Discussion Articles


Page 5 Nicholson AG et al. Refining the diagnosis and *EGFR* status of non-small cell lung carcinoma in biopsy and cytologic material, using a panel of mucin staining, TTF-1, cytokeratin 5/6, and p63, and *EGFR* mutation analysis. *J Thorac Oncol* 2010;5:436-441 (editorial by Bill Travis et al also)


Articles for Notation

I. Original research articles from the pared-down journal list

*Non-neoplastic diseases*


*Neoplastic diseases*

Ou SI et al. Primary signet-ring carcinoma (SRC) of the lung. A population-based epidemiologic study of 262 cases with comparison to adenocarcinoma of the lung. *J Thorac Oncol* 2010;5:420-427


Monego G et al. Parathyroid hormone-related peptide and parathyroid hormone-related peptide receptor type 1 expression in human lung adenocarcinoma. *Chest* 2010;137:898-908
Maeshima AM et al. Clinicopathologic analysis of multiple (five or more) atypical adenomatous hyperplasias (AAHs) of the lung. Evidence for the AAH-adenocarcinoma sequence. J Thorac Oncol2010;5:466-471

Page 11 Krajnik M et al. Enkephalin, its precursor, processing enzymes, and receptor as part of a local opioid network throughout the respiratory system of lung cancer patients. Hum Pathol 2010;41:632-642
Findeis-Hosey JJ et al. IMP3 expression is correlated with histologic grade of lung adenocarcinoma. Hum Pathol2010;41:477-484

II. Original research articles from the previously used extended list

Wislez M et al. Non-mucinous and mucinous subtypes of adenocarcinoma with bronchiole alveolar carcinoma features differ by biomarker expression and in the response to gefitinib. Lung Cancer 2010;68:185-191

III. Case reports, letter to the editor, editorial, etc. from both lists


Discussion Articles

Fell CD et al. Clinical predictors of a diagnosis of idiopathic pulmonary fibrosis. 
Am J Respir Crit Care Med 2010;181:832-837

-Purpose: To determine if clinical variables could predict a histopathologic dx of IPF in pts without honeycomb change on HRCT

-Methods: A retrospective study of 135 pts (97 bx-proven IPF/UIP, 38 other lIPs including 19N5IP, 9 HP, 9 RBILD/DIP, 1 COP)

- Patient selection: 664 pts in data base 1995-2006: 206 excluded (1 cancer, 2 inf, 4 sarcoid, 23 CTD-ILD, 87 clinical dx ofIPF w/o bx, 89 unable to reach consensus dx); 458 pts with lIP and a lung bx: 215 excluded (HRCT, PFT, or 6MWT >6m from lung bx, 108 excluded (HRCT interstitial score 2:2)

- HRCT scoring separately on alveolar and interstitial changes for each lobe by 2 expert thoracic radiologists blinded for dx (kappa=0.727): 0-no alveolar or interstitial ds; 1 GGO <5% of lobe, septal thickening w/o honeycomb; 2-5 GGO and honeycomb change <25%. 25-49, 50-75, >75%

- Demographic data, PFT, 6 MWT and HRCT scores are compared with IPF and non-IPF lIP using Student t-test or chi-square test; univariate and multivariate analyses done for positive predictive values, specificities, sensitivities, and negative predictive values

-Results

- On univariate model, older age, lower HRCT alveolar score, and higher interstitial scores were significant predictors of IPF dx (100% in 75 yrs or older)

- On multivariate model, increasing age and increasing HRCT interstitial score best predicted a dx of IPF

- They gave PPV, specificity, sensitivity and NPV by age alone and by composite age and HRCT interstitial score in 2 separate tables

- "IPF score"=[(0.084 x Age + 2.346 x HRCT interstitial score - 3.31)/5.856]; they provided a "user-friendly" table that can be applied in individual patient and a histogram illustrating the frequency of the probability of IPF scores for pts with a bx proven dx of IPF (n=97, solid) and non-IPF (n=38, striped)

-Conclusion: a higher HRCT interstitial score and older age, but not FVC, DLCO, and 6MWT, are predictive of IPF. Got algebra?; surgical bx might be spared!

