Conclusions: In all lung transplant patients, a negative pCMV-PCR had a NPV=100% and specificity=93%. This implies that in asymptomatic patients, a negative pCMV-PCR excludes CMV pneumonitis with high reliability, specificity=93.8%, superior to clinical impressions. We recommend that CMV-IHC should not be performed for asymptomatic patients with negative pCMV-PCR.

Table1. CMV IHC vs PCR

	IHC +	IHC -	Total
pPCR +	1	11	12
pPCR -	0	143	143 (PPV=100%)
Total	1	154 (Spec=93%)	155

Table2. Clinical Symptoms vs pCMV-PCR

	Symptomatic	Asymptomatic	Total
pPCR+	6	6	12
pPCR-	51	92	143
Total	57	98 (Spec=93.8%)	155

1500 Value of Silver Stains on BAL Fluid in Lung Transplant Recipients

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Background: Lung transplantation is a viable treatment for patients with end stage disease. Pneumocystis carinii pneumonia (PCP) is uncommon in lung transplant patients on lifelong prophylaxis. During bronchoscopy, either for clinical symptoms or routine surveillance protocols, transbronchial lung biopsies (TBBx) and bronchoalveolar lavages (BAL) are obtained and sent, in accordance with the Lung Rejection Study Group, for H&E and Papanicalou staining, respectively. Many transplant institutions stain TBBx and BAL fluid with Gomori Methenamine Silver (GMS) to exclude PCP. In effort to better understand the value of GMS stained BAL fluid, we conducted a retrospective analysis of patients who had concurrent BALs and TBBxs stained with GMS for PCP.

Design: Fifty consecutive patients on PCP prophylaxis with GMS stained TBBxs and concurrent BALs, between 1996 and 2006, were identified. Bronchoscopies were performed on both asymptomatic/surveillance patients and symptomatic (fever and/or decrease in FEV1) patients. TBBxs were fixed in 10% buffered formalin, processed by pulmonary biopsy protocol, embedded in paraffin, and 4µm sections were stained with H&E and GMS. BAL specimens were treated with Cytolyt, centrifuged 5 minutes, resuspended and processed in a Wescor Cytopro for 3 minutes. The slides were then stained with GMS.

Results: We compared 393 GMS stained TBBxs with concurrent GMS stained BALs, from 50 consecutive patients. There were 283 biopsies from asymptomatic patients and 110 from symptomatic patients. None of the GMS stained TBBxs or BALs were pneumocystis positive. The negative predictive value (NPV) and specificity were 100% (Table1).

Conclusions: None of the 283 asymptomatic and 110 symptomatic patients' biopsies were pneumocystis positive, either on BAL or TBBx (gold standard). In all lung transplant patients on PCP prophylaxis, there were no positives by either GMS stained BAL or TBBX. This suggests that in patients on PCP prophylaxis, routine GMS staining on BAL and TBBx may not be necessary. Despite no positive tests in even the symptomatic patients, clinicians remain obligated to exclude infectious etiologies. While limited by the lack of PCP infected patients in our study, it is likely that in certain clinical scenarios GMS staining is indicated. However, based on our results, the risk of PCP under these clinical circumstances appears to be very low.

GMS Stained TBBx vs BAL

	PCP BAL +	PCP BAL -	Total
PCP TBBx +	0	0	0
PCP TBBx -	0	393	393 (NPV=100%)
Total	0	393	393

1501 Clinicopathologic Study of Type 4 Congenital Pulmonary Airway Malformation (CPAM): Evidence for Distal Acinar Origin

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Background: CPAMs are a group of cystic developmental malformations of the lung that are classified based on the putative anatomic region of origin. Type 4 CPAM was first described in 1994 and subsequently there are only anecdotal reports. Recently there has been increased concern that some of these lesions may represent cystic pleuropulmonary blastoma (PPB). We describe the largest series of type 4 CPAM with detailed clinicopathologic analysis.

Design: All cases of congenital/developmental cystic lesions of the lung accessioned to our consultation service were retrieved and cases of type 4 CPAM identified. Additional cases sent in consultation to one of us were also included. Clinical histories, surgical descriptions and histology slides were evaluated. Lesions were evaluated for cyst lining epithelium, subepithelial stromal components, presence or absence of cambium layer, and TTF-1, p63 and desmin immunostaining.

