Update on Classification and Staging of Pulmonary Tumors

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Disclosures

Relevant financial relationships:
None

Off-label usage:
None
Learning Objectives

At the end of this talk and the accompanying case presentations, the participant should be able to do the following:

• Explain the most important updates to the WHO lung tumor classification in 2015
• Describe the changes to AJCC staging of lung tumors in the new 8th Ed.
• Describe common diagnostic challenges with lung tumor diagnosis and possible solutions

4 Important Thematic Questions

1. If “tissue is the issue” why is the “sample not ample”?  
2. Adenocarcinoma in situ: what, when, and how? 
3. Am I staging lung cancers accurately? 
4. What other new entities should I know about?
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Musings on the “vanishing biopsy”

• Growing *inverse relationship* between sample size and the data required for patient management
Musings on the “vanishing biopsy”

• Growing *inverse relationship* between sample size and the data required for patient management

• “Learn to do more with less, or we will find *something* that can!”

Case example:

A 66-year-old woman is found to have a 3 cm lung mass. A transbronchial biopsy is performed…a rapid interpretation is requested and you do a FS.
You call the pulmonologist in the Bronchoscopy Suite after you decide the included cell groups are malignant, and “non-small” cell….

…really more like adenocarcinoma on the morphology, if you had to bet.

You comment further that only one TBBx sample has tumor and not much at that.

The pulmonologist thanks you for your help and promises to get more samples.
The next day, you attempt IHC to confirm lung origin. No additional biopsies received.

Results: TTF-1 neg, CK7 pos

Napsin A, CK20, synaptophysin, chromogranin, and p40 ...insufficient tumor in the recuts.

After signing the case out as “non-small cell carcinoma, NOS”, the oncologist calls to ask if the tumor could be from the patient’s prior breast cancer… “after all, that was the clinical question”.

…and if you think it is, please test for Her2.
…but if you really think this is more like a lung primary, could you send it to Bill Travis for a more accurate classification?

And of course, because of those liver nodules… we will need EGFR, ALK1, ROS1 and a NextGen sequencing panel…ASAP!

If this scenario sounds familiar, you are not alone.

The problem is most often a result of a “failure to communicate”.

However, to the surgeon, pulmonologist, interventional radiologist, oncologist…and even the molecular laboratory, this is a pathologist problem.
To these “upstream clients”, we are judged responsible for making sure that:

a. The sample is ample.
b. The diagnosis is accurate.
c. The immunohistochemistry is thorough.
d. The specimen is appropriately triaged for “all appropriate” special studies.
e. A composite final report goes to all relevant parties.

Lung Cancer: The Problem

• 2014 estimated 224,210 new cases
• By 2019 only 40,000 of these will be alive
• Approximately 437 people die of lung cancer every day
• Only 25% of lung cancer is surgically removable for intended cure at time of diagnosis

Siegel R, et al., CA Cancer J Clin 2014; 64;9-29
“Lung cancer offers a challenge for earlier diagnosis and better treatment results.

At present lung cancer is recognized late.

Opportunities to improve survival are through early detection, accurate diagnosis, absolute localization, and curative therapy.”
Various Cancers: 5 year Survival (%)

<table>
<thead>
<tr>
<th>Cancer</th>
<th>1960-63</th>
<th>2001-07</th>
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<tbody>
<tr>
<td>Lung</td>
<td>8</td>
<td>16*</td>
</tr>
<tr>
<td>Colon</td>
<td>43</td>
<td>64*</td>
</tr>
<tr>
<td>Breast</td>
<td>63</td>
<td>89*</td>
</tr>
<tr>
<td>Prostate</td>
<td>50</td>
<td>99*</td>
</tr>
</tbody>
</table>

*(P<0.05)

Landis SH, et al., CA Cancer J Clin 1999;49:8-31

Primary Lung Carcinoma: Classification

Non-Small Cell Carcinoma (80%)

- Adenocarcinoma 50%
- Squamous Cell Carcinoma 20%
- Large Cell Carcinoma 10%

Chemoresistant
Surgically treated if possible

Small Cell Carcinoma (20%)

- Small cell carcinoma 20%

Chemosensitive
Not treated surgically
Immunohistochemical Profiles of Lung Cancer

Adenocarcinoma:
CK7, TTF1, Napsin A

Large Cell Neuroendocrine Ca
PanCK, TTF-1, chromogranin, synaptophysin, Napsin A (+/-)

Squamous Cell Carcinoma:
PanCK, CK5/6, p40, p63

Large Cell Carcinoma:
PanCK

Small Cell Carcinoma:
PanCK, TTF1, Synaptophysin (+/-), Chromogranin (+/-)

Mucoepidermoid Carcinoma:
CK5/6, CK7, p63/40, MAML2
DIAGNOSIS

Morphological diagnosis superseded by molecular profile?
If oncologists were performing biopsies the “samples might be more ample”!

