PULMONARY PATHOLOGY JOURNAL CLUB – NOVEMBER 2018
(October 2018 articles)
December 3, 2018

Dr. Jeffrey L. Myers, MD
A. James French Professor of Pathology
Department of Pathology, University of Michigan
myerjeff@med.umich.edu

Dr. Jian J. Jing, MD
Pulmonary Pathology Fellow
Department of Pathology, University of Michigan
jiajing@med.umich.edu

Table of Contents

Discussion articles

Articles for notation

Page 9 Yokoyama et al. Tumor Spread Through Air Spaces Identifies a Distinct Subgroup With Poor Prognosis in Surgically Resected Lung Pleomorphic Carcinoma. CHEST 2018; 154(4): 838-847.

Toyokawa et al. Computed tomography features of resected lung adenocarcinomas with spread through air spaces. J Thorac Cardiovasc Surg 2018; 156: 1670-1676.

Arulananda et al. Mismatch Repair Protein Defects and Microsatellite Instability in Malignant Pleural Mesothelioma. Journal of Thoracic Oncology 2018; 13(10): 1588-1594.

Churg et al. Highlights of the 14th international mesothelioma interest group meeting: Pathologic separation of benign from malignant mesothelial proliferations and histologic/molecular analysis of malignant mesothelioma subtypes. Lung Cancer 2018; 124: 95-101.

Page 10 Montecalvo et al. Type A thymoma presenting with bone metastasis. Histopathology 2018; 73: 701-711.

Hsieh et al. Solitary pulmonary capillary hemangioma: An under-recognized pulmonary lesion mimicking early lung cancer on computed tomography images. Lung Cancer 2018; 124: 227-232.

Montero et al. The role or transbronchial cryobiopsy in lung transplantation. Histopathology 2018; 73: 593-600.

Kolaitis et al. Pirfenidone-Induced Sarcoid-Like Reaction. CHEST 2018; 154(4): e89-e92.

Page 11 Bonnefoy et al. Bronchial Dieulafoy's Disease: Visualization of Embolization Particles in Bronchial Aspirate. Am J RespirCrit Care Med 2018; 198(7): 954-955.

Konopka et al. A review of Smoking-Related Interstitial Fibrosis, Respiratory Bronchiolitis, and Desquamative Interstitial Pneumonia: Overlapping Histology and Confusing Terminology. Arch Pathol Lab Med 2018; 142: 1177-1181.

Discussion articles

Marchevsky et al. The use of Ki-67 labeling index to grade pulmonary well-differentiated neuroendocrine neoplasm: current best evidence. Modern Pathology 2018; 31: 1523-1531.

Purpose: To learn whether, 1) disparate language and use of Ki-67 labeling index as a diagnostic/risk stratification criterion in pulmonary neuroendocrine tumors (NETs) compared to NETs of GI/pancreatic origin poses challenges for treating oncologists, and 2) there is a meaningful and potentially reproducible role for Ki-67 labeling indices in risk stratification of typical carcinoid tumors of the lung.

Methods:

- Survey of 189 physicians participating in the October 2017 annual meeting of the North American Neuroendocrine Tumor Society
  - Is Ki-67%, 1-useful for selecting therapy, 2-useful for informing patients re prognosis, 3-associated with a value ≈ "poor prognostic" feature?
  - Does variability in terminology create problems in your practice?
  - Is it important to know origin of met NET to elect therapy?
- Systematic evidence-based review of relevant literature (PubMed: Ki-67 + carcinoid + lung neoplasms; English language, ≥ 10 patients)
  - N, method for Ki-67%, cutoff significantly associated with prognosis (expressed/measured how)?
- Retrospective cohort of 256 consecutive typical/atypical carcinoids with available Ki-67%
- A = typical carcinoid, Ki-67 < 5%; B = typical carcinoid, Ki-67 ≥ 5%; C = atypical carcinoid

Results:

- *33 (17.5%) respondents to survey*: Ki-67% important for therapy (100%), useful for informing patients re prognosis (81.8%), cutoff of >10% a more guarded prognosis/rationale for adjuvant therapy (90.9%), terminology problematic (63.6%), knowing site of origin for met NET important for therapy (78.8%)
- 42 papers → 11 "provided best available evidence" + retrospective cohort
  - 225 typical (A = 187; B = 38) and 31 atypical (C) carcinoid tumors
  - A vs B: no difference in sex ratio, median age @ dx, median tumor size
- random-image analysis (4) > hotspot-manual (3) > ? random-manual (2) > random (1)/hotspot (1)-manual and image analysis
- overall survival significantly worse in group B and C patients; progression-free survival significantly longer in group A compared to group B patients; trend toward higher percentage of tumor recurrence (12.5% vs 4.3%; $p<0.12$) and shorter mean times to recurrence (38.0±18.4 vs 64.6±47.6 mos; $p<0.3$).