Results: Among 27 cases, 78% presented in the first six months of life (range prenatal to 4 years), without gender predilection. Respiratory distress and/or tachypnea were the most frequent symptoms (59%). The middle/lower lobes were more often affected (53%), with multiple lobes being involved in 20%. The mean size was 7.2 cm (range 1.7 to 12.5 cm). The cysts predominantly contained air, suggesting a connection with the tracheobronchial tree. Cyst lining epithelium was of alveolar type. The underlying stroma was variably cellular, with lesions from older children showing a more collagenous stroma. Lymphocytes, siderophages, foamy histiocytes and prominent thick-walled vessels were common. Foci of cartilage were seen in eight (29%) cases. Lining cells were keratin and TTF-1 positive and p63 negative. Desmin immunostain was negative for rhabdomyoblasts in all cases.

Conclusions: Type 4 CPAM is predominantly a disease of infancy. The histologic features and immunohistochemistry favor a distal acinar origin with cysts being lined by alveolar-type cells. The presence of thick-walled vessels and focal cartilage supports a hamartomatous origin. Lack of desmin staining in subepithelial small round cells may help prevent a misdiagnosis of cystic PPB.

1502 Differences of Fibroblastic Foci of UIP and Intraalveolar Buds of COP/BOOP, as Measured by Cellular Markers and Growth Factors

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Background: Fibroblastic foci and profusion of fibroblastic foci contribute to irreversible fibrosis in UIP and are correlated with increased mortality. On the other hand, the polypoid granulation tissue plug (intraalveolar bud or Masson's body) is one of the pathologic characteristics in COP/BOOP but is not related to progressive interstitial fibrosis. We compared the spatial and quantitative expression of various cell markers and growth factors in UIP and COP/BOOP.

Design: Immunostaining for Transforming growth factor (TGF) beta-1, connective tissue growth factor (CTGF), alpha-SMA, CD34, triptase, S-100, beta-catenin, pSmad 2/3, vascular endothelial growth factor (VEGF), fms-related tyrosine kinase 1 (Flt-1), kinase insert domain region containing receptor (KDR) / Fetal liver kinase (Flk1) and proliferation cell nuclear antigen (PCNA) was carried out in paraffin embedded sections of lung from 12 video-assisted thoracosurgery (VATS) biopsies with UIP and from 10 VATS biopsies with COP/BOOP using a standard indirect avidin-biotin horseradish peroxidase method.

Results: Myofibroblastic proliferation was greater in the fibroblastic foci in UIP than in the intraalveolar buds in COP/BOOP. Capillary proliferation is frequent in intraalveolar buds but scarce in fibroblastic foci. TGF beta-1 and CTGF were expressed strongly in fibroblastic foci but faintly in intraalveolar buds. TGF beta-1, beta-catenin, pSmad 2/3, VEGF, Flt-1 and Flk-1 were seldom observed in pneumocytes adjacent to the lesions in COP/BOOP but were frequently observed in regenerating type 2 pneumocytes and bronchiolar epithelial cells in UIP. PCNA-positive pneumocytes, bronchiolar epithelial cells and myofibroblasts were frequent in UIP not in COP/BOOP.

Conclusions: Differences in expression of growth factors in myofibroblasts and regenerating pneumocytes in UIP when compared to COP/BOOP may explain the difference in the natural history of the two diseases.

1503 Novel Benign Pulmonary and Chest Wall Lesions as Part of the Von Hippel Lindau Syndrome Mimicking Metastatic Renal Cell Carcinoma

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Background: VHL is an autosomal dominant cancer syndrome in which affected individuals and kindreds are at risk to develop renal cell carcinomas (RCC), and other tumors. Distinct lung/chest wall lesions have not been previously reported in patients with this syndrome.

Design: Ten patients, members of VHL families, were evaluated for renal and or other tumors as part of clinical screening. Patients ranged in age from 15 to 59 years. Four were female and 6 were male. Clinical symptoms included chest pain, presence of a chest wall mass and in four patients the lesions were an incidental finding. Five patients had RCC and one a pancreatic neuroendocrine tumor. One patient had been diagnosed as Malignant Mesothelioma.