In the current paradigm, we become the oncologist’s surrogate at FS and ROSE. Unfortunately, we are rarely privy to the therapeutic options for a given patient at the time of biopsy.
Mutations in NSCLC

Driver Mutations Define Treatment Options

- Testing for EGFR and BRAF mutations and ALK and ROS1 rearrangements now standard
  - KRAS, HER2, RET, PIK3CA, others can define trial eligibility & potential treatments
- Resistance essentially universal due to acquisition of additional mutations
  - Bx at progression can guide next steps
- Tissue bx is invasive, and amount of tissue is often limited
- “Liquid bxs” could overcome limitations
What is a “Liquid Biopsy”?

Biopsy: “An examination of tissue removed from a living body to discover the presence, cause, or extent of a disease”
---Oxford English Dictionary

Liquid biopsy: An examination of liquid removed from a living body to discover the presence, cause, or extent of a disease?
What is a “Liquid Biopsy”? 

• Misnomer?
• Sexy marketing term?
• Blood-based assay to capture and analyze:
  • Circulating cell-free DNA (cfDNA)
  • Circulating tumor cells
  • Circulating cell-free RNA and microRNA

Advantages of “Liquid Biopsy”

- Easier to obtain than tissue bx
- Non-invasive
- Inexpensive
Potential Applications for “Liquid Bx”

- Profiling mutations
- Profiling acquired resistance mutations
- Monitoring treatment response earlier
- Monitoring for acquisition of resistance
- Assessing tumor heterogeneity
- Prognostic and predictive applications?
- Primary diagnosis?
- Screening?

Morphology Still Matters!

By Ryan E. Poplin, public domain, monarch butterfly, commons.wikimedia.org

By Thomas Bresson, public domain, monarch butterfly, commons.wikimedia.org
Morphology Still Matters!

Inflammatory myofibroblastic tumor of lung with EML4-ALK

Morphology Still Matters!

A few neoplasms with \( \text{BRAF}^{600E} \) mutation:

- Lung adenocarcinoma
- Papillary thyroid carcinoma
- Colorectal adenocarcinoma
- Melanoma
- Ovarian serous carcinoma
- Hairy cell leukemia
- Acute lymphoblastic leukemia
- Langerhans cell histiocytosis
- Erdheim-Chester disease
- Papillary craniopharyngioma
- Pleomorphic xanthoastrocytoma
- Ganglioglioma
- Dysembryoplastic neuroepithelial tumor
- Subependymal giant cell astrocytoma
Morphology Still Matters!


Morphology Still Matters!

Nitta H et al., Diagn Pathol 2012 May 30;7:60
Will “Liquid Biopsy” Replace Conventional Tissue-Based Sampling?

- Probably not anytime soon, especially in pretreatment setting
- Tissue bx provides morphologic context that liquid bx cannot:
  - Tumor type
  - Tumor behavior (lymphatic invasion, proliferation index, etc.)
  - Tumor heterogeneity
  - Gene-protein correlation
- Assessment of immune cell infiltration / PD-L1 requires tissue bx
- Data on efficacy of treatment is based primarily on tissue assays
- Efficacy data based on liquid bx results alone are limited
- Liquid bx has not been validated in the pretreatment setting
- Liquid bx tends to be less sensitive than tissue bx (could cause delays in diagnosis if negative)
- Many lung cancers do NOT have a tumor-specific mutational profile
- Mutational overlap with some hematolymphoid neoplasms

Will “Liquid Biopsy” Complement Conventional Tissue-Based Sampling?

