# Table of Contents

## Articles for discussion

<table>
<thead>
<tr>
<th>Page</th>
<th>Article</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Moreira, AL et al. Cribriform and fused glands are patterns of high-grade pulmonary adenocarcinoma. Human Path 2014;45:213-220</td>
</tr>
<tr>
<td>5</td>
<td>Schultheis AM et al. Fibroblast growth factor receptor 1 (FGFR1) amplification is a potential therapeutic target in small-cell lung cancer. Mod Pathol 2014;27:214-221</td>
</tr>
</tbody>
</table>

## Articles for notation – Neoplastic

<table>
<thead>
<tr>
<th>Page</th>
<th>Article</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Krasinskas, AM et al. KRAS mutational analysis and immunohistochemical studies can help distinguish pancreatic metastases from primary lung adenocarcinomas. Mod Pathol 2014;27:262-270</td>
</tr>
<tr>
<td>11</td>
<td>Sun, JM et al. Clinical characteristics associated with ALK rearrangements in never-smokers with pulmonary adenocarcinoma. Lung Cancer 2014;83:259-264</td>
</tr>
<tr>
<td>12</td>
<td>Surrey, et al. TTF-1 and Napsin -A are expressed in a subset of cholangiocarcinomas arising from the gallbladder and hepatic ducts.</td>
</tr>
</tbody>
</table>


Articles for notation – Non-neoplastic

Page 12 Verleden et al. The site and nature of airway obstruction after lung transplantation. Am J Respir Crit Care Med 2014;189:292-300


Page 15 Best, DH et al. EIF2AK4 mutations in pulmonary capillary hemangiomatosis. Original research: Pulmonary vascular disease. Chest 2014;145:


Reviews and letter to the editor

Page 15 Husain, AN. Mesothelial proliferations. Useful marker is not the same as a diagnostic one. Am J Clin Pathol 2014;141:152-153


Articles for Discussion
Moreira, AL et al. Cribriform and fused glands are patterns of high-grade pulmonary adenocarcinoma. Human Path 2014;45:213-220

Background:
- IASLC/ATS/ERS classification of lung ADC proposed in 2011 (JTO paper) included 5 predominant patterns: lepidic, acinar, papillary, micropapillary and solid.
- A grading system of lung ADC based on these histologic patterns was reported to be predictive of disease recurrence in stage I tumors (Sica et al, AJSP 2010;34:1155-62): grade I- lepidic (BAC) pattern, with low metastatic potential; grade II- acinar and papillary, with intermediate metastatic potential; grade III- solid and micropapillary, with high metastatic potential.
- The scoring based on 2 most predominant grades was able to stratify patients into low to high risk of recurrence or death of disease.
- The same PI now extended their previous work by evaluating the prognostic importance of variant patterns of ADCs that were not recognized in 2011 proposal.

Methods:
- Specimens: retrospectively identified 249 resected stage I ADCs at MSK between 1995-2010 (7th edition TNM system);212 lobectomies (85%), 17 segmentectomies (7%), 20 wedge resection (8%)
- Histologic evaluation:
  -First classified as predominantly lepidic, acinar, papillary, solid or micropapillary
  -Comprehensive histology subtyping of ADCs by recording % of each type in 10% increments
  -Nonstandard types of complex glandular patterns including cribriform pattern (defined as nests of tumor cells with sieve-like perforation) and fused gland pattern (defined as fused glands with irregular borders, back-to-back glands without intervening stroma, or ribbon-like formations) were recorded in addition to the above 5 main subtypes,
- The 5 main patterns were graded as 1, 2 or 3 as in their previous study (Sica et al, 2010). A histologic score, the sum of the grades of the 2 most predominant patterns was used for the analysis, resulting in scores of 2-3 (low grade), 4 (intermediate grade) and 5-6 (high grade).
- Molecular studies: EGFR and KRAS point mutations by Sequenom Mass Array spectrometry based multiplex genotyping system and EGFR exon 19 indels by PCR
- Statistics:
  -χ² test for comparing the association between complex glandular patterns, the 5 predominant histologic subtypes, and the histologic score of the tumors and for the association between tumor grade and molecular alterations
  -Disease free survival (DFS) was estimated by K-M method
  -Associations between the proposed scoring system, the presence of complex glands and DFS were evaluated using Cox proportional hazards models
Results:
- 91M / 158F; av age 68 ± 9 yrs; all underwent R0 resection of previously untreated pathologic stage I ADCs at MSKCC, without adjuvant chemo or radiotherapy
- 74% current smokers, 10% former smokers, 16% never smokers
- Av tumor size 2.2 ± 0.9 cm
- 12 (5%) lepidic predominant, 70 (28%) papillary predominant, 111 (45%) acinar predominant (counting complex glandular patterns as acinar pattern), 50 (20%) solid predominant, and 6 (2%) micropapillary predominant
- Histologic scores (sum of 2 most predominant patterns) 56 (22%) score 3, 96 (39%) score 4, 88 (35%) score 5, 9 (4%) score 6; no score 2 (AIS); none was MIA
- Cribriform pattern was present in 37 cases (15%), ranging from 10-100% of total tumor volume (34 ± 26 %); predominant pattern (range 30-100%) in 12 cases (5%)
- Fused gland pattern in 71 cases (29%), ranging 10-80% of total tumor volume; predominant pattern (40-80%) in 18 cases (7%)
- The presence of both cribriform and fused glands in the same specimen was in 10 cases
- Presence of any amount of cribriform and fused glands in each case by predominant type or histologic scores:

