Pulmonary Pathology Journal Club (January 2017)
Articles from December 2016

ARTICLE INDEX

Kim Y, et al. Overexpression of β-Catenin and Cyclin D1 is Associated with Poor Overall Survival in Patients with Stage IA-IIA Squamous Cell Lung Cancer Irrespective of Adjuvant Chemotherapy. J Thorac Oncol. 2016 Dec;11(12):2193-2201.

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ARTICLES FOR DISCUSSION

Davidson B. CD24 is highly useful in differentiating high-grade serous carcinoma from benign and malignant mesothelial cells. Hum Pathol. 2016 Dec;58:123-127.

Purpose: Ovarian serous carcinoma and malignant mesothelioma have overlapping morphologies and immunoprofiles. The goal of this study is to establish the utility of CD24 as a marker in the differential diagnosis of ovarian serous carcinoma and malignant mesothelioma. This IHC stain was identified based on prior gene expression analysis on effusion specimens by the same researchers.

Methods:

IHC: CD24 (clone SN3b; mouse monoclonal, Thermo Fisher Scientific)

Staining extent graded semiquantitatively (0-4): 0=None; 1=1-5%; 2=6-25%; 3=26-75%; 4=76-100%

Effusions and Surgical Specimens were tested:

Cohort	**Effusion (type not specified)**		**Surgical (via Tissue Microarray)**		
	Total	*Tumor Types*	*Total*	*Tumor Type*	*Tumor location*
Ovarian Carcinoma	116	100 HGSC 12 clear cell 4 endometrioid	117	96 HGSC 9 LGSC 10 clear cell 2 endometrioid	43 ovarian 74 extra-ovarian
Malignant Mesothelioma (MM)	36	Epithelioid or biphasic (not quantified)	65	49 epithelioid 13 biphasic 3 sarcomatoid	47 pleura 18 peritoneal
Breast Carcinoma (comparative)	54	44 IDC 2 lobular 2 mixed mammary 6 unavailable	--	--	--
Total	206		182		

HGSC/LGSC=High grade/Low grade serous carcinoma

Results:

Membranous staining (as expected)

Effusions ($p<0.001$ for all analyses, multi- and univariate analysis):

- 91% ovarian carcinomas (all types, n=116)
- 30% breast carcinomas (n=54)
- 0% MM (n=36)
- Reactive mesothelial cells were negative

Tissue ($p<0.001$):

- 46% ovarian carcinomas (n=117)
- 3% MM (n=65), both showed focal (<5%) staining; one biphasic, one sarcomatoid

Table CD24 immunostaining results

Diagnosis	CD24 staining extent				
	0%	1%-5%	6%-25%	26%-75%	76%-100%
OC effusions (n = 116)					
HGSC (n = 100)	6	39	19	28	8
CCC (n = 12)	3	5	2	2	0
EC (n = 4)	0	3	1	0	0
BC effusions (n = 54)	38	8	2	4	2
MM effusions (n = 36)	36	0	0	0	0
OC surgical specimens (n = 117)	63	39	11	4	0
MM surgical specimens (n = 65)	63	2	0	0	0

Abbreviations: OC, ovarian carcinoma; HGSC, high-grade serous carcinoma; CCC, clear cell carcinoma; EC, endometrioid carcinoma; BC, breast carcinoma; MM, malignant mesothelioma.

Take home points:

Traditional MM markers (WT1, D2-40, CK5/6) overlap significantly with that of ovarian carcinomas, necessitating the need for other IHC antibodies to assist with the differential

CD24 is among other "newer" antibodies, including:

- PAX8 (positive in majority of HGSC, but mostly absent in MM)
- PAX2 (sensitivity for serous carcinoma inferior to PAX8, at 56%-61%)
- Claudin 4 (performed well in MM vs carcinoma, 100% sens and 94% spec)
- BAP1 loss (more prevalent in MM vs serous carcinoma)

More robust in effusions than in tissue resections, both peritoneal and pleural

- Could the TMA methodology have contributed to this result?

Requires specific differential in specific specimen type to be of utility

- Given the high number of breast cancers staining, one would have to only use it in very specific clinical scenario, but performs well in this context
- Effusions > Surgical specimens

Hashisako M, et al. Interobserver Agreement of Usual Interstitial Pneumonia Diagnosis Correlated With Patient Outcome. Arch Pathol Lab Med. 2016 Dec;140(12):1375-1382.

Purpose: The 2002 histopathologic criteria for IPF were revised in the ATS/ERS/JRS/ALAT guidelines in 2011. The objective of this study was to examine whether the revised histopathologic criteria for IPF improved interobserver agreement among pathologists and the predicted prognosis in patients with interstitial pneumonia.

Methods:

- Twenty consecutive surgical lung biopsy specimens from cases of interstitial pneumonia were examined for histologic patterns by 11 pathologists without knowledge of clinical and radiologic data.

- Diagnosis was based on 2002 and 2011 ATS/ERS criteria.

- Pathologists were grouped by cluster analysis, and interobserver agreement and association to the patient prognosis were compared with the diagnoses for each cluster.

Results:

- The generalized kappa coefficient of diagnosis for all pathologists was 0.23.

- If the diagnoses were divided into 2 groups: UIP/probable UIP (the UIP group) or possible/not UIP (the non-UIP group), according to the 2011 guidelines, the kappa value improved to 0.37.

- When pathologists were subdivided into 2 clusters, only 1 showed an association between UIP group diagnosis and patient prognosis ($P < .05$).

