
**Purpose:** Tumor island is defined as an isolated, large collection of tumor cells within alveolar space without micropapillary pattern, present at the periphery of the lesion and separated from the main mass by a distance of at least a few alveoli.

- the prevalence and clinicopathologic and molecular characteristics of subjects with tumor islands
- the prognostic significance of tumor islands in resected early-stage lung adenocarcinomas

**Methods:** 261 pts with lung resection with curative intent for stage I or II lung adenocarcinoma without neoadjuvant therapy between Jan 1998 and Dec 2010. 92 of 261; during 2009-10, SNaPshot for point mutations and small insertions and deletions in 13 cancer genes, including KRAS and EGFR. Clinical and demographic information obtained from medical record.

- Two pathologists jointly reviewed for histologic subtyping and predominant histologic pattern was recorded.
- One author recorded the tumor islands; 3-D reconstruction of 50 whole-slide images of a serial-sectioned specimen to reveal connecting neighboring islands and merging with the main solid tumor
- Recurrence free survival using KM curve with pts from time of surgery until recurrence. The log rank test for assessing for differences. Multivariate analysis using Cox regression model.

**Results:** 59.8% women, median age 69 (37-92), 31.4% wedge resection, median tumor size 2.2 cm(0.4-15cm), stage IA 57.9%, IB 25.3%, IIA 8.8%, IIB 8%. 11.9% MIA. Acinar pattern predominant in 44.1%

- Tumor islands in 58 of 261 (22.2%) with mean greatest dimension 155 μm (35-366 μm), 2-29 tumor islands per case (3-8 slides per case).
- 18 of 58 cases also had micropapillary structures in adjacent alveolar spaces
- Similar median tumor size: 2.05 cm with vs. 2.3 cm without, p=0.283
- Predominant solid pattern: 22.4% vs. 7.9%, p=0.004
- Less likely MIA: 3.5% vs. 14.3%, p=0.022
- A trend toward a predominant micropapillary pattern: 10.3% vs. 3.9%, p=0.090
- A trend less likely to be lepidic predominant: 6.9% vs. 16.8%, p=0.089
- Higher nuclear grade (p=0.011), smoking (p=0.031)
- No differences in age, sex, pT, pN, AJCC stage, presence of pleural, lymphatic or vascular invasion
- Of 92 pts tested, 20 EGFR (22%), 37 KRAS (40%), 1 BRAF, 2 ERB2, 1 PIK3CA, 1 TP53, 30 no mutation
- Pts with tumor islands had a worse outcome with 5 year recurrence free survival at 44.6% vs. 74.4% (log rank p=0.010); multivariate analysis with stage and invasiveness included, survival difference significant (p<0.020) with the adjusted hazard ratio of 1.9 for increase in the risk of recurrence

Take home points: Tumor islands are associated with a solid growth and KRAS mutations, likely have worse px after resection in early-stage lung adenoca; over half of those pts had recurrence within 5 years, even in the stage IA cohort

Purpose: Bronchiolitis obliterans syndrome (BOS) is a manifestation of chronic rejection and a major barrier of long term survival. Known risk factors are acute rejection and small airways lymphocytic bronchiolitis in Tbx. This study from UCSF sought to evaluate lymphocytic bronchitis on endobronchial biopsies (in early post-transplant period) as a risk factor for BOS and mortality in lung transplantation patients.

Methods:
- Subjects:
  - Between 1997-2011, endobronchial bx and transbronchial bx (Tbx) were collected and scored during surveillance bronchoscopy, at 0.5, 1, 2, 3, 6, 12 mos after tpx, with additional bx as dictated by sx changes or fall in FEV1.
  - Pts were treated for all but minimal grade rejection (grade A1) detected by Tbx. Primary analysis included all subjects alive and BOS free 90 days after tpx that had had at least one endobronchial or Tbx in the first 90 days.
  - Bx from pts with concurrent infection, (defined as positive bacterial, fungal or viral studies from BAL taken at the time of bx) excluded.
  - Reports of pathology and PFT reviewed (slides not re-reviewed except a random fraction of cases to verify).
- Def of BOS per ISHLT: ≥ 20% decrease in FEV1 from baseline, which is defined as the ave of the two best values measured after tpx, at least 21 days apart. also, they required the decline in FEV1 to persist at least 21 days and not resolve by the end of the study to exclude reversible conditions that might misdiagnosed as BOS.
- Large-airway lymphocytic bronchitis grading: E0 (no), E1 (minimal to mild), E2 (moderate to severe) chronic inflammation with a prominent subepithelial band of lymphocytes scattered intraepithelial Lc and at least rare epithelial cell necrosis.