-Purpose: To evaluate the ability of IRC markers and mucin staining to predict the NSCLC subtype in small bx in retrospective set (NSCLC-NOS on bronchial bx with definite dx on subsequent resection) and to test on prospective cases of small biopsies

-Methods:
- **AB/PAS** and IRC stains with Ab's against s100A7, p63, CK5/6, 34PE12-HMWCK, TIFI (AB/IP AS) on 44 bronchial bx diagnosed as NSCLC-NOS
- Any intracytoplasmic mucin droplet stain considered + for ABIP AS
- IRC scored for intensity (0, 1, 2 and 3 for absent, light, intermediate and strong) and proportion (0, 1, 2, and 3 for none, 1-10%, 10-60%; >50%) by 2 pathologists
- Neural nets used to optimize MC scores into + or -; analysis of net outputs for each of the observed staining patterns for each marker into nonpredictive (-), predictive (+), and inconclusive are (no data).
- Positive and negative predictive values, sensitivity, specificity calculated, then a set of predictive tests established: ABIPAS plus TTFI, p63, CK5/6
- Applied prospectively in 82 small bx samples including 65 bronchial bx, 12 transthoracic needle bx, 3 liver bx, 2 LN bx

-Results:
1. Final diagnosis of 44 resected cases and IRC-predicted subtypes on bronchial bx

<table>
<thead>
<tr>
<th>Resection histology</th>
<th>N</th>
<th>Squamous</th>
<th>Adeno-c Null (non predictive)</th>
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<tbody>
<tr>
<td>Squamous ca</td>
<td>23</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Adeno-c</td>
<td>11</td>
<td>8</td>
<td>3</td>
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<tr>
<td>Large cell ca</td>
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<td>4</td>
<td>1</td>
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<tr>
<td>Adeno-squamous ca</td>
<td>2</td>
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2. Test on prospective cases (only 8 subsequent resection)

-Conclusion: a higher HRCT interstitial score and older age, but not FVC, DLCO, and 6MWT, are predictive ofIPF. Got algebra?; surgical bx might be spared!

-Purpose: To determine the utility of a panel of ab's in refining the diagnosis on small bx's and to determine whether cytologic material (TBNAIEBUS and EUS) is suitable for EGFR genotyping in a prospective cohort

-Methods:
- Reviewed by AGN and initial dx made as NSCLC-NOS, SQCC, ADC, or SCLC
- Positive bx's and cell pellets then stained with CK5/6, p63, TTF-1, 34PE12, D-PAS, with additional stains with MNF116 (broad spectrum CKs) and CD56 when appropriate, reviewed by AGN again and a final dx made
- Two additional pathologist (one thoracic specialist and one general pathologist) independently assess the cases in similar fashion and reassigned their dx using a validation panel CK5/6, p63, TTF-1, and D-PAS (34PE12 excluded due to the poor specificity for SQCC; all ADCC cases were positive)
- 10 cases of adenoca, including 8 derived from cytology samples (cell pellets), sent for EGFR mutational analysis

-Results:
- 38 consecutive bx's (5/2008~3/2009) confirmed by primary lung ca in Royal Brompton and Royal Marsden Hospitals; 6 dx'ed as SLCL
- 32 NSCLC cases, 12 endobronchial bx, 5 core bx (4 lung, 1 liver), 13 TBNAs (blind, EBUS and EUS guided), 2 pleural fluid
- Refinement of dx in 65% of NSCLC to either SQCC or AD in the test phase, even in TBNA, validated by two other pathologists with increased refinement and concordance.; major problem is that no confirmation by resection specimen
- Sufficient quantity and quality of the DNA present in all samples for EGFR mutation analysis, but the test was negative in all cases

-Conclusions: Similar as the previous article

-**Purpose:** To evaluate the prognostic impact of LN involvement patterns in pulmonary pN1 SqCC patients.