Take-home message: No getting around it now – going to have to do Ki-67 on all "well differentiated NETs" of the lung and suspect terminology change in store for next WHO. Molecular testing also on horizon to select patients for everolimus (mTOR inhibitor).

Sakata et al. Comparison of programmed death ligand-1 immunohistochemical staining between endobronchial ultrasound transbronchial needle aspiration and resected lung cancer specimens. CHEST 2018; 154(4): 827-837.

Purpose: To establish sensitivity, specificity, PPV, NPV and concordance rates for PD-L1 IHC staining on EBUS-TBNA cell blocks versus surgical resection specimens.

Methods: Retrospective cohort of patients who underwent EBUS-TBNA of either lymph nodes or tumor followed by surgical resection.

- semi-quantitative assessment of cell block cellularity
- ≥ moderate/membranous staining = "positive" expressed as 0, < 1%, and ≥ 1% in 5% increments
- ≥ 1% and ≥ 50% the cutoffs used for analysis

Results:

- 61 of 73 patients available for assessment (12 had no residual tumor in cell block)
- adenoca – 39 (64%); sq cell ca – 21 (34%); lge cell ca – 1 (2%)
- neoadjuvant therapy in 24 (39%); days from EBUS to surgery: median 32, mean 60.7 ± 62.7 (range 3-329)
- 32 (52%) negative in both; 14 (23%) ≥ 1% and 15 (25%) ≥ 50% in surgical specimens

	Tumor +	Tumor –
PD-L1 ≥ 1%		
EBUS-TBNA +	21	0
EBUS-TBNA –	8†	32
	SENS 72%, *SPEC* 100%, *PPV* 100%, *NPV* 80%, CONC 87% †≤ 1,000 cells/hpf	
PD-L1 ≥ 50%		
EBUS-TBNA +	7	3†
EBUS-TBNA –	8‡	43
	SENS 47%, *SPEC* 93%, *PPV* 70%, *NPV* 84%, CONC 82% †PD-L1 ≤ 30% in resected specimen; ‡5/8 ≤ 1,000 cells/hpf	

- no significant difference in performance characteristics in treatment naïve vs neoadjuvant therapy group, or in patients for whom EBUS-TBNA targeted lymph nodes (n = 42)

Take-home message: EBUS-TBNA is a reliable tool for predicting PD-L1 expression, although the higher the threshold (≥ 50% vs ≥ 1%) the lower the sensitivity. Some discordance likely attributable to intratumoral heterogeneity. Low cellularity associated with false negative results.

Suda et al. Innate genetic evolution of lung cancers and spatial heterogeneity: analysis of treatment-naïve lesions. Journal of Thoracic Oncology; 13(10): 1496-1507.

Purpose: To study intertumor heterogeneity in treatment naïve advanced stage lung cancer.

Methods: Tumor samples from 5 autopsied lung cancer patients (adenoca – 2, sq cell ca – 2, SCLC – 1) who did not receive systemic treatment.

- extracted RNA → cDNA library → NGS (Illumina HiSeq 4000 sequencer)
- sequencing reads mapped using various libraries and databases including method for detecting gene fusions
- mutations: "only called high-confidence somatic variants if the mutations were detected as somatic (after comparing with the paired normal samples), nonsynonymous, and deleterious mutations with total read counts 20 or more and variant read counts 5 or greater and 2% or greater."
- PD-L1 (E1L3N) IHC
- constructed phylogenetic trees for the multiple lesions of each patient

Results:

- 3 M:2 W (77, 82, 85, 86, & 96 yrs of age); 4-9 lesions/patient, including extrathoracic sites in 3
- 2 adca (1 never smoker, 1 smoker); 2 sq cell ca (2 smokers, 1 "heavy" [≥ 50 pk-yr]), 1 SCLC (heavy smoker)
- Global unsupervised clustering analysis of expression data showed that, 1) lesions from each patient clustered together; 2) NSCLC patients clustered together in contrast to SCLC patient; 3) the 2 adenoca patients clustered together as did the 2 sq cell ca patients.
- 27-98 dysregulated pathways in each patient
  - Dysregulated pathways were conserved across sites for 1) 52 pathways from the never smoker, 2) 15 & 35 pathways in "non-heavy" smokers, and 3) in 1 (sq cell ca) & 5 (SCLC) pathways in heavy smokers.
  - Primary lesions always distinct from mets.
  - Metastatic lesions often clustered based on site (*ie*, lymph nodes, lung and pleura, extrathoracic)
  - Metastatic sites showed upregulation of cell proliferation pathways and downregulation of immune-related pathways compared to primary sites. Multiple immune-regulated pathways downregulated in pleural mets.
- Mutational analysis showed a distinct mutational profile in the primary compared to mets; "trunk" (conserved across all sites) and "metastatic trunk" (present in all mets but not the primary) mutations variable

