Proposed Revisions to the Classification of Pulmonary Carcinomas

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5) Dept of Pathology, Wake Forest University, Winston-Salem, NC
6) Dept of Pathology, Aichi Cancer Center, Nagoya

Adenocarcinoma is the most common histologic type of lung cancer in most countries. In order to address advances in pathology, oncology, molecular biology, radiology and surgery of lung adenocarcinoma, an international multidisciplinary classification was sponsored by the IASLC, ATS, and ERS.1

An international core panel of experts representing all three societies was formed of pathologists, oncologists, respiratory physicians, radiologists, molecular biologists and thoracic surgeons.

The classification addresses resection specimens as well as small biopsies and cytology. Because no classification guidelines have been proposed for lung cancer diagnosis in such samples, criteria and diagnostic terms for histologies other than adenocarcinoma are also addressed. We recommend that the terms bronchioloalveolar carcinoma (BAC) and mixed subtype adenocarcinoma no longer be used. For resection specimens, new concepts are introduced such as adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) for small solitary adenocarcinomas to define patients who have near 100% disease specific survival if completely resected. We propose AIS for tumors with pure lepidic growth and MIA for predominant lepidic growth and ≤5mm invasion (MIA). Invasive adenocarcinomas have greater than 5mm of invasion and are classified by the predominant pattern after using comprehensive histologic subtyping with lepidic (formerly most mixed subtype tumors with nonmucinous BAC), acinar, papillary and solid patterns, with the addition of micropapillary as a new histologic subtype. Variants include mucinous adenocarcinoma (formerly mucinous BAC).

This classification provides specific guidelines for small biopsies and cytology specimens, as approximately 70 percent of lung cancers are diagnosed in such samples.1,2 Non-small cell lung carcinomas (NSCLC) are to be classified into more specific types such as adenocarcinoma or squamous cell carcinoma, whenever possible for several reasons: If the tumor cannot be classified based on light microscopy alone, special studies such as immunohistochemistry and/or mucin stains should be applied to classify the tumor further. As EGFR mutation is a validated predictive marker for response to EGFR tyrosine kinase inhibitors (TKIs) in the first line therapy in advanced lung adenocarcinoma, we recommend that patients with advanced adenocarcinomas be tested for EGFR mutation when clinically indicated. Strategic management of tissue is recommended including for small biopsies and cytology samples to maximize high quality tissue available for molecular studies.

Potential implications for TNM staging include adjustment of the size T factor according to only the invasive component 1) pathologically in invasive tumors with lepidic areas or 2) radiologically by measuring the solid component of part-solid tumors.

Based primarily on histology, this new strategy provides a multidisciplinary approach to classification of lung adenocarcinoma. Hopefully it will provide a useful standard for clinical practice as well as for histologic correlations with clinical, molecular, radiologic and surgical studies.
Reference List


Proposed Revisions to the Classification of Pulmonary Carcinomas

PULMONARY PATHOLOGY SOCIETY
COMPANION MEETING
USCAP, SAN ANTONIO
FEBRUARY 26, 2011

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International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society International Multidisciplinary Classification of Lung Adenocarcinoma

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Journal of Thoracic Oncology • Volume 6, Number 2, February 2011

Journal of Thoracic Oncology 6(2):244-485, 2011

244-485
RATIONALE FOR NEW ADENOCARCINOMA CLASSIFICATION

- Lung cancer – most frequent cause major cancer 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

WHO/IASLC CLASSIFICATION OF LUNG AND PLEURAL TUMORS

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

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
LUNG ADENOCARCINOMA

CLASSIFICATION IN SMALL BIOPSY AND CYTOLOGY SPECIMENS

Because this was never addressed by WHO, by necessity other histologies needed to be addressed

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

Percent

- Advanced Stage
- Early 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

CLINICAL RECOMMENDATION

- In patients with advanced lung adenocarcinoma we recommend testing for EGFR mutation (strong recommendation, moderate quality evidence).
- Remarks: This is a strong recommendation because potential benefits clearly outweigh harms. This recommendation assumes that correct classification by EGFR mutation status is associated with important benefit based upon randomized phase 3 clinical trials of EGFR TKI therapy which demonstrate a predictive benefit for response rate and progression-free survival, but not overall survival, as well as subset analyses of multiple additional studies.

