Pulmonary Pathology Journal Club
(February 2012 Articles)
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**Articles for Discussion**


Purpose: To document 5 cases showing diffuse cystic lung disease on HRCT and coexisting small airway ds (SAD) on examination of surgical lung biopsies

Methods: 5 cases from Royal Brompton (n=3) and Mayo Clinic AZ (n=2 TVC’s consult). Clinical data regarding presentation and F/U from medical records or referral letters. HE and EVG examined on all cases; IHC for S100, CD1a, SMA, desmin, HMB, CD56 in select cases. Birt-Hogg-Dube (BHD) tested by direct sequencing of folliculin gene in 2 cases.

Results:

**Clinical**
- 4 women, 1 man with age range 27-60 (mean 43)
- 4 never smokers, 1 unknown smoking hx
- 2 patients was found incidentally
- Sx’s: dyspnea, chest pain and/or chronic cough, or none
- Hx: 1 had pneumothorax 13 yrs earlier and 1 had asthma (also with family hx) and SLE
- PFT: decreased FEV1 54-67% predicted; 1 recorded as severe obstruction
- Autoantibodies: Ro and La positive in the pt with SLE; not known in others
- BAL: 2 pt’s WNL; not performed in 3 pt
- Pre-op dx: LAM in 4 pt’s and LCH in 1 pt (who was never smoker, 60M)

**HRCT and histopathologic findings**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Size Range (cm)</th>
<th>Profusion</th>
<th>Distribution</th>
<th>Strands Within Cysts</th>
<th>Vessels in Walls</th>
<th>Localized Cystic Change</th>
<th>Extent of Chronic Bronchiolitis</th>
<th>Other Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5-2</td>
<td>++</td>
<td>All zones (random)</td>
<td>++ +</td>
<td>Yes</td>
<td>Present</td>
<td>Mild</td>
<td>Features of asthma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Eosinophilic pneumonia-like reaction with occasional non-necrotizing granulomas</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.3-3</td>
<td>++ +</td>
<td>All zones (random)</td>
<td>+</td>
<td>Yes</td>
<td>Present</td>
<td>Mild</td>
<td>Overlying pleural thickening</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Focal collapse with associated fibrosis</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.5-2.5</td>
<td>++</td>
<td>All zones (random)</td>
<td>+</td>
<td>Yes</td>
<td>Present</td>
<td>Mild to moderate</td>
<td>Some airways show bronchiectatic change</td>
</tr>
<tr>
<td>4</td>
<td>0.5-4</td>
<td>++ +</td>
<td>All zones (random)</td>
<td>+</td>
<td>Yes</td>
<td>Present</td>
<td>Mild</td>
<td>No further features</td>
</tr>
<tr>
<td>5</td>
<td>0.5-3</td>
<td>++</td>
<td>Unilateral (random)</td>
<td>+</td>
<td>Yes</td>
<td>Present</td>
<td>Mild</td>
<td>DIPNECH and focal obliterative bronchiolitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DIPNECH and focal obliterative bronchiolitis</td>
<td></td>
</tr>
</tbody>
</table>

DIPNECH indicates diffuse idiopathic neuroendocrine cell hyperplasia.
Conclusions/take home points: 5 cases with a novel constellation of diffuse cystic change with SAD; unusual HRCT and clinical findings for both PLCH and LAM. HRCT might mimic BHD but SAD on histopathology would be unusual for BHD. Authors hypothesized that chronic damage to small airways may lead to cystic degeneration in a minority of pt’s and suggested a causal association between cystic parenchymal change and SAD (possibly due to air trapping, etc).


Purpose: To apply newly proposed classification on 87 resected adenoca and to assess the impact on tumor staging when using the new criteria

Methods: A retrospective review of 87 resected adenoca (2007-10) at U of Maryland Med Center, for morphometric measurement of invasion, histologic subtype, extent of lepidic component and predominant histologic pattern. Correlation with LN mets and clinical follow up (17-28 mos)
Results: 30 of 87 cases with lepidic growth and without high high-grade invasive areas

Table 2. Tumors with a prominent lepidic component (n=30); analysis of LN involvement by revised and 2004 WHO criteria

