PULMONARY PATHOLOGY JOURNAL CLUB
(July 2016 articles)

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Case reports

1. TPD52L1-ROS1, a new ROS1 fusion variant in lung adenosquamous cell carcinoma identified by comprehensive genomic profiling. Zhu et al. Lung Cancer 2016; 97:48

I. ARTICLES FOR DISCUSSION

1. Could prominent airway-centered fibroblast foci in lung biopsies predict underlying chronic microaspiration in idiopathic pulmonary fibrosis patients? Bois et al. Human Pathol 2016; 53:1

Background and Aim

- High prevalence of GERD in patients with IPF (87% vs 12% general population).
- Some authors have hypothesized that repeated small injuries from microaspiration of acidic contents leads to progressive fibrosis
- Occult aspiration occurs in patients with GERD, OSA and increased BMI
- Patients with IPF treated for their GERD have shown to have more stable disease
- The authors had an index case of classic UIP with evidence of aspiration with airway centered FF, constrictive bronchiolitis like, with foreign particles. This led them to study the meaning of such airway centered FF in UIP and potential relationship to microaspiration

Methods

- Surgical biopsies with diagnosis of UIP, correlated clinically and radiologically
- 2 pathologists score airway centered FF as rare, mod and severe. For analysis, rare and mod lumped as low score and severe as high score. Additional histologic findings recorded including acute inflammation, granulomas.
- Extensive clinical information abstracted including clinical diagnosis of GERD, some of which had more extensive investigation, OSA, smoking, BMI
- Extensive radiologic findings recorded upon radiology review.
- Statistical analysis

Results

- Total of 49 patients dx with UIP. After excluding patients with CTD and likely HP, and 1 patient with acute exacerbation (for practical purpose of assessing FF), 37 patients were diagnosed with IPF
- 20 GERD, 19 treated with PPI or other, 7 OSA, 1 dysphagia, BMI of 17-46, 21 smokers past or current, 3 HH
- 11 slides med from at least 2 lobes
    - 1 with evidence of aspiration
    - 15 with poorly formed granulomas
    - 13 with score of severe
        - Positive association only with HH, no other clinical features
        - Association with acute inflammation and granulomas
- No radiologic features associated with aspiration

Conclusions

Basically negative study but questions remain as to the significance of airway centered FF, if any. And in this study large number of cases had granulomas. Authors make a case for why these are not HP cases but still a possibility or possibility of subclinical infection?

2. Morphological and molecular approach to synchronous non-small cell lung carcinomas: impact on staging. Schneider et al. Mod Pathol 2016; 29:735

Background

- Multiple synchronous tumors up to 20% rate
- Distinguishing independent 1ary tumors from intrapulmonary metastasis challenging
- Martini et al criteria insufficient. Different molecular approaches have been studied and based on methodology discrepancy between morphology and molecular classification ranges 18-30%
- Since mutational profiling is done routinely, suggestions about using that data to classify and stage multifocal tumors. But SQCC is not routinely profiled and even more difficult to distinguish based on morphology alone

Aim

Assess possible impact of histological assessment and mutational profiling performed in clinical practice on the staging of surgically resected NSCLC

Material and methods

- 60 patients with 2 nodules:
    - 42 AD, 33 pT3 and 9 pT4
    - 18 SQCC, 15 pT3 and 3 pT4
    - All considered intra-pulm mets according to Martini
- Morphological subtyping using WHO 2015
    - If similar morphology = met
    - If different = ind 1ary
- Molecular analysis
    - Mutational profile only state did Sanger Sequencing no mention of which genes (later in the results there is a mention to 8 gene done)
    - FISH for MET amp, ALK and ROS. Although we find out p16 was done on SQCC in results not mentioned in methods

Results

- Of 42 AD
    - Concordance between Martini and morphology was 50%
    - Molecular alterations in 27 (64%) which means non informative in 15 cases
    - Kras in 22, EGFR in 2, MET in 2, ALK in 1
    - Concordance between histology and mol in 24 of 27 (89%)
    - But what to say about the 15 wild types? Absence = met? Basically all these cases would be indeterminate
- Of 18 SQCC
    - Concordance between Martini and morphology was 50%
    - Molecular alterations identified in only 44%
    - Concordance between molecular and histology was 57%
- Survival analysis could be done only on 35 and no difference upon re-staging the tumors. Only LN mets and age >65 were significant on the OS