Results: Eight patients had lung lesions, one a pleural mass, and another one a chest wall tumor. Six patients underwent surgical procedures: thoracotomy in 5 and excision of chest wall mass in 1. Four patients are being followed clinically for benign lung cysts. The clinicoradiological impression was metastatic RCC in 4 patients and malignant mesothelioma in the remainder patient. Morphologically, three of the lung lesions consisted of multiple, variable sized cysts lined by cuboidal cells with clear cytoplasm of uncertain histogenesis. They were distributed within the lung parenchyma, near bronchial structures or in pleural/subpleural locations. The fourth lung lesion consisted of an intraparenchymal proliferation of tubuloglandular structures, lined by clear cells and surrounded by dense myofibroblastic stroma. The chest wall lesion consisted of a small tumor mass characterized by clear cells arranged in tubuloglandular structures with myoepithelial proliferation in the walls. The pleural tumor consisted of a proliferation of papillary structures lined by clear cells. Immunohistochemistry was performed for TTF1, calretinin, CK, SMA, CEA, neuroendocrine and other markers markers. All patients are alive 1 to 7 years after diagnosis.

Conclusions: We describe novel lung and chest wall lesions and propose their inclusion in the spectrum of tumors associated with VHL syndrome. Lung lesions can be cystic or solid. Chest wall tumors are solid and frequently misdiagnosed as metastatic RCC. Recognition of these new lesions as part of the VHL syndrome is important to avoid unnecessary surgery and wrong forms of treatment.

1504 Convergence of College of American Pathologists (CAP) Protocol Model and North American Association of Central Cancer Registry (NAACCR) Elements for the Development and Deployment of Common Data Elements: An Emerging Standard for Mesothelioma Virtual Biorepository

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Background: The rise of molecular and systems biology in medicine is driving development of well annotated and properly characterized bio-repositories to provide tissue to support translational research. Clinical annotation of tissue samples – is central to the success of these repositories as such annotation allows samples can be better matched to the research question at hand and experimental results better understood and verified. To facilitate and standardize clinical annotation in bio-repositories, we have

combined two accepted and complementary sets of data standards, the CAP (pathology data) and NAACCR elements (epidemiology, therapy and progression). Combining these approaches one can create a set of ISO-compliant common data elements (CDE) for oncology tissue banking.
Design: The purpose of the project is to develop a core set of annotation data elements for mesothelioma based on the elements from CAP protocol and the NAACCR checklist. We have associated these elements using modeling architecture to enhance both syntactic and semantic interoperability. The system has a Oracle based three- tiered architecture. The application uses the http server to generate dynamic pages from the database to the users.
Results: We have developed the CDEs for the tissue banks using controlled vocabulary, ontology and semantic modeling methodology. The CDEs included for each case are of different types that include demographic & epidemiologic data, clinical history, pathology data including block level annotation, and outcome data including treatment, recurrence and vital status.
Conclusions: The CAP and the NAACCR elements represent widely established data elements that are used in many cancer centers. Herein we have shown that these representations can be combined and formalized to create a core set of annotation for banked mesothelioma specimens. Because these data elements are collected as part of the normal workflow of a medical center, data sets developed on the basis of these elements can be easily implemented and maintained.