<table>
<thead>
<tr>
<th>Classification</th>
<th>Total Size (cm ± SE)</th>
<th>Invasive Size (cm ± SE)</th>
<th>LN Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revised</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIS (n = 3)</td>
<td>0.9 ± 0.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MIA (n = 8)</td>
<td>1.4 ± 0.7</td>
<td>0.3 ± 0.5</td>
<td>0</td>
</tr>
<tr>
<td>LPA (n = 19)</td>
<td>2.9 ± 0.6</td>
<td>2.4 ± 0.4</td>
<td>5</td>
</tr>
<tr>
<td>WHO 2004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAC (Tis) (n = 3)</td>
<td>0.9 ± 0.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BAC + acinar (n = 15)</td>
<td>2.2 ± 0.4</td>
<td>1.6 ± 0.6</td>
<td>2</td>
</tr>
<tr>
<td>BAC + acinar + papillary (n = 7)</td>
<td>3.2 ± 1.1</td>
<td>2.6 ± 0.7</td>
<td>1</td>
</tr>
<tr>
<td>BAC + mucinous (colloid) (n = 3)</td>
<td>2.5 ± 1.6</td>
<td>0.4 ± 1.0</td>
<td>0</td>
</tr>
<tr>
<td>BAC + solid (n = 1)</td>
<td>3.0</td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td>BAC + microcystic (n = 1)</td>
<td>1.0</td>
<td>0.5</td>
<td>1</td>
</tr>
</tbody>
</table>

AJCC/UICC indicates American Joint Cancer Commission/Union Internationale contre le Cancer, reference.

Table 3. Tumors with prominent lepidic component; analysis of LN involvement and tumor dimensions

<table>
<thead>
<tr>
<th>Classification</th>
<th>Pattern of Invasive Tumor</th>
<th>Tumor Size (cm ± SE)</th>
<th>Invasive Size (cm ± SE)</th>
<th>LN Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIA (n = 8)</td>
<td>Complex acinar/papillary (4)</td>
<td>0.7 ± 0.8</td>
<td>0.3 ± 0.05</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Invasive with desmoplasia (4)</td>
<td>2.2 ± 0.8</td>
<td>0.4 ± 0.1</td>
<td>0</td>
</tr>
<tr>
<td>LPA (n = 19)</td>
<td>Complex acinar/papillary (3)</td>
<td>2.8 ± 1.3</td>
<td>2.2 ± 1.2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Invasive with desmoplasia (9)</td>
<td>2.8 ± 0.4</td>
<td>2.1 ± 1.2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Invasive with desmoplasia and single cells(6) or lymphovascular invasion (1)</td>
<td>3.2 ± 1.2</td>
<td>2.4 ± 1.1</td>
<td>5</td>
</tr>
</tbody>
</table>

Comparison between revised classification and total tumor size by TNM criteria.11
*LN2 (3), N1 (2), invasive component 5, 11, 15, 21, 36 mm.
†Microcystic type, N2.

Table 4. Tumors with lepidic spread, Follow-up

<table>
<thead>
<tr>
<th>Classification</th>
<th>LN Initially</th>
<th>Follow-up (mo, Mean)</th>
<th>Disease Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIS (3)</td>
<td>0</td>
<td>28</td>
<td>3 NED</td>
</tr>
<tr>
<td>MIA (8)</td>
<td>0</td>
<td>22</td>
<td>7 NED†</td>
</tr>
<tr>
<td>BAC with invasion as acinar papillary structures, without desmoplasia (3)</td>
<td>0</td>
<td>22</td>
<td>2 NED</td>
</tr>
<tr>
<td>BAC with desmoplasia, acinar or papillary invasive component (9)</td>
<td>0</td>
<td>17</td>
<td>7 NED</td>
</tr>
<tr>
<td>BAC with desmoplasia, and single-cell or compressed gland invasion (7)</td>
<td>4</td>
<td>17</td>
<td>4 distant metastases*</td>
</tr>
</tbody>
</table>

*One patient presented with brain and bone metastases; all lymph nodes were negative. Among the 4 patients, the invasive tumor sizes were 5, 11, 15, and 18 mm. The 5-mm tumor had lymphovascular invasion by microcystic tumor.
†One patient had concomitant breast cancer with metastases confounding lung tumor status.
NED indicates no evidence of disease.
Acinar adenoca, invasive without desmoplastic invasion.

(there is a problem; to me, B and D could be AIS or BAC...)