-**Methods:**
  - Among 2546 consecutive surgical resections for primary lung cancers from 7/1992 to 12/2005, 124 pts had complete resection and staged as N1 SqCC with lobectomy or more extensive resection with systematic ipsilateral hilar and mediastinal LN dissection with clear RM.
  - Preop anticancer therapy or limited resection less than lobectomy not included.
  - 4 pts with incomplete pathologic records excluded.
  - Remaining 120 pt included in this study; to compare the survival probability, 302 pNO and 59 pN2 SqCC cases undergoing complete resection during the same period also studies were also investigated.
  - Age, sex, location, type of resection, pT classification, tumor size, clinical N classification, node involvement pattern, #10 LN involvement, number of metastatic N1 (main bronchial) nodes, lymphatic permeation, vascular invasion and pleural invasion reviewed.
  - "direct N1" as all N1 nodes completely inside, or partly connected to, to the primary tumor, or: 3mm apart from the main tumor; "separate N1" as at least one N1 node connected with the primary tumor only preexisting normal bronchovascular structures and located >3mm away from the main tumor.
  - X2 test or Fisher's exact test, as appropriate; Cox's proportional hazards regression model, Kaplan-Meier curve, log-rank tests; end point for analyses was overall survival, measured from the date of surgery to the date of death, from any cause.

-**Results/conclusions:** Univariate and multivariate analyses showed that N1 node involvement pattern significantly associated with pt's px; direct N1 metastasis is similar to pNO, while separate N1 metastasis behaves similar to pN2.

-Purpose: To examine the prognostic value of morphometric cytologic atypia in small pulmonary adenocarcinomas C<:3:2cm; current Tla)

-Methods:
- 139 primary adenocarcas of :s2cm with surgical resection along with lymphnode dissection (Jan 1999–Dec 2000); no chemo or radiotherapy before or after surgery
- 6 excluded who died of causes other than lung ca
- tumor classified as WHO types (BAC, mixed subtypes, acinar, papillary, solid); as Noguchi type A, B, C, D, E, F; TNM staging by 5th AICC system;FIIU 8-150 mos
- Morphometry using image analysis on 50 cells per case (10 cells per field and 5 400x fields) for mean nuclear size (area and diameter, perimeter, roundness); cutoff point for nuclear size by receiver operating characteristic (ROC) curve analysis: 67 fl/m² of nuclear area or 10.7 um of nuclear diameter
- In randomly selected 60 cases, they attempted to apply on routine histologic exam by compare the nuclear size to smallymphocytes( considered as large if thecells are 5x nuclear area or 3x nuclear diameter of a small lymphocytes; considered a positive case if there were ~3 positive fields that have ~ 5 positive cells in a field)
- Survival curves by K-M method and evaluated with log-rank test; independent staging factors for pulmonary adenoca by multivariate analysis for nuclear size; interobserver variability and accuracy by kappa statistics

-Results:

- very similar curve with nuclear diameter
- also correlates very well with clinicopathological characteristics, WHO classification and Noguchi's classification
- on multivariate analysis to determine the factors most significantly to 5 yr recurrence free survival rate were nuclear size, pleural invasion, T - stage (T1 vs. higher and N stage (NO vs. higher)
- kappa among 4 pathologists were 0.56 ± 0.10 (range, 0.47-0.76)

-Conclusions: Nuclear area and nuclear diameter (but not nuclear roundness) are independent markers for px of lung adenoca; analogous to breast, bladder & renal cell ca
• Articles for Notation Only

I. Original research articles from the pared-down journal list

Non-neoplastic diseases

-Purpose: To describe unique biopsy findings in 4 cases of acute pulmonary histoplasmosis
-Methods: 4 surgical lung bx's from consultation (n=3) and surg path files (n=1)
-Results:
  - 3 men and 1 woman (40-68 yrs), only 1 was immunocompromised due to inflixamib tx for 5 yrs due to RA; all presenting with fever and flu-like sx
  - Radiographically, solitary nodular in 3 or bilateral reticulonodular infiltrate in 1
  - Histologically, all showed a nodular parenchymal inflammatory infiltrate composed of lymphocytes and histiocytes filling alv spaces and expanding adjacent interstitium. Parenchymal necrosis in 3, vasculitis in all and striking in 3 with close resemblance to grade 1 LyG; small necrotizing granulomas, histiocytic aggregates or a few multinucleated giant cells are helpful tip-offs; all + for GMS
-Conclusion: Important d.dx for LyG; don't forget bug stains