Results:
- 356 subjects transplanted during study period, 58 subjects excluded during 90 days (death, BOS, bleeding disorder, f/u in diff hosp, 17 infection), 298 included and 29 with no endobronchial bx leaving 269 with endobron bx and 1 infection during all tbx, leaving 297 tbbx.
  - within the 1st 90 days, 1151 bx's performed and 825 remained after excluding samples with positive cultures; median of 3 bx's during the 1st 90 days.
  - 5 year BOS and mortality rates at 48% and 44%, respectively (49% and 47% in ISHLT registry).
- Large and small airway bx scores positively correlated but are not sufficiently concordant that one can substitute for the other.
- Maximum E-score in 90 days predicts BOS and increasing E score was associated with more rapid development of BOS, even adjusted for age, sex, transplant indication, transplant type, and CMV status.
Take home points: 3% of subjects had a maximum E-score of 2 and showed a 10-fold increased risk for BOS. The association with a maximum score of 1 was not significant. In this single center analysis, the maximum inflammation score in endobronchial bx at 90 days was more accurate than acute cellular rejection or bronchiolitis (A grade or BR scores) of tbbx in predicting development of BOS

**Purpose:** To expand on our understanding of adsq ca by establishing Thymidylate synthase (TS) expression levels in adsq ca with correlation for molecular alterations, in both the overall tumor and the individual glandular/sq components, to ultimately provide guidance to the clinician with the regard to appropriate testing and therapeutics.

**Background:**
- Adenosquamous carcinoma (adsq ca) is defined as a mixed tumor type composed of both adeno (glandular) and squamous cell components with each one comprising at least 10% of the whole tumor
- Adsq ca accounts for 1% of invasive lung cancers (though it is possible that the use of markers may impact the frequency)
- The molecular background for mixed differentiation patterns is unclear and some studies reported that the px of adsq ca is poorer than other non-small cell lung ca.
- Sq cell carcinomas are known to have higher levels of TS and is speculated that the efficacy of pemetrexed partially depends on the level of TS expression. Accordingly, pmetrexed is approved solely for the tx of pts with non-sq tumors
- No standard of care exists for the tx of adsq ca. further more TS expression levels in the different histological components of adsq tumors have not been elucidated. It is unclear whether or not the same TS expression differential exists for these components as for the pure adenoca and sq cell ca
- Given early data on mutations for EGFR and KRAS in adsq ca mimicking the frequency in adenoca, the question pemetrexed responsiveness remains in adsq ca

**Methods:**

**Samples:** word search “adenosquamous” or “squamous” among resection specimens from 1997-2011; n=26, after slide review, 19 cases met the criteria. From their previous TMA, 121 adenoca and 17 sq cell ca were used to compare with adsq ca

**Quantitation of TS levels:** IHC with anti-TS ab (Life technologies Clone 106, Grand Island NY); two observers assessed the intensity of the staining with score 0 to 2, 0=no staining, 1=low-intensity, 2=strong staining; % of cells that stained positive. An H-score (range 0-200) was generated, based on the cross-product of the intensity score and the % of + cells. For adsq cases, sq and glandular components were separately assessed using the same histological scoring system

**Microdissection and mutation status:** manual needle dissection to enrich for tumor cells.

**EGFR and KRAS mutation study by Sanger sequencing:** For cases with mutation, a separate round of manual microdissection for sq and adenoca areas, guided by TTF1 and p63 immunostains with only including characteristic areas of the two histologies of the tumor were chosen.

