I. **Discussion-original articles**

**Neoplastic Diseases**


**Non-neoplastic diseases**


II. **Review articles, perspectives, and editorials**


III. **Clinically oriented**


**IV. Case report**
Original articles for Discussion

Neoplastic


- Methods: Evaluation of immunohistochemical detection of X-linked inhibitor of apoptosis protein (XIAP) in 31 malignant mesotheliomas (29 pleural and 2 peritoneal), 2 well differentiated peritoneal mesotheliomas, 13 pleural mesothelial hyperplasias and 9 normal mesothelial tissue. Granular or nonhomogeneous cytoplasmic staining was considered positive. Intensity of staining was graded as weak (1+), moderate (2+) or strong (3+). Extent of staining was evaluated as <10% of tumor cells (1+), 10-50% (2+) and >50% (3+).

- Results:

<table>
<thead>
<tr>
<th>Histopathologic Diagnosis</th>
<th>N+/N (%)</th>
<th>Intensity/Extent of Expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal mesothelium</td>
<td>0/9 (0)</td>
<td>0/0</td>
</tr>
<tr>
<td>Mesothelial hyperplasia</td>
<td>1/13 (8)</td>
<td>1+/1+</td>
</tr>
<tr>
<td>Well-diff meso of peritoneum</td>
<td>1/2 (50)</td>
<td>1+/1+</td>
</tr>
<tr>
<td>Biphasic mesothelioma</td>
<td>10/12 (83)</td>
<td>1+/1+ (1 case, epithelial only), 1 to 3+/2 to 3+ (other cases, 9/9 epithelial and 7/9 spindle components)</td>
</tr>
<tr>
<td>Epithelioid mesothelioma</td>
<td>13/14 (93)</td>
<td>1+/1+ (1 case), 1 to 3+/3+ (12 cases)</td>
</tr>
<tr>
<td>Sarcomatoid mesothelioma</td>
<td>2/5 (40)</td>
<td>1 to 3+/2 to 3+</td>
</tr>
</tbody>
</table>

2 to 3+/2 to 3+ staining occurred in 74% of overall malignant mesotheliomas and 92% of the epithelioid samples, which were therefore distinguishable from hyperplasia (0 to 1+/0 to 1+).

- Conclusions: XIAP can be useful to distinguish malignant mesotheliomas from benign and hyperplastic mesothelial proliferations. XIAP might also be involved in the pathogenesis of mesothelioma and could be a potential therapeutic target.


- Methods: Histologic reports from malignant mesothelioma patients undergoing surgery (75 extrapleural pneumonectomy, 9 pleurectomy/decortication and 11 pleurectomy) were compared to initial thoracoscopic diagnosis. Cases were confirmed by a panel of pathologists in a standardized fashion.

- Results:

<table>
<thead>
<tr>
<th>Initial histology (N)</th>
<th>Final histology (N)</th>
<th>Total (N=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial</td>
<td>87</td>
<td>Epithelial 80</td>
</tr>
<tr>
<td>Biphasic</td>
<td>4</td>
<td>Biphasic 15</td>
</tr>
<tr>
<td>No subtype</td>
<td>4</td>
<td>Epithelial 4</td>
</tr>
</tbody>
</table>

For the epithelial subtype diagnosis by thorascopic pleural
biopsy, the sensitivity is 94%, specificity 20%, PPV 86% and NPV 37%. For the biphasic subtype, the sensitivity is 20%, the specificity 98%, PPV 75% and NPV 87%.

- **Conclusions:** Thorascopic pleural biopsy does not accurately subclassify the malignant mesotheliomas as epithelial or biphasic subtypes (80% of biphasics are misclassified as epithelial).


- **Methods:** 28 endocervical adenocarcinomas (9 well, 12 moderately and 7 poorly differentiated), 32 endometrioid adenocarcinomas (11 FIGO grade I, 8 grade II and 13 grade III) and 13 uterine serous carcinomas were evaluated for TTF-1 immunostaining (in 2 laboratories, different antibodies and techniques). TTF-1 nuclear staining was graded as: 0=negative, 1+=<5%, 2+=5-25%, 3+=26-50%, 4+=51-75% and 5+=>75%.
- **Results:** TTF-1 was positive in 6/32 (19%) of endometrioid adenocarcinomas: 1 FIGO grade I case (1+), 2 grade II cases (1+ and 4+) and 3 grade III cases (2 cases 1+, 1 case 4+). TTF-1 was positive (4+) in 1/28 (4%) of endocervical adenocarcinomas (2 cases had cytoplasmic staining considered negative). TTF-1 was positive in 3/13 (23%) of uterine serous carcinomas (2 cases 1+ and 1 case 5+).
- **Conclusions:** TTF-1 is relatively specific for lung and thyroid neoplasms, but occasional expression by endometrial and endocervical adenocarcinomas can occur. TTF-1 should be interpreted in the context of clinical setting, radiologic findings and the results of other markers.