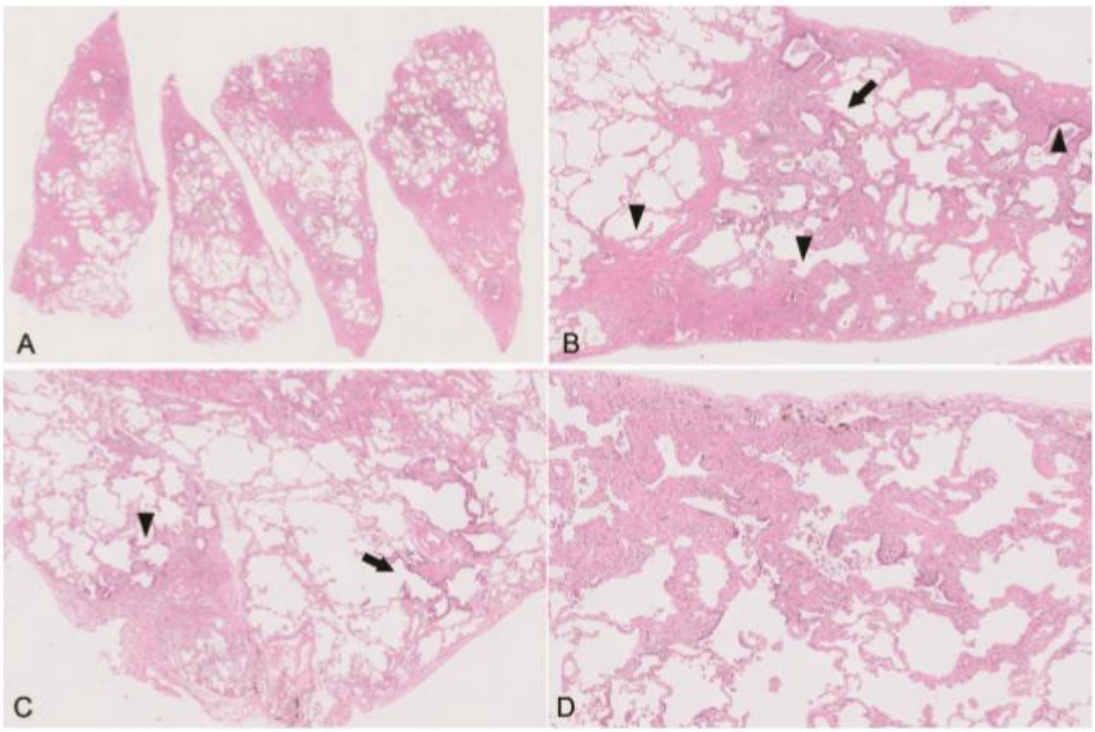

Figure 5. *Case with low interobserver agreement. This case was classified as usual interstitial pneumonia (UIP) by 6 pathologists (55%) and as non-UIP by 5 pathologists (45%). The major reason for making a diagnosis of non-UIP was a judgment of predominantly airway-centered change. A, Low magnification shows patchy, dense fibrosis. B and C, There are areas showing a mixture of peripheral, accentuated fibrosis (arrowheads) and airway-centered (arrows) fibrosis. D, Some areas show hyalinized fibrosis of uncertain distribution (hematoxylin-eosin, original magnifications ×5 [A] ×20 [B and C], and ×50 [D]).*

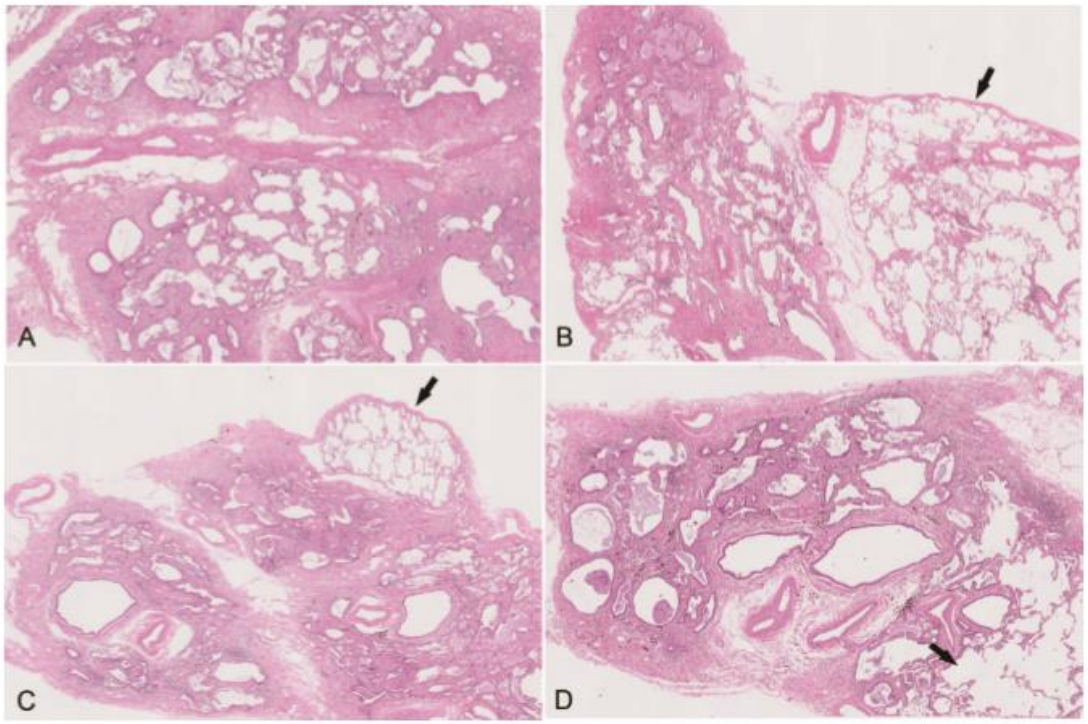

Figure 6. *Another case with low interobserver agreement. This case was classified as usual interstitial pneumonia (UIP) by 5 pathologists (45%) and as non-UIP by 6 pathologists (55%). The major reason for making a diagnosis non-UIP was a judgment for an alternative diagnosis of nonspecific interstitial pneumonia. A, Major histologic findings are diffuse, dense fibrosis with microscopic honeycombing. B through D, Mixture of fibrotic areas and normal-looking areas (arrows) are shown. Fibroblastic foci is inconspicuous (hematoxylin-eosin, original magnifications ×10 [A through C], and ×20 [D]).*

Take home points:

- Agreement about pathologic diagnosis of fibrotic IPs is poor, even among pulmonary pathologists (no surprise here).
- 2011 criteria did not improve agreement compared to 2002 criteria (also no surprise).
- Agreement is modestly improved with simplification into two (UIP and non-UIP) groups, but is still only "fair" (again, no surprise).
- The most frequent reason for disagreement was inconsistent judgment of airway-centered changes and cellular interstitial pneumonia away from honeycombing.
- It sure would be good to have better biomarkers! Otherwise, we may never get any better at subclassifying these disorders in an accurate, reproducible, and clinically meaningful fashion.

Kadota K, et al. KRAS Mutation Is a Significant Prognostic Factor in Early-stage Lung Adenocarcinoma. Am J Surg Pathol. 2016 Dec;40(12):1579-1590.

Purpose: The potential clinical impact of KRAS and epidermal growth factor receptor (EGFR) mutations has been investigated in lung adenocarcinomas; however, their prognostic value remains controversial. The authors investigated the prognostic significance of driver mutations using a large cohort of early-stage lung adenocarcinomas.

Methods: Cases of surgically resected solitary lung adenocarcinomas were reviewed that were pathologic early-stage and lymph node–negative (1995 to 2005; stage I/II=463/19). Tumors were classified according to the IASLC/ATS/ERS classification and genotyped by Sequenom MassARRAY system and PCR– based assays. In stage I disease, the Kaplan-Meier method and cumulative incidence of recurrence analyses were used to estimate the probability of overall survival (OS) and recurrence, respectively.

Results:

- Of 482 patients, mutations included:
    - 129 (27%) KRAS
    - 86 (18%) EGFR
    - 8 (2%) BRAF
    - 8 (2%) PIK3CA
    - 4 (1%) NRAS
    - 1 (0.2%) AKT1

- EGFR L858R mutation correlated with lepidic predominant histology.
- Exon 19 deletion correlated with acinar predominant histology.