**Results:**
- 19 adsq pts: 53% men and 47% women, age 45-83 (median age 72), stages IA-III A
- Overall TS expression:
- H-scores for TS expression: 53.4 in adeno and 61.6 in squamous part of adsq ca
- 2 of 19 adsq ca had EGFR mutations (11%) and 6 of 18 (one failure) harbored KRAS mutations (33%); all were mutually exclusive.
- Upon microdissection, all of the mutated specimens revealed their specific mutations in both glandular and squamous cell component (one specimen could not be accurately dissected)
- Mean H score of mutated cases was 60 (as compared with the overall H score for adsq ca of 64.7) despite the mutations of adenoca (KRAS and EGFR), suggesting the TS results are independent of mutation status
- Again, adsq ca are not simple mixtures of their two histological tumor counterparts
- Dx of sq cell ca in small specimens can be problematic
- Convergence of molecular markers in microdissected specimens suggest clonal origin for these oncogenic driver mutations
- Limitations: subjective nature of IHC scoring and small sample size (n=19).

**Take home points:** Adenosq ca might not be a simple mixture of sq cell and adenoca. High expression of TS (comparable to sq cell ca) suggests that pemetrexed may not be effective in adsq ca

**Purpose:** To assess hepatocyte nuclear transcription factor 4 alpha (HNF4α) expression in lung adenocarcinomas (including mucinous adenocarcinomas) and other types in lung cancers.

**Methods:**
- Various cancers in 2 series of TMAs including 358 lung cancers were stained with anti-HNF4α and assessed as positive or negative, along with TTF1 and CDX2; 36 benign lesions (in addition to 134 non-neoplastic areas neighboring the tumors) also examined
- Mutational analysis: EGFR, KRAS, ALK, p53 (in an other study)

**Results:**
- HNF4α positivity is limited to adenocarcinomas and all squamous cell cancers are negative; 7 adenocarcinomas were also negative.
- All GI and pancreatic cancers were positive for HNF4α, while all esophageal adenocarcinomas were negative.
- All HNF4α-positive ovarian cancers were mucinous type.
- In lung, most HNF4α-positive tumors were adenocarcinomas but carcinoid tumors (2 of 2), large cell carcinomas (1 of 6), LCNEC (1 of 6) were also positive.
- Invasive mucinous adenocarcinomas (IMCs): 37 (4.9%) IMCs in lung adenocarcinomas were identified. They were more females and nonsmokers; no correlations with age or pathologic stage; harbored frequent KRAS mutations (52%) and rare EGFR mutations (3%)
- HNF4α expression was seen in all but 4 of the IMCs; intense and uniform stain, suggesting that HNF4α could be a useful marker in small biopsy samples, given the lack of HNF4α positivity in any normal tissues.
- HNF4α expression in other lung adenocarcinoma subtypes including acinar and solid predominant subtypes. Of note, majority of HNF4α-positive adenocarcinomas were classified as columnar (15/16, 94%) and the cuboidal cell type was rarely positive for HNF4α (1/82, 1%)
- Negative correlation between HNF4α and TTF-1 expressions; cuboidal cell type was positive for TTF-1 but not for HNF4α.
- Interestingly, not all of the IMCs show HNF4α expression; 4 of 37 IMCs were HNF4α-negative, AND all of these 4 adenocarcinomas harbored an ALK fusion. Therefore, they also examined 31 adenocarcinomas with ALK fusion for HNF4α; none of them was positive for HNF4α, although 3 of the tumors were categorized as IMCs.
- HNF4α expression is distributed in normal GI mucosa and in cancers arising from the GI tracts, ovary, pancreas, uterine cervix, and lung with certain features including CDX2 and CD20 positivities, goblet cell morphology, and KRAS mutation.

**Take home points:** HNF4α is expressed in more cell specific than organ specific manner. IMC of the lung may be a heterogeneous group comprised of HNF4α-positive/KRAS mutated and HNF4α-negative/ALK mutated tumors.
Articles for notation – Neoplastic

Matsuguma H et al. Characteristics of Subsolid Pulmonary Nodules Showing Growth During Follow-up With CT Scanning. CHEST 2013;143(2):436-443

Purpose: The positive results of the National Lung Screening Trial that started in 2002 led to an increase in the use of CT screening with a likely increase in the detection of subsolid nodules. To determine which nodules require invasive procedure for dx and surgical tx, or follow up with noninvasive CT scanning

Methods: A retrospective review of 174 subsolid nodules identified from >60,000 examinations between 2000 and 2008, with a GGO area >20% of the nodule and measured ≤2cm, in 171 patients. They investigated the clinical characteristics and CT images of the subsolid nodules in relation to changes identified during the f/u period

