Discussion Articles


Articles of Notation


Page 7 Saito et al. Correlations between thin-section CT findings, histopathological and clinical findings of small pulmonary adenocarcinomas. Lung Cancer 2011;71:137-143.


Original Articles


Page 9 Kristensen et al. Methylation of MGMT in malignant pleural mesothelioma occurs in a subset of patients and is associated with the T allele of the rs16906252 MGMT promoter SNP. Lung Cancer 2011;71:130-136.


Reviews and Case Reports


Discussion Articles

Purpose: A retrospective study to assess changes in CT findings over time and to correlate the baseline CT findings with mortality in NSIP patients

Methods: Evaluated 50 idiopathic NSIP cases with initial HRCT scans within 1 month before the bx and latest HRCT (interval between the two scans 3-216 months; median 72)
- Patient selection: pts with histologic dx of NSIP by surgical lung bx between 1992-2006 (n=99);
- Histologic dx: made by consensus of two or more pathologists (9-30 yrs of experience in lung pathology); excluded cases with underlying connective tissue disease (before bx or during follow-up), HP, drug induced lung disease, and those without follow up CT scans
- Radiology review: by two radiologists without the knowledge of clinical information, histologic dx, or whether the scans were initial or follow up studies; divide the lung fields as six zones, score based on % involvement, overall involvement by averaging the six lung zones, parameters (see the table below); categorized as compatible with NSIP, UIP or suggestive of alternative dx
- Analysis: kappa statistics, group comparisons by paired t test or $\chi^2$ statistic. Univariate and multivariate Cox proportional hazards regression to identify independent CT predictors. Age, sex, smoking habit, FVC, DLCO, PaO2 was factored in the model. Log-rank test with Kaplan-Meier curve display to see the relationship of patient survival in different CT patterns

Results:

<table>
<thead>
<tr>
<th>HRCT findings</th>
<th>Initial CT scan</th>
<th>Last CT scan</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall extent</td>
<td>16.6±11.5</td>
<td>20.9±24.3</td>
<td>0.329</td>
</tr>
<tr>
<td>GGO extent</td>
<td>11.4±9.3</td>
<td>12.5±18.7</td>
<td>0.752</td>
</tr>
<tr>
<td>Reticulation extent</td>
<td>6.6±7.4</td>
<td>9.8±11.3</td>
<td>0.146</td>
</tr>
<tr>
<td>Fibrosis coarseness grade</td>
<td>2.1±2.3</td>
<td>3.9±3.0</td>
<td>0.005</td>
</tr>
<tr>
<td>Traction bronchiectasis score</td>
<td>4.2±4.0</td>
<td>7.1±5.0</td>
<td>0.007</td>
</tr>
<tr>
<td>Honeycombing</td>
<td>4 (8)</td>
<td>17 (34)</td>
<td>0.003</td>
</tr>
<tr>
<td>Honeycombing extent</td>
<td>0.2±0.6</td>
<td>2.3±5.9</td>
<td>0.031</td>
</tr>
<tr>
<td>Consolidation</td>
<td>28 (56)</td>
<td>10 (20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Consolidation extent</td>
<td>2.6±3.5</td>
<td>0.6±1.4</td>
<td>0.002</td>
</tr>
<tr>
<td>Emphysema</td>
<td>1.0±3.3</td>
<td>1.0±3.3</td>
<td>1.000</td>
</tr>
<tr>
<td>Cysts</td>
<td>6 (12)</td>
<td>11 (22)</td>
<td>0.264</td>
</tr>
</tbody>
</table>

* Data are numbers of patients, with percentages in parentheses.