Neoplastic-lung diseases

-Purpose: Presence of signet ring cell component has been implicated as a prominent factor in NSCLC with EML4-ALK translocation. To compare clinicopathologic features and survival outcome of primary SRC of the lung with pulmonary adenocarcinoma NOS
-Methods: A retrospective population-based analysis using California Cancer Registry (CCR) during a 7-year period (1989 ~ 2006)
  - Histology abstracted using ICD third edition; no central histology review
  - Adenoca (ICD code 8140) and SRC (ICD code 8490) with complete follow-up data included; did not include any subtypes such as acinar, papillary, fetal scirrrous, etc; no mixed type included
  - AICC (6th edition), age, sex, ethnicity, surgery, radiation, chemotx during the 1st course oft
  - Subgroup analysis of pts with smoking status available between 1991 and 2005 from Cancer Surveillance Programs of 3 counties in southern CA
  - Appropriate statistical analysis
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  • AJCC (6th edition), age, sex, ethnicity, surgery, radiation, chemotx during the 1st course of tx
  • Subgroup analysis of pts with smoking status available between 1991 and 2005 from Cancer Surveillance Programs of 3 counties in southern CA
  • Appropriate statistical analysis
-Results:
  - A total of 50,351 patients including 262 cases of SRC.
  - Primary SRC of the lung pts were significantly younger, with a higher proportion of poorly differentiated tumor and stage IV ds.
  - No difference in gender and ethnicity.
  - Never smokers comprised of significantly higher proportion of SRC pts (30.8%) vs. adenoca pts (11.0%; p=0.0013).
  - Never smokers with SRC tend to be younger with a trend of improved survival than ever smokers with SRC.
  - SRC pts had decreased overall survival and an independent unfavorable prognostic factor by multivariate analysis (vs. adenoca p<0.0030).

-Conclusions and Comment:
  - Primary SRC of the lung carries a worse px than adenoca NOS and shares many of the recently identified clinicopathologic characteristics ascribed to EML4-ALK positive non-small cell lung cancers (Shaw AT et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 2009;27:4247-53).
  - This study is likely limited by underreporting of SRC in cancer registries.

Remaining questions: definition of SRC seems to be a bit of problem, too; how much signet ring cell component for dx of SRC is not set; 5, 10, 30, 75% in the literature; also what cells constitute signet ring cell is not entirely clear as well.

- Purpose: To evaluate the sensitivity and accuracy of CT-guided percutaneous needle bx (PNB) in pts with hilar adenopathy, in comparison to EUS-guided F ANB.
- Methods: A retrospective review of 80 pts who underwent PNB including FNAB and core bx (CB) during 10/02~12/06; PNB sensitivity and accuracy calculated in each case with review for complications (pneumothorax and subsequent thoracostomy tube insertion); true positive or negative was determined by surgical confirmation of the dx and CT follow up.
- Results: PNB had a sensitivity of 91.4% and accuracy of 92.8% that are comparable to EUS FNAB and allow more tissue than such procedure, at higher rates of pneumothorax, however.
- Conclusions: When larger samples are needed for molecular study or biomarker analysis, PNB is a viable alternative for EBUS or EUS-guided FNAB.

- Purpose: to report 10 cases of carcinoid tumor with extensive sclerotic changes resected from 1988-2003; to highlight the difficulty of dx and grading.
- Methods: A retrospective review.
- Results: on their description, it sounds like all typical carcinoid (little or no mitotic activity and no necrosis) though not said that way. all are alive in on 1-5 yrs offF/u, except 2 cases who were lost to F/I/V.
- Conclusions: Be aware of unusually severe sclerosis esp. in small bx.

