PULMONARY PATHOLOGY JOURNAL CLUB
September 2007 articles

Neoplasia

**Airway Disease**


**Interstitial Lung Disease**


**Miscellaneous**


This supplement to the September issue of Chest presents approximately 25 sets of recommendations from an evidence-based review of the literature since 2002. The guidelines are evaluated by a rating system. The grade of recommendation scale is as follows:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>1A</td>
<td>Strong</td>
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<tr>
<td>1B</td>
<td>Strong</td>
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<td>1C</td>
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<td>2B</td>
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<td>2C</td>
<td>Weak</td>
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I have included the executive summary and its recommendations as one of the PDF files.

I have included two additional guidelines with the summary recommendations in their entirety below as they have a direct bearing on what we do as pathologists and highlight areas of discussion that we have had in the past at this journal club.

Summary of recommendations:
1. When pathologically diagnosing patients with lung cancer, the reporting of histologic type, tumor size and location, tumor grade (if appropriate), lymphovascular invasion, involvement of pleura, surgical margin, and status and location of lymph nodes by station is recommended. Grade of recommendation, 1B.
2. In individuals who are at risk for lung cancer but do not have symptoms or history of cancer, use of single or serial sputum cytologic examinations to screen for the presence of lung cancer is of insufficient clinical benefit and is not recommended. Grade of recommendation, 1A.
3. In individuals with pleural-based tumors, when distinguishing between pleural adenocarcinoma and malignant mesothelioma, a structured approach using a limited panel of histochemical and immunohistochemical assays is recommended to increase the diagnostic accuracy. More challenging cases may need additional studies, including ultrastructural analysis. Grade of recommendation, 1B.
4. In individuals with parenchymal-based tumors, distinguishing between small cell carcinoma and non-small cell carcinoma of the lung is recommended. For challenging cases, a diagnostic panel of immunohistochemical assays is recommended to increase the diagnostic accuracy. More challenging cases may need additional studies, including ultrastructural analysis. Grade of recommendation, 1B.
5. For individuals with glandular-producing tumors, distinguishing pure BAC from adenocarcinoma with or without BAC component is recommended. Grade of recommendation, 1C.
6. For individuals who have lung tumors and whose differential includes primary lung carcinoma vs metastatic carcinoma, a directed panel of immunohistochemical assays is recommended to increase the diagnostic accuracy. Grade of recommendation, 1C.
7. For individuals who have lung tumors and have had an assessment of pathologic features and staging parameters, the evaluation of pathobiological and molecular markers is appropriate for protocol investigation and is not routinely recommended for clinical management. Grade of recommendation, 1C.
8. For individuals who have lung tumors and have had an assessment of pathologic features and staging parameters, the determination of occult or micrometastatic disease, using enhanced pathologic or molecular techniques, is not of sufficient clinical utility and is not recommended. Grade of recommendation, 1C.

Summary of recommendations:
1. We recommend that the use of the term bronchioloalveolar carcinoma be reserved for lung cancers that meet the criteria established in the revised WHO classification system for lung tumors. Grade of recommendation, 1B.
2. For patients with suspected BAC, we recommend that a surgical biopsy be used to establish a histopathologic diagnosis. Grade of recommendation, 1C.
3. For patients who are unable to undergo surgical biopsy, the diagnosis of BAC should be made only with compatible histopathologic pattern on transbronchial or core needle biopsy and a CT demonstrating a pure ground-glass or pneumonic appearance. Grade of recommendation, 1C.
4. For patients whose CT scans show ground-glass attenuation or pneumonic consolidation (suggesting BAC), PET scans often have false-negative results, and therefore we recommend that a PET scan with negative results be followed by additional diagnostic testing to exclude the presence of cancer. Grade of recommendation, 1C.
5. In patients who have suspected BAC and are good surgical candidates, a sublobar resection may be appropriate, provided that the CT scan shows a pure ground-glass appearance, intraoperative pathologic consultation confirms pure BAC without evidence of invasion, and surgical margins are free of disease. Grade of recommendation, 1B.
6. For patients with good PS and unresectable BAC, we recommend the use of standard chemotherapy. The use of first-line EGFR-targeted agents should be reserved for patients with poor PS or those who are enrolled in clinical trials. Grade of recommendation, 2C.

The purpose of this study was to evaluate if ancillary studies for EGFR can be useful in cytologic diagnosis on NSCLC. 50 patients with cytology specimens (bronchial washings/brushings or FNAB) and corresponding lung biopsies were studied for EGFR expression by FISH and IHC.