Results: Nodule size 4-20 mm, nonsolid nodules 98 (of 174); resolution or shrinkage in 18 nodules, growth of 2 mm or more in 41 nodules with higher rate of such growth in part-solid than in nonsolid nodules at 2 and 5 years f/u. Large nodule size (>10 mm) and hx of lung ca were significant predictive factors of growth in nonsolid tumors on multivariate analysis.
Take home points: Subsolid nodules show different natural histories: some subsolid nodules show growth, some show shrinkage, and some remain stable for long periods. Factors associated with growth are the type of subsolid nodule, initial nodule size and hx of lung ca. Intervals of f/u of CT scanning for subsolid nodules should be determined considering these factors.


Purpose: To examine the clinical characteristics and therapeutic strategies of primary pulmonary sarcomas (PPS) and their impact on overall survival (OS)
Methods: A retrospective analysis from the SEER data base of the NCI from 17 population-based cancer registries covering 28% of the US population (1988-2008) on pts with PPS who underwent local therapy. Eligible pts had histologically confirmed invasive soft tissue sarcoma of the lung, bronchus, carina or hilum with no known metastasis. Pts restricted to age of 20 and older. Kaposi’s sa was excluded given the association with AIDS. Pts with rhabdomyosarcoma, Ewing’s sa, Askin tumor of soft tissue, peripheral neuroectodermal tumor of soft tissue, and extrarenal rhabdoid tumor were also excluded because the primary tx of these tumors includes chemotherapy. Survival estimation by K-M method and the Cox regression model. OS of PPS were compared with a cohort of 10,909 pts having soft tissue sarcomas of extremity

Results: 365 PPS with a median f/u of 21 months. 55% had tumors >5 cm, 76% high grade, 16% node positive ds. 75% had surgery alone, 14% surgery and RT, 11% RT alone. On multivariate analysis, pts with tumor >5 cm, high tumor grade and unresectable ds had reduced OS. OS at 5 year of PPS vs sarcomas of extremities was 35% vs. 71% (p<0.0001).

Take home points: PPS has a high rate of nodal involvement and significantly worse OS than pts with extremity sarcomas

Takahashi Y et al. Distinctive histopathological features of lepidic growth predominant node-negative adenocarcinomas 3 – 5 cm in size. Lung Cancer 2013;79:118-124

Purpose: To examine the prognostic implication of lepidic growth (LG) in node negative large ADCs (3-5cm) (i.e. T2aN0)

Methods: 135 lung ADCs 3-5 cm in size without LN mets were classified according to LG component and LG% was correlated with clinical factors.

Results: 41 (30.4%) tumors had 50% or more LG (i.e. lepidic predominant ADC). Female gender, smoking hx of <20 pack years, absence of pleural invasion and absence of vascular invasion were significantly more frequently seen in lepidic predominant group. Both recurrent-free survival and overall survival were better in lepidic predominant group (p<0.001 for both), which was an independent prognostic factor in multivariate analysis (p=0.014) as was the absence of pleural and vascular invasion (0.001 and 0.041, respectively), when consider age, gender, smoking hx, preop CEA level, and pleural, vascular and lymphatic invasions covariates. Additionally, they evaluated “non-cancerous cell area” (NCCA) that is defined as the areas without cancer cells and separated from the closest cancer cells by > 1 mm (represented as % of maximum tumor surface area). NCCA% was significantly higher in LG-predominant tumors.

Take home points: LG predominant pattern is an independently favorable prognostic factor in node-negative ADC of 3-5 cm


Purpose: To describe clinicopathologic and immunohistochemical characteristics of 24 primary intrapulmonary SFTs from multiple centers

Methods:
- Particular attention to the location of the tumor to avoid the cases with an inward growth of a pleural lesion. Excluded the case with hx or evidence of origin of the tumor outside of the lung, and bearing the standard histopathologic features of SFT and appropriate results of IHC

- Tumor graded as low, intermediate and high grades, on the basis of the degree of cytologic atypia, cellularity, mitotic activity and areas of necrosis
  
  **Low grade**- bland nuclear features without nucleoli, mitotic counts <5/10 HPF, absence of coagulative tumor necrosis, abnormal mitoses or nuclear pleomorphism.