Conclusion

Using routine mutational profiling is insufficient for staging of multifocal lung tumors: 1- too many cases without alterations in known targets or driver mutations so uninformative 2- mutations in for example k-ras can be the same just by chance since involves only a few codons (like in this study 21 of 22 k-ras mutations were all in the same codon so you would not be able

to even distinguish 2 tumors from different patients) 3- depending how early a mutation arise in a tumor or how homogeneous a tumor is for a mutation ie all cells with the same mutation, differences in mutational profile does not indicate necessarily independence but could reflect tumor heterogeneity

3. A Validation Study for the Use of ROS1 Immunohistochemical Staining in Screening for ROS1 Translocations in Lung Cancer. Viola et al. JTO 2016; 11:1029

Background

- FISH is time consuming, complex to interpret, more expensive than IHC which has led to recommendations to do IHC for ALK
- Same principal applies to FISH *ROS1*

Aim

To assess if IHC can be used to screen for *ROS1* rearrangement

Methods

- Enriched to finding *ROS1* rearranged cases by using a cohort of 103 patients that were wild type for *EGFR*, *K-ras*, *BRAF* and no *ALK* rearrangements
- IHC for ROS1 and used H-score of >100 to call case +
- FISH for *ROS1* 15% split signal to call +

Results

- Of 103 cases, 39 AD and 2 ADSQCC
    - All others SQCC, SCLC, LCC, LCNC, NSCLC NOS and 6 carcinoids IHC negative so not used further in the analysis
    - IHC for ROS1
        - Of 39 AD
            - 2 + with H score >100
            - 10 cases with staining of weak to mod, <5 to >90% + cells
        - No mention of ADSQC but one assumes both neg
    - FISH for *ROS1*
        - 38 cases with enough tissue, 34 neg and 3 failed
        - Of 36 AD- 1 +
        - The positive case correlates with 1 of the 2 + IHC (the strongest of the 2 i.e. mod staining >90% cells)
- Went to archives to find + FISH cases to enrich more and identified 4 new cases
    - IHC for these 4 cases showed:
        - 1 strong 90% H score 270
        - 2 mod 80 and 100% H score 200 and 160
        - 1 weak in 60 and mod in 30% H score 120
- So 5 of 6 IHC pos cases (ie H score >100) correlated with positive FISH
- Sensitivity of 100% (ie all FISH + detected by IHC) and specificity of 83% (1 called + by IHC neg by FISH but didn't do PCR or other studies to see if truly neg)
- 4 of 5 IHC and FISH+ cases treated with crizotinib, 3 with excellent response

Conclusions

- Similar results to other studies and plagued by same problem which is low number of FISH+ cases

- Nice Table that summarizes all studies performed to date: 8 studies with sensitivity and specificity measurements, of these only 2 had >10 + cases (all below 20). 6 had a 100% sensitivity (the other 2 33 and 94%) and specificity very variable ranging 15-99%

4. Natural History of Pulmonary Subsolid Nodules: A Prospective Multicenter Study. Kakinuma et al. JTO 2016; 11:1012

Aim

To evaluate the natural course of the progression of pulmonary subsolid nodules (SSNs).

Method

- 795 patients consisted of 454 women and 341 men (mean age 62 ± 9.4 years, median age 62 years) with 1229 pulmonary SSNs (549 solitary and 246 multiple)
- SSNs were classified into 3 categories:
    - Pure ground-glass nodules (PGGNs);
    - Heterogeneous GGNs (HGGNs), solid in lung but not in mediastinal window;
    - Part-solid nodules (PSNs), solid in both lung and mediastinal windows.

Results:

	Baseline	**Progression time**	**At Followup 4.3yrs (med 3.5)**	**# Resected and pathologic diagnosis**	
PGGN	**1046**		**977**		**35**
Progressed to HGGN		---	13	AAH	5
Progressed to PSN		3.8 yrs (med 3.4)	56	AIS	21
Progressed to >/= 3.3 mm solid		Min. 1.8 yr	20	MIA	9
				Inv. Adeno	0
HGGN	**81**		**78**		**7**
Progressed to PSN		2.1 yrs (med 1.0)	16	AAH	0
Progressed to >/= 3.3 mm solid		Min. 2.5 yr	5	AIS	2
				MIA	5
				Inv. Adeno	0
PSN	**102**		**174**		**49**
Progressed to >/= 3.3 mm solid		Min. 6 mon.	22	AAH	1
				AIS	10
				MIA	26
				Inv. Adeno	12

