

Pulmonary Pathology Journal Club (December 2016)
Articles from November 2016
- December 19, 2016 -

ARTICLE INDEX

Boussiotis, Vassiliki. Molecular and Biochemical Aspects of the PD-1 Checkpoint Pathway. *N Engl J Med* 2016;375:1767-78.

Bubendorf, Lukas et al. Testing for ROS1 in non-small cell lung cancer: a review with recommendations. *Virchows Arch* (2016) 469:489-503

Casagrande, Arianna, et al. Association between Congenital Lung Malformations and Lung Tumors in Children and Adults: A Systematic Review. *Journal of Thoracic Oncology*. Vol 11 No. 11:1837-1845

Cottin V et al. Respiratory manifestations of eosinophilic granulomatosis with polyangiitis (Churg–Strauss) . *Eur Respir J* 2016; 48: 1429–1441

Cottin V. Lung biopsy in interstitial lung disease: balancing the risk of surgery and diagnostic uncertainty . *Eur Respir J* 2016; 48: 1274–1277

Eguiluz-Gracia, Ibon et al. Long-term persistence of human donor alveolar macrophages in lung transplant recipients. *Thorax* 2016;71:1006-101

Facchinetti, Francesco, et al. Moving Immune Checkpoint Blockade in Thoracic Tumors beyond NSCLC. *Journal of Thoracic Oncology* Vol. 11 No. 11:1819-1836

Gray, Steven, et al. PD-L1 as a Companion Biomarker for Immune Checkpoint Inhibitors in NSCLC: Should RNA ISH (RISH) Be Considered? Letter to the Editor. *Journal of Thoracic Oncology*. Vol. 11 No. 11:143

Huynh, Tiffany et al. Programmed Cell Death Ligand 1 Expression in Resected Lung Adenocarcinomas: Association with Immune Microenvironment. *Journal of Thoracic Oncology*. Vol. 11 No. 11:1869-1878

Hutchinson et al. Surgical lung biopsy for the diagnosis of interstitial lung disease in England: 1997–2008. *Eur Respir J* 2016; 48: 1453–1461.

Jang, Sin Sung et al. Custom Gene Capture and Next-Generation Sequencing to Resolve Discordant ALK Status by FISH and IHC in Lung Adenocarcinoma. *Journal of Thoracic Oncology* Vol. 11 No. 11:1891-1900

Kao, Hua-Lin et al. Diagnostic algorithm for detection of targetable driver mutations in lung adenocarcinoma: Comprehensive analyses of 205 cases with

immunohistochemistry, real-time PCR and fluorescence in situ hybridization methods. *Lung Cancer* 101 (2016) 40-47

Khanna, Swati, et al. Malignant Mesothelioma Effusions Are Infiltrated by CD3+ T-Cells Highly Expressing PD-L1 and the PD-L1+ Tumor Cells within These Effusions Are Susceptible to ADCC by the Anti-PD-L1 Antibody Avelumab. *Journal of Oncology*. Vol. 11 No. 11:1993-2005

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Maher, Toby. Blood-based Diagnosis of Idiopathic Pulmonary Fibrosis. Fantasy or Reality? (Editorial). *American Journal of Respiratory and Critical Care Medicine*. Volume 194 Number 10. November 15, 2016.

Marisa Dolled-Filhart, et al. Development of a Companion Diagnostic for Pembrolizumab in Non-Small Cell Lung Cancer Using Immunohistochemistry for Programmed Death Ligand-1. *Arch Pathol Lab Med*-Vol 140, November 2016

Michal M et al. Histiocytosis With Raisinoid Nuclei: A Unifying Concept for Lesions Reported Under Different Names as Nodular Mesothelial/Histiocytic Hyperplasia, Mesothelial/ Monocytic Incidental Cardiac Excrescences, Intralymphatic Histiocytosis, and Others A Report of 50 Cases. *Am J Surg Pathol* 2016;40:1507–1516

Miller, Ross A. et al. PD-1/PD-L1, Only a Piece of the Puzzle. *Arch Pathol Lab Med*-Vol 140, November 2016

Nakahira, Kiichi et al. Autophagy in Pulmonary Diseases. *American Journal of Respiratory and Critical Care Medicine*. Volume 194 Number 10. November 15, 2016.

Neuman, Tzahi et al. A Harmonization Study for the Use of 22C3 PD-L1 Immunohistochemical Staining on Ventana's Platform. *Journal of Thoracic Oncology*. Vol. 11 No. 11:1863-1868

Raparia, Kirtee et al. Transbronchial Lung Cryobiopsy for Interstitial Lung Disease Diagnosis. A Perspective From Members of the Pulmonary Pathology Society. *Arch Pathol Lab Med*-Vol 140, November 2016

Righi, Luisella et al. BRCA1-Associated Protein 1 (BAP1) Immunohistochemical Expression as a Diagnostic Tool in Malignant Pleural Mesothelioma

Classification: A Large Retrospective Study. *Journal of Thoracic Oncology*. Vol. 11 No. 11:2006-2017

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Roy-Chowdhuri, Sinchita et al. Biomarker Testing in Lung Carcinoma Cytology Specimens. A Perspective From Members of the Pulmonary Pathology Society. *Arch Pathol Lab Med*. 2016;140:1267-1272

Ruano-Ravina, Alberto et al. Residential radon, EGFR mutations and ALK alterations in never-smoking lung cancer cases. *Eur Respir J* 2016; 48: 1462-1470

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Williams, Andrew S. et al. ALK+ lung adenocarcinoma in never smokers and long-term ex-smokers: prevalence and detection by immunohistochemical and fluorescence in situ hybridization. *Virchows Arch* (2016) 469:533-540

Yanagawa, Naoki et al. The Clinical Impact of Solid and Micropapillary Patterns in Resected Lung Adenocarcinoma. *Journal of Thoracic Oncology*. Vol. 11 No. 11:1976-1983

ARTICLES FOR DISCUSSION

1. White, Eric et al. Plasma Surfactant Protein-D, Matrix Metalloproteinase-7, and Osteopontin Index Distinguishes Idiopathic Pulmonary Fibrosis from Other Idiopathic Interstitial Pneumonias. American Journal of Respiratory and Critical Care Medicine. Volume 194 Number 10. November 15, 2016.

Purpose:

To identify potential biomarkers that might assist in distinguishing IPF from other types of ILD.

Methods:

- 86 patients were used as a derivation cohort
- Plasma samples and data from the lung tissue research consortium (NHLBI) used.
- Validation cohort included 63 patients with IPF and 33 with RA-ILD and 41 other ILDs (14 NSIP, 15 NOS, 6 COP, 4 RB-ILD, 2 DIP). All diagnoses were made by multidisciplinary review.
- 127 healthy controls also examined
- Complex biomarker screening strategy was employed (Fig 1). ROC characteristics were used to evaluate the sensitivity and specificity of each potential biomarker, and binary threshold variables were created.

