"Radiologic Implications of the New IASLC/ATS/ERS Classification of Lung Adenocarcinoma"
Benjamin Felson Memorial Lecture
March 7, 2011
Society of Thoracic Radiology
Bonita Springs, FL
William D. Travis, M.D.
Attending Thoracic Pathologist
Memorial Sloan Kettering Cancer Center
New York, NY

RATIONALE FOR NEW ADENOCARCINOMA CLASSIFICATION
- Lung cancer – most frequent cause major cancer incidence/mortality worldwide
- Adenocarcinoma – the most common histologic subtype
- Widely divergent clinical, radiologic, molecular & pathologic spectrum
- Bronchioloalveolar carcinoma (BAC) – confusing used many different ways despite 99/04 WHO; mucinous/nonmucinous
- Rapid evolving molecular advances (EGFR)

EPITHELIAL TUMORS
Invasive Malignant - 2004
Adenocarcinoma
Mixed subtype
Acinar
Papillary
Bronchioloalveolar carcinoma
Solid adenocarcinoma with mucin formation
Variants

Small Adenocarcinoma 2cm or <
Noguchi M. et al; Cancer 75:2844, 1995

Small Adenocarcinoma 2cm or <
Noguchi M. et al; Cancer 75:2844, 1995
60% are Type C - with very heterogeneous mixture of patterns

LUNG ADENOCARCINOMA CLASSIFICATION - 2009
- Ladanyi M and Pao W; Mod Pathol: Suppl 2:314-22
MULTIDISCIPLINARY APPROACH

- Prior WHO classifications: by pathologists
- Due to remarkable advances in past 10 yrs: oncology, molecular, radiology, surgery: need for integrated multidisciplinary approach
- International Association for the Study of Lung Cancer (IASLC); American Thoracic Society (ATS), European Respiratory Society (ERS)
- Panel: Pathologists, Oncologists, Radiologists, Molecular Biologists, Surgeons

IASLC/ATS/ERS ADENOCARCINOMA MULTIDISCIPLINARY PANEL
MARCH 12-13, 2009 (In Situ Wine Toast)

LUNG ADENOCARCINOMA
CLASSIFICATION IN SMALL BIOPSY AND CYTOLOGY SPECIMENS

NON-SMALL CELL LUNG CANCER: 70% PRESENT IN ADVANCED STAGE

Percent

30%
70%
Early Stage
Advanced Stage

SMALL BIOPSY/CYTOLOGY LUNG CANCER DIAGNOSIS: IN USA OVER 130,000 CASES IN 2009

- 2009: ACS estimates for USA:
  - 219,440 Lung Cancers
  - 85% NSCLC = 186,524 (15% SCLC)
  - 70% Advanced Stage = 130,567
    - Unresectable: Diagnosed by small biopsies /cytology

In Advanced NSCLC HISTOLOGY MATTERS

- Predictive of response
  - EGFR mutation (in adeno) – EGFR TKI’s
  - Adenoca or NSCLC-NOS - pemetrexed
- Predictive of toxicity
  - Bevacizumab – contraindicated in life-threatening hemorrhage in squamous carcinoma
Initial Therapy of Lung Advanced Adenocarcinoma

- EGFR Mutation
  - Exon 19 del
  - Exon 21 L858R, L861X
  - Exon 18 G719A/S

- No EGFR Mutation
- Unknown EGFR Mutation Status

- Erlotinib/Gefitinib
- ± Pem/Bev/Cis
- Pemetrexed
- Bevacizumab
- Cisplatin

PHASE III STUDY COMPARING CISPLATIN PLUS GEMCITABINE WITH CISPLATIN & PEMETREXED IN ADVANCED NSCLC

SQUAMOUS CELL CARCINOMA

IMMUNOHISTOCHEMICAL MARKERS

- ADENOCARCINOMA
  - TTF-1 (best), Napsin, PE-10
- SQUAMOUS CARCINOMA
  - p63 (best), CK5/6, 34BE12
  - Desmocolin-3 (need more testing)
- Cocktails – nuclear/cytoplasmic antibodies
  - Adenoma – TTF-1/Napsin
  - Squamous – p63/CK5/6