- EGFR mutations were not detected in invasive mucinous adenocarcinomas.

- The 5-year OS of patients with KRAS-mutant tumors was significantly worse (n=124; 5-year OS, 63%) than those with KRAS wild-type (n=339; 77%; P<0.001).

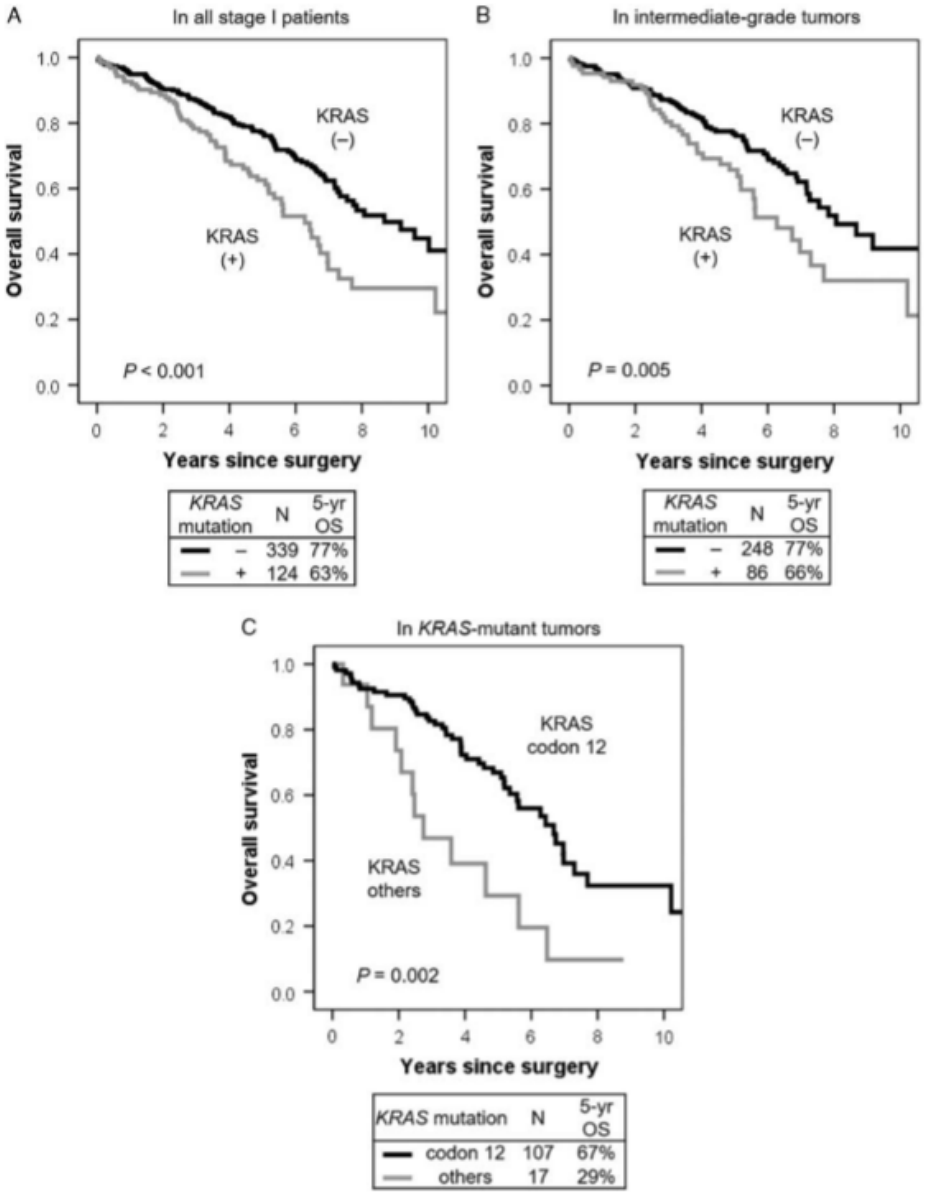

FIGURE 1. *KRAS* mutation associations with OS. A, 5-year OS of patients with *KRAS*-mutant tumors was significantly worse (n = 124; 5-y OS, 63%) than those with *KRAS* wild-type tumors (n = 339; 77%; $P < 0.001$). B, In architecturally intermediate-grade tumors (acinar predominant and papillary predominant subtypes), 5-year OS of patients with *KRAS*-mutant tumors was significantly worse (n = 86; 5-y OS, 66%) than those with *KRAS* wild-type tumors (n = 248; 77%; $P = 0.005$). C, 5-year OS of patient with *KRAS* codon 12 mutated tumors were significantly better (n = 107; 5-y OS, 67%) than those with other *KRAS*-mutant tumors (n = 17; 29%; $P = 0.002$).

- In solid predominant tumors, KRAS mutations correlated with worse OS (P=0.008) and increased risk of recurrence (P=0.005).

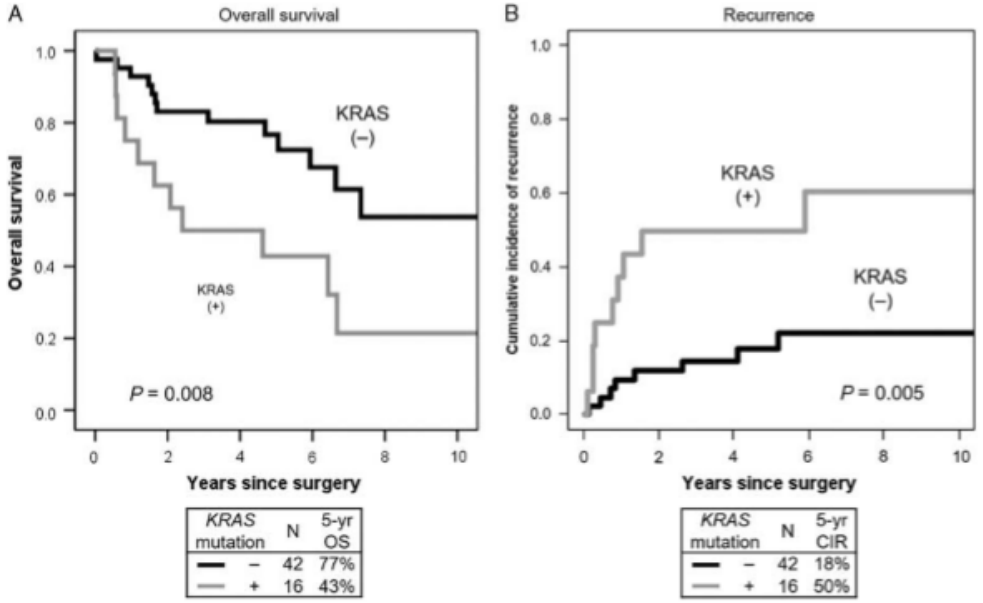

FIGURE 2. *KRAS* mutation associations with OS and CIR in solid predominant tumors. A, In solid predominant tumors, 5-year OS of patients with *KRAS*-mutant tumors was significantly worse (n = 16; 5-y OS, 43%) than those with *KRAS* wild-type (n = 42; 77%; $P = 0.008$). B, In solid predominant tumors, 5-year CIR of patients with *KRAS*-mutant tumors was significantly higher (5-y OS, 50%) than those with *KRAS* wild-type tumors (18%; $P = 0.005$).