Discussion:

- If the growth of the solid component has not exceeded 3.3 mm, an option for the management of SSNs could be a follow-up examination:
    - Every 6 months in cases with a part-solid nodule;
    - Every 1 or 2 years in cases with a PGGN or an HGGN.
- In the 49 resected part-solid nodules, 75.5% (37 of 49) were preinvasive lesions or MIAs; authors suggest the appearance of solid components might not always be an appropriate parameter for a "prompt" resection from the standpoint of avoiding overdiagnosis.
- The solid components in mediastinal windows are not equal to the invasive foci in pathological specimens. The size of the solid component could be smaller histologically due to alveolar collapse, inflammatory cells, and miscellaneous changes, as well as invasive adenocarcinoma.

Conclusion: Invasive adenocarcinomas were diagnosed only among the resected part-solid nodules in this study. The results could aid in the development of guidelines on follow up intervals for pulmonary SSNs.

II.ARTICLES FOR DISCUSSION/NOTATION

1. Allergen-induced Changes in Bone Marrow and Airway Dendritic Cells in Subjects with Asthma. El-Gammal et al. AJRCCM 2016; 194 (2): 169

Background

- Dendritic cells (DC) are potent Ag-presenting cells in airways
- DC are derived from CD34+ marrow progenitors along myeloid differentiation in the BM
- DCs then go through the blood into LN or mucosal associated lymphoid tissue there they mature, take up Ag and then present Ag to the naïve T-cells
- This mechanism important in asthma
    - Decrease in circulating DC with increase of DC in airway mucosa
    - Increase of DC in BALs
    - In animal models, expansion of the myeloid progenitors to meet increased demands of DCs

Aim

Test the hypothesis that allergen inhalation expands DCs and precursors in BM and assess trafficking of the DCs into the airways.
Also assess role of IL-33 and TSLP through their surface receptors

M&M

- 10 subjects with mild asthma not on regular asthma treatment. Inhalation with diluent and allergen, cross over study.
- Provocative concentration of methacholine, PB, and BM aspirate at baseline day 1.
- Day 2 inhalation and Day 3 spirometry, PB, BM aspirate and BAL with bronchial bx. Repeat at 4-week.
- CD34+ cells isolated from BM and cultured. BX routine and with multicolor IF. Flow on blood and BM

Results

- All subjects with allergen induced response
- BAL with significant increase in eosinophils in allergen vs diluent, but not for neutrophils or macrophages
- No increase in BM CD34+ allergen vs diluent or in the % of CD34+ cells expression IL4R
    - *But in culture, increase if the number of clusters of DCs after allergen vs diluent*
    - By flow, the CD11c+ cells and co-expressed CD11c and CD83+ cells increased after allergen vs diluent
- cDCs and pDCs both significantly increased in BM with allergen vs diluent, including ones with CCR5 and TSLPR
- In PB, no changes in DCs or surface receptors for interleukines
- In BAL, increase in numbers of cDC2 with allergens. No changes in surface receptors.
- In bronchial biopsies, HLA-DR+ cells identified with co-expression for DC1 and DC2, with increase of the DC2 after allergen

Conclusions

- Increased number of cultured DCs in BM both immature and mature, with increased of TSLPR. Increased cDC1 and cDC2 in BAL and of cDC2 in bx after inhalation of allergens in subjects with mild asthma
- TSLP plays a role in maturation of DCs from the BM and prior work showed that likely orchestrates progenitors for eosinophils. So blocking TSLP with monoclonal Ab may be a treatment for asthma.
- Increased airway DCs due to migration and increased production in BM.

2. Napsin A/p40 Antibody Cocktail for Subtyping Non-Small Cell Lung Carcinoma on Cytology and Small Biopsy Specimens. Nishino ell. Cancer Cytopath 2016; p472

Background

- Distinguishing SQCC from AD and other important for therapeutic decisions and mostly for triaging tissue for additional molecular studies
- On small specimens like TBNAs very important to minimize the number of immunostains to use.