![Diagram A](image1)

![Diagram B](image2)

- DFS by predominant type, histologic score and complex glands

![Diagram A](image3)

![Diagram B](image4)

**Take home message:** Cribriform and fused glands should be considered as patterns of high grade ADCs (solid and micropapillary), but not as an acinar pattern.
Schultheis AM et al. Fibroblast growth factor receptor 1 (FGFR1) amplification is a potential therapeutic target in small-cell lung cancer. Mod Pathol 2014;27:214-221

Background:
- Tx of SCLC has remained unchanged over the last decades and no actionable molecular targets have been found
- FGFR1 is a member of the type IV receptor tyrosine kinase family (FGFR1-4)
- Amplification of the FGFR1 locus at chromosome 8p has been reported in breast, esophageal and head and neck cancers and the authors of this study previously reported the oncogene dependency for a focal FGFR amplification in a large subset of lung carcinomas
- Targetable FGFR1 amplification in about 20% of lung Sq cell ca affecting smokers; several phase I & II clinical trials using FGFR1 inhibitors currently
- The authors evaluated amplification patterns in SCLCs and correlated FGFR1 status with clinical data in a large cohort of SCLCs.

Methods:
- 307 SCLC tumor samples with sufficient material for molecular studies (269 primary SLCL, 29 LN mets, 9 distant mets (liver, adrenal, soft tissue, breast, pleura, ovary); 6 combined SCLCs and only small cell component was analysed
- Pts were screened for FGFR1 amplification as a part of routine molecular diagnostics program of the Network Genomic Medicine (a multicenter non-profit group that provides molecular testing for personalized tx of lung cancer pts including early clinical trials) between Jan 2010 and Dec 2012
- FISH on FFPE using FGFR1/CEN8 dual probe; vessels, fibroblasts, lymphocytes or non-tumor lung tissue as internal positive control to verify one or two clearly distinct signals of each color in the nuclei.
- Tumor tissue was entirely scanned for amplification hot spots by using 63x objective; if FGFR1 signals showed a homogeneous distribution, random areas were used for counting the signals; 60 nuclei were counted (20 contiguous tumor cell nuclei from three areas, by counting green FGFR1 and orange centromere 8 signals; SCLC by nature often presents with overlapping cells and dense tumor areas, they tend to use the tumor cells at the periphery
- FGFR1/CEN8 ratio, % of the cells with ≥5 and ≥15 FGFR1 signals and the average FGFR1 copy number per cell
- High level amplification: FGFR1/CEN8 ratio ≥ 2.0 or an av FGFR1 gene count per tumor cell ≥6.0 or a % of tumor cells containing ≥ 15 FGFR1 gene copies of ≥10%
- Low level amplification: the absence of high-level criteria and % tumor cells containing ≥5 FGFR1 gene copies of ≥ 50%

Results:
- FGFR1 amplification patterns: 56 of 307 cases (18%) failed for FISH, technical failure rate is higher in SCLC than in sq cell ca (<5%)
- All amplified cases showed even signal distribution in the entire tumor without hot spots
All amplified tumors showed a homogenous amplification pattern with approximately the same number of FGFR1 signals in all tumor cells, with only small variation.

No co-localized clusters with both enhanced FGFR1/CEN8.