**Results:**

<table>
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<tr>
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<th>Tumor</th>
<th>Non-tumor</th>
<th>Total</th>
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<tbody>
<tr>
<td>Positive</td>
<td>12</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Negative</td>
<td>13</td>
<td>24</td>
<td>37</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>25</td>
<td>50</td>
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Sensitivity = 12/25 = 48%; specificity = 24/25 = 96%; PPV = 12/13 = 92%.

**FISH** showed only balanced aneuploidy of EGFR, no gene amplification was detected. EGFR chromosomal abnormalities in NSCLC were almost always accompanied by other chromosomal abnormalities in c-myc, 5p15.2 or chromosome 6, suggesting genetic instability. 48% of malignant cases showed balanced aneuploidy by FISH, but gene copy number did not correlate with protein expression by IHC in many cases. Atypical or suspicious cytology samples, if + for EGFR by FISH, have a high probability of being malignant (92% PPV). Specificity was very high (96%), and only 1/25 benign cases on biopsy (which was atypical by cytology) showed low trisomy aneuploidy.

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<th>Tumor</th>
<th>Non-tumor</th>
<th>Total</th>
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<tbody>
<tr>
<td>Positive</td>
<td>22</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>Negative</td>
<td>3</td>
<td>22</td>
<td>25</td>
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<tr>
<td>Total</td>
<td>25</td>
<td>25</td>
<td>50</td>
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Sensitivity = 22/25 = 88%; specificity = 22/25 = 88%; PPV = 22/25 = 88%.

**IHC:** SqCC stained more than ADK. Staining was heterogeneous within single tumors, peripheral cells stained more intensely (possible edge effect) and there was non-specific staining of benign basal cells and normal squamous epithelial cells.

**Discussion:** There is conflicting data regarding EGFR amplification in NSCLC, with reported frequencies ranging from 0 to 23% (0% in this study). Patients with high-polysomy EGFR (4 copies or more in more than 40% of cells) and gene amplification are regarded as FISH +, and are more likely to respond to EGFR tyrosine kinase inhibitors, and have longer overall and disease-free survival.

**Conclusion:** EGFR expression by FISH and IHC may be useful to classify difficult cytology cases. If atypical or cytology cases are positive for EGFR, the positive predictive value for malignancy is 96% for FISH and 88% for IHC.

EGFR gene mutations have been reported in ADK, especially nonmucinous BAC component. Theses cancers respond well to EGFR tyrosine kinase inhibitors. Mucinous BAC have been associated with K-ras mutations. The purpose of this study is to evaluate the frequency of mutations in exons 19 and 21 of EGFR gene and in codon 12 of K-ras gene in 54 cases of atypical adenomatous hyperplasia using loop-hybrid mobility shift assay (LH-MSA) PCR and compare AAH results with those of BAC and ADK.

Results: EGFR mutations were detected in 17/54 cases (32%) of AAH. 10 tumors had a deletion mutation at exon 19 and 7 had a point mutation at exon 21 (L858R). There was no histological difference between AAH with and without EGFR mutations. No association was found between EGFR mutation and age, sex, smoking history, tumor size and tumor Ki-67 index. K-ras mutation (G12S) was detected in only 1/49 cases (2%).

Discussion: Frequency of EGFR mutation in this study (32%) is higher than that reported for AAH in 3 previous studies (0%, 3% and 28%), which authors explain by the higher sensitivity of LH-MSA to detect mutations than direct sequencing used in prior studies. 32% frequency of EGFR mutation for AAH is significantly lower than that found by this study’s authors in a prior study for both nonmucinous BAC (88%) and invasive adenocarcinoma with nonmucinous BAC features (75%). This study found a significantly lower frequency of K-ras mutation in AAH (2%) than prior studies analyzing AAH (15-39%) and mucinous BAC (67%). Authors surmise that AAH progresses sequentially to nonmucinous BAC, but not to mucinous BAC.

Conclusion: EGFR mutated AAH are more likely to progress to nonmucinous BAC and then invasive ADK with nonmucinous BAC features than wild-type EGFR AAH.

The purpose of this retrospective study was to evaluate prognostic factors in 445 patients with stage I NSCLC of 3 cm or less resected at a veterans hospital in Taiwan between 1980 and 2000.