Results:

Table 3. Demographic Data of the Validation Cohort

	IPF	RA-ILD	P Value*
N	63	33	
Age, yr (mean \pm SD)	65.4 \pm 9.1	65.5 \pm 11.3	0.96
Male, n (%)	41 (63.1)	23 (69.7)	0.52
Ever smoked, n (%)	43 (66.2)	21 (63.6)	0.80
FVC, % predicted (mean \pm SD)	63.3 \pm 17.7	74.3 \pm 23.7	0.013
FEV ₁ , % predicted (mean \pm SD)	68.4 \pm 18.8	73.5 \pm 26.2	0.35
DL _{CO} , % predicted (mean \pm SD)	42.3 \pm 18.1	48.5 \pm 19.4	0.15

Definition of abbreviations: DL_{CO} = diffusing capacity of the lung for carbon monoxide; IPF = idiopathic pulmonary fibrosis; RA-ILD = rheumatoid arthritis-associated interstitial lung disease.

*P value represents the comparison between the IPF and RA-ILD cohort.

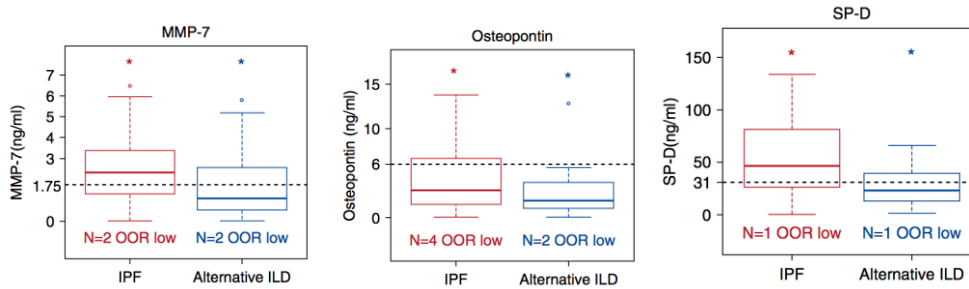


Table 4. Specificity, Sensitivity, and Threshold Values of Three Biomarkers with Unadjusted Area under the Receiver-Operating Characteristic Curve >0.6, Ordered by Decreasing Adjusted Odds Ratio

Biomarker	Spec	Sens	Threshold	Adjusted*				Unadjusted			
				OR	95% CI	P Value	AUC	OR	95% CI	P Value	AUC
OPN, ng/ml	0.91	0.35	6	3.8	1.0–14.3	0.045	0.743	4.7	1.5–14.5	0.007	0.620
SP-D, ng/ml	0.65	0.7	31	3.1	1.2–7.8	0.016	0.747	3.8	1.0–8.3	0.0008	0.660
MMP-7, ng/ml	0.63	0.71	1.75	3.1	1.2–7.7	0.015	0.771	3.9	1.7–8.7	0.0009	0.662

Definition of abbreviations: AUC = area under the receiver-operating characteristic curve; CI = confidence interval; MMP-7 = matrix metalloproteinase-7; OPN = osteopontin; OR = odds ratio; Sens = sensitivity; SP-D = surfactant protein-D; Spec = specificity.

*Adjustment variables include sex, age, smoking status, and FVC (% predicted).

- 35 biomarkers assayed.
- At final screening analysis only 3 biomarkers yielded an area under the curve >0.6, which meant that the odds of an IPF diagnosis in both adjusted and unadjusted analyses were enhanced (ORs 3.1 – 4.7).

Take home points:

- The ECM is remodeled in ILD.
- SP-D, MMP-7 and Osteopontin, when included in a 3 analyte panel of peripheral plasma biomarkers enhanced the odds of IPF diagnosis in ILD patients
- When used in concert with clinical presentation and radiology, may improve yield and help in cases of patients that can't tolerate surgical biopsy

2. Righi, Luisella et al. BRCA1-Associated Protein 1 (BAP1) Immunohistochemical Expression as a Diagnostic Tool in Malignant Pleural Mesothelioma Classification: A Large Retrospective Study. Journal of Thoracic Oncology. Vol. 11 No. 11:2006-2017

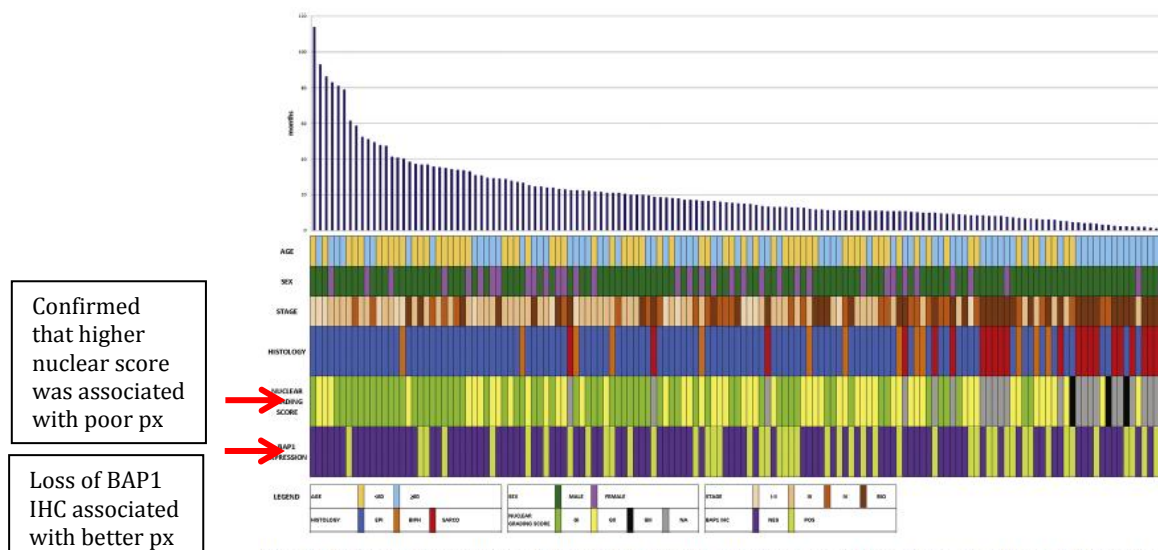
Purpose:

To evaluate the usefulness of BAP1 IHC in the diagnosis of MPM (particularly epithelioid type with reactive stroma vs biphasic) and correlate BAP1 IHC with clinical features.

Methods:

- Retrospective review of 101 consecutively resected MPM from two hospitals in Turin, Italy (2000-2012), plus 42 biphasic and sarcomatoid MPM biopsies.
- All 143 samples were classified by 2 pathologists according to 2015 WHO criteria.
- Nuclear grade for epithelioid component of tumor was recorded as the sum of atypia (1-3) and mitotic count scores (1=up to 1 mit/10hpf; 2=2-5; 3=>5) (Kadota score: *Kadota et al. Mod Pathol. 2012;25:260-271*).
- Tumor associated stromal atypia was recorded as low, moderate and high based on cellularity, nuclear pleomorphism, size, and hyperchromasia.
- BAP1 IHC (clone C4, rabbit monoclonal; Santa Cruz Biotechnology) was performed; positive was defined as weak to strong nuclear immunoreactivity.
- Mutation analysis of 20 cases (16 epithelioid; 4 biphasic) with mixed IHC results was performed by Sanger sequencing (coding regions and exon/intron junction sites).
- Cases with discrepant IHC/Sanger results underwent FISH testing (BAP1 deletion= \geq 30% of cells).