Most tumors (n=237, 94% of evaluable tumors) were homogeneously non-amplified with 2.8 FGFR1 signals per cell on average.

Polysomy, defined as average CEN8 signal count / tumor cell ≥3, occurred in 6%.

5.6% (14 of 251 evaluable tumors) showed FGFR1 amplification, 13 of 14 tumors reaching the criteria for high-level amplification (5.2% of evaluable tumors) and only one tumor met the criteria for low-level amplification.

All high level amplified tumors showed an av number of FGFR1 signals ≥6 (mean 9.5); seven of 13 (54%) had ≥10% of tumor cells containing >15 FGFR1 signals or large clusters, and all 13 high level amplified tumors had a FGFR1/CEN8 ratios ≥2.

4 of 13 high level amplified tumors were negative TTF1, with significantly higher FGFR1 gene copy numbers than the other TTF+ high level amplified tumors.

No difference in gender or age between amplification-negative and -positive pts (p=0.75 and 0.88, respectively).

Stage info available in 78 pts (13 of 14 amplified and 65 of 237 non-amplified pts); 43 presented at 1st dx with an extensive-stage and 35 with limited stage ds; no difference in stage at first dx between FGFR1 amplified and non-amplified pts (p=0.083).

In 78 pts with survival info, pts in all stage or in extensive-stage at dx, no difference in mean OS for FGFR1 amplified vs. non-amplified (p=0.56 and 0.11, respectively); a worse outcome in amplified pts with limited stage SCLC than in non-amplified pts with limited stage SCLC (p=0.005).

**Take home message:** FGFR1 amplification, a potential therapeutic target, was found in 5.6% of SCLC and its screening may be warranted in SCLCs in the future.

**Mokhtar, M et al. Methylation and expression profiles of MGMT gene in thymic epithelial tumors. Lung Cancer 2014;83:279-287**

**Background:**

- Thymic epithelial tumors (TETs) have heterogeneous clinical and histologic manifestations and their molecular characteristics are not well known.
- Aberrant DNA methylation is a common epigenetic lesion in tumorigenesis, and more prevalent than gene alterations.
- Hypermethylation of promoter of CpG islands causes gene silencing of tumor suppressor genes in cancers.
- The reversibility of epigenetic changes can be exploited as a therapeutic target by using demethylating drugs.

**Methods:**

- Methylation specific PCR and IHC to profile the methylations status of DNA repair gene O6-methylguanine DNA methyl transferase (MGMT) and its protein...
expression to examine the association between MGMT status and clinicopathological features, response to chemotherapy and overall survival

- Patients: 66 TET (57 surgical, 9 bx) 1985-2006; *numbers don’t match in abstract and tables* (23 thymic carcinomas and 44 thymomas in abstract; 21 ca in table 2)
- WHO classification for dx, Masaoka staging
- Nested methylation-specific PCR
- IHC on FFPE with mouse monoclonal Ab (abcam, Cambridge, MA); entire tissue section was scanned and scored for intensity (0=neg, 1=weak, 2=intermediate to strong, compared to the non-neoplastic cells), and % of + cells (200 cells/HPF evaluated, 0=none, 1=<30%, 2= 30-80%, 3 = >80%); the sum of intensity and extent scores; score 5 as a positive expression pattern and score 0-4 as loss of protein expression pattern; 3 observers evaluated the IHC

**Results:**

- MGMT methylation and loss of MGMT correlated (p=0.0003)
- MGMT methylation and loss of MGMT protein expression were more frequent in thymic carcinoma than in thymoma (74% vs 29%, p<0.001; 87% vs. 23%, p<0.0001, respectively); no correlation with thymoma subgroups
- MGMT methylation and loss of MGMT protein expression were more frequent in advanced (III/IV) than in early TETs (I/II); but no difference in thymomas; no difference in OS

**Take home message:** MGMT methylation might play a role in development of thymic carcinoma and could be a potential target for therapies in TET