  **Intermediate grade**- increases in overall cellularity, more pronounced cytologic atypia, increase in chromatin density, prominent nucleoli, with mitoses 5-10/10 HPF. Focally collagenized areas adjacent to hypercellular areas, many of which had a fascicular, fibrosarcoma-like appearance admixed with areas of necrosis. Hemagipericytic and angiofibromatous patterns also present.

  **High grade**- >10/10 HPF, high cellularity, areas of coagulative tumor necrosis, and marked nuclear pleomorphism resembling a high-grade pleomorphic sarcoma at initial dx, but with focal areas showing the conventional features of low-grade SFT

**Results:** looked pretty much similar to that of extrapulmonary SFT

- 21 of 24 were low-grade; 14 of 21 did not have any mitotic activity (<1/10 HPF); 7 of 21 had 2-4/10 HPF. In 2 of 21 low grade patients subsequently went on to develop metastasis and died 4 and 7 years after dx. On patient had a 0.6 cm nodule in the contralateral lung on imaging at the time of initial presentation, which may have presented a metastasis.

- 1 of 24 showed intermediate morphology

- 2 of 24 had high grade morphology. One of 2 had at least 2 separate nodules. CD34 was negative in high-grade areas but there were focal areas with conventional SFT morphology

**Take home points:** Even tumors with low grade morphologic features at initial presentation might follow an aggressive course as do the tumors with overtly malignant histologic features, which has been well known in extrapulmonary SFTs. Adequate excision with close clinical follow up is recommended


**Purpose:** To characterize mucoepidermoid ca (MEC)

**Methods:** 28 MEC (13 FFPE and 15 fresh frozen). Dx reviewed by 3 pathologists and histopathological grading according to the WHO classification. Clinical f/u data obtained from medical records. ArrayCGH, nested RT-PCR for CRTC1-MAML2 fusion transcript, and FISH for CRTC1-MAML2 and EWSR1-POU5F1 were performed using break-apart probes for MAML2 and EWSR1 genes were performed. was done.

**Results:** Low-grade ME ca have normal or near-normal genomic profiles, express the CRTC1-MAML2 fusion and have a favorable clinical outcome. The majority of high-grade ME ca had multiple genomic imbalances, were negative for CRTC1-MAML2 fusion and developed frequent metastasis and/or recurrence

**Take home points:** Molecular genetic analysis can be a useful adjunct to histologic scoring of ME ca and may possibly lead to new therapeutic strategies

Purpose: To investigate the clinical characteristics and EGFR mutation rate in NSCLC with miliary intrapulmonary carcinomatosis (MIPC) at presentation.

Methods: Newly diagnosed NSCLC pts were screened for MIPC using image-based criteria during 6/2004-12/2008 period. Clinical data and EGFR mutation status were analyzed. For comparison, stage IV NSCLC cases without MIPC were tested for EGFR mutations during 4/2001-11/2008.

Results: 85 pts with MIPC were identified among 3612 NSCLC patients; 81 were adenoca. 60 of these 85 cases underwent EGFR mutational analysis and 42 (70%) were positive. Compared to 673 stage IV pts without MIPC, pts with MIPC had higher EGFR mutation rate (p=0.036, even in male smokers (91%). In 85 pts with MIPC, adenoca histology, absence of extrapulmonary metastasis and positive EGFR mutation status were associated with longer overall survival on multivariate analysis.

Take home points: NSCLC pts with MIPC had a higher rate of EGFR mutation and EGFR inhibitor may be the tx of choice for those with MIPC at initial dx among Asians, regardless of gender and smoking status


Purpose: Unlike EGFR exon 19 deletions and exon 21 point mutations, exon 20 insertions are not sensitive to EGFR TKIs. To examine the role of EGFR exon 20 insertions other than its known implication of predicting lack of responses to EGFR inhibitors

Methods: A retrospective evaluation of clinical characteristics and survival in cancers harboring common EGFR mutations and cancers with wild-type EGFR

Results: 27 (2.5%) of 1,086 pts tested for EGFR genotyping harbored exon 20 insertions, making up 9.2% of all cancers with documented EGFR mutations. Compared with wild type cancers, those with exon 20 insertions were more commonly found in never smokers and Asian pts. Insertion sequences were highly variable with the most common variant V769_D770insASV making up only 22% of cases. Median survival of pts with exon 20 insertions was 16 months, similar to the survival of wild-type cancers and shorter than the survival of cancers with common EGFR mutations