- Probably, especially after initial diagnosis is confirmed
- Liquid bx is feasible, inexpensive, non-invasive
- Liquid bx appears reflective of tumor status in trials to date
- Serial assessments / monitoring for relapse
- Assessment for acquisition of resistance mutations
- Alternative if tissue is unavailable?
- Rigorous clinical and laboratory validation must occur before liquid biopsies become part of standard practice
- STAY TUNED!!!
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2. Adenocarcinoma in situ: what, when, and how?

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Fig 2. Survival according to the histologic subtype of adenocarcinoma (Ad). The 5-year survival rates were 100% for bronchioloalveolar carcinoma (BAC) and 63.5% for adenocarcinoma other than BAC.
Rationale for recognizing AIS

- Other cancers have an \textit{in situ} phase
- Might explain why some small singular BACs have better survival
- Lack of consistent relationship between AAH and established invasive adenocarcinomas, suggests a missing link

We recommend discontinuing the use of the term “BAC”. (Strong recommendation, low quality evidence)

For small (≤3.0 cm), solitary adenocarcinomas with pure lepidic growth, we recommend the term

“Adenocarcinoma in situ” (AIS)

…that defines patients who should have 100% disease-specific survival, if the lesion is completely resected. (strong recommendation, moderate quality evidence).

Remark: Most AISs are non-mucinous, rarely are they mucinous.

Adenocarcinomas with predominantly lepidic growth and small foci of invasion measuring 0.5 cm or less, we recommend a new concept of:

“Minimally invasive adenocarcinoma” (MIA)

to define patients who should have near 100% disease specific survival, if completely resected. (strong recommendation, low quality evidence).

Remark: Most MIAs are non-mucinous, rarely are they mucinous.
How do we distinguish AAH from AIS?

Lung structure intact, minimal atypia, spaces between cells -- AAH

= lesion 5mm or less
What criteria are required for AIS?

No Invasion. Lung structure intact
larger cells, more overlap -- AIS

= lesion 3 cm or less
Invasion. Lung structure altered—MIA

How do we determine "invasion" in AIS?

- lesion 3 cm or less
- invasion no more than 5.0 mm

NO! Do not sum separate foci…

How do we measure "invasion" in MIA?

"9.0 mm"

NO! Do not sum separate foci…
Test your skills
Helpful Tip
Final Thoughts on AIS

- Lung cancer is still a "bad" cancer in 2018, with poor survival
- \textbf{AIS is exceedingly rare} (<0.2\% of Stage I tumors) -- essentially ALL resected tumors are at least focally invasive
- Have a very low threshold for diagnosing invasion; err on the side of MORE therapy, follow-up, etc.

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AJCC 8\textsuperscript{th} Edition
TNM Staging System

Based on 76,156 patient outcomes
IASLC 1999-2010

7\textsuperscript{th} Edition Staging System (IASLC ’07)
J Thorac Oncol. 2007 Aug 2; 8:706-714; Histopathol 2009, 54:3

<table>
<thead>
<tr>
<th>6th Ed T/M Descriptor</th>
<th>7th Ed T/M</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
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<tbody>
<tr>
<td>T1 (≤ 3 cm)</td>
<td>T1a (≤ 2 cm)</td>
<td>IA</td>
<td>IIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T1b (&gt;2 up to 3 cm)</td>
<td>IA</td>
<td>IIA</td>
<td>IIIA</td>
<td>IIIB</td>
<td></td>
</tr>
<tr>
<td>T2 (&gt;3 … or larger !)</td>
<td>T2a or PL1, PL2</td>
<td>IB</td>
<td>IIIB</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T2b (5 to &lt; 7 cm)</td>
<td>IIIB</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
<td></td>
</tr>
<tr>
<td>T3 (≥ 7 cm)</td>
<td>IIIB</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
<td></td>
</tr>
<tr>
<td>T3 invasion</td>
<td>T3 or PL3</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T4 (same lobe nodules)</td>
<td>T3</td>
<td>IIB</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T4 (extension)</td>
<td>T4</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IIIB</td>
</tr>
<tr>
<td>M1 (ipsilateral Lung)</td>
<td>T4</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IIIB</td>
</tr>
<tr>
<td>M1 (pleural effusion)</td>
<td>M1a</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>M1 (contralateral lung)</td>
<td>M1b</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>M1 (distant)</td>
<td>M1b</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
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</table>
## AJCC 8th Edition Staging System