Results: Median follow-up was 70.4 months. For 5 and 10 years, overall survivals were 61.4% and 40%, and disease-free survivals were 74.5% and 73.4%, respectively. Tumor size, smoking, and number of mediastinal lymph nodes dissected were independent prognostic factors for both disease-free survival and overall survival in multivariate analyses. Age also correlated with overall survival. No association was found between visceral pleural invasion and disease-free or overall survival.

Discussion: There is controversy regarding the cutoff value for tumor size in lung cancer staging system (2 vs 3 cm). Visceral pleural invasion is associated with a higher frequency of lymph node involvement.

Conclusion: Stage IB (T2N0M0) NSCLC of 3 cm or less with visceral pleural invasion should be treated as T1 disease and not as T2.

| TABLE 3. Multivariate analyses for overall survival and disease-free survival in patients with resected stage I non–small cell lung cancer with a diameter of 3 cm or less |
| Variables | Hazard ratio (95% CI) | P value |
| Overall survival | | |
| Age, y | 1.024 (1.007–1.041) | .005 |
| Smoking index, pack-yr* | 1.010 (1.005–1.015) | <.001 |
| Tumor size | 1.348 (1.098–1.655) | .004 |
| No. of LNs dissected (< > 15) | 0.622 (0.470–0.822) | .001 |
| Disease-free survival | | |
| Smoking index, pack-yr* | 1.011 (1.004–1.018) | .002 |
| Tumor size | 1.549 (1.116–2.151) | .009 |
| Number of LNs dissected (> > 15) | 0.544 (0.352–0.840) | .006 |

The purpose of this retrospective study was to compare clinical features, therapy, and natural course of 11 cases of extrapulmonary small cell carcinoma (EPSCC) with 54 cases of SCLC, documented in medical records between January 1999 and May 2006.

Results: Overall survival was significantly better in patients with EPSCC than SCLC. Smoking history was less in EPSCC than SCLC. There was a trend for more brain metastasis in SCLC than EPSCC.

Discussion: There is no standard treatment for limited stage EPSCC (combination of surgery, chemotherapy, radiotherapy?). Extensive EPSCC is treated by chemotherapy. Brain metastases are rarer in EPSCC and there is no evidence to support prophylactic cranial irradiation. There is no standard stage system for EPSCC (TNM system may be more valuable). Bias in this study: low number of patients, heterogeneous groups and retrospective data collection.

Conclusion: EPSCC and SCLC are usually treated in a similar fashion, but this study suggests that these entities might differ in etiology, clinical course, and survival, which may influence the therapeutic approach.

Small cell carcinoma (SCC) of lung (SCCLu) and of cervix (SCCCx) can present as ovarian masses and mimic an ovarian primary SCC. The purpose of this study was to distinguish SCC of the ovary, SCCCx and SCCLu, and potentially determine the histogenesis of small cell carcinoma of the ovary, hypercalcemic type (SCCOH).

**Results:** Tumors showed overlapping morphological features, but SCCOH had some distinctive features such as follicular-like spaces (5/7 cases) and large cell morphology (1/7 cases). HPV was detected only in SCCCx (5/6+ cases, including 4 cases+ by ISH and 1 case+ by PCR).

<table>
<thead>
<tr>
<th></th>
<th>SCCOH</th>
<th>SCCOP</th>
<th>SCCCx</th>
<th>SCCLu</th>
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<tbody>
<tr>
<td>WT-1</td>
<td>6/7 (86%)</td>
<td>0/2 (0%)</td>
<td>1/8 (13%)</td>
<td>1/22 (5%)</td>
</tr>
<tr>
<td>TTF-1</td>
<td>0/7 (0%)</td>
<td>1/2 (50%)</td>
<td>3/8 (38%)</td>
<td>20/22 (91%)</td>
</tr>
<tr>
<td>p16</td>
<td>6/7 (86%)</td>
<td>2/2 (100%)</td>
<td>7/8 (88%)</td>
<td>21/22 (95%)</td>
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<tr>
<td>cKIT</td>
<td>0/7 (0%)</td>
<td>0/2 (0%)</td>
<td>2/8 (25%)</td>
<td>16/22 (73%)</td>
</tr>
<tr>
<td>OCT3/4</td>
<td>0/7 (0%)</td>
<td>0/2 (0%)</td>
<td>0/8 (0%)</td>
<td>0/21 (0%)</td>
</tr>
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</table>

**Discussion:** cKIT staining found in 73% of SCCLu is not reported to be associated with Bcr/Abl fusion protein or Kit mutations (therefore not subject to respond to Gleevec therapy).