Take home points: Pts with EGFR exon 20 insertions have poorer px than those with common TKI sensitive EGFR mutations despite the similar clinical characteristics and would be a population of interest for trials of new targeted therapies


Purpose: To evaluate if the diagnostic yield using histology analysis of core needle bx is higher than cytologic preparations alone

Methods: 177 consecutive pts with mediastinal abnormalities were evaluated and EBUS was done by interventional pulmonologist or thoracic surgeon. Diagnostic yields of cytology and histology were compared. Results were categorized as malignant, benign (infectious, inflammatory), normal nodal tissue or inadequate sampling (nondiagnostic). Malignancy, a defined benign process, and normal LN were considered diagnostic.
Results: the diagnostic yield for benign processes was higher by histology (n=37) than in cytology (n=22; p=0.0064), but it was comparable for malignancy (p=0.7530). The combination of both techniques provided a higher overall diagnostic rate: 84% by histology, 82% by cytology and 89% using both. Discordance was found in 23%, demonstrating that the use of one technique would have missed the diagnosis.

Take home points: A routine use of both cytology and core bx histology is ideal in EBUS.


Purpose: To investigate possible causes for false negative findings on PET scans for solid type lung cancers.

Methods: A retrospective comparison of PET findings to clinical and pathologic features using multivariate analysis in solid type lung cancers

- Review of PET/CT, clinical records, preoperative thin-section CT images and post op path reports
- Selected only solid-type primary lung cancers with lesions ≤40mm in diameter that had been definitely dxed by surgical resection
- PET images with SUVmax of ≥2.5 were considere PET-positive.
- Logistic regression analysis was used to identify independent predictors of PE-positive or negative among 5 factors: body wt, blood glucose level, lesion size, location and histologic type.

Results: a total of 187 solid type primary lung cancers were selected. 40 (21.4%) were judged as PET-negative and 147 lesions (78.6%) were PET-positive. Multivariate logistic analysis for the 187 lesions revealed that lesion size and histologic type (both p<0.001) were significant factors for determining PET status.

Take home points: More attention should be paid to the lesions ≤2cm as well as BAC and well diff adenoca as they tend to be PET negative.


Purpose: To evaluate immunohistochemical expression of napsin A in primary pulmonary mucinous tumors.

Methods: Napsin A IHC on 43 mucin-producing adenocas of lung (18 mucinous BAC, 15 colloid adenoca, 5 solid predominant adenoca with mucin production, 5 adenoca with SRC features) and 25 extrapulmonary mucinous adenocarcinomas from various sites, in comparison with TTF1.

Results: 33% and 42% of mucinous lung tumors were positive for napsin and TTF1, respectively. All 25 extrapulmonary mucinous tumors were negative for napsin and TTF1.

Take home points: Napsin is not a very sensitive marker in mucin producing adenoca of the lung and less sensitive than TTF1 in this context.

**Purpose:** To evaluate the role of BRCA1 as a biomarker predicting the risk of recurrence in early stage NSCLC.

**Methods:** Methylation-specific PCR was performed to assess promoter methylation of BRCA1 in 70 pts who underwent curative resection of stage I NSCLC.

**Results:** 13 of 70 (18.6%) had methylation the BRCA1 promoter, which was an independent risk factor of tumor recurrence. BRCA1 methylation status was not associated with any specific clinicopathologic features including pathologic stage.

**Take home points:** BRCA1 methylation status may play an important role in the progression of NSCLC and could be a biomarker predicting the outcome of ds after curative resection of stage I NSCLC. Also, it could be a useful information for tailored adjuvant therapy in that BRCA1 plays a role in chemotherapy induced apoptosis.

**Articles for notation – Non-neoplastic**


**Purpose:** To assess the frequency of mediastinal lymphadenopathy (MLAD) in pts with idiopathic pulmonary arterial hypertension (IPAH) and to describe the correlative clinical features.

**Methods:** a retrospective review of pts with IPAH who underwent rt heart cath (RHC) and chest CT within 3 months of each other. CT scans were reviewed for MLAD with correlating demographic and clinical data including LN size and of pleural and pericardial effusion.