Travis WD et al; JTO 6:244-285, 2011
Initial Therapy of Lung Advanced Adenocarcinoma

-EGFR Mutation
  -Exon 19 del
  -Exon 21 L858R, L861X
  -Exon 18 G719A/S
  -Unknown EGFR
  -Mutation Status
  -Pemetrexed
  -Bevacizumab
  -Cisplatin

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

ALL DIAGNOSES – BY LIGHT MICROSCOPY VS LM & IHC

NEED TO DISCRIMINATE BETWEEN DIAGNOSES BASED ON LIGHT MICROSCOPY VS LM & IHC

- The only validation of histology for EGFR mutation/TKI’s, Pemetrexed and Bevacizumab is by light microscopy alone
- The use of IHC for diagnosis is not validated in clinical trials
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

Travis WD et al; JTO 6:244-285, 2011

IMMUNOHISTOCHEMICAL MARKERS

- ADENOCARCINOMA (ONE MARKER)
  - TTF-1 (best), Napsin, PE-10
- SQUAMOUS CARCINOMA (ONE MARKER)
  - p63 (best), CK5/6, 34βE12
  - Desmocollin-3 (need more testing)
- Cocktails – nuclear/cytoplasmic antibodies
  - Adenoca – TTF-1/Napsin
  - Squamous – p63/CK5/6

Travis WD et al; JTO 6:244-285, 2011
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

SMALL BIOPSY AND CYTOLOGY
IASLC/ATS/ERS SPECIFIC TERMINOLOGY
RECOMMENDED FOR LUNG CANCER DIAGNOSES

<table>
<thead>
<tr>
<th>WHO Classification</th>
<th>IASLC/ATS/ERS Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosquamous</td>
<td>Adenosquamous</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Mixed squamous</td>
<td>Mixed squamous</td>
</tr>
<tr>
<td>Squamous</td>
<td>Squamous</td>
</tr>
<tr>
<td>Clear cell</td>
<td>Clear cell</td>
</tr>
<tr>
<td>Small cell</td>
<td>Small cell</td>
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<tr>
<td>Large cell</td>
<td>Large cell</td>
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<tr>
<td>Clear cell</td>
<td>Clear cell</td>
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<td>Small cell</td>
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</tbody>
</table>

Journal of Thoracic Oncology • Volume 6, Number 2, February 2011
### IASLC/ATS/ERS Classification

#### Squamous Cell Carcinoma

**Small Biopsies/Cytology**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Diagnosis Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant squamous cell carcinoma</td>
<td><strong>Morphology:</strong> squamous cell patterns with dysplasia. <strong>Treatment:</strong> referral to dermatologist.</td>
</tr>
</tbody>
</table>

#### Large Cell Carcinoma

**Small Biopsies/Cytology**

- **Large Cell Carcinoma – cannot be diagnosed in small biopsies or cytology (2004 WHO)**

#### Adenosquamous Carcinoma

**Small Biopsies/Cytology**

- **Adenosquamous Carcinoma – cannot be diagnosed in small biopsies or cytology (2004 WHO)**

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*Journal of Thoracic Oncology • Volume 6, Number 2, February 2011*
KEY PRINCIPLES

- Minimize diagnostic stains to maximize tissue for molecular studies
- Approach to workup needs to address possible diagnoses other than AD or SQC: metastatic carcinomas or other tumors (lymphoma/melanoma)
- Immunostains are not needed to diagnose most adenocarcinomas or squamous cell carcinomas
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
IASLC/ATS/ERS ADENOCARCINOMA CLASSIFICATION

- PREINVASIVE LESIONS
  - ATYPICAL ADENOMATOUS HYPERPLASIA
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  - non-mucinous
  - mucinous
- INVASIVE ADENOCARCINOMA