Conclusions/take home points: ~1/3 of lung adenoca showed significant lepidic spread and nearly 1/3 of these were MIA. Measurement can be difficult in cases without elastotic desmoplasia. LN and distant metastases occurred only in those with complex invasive patterns, but lung recurrence occurred in all subtypes, including MIAs

3. Kadota K et al. A nuclear grading system is a strong predictor of survival in epithelioid diffuse malignant pleural mesothelioma. Mod Pathol 2012;25:260-71

Purpose: To investigate prognostic utility of nuclear features in pleural epithelioid mesothelioma

Methods: 232 patients in MSK Cancer Center between 1989-2009 were studied.
- Clinical variables: age, gender, laterality, TNM stage (based on imaging and surgeon’s intraoperative findings and pathologic evaluation using the 6th edition AJCC manual), surgical procedure
- Pathologic dx: histologic, histochemical and immunohistochemical criteria
- Histologic evaluation: for nuclear features, 1) nuclear atypia, 2) nuclear/cytoplasmic ratio, 3) chromatin pattern, 4) intranuclear inclusion, 5) prominence of nucleoli, 6) mitotic count
Results:
-Demographic and procedures: 232 pts, median age 64 yrs (29-85), 72% males, stage I 6%, II 23%, III 56, IV 15%; extrapleural pneumonectomy 50%, pleurectomy-decortication 39%, other procedures 11%; lymphatic invasion 44%, vascular invasion in 23%
-Median overall survival: 16 mos, with a 2-yr OS of 34% and 5-yr OS of 11%; older age (>65), right -sided ds, higher T stage (T3-4) and advanced stage (III-IV), lymphatic and vascular invasion were associated with worse survival on univariate analyses
-Nuclear features and their association with OS: 5 of 7 were significant predictors on univariate analyses- nuclear atypia, chromatin, prominence of nucleoli, mitotic count, atypical mitoses.
-On multivariate analysis nuclear atypia and mitotic count were independent prognostic factors, on which they devised a nuclear grading system: nuclear atypia score 1-mild, 2-moderate, 3-severe; mitoses 1-low (0-1/10 HPF), 2-intermediate (2-4), 3-high (≥5); in each case, total score from the sum of the two parameter scores, ranging from 2 to 6; and then simplified the system into a three-tier grade: grade I (score sum 2, 3), II (4, 5), and III (6).
-Patients with nuclear grade III (n=34) with median OS 5 months; grade II (n=91, 14 months), and grade I (n=107, 28 months), with significant difference between each grade; grades I vs. II, p <0.001, grade II vs. III, p=0.001). these observations replicated in a cohort of 68 early stage pts (stage I-II) and in 130 stage III pts (both p<0.001)
-Nuclear grade was a strong independent predictor or worse OS on multivariate analysis including all factors found to be prognostic
-Association between nuclear grade and time to recurrence
-Association between nuclear features and clinicopathologic factors: nuclear atypia with lymphatic invasion, vascular invasion and increased T stage; high mitotic counts with lymphatic invasion, LN mets, advanced stage. high nuclear grade with male gender, lymphatic invasion, vascular invasion, advanced stage and tendency for higher T stage and LN mets
-MIB-index is associated with nuclear grade and prognosis

Conclusions/take home points: one more thing to grade in epithelioid mm. interobserver variability and reproducibility are still issues in the application


Purpose: Authors hypothesized circulating pathogenic antibodies in idiopathic pulmonary hypertension (IPAH) pts might be generated in tertiary or ectopic lymphoid tissue in the lung. To assess the frequency of tertiary lymphoid tissue (tLT) in IPAH lungs, with comparison to control subjects and flow-induced PAH in pts with Eisenmenger syndrome and to identify local mechanisms responsible for their formation, perpetuation and function

Methods:
-Dx and classification of PAH by right heart catheterization
Lung tissue for pulmonary tLT quantification: explanted lungs from IPAH (n=21) and Eisenmenger synd (n=5). 15 paraffin blocks of randomly chosen lung parenchyma sections; controls from 21 lobectomy specimens for cancers, lung parenchyma distal to the tumor. 2 blocks per pt; evaluated by 2 pathologists and results were expressed as tertiary follicles per cm² (tLT/cm²)

-IF on frozen tissue and real-time PCR for quantification of cytokines/chemokines and growth factors; some were done on IHC using paraffin sections
-Flowcytometry on circulating lymphocytes from peripheral blood samples for systemic mark of pulmonary lymphoid neogenesis

