Pulmonary Pathology Journal Club

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**Case reports**

Pilotto, et al. Lung adenocarcinoma patient refractory to gefitinib and responsive to crizotinib, with concurrent rare mutation of the epidermal growth factor receptor (L861Q) and increased ALK/MET/ROS1 copy number. J Thorac Oncol 2013; 8: e105-106.


For discussion

Prognostic impact of tumor size eliminating the ground glass opacity component - Modified clinical T descriptors of the tumor, node, metastasis classification of lung cancer. Nakamura, et. al., JTO

Background: Lepidic pattern adenocarcinomas are now more commonly encountered (incidental or screening detected cancers), many of which have a ground glass opacity (GGO) component on high resolution CT (HRCT), thought to correlate with the lepidic/in situ component of the tumor. With the new proposed classification (AIS/MIA), it has become unclear how we should measure these tumors.

Methods: They studied 475 NSCLC patients who had preoperative high resolution CT (HRCT) and were staged as T1a-T2b N0M0 at surgical resection with follow-up data available. They selected a transverse slice through the center of the tumor for measurement via HRCT. Size was manually measured by two radiologists, measuring the maximum tumor size (including areas of GGO) and the maximum solid tumor size (excluding areas of GGO). Discrepancies were averaged. Cases were re-categorized into modified T descriptors (mT) based on the solid tumor size ONLY: mTis, mT1a, mT1b, mT2a and mT2b.

Results:

- Their cases were comprised of 353 adenocarcinomas, 77 squamous cell carcinomas, and 45 “other.”

- The reclassification resulted in increase in mT1a and mTis tumors with decrease in other stages.

- There was statistical difference in OS and DFS between mT1a and mT1b in the modified system (p=0.04), but not in the current T staging system (p=0.22) (multivariate analysis). There were significant differences in survival between mT1a and all other groups except mTis using the modified system, and significant differences between T1a and all other groups except T1b using the current system.
All down-staged tumors except one were adenocarcinomas (one SQCC with obstructive pneumonia)

Discussion:

- Measuring the tumor diameter including areas of GGO/lepidic/in situ growth may overestimate T stage.
- They argue that in the TNM supplement, it directs that generally only the invasive component should be measured in organ systems where T stage is determined by size.
- In this data set, their modified system provided clearer separation of stage groups with superior “separation index”, which provides evidence that this modified system is a better predictor of prognosis.

Take home message: Interesting study. It seems that we are moving the direction of measuring the invasive component only for staging purposes. I must admit, I think this may be easier to do using the preoperative CT than trying to measure from the slides or from the gross specimens, especially for tumors that will not fit entirely in one microscopic section.

Background: The secondary EGFR mutation T790M accounts for about half of acquired EGFR TKI resistance in lung cancer. Recent reports suggest that development of this mutation is associated with indolent course/favorable prognosis.

Methods: Retrospective study of 78 patients who had undergone re-biopsy, who had sensitive EGFR mutations in their original tumor, and had acquired resistance to EGFR TKI (initial response or durable stable disease for >6 months while taking TKI, followed by disease progression despite ongoing therapy).

Results:

● EGFR mutations included 42 (54%) exon 19 deletions, 33 (42%) L858R, and 3 (4%) exon 18 G719X. Median interval between progression despite TKI therapy and biopsy was 4.1 months (0-60.1 months).

● T790M mutations were less common in CNS mets (4 of 24 cases, 17%; CSF tested in 20, brain tumor sample in 4) than at other sites (22 of 54 cases, 41%, p=0.0417; lung/pleural fluid in 51, distant LNs in 3).

● Multivariate analysis showed T790M mutation, good functional status, and lack of meningeal carcinomatosis to be independent predictors of improved post-progression survival.

● 76% of patients underwent TKI re-challenge after initial failure (median TKI-free interval 1.8 months, range 0-28.2): 12 of 59 received a partial response, and 23 of 59 had stable disease, but median PFS was less than 3 months. There was no difference in response between those with and without T790M.

Discussion:

● Development of T790M leads to indolent tumor behavior, which is less common in the CNS (poor TKI penetration?). TKI re-challenge/continuation may provide benefit by promoting T790M cell population.

Take home message: T790M in patients with acquired EGFR TKI resistance is associated with quite remarkably better prognosis. Retesting for this mutation may be important when considering prognosis and continued therapy, and may become more routine. Although they called it “re-biopsy” in the title, more than half of cases were successfully tested from accessible fluid such as CSF or pleural fluid.
Diffuse lung disease in infancy and childhood: Expanding the chILD classification. Rice et. al., Histopathology.

**Background:** Diffuse lung diseases of infancy (<2 years) are quite different than those seen in adults, and patterns that look similar often have a different etiology (i.e. DIP). When looking at diseases affecting older children, you begin to see a mix of adult type ILD as well as persistence of diseases seen in infancy. The goal of this study was to validate the chILD classification system in babies <2 years, for which it was developed, and see if it applies to older kids <18 years.

**Methods:** Slides from 211 patients (0-18 years) who underwent biopsy for diffuse parenchymal lung disease (1991-2007) were reviewed by two thoracic pathologists. This constituted 197 wedges, 8 autopsies, 3 lobectomies, 2 CT guided biopsies and 1 transbronch. 7 biopsies were considered normal.

**Results:**
- There was agreement between the pathologists regarding the major pathologic pattern in 90% of cases, with a consensus diagnosis reached in the remaining cases.
- 93 patients (44%) were <2 years: of these, 58% fell into the group of diseases in the chILD classification
  - Patterns associated with surfactant deficiency were the most common: chronic pneumonitis of infancy (CPI), NSIP (8 cellular, 2 fibrotic), PAP, endogenous lipid pneumonia.
  - Next most common were diffuse developmental/growth anomalies (alveolar capillary dysplasia, congenital alveolar dysplasia, pulmonary hypoplasia).
- PIG: Only 6 occurred in relative isolation, seen in patients with CLO, CAD, ACD, and hypoplasia.

- Only 3 cases of NEHI, but they did not go back and stain cases that showed mild chronic bronchiolitis or “normal” biopsies that occurred before 2006 when they got bombesin stain

- The remaining children had diseases seen in older kids and adults (not included in chILD) like DAD, OP, and infection; or frequently had conditions that were “masquerading” as diffuse lung disease, including chronic bronchiolitis, follicular bronchiolitis, asthma, and vascular disease.

● There were 118 patients (56%) 2-18 years, of which 23% were in the chILD diagnostic groups (and half of these 23% showed NSIP pattern: 7 cellular, 8 fibrotic).