Aim

- Determine optimal antibodies to create cocktail and assess ability of the cocktail to accurately subtype NSCLC

Methods

- TMA constructed from "proven" AD and SQCC. Assessed 4 commonly used Abs: TTF-1 (8G7G), Napsin A, TTF-1 and Ck5/6. Unfortunately did H-scores which doesn't apply well to clinical practice to determine specificity and sensitivity, ROC of H-scores used to determine cutoffs
- Based on the results from above, created cocktail of Napsin A/p40 that they assessed using TMA
- Then looked at NapsinA/p40 in a cohort of cases with pre-op small biopsies and corresponding resected tumors.

Results

- Individual Abs
    - Sensitivity of p40 and CK5/6 100% but specificity for p 40 much higher **94** vs 59%. *Not surprised about CK5/6 low specificity but I am for p40 and this low specificity has trickle down effect on the rest of the results*..
    - Sensitivity for TTF-1 and Napsin A 94% and specificity similar 99 and 91% respectively
    - ROC for H scores similar for NapsinA and TTF-1 30 and 10 while for CK5/6 is 100 vs 20 for p40
    - So since p40 superior to CK5/6 and Napsin A and TTF-1 similar, developed cocktail of Napsin A/p40
- NapsinA/p40 cocktail on TMAs
    - Correlation between H scores of single to dual Ab excellent with r=0.9845 for Napsin and 0.9774 for p40
    - Of 142 AD
        - 124 Nap+/p40-
        - 0 Nap-p40+
        - **9 Nap+/p40+**, **9 were TTF-1 +** by morphology many would be lepidic and acinar

        - **9 Nap-/p40- ,** 5 were TTF-1+, and 4 TTF-1 but 4 would be mucinous.
        - **So Napsin A trumps the p40** *mostly based on TTF-1 results and in the face of better specificity for p40 than Napsin*
- NapsinA/p40 in small biopsies versus resection
    - 80 cases, 45 AD, 25 SQCC, 9LCC, 1 sarcomatoid
    - Based on H scores devised a scoring system of
        - A+ or ++/p40 +/- = favor AD
        - A-/p40+/++ = favor SQCCC
        - A-/p40- = NOS
        - There was no A+ or++ and p40++?
    - 38 biopsies called favor AD were resected AD
    - 26 biopsies called favor SQCC were 25 SQCC and 1 LCC (because p40 focal?)
    - 15 NOS were 7 AD based on morphology or TTF-1, 7 LCC and 1 sarcomatoid ca, none were SQCC

Conclusions

Important study to help determine optimal cocktail to use allowing us best dx for clinical purposes with minimal use of tissue. Main issue to me was the low sensitivity of p40 to start with….

3. A proposal for cellularity assessment for EGFR mutational analysis with a correlation with DNA yield and evaluation of the number of sections obtained from cell blocks for immunohistochemistry in non-small cell lung carcinoma. da Cunha Santos et al. JCP 2016; 69:607

Background

- Different approaches exist to report adequacy of a specimen for molecular testing but limited information exists for cell blocks

Aim

- Assess their reporting methods for cellularity and correlate with yield of DNA
- Document number of IHC made prior to cutting block for molecular testing
- Evaluate role of doing H&E pre and post cutting block for molecular testing

Methods

- Cellularity counts
    - Total 1-100, 100-250, 250-500, 500-750, 750-1000, >1000
    - Tumor cells 0, 1-50, 50-100, 100-300, >300
    - Overall % tumor cells
    - Details of how they counted explained in their methods, pretty similar to what we would do in practice

Results

- 110 cases, majority 47 LN TBNA and 43 lung FNA
- 83 cases had IHC done, 1-10 IHC per case, med 3. But did not specifically correlate if higher number of IHC linked to lower cellularity for molecular testing or not.
- Cellularity
    - Total 64.5% (71cases) with >1000 and 5.5% (6) 100-250
    - Tumor 65 cases >300, 9 with 1-50
    - Med 50% tumor, 5-90% range.
- Correlation with DNA yield

    - >1,000 cells yield average 0.55µg vs 0.15 for 100-250
    - >300 tumor cells 0.60 vs 0.24 for 1-50
    - 60-90% 0.65 vs 0.36 for <5-10%
- 46 with pre-and post H&E and 43 had similar counts

Conclusions

- DNA yield correlates with cellularity
- Most CB were adequate even after IHC done, but no specification of how many were adequate.
- For comparison here at Mayo an average 10ng (0.01 µg) is needed for most molecular testing.