- On multivariate analysis, KRAS mutation was an independent prognosticator of OS in all patients (hazard ratio, 1.87; P<0.001) and recurrence in solid predominant tumors (hazard ratio, 4.73; P=0.012).

TABLE 6. Multivariate Analyses

Variables	HR	95% CI	*P*
For OS			
Age (y)			
> 65 vs. ≤65	1.78	1.24-2.55	**0.002**
Sex			
Male vs. female	1.73	1.26-2.36	**0.001**
Surgery			
Limited resection vs. lobectomy	2.31	1.62-3.29	**< 0.001**
Pathologic stage			
IB vs. IA	1.40	1.02-1.93	**0.039**
Vascular invasion			
Positive vs. negative	1.45	1.04-2.01	**0.027**
KRAS mutation			
Mutant vs. wild-type	1.87	1.36-2.58	**< 0.001**
For disease recurrence			
Sex			
Male vs. female	1.63	0.98-2.71	0.058
Smoking			
Ever vs. never	1.31	0.61-2.81	0.49
Necrosis			
Present vs. absent	1.27	1.14-1.41	**< 0.001**
Pathologic stage			
IB vs. IA	1.81	1.1-2.97	**0.019**
KRAS mutation			
Mutant vs. wild-type in solid predominant tumors	4.73	1.41-15.9	**0.012**
Mutant vs. wild-type in nonsolid predominant tumors	0.91	0.49-1.66	0.75

Significant *P*-values are shown in bold.

Take home points:

- In patients with resected stage I lung adenocarcinomas, KRAS mutation was an independent prognostic factor for OS and recurrence, especially in solid predominant tumors.

Newton CA, et al. Telomere-related lung fibrosis is diagnostically heterogeneous but uniformly progressive. Eur Respir J. 2016 Dec;48(6):1710-1720.

Purpose:

Telomere shortening has been implicated in the pathogenesis of IPF. Six telomere-related genes (TERT, TERC, RTEL1, PARN, DKC1 and TINF2) so far have been linked to familial pulmonary fibrosis (FPF). The authors sought to test the hypothesis that patients with pulmonary fibrosis due to heterozygous genetic mutations in TERT, TERC, RTEL1 or PARN share a common clinical phenotype (IPF) and a progressive clinical course.

Methods:

- Observational cohort study of patients with FPF identified at single center and referrals.

- Genomic DNA extraction and telomere length measured from circulating leukocytes.
- Available HRCT chest reviewed by a chest radiologist and available surgical specimens reviewed by a pulmonary pathologist, both blinded to clinical and molecular data.
- Statistical analysis on characteristics, PFTs, and transplant-free survival.

Results:

- 115 patients (from 64 families) with mutation in telomere shortening genes: TERT (n=75), TERC (n=7), RTEL1 (n=14) and PARN (n= 19); no DKC1 or TINF2.
- Mean age of Dx of genetic groups: TERC(51y)<TERT(58y)<RTEL1(61y)<PARN(64y).
- Orders of mean telomere lengths of genetic groups: TERC<TERT<RTEL1<PARN.
- Leucopenia, thrombocytopenia, aplastic anemia/MDS more often in TERC.
- Genetic anticipation seen in carriers of TERT and RTEL1.
- In 15 different families with MDD diagnosis made for ⩾2 affected family members, a discordant diagnosis was seen across affected individuals in 12 (80%) families and a concordant diagnosis of IPF was found for three (20%) families.
- No statistically significant difference in histopathological patterns across subjects with different genetic mutations.
- No difference in transplant-free survival across mutations or IPF vs non-IPF diagnoses

	Total	*TERT*	*TERC*	*RTEL1*	*PARN*
Subjects n	115	75	7	14	19
Age at diagnosis mean±SD years	58±10	58±10	51±11	60±11	64±8
Male	58 (50.4)	40 (53.3)	1 (14.3)	8 (57.1)	9 (47.4)
Diagnosis n	77	54	5	10	8
IPF	35 (45.5)	27 (50)	1 (20)	3 (30)	4 (50)
NSIP	2 (2.6)	2 (3.7)	0 (0)	0 (0)	0 (0)
DIP	1 (1.3)	1 (1.9)	0 (0)	0 (0)	0 (0)
PPFE	8 (10.4)	5 (9.3)	1 (20)	2 (20)	0 (0)
Unclassifiable	15 (19.5)	9 (16.7)	1 (20)	3 (30)	2 (25)
Chronic hypersensitivity pneumonitis	9 (11.7)	6 (11.1)	1 (20)	1 (10)	1 (12.5)
CTD-ILD	2 (2.6)	1 (1.9)	1 (20)	0 (0)	0 (0)
IPAF	5 (6.5)	3 (5.6)	0 (0)	1 (10)	1 (12.5)

Gene	Mutation	Multidisciplinary diagnoses of family members with ILD
Concordant		
TERT	p.Thr874Arg	IPF, IPF
TERT	p.His925Gln	IPF, IPF
TERT	p.Gly1063Ser	IPF, IPF
Discordant		
TERT	p.Val144Met	PPFE, chronic hypersensitivity pneumonitis, unclassifiable
TERT	p.Arg486Cys	IPF, IPAF
TERT	p.Arg631Gln	IPF, PPFE
TERT	p.Pro702Leu	IPF, IPF, unclassifiable
TERT	p.Arg865His	IPF, IPF, IPF, DIP, unclassifiable
TERT	p.Arg951Trp	PPFE, IPF
TERT	p.Leu1019Phe	Chronic hypersensitivity pneumonitis, IPAF
TERC	r.182g>c	Chronic hypersensitivity pneumonitis, PPFE
RTEL1	p.Gly201GlufsX15	IPF, IPAF
RTEL1	p.Pro484Leu	Unclassifiable, IPF
RTEL1	p.Gln669X	Chronic hypersensitivity pneumonitis, PPFE
PARN	c.246–2A>G	Unclassifiable, IPAF

Take home points:

- Telomere-related lung fibrosis appears to be a uniformly progressive fibrotic ILD irrespective of the fibrotic patterns.

ARTICLES FOR NOTATION

Neoplastic

He P, et al. Diagnosis of lung adenocarcinoma in situ and minimally invasive adenocarcinoma from intraoperative frozen sections: an analysis of 136 cases. J Clin Pathol. 2016 Dec;69(12):1076-1080.