- True infantile disease diagnoses: 3 alveolar hypoplasia, 1 NEHI, 1 CPI

- Two interesting etiologies for common patterns: DIP pattern in a patient with Gaucher’s disease, and endogenous lipid pneumonia in a patient with Nieman-Pick

- The remainder were patterns commonly seen in adults: DAD, OP, AFOP, UIP (1 case, 18 yo), bronchiolitis/airway disease, LIP/lymphoid hyperplasia, hemosiderosis, HP, sarcoid, alveolar microlithiasis, LCH, vascular disease and infection

**Discussion:**

● In order to capture all pediatric patients biopsied for suspected ILD, the chILD classification needs to be expanded, especially for kids 2-18 years, to include many diseases seen in adults.

● It is increasingly recognized that disorders of surfactant metabolism, especially mutations in SPC and ABCA3, can present in the older child and adult. Thus this should be included on the differential diagnosis of the associated patterns in these age groups.

● Evidence continues to accumulate indicating that PIG only occurs in babies <2 years, where it may represent simple persistence of embryological interstitial mesenchymal cells or a non-specific pattern of injury, as it is commonly seen in association with other abnormalities.

● Presence of more than one pattern is not uncommon, especially in patients with surfactant disorders

**Take home message:** This is a good reference to frame your mindset and differential diagnosis when looking at a biopsy in a child <18 years. You are much more likely to encounter developmental and growth disorders, NEHI, PIG and surfactant protein disorders in children <2, but also think of them in the older child, along with more “run of the mill” ILD patterns we see in adults. Age is critical to formulating a differential for the most likely underlying etiology for the observed pattern.
GROUP A: HISTOLOGICAL PATTERNS MORE PREVALENT IN CHILDREN <2 YEAR

Diffuse developmental and growth disorders
- Alveolar capillary dysplasia
- Congenital alveolar dysplasia
- Alveolar hypoplasia/simplification
- Other

Specific conditions of undefined aetiology
- Neuroendocrine cell hyperplasia of infancy
- Pulmonary interstitial glycogenosis

Surfactant protein disorder-associated histological patterns
- Chronic pneumonitis of infancy
- Pulmonary alveolar proteinosis
- Desquamative interstitial pneumonia
- Non-specific interstitial pneumonia (cellular and fibrotic)

GROUP B: HISTOLOGICAL PATTERNS MORE PREVALENT IN CHILDREN OF 2-18 Y

Interstitial pneumonias (idiopathic, or with known cause/association other than SPD)
- Organising pneumonia
- Acute fibrinous organising pneumonia
- Diffuse alveolar damage
- Usual interstitial pneumonia
- Desquamative interstitial pneumonia
- Non-specific interstitial pneumonia (cellular and fibrotic)
- Other

Other patterns of diffuse lung disease
- Haemosiderosis
- Alveolar microlithiasis
- Sarcoidosis
- Langerhan cell histiocytosis (localised and systemic)
- Other

Lymphoproliferative disease
- Lymphoid interstitial pneumonia
- Diffuse lymphoid hyperplasia
- Lymphomatoid granulomatosis
- Follicular bronchiolitis
- Other

GROUP C: DISORDERS MIMICKING DIFFUSE LUNG DISEASE

Small airways disease
- Acute, acute and chronic, chronic bronchiolitis
- Obliterative bronchiolitis
- Follicular bronchiolitis
- Eosinophilic bronchiolitis/asthma
- Other

Vascular disorders (primary and secondary pulmonary involvement)
- Primary pulmonary arterial hypertension
- Pulmonary veno-occlusive disease
- Pulmonary capillary haemangiomatosis
- Thromboembolic disease
- Lymphangiomatosis
- Lymphangectasia (primary and secondary)
- Secondary vasculopathies (e.g. due to cardiac disease)
- Primary and secondary pulmonary vasculitis
- Other

INFECTIONS (Viral, Bacterial, Fungal, Parasitic)
NEOPLASMS (Any)
Primary salivary-type lung cancer-clinicopathological analysis of 88 cases from China. Zhu et. al., JTO

**Background:** Primary salivary gland-type tumors represent <1% of all lung tumors, and are mainly comprised of mucoepidermoid carcinoma and adenoid cystic, with epithelial-myoepithelial carcinoma occurring more uncommonly. Since they are rare, they are mainly reported in small studies.

**Methods:** Cases were collected from two oncology centers between 2001-2013, comprising 88 cases.

**Results:**
- They observed 69 MEC, 12 ACC, and 7 EMC; no differences were observed in demographics. There was generally a wide age range (7-75 years), and most patients (84%) were non-smokers.
- Radiologically, the lesions were more often central (26 cases) but could also be peripheral (12 cases). Contour was round, oval or lobulated in all cases. Central lesions could often be seen projecting into the bronchus. PET was done in one case of ACC, which showed “slight but obviously increased” uptake.
- Grading of MEC showed 45 low grade, 11 intermediate and 13 high grade
- Average follow up was 49 months (3-134). 15 (17%) patients had recurrence/metastasis (4 of whom had positive margin). This constituted 42% of ACC, 13% MEC and 14% EMC (p=0.057):
- OS at 3, 5 and 10 years was 96%, 86% and 81%; DFS was 90%, 79% and 55%. There was no significant difference among the histologic groups, but it looks like ACC was on its way to worse DFS (p=0.082; 46% 5 year DFS for ACC compared to 86-87% in other two subtypes) if there was a larger cohort.
- Worse OS and DFS was seen in high grade MEC than low-intermediate grade (p<0.001)
- Multivariate analysis showed “intrathoracic invasion” and high grade MEC to be significant; univariate also included margin status, TNM stage and lymph nodes status

**Discussion:**
- Clinical and radiographic findings are characteristic but not specific
- MEC is the most common subtype, where grade predicts outcome.
- Optimal treatment strategy isn’t standardized, but they propose complete surgical resection, with consideration of post-op radiation if positive margin

**Take home message:** Although they state that there is no significant difference in subtypes, it seems to me that ACC and high grade MEC are the bad actors; that being said, even the low grade MEC and EMC can sometimes recur/metastasize, necessitating long term follow-up. No surprisingly, staging parameters predict outcome.
**Articles for Notation**

**Neoplastic**


**Summary:** They tested 594 NSCLC by tissue microarray (470 ADCA, 83 SQCC, 26 large cell and 15 other). They used all 3 ALK antibodies (ALK1, 5A4 and D5F3), read by 2 pathologists, and scored any amount of cytoplasmic staining to be positive (1+ weak/faint, 2+ moderate, and 3+ intense); discrepancies settled by consensus. They found 7 ALK+ by FISH (1% of all cases; 6 of 478 ADCA, the other one was technically a pleomorphic/sarcomatoid ca, but had ADCA component). All ALK+ were also positive for all 3 ALK antibodies by IHC (5A4 and D5F3 were generally stronger intensity than ALK1). The immunostains were positive in 13/594 with ALK1 (2%); 18/594 with 5A4 (3%); and 13/594 with D5F3 (2%). Interestingly they had one case with a subtle ALK probe separation that is technically FISH negative by manufacturer criteria, but it was positive with all 3 antibodies.