4. Prognostic Significance of PD-L1 in Patients with Non–Small Cell Lung Cancer: A Large Cohort Study of Surgically Resected Cases. Sun et al. JTO 2016; 11:1003

Background

- Prognostic relevance of PD-L1 as a prognostic marker remains unclear
    - Some studies indicate better, others worse and finally some no relevance
    - A metanalysis suggested likely worse
- All these studies hampered by non-standardized methods, different Abs and small sample size

Aim

Basically aiming at doing better!

Methods

- 1070 (of 4054) surgically resected lung cancers in South Korea
- IHC using 22C3 Ab and a scoring system of strong if >95%+, weak 1-94% and negative if 0%
- Statistical analysis

Results

- 63 yo med age, 67% male, 49% Stage I, 47% chemotherapy, 29% Rad, 11% EGFR inhibitors, 664 AD, 6.4%strong and 38.3% weak PD-L1
- Univariate significant, old age, male, poor ECOG, smoker, LCC, high tumor stage
- Multivariate significant histology and stage
- OS and PFS shorter in strong PD-L1 overall but remained significant only on non-treated patients. Any type of post-op treatment made PD-L1 non relevant

Conclusions

PD-L1 appears to be prognostically significant only in patients that had surgery alone but these patients also tended to be the ones with better features such as female, nonsmokers, with AD and stage I. As much as studies can be comparable these findings are different yet from another study published the same month in Lung Cancer (see below)

III. Articles for notation

1. Thymomas With Extensive Clear Cell Component. A Clinicopathologic and Immunohistochemical Study of Nine Cases. Weissferdt et al. AJCP 2016; 146:132

The authors describe 9 cases of thymoma with extensive clear cell changes (comprising 80-90% of the tumor). Clinically and radiologically, no distinctive features. Histologically, besides the clear cell changes, many lymphocytes and focally more classic thymoma. IHC show the clear cells to be CK5/6+, CD5 and c-kit – and lymphocytes are tdt+. 8/9 are either encapsulated or minimally invasive. FU too short to make any conclusions. The authors argue that one should wait for resection to distinguish thymoma from thymic carcinoma because of risk of misinterpretation as would be the case with clear cell changes. But all their cases had tdt+lymphocytes and morphologically the cells weren't atypical and no mitosis reported. So shouldn't really be a problem. Based on images, the H&E differential would be with seminoma. Of note, they use their own staging system called the MD Anderson staging protocol….

2. Galectin-3 Is Associated with Restrictive Lung Disease and Interstitial Lung Abnormalities. Ho et al. AJCCRM 2016; 194:77. Accompanied by an Editorial.

Galectin-3 is thought to play a role in fibrosis. It has been shown to be a prognostic and predictive marker of heart failure. Some studies have shown increase of Gal3 in the serum and BAL of patients with IPF. The authors hypothesized that Gal3 should be increased in early pulmonary fibrosis. Looking at patients enrolled in the FHS, they identified 2596 patients with PFTs, 1148 of which had CT scan. Patients with higher Gal3 were older, had more DI and higher BMI. Higher Gal-3 associated with lower lung volumes and DLCo, even after multivariate. Higher Gal3 associated with 2 folds increase of having interstitial abnormalities on imaging. So interesting findings but authors did not show changes overtime associated with increased Gal3 and no outcome data, how many actually diagnosed with ILD, what happened to the lung abnormalities in subsequent imaging etc

3. Clinical Validation of a Novel Commercial Reverse Transcription–Quantitative Polymerase Chain Reaction Screening Assay for Detection of ALK Translocations and Amplifications in Non–Small Cell Lung Carcinomas. Liu et al. Arch Pathol Lab Med 2016; 140:690

The authors validate a new RT-PCR assay for ALK. The advantage of looking at ALK in this manner instead of using FISH would be the need of using less tissue if done in combination with EGFR (ie no need to cut block for FISH and then block to get DNA for EGFR, instead same tissue sections used for both EGFR and ALK with RT-PCR). And potentially increase the TAT. The authors looked at 43 samples with known ALK FISH results, 20 + and 23-. The analytic sensitivity was 15% dilution with Ct<36.9. The clinical sensitivity was 100% and specificity 100% so perfect correlation between FISH and RT-PCR. 2 samples were duplicated 5 times and intra-run reproducibility was 100%, 29 samples repeated in multiple runs with inter-run reproducibility of 100%. So seems to be a great option to FISH and easily combined with EGFR in same test.