1505 Molecular Profiling of Large Cell Neuroendocrine Carcinoma of Lung and Evaluation of ASCL-1 and KLK11

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Background: Large cell neuroendocrine carcinoma of lung (LCNEC) is a diagnostic challenge, because of its morphological spectrum. Although there are published morphologic criteria and several useful immunohistochemical markers, these lack specificity. More specific and sensitive biomarkers are needed for accurate diagnosis and to better define biological features of neuroendocrine tumors.
Design: 108 tumor specimens (7 LCNEC,100 adenocarcinomas (AD) and 1 small cell carcinoma (SCLC)) were examined for gene expression profile using Affymetrix U133 genechip. Diagnosis was established by morphology and immunohistochemistry (IHC) for synaptophysin (syn), chromogranin A (chr) and CD56. Expression of mRNA was analyzed by t test, and two candidate genes (achaete scute complex, drosophila, homolog of, 1, ASCL1, and kallikrein 11, KLK11) were selected as neuroendocrine markers, and examined by quantitative realtime PCR (qRT-PCR), using RNA from frozen and formalin-fixed paraffin-embedded (FFPE) samples.
Results: 154 probe sets were differentially expressed between LCNEC and AD ($p<0.005$ and > 3-times fold change). ASCL1 and KLK11 were selected for further examination. qRT-PCR of RNA from frozen samples showed ASCL1 expression of LCNEC (mean of relative ratio to TBP = 438) and SCLC (1052) was higher than that of AD (49) and NL (9) ($p<0.001$). KLK11 expression was also higher in LCNEC (6.1) than SCLC (0.2), AD (3.2) and NL (0.9) ($p<0.001$). Using FFPE specimen, reliable results of qRT-PCR were obtained in 27 out of 38 samples (7 LCNEC and 20 AD). RNA quality was inadequate for the remaining 11. The ASCL1 expression was higher in LCNEC (13901) than AD (176) ($p=0.015$), although that of KLK11 did not show significant difference (LCNEC 2.0 vs. AD 2.1). ASCL1 expression ($p=0.001$) and immunoreactivity of chr ($p=0.002$) showed association with histology, but KLK11 expression, immunoreactivity of syn and CD56 did not. ASCL1 expression associated with immunoreactivity of syn ($p=0.002$) and chr ($p=0.003$), but not with CD56. The sensitivity of qRT-PCR of ASCL1 in LCNEC (LCNEC 100%) was higher than immunohistochemical reactivity (syn 83%, chr 83%, CD56 67%).
Conclusions: ASCL1 is a potential useful marker for neuroendocrine differentiation of lung cancer (both of LCNEC and SCLC). The qRT-PCR for detecting gene expression can be applied to FFPE samples as well as fresh frozen samples if the RNA quality is good. KLK11 seems to be a less specific marker and needs further evaluation.

1506 Necrotizing Granulomas Negative for Microorganisms: Clinical Course of 50 Cases

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Background: No organisms are identified using histochemical techniques in a subset of necrotizing granulomas with histologic features suggestive of infection. Some of these are granulomatous infections in which organisms are undetected by light microscopy while others may represent non-infectious disorders. This study was performed to determine the clinical course of patients with unexplained necrotizing granulomatous inflammation.
Design: We retrospectively reviewed 50 cases of necrotizing granulomas in surgical lung specimens that were negative for microorganisms using Grocott Methenamine Silver and Auramine-Rhodamine stains. Only patients with radiologically solitary or multiple nodules were included. Microbiological, clinical and radiographic data were reviewed till the date of last follow-up.
Results: 28 women and 22 men had a mean age of 57 (range 10-82 years). Radiographically, nodules were solitary in 24 and multiple in 26. The nodules were mainly excised by wedge resection (88%). Cultures of the tissue specimens were positive in 9 cases: M. avium-intracellulare complex (8) and M. tuberculosis (1). M. avium-intracellulare complex was isolated from induced sputum in one additional patient. Following lung biopsy, clinical diagnoses were established in 22 patients: granulomatous infection (13), sarcoidosis (4), rheumatoid nodule (2), limited Wegener's granulomatosis (1), pulmonary vasculitis of indeterminate etiology (1) and ANCA-negative necrotizing granulomatous vasculitis (1). Follow-up was available in 45 patients and ranged from 1-134 months (mean, 34 months). Only 10 patients received therapy following resection, including Itraconazole (3), anti-tubercular therapy (3), immunosuppressants (2), Infliximab (1) and trimethoprim-sulfamethoxazole (1). There was no recurrence of nodules in 43 patients. Two patients developed an additional pulmonary nodule, but these remained stable on follow-up.
Conclusions: More than half of patients with necrotizing granulomas in surgical lung biopsies that are negative for microorganisms on special stains have unexplained disease. Infections account for the largest group of patients with specific diagnoses. M. avium-intracellulare, in particular, may be more common than previously recognized. In patients without specific etiologies the nodules do not recur and can likely be managed effectively without therapy.