_de Krijger RR, Claessen SMH, van der Ham F, et al. Gain of chromosome 8q is a frequent finding in pleuropulmonary blastoma. Mod Pathol 2007;20:1191-1199_

- **Methods:** 5 cases pleuropulmonary blastoma (PPB) were analyzed for genetic alterations by comparative genomic hybridization (CGH) and five genetic loci by FISH. Patients were treated by surgery and chemotherapy.
- **Results:** 5 patients were aged from 20 to 35 months, 4/5 were females, 1 case was a type 1 PPB, 2 were type 2 PPB and 2 were type 3 PPB.
  - **Histology:** Cysts were lined by flat to cuboidal epithelium with a subjacent cambium layer of atypical mesenchymal cells. Areas of epithelioid mesenchymal cells and chondroid differentiation were found in some cases.
  - **Immunostaining:** was strong and diffuse for myogenin, vimentin and desmin (except 1 case of type 3 PPB with only focal staining). There was focal staining for myoglobin, MyoD1 and actin. Pankeratin, CD34, SMA and S100 were negative.
  - **CGH:** Most frequent alterations were 8q11-22.2+ (4/5 cases), 20q+ (2/5), 9p21-24- (2/5) and 11p14- (3/5). 3 tumors showed amplification at 5p33-34, 11q22.2-ter, 15q25-ter and/or 19q11-13.2.
o FISH: confirmed 8q+ found by CGH and detected up to 5 copies of chromosome 8 centromeres per nucleus. 19q11-13.2 amplification was confirmed by AKT-specific probe.

o Prognosis: In the 2 surviving patients, 8q+ were the only genetic abnormality, suggesting this might be an early event in PPB carcinogenesis.

• Conclusions: This study confirms prior reports that 8q+ is a frequent finding in PPB (along with 9p- and 11p-). Additional studies with more cases are required.


• Methods: Retrospective review of 62 cases of primary salivary-type lung cancer (1972 to 2002). Slides were reviewed and tumors classified similar to primary salivary gland tumors of head and neck. The Brandwein grading system was used for mucoepidermoid carcinomas (MEC). Adenoid cystic carcinoma (ACC) were graded as 1 for tubular, 2 for cribriform and 3 if >30% of solid architectural pattern.

• Results:
  o Demographics: Median age was 40 y for MEC vs 54 for ACC (p=.02). A smoking history was found in 69.2% of ACC vs 42.1% of MEC.
  o Symptoms: at presentation were similar in ACC and MEC, and included cough (70%), dyspnea (51.7%), wheezing (38.3%), obstructive pneumonia (30%), hemoptysis (28.3%) and fever (16.7%).
  o Tumor characteristics:
    ▪ Type: ACC was found in 64.5% of cases, MEC in 32.3%, and 3.2% had a mixed (ACC-MEC) tumor or epithelial-myoepithelial carcinoma.
    ▪ Grade: Of ACC, 17.9% were tubular (grade 1), 74.4% cribriform (grade 2) and 7.7% solid (grade 3). Of MEC, 30% were low grade (1) and 65% were intermediate grade (2).
    ▪ Site: 82% of ACC vs 44.4% of MEC presented in the trachea, carina or main stem bronchus (p=.01).
    ▪ Median size: was 3 cm for ACC vs 1.9 cm for MEC (p<.01).
    ▪ Lymph node involvement: was found in 30.8% of ACC and 11.8% of MEC (p=.36, LN1).
    ▪ Positive margins were found in 21.7% of ACC vs none of MEC (p=.05).
  o Treatment: 71.7% had surgery (any), 44.2% had lobectomy, 25.6% tracheal resection, 18.6% pneumonectomy, 9.3% sleeve resection and 2.3% enbloc resection. More patients with MEC than ACC had surgery (95 vs 60%, p<.01) and lobectomy (63.2 vs 29.2%, p=.03). Radiation was given more in ACC than MEC (32.5 vs 5.3%, p=.02).
  o Metastasis: were more common in ACC than MEC (40.5 vs 10.5%, p=.03). Sites were diaphragm and cervical spine for MEC, and mostly lung for ACC.
  o Survival: Relative risk of death for ACC compared to MEC was 4.19 (p<.01) and nearly 3 after adjusting for age (p=.02).

<table>
<thead>
<tr>
<th>Survival</th>
<th>3 years</th>
<th>5 years</th>
<th>10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>80%</td>
<td>65%</td>
<td>53%</td>
</tr>
<tr>
<td>Complete resection</td>
<td>82%</td>
<td>70%</td>
<td>63%</td>
</tr>
</tbody>
</table>
MEC | 94% | 87% | 87%
Surgical ACC | 73% | 57% | 45%
Non surgical ACC | 74% | 53% | 31%

- Conclusions: ACC has poorer survival rates than MEC (but better than NSCLC). ACC also have a higher propensity to metastasis. Complete surgical resection is warranted to prevent recurrence.