**Conclusion:** WT-1 and TTF-1 were useful to establish origin of SCC of female genital tract, as WT-1+/TTF-1− profile was 86% sensitive and 97% specific for SCCOH, but cKIT, OCT3/4 and p16 were not useful. Absence of OCT3/4 and cKIT staining argues against a germ cell origin for SCCOH, but staining for WT-1 supports a Mullerian origin.

This letter to the editor seemed like a nice follow-up to the previous articles. It reports three cervical large cell neuroendocrine carcinomas which exhibited diffuse nuclear TTF1 reactivity. **Conclusion:** No stain is ever perfect!

**Background:** Several studies have investigated the histologic features of carcinomas with pleomorphic sarcomatoid or sarcomatous elements. This study evaluates 39 patients with this diagnosis.

**Methods:** 39 patients identified by like microscopic means were identified at a French teaching hospital. Pre-op and post-op data were collected and survival calculated using K/M methods.

**Results:** 19 patients were diagnosed pre-op but interestingly only one had a sarcomatoid component identified at this time.

**Histopathology:** 34 pleomorphic (NSLC with at least 10% spindle cells, giant cells or both), three spindle cell and two giant cell carcinomas. Five year survival rate (33%; median, 11 months) was negatively influenced by large tumors (7.5% survival for greater than or equal to 7 cm versus 56% for less than 7 cm, \(P=.0026\)). Disease free interval was significant for patients who relapsed. Relapses tended to be hematogenous rather than local.

**Conclusions:** These tumors are highly heterogeneous. Five year survival rates were lower than for other non-small cell carcinomas (no direct comparison in this study).

**Comments:** Not much new here despite the author’s initial contention that this represented a “large series”. The paper discussed last month by Yuki, et al actually had 45 patients but the survival results were very similar.

Article of note – primarily a surgical paper although first author is a pathologist.

Purpose: To determine the current epidemiology, pathology and patterns of care for patients with non-small cell lung cancer (NSCLC) in the U.S.

Methods: Under the auspices of the American College of Surgeons data in the National Cancer Database in 2001 was surveyed to determine patient demographics, history, diagnostic and staging methods, pathology, and initial treatment for patients with NSCLC.

Results:
- 40,909 patients, 93% of whom were smokers. Approximately half were over 70 years of age and 58% were male.
- Adenocarcinoma = 35.3%; squamous carcinoma = 26.6%;
- Males tended to have squamous carcinoma and females adenocarcinoma including BAC. Among patients with BAC twice as many were women (4.8 vs 2.6%).
- White patients were more likely than black, Hispanic or Asian to be stage I ($P < 0.01$).
- Blacks, Hispanic and Asian patients were more likely than whites to have stage IV disease ($P < .01$).

Discussion and Conclusion: Not much new in this study.

**Background:** There have been three previous case reports of bronchioloalveolar carcinoma with rhabdoid cells reported, all of non-mucinous type. This is the first case of mucinous BAC with rhabdoid component.

**Case:** A 59-year-old man with ill-defined ground-glass opacities and patchy consolidation with air bronchograms. At the time of right lower lobectomy a tumor was identified with three components: mucinous BAC (50%), well differentiated adenocarcinoma with stromal invasion (20%), and rhabdoid cells (30%). Rhabdoid cells were CK7, AE1-3 and vimentin positive. They were negative for TTF1 (which was positive in other components). EM showed intermediate filaments in the rhabdoid cells at a paranuclear location.

**Discussion:** There have been 33 lung tumors with a rhabdoid component reported previously.
- 12 adenocarcinoma
- 8 LCC
- 4 poorly diff CA NOS
- 4 sarcomatoid
- 3 LCNEC
- 1 sarcoma
- Assoc type not specified

The literature indicates this is an aggressive tumor and patients with greater than 10% rhabdoid cells may show more aggressive clinical behavior than those with less than 10% rhabdoid cells (Shimazaki et al. Histopathology 2001).

**Comment:** Although the title makes it sound as though this is a case of mucinous BAC with a rhabdoid component alone, it is clear that this really just represents a case of adenocarcinoma with a rhabdoid component.

Case Report: A 66-year-old woman with no prior asbestos exposure who developed pleural mesothelioma 17 years after pneumonectomy and adjuvant radiation therapy for NSCLC. Tumor histology was that of an epithelioid MM with appropriate immunohistochemical profile. This represents yet another case of MM following radiation therapy.