<table>
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<tr>
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<td>T1a (≤ 2 cm)</td>
<td>T1a ≤ 1.0 cm</td>
</tr>
<tr>
<td>T2 (≥ 3 cm)</td>
<td>T1b (≥ 2 cm up to 3 cm)</td>
<td>T1b &gt; 1.0 cm up to 2 cm</td>
</tr>
<tr>
<td>T2b (≥ 5 cm up to 7 cm)</td>
<td>T1c &gt; 2.0 cm up to 3 cm</td>
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</tr>
<tr>
<td>T3 (≥ 7 cm)</td>
<td>T2a &gt; 3.0 cm up to 4 cm</td>
<td></td>
</tr>
<tr>
<td>T3 invasion</td>
<td>T2b &gt; 4.0 cm up to 5 cm</td>
<td></td>
</tr>
<tr>
<td>T4 (same lobe nodules)</td>
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<td>T4</td>
<td></td>
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<tr>
<td>M1 (pleural effusion)</td>
<td>M1a Any endobronchial tumor = T2</td>
<td></td>
</tr>
<tr>
<td>M1 (contralateral lung)</td>
<td>M1b With atelectasis or pneumonitis = T2</td>
<td></td>
</tr>
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<td><strong>T1</strong></td>
<td><strong>T1a</strong></td>
<td><strong>Tis Adenocarcinoma in situ</strong></td>
</tr>
<tr>
<td>(≤ 3 cm)</td>
<td>(≤ 2 cm)</td>
<td><strong>T1mi</strong> Minimally Invasive Adenocarcinoma</td>
</tr>
<tr>
<td><strong>T2</strong></td>
<td><strong>T2a</strong></td>
<td><strong>T1a</strong> &lt;= 1.0 cm</td>
</tr>
<tr>
<td>(&gt;3 … or larger !)</td>
<td>(3 to ≤ 5 cm)</td>
<td><strong>T1b</strong> &gt; 1.0 cm up to 2 cm</td>
</tr>
<tr>
<td><strong>T3</strong></td>
<td><strong>T2b</strong></td>
<td><strong>T1c</strong> &gt; 2.0 cm up to 3 cm</td>
</tr>
<tr>
<td>invasion</td>
<td>(5 to &lt; 7 cm)</td>
<td></td>
</tr>
<tr>
<td><strong>T4</strong></td>
<td><strong>T3</strong></td>
<td><strong>T2a</strong> &gt; 3.0 cm up to 4 cm</td>
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<td><strong>M1b</strong></td>
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</tr>
<tr>
<td>(distant)</td>
<td></td>
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</table>

**Stage = Destiny!**
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New Entities To Know

• NUT carcinoma
• Primary pulmonary myxoid sarcoma
NUT Carcinoma

- No specific cytologic / histologic features
- Undifferentiated carcinoma, bearing translocation t(15;19) involving NUT gene
  - Small-to-medium sized malignant cells
  - Monotonous round-to-oval nuclei
  - Clear/vesicular cytoplasm
  - Prominent nucleoli
  - Might mimic small cell carcinoma
- +/- Abrupt squamous differentiation

French CA. Annu Rev Pathol 2012. 7: 247-65
Abrupt squamous differentiation
Primary Pulmonary Myxoid Sarcoma With *EWSR1-CREB1* Fusion: A New Tumor Entity

Khin Thway, FRCPath, Andrew G. Nicholson, DM, FRCPath, Kay Lawson, MBBS,
David Gonzalez, PhD, Alexandra Rice, FRCPath, Bonne Balk, MD, John Swansbury,
FRCPath, Toon Mia, PhD, Lisa Thompson, PhD, Kwame Adu-Poku, FRCPath,
Anne Campbell, MD, FRCPath, and Cyril Fisher, MD, DSc, FRCPath

Primary Pulmonary Myxoid Sarcoma

- Younger women (30s, 40s)
- Well-circumscribed, lobulated endobronchial mass
- Spindled, stellate, polygonal cells
- Arranged in strands and cords, myxoid stroma
- Mild to moderate atypia, low mitotic rate
- Non-specific immunophenotype
- EWSR1-CREB1 fusion described in 79%
- Usually indolent but can metastasize and cause death
EWSR1 break apart probe
QUESTIONS?