Histology	Smoking Status	Total Mutations	Trunk Mutations	Metastatic Trunk Mutations
adenoca	never smoker	351	51 (KIF5B-RET)	77
	smoker	362	81 (RICTOR / DUSP5)	18
sq cell ca	smoker	442	53 (NFE2L2 / CDKN2A)	11
	heavy smoker	272	7 (NFE2L2)	5
SCLC	heavy smoker	316	63 (TP53 / PARP2)	69

- No correlations between mutation burden and PD-L1 expression which were highly variable across sites. Adenoca in never smoker positive (60%) in primary and negative in all mets c/w RNA expression data.

Take-home message: Metastatic lesions can be used as surrogates for the primary at the level of global gene expression pattern. Intertumor heterogeneity in dysregulated pathways and somatic mutations is variable and correlates with smoking status (higher in heavy smokers). Mets have upregulated cell proliferation and downregulated immune-related pathways that may promote metastatic potential and adaptation to foreign microenvironments. PD-L1 expression is highly variable across sites complicating an already complicated story.

Stone et al. Does presentation at multidisciplinary team meetings improve lung cancer survival? Findings from a consecutive cohort study. Lung Cancer 2018; 124: 199-204.

Purpose: To assess the relationship, if any, between multidisciplinary team (MDT) presentation and outcomes in lung cancer patients.

Methods:

- *Post hoc* analysis of prospectively collected data in a consecutive cohort of lung cancer patients registered with an Australian institutional cancer registry and tissue diagnoses between 1JAN06 (the year MDT was initiated at the study hospital) and 31DEC12.
  - survival data collected through/follow-up censored on 23MAY14
- Comparison of survival after diagnosis (primary aim) and demographic data (age, gender, ECOG status, rates of referral to palliative care, tumor pathology) between *MDT* and *non-MDT* patients.
  - patients referred to MDT at the discretion of treating clinicians at various points in their care

Results:

Characteristic		MDT	non-MDT	*p* value
Stage	I & II	33%	14%	$p < 0.001$
	IV	39%	56%	
	unknown	3%	16%	
ECOG status	0 & 1	60%	32%	$p < 0.001$
Age	< 69	58%	45%	$p < 0.001$
	> 80	18%	28%	
Year of diagnosis	2006	19%	81%	$p < 0.001$
	2012	34%	66%	

- 1197 cases: 295 (24.6%) MDT and 902 (75.4%) non-MDT
- MDT patients younger, earlier stage and stage more likely to be known, and better performance status
- Rate of referral to MDT increased from 2006 (19%) to 2012 (34%) after peaking in 2010 (42%) and 2011 (52%)
- No difference in gender distribution or distribution of NSCLC (89% vs 87%) and SCLC (11% vs 13%) although proportion of NSCLC (30%) cases presented at MDT was significantly higher ($p = 0.03$) than proportion of SCLC cases (21%)
- In multivariate analysis adjusted for age, sex, performance status, pathology, stage, and year of diagnosis, MDT associated with improved survival at 5 years ($p < 0.001$).
- No significant difference in rates of referral to palliative care for stage IV patients (78% vs 85%) although median time to referral was shorter for non-MDT patients (26 days vs 69 days).

Take-home message: Despite methodological vulnerabilities in lack of standardization for MDT referral and available data sources (ie, cancer registry), MDT presentation may be an independent, clinically significant component of lung cancer care. So whatever your feelings about the work entailed, it is important work that is here to stay as a standard of care in peer cancer treatment centers!

Articles for notation

Neoplastic

Sanchez-Font et al. Molecular analysis of peripheral lung adenocarcinoma in brush cytology obtained by EBUS plus fluoroscopy-guided bronchoscopy. Cancer Cyopathology 2018; 126: 860-871.

Purpose: To explore the feasibility of performing mutational profiling for *KRAS* and *EGFR* in brush cytology samples obtained by EBUS plus fluoroscopy guided bronchoscopy by comparing results with those obtained from histological samples in patients with peripheral lung adenocarcinoma.