- Methods: CISH and FISH were performed for detection of EGFR gene copy number in 58 NSCLC (43% ADK, 39% SCC, 9% large cell carcinomas and 9% others), including 31 paraffin and 27 frozen samples. 200 tumors cells were counted in at least 3 fields. Samples were considered positive when 4 or more dots per nucleus were seen in >40% of tumor cells, or when tight EGFR gene clusters were seen in >10% of cells.
- Results:
  - Success rate: CISH could analyze all frozen and paraffin cases. FISH could not analyze 45% of the paraffin cases (because of autofluorescence, low signal, unrecognizable morphology or detachment of tissue). FISH was easier to interpret in frozen samples.
  - Interobserver concordance: was 93% for CISH (k=.74, 3/4 borderline cases, other case attributed to tumor heterogeneity) and 100% for FISH (k=1).
  - CISH-FISH concordance: was 93% (k=.64) and 95% (k=.76) for observers 1 and 2. Discordances were attributed to borderline positive cases.
- Conclusions: CISH may be a good alternative to FISH in determining EGFR gene copy number in NSCLC, especially in paraffin samples.


- Methods: 322 surgically treated NSCLC (including 205ADK) frozen samples were analyzed for EGFR mutations of kinase domains by direct sequencing (PCR assays).
- Results:
  - EGFR exon 20 insertion mutations: were found in 7/322 (2.17%) of NSCLC which showed a trend for higher rates in never smokers (4.4 vs 1.3% in smokers, p=.0996) and in females (4.5 vs 1.3% in males, p=.0917). Age, histologic type, grade, node metastasis and stage showed no association with mutational status. Overall survival was similar for patients with or without mutations (2/7 vs 102/315 dead, p=7186). 2 cases were treated with gefitinib and failed to respond.
  - Exons 18, 19 and 21: Deletion type mutation in exon 19 was found in 18 patients. Missense point mutations in exon 18 or 21 were found in 29 patients
(25 L858R, 2 G719S, 1 G719C and 1 L861Q). Mutational status correlated with female gender, non-smoking status and adenocarcinoma subtype (p<.0001).

- Conclusions: EGFR exon 20 insertion mutations are found in 2.17% of Japanese NSCLC and do not seem to respond to gefitinib.

**Non-neoplastic**


- Methods: Collagen/elastic fiber density (evaluated with Sirius red/Picrosirius-polarization and Weigert’s Resorcin-Fuchsin methods), myofibroblast proliferation (evaluated with a-SMA antibody), microvascular density (evaluated with CD34 antibody) and endothelial activity (evaluated with VCAM-1 and E-selectin antibodies) were compared in 12 cases of idiopathic organizing pneumonia (OP) vs 11 cases of secondary OP (1 SLE, 3 HIV, 4 hematological disorders and 1 hyperthyroidism) at open lung biopsy. Intraluminal plug area was determined by optical density using an image analysis system in 10 randomly selected plugs at 200x. Immunostaining was evaluated by the point-counting technique at 400x with a grid.

- Results: Intraluminal plugs of idiopathic OP showed more collagen density than secondary OP (0.20 vs 0.07, p<.001). Neither group had elastic fibers in the plugs. Idiopathic OP plugs, compared to secondary OP plugs, showed fewer a-SMA+ myofibroblastic cells (16.38 vs 24.41, p=.01), fewer CD34+ endothelial cells indicative of a lower microvascular density (1.69 vs 2.57, p=.008), lower endothelial cell activity as measured by VCAM+ (0.55 vs 1.30, p<.001) and E-selectin (0.95 vs 1.45, p=.004).

- Conclusions: Increased collagen synthesis, but lower myofibroblast proliferation, microvascular density and endothelial activity, were found in idiopathic OP compared with secondary OP. This may reflect a remodeling process more than repair.


- Methods: Review of current literature pertaining to acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF).

- Results:
  - Definition of AE-IPF requires 6 criteria: (1) previous or concurrent diagnosis of UIP, (2) unexplained worsening or development of dyspnea < 30 days, (3) HRCT with new bilateral ground glass opacities and/or consolidation superimposed on a background c/w UIP, (4) worsening hypoxemia on arterial blood gas, (5) no evidence of infection by endotracheal aspiration or BAL and (6) exclusion of left heart failure, pulmonary embolism and other identifiable causes of acute lung injury.
Overall incidence of AE-IPF is unknown but appears to be in the range of 5 to 19% per year. Difficulties in evaluation of incidence may be because of reporting biases (including only biopsy or autopsy patients or excluding patients with advanced disease) and difficulty excluding infection.