Purpose: To determine the diagnostic accuracy and contraindications for intraoperative diagnosis of lung adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) from frozen sections.

Methods: A retrospective analysis of data from 136 patients pathologically diagnosed with early-stage (T1N0M0) AIS or MIA from paraffin-embedded sections. The rate of concordance between the diagnoses from intraoperative frozen sections and paraffin-embedded sections was determined, and the interpretive features that contributed to errors and deferrals in frozen-section diagnoses were identified.

Results: Of the 136 patients, diagnoses from frozen sections and paraffin-embedded sections were concordant in 86 (63.24%) cases intraoperatively

diagnosed with AIS or MIA, and 44 (32.35%) cases were intraoperatively diagnosed with adenocarcinoma as the range of infiltration could not be determined from the frozen sections. From the remaining six (4.41%) cases, the frozen section and paraffin-embedded section diagnoses were discordant. The reasons for frozen section errors and deferrals included larger tumor volume, tumor located close to the visceral pleura, interstitial inflammation or fibrosis, absence of prominent atypia, and differential morphology in the deeper levels of the paraffin block.

Take home points:

- Diagnosis of AIS and MIA from intraoperative frozen sections is feasible in many cases.

Ibrahim M, et al. ALK Immunohistochemistry in NSCLC: Discordant Staining Can Impact Patient Treatment Regimen. J Thorac Oncol. 2016 Dec;11(12):2241-2247.

Purpose: To gauge the quality and variability of anaplastic lymphoma kinase (ALK) IHC among laboratories in numerous countries.

Methods: Unstained tissue and cell line samples were distributed on a quarterly basis to participating laboratories from 30 countries. Participants stained the slide using their routine diagnostic ALK IHC method and returned the slide along with their in-house control and methodology details. Slides were assessed by a team of pathologists and scientists.

Results: Overall, there was a mean pass rate of 83% (range 71%-98%), with 38 variations in staining protocol. Methods included the following: the Roche D5F3 assay (65% of users, pass rate 93%); Novocastra 5A4 (15% of users, pass rate 65%); Cell Signaling Technology D5F3 (7% of users, pass rate 91%), and Dako ALK1 (5% of users, pass rate 50%). Choice of methodology directly affected final interpretation of distributed ALK-positive and ALK-negative NSCLC cases, which were correctly identified by 89% and 88% of participants, respectively. Antibody detection method was a contributing factor in false-negative staining results. The choice of laboratory controls was found to be unsuitable, and as such, in-house control recommendations are also provided.

Take home points:

- ALK IHC may be adversely affected by inadequate staining methods, which has a direct impact on final interpretation.
- As with any other type of laboratory or IHC assay, external assessment helps provide laboratories with continued confidence in their ALK IHC testing.

Ilie M, et al. PD-L1 expression in basaloid squamous cell lung carcinoma: Relationship to PD-1(+) and CD8(+) tumor-infiltrating T cells and outcome. Mod Pathol. 2016 Dec;29(12):1552-1564.

Purpose: To determine the expression pattern of PD-L1 and the presence of CD8+ and PD-1+ tumor-infiltrating T cells in the basaloid variant of squamous cell carcinoma.

Methods: Immunohistochemistry analysis of PD-L1 expression, with three recently validated monoclonal antibodies used in clinical trials (clones SP142, SP263, and 28-8), and detection of CD8+ and PD-1+ tumor-infiltrating T cells was performed on whole-tissue sections from 56 patients following surgery for basaloid squamous cell carcinoma. Data were correlated to clinicopathological parameters and outcome.

Results: Fair to poor concordance was observed between the SP142 vs SP263 clones, and SP142 vs 28-8 (κ range, 0.018–0.412), while the 28-8 and SP263 demonstrated a strong correlation in both the tumor cell and immune cell compartments (κ=0.883, and κ=0.721). Expression of PD-L1 correlated with a high content of CD8+ and PD-1+ tumor-infiltrating T cells when using SP142 (P=0.012; P=0.022), but not with SP263 or 28-8 (P=0.314; P=0.611). In the multivariate analysis, they found significantly better disease-free and overall survival rates for high PD-L1 expression with SP142, CD8+ and PD-1+ tumor-infiltrating T cells (P=0.003; P=0.007). No significant prognosis value was observed for SP263 and 28-8 clones, except a correlation between improved overall survival and SP263 in the univariate analysis (P=0.039), not confirmed in the multivariate model.

Take home points:

- Expression of PD-L1 and the content of CD8+ and PD-1+ tumor-infiltrating T cells is an independent indicator of better outcome in basaloid squamous cell carcinoma patients, although the observed effect is dependent on the PD-L1 antibody clone used.

Kim S, et al. PD-L1 expression is associated with epithelial-to-mesenchymal transition in adenocarcinoma of the lung. Hum Pathol. 2016 Dec;58:7-14.

Purpose: To investigate the association between PD-L1 expression and EMT phenotype in pulmonary adenocarcinoma (pADC).

Methods: Immunohistochemistry for E-cadherin (epithelial marker), ZEB1, SNAIL, SLUG, vimentin (mesenchymal markers), PD-L1, CD8, and PD-1 was performed on 477 cases of pADC. Cases were classified into epithelial, mesenchymal, epithelial-mesenchymal, and unspecified types based on immunohistochemical results.

Results: PD-L1 expression was scored as 0 in 14.0% (n=67), 1 in 26.4% (n=126), 2 in 51.2% (n=244), and 3 in 8.4% (n=40). PD-L1 score was positively correlated with SNAIL and vimentin H scores (P<.001, both). After dichotomizing patients into PD-L1-negative and PD-L1-positive groups, PD-L1 positivity was significantly higher in patients with mesenchymal (71.2%; 84/118) and epithelial-mesenchymal (62.7%; 84/134) phenotypes compared with those with epithelial (50.6%; 44/87) and unspecified (50.0%; 35/70) phenotypes (P=.005). The significant association between PD-L1 expression and EMT phenotype was maintained in EGFR-mutated pADCs. Moreover, cases with EMT phenotype (ie, mesenchymal and epithelial-mesenchymal) were infiltrated by higher numbers of CD8+ and PD-1+ cells than those with epithelial and unspecified phenotypes in EGFR-mutated pADCs (P=.043 for CD8+ cells and P<.001 for PD-l+ cells). Particularly, cases with EMT phenotype and PD-L1 expression showed the greatest amount of CD8+ and PD-1+ cells in EGFR-mutated cases (P=.043 for CD8+ cells and P=.005 for PD-1+ cells).

Take home points:

- EMT phenotype is related to PD-L1 overexpression in pADC cells.
- Patients with EMT-phenotype pADC may benefit from PD-1/PD-L1-blocking immunotherapy.