4. Folate Receptor α Expression Level Correlates With Histologic Grade in Lung Adenocarcinoma. Driver et al. Arch Pathol Lab Med 2016; 140:682

Folate receptor α (FRA) is being studied as a drug target. In breast cancers, FRA expression is associated with high grade and triple negative tumors. The authors studied FRA expression in

lung AD. They used TMAs 119 NSCLC with 3 cores grade 0 to 3+ and cores averaged out. Low expression was 0-1.4 and high expression >1.4. RFA expressed more in AD (77%) versus SQCC (10%). In AD, RFA expression correlated only with grade (not age, sex, TNM, stage). RFA expression was higher in grade 1 (including LPA) AD (85%) versus grade 2 (58%) and grade 3 (including solid) (48%). No correlation with TTF-1 and Napsin. No difference in survival between low and high expression.

5. Detection of PIK3CA Mutations, Including a Novel Mutation of V344G in Exon 4, in Metastatic Lung Adenocarcinomas: A Retrospective Study of 115 FNA Cases. Allison et al. Cancer Cytopath 2016; p485

The authors sought to study the role of *PIK3CA* mutation in metastatic NSCLC. The literature shows that approximately 1-2% of AD have *PIK3CA* mutation, often co-existing with other mutations in *EGFR* and *Kras.* In contrast, *PIK3CA* mutation is more common in SQCC, in about 16%, mutually exclusive from *FGFR* amplification. The authors studied 115 FNAB of metastatic NSCLC, 97 AD and 18 NOS. They found 7 (6.1%) in 6 AD and 1 NOS *PIK3CA* mutations including 2 in exon 4 (VAF of 24 and 17%), not previously described. 6 of these were associated with mutations in EGFR mutations including 2 with the resistant mutation and Kras. The authors also claimed that since the rate of *PIK3CA* mutation was higher in their cohort of AD and NOS compared to literature implied that this mutation plays a role in metastatic disease. Weak argument as we don't know what the status is in the primary tumor corresponding to the met, 2 had EGFR resistant mutation, and the increase rate could be just by luck….

6. Epidemiology and survival of idiopathic pulmonary fibrosis from national data in Canada. Hopkins et al. Eur J Respir 2016; 48:26

In this study, the authors used the National administrative institutional database to look at prevalence, incidence, survival and QOL of patients with IPF. This database is based on a standardized mandatory reporting for all hospital admissions and day surgeries which allows a 100% capture of patient info. They also used the ICD10 coding which has IPF terminology not existent in the ICD9. They showed higher prevalence and incidence of IPF in Canada compared to other countries (perhaps under reporting from others). In Canada, prevalence is 4.8/100,000 and 19% higher in males, incidence 18.7 31% higher in males, rare under 50yo, 41% deaths at 4 yrs, and low quality of life, lower than patients with severe COPD.

7. Incidence and prevalence of idiopathic pulmonary fibrosis in US adults 18–64 years old. Raghu1 et al. Eur J Respir 2016; 48: 179

The incidence of IPF is increasing overtime in most countries, likely due to increase awareness of the disease. Data in USA is limited. 5 studies have looked at the incidence and prevalence of IPF in the USA and only 1 has looked at it over time. In that study, Medicare patients i.e. 65 and older were studied. That study showed that the incidence of IPF has been stable over time at about 93.7/100,00 between 2001-2011. The prevalence has increased during the same time period from 202.2 to 494.5/100,000.

The authors wanted to look at the incidence and prevalence of IPF in adults younger than 65 and searched data for 45 managed care health plans from 2004-2010. They used varying levels of restriction to insure a diagnosis of IPF. The mean age was 53 yo and 50.6% were women. The data showed an increase of the annual prevalence until 2008 then stable prevalence (4.6-6.7 for the most restrictive definition and 13.4-18 for the least) and decrease incidence (2.9 to 2.4 for

most and 7.9 to 5.8 for the least) and this decreased was seen in the younger than 44 while tin the 54-65 remained stable, likely due to increase accuracy in the diagnosis of IPF.