**SUGGESTED TERMINOLOGY**

**NSCLC: SMALL BIOPSIES/CYTOLOGY**

- Light microscopy – clear differentiation
  - Squamous Cell Carcinoma or Adenocarcinoma
- Light microscopy – NSCLC-NOS – do IHC
  - Clear IHC differentiation
    - Non-small cell carcinoma, favor squamous cell carcinoma (IHC: positive squamous, negative adeno)
    - Non-small cell carcinoma, favor adenocarcinoma (IHC: positive adeno, negative squamous)
  - IHC negative or not clear: NSCLC-NOS
    - All staining negative
    - Conflicting staining

**NSCLC-NOS**

**BY LIGHT MICROSCOPY**

**NSCLC – FAVOR ADENOCARCINOMA**

**NSCLC – FAVOR ADENOCARCINOMA**

**TOUCH PREP CYTOLOGY**

**NSCLC-NOS, FAVOR ADENOCARCINOMA**

**BY LIGHT MICROSCOPY**

- EGFR mutation - negative
  - Exon 19 deletion
  - Exon 21 L858R mutation
- KRAS mutation - positive
  - G12V
- Results favor adenocarcinoma

**TISSUE MANAGEMENT**

- Each group of thoracic physicians (clinicians, radiologists, surgeons, pathologists, molecular biologists) must develop a strategy to manage tissues
- Obtaining biopsies or cytology samples
- Optimal processing by laboratories/pathologists for diagnosis AND molecular studies
LUNG ADENOCARCINOMA
CLASSIFICATION IN
RESECTION SPECIMENS

IASLC/ATS/ERS ADENOCARCINOMA
CLASSIFICATION

- PREINVASIVE LESIONS
  - ATYPICAL ADENOMATOUS HYPERPLASIA
  - ADENOCARCINOMA IN SITU (≤3 cm, formerly BAC pattern)†
    - non-mucinous
    - 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
MUCINOUS

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MINIMALLY INVASIVE ADENOCA NONMUCINOUS

IASLC/ATS/ERS ADENOCARCINOMA CLASSIFICATION

INVASIVE ADENOCARCINOMA
- Lepidic pattern predominant (formerly non-mucinous BAC pattern)
- Acinar pattern predominant
- Papillary pattern predominant
- Micropapillary pattern, predominant
- Solid pattern predominant

(Comprehensive histologic subtyping: semiquantitative assessment of patterns in 5-10% increments)

LEPIDIC PREDOMINANT

OLD 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. Mucinous adenocarcinoma with lepidic pattern
STAGE 1 SOLITARY ADENOCARCINOMA AGE AND SEX (N=514)

- AGE: Mean 68 yr, Median 69 yrs (range 33-89 yrs)

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>I A</td>
<td>233 (62%)</td>
<td>143 (38%)</td>
<td>376 (73%)</td>
</tr>
<tr>
<td>I B</td>
<td>90 (65%)</td>
<td>48 (35%)</td>
<td>138 (27%)</td>
</tr>
<tr>
<td>Total</td>
<td>323 (63%)</td>
<td>191 (37%)</td>
<td>514 (100%)</td>
</tr>
</tbody>
</table>

Yoshizawa A, Motoi N, Sima C, Gerald W, Kris, M. Park B, Rusch V, Travis WD (submitted)

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

<table>
<thead>
<tr>
<th>Histologic Type (N)</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>Mucinous Adca (13)</td>
<td>76</td>
</tr>
<tr>
<td>Solid (87)</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>

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

<table>
<thead>
<tr>
<th>Histologic Type (N)</th>
<th>5 Year RFS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIS/MIA (9)</td>
<td>100</td>
</tr>
<tr>
<td>Lepidic NM, Papillary, Acinar (404)</td>
<td>84</td>
</tr>
<tr>
<td>Mucinous Adca, Colloid, Solid, Micropapillary (101)</td>
<td>71</td>
</tr>
</tbody>
</table>