- 30 NSIP, 4 UIP, 16 alternative dx (4 COP, 5 CHP, 1 LIP, 1AIP 5 unclassifiable) on CT
- All e-NSIP were alive with improvement, so only with mixed or f-NSIP evaluated for px
- Mean survival for pts with HRCT pattern of NSIP (160mos) is significantly longer than those with UIP (42 mos) or others (122 mos); p<0.001 and p=0.022, respectively

Conclusion/take home message/discussion: HRCT finding changes over time in idiopathic NSIP and initial HRCT dx may impact survival. I wondered if the patients having initial HRCT pattern of NSIP have different survival depending on their histologic diagnosis of UIP vs. NSIP

**Purpose/Background:** Translocation of ALK gene has been shown to be associated with responsiveness to ALK inhibitors and used to identify patients for this therapy. ALK gene copy number changes and amplification are not well characterized in NSCLCs. This study looked into the prevalence of ALK copy number changes and their correlation with ALK protein expression, EGFR status, and clinicopathological data.

**Methods:**
- Patient inclusion criteria: the availability of tissue for biomarker studies (did not show time period); 107 patients with stage I in 46%, adeno (65%), squa ca (28%), NSCLC NOS (2%), and LCC and BAC (5%); median follow up only 10.6 months (0.1-61.2).
- FISH for EGFR and ALK; EGFR/CEP7; ALK/CEP2, EML4, KIF5B, TFG
  - ALK gene copy gain: mean copy number of 3 to 5 fusion signals in ≥10% of tumor cells
  - ALK gene amplification: mean gene copy number of ≥6 or fusion clusters in ≥10%
- IHC for EGFR and ALK: EGFR Ab (DAKO cytomation)- membranous stain with score 0 to 3+; ALK Ab(D5F3, Cell Signaling, Danvers, MA)- cytoplasmic stain using H score (intensity 0 to 4+, multiplied by % positive cells) – does not say what number is the cut-off value, this Ab is not commercially available yet
- EGFR mutational analysis: exons 18 to 21 of the EGFR gene by direct sequencing using paraffin tissue

**Results:**
- 3 cases (2.8%) show ALK translocation: 2 cases with ALK-EML4 translocation (both adenocarcinomas, 1 ex smoker 74M, 1 never smoker 72F); 1 case mixed adeno and LCNEC current smoker 74M, shows atypical pattern with a deletion of the 5’ region of ALK without abnormalities in currently known ALK translocation partners EML4, KIF5B or TFG: all three cases negative for EGFR mutation
- 11 cases (10%) show amplification of ALK (5 adeno, 1 BAC, 5 squam). A significant association between amplification and early stage (I and II) but not with gender, age, smoking hx, or histology
- 68 cases (63%) show ALK copy number gains in a high proportion of cells (50-95%) without any association with any clinical or pathologic parameter
- Only two cases with ALK-EML4 translocation are positive for ALK IHC
- Significant association between ALK amplification and EGFR FISH positivity (p <0.001), but not with EGFR mutation or protein expression
- Survival analysis does not seem to be very meaningful even with many complicated ways

**Conclusion:** ALK gene amplification is probably not a biologically relevant event or predictive of responsiveness to ALK inhibitors such as Crizotinib

**Purpose:** To assess the utility of immunohistochemical markers in subtyping poorly differentiated NSCLC and to compare the results of IHC on bx's with corresponding resections

**Methods:** Poorly differentiated NSCLC diagnosed by bronchoscopic bx's or CT-guided needle bx's over 12-yr period (1998-2009) that had subsequent resection at a single institution (n=71)

- Inclusion criteria: 1) NSCLC dx confirmed, 2) no differentiation on HE morphology, 3) glass slides and blocks available on both bx's and resection specimens; 26 cases excluded n=23 HE morphology enough for dx, n=2 sarcomatoid ca, n=1 small cell ca
- 39 cases selected: 27 CT-guided needle bx, 4 endobronchial bx, 8 TBbx

- Gold standard: subtyping on resected tumor by 2 pathologists (SM and AK) as AC if gland formation and/or mucin production, SCC for intercellular bridges or keratinization, LCC if lacking the features of AC and SCC

- IHC done on both bx and resection with CK7, TTF1, napsin A, p63, CK5/6 and 34βE12