8. Transbronchial needle aspiration in peripheral pulmonary lesions: a systematic review and meta-analysis. Mondoni1 et al. Eur J Respir 2016; 48:196

The authors aimed at performed a pool estimate of the diagnostic yield of TBNA and predictive factors for a positive cancer result for peripheral lung lesions, since a bronchoscopic procedure is often the first procedure and a procedure that allows a more thorough assessment for lung cancer than a transthoracic procedure would (also see opinion piece in Cancer Cytopath of this month)
Of 2089 articles on the topic, 18 allowed for a qualitative and quantitative analysis.
Total 1687 patients across 10 countries med age 60.4yo, majority was prospective studies and 50% enrolled patients with suspected or know lung cancer.
Pooled TBNA yield was 0.53: ↑ 0.70 with bronchus sign present
↑ 0.62 with ROSE assessment
↑ in malignant vs benign dx (0.55 vs 0.17)
↑ 0.81 in >3 cm nodule
Higher yield for TBNA than TBBx (0.60 vs 0.45)
So reasonably good yield for dx.
One thing to keep in mind remains the quality and amount of tissue for molecular studies….Not addressed in this study.

9. Double staining of bacilli and antigen Ag85B improves the accuracy of the pathological diagnosis of pulmonary tuberculosis. Che et al. J Clin Pathol 2016; 69:600

The authors developed an antibody that is directed a specific protein Ag85B protein seen in *M.tuberculosis*. And then developed a method that allows performing at the same time this IHC and regular AFB stain called ZC staining. Using cases of granulomatous disease with proven TB by cultures and controls, they showed increased sensitivity of their ZC staining vs AFB alone (66% vs 34%) with no false positive. The main issue is the type of controls, none were other causes of granulomatous diseases like nonTB mycobacteria, or fungal, or vasculitis. But interesting method.

10. Prognosis in Resected Invasive Mucinous Adenocarcinomas of the Lung: Related Factors and Comparison with Resected Nonmucinous Adenocarcinomas. Lee et al. JTO 2016; 11:1064

The authors sought to study the clinicopathologic, radiologic and survival of patients with invasive mucinous AD compared to non mucinous inv AD since it was re-defined in 2011. Good premise with thorough data but biased by the way they interpreted the definition of inv mucinous AD. Indeed, they read that inv mucinous AD includes only mucinous tumors with a predominant lepidic pattern and excluded tumors that may have had other predominant patterns, which would have been interesting to study in itself to see if these different architectural patterns influenced survival like for non mucinous. In the end, they showed that their mucinous LPA had worse DFS than non mucinous LPA but better than acinar/papillary AD. Similarly they had worse OS than LPA but same as acinar/papillary. And that is adjusted for stage. They looked at nodular versus consolidative radiologic appearance and showed that the nodular were smaller cancers with less SUV max but no stat difference in survival. Only size mattered….

11. High prevalence of ALK+/ROS1+ cases in pulmonary adenocarcinoma of adolescents and young adults. **Scarpino et al. Lung Cancer 2016; 97:95**

The authors studied a large # AD (not clear what the total number was, possibly 789 with the other 2 being subgroups?), 789 tested for EGFR, 637 for ALK and 376 for ROS1 (the latter 2 groups were from EGFR WT tumors).

Out of the 6 patient aged <30 yo, 100% had either ALK or ROS rearrangements
Of the 17 aged 31-40 yo, 29% had either
Of the 46 aged 41-50 yo, 13% had either
Of the 568 aged >50 yo, 7% had either.
So a significant trend of ALK or ROS rearrangements associated with younger age (bias of small numbers studied in the younger age?).

A similar trend was not observed for EGFR mutant tumors.

12. Clinicopathological and prognostic significance of programmed cell death ligand-1 expression in lung adenocarcinoma and its relationship with p53 status. Cha et al. Lung Cancer 2016; 97:73

The authors studied 323 lung AD looking at prognostic value of PD-L1 and p53 as a surrogate of mutational tumor burden. All AD were also assessed for EGFR, K-ras, ROS1 and ALK.
60 (18.6%) of cases were PD-L1+ and PD-L1+ cases were statistically more common in males, large tumors, solid subtypes, p53 aberrant expression and less EGFR mutated tumors.
The effect of PD-L1 status was studied only in resected tumors, Stage I to IIIA (no mention if any patients had additional therapy). PD-L1+ tumors were associated with poorer RFS and OS, and p53 with poorer OS.
By multivariate, only stage, age and solid histologic subtypes were associated with poor prognosis, not PD-L1 and p53.