Kim Y, et al. Overexpression of β-Catenin and Cyclin D1 is Associated with Poor Overall Survival in Patients with Stage IA-IIA Squamous Cell Lung Cancer Irrespective of Adjuvant Chemotherapy. J Thorac Oncol. 2016 Dec;11(12):2193-2201.

Purpose: To understand the association of β-catenin and cyclin D1 overexpression on overall survival and response to adjuvant chemotherapy in patients with early-stage NSCLC.

Methods: Expression of β-catenin and cyclin D1 was analyzed retrospectively using immunohistochemistry in formalin-fixed paraffin-embedded tissues from 576 patients with early-stage NSCLC.

Results: The median duration of follow-up was 5.1 years. Overexpression of β-catenin and cyclin D1 was found in 56% and 50% of 576 cases, respectively. Overexpression of β-catenin and cyclin D1 was significantly associated with poor overall survival (p = 0.003 and p = 0.0009, respectively; log rank test) in squamous cell carcinomas, not in adenocarcinomas. The prognostic significance of each protein in the squamous cell carcinomas was limited to stages IA, IB, and IIA. In addition, simultaneous overexpression of β-catenin and cyclin D1 in the squamous cell carcinomas synergistically increased hazard ratios (HRs) 15.79 (95% confidence interval [CI] = 1.09-51.23; p =0.04) for stage IA, 10.30

(95% CI = 2.29-46.41; p = 0.002) for stage 1B, and 3.55 (95% CI = 1.22-10.36; p = 0.02) times for stage 2A compared to those without overexpression of the two proteins, after adjusting for confounding factors. In addition, the effect was not dependent on adjuvant chemotherapy.

Take home points:

- Simultaneous overexpression of β-catenin and cyclin D1 may be associated with poor overall survival irrespective of platinum-based adjuvant chemotherapy in stage IA-IIA squamous cell carcinoma of the lung.

Liu L, et al. Ciliated Muconodular Papillary Tumors of the Lung Can Occur in Western Patients and Show Mutations in BRAF and AKT1. Am J Surg Pathol. 2016 Dec;40(12):1631-1636.

Purpose: Ciliated muconodular papillary tumors (CMPTs) have previously only been reported in East-Asian patients, and bear alterations in BRAF and EGFR genes in some cases, supporting their neoplastic nature. However, they haven't been reported before in the West.

Methods: The authors report 4 cases of morphologically typical CMPT in Western patients.

Results: CMPT occurred in 1 man (60y) and 3 women (71 to 83y). Interestingly, 1 case occurred in background of pronounced small airway disease with necrotizing bronchiolitis and multiple carcinoid tumorlets. They further analyzed 1 tumor using a 50 gene next-generation sequencing oncology panel that identified 2 pathogenic mutations (BRAF V600E and AKT1 E17K).

Take home points:

- CMPT can occur in Western (non-Asian) patients.
- BRAF V600E mutation as a probable driver in a subset of these tumors, along with AKT1 mutation, which further supports the notion that CMPT is a neoplasm and not just a hamartomatous lesion.

Mansuet-Lupo A, et al. Intratumoral Immune Cell Densities Are Associated with Lung Adenocarcinoma Gene Alterations. Am J Respir Crit Care Med. 2016 Dec 1;194(11):1403-1412.

Purpose: To determine whether the tumoral immune environment is related to lung adenocarcinoma mutations.

Methods: This retrospective cohort included 316 consecutive patients with lung adenocarcinoma (225 men; 258 smokers) studied from 2001 to 2005 in a single center. The authors investigated the association of densities of intratumoral

mature dendritic cells (mDCs), CD8+ T cells, neutrophils, and macrophages with clinical and pathological variables and tumor cell mutation profiles obtained by next-generation sequencing.

Results: In 282 tumors, the authors found 460 mutations, mainly in TP53 (59%), KRAS (40%), STK11 (24%), and EGFR (14%). Intratumoral CD8+ T-cell density was high in smokers (P=0.02) and TP53-mutated tumors (P=0.02) and low in BRAF-mutated tumors (P=0.005). Intratumoral mDC density was high with low pathological tumor stage (P=0.01) and low with STK11 mutation (P=0.004). Intratumoral neutrophil density was high and low with BRAF mutation (P=0.04) and EGFR mutation (P=0.02), respectively. Intratumoral macrophage density was low with EGFR mutation (P=0.01). Intratumoral CD8+ T-cell and mDC densities remained strong independent markers of overall survival (P=0.001 and P=0.02, respectively).

Take home points:

- Intratumoral immune cell densities (mDCs, CD8+ T cells, neutrophils, macrophages) were significantly associated with molecular alterations in adenocarcinoma, suggesting interactions between cancer cells and their microenvironment.

Masai K, et al. Clinicopathological, Immunohistochemical, and Genetic Features of Primary Lung Adenocarcinoma Occurring in the Setting of Usual Interstitial Pneumonia Pattern. J Thorac Oncol. 2016 Dec;11(12):2141-2149.

Purpose: An association between UIP and carcinogenesis has been well established. However, few detailed analyses have investigated the clinicopathological, immunohistochemical, and genetic features of patients with primary lung adenocarcinoma (ADC) with UIP (UIP-ADC).

Methods: The authors identified 44 patients with ADC in the setting of UIP (the UIP-ADC group) (1.9%) from 2309 patients with primary ADC and compared clinicopathological, immunohistochemical, and genetic features between the UIP-ADC group and patients with ADC without UIP (the non-UIP-ADC group).

Results: Clinicopathological features of UIP-ADC included an older age at occurrence; male predominance; smoking history; predilection for the lower lobe; large tumor size; high incidence of lymph vessel invasion, pleural invasion, and lymph node metastasis; and poor survival rate. However, the cause of death of patients with UIP-ADC was largely influenced by respiratory complications. Histologically, patients in the UIP-ADC group could be stratified according to invasive mucinous-predominant subtype. Genetically, patients in the UIP-ADC group had lower EGFR and higher KRAS mutation rates compared with patients in the non-UIP-ADC group.

Take home points:

- UIP-ADC was associated with a poor prognosis owing to the high frequency of perioperative complications rather than the malignancy of the tumor itself.
- There was a high prevalence of the invasive mucinous-predominant subtype in cases of UIP-ADC.
- UIP-ADC also had a low prevalence of EGFR mutations and a high prevalence of KRAS mutations.

Nowak AK, et al. The IASLC Mesothelioma Staging Project: Proposals for Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Pleural Mesothelioma. J Thorac Oncol. 2016 Dec;11(12):2089-2099.

Purpose: To develop recommendations for the T stage of mesothelioma in the AJCC eighth edition.

Methods: Data elements including detailed T descriptors were developed by consensus. Tumor thickness at three pleural levels was also recorded.