Results:



- 143 cases; 107 epithelioid (including 12 pleomorphic), 13 biphasic, 23 sarcomatoid
- BAP1 IHC:
 - Lost in 89 of 143 cases (62%), most commonly lost in epithelioid and biphasic type
 - Atypical stromal cells in epithelioid MPM had intact staining
 - Nuclear staining retention had a worse prognosis (was not an independent predictor of prognosis in multivariate analysis, $p=0.055$).
- BAP1 IHC correlation with molecular
 - 100% (10 of 10) tumors with nuclear BAP1 loss and cytoplasmic BAP1 immunoreactivity had BAP1 mutation by Sanger.
 - 66% (6 of 9) cases with both nuclear and cytoplasmic BAP1 loss had BAP1 mutation by Sanger; remainder showed heterozygous deletions by FISH.
 - 5 of 13 (38%) cases of biphasic MPM had discrepant staining in the epithelioid component (BAP1 IHC loss) and the spindle cell component (BAP1 IHC retention).
 - Differential microdissection of epithelioid and spindled areas in 3 of these 5 tumors showed BAP1 mutation isolated to epithelioid component (consistent with IHC results).
 - Interpretation: (1) wrong diagnosis, with these being epithelioid MPMs with reactive stromal cells, vs (2) collision tumor of epithelioid and sarcomatoid MPM of two different clonal origins.
- Histology
 - High nuclear score (Kadota score) predicted poor survival ($p<0.0001$).

- High stromal atypia was seen in pleomorphic and biphasic MPM, and therefore correlated with worse outcome than epithelioid types (P=0.0004).

Take home points:

- BAP1 mutation is more commonly found in epithelioid and biphasic MPM and is associated with a better prognosis (but not an independent predictor on multivariate analysis).
- Two patterns of IHC correlate with BAP1 mutation: nuclear loss of immunoreactivity and cytoplasmic staining (75% of BAP1-mutated tumors were completely negative, 25% had cytoplasmic staining).
- BAP1 retention in atypical spindle cells may be helpful in differentiating epithelioid MPM with atypical reactive spindle cells from biphasic MPM

3. Eguiluz-Gracia, Ibon et al. Long-term persistence of human donor alveolar macrophages in lung transplant recipients. *Thorax* 2016;71:1006-1011

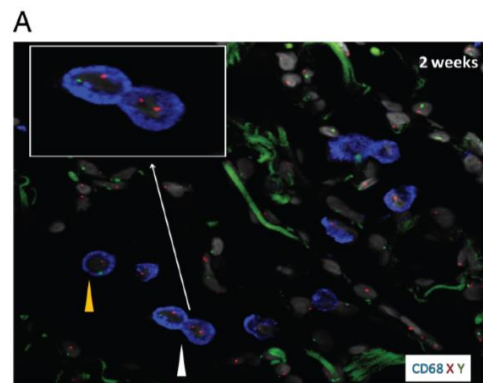
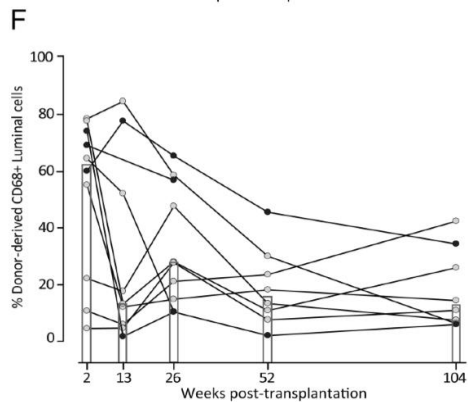
Purpose:

In recognition of the fact that little is known about the lifespan and turnover of human alveolar macrophages, this study set out to determine the turnover of alveolar macrophages in lung transplant for >100 weeks. They also evaluated AMF development in mice, with cord-derived cells

Methods:

- Transbronchial biopsies obtained per protocol from 10 lung transplant recipients from gender mismatched donors.
- 7 men, 3 women; 41-60 years old
- Any cases of cell-mediated rejection requiring treatment or infection were excluded
- Chimerism was evaluated by XY FISH-based cytogenetics at 2 weeks, 13 weeks, 26 weeks, 52 weeks, and 104 weeks post-tx
- Phenotype data seem to show that recipient-derived AMFs rapidly seed the graft and those AMFs stay there long-term, with minimal turnover.
- Mouse models show that the AMFs are largely derived from circulating monocytes

Results:



Take home points:

- Human AMFs are long-lived and self-maintained.
- Most donor macrophages that survive the transplant are still there at 2 years post-tx

- A fraction of these were Ki-67+, indicating that they may proliferate locally (suggesting that the recruitment from circulation may not be as important as previously believed)
- The finding that human AMFs are maintained provides rationale for transplant of MFs into lungs of people with MF diseases (PAP)

4. Huynh, Tiffany et al. Programmed Cell Death Ligand 1 Expression in Resected Lung Adenocarcinomas: Association with Immune Microenvironment. *Journal of Thoracic Oncology*. Vol. 11 No. 11:1869-1878

Purpose:

To perform a comparative analysis of PD-L1 expression and correlate the results with clinicopathologic variables, tumor-associated lymphocyte subtypes, and patient outcomes in lung adenocarcinoma.

Methods:

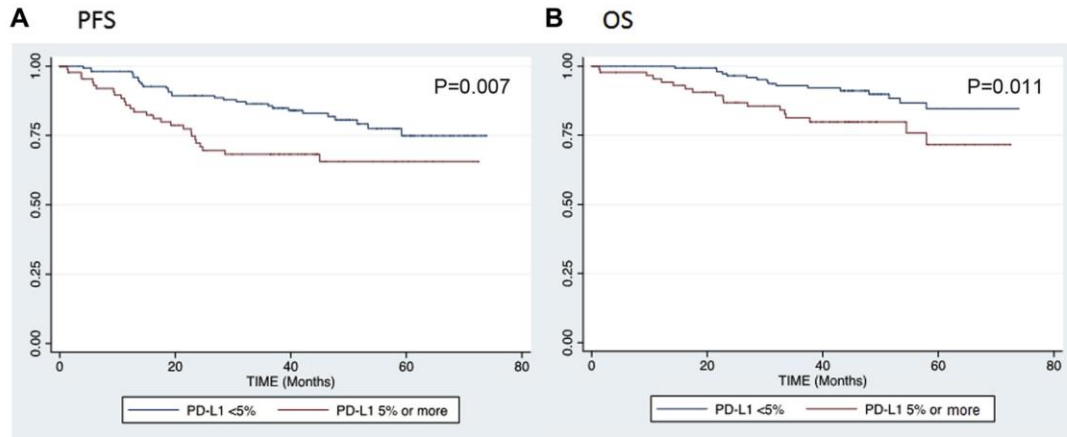
- Archives of MGH were queried for primary lung adenocarcinomas (2010-2012), identifying 461 cases.
- After exclusion for neoadjuvant therapy, multiple recurrent primaries, insufficient molecular testing and insufficient quantity of tumor, 261 cases remained.
- All cases tested for *EGFR*, *KRAS*, *BRAF*, *Her2*, *TP53*. Subset tested for *ALK* (248), *ROS1* (65), or rearrangement of *MET* (17), *EGFR* (4) or *Her2* (2).
- Demographic info, smoking hx, and post-op follow-up, and OS abstracted
- TMAs made, IHC performed PD-L1, GATA3, CD8, T-bet (marker of Th2 pathway activation)