**Take home message:** More evidence that IHC is a good screening strategy for finding the rare cases with ALK+, as the stains have high sensitivity and excellent negative predictive value, as long as any degree of positivity is reflexed to FISH (positive predictive value is only 39-54%). The only issue is staining can be patchy, which may lead to sampling issues on small biopsies. I think now the big question is- why is FISH gold standard, especially when this particular translocation is actually quite challenging to see by FISH and can be missed? We don’t really know that IHC+/FISH- patients (especially 2-3+) are not going to respond to crizotinib, and in fact there are reports of patients responding dramatically in this scenario. More study needed.

**The central nervous system as a sanctuary site for ALK positive non-small cell lung cancer.** Gainor et al, JTO.

**Summary:** Report of 2 ALK+ patients with CNS progressive disease on crizotinib, taking the rare forms of intramedullary spinal cord metastases (ISCM) and leptomeningeal carcinomatosis (LC). Look back at their 96 ALK+ cases showed 4/96 experienced ISCM (4%) and 5/96 had LC (5%). Most patients experienced these as late complications. There is evidence that crizotinib has poor blood-brain barrier penetration, making these patients susceptible to the much more common brain mets as well as these rare forms of CNS progression.

**Take home message:** The title says it all 😊. Some of the new generation ALK inhibitors in clinical trials have shown efficacy in brain mets, which may imply better penetration of the CNS. This is something that should be specifically studied in these clinical trials of new ALK inhibitors.

Summary: They tested 86 stage IIIb/IV patients with adenocarcinoma/adenosquamous carcinoma, using matched serum and tissue samples, and matched malignant pleural effusions (MPE) collected from a subgroup (27 patients), including DNA extracted from tissue, MPE cell block, MPE supernatant, and circulating free DNA from plasma. They compared amplification refractory mutation system (ARMS, a PCR-based method looking for known mutations), Sanger sequencing, and mutant-specific IHC.

Compared to tissue as the gold standard, sensitivity of MPE cell block was 82%, MPE supernatant was 64%, and plasma was 68%; Specificity was 80%, 100% and 100%, respectively. Sensitivity of Sanger sequencing was lower than ARMS in both tissue and cell blocks, with high specificity. Sensitivity of IHC was 55% for tissue and 50% for MPE cell blocks, with high specificity.

Take home message: Testing of MPE cell block or even MPE supernatant/plasma seem to be valid ways to test for *EGFR* mutations if tissue is not available, with the caveat that sensitivity is lower (thus tumor tissue followed by cell block would be preferred over supernatant/plasma if available). If you find a mutation in *EGFR* using plasma or supernatant, it seems to be quite specific. PCR based amplification tests definitely seem to be the most sensitive means to detect these mutations (although at this point it seems the serum tests are research only).

Multi-gene analysis from waste brushing specimens for patients with peripheral lung cancer receiving EBUS-assisted bronchoscopy. Tsai et al, Lung Cancer.

Summary: They looked at 84 patients with positive brushing cytology (which was about 69% of the patients with positive biopsy), and tested the EBUS brushing-derived waste specimen for *EGFR*, *KRAS* and *ALK* mutations (for *ALK* testing they used *EML4-ALK* RT-PCR in cases that were *EGFR* and *KRAS* negative). Basically the waste material consisted of the snipped off brush tip placed in fluid after it was used to create smears, and the brush/fluid was then frozen. They utilized the cell-derived RNA as a template which was amplified using RT-PCR and then sequenced. PCR amplification/sequencing failed in only 5% of cases. They detected *EGFR* mutations in 55% of their samples (44 cases, concordance with tissue mutation testing in 94%). 24 of these patients were treated with EGFR inhibitors, which achieved disease control in 83% and response in 63%. Their *KRAS* mutation rate was only 2.5% (study performed in Taiwan). As you might expect, they tested 19 patients proven to have lung cancer but with a negative brushing, and they did not detect any mutations in those samples. *EML4-ALK* was detected in 2 of 19 samples negative for both *EGFR* and *KRAS*.

Take home message: In the era of doing more with less, this looks like a promising way to use sensitive PCR methods to detect these mutations. The limitations are obviously that it only seems to work if your brushing is actually positive, and PCR is currently not accepted as a gold standard to approve crizotinib therapy in *ALK* rearranged patients, according to the FDA.
**Distinct clinicopathologic characteristics of lung mucinous adenocarcinoma with KRAS mutation.** Ichinokawa et al, Human Pathol.

**Summary:** Study of 45 mucinous adenocarcinomas, in which they found 49% with KRAS and 16% with EGFR, and they say they have two cases that showed BOTH. Their KRAS mutated cases were more likely to occur in the lower lobe and had less nuclear atypia.

**Take home message:** KRAS mutation seems more common among the mucinous tumors with bland nuclear features (classic “mucinous BAC” pattern) that more commonly occur in the lower lobes. They glaze over the fact that 2 cases had both EGFR and KRAS, and don’t give any important details about these two cases (mutation percentages, etc).

**Contributions of KRAS and RAL in non-small cell lung cancer growth and progression.** Guin et al, JTO.

**Summary:** RAL is a family of GTPases that lie downstream of KRAS, and are implicated in RAS-mediated tumor signaling. They looked at IHC and transcriptome analysis, and found that RALA and RALB expression was associated with poor survival, and there was higher expression in KRAS mutated cell lines.

**Take home message:** RAL seems associated with poor survival and KRAS mutation, and may be able to be targeted by novel therapeutic agents.

**Detecting EGFR alterations in clinical specimens- pitfalls and necessities.** Isaksson et al, Virchows Arch.

**Summary:** They look at EGFR testing in Southern Sweden in 350 patients with all types of lung cancer using a variety of techniques. They had trouble with the mutation specific antibody staining on TMA tissue, in that they had several discrepant cases with molecular based testing, and they saw heterogeneous staining in whole tissue sections. They also found mutations not covered by these antibodies, and thus do not advocate them for screening for EGFR mutations in this population. High expression of EGFR by IHC correlated with increased copy number but not mutation status.

**Take home message:** I think we knew most of this already, but now we know it about the Southern Swedish population in particular 😊.
Differences in the prognostic implications of vascular invasion between lung adenocarcinoma and squamous cell carcinoma. Usui et al, Lung Cancer.

Summary: They studied prognostic implications of vascular invasion in 81 peripheral SQCCs and 255 ADCAs, using the aid of VVG and D2-40 stains. Among all patients, 5-year survival for 160 patients with vascular invasion was 38.4%, compared to 76.3% in the 176 patients without (p<0.0001), which was a significant prognostic factor by multivariate analysis. The difference in cancer-free survival was significant for ADCA, but barely non-significant in SQCC (p=0.086). Vascular invasion was significant in predicting survival for lepidic, papillary and acinar ADCAs, but not solid subtype.