Avritscher R et al. Accuracy and sensitivity of computed tomography-guided percutaneous...
-Purpose: To establish (I guess they meant refine) cytologic criteria for LCNEC vs. SCLC
-Methods: Aspiration cytologic and/or imprint smears from 29 LCNEC and 26 SCLC
-Results: They used an analysis that required (a serious) algebra skill as well as morphologic examination
-Conclusions: Large cell clusters with tight cohesion and of small tumor cells without prominent nucleoli are useful

Monego G et al. Parathyroid hormone-related peptide and parathyroid hormone-related peptide receptor type 1 expression in human lung adenocarcinoma. Chest 2010;137:898-908
-Purpose: To examine the clinical relevance of the PTH1R expression in NSCLCs
-Methods: Quantitative IHC ofPTHrP and PTH1R in stage I and II 54 adenocarcinoma of mixed histologic type (using image analysis)
-Results: PTHrP and PTH1R were associated with LN involvement at presentation, but not with age, tumor size or histologic grading. Cox regression analysis showed coexpression of high levels of both proteins are associated with the risk of death and metastasis
-Conclusions: Possible role of these proteins in early-stage lung adenocarcinoma progression

-Purpose: To examine the associations of ERCC1 and Ki67, clinical features and survival in SCLC, TC, AC and LCNEC
-Methods: Consecutive series of 196 SCLC treated with platinum-based chemo and surgically treated pts with 48 TC, 15 AC and 27 LCNEC. ERCC and Ki67 IHC scored semiquantitatively by estimating the % of tumor cells -
- Results & Conclusions: No impact on survival for ERCC1 expression in SCLC treated with platinum-based chemo. a clue to the failure of such therapy for TC with high expression of ERCC1; ERCC1 expression has prognostic impact in TC and AC. a correlation between Ki67 and ERCC 1 present for all included patients

Maeshima AM et al. Clinicopathologic analysis of multiple (five or more) atypical adenomatous hyperplasias (AAHs) of the lung. Evidence for the AAH-adenocarcinoma sequence. J Thorac Oncol2010;5:466-471
-Purpose: To examine clinicopathologic characteristics of pts with multiple AAH
-Methods: 1639 pts who underwent lobectomy or pneumonectomy for lung tumors. the number and the sized of AAHs, incidence and histology of adenocas, and outcomes were studied
-Results: 42 of 1639 pts had 5 or more AAHs (range 5-171), more in the upper lobe (86%) and in women (75%).794 AAHs found and 62% measured less than 1mm, 22% 1-2mm, 15% 2-5mm, 1% 5-10mm. 28 of32 pts with AAHs had adenoca (1 in 18 pts, 2-6 in 10 pts). Of 51 adenocas in 28 pts, 19 were non-invasive (0.2-2.2cm), 8 were minimally invasive adenoca (0.3-3.6CM, 19 wee overtly invasive (1-4cm) without LN mets and 5 were overtly invasive with LN mets (2-4.7cm). 6% of total AAH (51 of845) had both AAHs and adenoca. 5 yr cancer free survival rate in these 28 pts was 71.4%
Conclusions: 5 or more AAH seen in 2%, most were small (<2mm) and associated cancer type was adenoca, suggesting the derivation from AAH. However, the incidence of AAH-Adenoca sequence appears to be low (6%) and the outcome of adenoca was not very favorable.

Krajnik M et al. Enkephalin, its precursor, processing enzymes, and receptor as part of a local opioid network throughout the respiratory system of lung cancer patients. Hum Pathol2010;41:632-642
-Purpose: To examine local opioid network of the respiratory system
-Methods: IHC of precursor and key processing enzymes in 12 resected lung cancers. Colocalization is also studied by double IF confocal microscopy in alveolar macrophages, submucosal glands, cancer cells, pulmonary neuroendocrine cells of bronchial epithelium.
-Results and Conclusions: they are present in these functionally relevant anatomical structures, encouraging future study for the role of local opioid peptides in resp system