Results:

Variable	PD-L1 expression (≥5% vs. <5%)		p Value
	PD-L1 ⁺	PD-L1 ⁻	
T-bet ⁺ TILs, n (%)			<0.001
0-1	70 (74)	161 (97)	
2-3	25 (26)	5 (3.0)	
T-bet ⁺ stroma, n (%)			0.087
≤5%	74 (78)	143 (86)	
>5%	21 (22)	23 (14)	
GATA3 ⁺ TILs, n (%)			1.000
0-1	94 (99)	164 (99)	
2 ^b	1 (1.1)	2 (1.2)	
GATA3 ⁺ stroma, n (%)			0.111
≤5%	53 (56)	110 (66)	
>5%	42 (44)	56 (34)	
Molecular alterations, n (%)			<0.001
<i>KRAS</i> mutations	50 (53)	58 (35)	
<i>EGFR</i> mutations	5 (5.3)	49 (30)	
<i>ALK</i> mutations	1 (1.1)	3 (1.8)	
Other alterations	4 (4.2)	9 (5.4)	
SNaPshot wild-type	35 (37)	47 (28)	

- 90 men, 171 women (mean age 69 years)
- 49% ≥1% PD-L1; 37% ≥5% PD-L1; 24% ≥50% PD-L1
- PD-L1 correlated with smoking history, solid pattern, high nuclear grade, and angiolymphatic invasion. Was also more prevalent in large tumors.
- No association with PD-L1 and AJCC stage

- T-bet lymphocytes and GATA3 TILs, as in Table above
- Logistical regression analysis revealed CD8+ TILs and high nuclear grade were independent predictors of PD-L1+



Take home points:

- PD-L1 expression was associated with wild-type *EGFR*, smoking history and aggressive pathologic features (basically the reverse of *EGFR*+ cases)
- Abundant CD8+ TILs and T-bet TILs are characteristic of PD-L1+ tumors
- While PD-L1 expression was associated with PFS and OS, it was not predictive of survival by multivariate analysis
- Association between PD-L1 and abundant CD8 or smoking hx was significant in *KRAS* mut and SNaPshot wt cases – suggests using PD-L1 may be helpful in at least a subset of *KRAS* mut cases.
- Reports have shown better and worse survival in PD-L1 expressed tumors, and it is unclear whether these are population-based reasons or testing/clone-based reasons (or a combination thereof)
- They used TMAs and classifying PD-L1 can be difficult on such small samples

ARTICLES FOR NOTATION

Neoplastic

1. **Jang, Sin Sung et al. Custom Gene Capture and Next-Generation Sequencing to Resolve Discordant ALK Status by FISH and IHC in Lung Adenocarcinoma. Journal of Thoracic Oncology Vol. 11 No. 11:1891-1900**

Purpose: To evaluate genetic alterations in cases of pulmonary adenocarcinoma with discordant FISH-IHC ALK status.

Methods: DNA was extracted from 38 cases (16 FISH+/IHC- and 12 FISH-/IHC+) and subject to NGS-based interrogation of 9 genes (ALK, EML4, KIF5B, SND1, RET, EZR, ROS1, TERT, BRAF). 26 concordant cases (16 positive, 10 negative) also included.

Results: In 4 ALK FISH-positive/IHC-negative cases, no EML4-ALK fusion gene was observed by NGS, but in one case using fresh frozen tissue, we identified EML4-baculoviral AIP repeat containing 6 gene (BIRC6) and AP2 associated kinase 1 gene (AAK1)-ALK fusion genes. Among the 12 FISH-/IHC+ cases, no evidence of ALK gene rearrangement was detected by NGS. Eleven of 12 FISH- /IHC+ cases detected by ALK1 clone were concordant by repeat ALK IHC. Among the 16 ALK positive controls, whole gene capture identified ALK gene fusion in 15 cases, including in one case with HIP1-ALK. No ALK fusion gene was observed in any of the 10 FISH-negative/IHC-negative cases. Other fusion genes involving ROS1, EZR, BRAF, and SND1 were also found.

Take home points:

- ALK FISH results appeared to be false- positive in 3/4 FISH+ /IHC- cases, whereas no false-negative ALK FISH case was identified among 12 ALK FISH- /IHC+ cases
- Our targeted whole gene capture approach using formalin- fixed paraffin embedded samples was effective for detecting ALK rearrangements with other genes

2. **Kao, Hua-Lin et al. Diagnostic algorithm for detection of targetable driver mutations in lung adenocarcinoma: Comprehensive analyses of 205 cases with immunohistochemistry, real-time PCR and fluorescence in situ hybridization methods. Lung Cancer 101 (2016) 40-47**

Purpose: To evaluate EGFR, ALK, and ROS1 in a panel of Taiwanese lung adenocarcinoma cases (microarray) via parallel IHC and FISH/PCR

Methods: 205 lung adenocarcinomas were examined for EGFR mutations and ALK and ROS1 rearrangements using PCR, FISH and IHC in parallel. The association between these driver mutations and clinicopathological characteristics was also analyzed.

Results: 58.5% were found to harbor EGFR mutations, 6.3% ALK rearrangements and 1.0% ROS1 rearrangements. Compared to molecular-based methods, IHC of EGFR mutations showed an excellent specificity but the sensitivity is suboptimal, while IHC of ALK and ROS1 rearrangements demonstrated high sensitivity and specificity. No significant difference regarding the performance of different antibody clones toward these driver mutations was observed, except that clone SP125 showed a higher sensitivity than 43B2 in the detection of p.L858R of EGFR.

Take home points:

- EGFR IHC can be used as a substitute when nucleic acid quality is poor
- EGFR tested first, then ALK and ROS1 in parallel.

3. Khanna, Swati, et al. Malignant Mesothelioma Effusions Are Infiltrated by CD3+ T-Cells Highly Expressing PD-L1 and the PD-L1+ Tumor Cells within These Effusions Are Susceptible to ADCC by the Anti-PD-L1 Antibody Avelumab. Journal of Oncology. Vol. 11 No. 11:1993-2005

Purpose: To study immune checkpoints, PD-1 and PDL-1 in mesothelioma.