Background:
- Survival after lung tpx is shorter than in other solid organ tpx; 5y survival ~55%
- Obliterative bronchiolitis (OB) was postulated as the result of chronic rejection via alloimmune mechanism; histopathologic confirmation by TBBx is difficult
- Bronchiolitis obliterans syndrome (BOS): clinical surrogate marker of chronic allograft dysfunction based on measurement of FEV1 decline
- The second revision (after the 1st 2002 publication) is in the process of publication (approved by ATS, ISHLT & ERS)-during the preparation of this revision, members acknowledged that a substantial cohort of pts had chronic FEV1 decline after lung tpx for which the previous definition of BOS was not the best descriptor
- This paper focuses on the description of additional entities that can lead to chronic FEV1 decline after lung tpx and proposes introduction of a new classification system which defines various terms that can be used to help the lung tpx community recognize distinct entities with important differences in their clinical manifestations and pathobiology
- CLAD (chronic lung allograft dysfunction)

Table 1.
Emerging Phenotypes of Chronic Lung Allograft Dysfunction: Key Features:

<table>
<thead>
<tr>
<th>Entity</th>
<th>Classic BOS</th>
<th>RAS</th>
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<tbody>
<tr>
<td>Pulmonary</td>
<td>Obstructive (FEV1 ≤ 80% baseline)</td>
<td>Restrictive (TLC ≤ 90% of stable baseline)</td>
</tr>
<tr>
<td>Entity</td>
<td>Classic BOS</td>
<td>RAS</td>
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<tr>
<td>-----------------------------</td>
<td>-------------------------------------------------</td>
<td>------------------------------------------</td>
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<tr>
<td>function</td>
<td>80% of stable baseline value)</td>
<td>value) and/or FEV₁/FVC normal or increased value) and/or FVC decline ≤ 80% of stable baseline value)</td>
</tr>
<tr>
<td>HRCT thoracic imaging</td>
<td>Air trapping usually present</td>
<td>Infiltrates usually present</td>
</tr>
<tr>
<td></td>
<td>No/minimal infiltrates</td>
<td>With/without bronchiectasis</td>
</tr>
<tr>
<td></td>
<td>With/without bronchiectasis</td>
<td>With/without air trapping</td>
</tr>
<tr>
<td></td>
<td>OB (difficult to diagnose)</td>
<td></td>
</tr>
<tr>
<td>Histopathology</td>
<td>by transbronchial biopsy specimen)</td>
<td>Parenchymal/pleural fibrosis with/without OB</td>
</tr>
<tr>
<td>Clinical course</td>
<td>Typically progressive but may stabilize</td>
<td>Tends to be relentlessly progressive</td>
</tr>
<tr>
<td></td>
<td>Recipients may have coexistent chronic bacterial infection</td>
<td>May start as or coincide with BOS</td>
</tr>
<tr>
<td></td>
<td>May evolve to RAS</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Usually responds poorly to pharmacologic therapies</td>
<td>Correlates with the presence of early DAD post-transplant</td>
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**Take home message:** ALAD and CLAD may soon replace the term and concept of acute rejection and chronic rejection, respectively.
**Articles for notation – Neoplastic**


**Summary:** In this study, the authors assessed divergence in KRAS mutation genotype between NSCLC and CRC in 2603 pts (838 CRC and 1765 NSCLC), the largest series. They found that KRAS mutations differed significantly between NSCLC and CRC in terms of overall frequency (25% vs. 39%), the % of smoking-associated G>T transversions (73% vs. 27%) and the ratio of transversions to transitions (3.5 vs. 0.79), suggesting that these distinct KRAS mutation patterns reflect differences in the carcinogenic process of each disease and provide a molecular rational for differences in impact of EGFR targeting therapies in the two malignancies. Distinct differences between the two malignancies likely reflect the dominance of tobacco-related carcinogenesis in NSCLC and subsequent patterns of KRAS-associated signaling pathways.

**Take home message:** KRAS mutation patterns are quantitatively and qualitatively distinct between NSCLC and CRC, with different therapeutic and prognostic implication.

**Krasinskas, AM et al. KRAS mutational analysis and immunohistochemical studies can help distinguish pancreatic metastases from primary lung adenocarcinomas. Mod Pathol 2014;27:262-270**

**Summary:** This study explored potential utility of KRAS mutational status in conjunction with IHC profile of adenocarcinoma in the lungs of patients with known pancreatic cancer. Metastatic pancreatic cancers had fewer solitary lung lesions, nor tumors with pure mucinous morphology, more frequent KRAS mutations than lung primaries. Presence of the KRAS G12C mutation had 96% specificity with good positive predictive value for lung primary, while G12R was 99% specific for pancreatic primary and 86% positive predictive value. KRAS mutation with nonsmoking status is significantly more common in pancreatic primary. KRAS G12C mutations, TTF and napsin A positivity are associated with primary lung adenoca whereas KRAS G12R mutations, CK20 and CDX2 favored pancreatic adenoca. Differences in KRAS mutations reflect differences in exposure to smoking and highlight biologic differences between two KRAS oncogene-driven cancers.

