morphology/special stains
Further Evaluation

- Available material from bronchoscopy was insufficient for additional pathologic evaluation
- Patient undergoes CT-guided core needle biopsy

- Diagnosis: Invasive Adenocarcinoma
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
- NE morphology, NE IHC(+), small cells, no nucleoli, TTF-1(+/-), CK(+)
- Keratinization, pearls and/or intercellular bridges
- Histology: Lepidic, papillary, and/or acinar architecture(s)
  Cytology: 3-D arrangements, delicate foamy/vacuolated (translucent) cytoplasm, fine nuclear chromatin and often prominent nucleoli, nuclei often eccentrically situated

**NSCLC (probably LCNEC)**

**SCLC**

**Classic Morphology: SQCC**

**Classic Morphology: ADC**

Molecular Analysis: e.g. *EGFR* mutation

ADC: adenocarcinoma; CK: cytokeratin; FOB: fiberoptic bronchoscopy; IHC: immunohistochemistry; LCNEC: large cell neuroendocrine carcinoma; NE: neuroendocrine; NOS: not otherwise specified; NSCLC: non-small cell lung carcinoma; SBx: surgical lung biopsy; SCLC: small cell lung carcinoma; SQCC: squamous cell carcinoma; TBBx: transbronchial biopsy; TTF: thyroid transcription factor;
Diagnostic Molecular Pathology Evaluation

• Diagnostic molecular pathology
  – Positive for *EGFR* exon 19 deletion, 18bp deletion
  – Negative for *ALK* rearrangement
Based on histology and molecular pathology evaluation, patient was initially treated with erlotinib.

Radiographic response lasted 16 months.
Patient # 2 – Clinical History

- 76 year old woman, former 50 pack-year smoker (1 pack per day for 50 years, quit 10 years ago) presents with intermittent, dry cough
- Past Medical History: COPD, coronary artery disease with prior bypass grafting
- Family History: no family history of cancer, father and mother died in their 70s of heart disease
- Abnormal chest X-ray leads to CT scan
CT Chest

Left lower lobe mass, juxtpleural nodules in left lower and upper lobes, right paratracheal, left tracheobronchial, and left hilar lymphadenopathy.
Initial Evaluation

- MRI Brain – unremarkable except for small vessel ischemic changes
- PET/CT scan – showed FDG-avid lung mass, hilar adenopathy, and mediastinal adenopathy
- Multiple FDG-avid bone lesions on PET with corresponding lesions seen on CT scan
Further Evaluation

- Bronchoscopy showed endobronchial lesions on left with proximal disease
- Transbronchial biopsy and endobronchial ultrasound-guided biopsy of mediastinal nodes was obtained
- Initial Pathology Report: Poorly Differentiated Carcinoma
• For small biopsies/cytology, NSCLC should be further classified into more specific histologic types (e.g. adenocarcinoma, squamous), whenever possible.

• The term NSCLC-NOS be used infrequently and only applied when a more specific diagnosis is NOT possible by morphology/special stains.
Further Classification of NSCLC-NOS  
(when morphology is indefinite)

**STEP 1.**
If morphology is not clear:
- NSCLC-NOS

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

- IHC(-) and Mucin(-)
  - NSCLC NOS
- ADC-marker(+) or Mucin(+)
  - NSCLC-NOS, possible adenosquamous
- ADC-marker(+) and/or Mucin(+)
  - NSCLC (favor ADC)
- SQCC-marker(+)
  - Non-NE Markers:
    - ADC: TTF1, Napsin-A
    - SQCC: P63, CK5/6, p40
  - NSCLC (favor SQCC)
- ADC-marker(-) or Mucin(-)
  - ADC-marker(+) and/or Mucin(+)
    - SQCC-marker(-) (or weak in same cells)

**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)
Further Evaluation

- Initial Pathology Report: Poorly Differentiated Carcinoma
- P63 IHC: positive
- TTF-1 IHC: negative
- After review of IHC and further light microscopy review: Squamous Cell Carcinoma
Treatment

Patient is treated with gemcitabine/cisplatin

Baseline

After 2 cycles
Patient # 3 – Clinical History

• 56 year old man, former 60 pack-year smoker (1½ packs per day for 40 years) presents with cough productive of copious amounts of clear sputum

• Past medical history: COPD, coronary artery disease with placement of coronary stents

• Family History: mother, who was a smoker, died of lung cancer at the age of 74

• Abnormal chest X-ray leads to CT scan
CT Chest

Consolidation encompassing right lower and right middle lobes
Initial Evaluation

- CT scan brain with IV contrast – no metastatic disease, no significant ischemic changes
- Bone Scan – no sites of specific tracer uptake
- Patient undergoes fluoroscopic core-needle biopsy
Pathology Evaluation