Methods: 65 cases of mesothelioma were evaluated for PD-L1 expression by IHC, and its prognostic significance was examined. Malignant effusions from patients with pleural and peritoneal mesothelioma were evaluated for PD-1+ and PD-L1+ infiltrating lymphocytes and their role in inducing PD-L1 expression in tumor cells. Antibody-dependent cellular cytotoxicity (ADCC) of avelumab, a fully humanized immunoglobulin G1 anti PD-L1 antibody against primary mesothelioma cell lines, was evaluated in presence of autologous and allogeneic natural killer cells

Results: Of 65 pleural and peritoneal mesothelioma tumors examined, 63% were PD-L1+, which was associated with slightly inferior overall survival compared to patients with PD-L1- tumors (median 23.0 versus 33.3 months). The frequency of PD-L1 expression was similar in patients with pleural and peritoneal mesothelioma, with 62% and 64% of samples testing positive, respectively. In nine mesothelioma effusion samples evaluated, the fraction of cells expressing PD-L1 ranged from 12%-83%. In seven patients with paired malignant effusion and peripheral blood mononuclear cell (PBMC) samples, PD-L1 expression was significantly higher on CD3+ T cells present in malignant effusions as compared with PBMCs. In addition, the numbers of CD14+ PD-1+ cells were increased in malignant effusions

compared with PBMCs. The lymphocytes present in malignant effusions recognized autologous tumor cells and induced interferon-g–mediated PD-L1 expression on the tumor cell surface. Of the three primary mesothelioma cell lines, 2 were susceptible to avelumab.

Take home points:

- Most MM (pleural and peritoneal) express PD-L1
- CD3+ T-cells in these tumors highly express PD-L1
- MM tumor cells are susceptible to avelumab.

4. Marisa Dolled-Filhart, et al. Development of a Companion Diagnostic for Pembrolizumab in Non-Small Cell Lung Cancer Using Immunohistochemistry for Programmed Death Ligand-1. Arch Pathol Lab Med-Vol 140, November 2016

Purpose: To develop a PD-L1 IHC assay on the dAko platform as a companion diagnostic to pembrolizumab in NSCLC.

Methods: Tumor samples from 146 patients with NSCLC treated with pembrolizumab for whom response data were available were scored according to their staining intensity by a single pathologist using 4 methods: percentage of tumor cells staining at any intensity (PS1), moderate/strong intensity (PS2), strong intensity (PS3). The cutoff score for predicting response to pembrolizumab was determined using receiver operating characteristic analysis. Progression-free and overall survival were assessed in patients

Results: The 4 scoring methods assessed performed similarly; PS1 with a 50% cutoff score is the simplest and easiest method to implement in practice. Response to pembrolizumab was observed in 43% with a PS1 score of 50% or higher in 8% with PS1 lower than 50%. Median progression-free and overall survival was 4.0 months and not yet reached, respectively, for patients with a PS1 of 50% or higher, and 2.1 and 6.1 months, respectively, for those with PS1 lower than 50%

Take home point:

The PD-L1 immunohistochemical assay shows the potential for enrichment of trial populations and as a companion diagnostic tool in non–small cell lung cancer

5. Michal M et al. Histiocytosis With Raisinoid Nuclei: A Unifying Concept for Lesions Reported Under Different Names as Nodular Mesothelial/Histiocytic Hyperplasia, Mesothelial/ Monocytic Incidental Cardiac Excrescences, Intralymphatic Histiocytosis, and Others A Report of 50 Cases. Am J Surg Pathol 2016;40:1507–1516

Purpose: To report on 50 cases of histiocytic proliferations that have previously been referred to as various terms (MICE, LAMM, NHA, REPs) and present a unifying lesional construct.

Methods: 50 cases of these histiocytic lesions were obtained from author's files. Microscopy and IHC were performed.

Results: Patients included 32 women and 15 men and 2 unknown. Age range 4-85 years. Size ranged from microscopic to 1-2 cm. All had similar morphology, by definition, consisting of polygonal to ovoid histiocytes with eosinophilic cytoplasm with admixed inflammatory cells. All stained with CD68, CD163, CD4 and CD64. CD1a, Langerin and S100 were consistently negative.

Take home point:

Author propose the term "histiocytosis with raisinoid nuclei" for this condition.

6. Neuman, Tzahi et al. A Harmonization Study for the Use of 22C3 PD-L1 Immunohistochemical Staining on Ventana;s Platform. Journal of Thoracic Oncology. Vol. 11 No. 11:1863-1868

Purpose: To study use of the 22C3 PD-L1 Ventana IHC platform as a companion for Pembrolizumab therapy.

Methods: 41 random cases of NSCLC were then independently evaluated by two pathologists. Each case was scored using Dako- or Ventana-stained slides. The scores obtained with the two 22C3 Ventana assays were compared with those obtained using the Dako 22C3 IHC platform.

Results: The Dako IHC platform stratified 8, 7, and 26 cases as being strongly positive, weakly positive, and negative for PD-L1, respectively, whereas 87.8% had the same results with Ventana's UltraView 22C3 protocol. Moreover, 85.3% had the same results with Ventana's OptiView 22C3 protocol.

Take home point:

The same PD-L1 IHC algorithm can reliably be applied to Ventana's platform (as the Dako platform) for use as a companion test for pembrolizumab therapy.

7. Ruano-Ravina, Alberto et al. Residential radon, EGFR mutations and ALK alterations in never-smoking lung cancer cases. Eur Respir J 2016; 48: 1462-1470

Purpose: To assess if residential radon exposure might cause EGFR mutations or ALK rearrangements in never-smokers.

Methods: Study was a multicenter case–control study in a radon-prone area; only lung cancer cases were included in the study. Residential radon measurements and clinical information were obtained for all the participants. Median values of residential radon between patients with EGFR mutations or ALK rearrangements versus those without them were compared.

Results: 323 patients (mean age 70 years; 19.5% men) included. 42//5 and 15% of patients were EGFR+ ALK+, respectively. The most frequent EGFR alterations were exon 19 deletions and exon 21 (L858R) single-point substitution mutations. ALK+ patients were 10 years younger than ALK- patients. Residential radon levels were two-fold higher in patients with exon 19 deletions compared with patients with exon 21 (L858R) single-point substitution mutations. There were no differences in residential radon levels by EGFR mutation status. ALK+ patients (n=12) essentially had two-fold residential radon levels compared with ALK-negative patients.

Take home point:

Residential radon may have a role in the molecular signature of lung cancer in never-smokers,

8. Shukuya, Takehito, et al. Relationship between Overall Survival and Response or Progression-Free Survival in Advanced Non-Small Cell Lung Cancer Patients Treated with Anti-PD-1/PD-L1 Antibodies. Journal of Thoracic Oncology. Vol. 11 No. 11:1927-1939

Purpose: Study tumor response and progression-free survival in patients with advanced NSCLC treated with anti-PD-1/PD-L1.

Methods: In a systematic review of the reported prospective clinical trials, data for response rate, median PFS, and median OS were extracted from 12 arms in 10 reported clinical trials using anti–PD-1/PD-L1 antibody, and their correlation was investigated. OS was compared according to tumor response on 5- to 9-week computed tomography scans and status of being progression-free at 8, 16, and 24 weeks by landmark analysis in 71 patients with advanced NSCLC treated with anti–PD-1/PD-L1 antibodies(2013-2015).