**Results:**

- Lymphocyte accumulation in highly organized lymphoid structures in the lung of patients with IPAH
- Lymphorganogenic chemokines are overexpressed in explanted IPAH lungs
- Pulmonary lymphorganogenic chemokines may impact on circulating lymphocytes
- Survival factors for lymphocytes are found in IPAH-associated pulmonary tLTs
- Molecular and cellular GC inducers are found in IPAH-associated tLTs
- Immunoglobulin class switching occurs in tLTs

Conclusions/take home points: There may be increased lymphoid neogenesis, with features of highly organized perivascular follicles in IPAH lungs, suggesting a specific immune-adaptive mechanism in the pathogenesis of IPAH. *But I don’t remember seeing these perivascular follicles in IPAH cases all that much...so, am not quite sure about this nice schematic diagram.*
Articles for Notation

Ordonez NG. Mesotheliomas with crystalloid structures: report of nine cases, including one with oncocytic features. Mod Pathol 25:272-81

Purpose: To provide a detailed ultrastructural description of nine epithelioid mesotheliomas containing abundant crystalloid inclusions, including one with oncocytic features.

Methods: An index case of mesothelioma showing intracytoplasmic crystalloids was noted and the author subsequently searched for these structures in 69 consecutive cases of mesothelioma (59 epithelioid, 7 sarcomatoid, 3 mixed-epithelioid sarcomatoid).

Results: Crystalloids were found in 9 of 59 (15%) epithelioid mesotheliomas. These inclusions were demonstrated in tumors exhibiting diverse histological patterns and were not confined to a single subtype of epithelioid mesothelioma, so when present it can assist in the subtyping. In addition, oncocytic features were also seen in one of the cases with crystalloid inclusions. Pathologists should be aware of the fact that even though uncommon mesotheliomas can present oncocytic morphology.

Conclusions/take home points: The crystalloid inclusions described in this study are not a rare finding in mesotheliomas, and because of their unique morphology, when present, they can serve as an ultrastructural marker of mesothelioma.


Purpose: To determine whether segmentectomy and lobectomy make any differences in survival and local recurrence in stage IA NSCLC by the new 7th edition AJCC stratification.

Methods: A retrospective review of 429 pts (2002-9) undergoing resection of pathologically confirmed stage IA NSCLC via lobectomy or segmentectomy. Primary outcome variables included mortality, recurrence, and survival. Recurrence-free and cancer-specific survival were estimated using the Kaplan-Meier method.

Results: No difference in mortality, recurrence rates, or 5 year cancer specific survival when comparing segmentectomy and lobectomy for pathologic stage 1A NSCLC when stratified by T stage.

Conclusions/take home points: Segmentectomy may achieve equivalent survival compared with lobectomy for pts with stage IA NSCLC.

Purpose: Report of 7 cases to describe the clinicopathologic, immunophenotypic and genetic features

Methods: Retrospective review in a single institution (1990-2010) for thymic epithelial tumor and 7 cases were identified. Clinical findings, stage by Masaoka, IHC (23 Ab's), CGH (n=4), and EBV ISH using EBER

Results: Ages 36-61 yrs, 5F 2M, none had myasthenia gravis, all Masaoka stage I and underwent a complete resection without adjuvant therapy. all survived in f/u ranging 11-172 mos (mean 81.7). tumor size 5-14cm (mean 8), epithelial mesenchymal transition with loss of E-cadherin expression. EBV ISH is negative in all cases. No genetic alteration on CGH

Conclusions/take home points: This tumors follow a benign clinical course and all survived with surgery alone


Purpose: To provide basis for a grading approach with mitoses and Ki-67 proliferations and also to define suitable diagnostic markers and to screen for putative therapeutic markers