**Results:** 85 pts were included with mean age of 48 and 82% of women. 15 of 85 (18%) had MLAD, with mean short axis diameter of 13.6mm. no association of MLAD with age, sex, RAP, or mPAP. MLAD was associated with presence of pleural effusion, but not pericardial effusion.

**Take home points:** MLAD without other identifiable causes is seen in 18% of IPAH and is associated with pleural effusions but not with other parameters.

Miyoshi K et al. Epithelial Pten Controls Acute Lung Injury and Fibrosis by Regulating Alveolar Epithelial Cell Integrity. Am J Respir Crit Care Med 2013;187(3):262-275

**Purpose:** Underlying mechanisms of maintenance, repair and remodeling of alveolar epithelial cells (AECs) integrity after injury is important for understanding the pathogenesis of acute lung injury (ALI) and lung fibrosis. Pten is a multifunctional phosphatase that negatively regulates the PI3K/Akt pathway and exerts tumor.
suppression and exerts tumor suppression. The role of Pten on epithelial cells in organ fibrosis, including lung fibrosis, remains unknown. Authors sought to determine the role of epithelial Pten in ALI and lung fibrosis.

**Methods:** Bronchioalveolar epithelium-specific Pten-deleted mice were studied for structural, biochemical, and physiologic analyses and compared with wild type mice. Also samples from IPF patients were analysed.

**Results:** Pten deficient mice demonstrated exacerbation of alveolar flooding and subsequent lung scarring with disturbed tight junctions of AECs and degradation of basement membranes. The induction of dominant negative Pten gene in lung epithelial cells led to increased TGF-1 induced disruptions of tight junctions. Epithelial derived myofibroblasts were increased in the epithelium specific Pten deficient mice. The lungs of bleomycin treated Pten deficient mice showed increased pAkt, pS6K, Snail, and MMP expressions and decreased claudin-4, E-cadherin and laminin-beta1 expressions. Akt inactivation saved Pten deficient mice through amelioration of ALI and retention of AEC integrity. In the AECs of human IPF lungs, there was a reduction of Pten expression and AKT hyperactivation.

**Take home points:** The epithelial Pten is essential for the prevention of ALI and lung fibrosis through the regulation of AEC barrier integrity. PI3K/Pten/Akt pathway in bronchioloalveolar cells was essential to the prevention of ALI and lung fibrosis and may be a therapeutic target against these diseases.

**Dakhllalah D et al.** Epigenetic Regulation of miR-17~92 Contributes to the Pathogenesis of Pulmonary Fibrosis. Am J Respir Crit Care Med 2013;187(4)397-405

**Purpose:** Molecular changes in the development of IPF is not well known. Recently, microRNAs (miRNA) have emerged as regulators of numerous genes and unique targets in IPF. The mechanisms by which miRNAs are altered in IPF remain unknown. The miR-17~92 miRNA cluster is critical for lung development and lung epithelial cell homeostasis and is predicted to target fibrotic genes and DNA methyltransferase (DNMT)-1 expression. This study is to investigate the miR-17~92 cluster expression and its role in regulating DNA methylation events in IPF lung tissue

**Methods:** Expression and DNA methylation patterns of miR-17~92 were determined in human IPF lung tissue and fibroblasts and fibrotic mouse lung tissue. The relationship between miR-17~92 cluster and DNMT-1 expression was examined in vitro. Using a murine model of pulmonary fibrosis, they examined the therapeutic potential of a demethylating agent.

**Results:** Compared to controls, miR17~92 expression was reduced in lung bx and lug fibroblasts from IPF pts while DNMT-1 expression and methylation of the miR-17~92 promoter was increased. Several miRNAs from the miR-17~92 cluster targeted DNMT-1 expression resulting in a negative feed back loop. Also, miR-17~92 expression was
reduced in the lungs of bleomycin treated mice and treatment with a demethylating agent in a murine bleomycin induced lung fibrosis model reduced fibrotic gene and DNMT-1 expression, enhanced miR-17~92 cluster expression and attenuated pulmonary fibrosis.

**Take home points:** A novel epigenetic feedback loop between miR17~92 and DNMT-1 in lung fibrosis is identified. This study reports the association between aberrant DNA methylation and miRNA expression in IPF. miRNA expression in IPF is susceptible to epigenetic regulation. Based on this observation, this study, suggests the potential for targeting DNA methylation events as a therapeutic approach for IPF.