Results: Moderate correlations between median OS and median PFS and between median OS and response rate were identified using the Spearman correlation coefficient, although these correlations were not statistically significant. In a retrospective analysis of patients, disease control, and progression-free status at 8, 16, and 24 weeks significantly predicted OS.

Take home points:

- Disease control and progression-free survival were correlated with OS
- Longer interval PFS is the best predictor of survival in NSCLC treated with anti-PD-1/PD-L1.

9. Song Zhengbo, et al. Clinicopathologic characteristics, genetic variability and therapeutic options of RET rearrangements patients in lung adenocarcinoma. Lung Cancer 101 (2016) 16-21

Purpose: Prevalence, clinicopathologic characteristics, genetic variability and therapeutic options in RET-positive lung adenocarcinoma patients was studied.

Methods: For 615 patients with lung adenocarcinoma, RET status was detected by RT-PCR. NGS and FISH were performed in positive cases. Thymidylate synthetase (TS) mRNA level was assayed by RT-PCR. Overall survival (OS) was evaluated by Kaplan-Meier method and compared with log-rank test.

Results: 12 RET+ patients were identified by RT-PCR. However, one patient failed the detection of RET rearrangement by FISH and NGS. Totally, 11 patients confirmed with RET rearrangements by 3 methods, including 6 women and five men with a median age of 54 years. The presence of RET rearrangements was associated with lepidic predominant lung adenocarcinoma subtype in five of 11 patients. RET rearrangements comprised of nine KIF5B-RET and two CCDC6-RET fusions. Four patients had concurrent gene variability by NGS detection, including EGFR, MAP2K1, CTNNB1 and AKT1. No survival difference existed between RET-positive and negative patients (58.1 vs. 52.0 months, $P = 0.504$). The median progression-free survival of first-line pemetrexed/platinum regimen was 7.5 months for four recurrent cases.

Take home points:

- RET fusion prevalence is ~2% in Chinese lung adenocarcinoma.
- RET rearrangements are lepidic and have a lower TS level.
- Patients with RET rearranged tumors may benefit from pemetrexed-based therapy.

10. Takada, Kazuki, et al. Clinical Significance of PD-L1 Protein Expression in Surgically Resected Primary Lung Adenocarcinoma. Journal of Thoracic Oncology Vol. 11 No. 11:1879-1890

Purpose: To examine PD-L1 in surgically resected primary lung adenocarcinoma and the association of PD-L1 status with clinicopathologic features, EGFR status and outcomes.

Methods: The expression of PD-L1 protein in 417 surgically resected primary lung adenocarcinomas was evaluated by immunohistochemical analysis. The cutoff value for defining PD-L1 positivity was determined according to the histogram of proportions of PD-L1–positive cancer cells.

Results: Samples from 85 patients (20.4%) and 144 patients (34.5%) were positive for PD-L1 protein expression according to 5% and 1% PD-L1 cutoff values, respectively. Fisher's exact tests showed that PD-L1 positivity was significantly associated with male sex, smoking, higher tumor grade, advanced T status, advanced N status, advanced stage, the presence of pleural and vessel invasions, micropapillary or solid predominant histological subtypes, and wild-type EGFR. Univariate and multivariate survival analyses revealed that patients with PD-L1 positivity had poorer prognoses than those without PD-L1 protein expression at the 1% cutoff value (disease-free survival $p < 0.0001$, overall survival $p < 0.0001$).

Take home points:

- PD-L1 expression is higher in adenocarcinoma from smokers and in EGFR- tumors
- PD-L1 expression associated with poor survival

11. Thomas, Anish et al. Expression of mesothelin in thymic carcinoma and its potential therapeutic significance. Lung Cancer 101 (2016) 104-110

Purpose: We sought to determine tumor expression and serum levels of mesothelin in patients with TETs.

Methods: Tissue samples were obtained from 71 patients with histologically confirmed, unresectable advanced TETs and evaluated for mesothelin expression by immunohistochemistry. The evaluation was blinded for clinical data and outcome. Mesothelin expression and its association with clinico-pathological parameters and survival were assessed.

Results: Thymic carcinoma, thymoma, and thymic neuroendocrine tumors (NETs) accounted for 34 (48%), 29 (41%), and 8 (11%) cases respectively. Mesothelin expression was seen in a significantly larger proportion of thymic carcinoma (27/34, 79%) than thymoma (3/29, 10%) ($P < 0.0001$) and was absent in thymic NETs. Among thymic carcinomas 13/34 (38%) showed expression in nearly all tumor cells. Immunoreactivity was membranous, strong, and homogenous. Patients with thymic carcinoma and high mesothelin expression (in $>50\%$ of tumor cells) had significantly improved overall survival (median not reached, $n = 19$) compared to patients with no or low mesothelin expression.

Take home points:

- Mesothelin expression is common in thymic carcinoma, infrequent in thymoma and absent in thymic NET.
- Mesothelin may be a therapeutic target in thymic carcinoma owing to the robust membranous expression.

12. Thongprast, Sumitra et al. The prevalence of expression of MAGE-A3 and PRAME tumor antigens in East and South East Asian non-small cell lung cancer patients. Lung Cancer 101 (2016) 137-144

Purpose: To investigate the expression rates of MAGE-A3 and PRAME in tumors from East Asian NSCLC patients, and the associations between TAA expression and clinico-pathologic patient characteristics

Methods: Archived FFPE tumor tissue specimens were tested for MAGE-A3 and PRAME expression by quantitative reverse transcription polymerase chain reaction. Exploratory analyses of the impact of patient and tumor characteristics on antigen expression were performed by multivariate logistic regression analyses.

Results: A total of 377 specimens were tested and a valid expression result was obtained for 86.5% and 92.6% for MAGE-A3 and PRAME, respectively. Of the specimens with valid test results, 26.4% expressed MAGE-A3, 49.9% PRAME, 20.0% both and 57.5% expressed at least one TAA. The same pattern of associations between antigen expression and patient and tumor characteristics was found for both TAAs: higher rates of antigen-positive tumors were found in squamous cell carcinomas compared to adenocarcinomas, and for smokers compared to non-smokers.

Take home points:

- MAGE-A3 and PRAME expression suggests an association between histology and smoking status
- Both may be future therapeutic targets.

13. Toki Maria I et al. EGFR-GRB2 Protein Colocalization is a Prognostic Factor Unrelated to Overall EGFR Expression or EGFR Mutation in Lung Adenocarcinoma. Journal of Thoracic Oncology. Vol. 11 No. 11:1901-1911

Purpose: EGFR-GRB2 PLA was compared with total EGFR expression levels and mutational status in a series of tumors in patients with NSCLC, and its role as a prognostic marker was assessed in two adenocarcinoma NSCLC cohorts.

Methods: A PLA developed to detect EGFR-GRB2 interaction was measured by quantitative immunofluorescence using Automated Quantitative Analysis

technology. EGFR pathway activation was assessed in patients with NSCLC with different mutation status along with overall EGFR expression. Additionally, the PLA to detect EGFR-GRB2 interaction was evaluated as a prognostic marker in two cohorts of patients with lung adenocarcinoma.