**Take home message:** TTF1, napsin A, CDX2, CK20 with KRAS mutational analysis may have diagnostic utility in differentiating lung vs. pancreatic primary


**Summary:** ROS1 translocations are described in 0.9-1.7% of NSCLC and associated with a response to crizotinib. In this study, 121 triple (EGFR, KRAS, ALK) negative lung adenoca cases were screened by both IHC (ROS1 D4D6 ab, Cell Signaling Technology) and FISH using two commercially available ROS1 break-apart probes. They also screened 80 additional cases with known EGFR, KRAS, PI3KCA, BRAF, HER2 mutations or ALK rearrangement, to address the possible cross reactivity of the ROS-1 ab. They found 9 ROS-1-rearranged adenoca with positivity for both FISH (51-87%) and IHC (2+/3+ cytoplasmic staining). One ROS-1 positive case by FISH showed split pattern and remaining 8 cases showed a loss of the 5’ telomeric probe. The sensitivity of ROS-1
IHC was 100% (using 2+ as positive) and the specificity was 96.9%, as two were negative for FISH; these two cases were HER2 mutated. All ROS1-positive cases were at an advanced stage and never or light smokers.

**Take home message:** A screening algorithm starting with IHC followed by ROS-1 FISH is feasible. Prevalence of ROS-1 positivity in triple negative cases reached 7.4%


**Summary:** They sought to identify tumor tissue protein biomarkers that might predict a benefit from platinum-based chemotherapy regimens for NSCLC. This study prospectively enrolled consecutive chemotherapy-naïve NSCLC patients at any stage (2005-10) at six hospitals in France. Of the 537 pts in the full analysis set, 460 had a complete histologic dx. They used the tumor tissue for IHC of 8 biomarkers: ERCC1, BRCA1, p53, p27kip1, class III β-tubulin (TUBB3), Bax, Fas, and FasL. They looked for associations between these biomarkers and the ds control rate after 2/3 cycles of platinum-based chemotherapy, progression-free survival and overall survival. In 289 pts, tissue sample was adequate for testing at least one biomarker. There was no significant association between biomarker expression levels and clinical or pathological variables, except for TUBB3 that showed a trend toward higher expression in adenoca.

**Take home message:** In a large cohort of predominantly advanced or metastatic NSCLC, none of the above protein biomarkers predicted the chemotherapy response or survival.

**Sun, JM et al. Clinical characteristics associated with ALK rearrangements in never-smokers with pulmonary adenocarcinoma. Lung Cancer 2014;83:259-264**

**Summary:** They showed that the prevalence of ALK rearrangements was high in the clinically enriched population of never-smokers with pulmonary adenocarcina. When accounting for the EGFR and KRAS mutation status in this population, the ALK-positive rate was 33% in their population. Patients with ALK-positive tumors had similar prognoses to those without ALK rearrangements, although the sites of disease recurrence are slightly different between ALK-positive and –negative groups.

**Take home message:** No new information from this study, except adding to the controversy in the prognostic significance of ALK status in NSCLC patients.


**Summary:** Frequency and functional role of ALK splicing isoforms are not well known and were evaluated in this study. They analyzed 270 cases of NSCLC for ALK kinase domain splicing aberrations and generated constructs with full-length EML-4-ALK (E13;A20) and a splicing isoform. Splicing isoforms of the kinase domain of ALK (including complete skipping of exon 23 and exon 27) were identified in 11.1% of NSCLC and these changes coexisted with ALK rearrangements, KRAS mutations, and EGFR mutations, suggesting that ALK splicing isoforms are “passenger” events in NSCLCs. Coexpression of EML4-ALK L1196M with EML4-ALK resulted in resistance to inhibition of ALK by crizotinib. The identification of mechanisms of resistance to crizotinib and other ALK TKIs in ALK rearranged NSCLC is important. Only ALK
kinase mutations and/or bypass tracks due to activation of other oncogenes (such as EGFR) have been described in developing crizotinib resistance. ALK kinase mutations, which are present in only approximately 1/3 of crizotinib resistant samples, have been characterized in vitro as crizotinib–resistant mutations using EML4-ALK driven models. They confirm that EML4-ALK with the gatekeeper ALK-L1196M indeed is resistant to crizotinib.

