Pathologic Staging Updates in Lung Cancer

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Dr. Sanja Dacic has no conflict(s) of interest to disclose.
OUTLINE

• T
  o Size
  o Multiple tumor nodules

• N
  o Number lymph nodes or stations
T STAGE

• It is all about size…
Survival According to Size Only

Every centimeter counts (1 cm)

Rami-Porta R. et al. JTO 2015; 10:990-1003
## T STAGE

<table>
<thead>
<tr>
<th>Tumor size (cm)</th>
<th>AJCC 7\textsuperscript{th} edition</th>
<th>AJCC 8\textsuperscript{th} edition</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1</td>
<td>T1a</td>
<td>T1a</td>
</tr>
<tr>
<td>&gt;1-≤ 2</td>
<td>T1a</td>
<td>T1b</td>
</tr>
<tr>
<td>&gt;2-≤ 3</td>
<td>T1b</td>
<td>T1c</td>
</tr>
<tr>
<td>&gt;3-≤ 4</td>
<td>T2a</td>
<td>T2a</td>
</tr>
<tr>
<td>&gt;4-≤ 5</td>
<td>T2a</td>
<td>T2b</td>
</tr>
<tr>
<td>&gt;5-≤ 7</td>
<td>T2b</td>
<td>T3</td>
</tr>
<tr>
<td>&gt;7</td>
<td>T3</td>
<td>T4</td>
</tr>
</tbody>
</table>

Rami-Porta R. et al. JTO 2015; 10:990-1003
HOW TO ACCURATELY MEASURE TUMOR SIZE?

• CT size
• Gross vs. microscopic size
• Three dimensional size includes not only tumor but also fibrosis, organizing pneumonia and inflammatory process
GROSS vs. MICROSCOPIC SIZE

- Mean gross size 2.5 cm (range 1-5 cm)
- Adjusted microscopic size 1.5 cm (range 0.4-3.5 cm)

- Tumor & Scar = 43.06 mm²
- Scar = 26.86 mm²
- 37.6% of the "gross size"
GROSS vs. MICROSCOPIC SIZE

Time (months)

Survival probability (%)

- Microscopic size
- Gross size (tm with fibrosis)
- Gross size (tm with no fibrosis)

P=0.1

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HOW TO STAGE LEPIDIC ADENOCARCINOMA?

- **Tis**
  - Adenocarcinoma in situ (AIS)

- **T1a-mi**
  - Minimally Invasive Adenocarcinoma (MIA)

- **T any**
  - Invasive adenocarcinoma, lepidic subtype

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Total tumor size should be recorded, but only the invasive component used as a descriptor of the T-categories.
WHAT IS THE REPRODUCIBILITY OF INVASION CRITERIA?
“EASY CASES”

($\kappa=0.55\pm0.06$)

IASLC Pathology Committee, October 2010;
Thunissen E. et al. Mod Pathol 2012; 25:1574-83.
“DIFFICULT CASES”

($\kappa=0.08\pm0.02$)

IASLC Pathology Committee, October 2010

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Thunissen E. et al. Mod Pathol 2012; 25:1574-83.
GEOGRAPHY SEEMS TO BE IMPORTANT

Group A
“invasion”

Group B
“no-invasion”

Thunissen E. et al. Mod Pathol 2012; 25:1574-83.
WHAT IS THE REPRODUCIBILITY OF HISTOLOGICAL SUBTYPING OF LUNG ADENOCARCINOMA?
## Reproducibility of Histological Subtyping

<table>
<thead>
<tr>
<th>Submitted pattern</th>
<th>Single pattern (%)</th>
<th>Predominant pattern (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinar (n=20)</td>
<td>17/26 (65)</td>
<td>25/26 (96)</td>
</tr>
<tr>
<td>Lepidic (n=19)</td>
<td>11/26 (42)</td>
<td>24/26 (92)</td>
</tr>
<tr>
<td>Micropapillary (n=16)</td>
<td>3/26 (12)</td>
<td>16/26 (62)</td>
</tr>
<tr>
<td>Papillary (n=19)</td>
<td>5/26 (19)</td>
<td>25/26 (96)</td>
</tr>
<tr>
<td>Solid (n=20)</td>
<td>17/26 (65)</td>
<td>26/26 (100)</td>
</tr>
</tbody>
</table>

“typical” cases \( \kappa = 0.77 \pm 0.06 \)
“difficult” cases \( \kappa = 0.38 \pm 0.14 \)

Thunissen E. et al. Mod Pathol 2012; 25:1574-83.
LEPIDIC VS. PAPILLARY
MULTIPLE TUMOR NODULES

- 15% reported incidence
- Increased detection
  - HRCT
  - Screening of smokers
  - Closer follow up of patients after initial surgical resection
SYNCHRONOUS LUNG NODULES

Tumor nodule 1

Tumor nodule 2
When multiple tumors are of the same cell type, they should only be considered to be synchronous primary tumors if in the opinion of the pathologist, based on features such as associated carcinoma in situ or differences in morphology, immunohistochemistry, and or molecular studies, they represent differing subtypes of the same histopathological cell type, and...
POTENTIAL CRITERIA TO DEFINE LINEAGE OF TWO MALIGNANT LUNG LESIONS

- Histologic type
- Histologic subtype
- Molecular characterization
  - Specific mutations, gene rearrangements
  - Comparative genomic hybridization
  - Next-generation sequencing
MOLECULAR CHARACTERIZATION OF MULTIPLE LUNG NODULES

• PCR clonality assays
  o DNA microsatellite analysis
  o X-chromosome inactivation analysis