Results: The PLA to detect EGFR-GRB2 interaction was unrelated to overall EGFR expression or mutation in a series of patients with NSCLC with known mutation status. EGFR- mutant and EGFR/KRAS wild-type tumors ($p=0.0049$) had significantly higher EGFR pathway activation compared with KRAS-mutant cases, with no significant difference shown between mutation sites. In two series of patients with lung adenocarcinoma, the PLA to detect EGFR-GRB2 interaction was independently associated with longer survival. Total EGFR protein expression alone was not correlated with outcome.

Take home point:

EGFR colocalization with GRB2 as assessed by PLA is not correlated with EGFR expression levels or mutation status, defining a patient group that may show EGFR pathway activation, as illustrated by its prognostic value

14. Viola P et al. Follicular dendritic cell tumour/sarcoma: a commonly misdiagnosed tumour in the thorax. *Histopathology* 2016, 69, 752–761.

Purpose: Present a case series that reviews the experience of clinical, imaging, and pathologic presentations of thoracic FDCCS.

Methods: Clinical, radiological and histological characteristics, including diagnosis on pre- resection material, were assessed in seven intrathoracic cases from 5 men and 2 women with a median age of 38 years.

Results: Clinical symptoms were related to mass location, six cases presenting within central and/ or posterior mediastinal compartments and one within the lungs. Positron emission tomography–computed tomography demonstrated marked FDG avidity and the prominent vessels traversing the lesions. 67% were misdiagnosed initially. HVCD was present in three cases. Two cases with high mitotic rates recurred after resection. All were positive for at least one of the follicular dendritic cell markers (CD21, CD35 and CD23). 86% show cyclin D1 expression ranging from 5% to 90%.

Take home points:

- FDCCS is often misdiagnosed on biopsy
- Often present in the central/posterior mediastinum
- Highly vascular

15. Weissferdt A et al. Ectopic Hamartomatous Thymoma—New Insights Into a Challenging Entity A Clinicopathologic and

**Immunohistochemical Study of 9 Cases. Am J Surg Pathol
2016;40:1571–1576**

Purpose: Present 9 cases of ectopic hamartomatous thymoma.

Methods: 9 cases of EHT were identified from authors files. Slides were reviewed and various stains were performed.

Results: The patients were 5 men and 4 women aged 34 to 52 years (mean, 43y). All patients presented with solitary lower neck masses ranging in size from 3.5 to 8.0 cm. Grossly, the lesions were circumscribed and lobulated masses with a fleshy white cut surface; cystic changes were identified in 3 cases. Histologically, the tumors were composed of varying proportions of spindle cells arranged in fascicles, mature adipose tissue, and an epithelial component composed of squamoid elements and glandular or ductal structures. Structures reminiscent of Hassall corpuscles were identified in 2 cases. No overt malignant changes were seen, and the mitotic activity ranged from 0 to 2 mitoses per 10 high-power fields. Immunohistochemically, the spindle cells coexpressed CK5/6, CD34, and smooth muscle actin, whereas the squamous component was positive for CK5/6 only. Bcl-2 was variably expressed in the spindle and epithelial elements, whereas Pax8 and STAT6 were uniformly negative. Clinical follow-up revealed that all patients were alive and well 2 to 5 years after diagnosis.

Take home points:

- EHTs have a wide morphologic spectrum
- Morphology and IHC are reminiscent of thymic differentiation, but are not related to thymoma.

16. Williams, Andrew S. et al. ALK+ lung adenocarcinoma in never smokers and long-term ex-smokers: prevalence and detection by immunohistochemical and fluorescence in situ hybridization. Virchows Arch (2016) 469:533-540

Purpose: To evaluate the prevalence of ALK rearrangement in non-smokers and long-term ex-smokers with lung adenocarcinoma and to assess the performance of IHC for the detection of ALK+ tumors when compared to FISH.

Methods: 251 cases of resected lung adenocarcinoma were retrospectively reviewed, including non-smokers (n=79) or long-term ex-smokers (n=172). ALK IHC and ALK FISH were performed on each case.

Results: 4 cases demonstrated ALK rearrangement by FISH. All cases were non-smokers (4/79; 5.1 %), and all were positive for ALK by IHC. No additional cases were considered positive by IHC, and only 26 (10.4 %)

cases were considered equivocal using a conservative approach to interpretation, resulting in a sensitivity of 100 % and specificity of 89.5 %. ALK rearrangement was not observed in lung adenocarcinoma arising in long-term ex-smokers, whereas it is seen in up to 5.1 % of lifetime non-smokers.

Take home point:

ALK IHC using the 5A4 antibody demonstrates high sensitivity, supporting its use as a screening test.

17. Yanagawa, Naoki et al. The Clinical Impact of Solid and Micropapillary Patterns in Resected Lung Adenocarcinoma. Journal of Thoracic Oncology. Vol. 11 No. 11:1976-1983

Purpose: To investigate the proportion of S and MP patterns in patients with resected lung ADC and validated the relationship between their proportion and the clinicopathological backgrounds, including outcomes.

Methods: A total of 531 ADCs were examined. We classified the patients into five subgroups according to the proportion of S and/or MP patterns: (1) both patterns absent (S-/MP-), (2) S predominant (S pre), (3) MP predominant (MP pre), (4) S pattern present although not predominant and MP pattern absent (Sp not pre/MP-), and (5) MP pattern present although not predominant (MPp not pre).

Results: Of the 531 ADCs, 384 (72.3%) were classified as S-/MP-, 55 (10.4%) as S pre, 11 (2.1%) as MP pre, 42 (7.9%) as Sp not pre/MP-, and 39 (7.3%) as MPp not pre. In a univariate analysis, the recurrence-free survival (RFS) and overall survival differed significantly among the five subgroups ($p < 0.01$ and $p < 0.01$, respectively). In a multivariate analysis, patients with S-/MP- had significantly higher RFS rates than did those with other subgroups. On the other hand, patients with MP pre had lower RFS rates than did those with other subgroups.

Take home point:

Patients with S and/or MP have worse prognosis (even if not predominate)

Non-neoplastic

- 1. Cottin V et al. Respiratory manifestations of eosinophilic granulomatosis with polyangiitis (Churg–Strauss) . Eur Respir J 2016; 48: 1429–1441**

Purpose: To study the respiratory manifestations of EGPA.

Methods: All institutional cases of EGPA were collected at multiple centers. Criteria included asthma, eosinophilia, and at least one new onset extra-bronchopulmonary organ involved.

Results: The study population included 157 patients (mean±SD age 49.4±14.1 years), with a mean±SD blood eosinophil count of 7.4±6.4×10⁹ L⁻¹ at diagnosis. There was a mean±SD of 11.8±18.2 years from the onset of asthma to the diagnosis of EGPA, of 1.4±8.4 years from the first onset of peripheral eosinophilia to the diagnosis of EGPA, and of 7.4±6.4 years from EGPA diagnosis to the final visit. Despite inhaled and oral corticosteroid treatment, the severity of asthma increased 3–6 months before the onset of the systemic manifestations. Asthma was severe in 57%, 48%, and 56% of patients at diagnosis, at 3 years, and at the final visit, respectively. Persistent airflow obstruction was present in 38%, 30%, and 46% at diagnosis, at 3 years, and at the final visit, respectively.