**Take home message:** Splicing isoforms of the kinase domain of ALK (either ALK del23 or ALK del27) were identified in 11.1% of NSCLCs and these ALK kinase splicing variants were nonfunctional genomic events in NSCLC.


**Summary:** They studied liver, GB, pancreato-biliary resections with cholangiocarcinoma (n=33) and non-neoplastic intrahepatic and extrahepatic biliary epithelium control tissue (n=26) with IHC for TTF-1 (SPT24 clones from 2 different companies) and Napsin A (clone KCG1.1 Abcam) by grading both intensity and quantity. TTF1 was negative in control biliary tissue but positive in 27.2% of cholangiocarcinomas. All TTF positive cases were extrahepatic and mostly upper biliary tract (GB and hepatic ducts). TTF1 positivity was associated with age 60 years or older but not with gender. 3 cases were positive for both TTF and Napsin. This study shows that 47.4% of extrahepatic cholangiocarcinomas can express TTF-1 with the monoclonal SPT24 antibody and up to 33.3% of those cases also coexpress Napsin A. All TTF-positive choangiocarcinomas were also CDX2 positive.

**Take home message:** Another cautionary note in using TTF-1 and Napsin-A antibodies as the markers of lung primary; in addition to endometrial, nasopharyngeal, colon, gastric, serous ovarian and prostate cancers, now cholangiocarcinomas!


**Summary:** Dx of clear cell carcinoma (CCC) of the endometrium may be subject to significant interobserver variability. They studied 77 cases of CCC from 9 institutions. Dx was confirmed by 3 pathologists in 60 cases and used as a gold standard to which napsin A performance was assessed. Duplicate 1.1mm core TMA were constructed from 54 cases in the consensus group with available tissue, 49 endometrioid adenoca of all grades, 17 endometrial serous carcinomas were also tested. Scoring as 0 (0%), 1+ (1-25%), 2+ (26-49%), and 3+ (>50%). Napsin A immunoreactivity was significantly higher in CCCs than in endometrioid and serous carcinomas.

**Take home message:** Napsin A expression displays a high sensitivity and specificity for CCC of the endometrium and may carry some diagnostic utility, though a small subset of other subtypes of endometrial ca may be positive for Napsin as well. Also, it highlights that we should be cautious using this as the lung adenocarcina marker.

**Articles for notation – Non-neoplastic**

Verleden et al. The site and nature of airway obstruction after lung transplantation. Am J Respir Crit Care Med 2014;189:292-300
Purpose: To determine the site and nature of small airway obstruction in chronic rejection of lung allograft

Methods: Rejected lung allografts from patients who underwent a second transplantation (n=7) and unused donor lung (n=7; as controls) were examined using multidetector CT (MDCT) to determine the % of visible airways obstructed in each airway generation, microCT to visualize the site of obstruction, and histology to determine the nature of this obstruction

Results: The number of airways visible with MDCT was not different between rejected and control lungs. However, $10 \pm 7\%$ of AW >2mm, $50 \pm 22\%$ 1-2 mm, $73 \pm 10\%$ <1mm in diameter were obstructed in the rejected lungs. MicroCT confirmed that the mean lumen diameter of obstructed AW was $647 \pm 317 \mu m$; no difference in either total number and cross-sectional area of the terminal bronchioles or in alveolar dimensions between rejected and control lungs. Histology showed expansion of granulation tissue or collagen-rich scar in obstructed airways.

Take home message: chronic lung rejection is associated with constrictive bronchiolitis that targets conducting airways with sparing of larger airways, terminal bronchioles and the alveolar surface.


Background: The current classification of PHT includes 5 major categories: PAH, PH due to left heart disease, PH due to lung disease, PH due to chronic thromboemboli, and a miscellaneous category). There are far more than 5 phenotypes exist among the pts with PH. Understanding and describing genetic, pathobiologic, hemodynamic and clinical heterogeneity within each category of PH are crucial in individualized care and further advance in treatment.