Take-home message: It works! Brushing specimens conserved in RPMI medium and obtained by R-EBUS plus fluoroscopy-guided bronchoscopy are valid for molecular studies, allowing the detection of *EGFR*/*KRAS* mutations in patients with peripheral adenocarcinoma.

Sharpnack et al. Proteogenomic analysis of surgically resected lung adenocarcinoma. Journal of Thoracic Oncology 2018; 13(10): 1519-1529.

Purpose: To predict lung adenocarcinoma recurrence with matched transcriptomic and proteomic data using a novel supervised classification algorithm.

Take-home message: The combined analysis of RNA and protein abundances can be used to define candidate biomarkers of recurrence risk for surgically resected lung adenocarcinomas. However, independent validation is necessary to reduce the potential for over-fitting explaining the observed results.

Fu et al. Novel gene mutations in well-differentiated fetal adenocarcinoma of the lung in the next generation sequencing era. Lung Cancer 2018; 124: 1-5.

Purpose: To investigate the clinic-pathologic details and potential driver genes of well-differentiated fetal adenocarcinoma of lung (WDFA).

Take-home message: Three novel gene mutations were identified in two WDFA cases: missense mutations of BRCA2 and TSC2, and a silent mutation of DDR2

Rodriguez et al. Molecular genetic alterations in thyroid transcription factor 1- negative lung adenocarcinoma in cytology specimens: a subset with aggressive behavior and poor prognosis. Cancer Cytopathology 2018; 126: 853-859.

Purpose: To investigate the molecular alterations and survival in cytology samples diagnosed with TTF-1 negative adenocarcinoma.

Take-home message: Patients with TTF1- negative lung ADC have worse overall survival, a lower frequency of known mutations, and a higher frequency of ALK alterations.

Davies et al. Comparison of molecular testing modalities for detection of ROS1 rearrangements in a cohort of positive patient samples. Journal of Thoracic Oncology; 13(10): 1474-1482.

Purpose: To compared the performance of three common molecular testing approaches (FISH, DNA and RNA based library followed by NGS) on a cohort of ROS1 rearrangement/fusion-positive patient samples.

Take-home message: Break-apart FISH, RNA-based NGS, and DNA-based NGS each have inherent deficiencies that can lead to false-negative results in the testing for ROS1 rearrangements/fusions.

Young et al. Concordance of PD-L1 expression detection in non-small cell lung cancer (NSCLC) tissue biopsy specimens between OncoTect iO lung sssay and immunohistochemistry (IHC). Am J Clin Pathol 2018; 150: 346-352.

Purpose: Comparison of a fully quantitative technology and a standard immunohistochemical (IHC) assay for determining PD-L1 expression in non–small cell lung cancer.

Take-home message: The nonsubjective OncoTect iO Lung Assay (Flow Cytometry based assay) has been shown to be at least as accurate and sensitive as IHC for the detection of PD-L1 expression while providing additional information (quantification of tumor-infiltrating lymphocytes) to guide treatment.

Munari et al. PD-L1 Assays 22C3 and SP263 are not interchangeable in non-small cell lung cancer When considering clinically relevant cutoffs. Am J Surg Pathol 2018; 42: 1384-1.

Purpose: To compare 22C3 and SP263 assays in a large cohort of non–small cell lung cancer cases taking into account interobserver variability between trained pathologists.

Take-home message: Assays 22C3 and SP263 show important discrepancies in identifying PD-L1 positive cases at clinically relevant cutoffs, with possible underestimation of patients suitable for pembrolizumab therapy.

Katsumata et al. Differences of tumor microenvironment between stage I lepidic-positive and lepidic-negative lung adenocarcinomas. J Thorac Cardiovasc Surg 2018; 156: 1679-1688.

Purpose: To investigate the biological differences between the invasive components of Lep+ and Lep- adenocarcinoma.

Take-home message: Lower cancer cell–specific expression levels of hypoxia markers and a smaller number of tumor-promoting stromal cells in invasive component were characteristic features of Lep+ adenocarcinomas.

Yokoyama et al. Tumor spread through air spaces identifies a distinct subgroup with poor prognosis in surgically resected lung pleomorphic carcinoma. CHEST 2018; 154(4): 838-847.

Purpose: Retrospective cohort study of 35 resected pleomorphic lung carcinomas to characterize the significance of STAS (groups 1-3 – not to be confused with STAKS) in this narrow context.

Take-home message: STAS of one form or another observed in 40% of cases and was associated with recurrence-free and overall survival.

Toyokawa et al. Computed tomography features of resected lung adenocarcinomas with spread through air spaces. J Thorac Cardiovasc Surg 2018; 156: 1670-1676.