Take home message: Vascular invasion is a poor prognostic factor in NSCLC. It seems to lose its prognostic power in tumors that are known to be bad actors, i.e. SQCC and solid ADCA.

In compressed lung tissue microscopic sections of adenocarcinoma in situ may mimic papillary adenocarcinoma. Thunnissen et al, Arch Pathol Lab Med.

Summary: I’m sure we have all seen and struggled with this (or maybe only I have struggled 😊), when lepidic pattern becomes artfactually compressed and starts to look quite papillary. They used 3D reconstruction and elastic stains to examine 2 cases which looked quite papillary but they argue are actually lepidic. They used discontinuous elastin staining in apparent fibrovascular cores as a sign they were really compressed alveoli with lepidic carcinoma, while true papillary carcinoma lacked elastic layer. They argue against statements in the new classification system that state desmoplasia is not required to diagnose papillary pattern adenocarcinoma, and if a tumor has a lepidic pattern but the alveoli are filled with papilla, it should be called papillary adenocarcinoma, since many such tumors may represent compressed lepidic tumors. But I have to say, I would have some trepidation calling AIS based on some of their images with tall, almost mucinous pattern and apparent papilla.

Take home message: I think most of us knew compressed lepidic could look papillary, but now it is in the literature. More evidence that, in particular, lepidic, papillary, and micropapillary patterns are often in the eye of the beholder, and could use some standardization before globally applied for prognosis.

Association of c-Met phosphorylation with micropapillary pattern and small cluster invasion in pT1-size lung adenocarcinoma. Koga et al, Lung Cancer

Summary: Micropapillary pattern (MPP) is well known to be associated with lymph node mets and poor outcome, and this group had previously associated it with a type of invasion they call “small cluster invasion”, which they define as “markedly resolved acinar-papillary tumor structures with single or small clusters of carcinoma cells invading stroma within fibrotic foci.” So in other words, the weird pattern that MPP tumors show when they invade. C-Met plays a role in tumor invasion and mobility. They looked at 125 cases of surgically treated adenocarcinoma <3cm with antibodies against c-Met and phosphorylated c-Met (pc-Met). 60% of their cases had MPP (>10% of the tumor; seems like a lot!)
Enriched somehow?) and small cluster invasion. Breakdown by predominant growth pattern showed 58% papillary, 16% acinar, 9% micropapillary, 6% mucinous, 4% solid, 3% AIS, 2% lepidic, 2% MIA. All cases were positive for c-Met. 95% of cases were positive for pc-Met, but they were able to discern that 22% showed high expression of pc-Met (at least 10% of cells showing 3+ strong positivity and weak to moderate positivity in at least 40% of tumor cells). Cases with high pc-Met were associated with MPP, small cluster invasion and worse survival.

**Take home message:** There may be some association here, but looks like there were plenty of tumors showing MPP that did not have high pc-Met, and high pc-Met cases that did not have MPP, and the stain sounds very hard to interpret.

A panel of four immunohistochemical markers (CK7, CK20, TTF-1 and p63) allows accurate diagnosis of primary and metastatic lung carcinoma on biopsy specimens. Montezuma et al, Virchows Arch.

**Summary:** They looked at 443 lung biopsies by IHC. If it looked like SQCC, they ordered only p63 to confirm. They ordered CK7, 20 and TTF1 on all ADCAs, and if they could not tell SQCC vs. ADCA, they ordered all 4 stains. After the staining panel, 44.7% were NSCLC favor ADCA, 28.7% were SQCC, 13% were metastatic adenocarcinoma, 9% were NSCLC NOS, 2% were adenocarcinoma of unknown primary, 2% were probable adenosquamous. Mets were 43% colorectal, 36% breast, 9% GYN, 5% GI, 3% prostate, and 4% other. Definitive site of origin was determined in 81% of cases, and ADCA vs. SQCC subtyping was achieved in 87%. 18% of primary lung cancers had clinically been suspected to be a met.

**Take home message:** I don’t think it is a shock to any of us that a panel like this works. But in my opinion, it is overkill in most routine cases.


**Summary:** This 3 stain panel was applied to whole tissue sections from 107 SQCC (including 12 pulmonary SQCC) and 49 urothelial cancers (UC). They found p40 in 99% of SQCC (including all 12 pulmonary tumors) and 94% of UC. Pax8 was positive in 3% of SQCC (all originating in uterine cervix, all 12 lung tumors were negative) and 10% of UC. Glypican 3 was found in 20% of SQCC (actually 50% of those arising in lung, but present in tumors from other sites as well) and 12% of UC.

**Take home message:** p40 is a very sensitive squamous marker regardless of anatomic site. Pax8 was not positive in any pulmonary SQCC. Glypican 3 was positive in 50% of pulmonary SQCC- good to remember since it is touted as a marker of hepatocellular carcinoma- they anecdotally describe a case of metastatic squamous lung cancer misdiagnosed as HCC on the basis of this stain.
Serpin B3 is associated with poor survival after chemotherapy and is a potential novel predictive biomarker in advanced non-small cell lung cancer. Urquhart et al, JTO.

Summary: In their previous biomarker discovery project, this group found that serine protease serpin B3 expression was associated with poor response to platinum chemo, and this is their prospective validation. They used IHC for serpin B3, and scored based on percentage of positive tumor cells (1+=1-10% of cells positive, 2+=10-50%, 3+=50-100%). They studied 197 stage IV patients treated with first line platinum chemo. Staining was seen in 36% of NSCLC (25% showed 1+, 11% 2-3+). Overall positivity was more common in SQCC, although usually weak. Expression was independently associated with survival: median survival was 332 days in score 0, 268 days in score 1, and 120 days in score 2-3 (p=0.004).

Take home message: Serpin B3 expression seems to predict a subgroup of patients that will fail to respond to traditional platinum chemotherapy, who may be better served by supportive care or consideration of alternative therapies.

The prognostic significance of aldehyde dehydrogenase 1A1 (ADH1A1) and CD133 expression in early stage non-small cell lung cancer. Alamgeer, et al, Thorax.

Summary: They looked at expression of these two stem cell markers in 205 invasive stage I NSCLCs via immunohistochemistry (144 stage 1A and 61 stage IB). At a median of 5 year follow-up, they observed 62 relapses and 58 lung cancer deaths. Overexpression of ADH1A1 was seen in 68.7% of cases, associated with SQCC histology and stage IB; and overexpression of CD133 was observed in 50.7%, associated with invasive ADCA histology and stage 1A. Both were associated with poor overall survival (p=0.017 and p=0.039). Expression of ADH1A1 also predicted worse recurrence-free survival. When they combined the markers, patients with expression of both had the worst outcome, while patients who had tumors that were negative for both did the best.

