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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 of lymph nodes or stations

SURVIVAL ACCORDING TO SIZE ONLY
Every centimeter counts ( )

T STAGE

• It is all about size...

Tumor size (cm) | AJCC 7th edition | AJCC 8th edition
---|---|---
≤ 1 | T1a | T1a
>1≤ 2 | T1a | T1b
>2≤ 3 | T1b | T1c
>3≤ 4 | T2a | T2a
>4≤ 5 | T2a | T2b
>5≤ 7 | T2b | T3
>7 | T3 | T4

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

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HOW TO ACCURATELY MEASURE TUMOR SIZE?

- CT size
- Gross vs. microscopic size

PATHOLOGIC ASSESSMENT OF GROSS 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)

HOW TO STAGE LEPIDIC ADENOCARCINOMA?

Tis

Adenocarcinoma in situ (AIS)

Minimally Invasive Adenocarcinoma (MIA)

Invasive adenocarcinoma, lepidic subtype

T1a-mi

T any

WHAT IS THE REPRODUCIBILITY OF INVASION CRITERIA?

Total tumor size should be recorded, but only the invasive component used as a descriptor of the T-categories
“EASY CASES”
(κ=0.55±0.06)

Thunissen E. et al. Mod Pathol 2012; 25:1574-83.

“DIFFICULT CASES”
(κ=0.08±0.02)

Thunissen E. et al. Mod Pathol 2012; 25:1574-83.

GEOGRAPHY SEEMS TO BE IMPORTANT

Group A “invasion”
Group B “no-invasion”

MULTIPLE TUMOR NODULES

• 15% reported incidence
• Increased detection
  ○ HRCT
  ○ screening of smokers
  ○ closer follow up of patients after initial surgical resection

MARTINI AND MELAMED CRITERIA

• MULTIPLE PRIMARY LUNG CANCERS
  • Different histology
  • Same histology
    • Anatomically separated
    • Temporally separated (2-4 years, no systemic metastases)

• SATELLITE NODULES
  • Same histology
  • Same lobe
  • No systemic metastases

SYNCHRONOUS LUNG NODULES

Tumor nodule 1
Tumor nodule 2
SYNCHRONOUS CARCINOMA STAGING
AJCC 7TH EDITION

• 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...

DIAGNOSTIC APPROACH TO MULTIPLE LUNG NODULES

• Histologic type/subtype
• Molecular characterization
  □ Specific mutations, gene rearrangements
  □ Comparative genomic hybridization
  □ Next-generation sequencing

REPRODUCIBILITY OF HISTOLOGIC ASSESSMENT IN P STAGING OF MULTIPLE LUNG NODULES

• Overall assessment: kappa score 0.60
• Most useful features in distinction between multiple primary tumors vs. metastases:
  ▪ main tumor type
  ▪ predominant patterns
  ▪ acinus formation
  ▪ nuclear pleomorphism
  ▪ cell and nucleolar size
  ▪ mitotic rate

GENOMIC PROFILING OF MULTIPLE NSCLC

INTEGRATION OF CLINICAL, MOLECULAR AND HISTOLOGIC DATA

Route molecular testing for targeted mutations/gene rearrangements and staging of lung carcinomas

GENETIC ALTERATIONS IN LUNG ADENOCARCINOMA

CAP/IASLC/AMP 2017 BIOMARKER SELECTION PROPOSAL

- STRONG RECOMMENDATION
  - EGFR mutations, ALK rearrangement

- RECOMMENDATION
  - ROS1 rearrangement

- EXPERT CONSENSUS OPINION
  - BRAF, RET, ERBB2, KRAS, MET

HIGH CONCORDANCE OF GENOMIC CHANGES BETWEEN MATCHED PRIMARY NSCLC METASTASIS

CHROMOSOMAL REARRANGEMENTS BY NGS

- 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.
### Pathologic Criteria for Multiple Lung Nodules (8th AJCC)

<table>
<thead>
<tr>
<th>SECOND PRIMARY</th>
<th>RELATED TUMORS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different histologic type (adenocarcinoma vs squamous cell)</td>
<td>Separate tumors with a similar histologic appearance to a primary lung cancer</td>
</tr>
<tr>
<td>Different based on comprehensive histologic assessment</td>
<td>Multiple tumors with a different histologic appearance to a primary lung cancer</td>
</tr>
<tr>
<td>Squamous carcinoma arising from CIS</td>
<td>Not multiple tumors arising from CIS</td>
</tr>
</tbody>
</table>

#### Relative Arguments

- Different biomarker patterns
- Absence of nodal or systemic metastases
- Matching appearance on comprehensive histologic assessment

### N Stage and Survival

- Asamura H. et al. JTO 2015

### pN1/N2 Single and Multiple Positive Lymph Nodes

- Asamura H. et al. JTO 2015

### N Stage

- Lymph node descriptors
  - Single station N1: N1a
  - Multiple stations N1: N1b
  - Single station N2 without N1 (skip metastasis): N2a1
  - Single station N2 with N1: N2a2
  - Multiple station N2: N2b
  - Contralateral nodal stations: N3

- "...we recommend that physicians record the number of metastatic lymph nodes (or stations) and to further classify the N category using new descriptors..."
**HOW DO PATHOLOGISTS COUNT LYMPH NODES?**

- One (1) LN
- Three (3) fragments
- Four (4) fragments
- Few fragments
- Several fragments
- Multiple fragments
- No tumor seen

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**If we didn’t figure it out...**

“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.”

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**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