Lung Carcinoma – Pathologist Perspective

Scott Kantola, MD
UP Health System Marquette,
No Financial Relationships to Disclose
Outlines

• Review and classification of lung cancer

• Role of Immunohistochemistry

• Ancillary Molecular testing
Cytology

- Sputum

- Bronchoscopic specimens
  - Bronchial brushing
  - Bronchial washing
  - Bronchioalveolar lavage

- Fine needle aspiration
  - Transthoracic
  - Transbronchial EBUS

Histology

- Core needle biopsy

- Wedge biopsy
  - With / without frozen section

- Resection samples
Evolution of World Health Organizations
Classification of Lung Tumors

1967  HE
1981  HE & Mucin
1999  HE, Mucin & IHC
2004  HE, Mucin, IHC & Genetics
2015  HE, Mucin, IHC, Genetics & Radiology

for resections
includes small specimens
WHO Classification of Epithelial Tumors - 2015

- Adenocarcinoma
  - Lepidic
  - Acinar
  - Micropapillary
  - Solid
  - etc
- Squamous cell carcinoma
  - Keratinizing, Nonkeratinizing, basaloid
- Neuroendocrine tumors
  - Includes small cell, carcinoids, etc
- Large cell carcinoma
- Adenosquamous carcinoma
- Pleomorphic carcinoma
- Spindle cell carcinoma
- Carcinosarcoma
- Pulmonary Blastoma
- Unclassified
- Salivary gland type tumors
- Papillomas
- Adenomas
Diagnostic algorithm

- Malignant vs Benign
- Primary tumor vs metastasis
- Small cell (~15%) vs Nonsmall cell (~85%)
- Adenocarcinoma vs Squamous vs other
- Subtype
- Histologic Grade
Small cell Carcinoma - SCLC

- 45 K cases / year
- Median age 60
- 99% of cases occur in smokers
- Aggressive with early nodal involvement
- Paraneoplastic syndromes
- Centrally located
- Bx often crushed
- Neuroendocrine markers

Images from http://library.med.utah.edu/WebPath/
NSCLC- Squamous cell carcinoma- SCC

• Strongly associated with smoking
• Centrally located
• Cavitating
• Histologically graded:
  - Well
  - Moderately
  - Poorly
• Minimally role for molecular studies
• Better prognosis stage for stage compared to small cell and ADCA

Images from http://library.med.utah.edu/WebPath/
NSCLC - Adenocarcinoma

• Most common type of lung carcinoma in
  - Non-Smokers
  - Females
  - Younger males
  - Light smokers

• Targeted therapy available

• Molecular testing important
  – EGFR, ALK, ROS-1
NSCLC - Adenocarcinoma

- Peripherally located
- Pleural puckering or retraction.
- May cause pleural thickening
- May be poorly defined

Images from http://library.med.utah.edu/WebPath/
Histology - Adenocarcinoma

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

- Limited sample
- Spare tumor present
- Poor tumor differentiation
- Exclude metastasis
- Mixed phenotype
- 10-40% of cases can not be subtyped by morphology alone
- Need to accurate classification for treatment
- Knowledge of antibody and staining pattern necessary
Immunohistochemistry

Adenocarcinoma
- TTF-1
- Napsin
- BerEp-4
- Moc-31
- CK-7

Squamous cell carcinoma
-p63 /p40
-CK-5/6
-Desmogledin

Neuroendocrine (small cell)
-Chromogranin
-Synaptophysin
-CD56

Implications of Histopathologic Classification

**Adenocarcinoma**

- EGFR mutations → tryosine kinase inhibitors
- Rearrangement of ALK and ROS-1 → Crizotinib

**Squamous cell carcinoma**

- Bevacizumab contraindicated
- Nivolumunmab (PDL-1 antibody) recently FDA approved
Driver mutations in Adenocarcinoma

FDA approved treatments and testing

- **EGFR** → tyrosine kinase inhibitors
- KRAS → resistance to TKI
- ALK → Crizotinib
- ROS-1 → Crizotinib

![Mutations in Adenocarcinoma](image)

Iafrate, J., Molecular Pathology and Lung Cancer. USCAP 2016
EGFR mutations

- 10-15% of lung adenocarcinomas
- Transmembrane receptor tyrosine kinase involved in epithelial cell development and function
- Downstream mutations (KRAS, T790M, MET amplification) associated with resistance to TKI
- Testing PCR based on formalin fixed paraffin embedded tissue
- Current testing targets
  - Exons: 18, 19, 20, 21

https://www.aacc.org/publications/cln/articles/2013/october/egfr-mutations
Anaplastic Lymphoma Kinase - ALK

- 3% of ADCS’s
- Mutually exclusive w/ EGFR or KRAS
- Younger, non smokers
- Inversion creating a fusion oncogene
  - EML4-ALK
  - Constitutive kinase activity
- FISH based testing of formalin fixed paraffin embedded tissue
  - Break-apart probe

ROS-1 mutation in adenocarcinoma

- Rare, 1.5% of patients
- No histologic association
- Mutually exclusive with EGFR, KRAS, ALK
- Younger patients and nonsmokers
- Tryosine kinase insulin receptor family
- Chimeric protein with strong proliferative activity
- Identified with a FISH breakapart probe

Programmed death ligand -1

- Patients who progressed on or after platinum-containing chemotherapy or EGFR-or ALK-targeted agents in patients harboring those mutations.

- **Nivolumab**: (3/2015) 
  Squamous cell carcinoma

- **Penbrolizumab**: (10/2015) 
  Squamous cell carcinoma and adenocarcinoma

- PD-L1 IHC 22C3 pharm Dx test
  *Only available at several national reference laboratories*

Summary of Pathologist role

• Establish a diagnosis
  – Excluding benign neoplasms, infections, etc
  – Excluding metastasis
  – Stage tumor TMN system

• Accurately classify the histopathology of lesion

• Select tissue for ancillary molecular studies

• Oversight of molecular testing
References

2. Pathology images: http://library.med.utah.edu/WebPath/
6. Iafrate, J., Molecular Pathology and Lung Cancer. USCAP 2016