Lung Cancer Update 2012

Optimizing the diagnostic yield of small biopsy samples

Kevin O. Leslie, MD
Professor and Consultant
Mayo Clinic Arizona

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Slide 2

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Slide 3

Case example:

A 66 year old woman is found to have a 3 cm lung mass. A transbronchial biopsy is performed...
You decide the included cell group is malignant, and "nonsmall" cell... really more like adenocarcinoma on the morphology, if you had to bet.

You attempt IHC to confirm lung origin.

Results: TTF-1 neg, CK 7 pos
Napsin A, CH50, synaptophysis, chromogranin, and P40... insufficient tumor in the recuts.

After signing the case out as "nonsmall cell carcinoma, NOS", the clinician calls to ask if the tumor could be from the patient's prior breast cancer... and if it is, please send for Her2 neu.

However, if you really think it is more like an "adenocarcinoma" of the lung, we need to know if it is that "new Travis AIS tumor".

If not, as long as you are sure there is no evidence of squamous differentiation, please send the tissue for EGFR and ALK analysis.

Objectives
1. The Changing Histopathology of Lung Cancer
2. History lung cancer therapy- The first 60 Years. Evolution or Repetition.
3. Present and Future prospects for targeted therapies
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**Changing Lung Cancer Histology**

Small-cell (SCLC)
- Accounts for approximately 15% of all lung cancers
- Incidence declining

Non-small cell (NSCLC)
- Accounts for approximately 80% of all lung cancers
- NSCLC types: squamous-cell, adenocarcinoma, large-cell

<table>
<thead>
<tr>
<th>Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>45%</td>
</tr>
<tr>
<td>Squamous</td>
<td>25-30%</td>
</tr>
<tr>
<td>Small-cell</td>
<td>15%</td>
</tr>
<tr>
<td>Large-cell</td>
<td>5-10%</td>
</tr>
</tbody>
</table>

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**Non-small Cell Lung Cancer**

**Adenocarcinoma**
- Glandular pattern
- Mucin positivity (50%)
- CK7+/CK20-
- TTF-1+ Napsin A

**Squamous cell carcinoma**
- Cellular keratinization
- Intercellular bridges
- Keratin “pearl” formation
- CK7–CK20–
- TTF-1 neg
- P63+ CK5/6+

Common, but not 100%

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**Optimal Immunohistochemical Markers for Distiguishing Lung Adenocarcinomas From Squamous Cell Carcinomas in Small Tumor Samples.**

*Am J Surg Pathol* 2010;34:1885–1811
“When sufficient tissue is available, we suggest that the panel of choice is composed of P63, CK5/6, TTF1, CK7, Napsin A and a mucin stain. A subpanel of Napsin A and a mucin stain performs nearly as well and may be preferred when tissue preservation for other purposes is a priority, such as molecular testing for EGFR mutations.”

…”the optimal order in which to carry them out:

1. P63
2. TTF1
3. CK5/6
4. CK7
5. Napsin A
6. Mucicarmine”
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Now, assuming that you have figured out that the tumor is an adenocarcinoma…

New Proposed Classification for Adenocarcinomas
IASLC 2011

Slide 14

A Few Words On The Changing Face of BAC...

• Bronchioloalveolar carcinomas (BAC) are a subset of lung adenocarcinoma, with a distinctive and peculiar growth pattern of the tumor cells over pre-existing lung structure (alveolar walls).

• This gives rise to an “aerated” tumor, hence GGO on CT.

The incidence of BAC may be as high as 15% of all lung cancers, and over half of these tumors are asymptomatic at presentation, where they appear as a solitary peripheral GGO.

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A Few Words On The Changing Face of BAC...

• Patients are usually in the fifth and sixth decades, but this tumor can occur in young patients (under 30).

A sizeable proportion of BACs will present as solitary peripheral lung masses, not unlike other types of lung cancer.

The pneumonic or multifocal presentation happens frequently in this disease but should not be a sole criterion for judging whether or not a patient has a BAC.
A distinctive clinical characteristic of BAC is the propensity to spread within the lung, in contrast to other lung adenocarcinomas that frequently spread to extrapulmonary sites early in their development.

Two histopathological forms exist:

- Mucinous
- Nonmucinous

ALL Dx’d as “BAC” on Histopathology!
1. We recommend discontinuing the use of the term "BAC". 
(Strong recommendation, low quality evidence)

2. For small (less than or equal to 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 AIS are nonmucinous, rarely are they mucinous.
3. Adenocarcinomas with predominant 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 MIA are nonmucinous, rarely are they mucinous.


Critical Questions

• 3. How do we distinguish “invasion” in AIS?

No Invasion. Lung structure intact
3. How do we distinguish “invasion” in AIS?