Take home point:

In this population, asthma is severe, and antedates systemic manifestations by a mean of 12 years, and progresses to long-term persistent airflow obstruction despite corticosteroids in a large proportion of patients, which affects long-term management and morbidity.

2. Hutchinson et al. Surgical lung biopsy for the diagnosis of interstitial lung disease in England: 1997–2008. Eur Respir J 2016; 48: 1453–1461.

Purpose: To assess the risk of surgical lung biopsy in a cohort of patients with ILD.

Methods: Statistics data were gleaned from 1997 to 2008 to assess the frequency of surgical lung biopsy for ILD in England, UK. Cardiothoracic surgical patients using ICD-10 codes for ILD and OPCSCIP version 4 codes for surgical lung biopsy. Those with lung resections or lung cancer were excluded. In-hospital, 30-day and 90-day mortality following the procedure were estimated, and linked to cause of death using data from the UK Office of National Statistics.

Results: 2820 patients with ILD undergoing surgical lung biopsy were identified during the 12-year period. The number of biopsies increased over the time period studied. In-hospital, 30-day and 90-day mortality were 1.7%, 2.4% and 3.9%, respectively. Male sex, increasing age, increasing comorbidity and open surgery were risk factors for mortality.

Take home point:

- Surgical biopsy for ILD has a similar mortality to lobectomy for lung cancer

Reviews

1. Boussiotis, Vassiliki. Molecular and Biochemical Aspects of the PD-1 Checkpoint Pathway. N Engl J Med 2016;375:1767-78.

Purpose: To review the current state and understanding of the receptor PD-1.

Take home points:

- Nice review in a high impact journal – good to know about this.
- There are several nice images in here that outline the molecular pathways of PD-1/PD-L1.

2. Bubendorf, Lukas et al. Testing for ROS1 in non-small cell lung cancer: a review with recommendations. Virchows Arch (2016) 469:489-503

Purpose: To review the current state and understanding of the ROS1 in NSCLC.

Take home points:

- ROS1 fusion proteins comprise one of three oncogenic drivers for which there is approved targeted therapy
- Detection methods include break apart FISH, IHC and non-in situ methods
- Because of false(+) in both IHC and FISH, a second confirmation strategy is recommended (like targeted NGS)
- Authors propose testing EGFR, ALK and ROS in parallel in NSCLC

3. Casagrande, Arianna, et al. Association between Congenital Lung Malformations and Lung Tumors in Children and Adults: A Systematic Review. Journal of Thoracic Oncology. Vol 11 No. 11:1837-1845

Purpose: To review cases in which lung tumors associated with congenital lung malformations in pediatric and adult populations.

Findings & Take home points:

- 134 publications reviewed, including 168 patients with CPM and lung tumor
- Pleuropulmonary blastoma was most common in children and adenocarcinoma in adults
- CPMs should be followed up and carefully examined to ensure they don't conceal tumor – even in adulthood.

4. Facchinetti, Francesco, et al. Moving Immune Checkpoint Blockade in Thoracic Tumors beyond NSCLC. Journal of Thoracic Oncology Vol. 11 No. 11:1819-1836

Purpose: To review the biological and clinical rationale for immune checkpoint inhibition in SCLC, MPM, and TETs and present preliminary clinical results with available antibodies.

Take home points:

- A number of immune checkpoint blockers CTLA-4 and PD-1/PD-L1 have shown valuable as single or combination agents in patients with SCLC and MPM
- More phase III trials needed.

5. Nakahira, Kiichi et al. Autophagy in Pulmonary Diseases. American Journal of Respiratory and Critical Care Medicine. Volume 194 Number 10. November 15, 2016.

Purpose: To summarize the current understanding of the regulation and function of autophagy, with an emphasis on the importance of selective autophagy in the pathogenesis of lung diseases and its therapeutic targets

Take home points:

- Autophagy is involved in the pathogenesis of various pulmonary diseases and models thereof
- In the last 5 years, there has been great advances in the role that autophagy plays in COPD, cancer and pneumonia.
- Autophagy is a candidate for a therapeutic target and should be investigated as such.

6. Raparia, Kirtee et al. Transbronchial Lung Cryobiopsy for Interstitial Lung Disease Diagnosis. A Perspective From Members of the Pulmonary Pathology Society. Arch Pathol Lab Med-Vol 140, November 2016

Purpose: The authors seek to provide clarity on the topic and role of cryobiopsy in the diagnosis of ILD.

Findings & Take home points:

- Emerging data on cryobiopsy for ILD are encouraging
- The modality is useful for those that are considered to high risk for surgical biopsy
- Cryobiopsy is not sufficient to replace surgical biopsy at this point, with the limited available data

- Prospective studies demonstrating comparable diagnostic accuracy of the 2 procedures in the multidisciplinary context are needed, although the practical difficulty of performing these studies may be a limiting factor

7. Ritter JH et al. Pulmonary and pleural pathology: Contributions of Dr. Louis “Pepper” Dehner. Sem Diagn Pathol 33 (2016) 450–461.

Purpose: To review the life work of Dr. Dehner as it pertains to pulmonary and pleural pathology

Take home points:

- Nice review

8. Roy-Chowdhuri, Sinchita et al. Biomarker Testing in Lung Carcinoma Cytology Specimens. A Perspective From Members of the Pulmonary Pathology Society. Arch Pathol Lab Med. 2016;140:1267-1272

Purpose: To review steps and strategies for biomarker testing in pulmonary cytology specimens.

Take home points:

- Nice table is provided for review

Case Reports / Letters to the Editor / Editorials

- 1. Cottin V. Lung biopsy in interstitial lung disease: balancing the risk of surgery and diagnostic uncertainty . Eur Respir J 2016; 48: 1274–1277**
- 2. Gray, Steven, et al. PD-L1 as a Companion Biomarker for Immune Checkpoint Inhibitors in NSCLC: Should RNA ISH (RISH) Be Considered? Letter to the Editor. Journal of Thoracic Oncology. Vol. 11 No. 11:143**
- 3. Klinger JR. Plasma nitrite/nitrate levels: a new biomarker for pulmonary arterial hypertension? Eur Respir J 2016; 48: 1265–1267**
- 4. Miller, Ross A. et al. PD-1//PD-L1, Only a Piece of the Puzzle. Arch Pathol Lab Med-Vol 140, November 2016**
- 5. Todd, Nevins W et al. Microscopic organizing pneumonia and cellular non-specific interstitial pneumonia are widespread in macroscopically normal-appearing lung tissue in idiopathic pulmonary fibrosis. The Journal of Heart and Lung Transplantation, Vol 35, No 11, November 2016**

6. **Viola et al. Dieulafoy's disease of the airways: a comprehensive review of a rare entity. *Histopathology* 2016 69(5), 883-897.**