Take home message: These stem cell markers are associated with worse outcome, possibly because the tumor cells have superior self-renewal capacity because of their stem cell phenotype. They excluded all MIA/AIS, not sure I agree with that, would be interesting to see what they showed and also may introduce bias to systematically exclude cases with good prognosis.

Interobserver agreement and assay reproducibility of folate receptor alpha expression in lung adenocarcinoma- A prognostic marker and potential therapeutic target. Bremer et al, Arch Pathol Lab Med.

Summary: They looked at IHC for folate receptor alpha (clone 26B3) as a potential biomarker to predict response to folate antagonists. They found expression in 39/54 adenocarcinomas (72%) and 4 of 37 squamous cell carcinomas (11%). There was agreement among 3 pathologists 92% of the time when reading the stain in a semiquantitative fashion (which required assigning 0-3+ intensity and % of cells
staining with each of these intensities). They also found good reproducibility across staining platforms and different labs.

**Take home message:** The stain seems to work in a reproducible fashion, but since the antifotales in development have yet to finish clinical trials, who knows if the stain will predict response or if the drugs will work in lung cancer at all.....lots more to be done before this is ready for prime time.

**Quality gaps and comparative effectiveness in lung cancer staging. The impact of test sequencing on outcomes. Almeida et al, Chest.**

**Summary:** Current evidence based guidelines recommend mediastinal staging as the first invasive procedure for patients with suspected lung cancer and mediastinal adenopathy. They looked at practice patterns and outcomes in 137 patients fitting the aforementioned clinical scenario, and found guideline consistent care in only 22%. Instead, 46% of patients had CT-guided biopsy of the primary lung lesion, and 32% had bronchoscopic biopsy without TBNA staging of the mediastinum. The patients who had care within guideline recommendations underwent fewer invasive tests and fewer complications (most often pneumothorax related to CT-guided biopsy. EBUS-TBNA was/would have been sufficient to guide therapy without any additional testing in 64% of patients: 49% of patients were diagnosed with positive lymph node involvement, and the remaining 16% had negative lymph nodes but bronchoscopic biopsy performed at the same time was positive. This study was performed at MD Anderson, so they looked at patients that had complete workup there vs. patients that were referred with part of the workup already done outside. 71% of patients that had complete workup done at MD Anderson had guideline-consistent care, and no other invasive testing was required in 76% of these patients. In 96 patients that had received a prior biopsy but no mediastinal staging at an outside institution, 64% of these biopsies were deemed unnecessary since subsequent EBUS-TBNA provided diagnostic tissue with appropriate staging at the same time. There was a similar rate of inadequate tissue for genetic testing in EBUS samples and CT guided biopsies.

**Take home message:** Currently available evidence based guidelines are not being followed regarding the sequence of test ordering in patients with suspected lung cancer and probably mediastinal lymph node disease, leading to increased invasive tests, complications, and cost. EBUS-TBNA should be the first test for patients in this clinical scenario.

**Characteristics and outcome of patients with second primary lung cancer. Reinmuth et al, Eur Resp J.**

**Summary:** 139 of 2816 lung cancer patients developed a second malignancy, 78 of which were a second lung cancer (59 NSCLC, 13 small cell). The initial lung cancer diagnosis constituted 69 NSCLC and 9 small cell. 59 of the second tumors were considered metachronous (>2 years from diagnosis of first tumor) at a mean interval of 72 months. Those patients that were destined to get a second tumor presented with their first tumor at a younger age and lower stage than those patients who did not get a second lung
cancer, and the second tumors that were detected within 5 years of first lung cancer diagnosis presented at lower stage. Never and former smokers were more likely to get a second lung cancer than current smokers, but current smokers that ended up getting a second tumor had a higher mean cigarette consumption. The patients who got a second tumor had mean overall survival of 12.6 years from their first lung cancer, and 4.8 years from diagnosis of their second lung cancer, which was much better than patients who did not go on to get a second lung cancer (mean OS 1.5 years). This difference in OS was due to improved outcome of patients with NSCLC, not small cell.

**Take home message:** While getting a second lung cancer logically seems like a bad thing, it turns out that it likely means you were younger and healthier when you got your first lung cancer, and your first cancer probably wasn’t all that bad, so surviving long enough to get a second lung cancer means you actually have a better prognosis than the majority of lung cancer patients that do not survive their first battle. The propensity for second tumors in never/light smokers also probably indicates a high proportion of lepidic-pattern, *EGFR* enriched tumors, which we know will do better.

**Lung cancer in pregnancy:** Report of nine cases from an international collaborative study. Boussios et al, Lung Cancer.

**Summary:** Quite depressing report of nine pregnant European women (age 24-42 years, average 33) with lung cancer. Median gestation age at diagnosis was 16 weeks (range 6-28 weeks). All patients presented with metastatic disease. 4 patients had ADCA, 2 NSCLC NOS, 1 each SQCC, large cell and poorly differentiated carcinoma NOS. 5 were treated systemically during gestation, 3 more were treated post-gestation, none responded. One patient had spontaneous pregnancy loss, three pregnancies were terminated, and the remaining 5 babies were delivered prematurely via C-section due to poor maternal status at an average of 30 weeks (26-33 weeks). Maternal outcome was universally very poor, survival was less than one year (3 survived less than one week after delivery, and 75% less than one month). No placental or fetal metastases were observed, although this has been previously reported to occur in the literature.

**Take home message:** Lung cancer is very rare during pregnancy and has a horrible prognosis, although this seems to likely relate to the advanced stage at which all these patients presented. It is unknown whether the state of pregnancy leads to more aggressive behavior in lung cancer, or if it blunts the effects of chemotherapy, or if this is just typical stage-dependent behavior of this bad disease.

**Volumetric computed tomography screening for lung cancer:** Three rounds of the NELSON trial. Horeweg et al, Eur Resp J.

**Summary:** This trial uses more stringent criteria to be considered positive the NLST, using volumetric analysis. Positive screen criteria include >500 mm³ (which is about 9.8 mm diameter) or volume doubling times <400 days. This compares to NLST which considered positive anything 4mm or larger.
They screen 7,582 patients, and 87% of them were still coming for annual screening at three years. Their criteria yielded a 2% positive rate, and 11% indeterminate, with the rest being negative. Of 493 positive screens, about 40% were “true positive” (200 cases). The PPV of the screening scan increased slightly with every yearly scan, trending up from 35% to 45%. 6% of participants had at least one positive screen over the 3 year period. 273 patients had a false positive screen, and 67 of these patients underwent and invasive diagnostic procedure, most of which were surgical excision of some sort.

**Take home message:** Using their criteria (about 1 cm positive cutoff vs. 4 mm), they substantially reduced the number of false positive results compared to NLST. However, whether that resulted in missing a significant number of lung cancers (high false negatives) is still unknown.