Findeis-Hosey JJ et al. IMP3 expresion is correlated with histologic grade of lung adenocarcinoma. Hum Pathol2010;41:477-484.
-Purpose: To examine the correlation of insulin-like growth factor II mRNA binding protein 3, an oncofetal protein, with histologic grade of lung adenoca
-Methods: IHC on 89 cases (11 AAH, 10 BAC, 36 well diff adenoca, 41 mod or poorly diff adenoca
-Results: IHC for IMP3 is more frequent, stronger and more extensive in mod and poorly diff adenoca than in BAC and well diff adenocas, and negative in AAH
-Conclusions: IMP3 expression may be associated with aggressive biologic behavior

-Purpose: To assess the frequency and quantity of tumor present in bx samples, in order to examine the problem in molecular study using these samples
-Methods: proportion of tumor in bronchial bx measured by computer aided morphometry
-Results: onl 48% contained some tumor in all bx fragments. median number of fragments obtained bx was 4 and 3 frags had tumor. total tumor area in the positive frag was 33.4% for all cases and median area was 28%. SCLC tends to have more tumor than NSCLC
-Conclusions: Blind molecular analysis using a fragment of bronchial bx specimen can be false negative

-Purpose: To examine EGFR mutation status in pulmonary pleomorphic ca (PPC)
-Methods: Retrospective analysis of EGFR mutation and Ki-67 index in 17 PPCs
-Results: 13M, 4F, median age 72; 3 (18%) of 17 pts had EGFR mutation; median of Ki-67 index was 62%; 1 pt treated with gefitinib did have a minor and transient response
-Conclusions: Low incidence of EGFR mutation in PPCs and questionable response at best to gefitinib

II. Original research articles from the previously used extended list
-Purpose: To determine the longer-term effects of exposure among FDNY rescue workers (firefighters and EMS workers) exposed to dust at the time of 9-11 attack
-Methods: They analyzed FEV1 of both active and retired FDNY rescue workers on the basis of spirometry routinely performed at intervals of 12 to 18 months from 31/12/00–9/11/08 (61,746 quality-screened spirometric measurements)
-Results:
- Of the 13954 FDNY workers who were present between 9/11–14, 2001, a total of 12,781 participated in the study
- In the first year the mean FEV1 decreased significantly for all workers; more for the firefighters than for EMS workers among non-smokers (a reduction of 438 vs. 267ml)
- Little or no recovery in FEV1 during the subsequent 6 yrs (below normal in 13 % for firefighters and 22% for EMS workers)
-Conclusions: a large decline in lung function in the first year and persistent decline in the next 6 yrs without recovery, leaving a substantial proportion with abnormal lung func

Zlobec I et al. Assessment of mean EGFR gene copy number is highly reproducible method for evaluating FISH in histological and cytological cancer specimens. Lung Cancer 2010;68:192-197. The title says all; a reproducible scoring method for evaluating EGFR-FISH as an alternative to current methods of gene copy number assessment

Okereke IC et al. Prognostic indicators after surgery for thymoma. Ann Thorac Surg 2010;89:1071-9. I just ask Anja for any issue on the Masaoka staging system, original or modified; I can't remember even if I tried hard ...

Wislez M et al. Non-mucinous and mucinous subtypes of adenocarcinoma with bronchiole alveolar carcinoma features differ by biomarker expression and in the response to gefitinib. Lung Cancer 2010;68:185-191. PAS, TTF-1 stain and EGFR genomic mutational analysis distinguish the two types; as suspected, mucinous type was resistant to EGFR-TKIs

Shah SA et al. Differential matrix metalloproteinase levels in adenocarcinoma and squamous cell carcinoma of the lung. J Thorac Cardiovascular Surg 2010;139:984-990. MMP profile was different between the two types, which suggests a role in their different natural history and in identifying potential prognostic factor or therapeutic targets

III. Case reports, letter to the editor, editorial, etc. from both lists

Yokomine T et al. Pulmonary thrombotic microangiopathy caused by gastric carcinoma. J Clin Pathol2010;63:367-369. A case report postulating the role ofPDGF (produced by alveolar macrophages) and PDGFR (expressed in myointimal cells associated with carcinoma cells and blocking the lumens) in this often fatal condition resulting in acute, rapidly progressive pulmonary hypertension and right ventricular failure