**Results:**

<table>
<thead>
<tr>
<th>Resection Diagnosis by WHO Criteria (No. Cases)</th>
<th>Biopsy IHC Number Positive/Total Stained (%)</th>
<th>Biopsy Diagnosis After IHC (No. Cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC (20)</td>
<td>CK7 19/19 (100)*</td>
<td>AC (16/20) NSCLC, NOS (4/20)</td>
</tr>
<tr>
<td>SCC (15)</td>
<td>TTF-1 16/20 (80)</td>
<td>NSCLC, NOS (1/5)</td>
</tr>
<tr>
<td>LCC (4)</td>
<td>Napsin A 11/19 (58)*</td>
<td>AC (2/4) NSCLC, NOS (2/4)</td>
</tr>
<tr>
<td></td>
<td>p63 2/20 (10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CK5/6 0/20 (0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>34βE12 12/20 (60)</td>
<td></td>
</tr>
</tbody>
</table>

*No tumor was present on the immunostained slide in 1 case.

AC indicates adenocarcinoma; IHC, immunohistochemistry; LCC, large cell carcinoma; NSCLC, Non-small cell lung carcinoma; NOS, not otherwise specified; SCC, squamous cell carcinoma; WHO, World Health Organization.

<table>
<thead>
<tr>
<th>TTF-1</th>
<th>Napsin A</th>
<th>p63</th>
<th>CK5/6</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>-</td>
<td>Diffuse positive</td>
<td>+</td>
<td>-</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>-</td>
<td>Diffuse positive</td>
<td>-</td>
<td></td>
<td>Poorly differentiated non-small cell carcinoma, NOS</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Poorly differentiated non-small cell carcinoma, NOS</td>
</tr>
</tbody>
</table>

NOS indicates not otherwise specified.

**Conclusion:** TTF1, napsin A, p63, and CK5/6 are useful markers for subtyping of NSCLC. 34βE12 is not good. Discrepancies in IHC findings between bx's and resections are uncommon

**Purpose:** To evaluate the potential value of PET/CT along with other parameters in selecting the patients who need adjuvant therapy after a complete resection of stage I lung cancer

**Methods:** A retrospective study
- Patients: 201 patients with pathologic stages IA and IB selected from 356 patients who underwent surgery from Jan 2004 to Dec 2008 at a single institution, and had PET/CT scan with maximum SUV measurement
- Inclusion criteria: complete resection, no induction therapy, preop PET/CT, no severe diabetes (requiring insulin). Pts with pure GGO also excluded
- Follow-up and clinical information: age at dx, gender, smoking status, serum CEA level, time of surgery, TNM staging (looks like by 7th edition, though it did not specify), max SUV of primary tumor, extent of surgery, pathologic findings (histology, LVI), time of recurrence, time to last follow-up, time to death, and cause of death; patients were followed up every 3-4 months in outpatient clinic and annual CT was taken.

**Results:** On multivariate analysis using predictive factors after surgery, only max SUV (≥4.7 vs. <4.7) and LVI were significant (both <0.01); gender, age (≥75 vs. <75), smoking status, CEA, tumor size (≥3.1cm vs. <3.1cm), histology (non-adeno vs. adeno) and pleural invasion were not.

DFS based on the four groups

**Conclusion:** Patients with high max SUVs and LVI were more likely to have recurrence and might be candidates for adjuvant chemotherapy
Articles of Notation

Purpose: An approach to classify adenoca and sq ca based on the reverse engineering of the transcriptional network.