Invasion. Lung structure altered - MIA
Slide 28

1. How do we make an accurate distinction in small tissue samples?
A. Cannot be done in many cases (unless mucinous)

Slide 29

2. How do we make an accurate diagnosis of AIS, MIA, or "macro" invasive carcinoma in cytological samples?
A. Cannot be done in many cases (unless mucinous)

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[Diagram of signaling pathways]

Signal pathways:
Tyrosine kinase inhibitors
PTEN, PI3K, PDK1, AKT, RAS, BRAF, MEK, ERK, mTOR

Nucleus

Therapies:
Tipifarnib, Ionafarnib, Sorafarnib, CI-1040, Vornostat, despeptide

Therapy

Transmembrane receptor
PI3K
PDK1
AKT
RAS
BRAF
MEK
ERK
mTOR

PTEN
LY294002
HDAC
Sirolimus, et al
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TISSUE SAMPLE MANAGEMENT

To Pathology Lab

+ IHC + ISH

PCR

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FNA SAMPLE MANAGEMENT

Transport

Triage

Aliquot

Molecular Analysis

IHC and ISH

Culture

Cytology

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Pathology Challenges Remaining

1. Biopsy sample size
2. Tumor heterogeneity
3. Morphologic criteria for subclassifying NSCLC are not always easy to apply and require considerable experience
4. Consensus statement required regarding standardized molecular genetic testing in NSCLC
Lung Cancer Update 2012

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Clinical Target

Slide courtesy of Dr. Corey J. Langer. Fox Chase Cancer Center, Philadelphia, PA
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2010

Adenocarcinoma: 45%
Squamous-cell: 25-30%
Large-cell: 5-10%
Small-cell: 15%
Nonsmall Cell Lung Cancer

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WHO
- Common, but not 100%
Optimal Immunohistochemical Markers For Distinguishing Lung Adenocarcinomas From Squamous Cell Carcinomas in Small Tumor Samples

Jefferson Terry, MD, PhD,* Samuel Leung, MSc,* Janessa Laskin, MD,†
Kevin O. Leslie, MD,‡ Allen M. Gown, MD,§ and Diana N. Ionescu, MD*

(Am J Surg Pathol 2010;34:1805–1811)
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• Two histopathological forms exist:
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  - Nonmucinuous
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.
ALL Dx’d as “BAC” on Histopathology!
IASLC/ATS/ERS INTERNATIONAL MULTIDISCIPLINARY CLASSIFICATION OF LUNG ADENOCARCINOMA

William D. Travis† 1
Elisabeth Brambilla† 2
Masayuki Noguchi† 3
Andrew G. Nicholson† 4
Kim R. Geisinger† 5
Yasushi Yatabe† 6
David G. Beer† 7
Charles A. Powell† 8
Gregory J. Riely† 9
Paul E. Van Schil† 10
Kavita Garg† 11
John H.M. Austin† 12
Hisao Asamura† 13
Valerie W. Rusch† 14
Fred R. Hirsch† 15
Giorgio Scagliotti† 16
Tetsuya Mitsudomi† 17
Rudolf M. Huber† 18
Yuichi Ishikawa† 19
James Jett† 20
Montserrat Sanchez-Cespedes† 21
Jean-Paul Sculier† 22
Takashi Takahashi† 23
Masahiro Tsuboi† 24
Johan Vansteenkiste† 25
Ignacio Wistuba† 26
Pan-Chyr Yang† 27
Denise Aberle 28
Christian Brambilla 29
Douglas Flieder 30
Wilbur Franklin 31
Adi Gazdar 32
Michael Gould 33
Philip Hasleton 34
Douglas Henderson 35
Bruce Johnson 36
David Johnson 37
Keith Kerr 38
Keiko Kuriyama 39
Jin Soo Lee 40
Vincent A. Miller 41
Iver Petersen 42
Victor Ruggli 43
Rafael Rosell 44
Nagahiro Saijo 45
Erik Thunnissen 46
Ming Tsao 47
David Yankelewitz 48
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A. Cannot be done in many cases (unless mucinous)
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A. Cannot be done in many cases (unless mucinous)
Ligand Directed Tx
--Monoclonal antibodies
  EGF-Cetuximab
  VEGF- Bevacizumab

Tyrosine kinase inhibitors
  for EGFR- gefitinib, erlotinib, etc.
  for VEGFR- AZD2171, vandetanib, etc.

Transmembrane receptor

Plasma membrane

Signaling pathways

Tipifamib, lonafamib
Sorafamib
CI-1040

TSG Therapy

Nucleus

TISSUE SAMPLE MANAGEMENT

A bronchoscope is used to view the airways and check for any abnormalities.

To Pathology Lab

+ PCR + IHC + ISH
FNA SAMPLE MANAGEMENT

Transport

Triage

Aliquot

Culture

IHC and ISH

Cytology

Molecular Analysis
Pathology Challenges Remaining

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Suggested Reading

ASCO Provisional Clinical Opinion: Epidermal Growth Factor Receptor Mutation Testing in Practice

By Mary Beth Beasley, MD, and Daniel T. Milton, MD

Journal of Oncology Practice • Vol. 7, Issue 3 • May 2011

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Am J Surg Pathol • Volume 34, Number 12, December 2010

Molecular Diagnostics of Lung Carcinomas
Sanja Dacic, MD, PhD

Arch Pathol Lab Med. 2011;135:622–629

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