**Computed tomography screening for lung cancer: Results of ten years of annual screening and validation of COSMOS prediction model. Veronesi et al, Lung Cancer.**

**Summary:** They enrolled 1035 volunteers for low dose CT screening in 2001 and followed annually for 10 years with 65% compliance. Patients were smokers/former smokers of >20 pack years and were >50 years old. 71 lung cancers were diagnosed (about 7% of patients), 12 of which were diagnosed at baseline, and 23 patients died of their lung cancer. 61% were adenocarcinoma, and mean size of detected NSCLC was 12.5 mm. 67% were stage IA, which had 84% and 65% 5 and 10 year survival, compared to 64% and 57% for the whole lung cancer group. Ten patients had surgery for a benign lesion. They looked at the validity of the Bach and COSMOS risk models for predicting lung cancer, which are based on age, sex, smoking history, and asbestos expose: They found that COSMOS predicted the number of lung cancers found at baseline and in the first three years, while the Bach model predicted the number of lung cancers encountered thereafter. They argue that neither frequency nor proportion of stage I disease decreased with time, so screening should not be discontinued.

**Take home message:** They found no clear endpoint for screening, although there is undoubtedly a point of diminishing returns based on life expectancy, etc.

**Clinical indications and results after chest wall resection for recurrent mesothelioma. Burt et al, J Thoracic and CV Surg.**

**Summary:** They looked at surgically treated patients with mesothelioma who had localized ipsilateral chest wall recurrence amenable to resection, and treated with redo operation. This comprised 47 of 1142 patients (32 epithelioid, remainder biphasic), 32 treated with extrapleural pneumonectomy and 15 with pleurectomy and decortication. There was a mix of patients who received chemo and/or radiation adjuvant treatment and those who did not. Median time to recurrence was 16 mos, and most recurrences were incisional or costophrenic. Average hospital stay after redo surgery was 3 days, and they had no 30 day operative mortality or surgical complications. Those with biphasic tumors had
shorter time to recurrence. The expected survival benefit seemed to be heavily reliant on the time to recurrence; median 2.7 month survival for those <10 mos, 15.9 months for those >10 months).

**Take home message:** At surgical centers with the expertise to perform this kind of surgery, redo chest wall resection seems to be a viable treatment option, especially for younger patients with epithelioid histology that have a longer interval from initial surgery to recurrence.

**Long term outcome after en bloc resection of non-small cell cancer invading the pulmonary sulcus and spine.** Collaud et al, JTO.

**Summary:** Report of 48 patients s/p induction chemorads who then underwent en bloc resection of lung, spine and chest wall. They performed the operation in one or two steps, depending on complexity of vertebral resection. They were able to achieve complete resection with negative margins in 88% of cases. Post-surgical (30 day/in hospital) mortality was 6%. 50% of patients had achieved a complete or near complete response to induction therapy. 24 patients were alive without recurrence at last follow up (0-151 months, mean 26 months), and 5 year overall survival was 61%. Response to induction therapy was significant predictor of survival in multivariate, with margin status and length of ICU stay also being significant in univariable analysis.

**Take home message:** En bloc lung/chest wall/spine resection seems to be a viable option at centers with this kind of expertise in selected patients, who seemed to have quite a good outcome in this series.

**Pulmonary metastatic nodules of uterine low grade endometrial stromal sarcoma: Histopathological and immunohistochemical analysis of 10 cases.** Park et al, Histopathology.

**Summary:** Metastatic ESS in the lung can be notoriously tricky, since it can present long after the primary tumor or precede the primary diagnosis, and present with a variety of histologic/radiographic patterns. Of the 10 patients, 6 presented 0.6-5.8 years after surgery for ESS, 3 patients presented with pulmonary mets before their ESS was discovered, and in one patient the lung and uterine tumors were discovered simultaneously. Radiographically, 4 patients had solitary nodules, 5 had multiple nodules, and 1 had GGOs. Only 2 patients were symptomatic from their pulmonary metastases. 9 patients were alive at last follow-up, one patient with military pulmonary mets died 9.6 years after diagnosis of ESS. Not surprisingly, most tumor nodules were centered on airway, vessels, pleura or lymphatics. They identified several potential pitfalls, including: HPC-like vascular pattern, entrapment of bronchial epithelium often with cystic change, smooth muscle differentiation, myxoid change, collagen deposition, microcystic change, and abundant foam cells. Tumor cells coexpressed CD10 and ER (lots of background staining with ER), and they saw some early/“H&E occult” mets using these stains, which highlighted subtle early mets undermining the bronchial epithelium of small airways.
**Take home message:** They point out several important issues when considering ESS metastatic to the lung: ESS can first present as lung mets, and ESS can show lots of strange and interesting secondary patterns/pitfalls.

**Association of D2-40 and MMP-1 expression with cyst formation in lung metastatic lesions of cutaneous angiosarcoma on the scalp: Immunohistochemical analysis of 23 autopsy cases.** Masuzawa et al, Human Pathol.

**Summary:** Of their 23 patients with pulmonary metastasis of angiosarcoma arising in the scalp, 39% presented as thin walled cysts alone, 39% presented as nodules, 13% had a mix of cysts and nodules, and 9% with GGO. All but one of the patients with cystic mets had complicating pneumothorax, often recurrent/refractory, which was a common cause of death. Most of the cysts were very bland, and tumor cells were often inconspicuous, with only 2 cystic lesions demonstrating tumor necrosis as the apparent reason for cystic change. They found D2-40 to be positive in all primary skin lesions and 92% of the metastatic lesions. Even when the neoplastic cells were not apparent on H&E examination of the cysts, a thin layer of D2-40 positive cells could be demonstrating surrounding the cavity. ERG was also positive in 95% of the primary skin lesions and 92% of the metastatic lesions. They found MMP-1 staining in 95% of primary lesions and 83% of metastatic lesions, but there was no difference between cystic and nodular mets.

**Take home message:** D2-40 can be used as a tumor marker in cutaneous angiosarcomas metastatic to the lung with relatively low background. The mechanisms of cyst formation in metastasis may be from MMP-1 production by the tumor leading to breakdown of the pulmonary parenchyma, although no difference was seen in MMP-1 expression between cystic and nodular mets.

**Pulmonary inflammatory myofibroblastic tumor and IgG4-related inflammatory pseudotumor: A diagnostic dilemma.** Bhagat et al, Virchows Arch.