1507 The Diagnostic Accuracy of Fine Needle Aspiration Cytology Versus Core Needle Biopsy for Peripheral Lung Lesions: A Comparative Study

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Background: Fine needle aspiration biopsy (FNAC) of the lung has long been recognized as a useful diagnostic procedure, providing a rapid, accurate and cost-effective evaluation of pulmonary masses. However, there appears to be a growing movement in favor of core needle biopsy (CNB) over FNAC in detecting carcinoma in some organs such as the breast. In this study, we compared the sensitivity and specificity of these two methods in patients with lung masses.
Design: A computer search identified 76 patients with peripheral lung lesions, subjected to CT-guided CNB including 25 cases having concomitant FNAC, in a tertiary academic medical center between January 2003 and August 2006, and compared to a consecutive 100 FNAC of lung masses. FNAC was performed with 20-gauge spinal needle and CNB with 18-gauge needle. CNB samples were initially submitted for touch preparation to determine adequacy. All patients had follow-up histologic confirmation.
Results: In CNB group, 69/76 patients had malignant diagnosis (47 primary lung, 14 metastatic carcinoma, 2 mesothelioma, 2 melanoma, 2 lymphoma, 1 solitary fibrous tumor and 1 synovial sarcoma), 6/76 cases benign (4 granulomas, 2 reactive) and 1/76 atypical. Immunohistochemistry (IHC) was performed in 43 cases that helped in determining the origin of the tumor in 34/76 (45%) cases. The main indication for core biopsy was to perform IHC to identify the origin of the tumor based on past history of another primary or as a result of unusual presentation of primary tumor as multiple lesions at the time of the procedure. Ten and eleven patients developed postprocedure pneumothorax in CNB and FNAC groups, respectively. For FNAC group, 74/100 cases were positive, 20/100 negative, 4/100 cases false negative and 2/100 cases false positive. FNAC sensitivity was 95%, 91% specificity, 74% accuracy, positive predictive value (PPV) 97% and negative predictive value (NPV) 83%, while in core needle breast biopsy sensitivity was 100%, 86% specificity, 92% accuracy, PPV 99% and NPV 100%. The diagnostic accuracy of CNB was higher than the FNAC, which was statistically significant ($p<0.05$).
Conclusions: In our experience, both FNAC and CNB of the lung have similar sensitivity and specificity, although FNAC has slightly less accuracy. CNB contributed to a more definitive diagnosis in 45% of cases with the application of ancillary IHC studies.

1508 A Simple Inflation Method for Frozen Diagnosis of Lung Tissue

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Background: Evaluation of lung tissue by frozen section has often posed difficulties for the pathologist as uninflated lung tissue showed severe artificial atelectasis and frozen artifact. Recently, the demand for intraoperative pathology consultation for minute lung lesions including GGO (ground-glass opacity) has been increasing. Tissue inflation using fixative has been very helpful in the diagnosis of non-neoplastic lung lesions and minute cancerous lesions; however, this method has not been widely employed for frozen section diagnosis of lung tissue. To obviate this problem, we have inflated lung tissue with the embedding medium (OCT compound) for frozen section diagnosis.
Design: To evaluate the effect of embedding medium injection, we prepared serial dilutions of embedding medium with saline and compared the quality of the frozen sections after injection. Normal lung tissue was divided into five groups - no inflation, inflation with saline, and inflation with diluted embedding medium (1:1, 2:1, 2:3) - and processed for frozen section.
Results: On the basis of morphological assessment, inflating lung tissue by embedding medium diluted at a ratio of 2:3 yielded excellent frozen section quality. Frozen section after inflating saline made lung tissue ragged and difficult to cut on cryostat.
Conclusions: Inflation of lung tissue by embedding medium is a very simple and excellent method for frozen section diagnosis. The minute cancerous and non-neoplastic lesions could be detected more easily by this technique than by the usual method of non-inflated frozen section of specimen.

1509 Pulmonary Veno-Occlusive Changes: An Under-Recognized Finding in Advanced Pulmonary Langerhans Cell Histiocytosis

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Background: Pulmonary Langerhans cell histiocytosis is characterized in its early stages by multiple bronchiolocentric nodules composed of Langerhans cell histiocytes and eosinophils. The majority of patients undergo spontaneous remission or remission following smoking cessation; however, some patients progress to a chronic disease that is characterized by airspace enlargement with cyst formation and alveolar septal fibrosis. These patients show severe pulmonary hypertension. While the cystic nature of the chronic disease is emphasized in the pathology literature, the source of the nearly ubiquitous hypertension has not been as well-characterized.
Design: A search was performed of the surgical pathology and consultation files for cases of advanced Langerhans cell histiocytosis. The cases were reviewed and examined for histologic features including arterial intimal fibrosis and medial thickening, venous intimal fibrosis and muscularization, mineral encrustation of elastic tissue with giant