† Size should be specified. AIS and MIA should be completely sampled histologically

MINIMALLY INVASIVE ADENOCARCINOMA NONMUCINOUS

- Type A, B ADENOCA:
  - Pleural Invasion 9.7%
  - Vascular Invasion 9.4%

~Noguchi M et al: Cancer 75: 2844 1995
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
ACINAR PAPILLARY

MICRO-PAPILLARY SOLID WITH MUCIN DPAS STAIN

STAGE 1 SOLITARY ADENOCARCINOMA AGE AND SEX (N=514)

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Female</th>
<th>Male</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>233 (62%)</td>
<td>141 (38%)</td>
<td>374 (73%)</td>
</tr>
<tr>
<td>1B</td>
<td>90 (65%)</td>
<td>48 (35%)</td>
<td>138 (73%)</td>
</tr>
<tr>
<td>Total</td>
<td>323 (63%)</td>
<td>191 (37%)</td>
<td>514 (100%)</td>
</tr>
</tbody>
</table>

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

<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>Mucinous Adca (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

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

<table>
<thead>
<tr>
<th>Histologic Type</th>
<th>5 Year RFS %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIS, MIA, LEPIDIC NM, ONLY 7.4% OF ALL STAGE I ADENOCA</td>
<td>92.6%</td>
</tr>
<tr>
<td>AIS, MIA, LP NM, ONLY 7.4% OF ALL STAGE I ADENOCA</td>
<td>0.2%</td>
</tr>
<tr>
<td>Lepidic NM</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

P=0.003
STAGE I ADENOCARCINOMA (N=514)

RECURRENT-FREE SURVIVAL (RFS) BY IASLC HISTOLOGIC TYPE

<table>
<thead>
<tr>
<th>Histologic Type</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,</td>
<td>71</td>
</tr>
<tr>
<td>Colloid, Solid, Micropapillary (101)</td>
<td></td>
</tr>
</tbody>
</table>

P<0.001

IASLC/ATS/ERS ADENOCARCINOMA CLASSIFICATION

VARIANTS

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

MUCINOUS ADENOCARCINOMA

[Images of 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

n= 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
(Solid component, Cytologic atypia)

- 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
  - (10.7µm = diameter 3x small lymphocytes)
- 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>MP</th>
<th>SO</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>

Grade 1: BAC

Grade 2: Acinar, Papillary

Grade 3: Solid, Micropapillary

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

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

Stage IA Lung Adenocarcinoma, Grade by Sum of 2 Predominant Patterns


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
Multiple primary non-small cell lung cancer

At MSKCC: Testing for EGFR/KRAS mutations


Genomic profiling: similar profile = metastases


7th Ed TNM Staging System: Multiple Nodules, Same Histology

<table>
<thead>
<tr>
<th>Location</th>
<th>7th Ed AJCC/UICC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same lobe</td>
<td>T3</td>
</tr>
<tr>
<td>Ipsilateral different lobe</td>
<td>T4</td>
</tr>
<tr>
<td>Contralateral</td>
<td>M1a</td>
</tr>
<tr>
<td>Discontinuous pleural nodules</td>
<td>M1a</td>
</tr>
</tbody>
</table>

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 (s). In simultaneous bilateral cancers, each tumor should be classified independently.
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>Method</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martini Melamed</td>
<td>0.052</td>
</tr>
<tr>
<td>Molecular</td>
<td>0.013</td>
</tr>
<tr>
<td>Surgical Pathology</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

**IMPLICATIONS OF NEW CLASSIFICATION AND OUR DATA FOR TNM STAGING**

- 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>

Yoshizawa, Modern Pathology (in press)

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

<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>

P<0.001

Yoshizawa, Modern Pathology (in press)

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 (0.9 – 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 – 1.9)</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>

* Tumor size adjusted by subtracting percentage of lepidic growth

Yoshizawa, Modern Pathology (in press)
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

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