**Summary:** IMT and inflammatory pseudotumor (IPT) have overlapping morphologic characteristics, and were historically categorized under the same umbrella of “IPT.” Now that we know IMT is a neoplasm associated with ALK rearrangement which can occasionally behave in an aggressive fashion, and IPT in the setting of IgG4 disease can manifest in other organs, this distinction is important. They looked at 10 cases (4 IMT and 6 IgG4-related IPT), and found IMT patients to be younger than those with IPT. They found that bland spindle cell proliferation, fibrosis and inflammation with lymphocytes and plasma cells were common to both lesions. The spindle cell proliferation was more prominent in IMT whereas the lymphoplasmacytic infiltrate was more prominent in IPT. Obliterative phlebitis was only seen in IPT. The number of IgG4 positive plasma cells was significantly higher in IPT than in IMT (102-150/hpf vs. 4-10/hpf), while ALK was positive in 3 of 4 IMTs but none of the IPTs.
**Take home message:** While historically grouped together, it is important to distinguish the true neoplasm IMT from IPT due to treatment and prognostic implications. Important to note that some cases of IPT will be related to IgG4 disease which usually have the classic morphologic features.

**Comparative immunohistochemical analysis of pulmonary and thymic neuroendocrine carcinomas using Pax8 and TTF-1. Weissferdt, et al, Modern Pathol.**

**Summary:** 25 cases of pulmonary (21 typical and 4 atypical) and 25 cases of thymic (8 typical and 16 atypical) carcinoid tumors were stained with Pax8 and TTF-1. Interestingly, Dr. Moran used his own published criteria which do not align with the WHO: They allowed up to 3 mitoses per 10 hpf in the carcinoid group, and allowed necrosis if it was “only focally identified and did not amount to more than punctate necrosis”. 2 pulmonary tumors (8%) showed nuclear expression of Pax8 (weak but diffuse), while 19 (76%) were positive for TTF-1 (always diffuse but weak). 8 thymic tumors (32%) were positive for Pax8, and 2 (8%) were positive for TTF-1. They argue that the differentiation of primary site is important since thymic tumors have a worse prognosis, but to me it seems clinical evaluation of primary site is probably better than this IHC panel in many cases. Plus I am not sure if that “worse prognosis” is simply a reflection that most thymic carcinoids are atypical.

**Take home message:** Generally TTF-1 goes with lung primary site and Pax8 with thymic, but this seems to be far from definitive, since Pax8 expression was actually not that common in the thymic tumors, and both TTF-1 and Pax8 could rarely be positive in the “wrong” site of origin. Of note, Pax8 expression has also been reported in carcinoids arising in the pancreas, duodenum, and rectum.

**The IASLC/ITMIG Thymic Malignancies Staging Project- Development of a stage classification for thymic malignancies. Detterbeck et al, JTO.**

**Summary:** This group will address the lack of official AJCC stage classification for thymic malignancies. They have assembled a retrospective database of 8,994 worldwide cases of thymic malignancies from 77 centers in 16 countries, and have set out to create a prospective database as well. They aim to construct a TNM staging system applicable to thymoma, thymic carcinoma and thymic neuroendocrine tumors, based largely on outcome data from the retrospective database.

**Take home message:** Expect a proposed TNM thymic staging classification by 2014, expected to be incorporated into the AJCC 8th edition in 2016.
Analysis of *MAML2* rearrangement in mucoepidermoid carcinoma of the thymus. Roden et al, Human Pathol.

**Summary:** The t(11;19) translocation involving rearrangement of the *MAML2* locus has been implicated as a disease defining event in mucoepidermoid carcinoma of the salivary gland, but how this translates to other organs is not yet entirely clear. Here they study 2 thymic mucops (both intermediate grade), 5 thymic SQCC and 3 thymic adenosquamous carcinomas using *MAML2* FISH. They found rearrangement in the 2 thymic mucops but not the other tumors.

**Take home message:** Thymic mucops seem to show *MAML2* rearrangement, similar to mucops at other anatomic sites. This could be useful in the differential diagnosis between mucoep and other thymic malignancies.

Non-neoplastic


**Summary:** They looked at gene expression profiling from 119 cases of UIP vs. 50 normal controls. They identified differentially transcribed genes, and validated on 111 cases of UIP and 39 normal controls. Their UIP cases segregated into two groups based on expression of ciliary genes, fibrosis genes (MMPs, keratins, etc), and some genes of unknown function. The cases with high expression of ciliary genes were associated with more microscopic honeycomb change (as assessed by two pathologists) and higher expression of mucin gene *MUC5B*, as well as *MMP7*, which is thought to attenuate ciliated cell differentiation in the setting of repair.

**Take home message:** There appear to be two molecular subtypes of UIP based on ciliary gene expression. The prognostic/clinical/therapeutic implications are unknown. Very interesting. But I wonder- could it not be that cilia genes are turned on in areas of microscopic honeycombing, and therefore are simply a reflection of biopsy samples that have more of this abnormality? Is it possible ciliary genes are just a “honeycomb signature” rather than a defining characteristic of the underlying UIP? They have some arguments against this, I’m still not sure…

Pulmonary pathology in pediatric cerebral malaria. Milner et al, Modern Pathol.

**Summary:** Autopsy series of 55 children who died of malaria and 45 controls (6 mos-13 years) from Malawi. They found lots of malaria parasites in the alveolar capillaries, along with the malaria pigment hemozoin, especially in children who died of cerebral malaria (sequestered parasites in the brain histologically and/or seizures clinically). Acute pneumonia was a common comorbidity. Microthrombi were also commonly seen (probably related to malaria-associated DIC). Coinfection with *Schistosoma* was seen in 2 patients. Alveolar hemorrhage and fibrin were rarely observed.
Take home message: Kids with cerebral malaria probably have respiratory distress because of CNS depression/coma and/or acidosis, since there appears to be little anatomic parenchymal abnormalities besides parasite burden (no DAD, etc). Acute pneumonia is a common comorbidity in this setting.


Summary: CFTR dysfunction has been shown in the airways in smokers, and the authors noticed that other CF-related symptoms (male infertility, cachexia, and pancreatitis) are seen in smokers- so they looked at CFTR function at extrapulmonary sites. They found that healthy smokers, smokers with COPD and former smokers all had elevated sweat chloride levels compared to non-smoking healthy controls. Intestinal current measurements from rectal biopsy specimens taken at screening colonoscopy also showed 65% lower activity in smokers compared to controls. Mouse experiments showed decreased intestinal CFTR activity in mice exposed to smoke. In vitro exposure of normal human bronchial cells to plasma from smokers resulted in 68% decrease in CFTR activity, indicating that the compound implicated in this dysfunction may be a circulating agent, and they provide further evidence that the CFTR dysfunction is at least partially mediated by the compound acrolein found in cigarette smoke, which they show causes dysfunction but not reduced expression.

Take home message: Smokers seem to have systemic CFTR dysfunction, likely secondary to acrolein found in smoke, which may explain some of the extrapulmonary manifestations of smoking. The CFTR dysfunction seems to be long lasting, and was still detectible in former smokers.

In-vivo probe based confocal laser endomicroscopy in amiodarone-related pneumonia. Salaun et al, Eur Respir J.