Methods:
-training data inferred from 111 lung ca (58 adeno 53 sq with histologic dx)
-a transcriptional network classifier was constructed with Bayesian networks framework
-compute the probability of being adeno ca vs sq ca by the network model with differential analysis, and determine discrimination accuracy with receiver operator characteristic (ROC) curves
-testing its accuracy from the above data on 7 independent cohorts, including 422 subjects with different ethnic origin
-comparing performance with other methods and CGH data

Results:
-the 25-gene signature identified by the transcriptional network classifier is unique to discriminate adeno ca and sq ca with high accuracy (95.2%)
-discriminating power of a narrow cytoband on chromosome 12q12-13 harboring KRT6A, KRT6B, and KRT6C genes that were able to achieve a classification accuracy of 90.2% (accounting for 95% of the accuracy of the entire signature)
-gain of 12q13 appears more common in sq ca than in adenoca

Conclusion:
-Gene expression profiling is a powerful alternative to histology
-the ability of this small functional network to pinpoint a small region of chromosome 12 accounting for a large proportion of the differences between adeno ca and sq ca
-the possibility of developing high-throughput screening methods to identify candidates for defect-targeted drugs and potential for personalized therapeutic strategies

Saito et al. Correlations between thin-section CT findings, histopathological and clinical findings of small pulmonary adenocarcinomas. Lung Cancer 2011;71:137-143.
Purpose: Histologic correlation with radiological density of TOM (tumor opacity on mediastinal window images) in small adenocarcinomas of the lung

Methods:
-A retrospective review of preoperative thin-section CT scans of 134 pts who underwent surgical resection of peripheral adenoca ≤ 20mm by four thoracic oncologists with classification as "air containing type" (TDR ≥ 50%) or "solid density type" (TDR <50%)
-TDR (tumor shadow disappearance rate) = 1 - (TOM/tumor area of the lung windows)
- histologic review and correlation with TOM area in the resected tumor with HE and EVG stains; classified as 1) collapse (C), 2) collapse with BAC (CwB), 3) adenocarcinoma cells (Cells), 4) fibroblasts (F), and 5) mucus (M).

Results:
- 52 cases showed air-containing type and areas of TOM showed predominantly C and/or CwB (44 cases); conversely 8 cases (15.4%) showed Cell/F and M types
- 82 cases showed solid-density type and had Cells for F type in 67 cases; 15 (18.3%) cases showed C/CwB and M types
- 38 cases of Cell/F type also revealed microscopic evidence of pleural involvement, vascular or lymphatic invasion, or LN mets, but none of C/CwB type did

Conclusion: There is a correlation between the areas of TOM and histopathologic component in small adenocarcinoma depending on the radiologic type; air containing type mostly showed C/CwB type with better px while solid-density type demonstrated Cell/F with worse px. CT scan is useful aid, but still pathologic exam is crucial, given the discrepant cases

Purpose: To correlate amplification and activating mutation of Kras gene in Japanese lung cancers patients

Methods: 172 NSCLC cases with surgical excision in a single institution, these cases already have been evaluated for EGFR and Kras mutations; among these patients, they also analyzed the Kras amplified status by qPCR and FISH

Results: In 172 cases, increased Kras copy number was found in 19 (11%) cases, which correlated with Kras mutation. Increased Kras copy number by itself did not correlate with overall survival but had worse prognosis if Kras mutant, than Kras wild type or case without increase in Kras copy number

Conclusion: NSCLCs having both Kras mutation and increased copy number had poor clinical outcome

Original Articles; neoplastic and non-neoplastic


Purpose: To determine the clinical relevance of circulating tumor cells (CTCs) in surgically resected NSCLC patients

Methods: nested real-time RT-PCR for TTF1 and CK19 mRNA on presurgery and postsurgery blood samples from 79 patients who had surgical resection of NSCLC to detect CTC

Results:
- TTF-1+ CTCs in 36.1% of presurgery and 37.5% of postsurgery samples
- CK19+ CTC in 42.6% preop and 25.0% of postop samples
- cases with postsurgery TTF1+ and/or CK19+ CTCs are associated with more disease progression and shorter disease progression-free survivals (both p=0.004).
- CK19+ CTC status by itself did not show significant clinical relevance
Conclusion: TTF1- mRNA expressing CTCs might be a useful surrogate predictor of disease progression before clinical manifestations and the monitoring of TTF1-positive CTC status after surgery may be useful for identifying high-risk patients among surgically resected NSCLC cases

Kristensen et al. Methylation of MGMT in malignant pleural mesothelioma occurs in a subset of patients and is associated with the T allele of the rs16906252 MGMT promoter SNP. Lung Cancer 2011;71:130-136.