Results: A total of 3519 cases were submitted to the database. Of those eligible for T-component analysis, 509 cases had only clinical staging, 836 cases had only surgical staging, and 642 cases had both available. Survival was examined for T categories according to the current seventh edition staging system. There was clear separation between all clinically staged categories except T1a versus T1b (hazard ratio = 0.99, p = 0.95) and T3 versus T4 (hazard ratio = 1.22, p = 0.09), although the numbers of T4 cases were small. Pathological staging failed to demonstrate a survival difference between adjacent categories with the exception of T3 versus T4. Performance improved with collapse of T1a and T1b into a single T1 category; no current descriptors were shifted or eliminated. Tumor thickness and nodular or rindlike morphology were significantly associated with survival.

Take home points:

- A recommendation to collapse both clinical and pathological T1a and T1b into a T1 classification will be made for the eighth edition.
- Simple measurement of pleural thickness has prognostic significance and should be examined further with a view to incorporation into future staging.

Pass H,et al. The IASLC Mesothelioma Staging Project: Improving Staging of a Rare Disease Through International Participation. J Thorac Oncol. 2016 Dec;11(12):2082-2088.

This is an introductory paper that accompanies the other three papers describing proposed revisions to the TNM classification system for pleural mesothelioma, which provides a nice historical overview of the development of staging for mesothelioma and the IASLC mesothelioma database that is providing much of the data upon which the recommended changes hinge. Although it is just an introductory paper, it has nice information for talks.

Rice D, et al. The IASLC Mesothelioma Staging Project: Proposals for Revisions of the N Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Pleural Mesothelioma. J Thorac Oncol. 2016 Dec;11(12):2100-2111.

Purpose: To develop recommendations for the N stage of mesothelioma in the AJCC eighth edition.

Methods: Data from 29 centers were entered prospectively (n = 1566) or by transfer of retrospective data (n = 1953). Survival according to the seventh edition N categories was evaluated using Kaplan-Meier survival curves and Cox proportional hazards regression analysis. Survival was measured from the date of diagnosis.

Results: There were 2432 analyzable cases: 1603 had clinical (c) staging, 1614 had pathologic (p) staging, and 785 had both. For clinically staged tumors there was no separation in Kaplan-Meier curves between cN0, cN1 or cN2 (cN1 versus cN0 hazard ratio [HR] = 1.06, p = 0.77 and cN2 versus cN1 HR = 1.04, p = 0.85). For pathologically staged tumors, patients with pN1 or pN2 tumors had worse survival than those with pN0 tumors (HR = 1.51, $p < 0.0001$) but no survival difference was noted between those with pN1 and pN2 tumors (HR = 0.99, p = 0.99). Patients with both pN1 and pN2 nodal involvement had poorer survival than those with pN2 tumors only (HR = 1.60, p = 0.007) or pN0 tumors (HR = 1.62, $p < 0.0001$).

Take home points:

- A recommendation to collapse both clinical and pN1 and pN2 categories into a single N category comprising ipsilateral, intrathoracic nodal metastases (N1) will be made for the eighth edition staging system.
- Nodes previously categorized as N3 will be reclassified as N2.

Rusch VW, et al. The IASLC Mesothelioma Staging Project: Proposals for the M Descriptors and for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Mesothelioma. J Thorac Oncol. 2016 Dec;11(12):2112-2119.

Purpose: To develop recommendations for the M stage of mesothelioma in the AJCC eighth edition.

Methods: Data from 29 centers were submitted either electronically or by transfer of existing institutional databases. The M component as it currently stands was validated by confirming sufficient discrimination (by Kaplan-Meier analysis) with respect to overall survival (OS) between the clinical M0 (cM0) and cM1 categories. Candidate stage groups were developed by using a recursive partitioning and amalgamation algorithm applied to all cM0 cases.

Results: Of 3519 submitted cases, 2414 were analyzable and 84 were cM1 cases. Median OS for cM1 cases was 9.7 months versus 13.4 months ($p = 0.0013$) for the locally advanced (T4 or N3) cM0 cases, supporting inclusion of only cM1 in the stage IV group. Exploratory analyses suggest a possible difference in OS for single- versus multiple-site cM1 cases. A recursive partitioning and amalgamation-generated survival tree on the OS outcomes restricted to cM0 cases with the newly proposed (eighth edition) T and N components indicates that optimal stage groupings for the eighth edition will be as follows: stage IA (T1N0), stage IB (T2-3N0), stage II (T1-2N1), stage IIIA (T3N1), stage IIIB (T1-3N2 or any T4), and stage IV (any M1).

Take home points:

- The M component was validated as it currently stands.
- This first evidence-based revision of the TNM classification leads to substantial changes in the T and N components and the stage groupings.

Wu HH, et al. Utilization of Cell-Transfer Technique for Molecular Testing on Hematoxylin-Eosin-Stained Sections: A Viable Option for Small Biopsies That Lack Tumor Tissues in Paraffin Block. Arch Pathol Lab Med. 2016 Dec;140(12):1383-1389.

Purpose: To evaluate a tumor cell–enriched cell-transfer technique for isolating tumor cells from hematoxylin-eosin (H&E)–stained slides for the purposes of molecular testing, as an alternative method when insufficient material is present in the block.

Methods: Molecular testing was performed by using the cell-transfer technique on 97 archived H&E-stained slides from a variety of different tumors. Results were compared to the conventional method of molecular testing.

Results: PCR–based molecular testing via the cell-transfer technique was successfully performed on 82 of 97 samples (85%). This included 39 of 47 cases for EGFR, 10 of 11 cases for BRAF, and 33 of 39 cases for KRAS mutations. Eighty-one of 82 cell-transfer technique samples (99%) showed agreement with previous standard method results, including 4 mutations and 35

wild-type alleles for EGFR, 4 mutations and 6 wild-type alleles for BRAF, and 11 mutations and 21 wild-type alleles for KRAS. There was only 1 discrepancy: a cell-transfer technique with a false-negative KRAS result (wild type versus G12C).

Take home points:

- Molecular testing performed on H&E-stained sections via the cell-transfer technique is useful when tissue from cell blocks and small surgical biopsy samples is exhausted and the only available material for testing is on H&E-stained slides.

Non-neoplastic

Borie R, et al. Prevalence and characteristics of TERT and TERC mutations in suspected genetic pulmonary fibrosis. Eur Respir J. 2016 Dec;48(6):1721-1731.

Purpose: Telomerase reverse transcriptase (TERT) and telomerase RNA (TERC) gene mutations are major monogenic causes of pulmonary fibrosis, but little is known about the possible predictors of this mutation and its impact on prognosis.

Methods: The authors retrospectively analyzed all the genetic diagnoses made at their institution between 2007–2014 in patients with pulmonary fibrosis. They evaluated the prevalence of a TERT/TERC disease-associated variant (DAV), factors associated with a DAV, and the impact of the DAV on survival.