Purpose: In an effort to preoperatively predict what no oncologist is interested in after the fact, CT findings were retrospectively compared in 327 resected STAS-positive (58.4%) and STAS-negative lung adenocarcinomas.

Take-home message: In multivariate analysis, STAS status (feels funny to say that, doesn't it?) correlated with the presence of notch ("a portion of the surface of a lesion showing a shallow, wavy configuration") and the absence of GGO (odds ratio for a tumor with both as opposed to a tumor with neither 5.01).

Arulananda et al. Mismatch repair protein defects and microsatellite instability in malignant pleural mesothelioma. Journal of Thoracic Oncology 2018; 13(10): 1588-1594.

Purpose: To profile a large retrospective cohort of pleural mesotheliomas for any loss of MMR proteins suggesting an MSI-high phenotype.

Take-home message: MSI is not seen in pleural mesotheliomas and is unlikely to be the mechanism underlying occasional response to PD-L1 based immunotherapy.

Churg et al. Highlights of the 14th international mesothelioma interest group meeting: Pathologic separation of benign from malignant mesothelial proliferations and histologic/molecular analysis of malignant mesothelioma subtypes. Lung Cancer 2018; 124: 95-101.

Purpose: The title says it all!

Take-home message: IHC for methylthioadenosine phosphorylase (MTAP) in combination with BAP1, and a 117 gene panel improved sensitivity for distinguishing meso from non-neoplastic mesothelial proliferations. Pathologists don't agree much when it comes to distinguishing biphasic mesos. Transitional mesos behave like sarcomatoid mesos. And our histological distinctions (however relevant to prognosis) are artificial for a genetic continuum of neoplasms.

. . . oh yeh one more: meso in-situ is now a thing with criteria and everything!

Montecalvo et al. Type A thymoma presenting with bone metastasis. Histopathology 2018; 73: 701-711.

Purpose: To showcase an unusual example of type A thymoma metastatic at diagnosis.

Take-home message: Stuff happens.

Hsieh et al. Solitary pulmonary capillary hemangioma: An under-recognized pulmonary lesion mimicking early lung cancer on computed tomography images. Lung Cancer 2018; 124: 227-232.

Purpose: To alert the pathology community to a diagnosis that we're apparently not very good at making: 16 cases included in a retrospective cohort were unrecognized or misdiagnosed.

Take-home message: We should do better at recognizing these unique tumors on the one or two occasions they are likely to pop up in the course of your career!

Non-neoplastic:

Montero et al. The role of transbronchial cryobiopsy in lung transplantation. Histopathology 2018; 73: 593-600.

Purpose: To compare diagnostic yield of conventional forceps biopsies (41) and cryobiopsies (40) in the transplant setting. Patients with forceps biopsies in ICU; cryobiopsy in outpatient bronch unit (hmmmm . . .). One CB patient died 15 days post-procedure from pneumonia complicated by empyema.

Take-home message: Bigger and not-crushed specimens from less sick patients are better when it comes to diagnostic yield . . . but it may come with increased risk in this vulnerable population.

Kolaitis et al. Pirfenidone-induced sarcoid-like reaction. CHEST 2018; 154(4): e89-e92.

Purpose: To report a patient with UIP/IPF who developed evidence of sarcoidosis-related adenopathy 10 months after starting pirfenidone. Biopsy of LNs and subsequent transplantation pneumonectomies showed features of sarcoidosis in lungs and nodes.

Take-home message: Impossible to sort out the extent to which the findings were related to prifenidone as opposed to new onset sarcoidosis, but worth keeping on your radar screens!

Bonnefoy et al. Bronchial Dieulafoy's Disease: visualization of embolization particles in bronchial aspirate. Am J Respir Crit Care Med 2018; 198(7): 954-955.

Purpose: Dieulafoy's disease (abnormal superficial "dysplastic" bronchial artery in bronchial submucosa) is a rare cause of life-threatening hemoptysis.

Take-home message: Here' another one showing the effects of embolization.

Konopka et al. A review of smoking-related interstitial fibrosis, respiratory bronchiolitis, and desquamative interstitial pneumonia: vverlapping histology and confusing terminology. Arch Pathol Lab Med 2018; 142: 1177-1181.

Purpose: Terminology for overlapping histologies attributed to cigarette smoking are confusing and the authors set out to offer greater clarity.

Take-home message: Smoking-related lung lesions represent a spectrum of intra-alveolar and interstitial abnormalities that are overlapping and only easily separable at the extremes! In the middle choice of terms arbitrary and should be driven my synthesis of clinical, radiological and pathologic findings!