13. MiR-145 and miR-203 represses TGF- β-induced epithelial-mesenchymal transition and invasion by inhibiting SMAD3 in non-small cell lung cancer cells. Hu et al. Lung cancer 2016; 97:87

Functional study by which the authors have shown that the microRNA 145 and 203 can inhibit SMAD3. SMAD3 is the main stimulus for TGFβ which in turn activates EMT and allows for invasion and metastasis. So miR-145 and/or 203 was shown to be capable of suppressing invasion in NSCLC cell lines and thus potentially reduce metastasis. Next step would be to see if this can be actually targetable for treatment purposes…

14. Primary pulmonary clear cell sarcoma—the first two reported cases. Goh et al. Virchows Arch 2016; 469:111

The authors make a good case for one of the 2 tumors to be a clear cell sarcoma of the lung, well supported by FISH and RT-PCR to show the typical *EWSR1-ATF1* fusion. The second case morphologically not looking as classic as clear cell sarcoma (would like to know what Jenn thinks), the FISH was negative and tissue insufficient to perform the RT-PCR so not convinced that malignant melanoma is ruled out.

Review articles or consensus statements

1. PD-L1 Expression in Lung Cancer. Yu et al. JTO2016; 11:964
Excellent review on PD-L1 expression in lung cancer looking at detection of PD-L1 by IHC, discussing issues with different scoring systems, role of tumor infiltrating immune cells and mutation burden in treatment response, effect of tissue processing or chemotherapy on expression and need to look at other biomarkers such as other check-points. Nothing much new except that the authors report on results from 1 study comparing different antibodies staining the same set of lung cancers. Antibodies 22C3, 28-8 and SP263 had a similar staining profile while SP142 had lower expression and this could be a reflection of 3 Ab binding extracellular domains vs an Ab binding an intracellular domain. FYI another similar study is currently ongoing.

2. Transthoracic Needle Aspiration Biopsy for the Cytologic Diagnosis of Subsolid Lung Nodules. Klein. Cancer Cytopath 2016; p451
Opinion piece by Dr Kelin on the role of CT-TNB in the diagnosis of subsolid nodules. He tries to make the argument that although not as sensitive as a needle biopsy, it is nearly 100% specific. And that a false negative in these patients with slow growing tumor does not have the same level of negative impact on patient care. Also the advantage of ease of sampling difficult lesion or lesion of difficult access for needle biopsies.

3. Predictive Markers for the Efficacy of Anti–PD-1/PD-L1 Antibodies in Lung Cancer. Shukuya and Carbone. JTO2016; 11:976
Another excellent review on PD-L1 as a predictive marker for Anti-PD-1/PD-L1 antibodies. There is some reiteration of IHC issues for PD-L1 as in the prior review. But most of this review goes over the clinical trials looking at PD-L1, its different cut-offs, the different histologic subtypes ie SQCC, nonSQCC, and SCLC, and effect on RR, PFS, and OS. As these drugs are very expensive, and many patients do not respond, there is a need to identify the patients that will and despite its limitation PD-L1 IHC does seem to identify patients that are more likely to respond, exception being for SQCC. Table 2 nicely details the results of all these studies. However, there remains a fair number up to 10-15% depending on the studies of patients with neg PD-L1 that do show a response, which is significant. So the review also explores other ways that this marker could be improved upon or looking at other complementary markers.

4. The International Association for the Study of Lung Cancer Consensus Statement on Optimizing Management of EGFR Mutation–Positive Non–Small Cell Lung Cancer: Status in 2016. Tan et al. JTO2016; 11:946
Update of their 2013 consensus recommendations. Large section on molecular testing of *EGFR* that concerns us pathologists. Recommendations are to routinely do *EGFR* testing on all non-squamous cell carcinoma (and if clinically suspicious like SQCC in never smokers) in accredited lab. Table 1 goes over all the methods and performance status for each. New recommendation to do repeat biopsies in progressive disease. cfDNA likely to play a role, right now for *EGFR 790M* but needs further study. The remainder of the recommendations are in regards to treatment. Of interest to us pathologists: Nice Figure 1 to illustrate approach of patients with progressive disease and recommendation to assess tissue on new biopsy for *EGFR T790M* or other mechanisms of resistance. The presence of resistant *EGFR* in cfDNA is insufficient by itself to warrant treatment with 3rd generation TKIs. No data to support treating Stage I to III with EGFR TKIs. Only as part of clinical trials.

Case reports

1. TPD52L1-ROS1, a new ROS1 fusion variant in lung adenosquamous cell carcinoma identified by comprehensive genomic profiling. **Zhu et al. Lung Cancer 2016; 97:48**

The title says it all….