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IASLC/ATS/ERS ADENOCARCINOMA CLASSIFICATION

VARIANTS

- Invasive mucinous adenocarcinoma (formerly mucinous BAC)
- Colloid adenocarcinoma
- Fetal adenocarcinoma (low and high grade)
- Enteric adenocarcinoma

MUCINOUS ADENOCARCINOMA

GRADING

- There is no well established grading system for adenocarcinoma (or other non-small cell lung carcinomas)
- Two different approaches
  - Architectural
  - Nuclear

Grading in Lung Adenocarcinoma

- 85 patients
- Solid component → 90 ≤ score 1, 90: score 2
- Cytologic atypia → Mild/Moderate: score 1, Severe: score 2
- Mitotic count → Not predictive for prognosis
- Sum of the 2 scores
  - Well differentiated: score 2
  - Moderate differentiated: score 3
  - Poorly differentiated: score 4


Nuclear grading of primary pulmonary adenocarcinoma

139 lung adenocarcinoma (≥2cm) patients
(Stage I: 86, II: 20, III: 26, IV: 1)
Nuclear diameter (ND) evaluated using an imaging processor (computer software)
- Optimal cut-off value for Nuclear Diameter 10.7μm
- Small lymphocyte (≤ 3.9μm) was recommended as internal control to evaluate nuclear diameter.


Concordance Between Predominant Histological Patterns in the Primary Tumor and Metastases

<table>
<thead>
<tr>
<th>Histological Pattern</th>
<th>AC</th>
<th>PAP</th>
<th>NP</th>
<th>SQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Tumor</td>
<td>36</td>
<td>14</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Metastases</td>
<td>16</td>
<td>3</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>% concordance</td>
<td>44</td>
<td>21</td>
<td>89</td>
<td>80</td>
</tr>
</tbody>
</table>

PROGNOSTIC SIGNIFICANCE OF COMPREHENSIVE HISTOLOGIC SUBTYPING (CHS) AS BASIS FOR GRADING

- Example: adenocarcinoma with 40% acinar, 25% papillary, 20% solid, 15% micropapillary
- Sum of two most prominent patterns: Score 2+2=4.
- Example: adenocarcinoma with 60% solid, 20% micropapillary, 10% lepidic, 10% papillary.
- Sum of two most prominent patterns: Score 3+3=6


COMPREHENSIVE HISTOLOGIC TYPING OF ADENOCARCINOMAS: USEFUL FOR ARCHITECTURAL GRADING

- The semiquantitative data obtained from comprehensive histologic subtyping of lung adenocarcinomas can easily be translated into a grading system that has prognostic significance.
- Histologic classification is different from histologic grading.

IMPLICATIONS OF NEW CLASSIFICATION FOR TNM STAGING OF ADENOCARCINOMAS

- Multiple tumors: Metastasis vs synchronous/metachronous primaries
- Terminology: implication of AIS and MIA
- Tumor size

7th Ed TNM STAGING SYSTEM:
MULTIPLE NODES, SAME HISTOLOGY

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>7th Ed AJCC/UICC</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same lobe</td>
<td>T3</td>
<td>- In the case of multiple simultaneous tumors in one organ, the tumor with the highest T category should be classified and the multiplicity or the number of tumors should be indicated in parentheses, e.g., T2 (m) or T2 (5). In simultaneous bilateral cancers, each tumor should be classified independently.</td>
</tr>
<tr>
<td>Ipsilateral different lobe</td>
<td>T4</td>
<td></td>
</tr>
<tr>
<td>Contralateral</td>
<td>M1a</td>
<td></td>
</tr>
<tr>
<td>Discontinuous pleural nodules</td>
<td>M1a</td>
<td></td>
</tr>
</tbody>
</table>
- Multiple primary non-small cell lung cancer

- At MSKCC: Testing for EGFR/KRAS mutations


\[
\begin{align*}
\text{EGFR 19 del} & \quad \text{KRAS G12D}
\end{align*}
\]