Summary: This procedure allows in vivo imaging of the alveoli during bronchoscopy using endogenous fluorophores, primarily elastin. Of note smoker’s tar pigment also fluoresces, so smokers and non-smokers need to be considered differently. They studied 36 non-smoking patients: 33 with interstitial lung disease (17 of which were treated with amio) and 3 patients being treated with amio without interstitial lung disease. As a gold standard, they had an expert panel of 2 pulmonologists, 1 radiologist and 1 pathologist determine the cause of ILD blinded to the endomicroscopy results, based on clinical, radiographic, and pathologic data available to them, as well as patient’s course after amio discontinuation and/or steroid treatment and other underlying causes of ILD that were identified. For amio-treated patients, they also had three independent clinician reviewers review the cases, and determine high, intermediate, or low probability of amio-related ILD, based on the opinion of the panel and agreement by at least two of the independent reviewers. They categorized 9 of 17 patients as having a high probability of amio-related ILD: these patients had large strongly florescent cells in 32 out of 38 alveolar areas examined by endomicroscopy. This compares to seeing similar cells in 2 out of 39 alveolar areas in the patients they categorized as low risk (which were the 8 other patients undergoing
amio treatment with ILD), and one of 59 areas in ILD patients that were not receiving amio treatment, and in none of 10 areas examined in patients with amio treatment but no ILD. Based on this data, they think this technique has a sensitivity of 100%, specificity of 88%, NPV of 100% and PPV of 90%.

**Take home message:** This is a cool technique. I’m not sure how much expertise and expensive equipment it requires, but I am guessing quite a lot of both. If it becomes a more widespread technique, may spare some patients a biopsy. Not sure how this will hold up when looking at a larger group of all comers with ILD, smokers, etc, but worked well in this small highly selected cohort.

**Editorials and Reviews**

**Slowly growing lung cancer as an emerging entity- from screening to clinical management. Infante et al, Eur Resp J.**

**Take home message:** With the advent of CT screening and incidentally discovered lung cancer, it has become apparent that they aren’t all the super aggressive rapidly fatal cancers of the past, when patients did not come to clinically attention until they typically had very advanced disease. The evidence supporting the existence of slow growing lung cancers is discussed, along with their typical radiographic and pathologic findings, and the clinical dilemma they create (namely no clear guidelines regarding if, when and how to treat; patients may die with these types of cancer rather than from them, but the urge is to treat aggressively so the window of opportunity for a cure is not missed).

**Strategies for improving outcome in NSCLC: A look to the future. Stahel et al, Lung Cancer.**

**Take home message:** Summary of current knowledge of molecular landscape of NSCLC and currently available targeted therapies along with issues of drug resistance. They discuss some novel targets, as well as the issue of escalating drug costs and predictive biomarker assessment to optimize therapy.

**Lung cancer in the era of targeted therapy- A cytologist’s perspective. M. Zakowski, Arch Pathol Lab Med.**

**Take home message:** Most patients with lung cancer are diagnosed based on small biopsies or cytology material since they present at high stage. With this scant tissue we type the NSCLC and perform biomarker analysis to target therapy, which leads to increasing pressure on the cytologist/pathologists, but also more visible and integral part in treatment planning for patients. Although the literature is quick to say that cytology specimens do not provide enough tissue for typing and testing, the author argues that this is false, and cytology can provide much information to treating clinicians in most cases.

**Take home message:** Although mediastinal staging is recommended as the best first test for lung cancer since it provides the most “bang for the buck”, most patients are not treated according to these guidelines, with resulting increase in number of invasive procedures and complication rate. They endorse implementation of benchmarks and perhaps even reimbursement models that will push physicians to comply with these recommendations, with are both money saving measures and the best care for the patient.


**Take home message:** This seems to come up a lot at meetings and in lectures- if you want to know where the made up word lepidic comes from exactly, and why its origin does not relate to butterflies, this is a nice summary.

Low papillary structures in lung adenocarcinoma: Any relationship with micropapillary adenocarcinoma? D Jain, Human Pathol

**Take home message:** Letter to the editor- valid point about potential relationship between what the authors described a few months back as “low papillary structures” and micropapillary pattern- seems especially relevant since the authors put forth that this pattern is associated with aggressive behavior. Again points out that there is a ton of subjectivity in recognizing patterns of adenocarcinoma, especially lepidic, papillary and micropapillary.

Case Reports

Lung adenocarcinoma patient refractory to gefitinib and responsive to crizotinib, with concurrent rare mutation of the epidermal growth factor receptor (L861Q) and increased ALK/MET/ROS1 copy number. Pilotto et al, JTO.

**Summary:** 77 yo woman with the above listed EGFR mutation in exon 21 (known to be relatively resistant to targeted therapy), and no rearrangement of ALK, MET, or ROS1, but with 2.6, 2.6 and 2.9 mean signals per cell for each of these genes. She progressed on gefitinib and so crizotinib was tried given the increased copy number, and she has had stable disease for 4 months on this therapy.

**Take home message:** I guess I am skeptical. Given that the ratios for all 3 genes are about the same, I am totally unclear as to why this doesn’t simply represent polysomy in the cancer cells. Seems to me more likely that the effect was due to some occult mutation in a crizotinib responsive gene rather than attributable to increased copy number, but I guess we need more proof one way or the other.

**Take home message**: They report a novel fusion variant of the above named fusion in a 26 yo man with pulmonary IMT. Interestingly, the tumor was strongly positive for keratin AE1/3 (present in about 1/3 of IMTs, known diagnostic pitfall), as well as SMA with focal desmin. ALK1 staining was equivocal, and staining with ALK 5A4 was strong, which has been previously reported with this fusion variant. ALK FISH was positive.

Case of solitary pulmonary capillary hemangioma: Pathological features based on frozen section analysis. Isaka et al, Pathol International.

**Summary**: Had a case just like this a few weeks ago! 55 year old woman with a persistent partial GGO nodule, that was PET negative but appeared to be gaining some more solid component over time. At excision, turned out to be a 7 mm pulmonary capillary hemangioma, which is apparently quite rare and has (as expected) a good prognosis.

**Take home message**: Something interesting to keep in mind for the very limited differential diagnosis of a persistent/enlarging GGO.


**Summary**: Case of a 62 year old man with a history of bowel carcinoid, presenting with a PET avid 2.3 cm mass infiltrating the right PA. Clinically it was thought to most likely represent a PA sarcoma, but was found to represent Rosai-Dorfman after pathologic evaluation. Patient did well post-op.

**Take home message**: Very neat CT and gross images, nice photomicrographs, interesting example of Rosai-Dorfman mimicking PA sarcoma.


**Summary**: 56 yo man presents with recurrent pneumonia, found to have obstructing “foreign body” that proved to be a tophus by pathology evaluation. No known history of gout. Very nice bronchoscopic photo and polarized photomicrograph.

**Take home message**: Gouty tophi can rarely be endobronchial and cause obstruction.