Clinicopathological findings are heterogeneous. Patients with multifocal or diffuse pattern on CT have a worse prognosis. Histology usually shows DAD, and occasionally organizing pneumonia. Extent of DAD does not correlate with outcome. Mortality rate is around 81.8%, with the majority of deaths occurring in the first month.

Etiology is unknown, but an unrecognized infectious etiology or associations with bronchoscopic/surgical lung biopsy or lung resection have been speculated.

Markers of AE-IPF include an abrupt decline in FVC and DCO with new alveolar infiltrates and need for hospitalization. Elevation of serum ST2 protein, expressed during T-helper type 2 inflammatory responses, has been noted in AE-IPF.

Treatment with antiinflammatory therapies (corticosteroids, cyclosporine and pirfenidone) and anticoagulation have not been fully studied.

Conclusions: AE-IPF is increasingly recognized to play a major role in IPF and demands additional study to determine incidence, improve definition and identify risk or prognostic factors.

**Review, perspectives and editorial**


Excellent review with update on sarcoidosis based on the literature published over the last 10 years. Covered epidemiology, search for environmental and genetic causes, immunopathogenesis, clinical features, diagnostic approach and treatment options. But not a lot of pathology, though


Guidelines by Association of Directors of Anatomic and Surgical Pathology (ADASP) primarily intended for extrapleural pneumonectomy specimens


Review focused on the cytologic characteristics of a variety of occupational lung diseases. It grouped them into 2 broad diagnostic categories: reactive cellular changes and noncellular elements such as curschmann spirals, charcot-layden crystals, asbestos bodies and intra-alveolar granular materials in PAP associated with silica
Yesner R. Small cell lung cancer. Sex and survival

An editorial on the gender-related discrepancies in the susceptibility and survival of lung cancer patients. Female patients with SCLC or NSCLC live longer than male patients. The female sex was an independent prognostic factor in SLCL. However, the reason for longer survival is not clear. He cited Darwin’s treatise on evolution: women are biologically more fit to survive, despite their increased susceptibility.

Clinically oriented papers


Review of the current application of PET in patients with NSCLC discussing diagnosis, staging, and assessment of treatment response and prognosis with an emphasis on the appropriate clinical use of PET in management. 96.8% sensitivity and 78% specificity in a meta-analysis of 40 studies. False positive is commonly due to infection and inflammation; false negative tends to occur with carcinoid tumors and BAC.

Maldonado et al. Focal organizing pneumonia on surgical lung biopsy. Causes, clinicoradiologic features and outcomes.

A Mayo study on the cases OP that were resected under the impression of a mass lesion or lung cancer. 3 of 26 cases were related infections but the remaining cases were cryptogenic. F/U over a median interval of 11 months yielded no recurrence of OP.


A retrospective study on children with CF who were on the waiting list for lung transplantation during the period from 1992 to 2002. Proportional-hazards survival modeling analysis, using multiple clinically relevant covariates that were available before the children were on the waiting list and the interactions of these covariates with lung transplantation as a time-dependent covariate. Most of the children (509 of the 514 studied and 247 of the 248 patients who underwent TPX) did not derive a significant estimated survival benefit. Five patients had a significant estimated benefit, 315 had a significant risk of harm, 76 had an insignificant benefit and 118 had an insignificant risk of harm associated with lung TPX. This study concluded that prolongation of life by means of lung TPX should not be expected in children with cystic fibrosis.


A prospective cohort study on TRALI (ALI developing within 6 hours of transfusion) demonstrated that patients developing ALI were more likely to have sepsis, history of chronic alcohol abuse, as compared to those who did not. Plasma from alloimmunized donors (ex.
multiparous women) and the presence of donor-derived anti-leukocyte antibodies predicted ALI development.


A Norwegian study showed that immigration did not result in increased transmission of TB. The TB situation among resident non-immigrants and immigrants was not significantly affected by new arrivals.


A study on the prevalence of PHT in LAM patients. Exercise-induced hypoxemia is common in LAM patients and could be associated with PAH. Resting PHT is uncommon and occurring less than 10% of 95 LAM patients studied. But more than half of these patients had elevations in systolic PAP during exercise. This rise may be due to in part with the development of hypoxemia, suggesting that hypoxemia-mediated pulmonary vasoconstriction. Oxygen therapy was suggested to prevent hypoxemia and exercise-induced PHT.


An open-label study exploring the transition from parenteral prostanoid (subcutaneous tresprostinil) to oral sildenafil I patients with PAH of varied etiology and found the majority of patients remained stable symptomatically as well as in other parameters. Good for patients!!

**Case report**


Unusual location and presentation of a large multilocular thymic cyst…