• DNA mutational analysis

• Comprehensive aCGH, SNPs and gene expression analysis

• Next-generation sequencing

GENOMIC PROFILING OF MULTIPLE NSCLC

INTEGRATION OF CLINICAL, MOLECULAR AND HISTOLOGIC DATA

CLINICAL ASSESSMENT

MOLECULAR ASSESSMENT

Girard N. et al. AJSP 2009;33(12):1752

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Routine molecular testing for targeted mutations/gene rearrangements and staging of lung carcinomas
GENETIC ALTERATIONS IN LUNG ADENOCARCINOMA
CAP/IASLC/AMP 2016 BIOMARKER SELECTION PROPOSAL

• STRONG RECOMMENDATION
  o EGFR mutations, ALK rearrangement

• RECOMMENDATION
  o ROS1 rearrangement

• EXPERT CONSENSUS OPINION
  o BRAF, RET, ERBB2, KRAS, MET
DIFFERENT ASSAY CHOICES

- FISH
- SINGLE GENE
- MULTIGENE PANEL
- WHOLE GENOME
HISTO-MOLECULAR STAGING

Schneider F. et al. Mod Pathol 2016 Jul;29(7):735-42

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HIGH CONCORDANCE OF GENOMIC CHANGES BETWEEN MATCHED PRIMARY NSCLC METASTASIS

Table 4. Concordance Between Primary Tumor and Matched Metastasis for Recurrent Somatic Alterations and Likely Passenger Alterations

<table>
<thead>
<tr>
<th>Alterations</th>
<th>No. of Evaluated Alterations</th>
<th>Shared</th>
<th>Unshared</th>
<th>Concordance Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mutations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent</td>
<td>28</td>
<td>26</td>
<td>2</td>
<td>53</td>
</tr>
<tr>
<td>Passenger</td>
<td>144</td>
<td>88</td>
<td>56</td>
<td>61</td>
</tr>
<tr>
<td><strong>Large structural alterations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Passenger</td>
<td>15</td>
<td>7</td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td><strong>Global</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent</td>
<td>33</td>
<td>31</td>
<td>2</td>
<td>94</td>
</tr>
<tr>
<td>Passenger</td>
<td>159</td>
<td>95</td>
<td>64</td>
<td>63</td>
</tr>
</tbody>
</table>

Vignot S. et al. JCO 2013; 31 (17):2167-2172

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• 3 to 276 breakpoints per tumor identified
• independent primary tumors based on histology did not share any genomic rearrangements
• lung primary tumors and paired distant metastases shared rearrangements in all tumor pairs
• Concordance between histology and genomic data occurred in the majority of samples.

Murphy SJ et al. JCO 2014;32:4050-4058
PATHOLOGICAL CRITERIA FOR SEPARATE VS. RELATED LUNG TUMORS (AJCC 8TH)

• **SEPARATE PRIMARY TUMORS**
  - Different histologic type
  - Clearly different based on a comprehensive histologic assessment
  - Squamous carcinoma arising from carcinoma in situ

• **RELATED TUMORS**
  - Exactly matching breakpoints by CGH
PATHOLOGICAL CRITERIA FOR SEPARATE VS. RELATED LUNG TUMORS (AJCC 8\textsuperscript{TH})

- Relative arguments that favor \textit{separate tumors}:
  - Different biomarker pattern
  - Absence of nodal or systemic disease

- Relative arguments that favor \textit{related tumors}:
  - Matching appearance on comprehensive histologic assessment
  - The same biomarker pattern
  - Significant nodal or systemic metastases
“…we recommend that physicians record the number of metastatic lymph nodes (or stations) and to further classify the N category using new descriptors…”

Asamura H. et al. JTO 2015
N STAGE AND SURVIVAL

N0 vs N1 vs N2 vs N3 Comparisons
Adjusted for Histology (adeno vs others), Sex, Age 60+, R0 resection, and Region.
(Cox PH regression on all cases)

<table>
<thead>
<tr>
<th>comparison</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1 vs N0</td>
<td>2.13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>N2 vs N1</td>
<td>1.74</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>N3 vs N2</td>
<td>1.66</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Asamura H. et al. JTO 2015
pN1/N2 SingLe AND MultiPLe PoSiTiVe LympH NodeS

N1 Single = N1a
N1 Multiple = N1b
N2 Single N2 ("skip mets") = N2a1
N2 Single N2 + N1 = N2a2
N2 Multiple N2 = N2b

Asamura H. et al. JTO 2015
## N STAGE

<table>
<thead>
<tr>
<th>Lymph node descriptors</th>
<th>AJCC 8th edition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single station N1</td>
<td>N1a</td>
</tr>
<tr>
<td>Multiple stations N1</td>
<td>N1b</td>
</tr>
<tr>
<td>Single station N2 without N1 (skip metastasis)</td>
<td>N2a1</td>
</tr>
<tr>
<td>Single station N2 with N1</td>
<td>N2a2</td>
</tr>
<tr>
<td>Multiple station N2</td>
<td>N2b</td>
</tr>
<tr>
<td>Contralateral nodal stations</td>
<td>N3</td>
</tr>
</tbody>
</table>
HOW DO PATHOLOGISTS COUNT LYMPH NODES?

• One (1) LN
• Three (3) fragments
• Four (4) fragments
• Few fragments
• Several fragments
• Multiple fragments
• No tumor seen
“For consistency, nonspecific terms used in pathology reports were standardized: multiple was translated into four lymph nodes, aggregate into three, several into three, few fragments into three, and numerous into five. Concordance between the two reviews was within one lymph node 90% of the time.”
SUMMARY

• More emphasis on tumor size—every cm counts
• Staging of multiple lung tumors include clinical, pathological and molecular data
• Acknowledgement of lymph node counts
• Better prognostication groups, but no change in therapy