Methods: Multidiciplinary committee with expertise in clinical care, clinical and/or basic research in the areas of PH identified important questions and reviewed the literature

Results: They described the following PH phenotypes as an initial platform to define additional relevant phenotypes as new knowledge is generated:

1. Mixed pre- and postcapillary PH
2. “severe” PH in respiratory ds
3. Maladaptive RV hypertrophy
4. Connective tissue disease-associated PH
5. Portopulmonary hypertension
6. HIV-associated PAHPH in elderly individuals
7. PAH in children
8. Metabolic syndrome
9. Long-term survivors

Take home message: They tried to lay the framework to address a pressing need to develop accurate phenotyping in PH.

Purpose: It is not well known if CT performs as well in identifying the UIP pattern in ds other than IPF that manifest with a histopathologic pattern of UIP. This study is to determine the accuracy of CT in identifying the histopathologic UIP pattern in RA-ILD, given the important clinical implications of UIP vs. non-UIP pattern of RA-ILD for tx, ds progression and px

Methods: CT images of pts (n=69) enrolled in three tertiary care centers were reviewed by two experienced thoracic radiologists independently. CT pattern was categorized as definite UIP, possible UIP, and inconsistent with UIP by published criteria. All lung bx’s were reviewed by lung pathologists at the time of enrollment and re-reviewed by a second lung pathologist (TVC) if available

Results: 61% (42 of 69) pts had histopathologic pattern of UIP. 29% (20 of 69) had a definite UIP pattern on CT. Specificity of CT UIP pattern was 96% with 53% negative predictive value; Sensitivity was 45% with 95% positive predictive value

Take home message: Definite UIP pattern on a CT scan I RA-ILD is highly specific and moderately sensitive for histopathologic pattern of UIP, as in the setting of IPF cases


Purpose: ILD associated with EGFR inhibitors gefitinib and erlotinib in advanced NSCLC has been described but the overall risk remains unclear. A systematic review and meta-analysis to determine the incidence and the relative risk associated with their use

Methods: PubMed databases were searched for articles published from 1/2000 to 10/2012 and abstracts presented at ASCO and the European Society of Medical Oncology meetings held between 2000 and 2012. Eligible studies include randomized controlled trials with gefitinib and erlotinib in advanced NSCLC pts. Summary incidence rates, relative risks, and 95% CIs were calculated using fixed-effects or random-effects models, depending on the heterogeneity of the include studies

Results: overall incidence of all-grade ILD events was 1.2% among 15,618 pts from 29 randomized controlled trials used in this meta analysis, with 22.8% mortality among them. compared with controls, the relative risk of all grade ILD was 1.53, and relative risk of fatal ILD events associated with EGFR TKIs was 1.96. No significant difference in relative risk by drug type, study location, tx arm and tx line.

Take home message: Tx with EGFR TKIs may be associated with a significant increase in the risk of all-grade and fatal ILDs
Best, DH et al. *EIF2AK4* mutations in pulmonary capillary hemangiomatosis.

**Original research: Pulmonary vascular disease. Chest 2014;145:**

**Summary:** *EIF2AK4* gene belongs to a family of kinases that regulate angiogenesis in response to cellular stress. Exome sequencing done on the samples from two brothers in a family affected by PCH revealed *EIF2AK4* mutations in both brothers. Their parents and unaffected sister were heterozygous carriers. Additional 11 unrelated pts were screened with 1 familial and 10 sporadic PCH for mutation. Two *EIF2AK4* mutations were identified in each of two of unrelated individuals with sporadic PCH.

**Take home message:** *EIF2AK4* mutations might be causally associated with familial and some sporadic PCH cases

**Editorials, review and letter**


Editorial for the above paper on *EIF2AK4* mutations in PCH by Best et al

Husain, AN. Mesothelial proliferations. Useful marker is not the same as a diagnostic one. Am J Clin Pathol 2014;141:152-153

An editorial on an article published in Jan issue of AJCP by Minato et al who reported IMP3, GLUT1, EMA, CD146 and desmin in 34 mesotheliomas and 40 reactive mesothelial cases; the title says all in that they cannot tell for sure


A short review on the role of IL8, IL8 and anti-IL-8 autoantibody:IL8 complexes and those complexes's interaction with FcγRIIa receptor in the development of acute lung injury


Very nice review on the approach for surgical pathologists encountering lung specimens obtained in the context of pneumothorax repair based on literature review and consultation experience of the authors. Tables and figures are very helpful!


Reporting the first case of a phenotype of CPFE syndrome in a 41-year old nonsmoking man carrying mutations of the *ABCA3* gene, suggesting the role of surfactant metabolism in CPFE and possible underlying genetic predisposition