Purpose: MGMT is a DNA repair gene that removes alkyl adducts and prevents G>A mutations in the genome. Silencing of MGMT by promoter methylation is an early event in several lung cancers (such as colon cancers) but the status in malignant pleural mesothelioma (MPM) is not well known. Thus, they examined whether MGMT is silence in MPM.

Methods: 95 patients with dx of MPM (61 epithelial, 12 biphasic, 22 sarcomatous) were studied using FFPE blocks. Genotyping of the rs16906252 SNP and allelic Sensitive Melting Analysis After Real Time (SMART)-methylation specific PCR (MSP). IHC to see the loss of protein (positive internal controls served by lymphocytes)

Results: 80 (of 95) samples were homozygous for the C allele and 14 were heterozygous and 1 was homozygous for the T allele. cases carrying the T allele of the rs 16906252 SNP were more likely to have detectable MGMT methylation. On quantitative methylation estimation, most positive cases had low-level methylation. only one case with biallelic methylation and a methylation level of 93.3% was negative for MGMT IHC.

Conclusion: Complete silencing of MGMT is a rare event and thus is probably not a common driving force in MPM tumorigenesis.


Purpose: In US, black women are most commonly and severely affected by sarcoidosis but epidemiologic study focussing on black women are few.

Methods: Data on incidence, prevalence, and clinical characteristic of sarcoidosis among participants in the black Women’s Health Study, with a cohort of 58,000 black women in US, using biennial questionnaires and follow-up info in >80% through six completed cycles.

Results: incidence rate of 71/100,000 and current prevalence at 2.0%. lung is most commonly involved, also had extrapulmonary sites including LN, skin and eyes. dx confirmed in 96% of self reported cases (through physician questionnaire or medical record review; not clear how many had tissue dx).

Conclusion: useful information in this population and potential to identify risk factors, etc.

Frost et al. The Changing Picture of Patients With Pulmonary Arterial Hypertension in

Purpose: REVEAL (the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) for providing current demographics of patients with group I PAH in US

Methods: Description of 2,967 pts with type 1 PAH (idiopathic, inherited, associated with other conditions such as connective tissue disease, but without other pulmonary parenchymal, hypoxic, or thrombotic lung disease or left heart disease), diagnosed by right heart cath enrolled between March 2006 and September 2007 and comparison with historic US registry data (NIH PAH registry) and other contemporary US and non-US PAH registries; of note, this study is sponsored by Actelion Pharmaceuticals

Results/Conclusions: REVEAL patients were older than NIH registry patients at diagnosis, more likely to be women and obese. These findings differ from NIH registry in the 1980's, and also from the contemporary European and UK registries, suggesting that the presence of behavioral, environmental, racial, and pharmacologic factors are more prevalent and as yet unidentified in the Americans. these factors and the other observed differences in HIV PAH populations warrant further investigation

Reviews, Case Reports, etc.

Essentially summaries and highlights the article by Travis W et al published subsequently in the Feb issue of J Thorac Oncol. Emphasizes the role of surgical pathologists in the diagnosis adopting the new development

In depth review touching identification of potentially responsive patients as well as other treatment application problems

Concise highlights of the major changes in the 7th edition for lung cancer staging

Given the increasing literature using molecular techniques, it is useful to understand some principles and details of molecular testing in lung cancer diagnosis and tumors of extrapulmonary sites. This review is certainly helpful in that regard.

A useful update on sarcodosis in clinical field
A letter to the editor to describe a case of coexistent ABPA and active pulmonary TB, which has not been documented previously they say...

Unusual combination, against the current notion/dogma of their mutually exclusive status in tumorigenesis...