**Purpose:** Abnormal Ig responses and successful B-cell ablative therapy have suggest involvement of B cells in the pathogenesis of sarcoidosis. This study is to investigate how abnormal B-cell maturation and function in pts with sarcoidosis contribute to disease

**Methods:** 32 sarcoid pts were studied by IHC of tissue, flowcytometry of blood B-cell subsets, and serum Ig levels. Vaccination responses in pt with sarcoidosis to influenza virus and encapsulated bacteria and molecular analysis of Ig heavy chain transcripts were studied for functional analysis of Ig responses

**Results:** Perigranuloma localization of IgA producing plasma cells and numerous B cells were found in affected tissues. Total blood B cell numbers were normal, CD27+ memory B cells were significantly reduced and CD27- IgA+ B cells were significantly increased. The results are normalized in pts treated with TNF alpha blockers. Despite this, pts had normal serum Ig levels and normal Ag-specific Ig responses. IgA and IgG transcripts, however, showed high frequencies of somatic hypermutations and increased usage of downstream IgG subclasses, suggestive of prolonged or repetitive responses

**Take home points:** The large B cell infiltrates in granulomatous tissue and increased molecular signs of antibody maturation are indicative of direct involvement of B cells in local inflammatory processes in patients with sarcoidosis. B-cells could be involved in the pathogenesis of sarcoidosis.


**Purpose:** The effect of pretpx malignancy (PTM) in lung tpx and heart tpx.

**Methods:** A retrospective review of primary adult lung and heart recipients in UNOS database. Matched cohorts (2:1) and multivariable Cox regression models were used to evaluate mortality

**Results:** from 2000 to 2011, 13,613 lung and 19,817 heart tpx. PTM was present in 740 lung (5.4%) and 1,117 hear (5.6%) patients. In general, PTM does not increase mortality
in either cohort, except heart tpx patients with leukemia, lymphoma and myeloma with increased hazard of mortality.

**Take home points:** Carefully selected patients PTM should not be excluded from lung or heart tpx

**Reviews, Commentaries, and Case reports**

**Lang IM et al. Risk factors and basic mechanisms of chronic thromboembolic pulmonary hypertension: a current understanding. Eur Respir J 2013;41:462-468**

CTEPH is not simply due to the obliteration of central pulmonary arteries by pulmonary emboli but caused by complex factors, including infections, immune phenomena, inflammation, circulating and vascular resident progenitor cells, thyroid hormone replacement and malignancy. Both plasmatic factors and misguided vascular remodelling process contribute to major vessel and small vessel obliteration. Endothelial dysfunction and endothelial-mesenchymal transition may be also important.


Commentary on increased lung cancer over the last 20 years or so HIV infected patients after the dramatic increase in survival of combination antiretroviral therapy. The leading cause of mortality in the HIV-infected population is lung cancer, accounting for nearly 30% of all cancer deaths as opposed to 10% of non-HIV-related deaths. The average age of onset of lung cancer in the HIV-infected population is 25-30 years earlier than that in the general population and at lower exposure to cigarette smoke. This article provided an overview of the epidemiology of lung cancer in the HIV-infected population and discusses some of the important risk factors and pathways that may enhance the risk of lung cancer in this population


Nice review on the lung architecture by legendary Dr. Weibel!


A review on potential challenges for the multidisciplinary team implied by the move toward personalized therapy in NSCLC and the increasing need for molecular diagnoses and working roles and responsibilities of team members

A comprehensive review on EGFR mutation testing in lung cancers including available methods and their use for analysis of tumor tissue and cytology samples


The two lung tumors in a patient showed different activating EGFR mutations, EGFR amplification status, PT53 mutations status, and loss of heterozygosity patterns shown by targeted next generation sequencing with the Ion Torrent Personal Genome Machine. Molecular testing should be done on all tumor foci present

**Steinestel K et al.** Fatal thromboembolism to the left pulmonary artery by locally applied hemostatic matrix after surgical removal of spinal schwannoma: a case report. Human Pathology 2013;44:294-298

A 78 year woman developed fatal thromboembolism 8 hours after a neurosurgical procedure for removing extraforaminal spinal schwannoma using bovine gelatinous granules admixed with human thrombin to control bleeding.