Results: 237 patients with pulmonary fibrosis (153 with familial pulmonary fibrosis, 84 with telomere syndrome features without familial pulmonary fibrosis) were tested for a TERT/TERC DAV. DAV was diagnosed in 40 patients (16.8%), including five with non-idiopathic interstitial pneumonia. Prevalence of a TERT/TERC DAV did not significantly differ between patients with familial pulmonary fibrosis or with only telomere syndrome features (18.2% versus 16.4%). Young age, red blood cell macrocytosis, and low platelet count were associated with the presence of DAV; the probability of DAV was increased for patients 40–60 years. Transplant-free survival was lower with than without TERT/TERC DAV (4.2 versus 7.2 years; p=0.046).

Take home points:

- TERT/TERC DAV were associated with specific clinical and biological features and reduced transplant-free survival.

Tan J, et al. Expression of RXFP1 Is Decreased in Idiopathic Pulmonary Fibrosis. Implications for Relaxin-based Therapies. Am J Respir Crit Care Med. 2016 Dec 1;194(11):1392-1402.

Purpose: To gauge the potential efficacy of relaxin-based therapies in IPF and to study gene expression for relaxin/insulin-like family peptide receptor1 (RXFP1) in IPF lungs and controls.

Methods: The authors analyzed gene expression data obtained from the Lung Tissue Research Consortium and correlated RXFP1 gene expression data with cross-sectional clinical and demographic data. They also employed ex vivo donor and IPF lung fibroblasts to test RXFP1 expression in vitro. They tested GEN25009, a relaxin-like peptide, in lung fibroblasts and in bleomycin injury.

Results: They found that RXFP1 is significantly decreased in IPF. In patients with IPF, the magnitude of RXFP1 gene expression correlated directly with diffusing capacity of the lung for carbon monoxide ($P<0.0001$). Significantly less RXFP1 was detected in vitro in IPF fibroblasts than in donor controls. Transforming growth factor-b decreased RXFP1 in both donor and IPF lung fibroblasts. CGEN25009 was effective at decreasing bleomycin-induced, acid-soluble collagen deposition in vivo. The relaxin-like actions of CGEN25009 were abrogated by RXFP1 silencing in vitro, and, in comparison with donor lung fibroblasts, IPF lung fibroblasts exhibited decreased sensitivity to the relaxin-like effects of CGEN25009.

Take home points:

- IPF is characterized by the loss of RXFP1 expression.
- RXFP1 expression is directly associated with pulmonary function in IPF.
- The relaxin-like effects of CGEN25009 in vitro are dependent on expression of RXFP1.
- IPF with the highest RXFP1 expression might be the most sensitive to relaxin-based therapies.

Reviews

Berg K, Wright JL. The Pathology of Chronic Obstructive Pulmonary Disease: Progress in the 20th and 21st Centuries. Arch Pathol Lab Med. 2016 Dec;140(12):1423-1428.

Purpose: To review the pathology of COPD.

Take home points: A basic review of COPD, specifically directed at residents and general pathologists.

Hofman P, Popper HH. Pathologists and liquid biopsies: to be or not to be? Virchows Arch. 2016 Dec;469(6):601-609.

Purpose: To review "liquid biopsy" technology for pathologists and the potential applications and limitations of this technology, specifically as they relate to development and validation of assays and their potential clinical utility (or lack thereof).

Take home points: A nice review for anyone who's preparing a lecture on the topic and needs some pros and cons and bullet points.

Langer CJ, et al. Incremental Innovation and Progress in Advanced Squamous Cell Lung Cancer: Current Status and Future Impact of Treatment. J Thorac Oncol. 2016 Dec;11(12):2066-2081.

Purpose: To review the progress in development of novel targeted therapies and relevant clinical trials for advanced SqCC.

Take home points: A nice review for those of us who struggle to keep up on the nuances of and rapid advancements in thoracic oncology.

Mathai SK, et al. Pulmonary fibrosis in the era of stratified medicine. Thorax. 2016;71:1154-1160.

Purpose: To review the current landscape of common and rare genetic alterations in IPF and familial interstitial pneumonia.

Take home points: A nice review and reminder that we've only begun to scratch the surface when it comes to understanding the biology of these diverse disorders.

Torres A, et al. Laboratory diagnosis of pneumonia in the molecular age. Eur Respir J. 2016 Dec;48(6):1764-1778.

Purpose: To review molecular assay techniques used in laboratory diagnosis of infectious pneumonia, including rapid molecular assays for respiratory viral and bacterial pathogens and molecular assays for determining antibiotic resistance.

Take home points: A nice review for those needing to brush up on the tools that the microbiologists are using these days for more rapid and specific diagnosis of organisms.

Zhou F, Moreira AL. Lung Carcinoma Predictive Biomarker Testing by Immunoperoxidase Stains in Cytology and Small Biopsy Specimens: Advantages and Limitations. Arch Pathol Lab Med. 2016 Dec;140(12):1331-1337.

Purpose: To review advantages and limitations of IHC biomarker testing in cytology specimens and small biopsies.

Take home points: A nice review of preanalytic and analytic variables in IHC and specific data on EGFR, ALK, and other antibodies currently used for IHC detection of biomarkers in cytology specimens. This review highlights the paucity of data on cytology specimens and lack of rigorous validation in many cases, which has implications for clinical trial design.

Case reports and editorials

Fernández-Codina A, et al. A 40-Year-Old Woman With Back Pain. Chest. 2016 Dec;150(6):e159-e165.

A nice case of a large MPNST filling the hemithorax in a patient with NF1.

Hambly N, Kolb M. Pathways to Precision Medicine in Idiopathic Pulmonary Fibrosis. Time to Relax? Am J Respir Crit Care Med. 2016 Dec 1;194(11):1315-1317

A nice editorial suggesting that we start thinking more about relaxin-based therapies as we seek to develop more sophisticated therapies that target the molecular abnormalities in subsets of pulmonary fibrosis.

Merck SJ, Armanios M. Shall we call them "telomere-mediated"? Renaming the idiopathic after the cause is found. Eur Respir J. 2016 Dec;48(6):1556-1558.

A thoughtful editorial on IPF. The title says it all.

Shi R, et al. An Anaplastic Lymphoma Kinase Immunohistochemistry-Negative but Fluorescence In Situ Hybridization-Positive Lung Adenocarcinoma Is Resistant to Crizotinib. J Thorac Oncol. 2016 Dec;11(12):2248-2252.

An intriguing case report. Again, the title says it all.

Tay CK, et al. Primary angiomatoid fibrous histiocytoma of the lung with mediastinal lymph node metastasis. Hum Pathol. 2016 Dec;58:134-137.

An interesting case of an exceedingly rare primary pulmonary AFH.

Weissferdt A, et al. Pleuromediastinal Epithelial-Myoepithelial Carcinomas: A Clinicopathologic and Immunohistochemical Study of Two Cases. Am J Clin Pathol. 2016 Dec;146(6):736-740.

Two cases illustrating that epi-myoepi carcinomas can occur not only in the lung, but pretty much anywhere in the thorax.