Comment: The article lists all of the previous case reports and discusses the positive and negative epidemiologic retrospective cohort studies. For this reason this makes a good reference for this problem.

**Background:** A small number of IMTs have harbored HHV-8 implicating the virus and its pathogenesis.

**Methods:** 20 IMT were analyzed for HHV-8 with immunohistochemical (antibodies against HHV-8 latent nuclear antigen, and ALK) and molecular methods (real time PCR(4 separate open reading frames (ORF)).

**Results:** Four cases (20/M, 26/M, 26/M and 37/F) were ALK1 positive. IHC and RTPCR results for HHV8 negative in all cases.

**Conclusion:** This study suggests no role for HHV-8 in the development of pulmonary IMT. The authors go out of their way to address issues surrounding the occurrence of false positive and false negative results described in the literature (which has previously shown HHV-8 to be present in some ALK1 negative pulmonary IMTs).

**Comment:** The methods and justification are a bit beyond me but the ultimate message I understand!

This is under the brief communication section and reports on 15 patients. All tumors were subjected to immunohistochemical and FISH and the diagnosis of synovial sarcoma confirmed.

Factors that adversely affected survival included tumor dimension greater than 10 cm, incomplete resection, and no adjuvant therapy.

This study appears to have been done in order to determine which metastases from renal cell carcinoma might be more amenable to antiangiogenic chemotherapeutic agents. But no treatment data reported.

Nicely done review with a summary of recent cytogenetic analyses.

This represents a nice case report of “cysts” due to nodular amyloidosis and GI and pulmonary MALT. Similar to some previous cases (cystic amyloid and Sjögren’s) and nodular amyloid with bulla, the “cysts” in this case appeared to be formed by dilated bronchioles.
Airway Disease


Objective: To determine the association between small airway pathology and long-term survival after lung volume reduction surgery (LVRS) in COPD and the effect of corticosteroids on this pathology.

Methods: 101 patients with severe (GOLD-3) and very severe (GOLD-4) emphysema were studied after LVRS. Kaplan-Meier survival analysis and Cox proportional hazards models were used to determine the relationship between survival and small airway pathology. The effect of corticosteroids on this pathology was assessed by comparing treated and untreated groups. The size of small conducting airways was estimated by measuring the length of the BM and determining luminal area in both the partially collapsed state and in a simulated fully expanded state. The severity of luminal occlusion was expressed by determining the fraction of these luminal areas occluded by inflammatory exudate containing mucus. The thickness of the entire wall (epithelial, lamina propria, muscle and adventitial compartments) was determined by dividing their measured areas by the length of the basement membrane.

Results: The quartile of subjects with the greatest luminal occlusion died earlier than subjects who had the least occlusion (see Fig. 1)

- There was a trend towards a reduction in the number of airways containing lymphoid follicles and those receiving steroids but corticosteroid treatment had no effect on airway wall thickening or luminal occlusion.

Discussion: The authors hypothesize that the level of airway occlusion and early death in COPD might be related to the increased risk for lower respiratory tract infections.

Conclusion: Occlusion of small airways by inflammatory exudates containing mucus is associated with early death in patients with severe emphysema treated by LVRS. Comment: Another carefully done study emphasizing the importance of the small airways in COPD.

Not a pathology paper but a study which confirms the previous known association between diacetyl and OB. It also represents the first study of this association identified outside the United States.

Interstitial Lung Disease


Conclusion: HRCT determined extent of pulmonary fibrosis and/or main pulmonary artery diameter cannot be used to screen for pulmonary hypertension in patients with advanced IPF.

This is published in the “Recent Advances in Chest Medicine” section and is a review. There is a small section on pathology.
Miscellaneous


All you wanted to know about the current state of lung transplantation. Of note, the figures are available in slide form and can be downloaded for use in talks at http://www.ishlt.org
Go to transplant registry PowerPoint slides under “quick links”

“A 25-year-old female presented to a pulmonary clinic carrying a plastic sandwich bag containing 50 mL of bloody sputum!”

What’s the diagnosis?
   A. Haemoptysis due to her herbal supplements including oregano oil and extracts from grape seeds, black walnut, wormwood, and cloves.
   B. Thromboembolic disease
   C. Catamenial haemoptysis

The discussion includes a nice table summarizing recent case reports of catamenial haemoptysis due to parenchymal and/or endobronchial endometriosis.