Invasive Mucinous Adenocarcinoma
Diagnostic Molecular Pathology Evaluation

- Diagnostic molecular pathology
  - Negative for *EGFR* exon 19 deletion
  - Negative for *EGFR* exon 21 L858R mutation
  - Positive for *KRAS* G12C mutation
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<th>Term</th>
<th>Pathology</th>
<th>CT Appearance</th>
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<td>Adenocarcinoma <em>in situ</em> (AIS)</td>
<td>Small (≤ 3 cm), solitary, noninvasive adenocarcinoma with pure lepidic growth, usually nonmucinous, rarely mucinous</td>
<td>Usually pure ground-glass, but may be part-solid, bubble-like, or solid</td>
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<tr>
<td>Minimally invasive adenocarcinoma (MIA)</td>
<td>Small (≤ 3 cm), solitary adenocarcinoma with predominantly lepidic growth and ≤ 5 mm invasion, usually nonmucinous, rarely mucinous</td>
<td>Mainly ground-glass, plus a small (≤ 5 mm) central solid component**</td>
</tr>
<tr>
<td>Lepidic predominant adenocarcinoma</td>
<td>Invasive nonmucinous adenocarcinoma that has lepidic growth as its predominant component</td>
<td>Usually part-solid, including a ground-glass component; may be pure ground-glass or solid; occasionally bubble-like</td>
</tr>
<tr>
<td>Acinar, papillary, micropapillary, or solid predominant ADC, plus a lepidic component</td>
<td>Invasive adenocarcinoma that is predominantly acinar, papillary, micropapillary, or solid, plus a small proportion of a lepidic component</td>
<td>Solid, but may include a small portion of ground-glass opacity</td>
</tr>
<tr>
<td>Invasive mucinous adenocarcinoma</td>
<td>Invasive mucinous adenocarcinoma that has lepidic growth as its predominant component</td>
<td>Usually solid or mostly solid, single or multifocal or multilobar, formerly BAC</td>
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Patient # 4 – Clinical History

• 71 year old woman with 40 pack year history of smoking (1 ppd x 40 years, quit 13 years ago) without symptoms
• Past Medical History – breast cysts
• Family History – unremarkable
• Patient undergoes a screening CT scan after announcement of NLST data and discussion with physician
CT Chest

Multilobar ground glass opacities with left lower lobe consolidation
Further Evaluation

- PET/CT scan – no FDG-avid lesions
- PFTs – adequate for lobectomy
- Cardiac stress test – no evidence of ischemia
- After discussion with thoracic surgeon, elects to undergo subsegmental resection as diagnostic procedure
Pathology Evaluation

Diagnosis: Minimally Invasive Adenocarcinoma
• The use of term “BAC” to be discontinued

• Adenocarcinoma in situ (AIS):
  – Defines small (≤ 3 cm) solitary ADC with pure lepidic growth
  – Exclude if miliary spread or lobar consolidation
  – 100% disease-free survival (DFS) if completely resected

• Minimally Invasive Adenocarcinoma (MIA):
  – Defines small (≤ 3 cm) solitary ADC with pure lepidic growth and small foci of invasion measuring ≤ 0.5 cm
  – Near 100% DFS if completely resected
MIA (Criteria of Invasion)

- Invasive components:
  - Histological patterns other than lepidic (e.g. acinar, papillary, micropapillary, solid)
  - Tumor cells infiltrating myofibroblastic stroma
- MIA excluded with presence of:
  - Lymphatic, blood vessels or pleural invasion
  - Tumor necrosis
- Microinvasive areas found in one tumor:
  - Multiple foci of MIA invasive areas possible
  - Individual invasive areas measured separately
  - Size of largest invasive area measured in largest dimension ≤0.5 cm
Key Concepts of the IASLC/ATS/ERS Lung Adenocarcinoma Classification

- Discontinued use of the term “BAC”, replaced with:
  - Adenocarcinoma in situ
  - Minimally Invasive Adenocarcinoma
  - Lepidic Predominant Adenocarcinoma,
  - Invasive Mucinous Adenocarcinoma

- Use of the term “NSCLC-NOS” to describe small biopsies/cytology should be uncommon
  - Immunohistochemistry should be used to further characterize

- Molecular analysis of lung adenocarcinomas should be routine (e.g. EGFR mutation, ALK rearrangement)
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• Check www.IASLC.org for upcoming program and events registration dates, and IASLC member information