Genomic profiling: similar profile = metastases


Genomic profiling: different profile = multiple primary


DISTINGUISHING MULTIPLE PRIMARY LUNG TUMORS FROM METASTASES

- Genomic and mutational profiling were feasible to assess clonal relationships between multiple lung tumors
- Martini Melamed clinical criteria were inaccurate in 32% of cases
- Comprehensive histologic subtyping accuracy rate was
  - 91% on surgical pathology specimens
  - 64% on frozen specimens


DISEASE FREE SURVIVAL COMPARING MARTINI MELAMED VS MOLECULAR VS SURGICAL PATHOLOGY

<table>
<thead>
<tr>
<th>Group</th>
<th>Survival Rate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martini Melamed</td>
<td></td>
<td>0.052</td>
</tr>
<tr>
<td>Molecular</td>
<td></td>
<td>0.013</td>
</tr>
<tr>
<td>Surgical Pathology</td>
<td></td>
<td>0.001</td>
</tr>
</tbody>
</table>

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

In breast cancer, the size T-factor is measured based only on the size of the invasive component (excluding the size of the CIS component).

We sought to examine if in our Stage I tumors, the tumor size T factor may need to be adjusted from total tumor size to only the size of the invasive component.

STAGE 1 ADENOCARCINOMA
Standard Gross Size
T1a <= 2 cm vs. T1b >2-3 cm

<table>
<thead>
<tr>
<th>Stage (N)</th>
<th>5 Year RFS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a (259)</td>
<td>88</td>
</tr>
<tr>
<td>T1b (152)</td>
<td>80</td>
</tr>
</tbody>
</table>

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STAGE 1 ADENOCARCINOMA
Size adjusted by % invasion (not in situ)
T1a <= 2 cm vs. T1b >2-3 cm

<table>
<thead>
<tr>
<th>Stage (N)</th>
<th>5 Year RFS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a (320)</td>
<td>88</td>
</tr>
<tr>
<td>T1b (111)</td>
<td>73</td>
</tr>
</tbody>
</table>

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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</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 (I vs II)</td>
<td>1.7 (0.3 – 9.6)</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>WHO/WHO-80 classification</td>
<td>1.1 (0.6 – 1.9)</td>
<td>0.56</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 – 2.5)</td>
<td>0.085</td>
</tr>
</tbody>
</table>

* Tumor size adjusted by subtracting percentage of lepidic growth

IMPLICATIONS OF IN SITU CONCEPT ON CT MEASUREMENT OF TUMOR SIZE: GGO VS SOLID

POTENTIAL NEW APPROACH TO TUMOR SIZE MEASUREMENT

Contributed by C. Henschke & colleagues
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

SUBTYPING OF PULMONARY ADENOCARCINOMAS – DOES IT HAVE AN IMPACT ON TREATMENT AND OUTCOME?

- AIS/MIA – 100% DFS; potential for limited surgery or just follow-up – needs validation
- Early stage: Impacts on outcome; may help stratify pts for adjuvant Rx - more validation needed
- Grading: needs more validation
- Staging
  - Multiple tumors – impacts outcome & Rx
  - Tumor size – impacts outcome & Rx

CORE MULTIDISCIPLINARY PANEL MEMBERS

- Elisabeth Brambilla
- Marcella Nagahiro
- Gianluigi Boccato
- Roberto Carbone
- Giuseppe Carnevali
- Joseph Ferrence
- Franco Fumagalli
- Robert Fujioka
- Michael Graeven
- Abhijit Gupta
- Marc Haaga
- Doris Hruban
- David Lippman
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- Iver Petersen
- Victor Pons
- John Reznikov
- Richard Schilsky
- Keith Sondak
- G. John Thayer
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- oggi Yamamoto
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- Ariane Bertrand
- Also Oktay
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- Roger Spaans
- Eric Tubbs
- Yuki Toi
- Kevin Weir
- Thaddeus Wierzbicki
- Junichi Usui
- Stephen Vincent
- Marco Verri
- Bernard Valley
- Yajin Yang
- Carl Zepp

PULMONARY PATHOLOGY SOCIETY
2011 BIENNIAL MEETING
AUGUST 18-20, 2011
MEMORIAL SLOAN KETTERING CANCER CENTER
NEW YORK, NY

www.pulmonarypath.org

www.mskcc.org/PPS2011