Methods/Results: 200 resected pulm carcinoids (PC) specimens in a single institution (1986-2008), reclassified with 2004 WHO criteria as TC and AC
- Clinical data-age, sex, age at primary tumor surgery, location, LN/distant mets, overall survival, tumor recurrence, cause of death collected in 193 pts
- IHC with CD56, CD57, CD99, CD117, TTF1, synaptophysin, chromogranin, CK18, KL-1, EGFR, HER2, somatostatin receptor subtype 2A (SSTR2A), thymidylate synthetase, ERCC-1 using TMA (2 cores in the area with >50% tumor cells); ki-67 on full slide section for mean and maximum (hot spot) proliferation index (PI) in each tumor
- TC 57%, AC 43%; mean mitoses in TC 0.7 (SD 0.5, range ≤1) and AC 2.7 (SD 1.5, range 2-10). 22.1% of AC showed focal necrosis. 55 of 86 AC show only 2 mitoses, six of these with necrosis (did not indicate how they chose the fields for mitotic counting). Ki-67 index, at least 100 cells/HPF were manually counted in 4 different regions by 2 pathologists using double head scope (i.e. at least 400 cells counted), then max PI determined in the areas with the highest numbers of Ki-67 stained cells- (not entirely clear if they chose the highest % from 4 spots or what...)
- Applied grading system for GI neuroendocrine tumor: G1 (<2 mitoses per 2 mm² and/or Ki-67 index <2% 2 mm²) and G2 (2-20 mitoses per 2 mm² and Ki67 index 3-20%); mitoses count 11 or higher will not be technically AC on WHO criteria and not sure what they do about it...
- Positive phenotyping of PC: SSTR2A and EGFR may be used for therapeutic approaches in progressive PC

Conclusions/take home points: They concluded that using the GI grading system is superior to the current WHO TC/AC classification. Also, Ki-67 index in addition to mitotic count may improve prediction of the biological behavior of PC. Not entirely sure if they proved that point with their results, however.

Purpose: To describe the clinical radiologic and pathologic characteristics of pts with DIPNECH and the effect of various therapeutic modalities on patient well being

Methods: A retrospective review of 11 consecutive pt with DPNECH followed at 2 referral centers in Israel during a 10-year period (2000-10)

Results: All were women, mean age 62.8, all Caucasi ans, greatest tumor size 19.4 ± 9.6 mm, pulm sx in 6 (55%), all had bilateral diseases, previous malignancy in 3 (27%)-breast ca, endometrial adenoca, papillary thyroid ca, each. In 10 pts, at least 1 carcinoid tumor was present (1.2-2.4cm) with multiple tumorlets. In 1 pt, multiple carcinoid tumors present. In 3 (27%), metastasis was seen-ipsilateral hilar LN in 2 and let adrenal in 1; PET CT at dx shows high uptake in the largest lesions in 10 of 11 (91%). In 1, intitial octroscan was negative but a repeat scan after 4 yrs revealed uptake by the largest lesion with a size increase. PFT with obstructive pattern with mean FEV1 63.5% and with moderate to severe degree in 4 of 9 (44%); Ki67 was <5% in 7 of 11 who had data available. Low-grade, TC in 8 (73%) based on Ki-67 index and/or lack of signs of invasiveness; in other 3 (27%), intermediate grade, AC as result of metastatic involvement of the regional LNs and 1 adrenal met (what criteria are these from??); all were alive at the end of F/U (mean 4.63 ± 2.04 yrs; ongoing)

Conclusions/take home points: The association of lung neuroendocrine tumor with multiple nodules in women who present with chronic cough and wheezing should raise suspicion for DIPNECH. Whenever possible, these patients should undergo surgical excision of the dominant lesion and somatostatin analogs may be considered for symptomatic or tumor control in pats with progressive disease

Vilmar A et al. RT-PCR versus immunohistochemistry for correlation and quantification of ERCC1, BRAC1, TUBB3 and RRM1 in NSCLC. Lung Cancer 2012;75:306-12

Purpose: To find the most reliable method determine biomarker status relevant in treating advanced NSCLC pts, they evaluated predictive efficiency of qRT-PCR and IHC on ERCC-1, BRACA1, ribonucleotide reductase subunit M1 (RRM1) and class III β-tubulin (TUBB3) excision across complementation group.

ERCC-1: involved in DNA repair and may predict platinum sensitivity
BRCA1: a tumor suppressor gene. Loss of BRCA1 function leads to more sensitivity to cross linking agents like cisplatin in cell lines
RRM1: regulatory component of a key enzyme in DNA synthesis. Overexpression of RRM1 in cell lines leads to resistant to gemcitabine-based chemotherapy
TUBB3: involved in spindle-microtubule dynamics and high expression level is associated with paclitaxel resistance
Methods: A total of 261 out of 443 pts enrolled in LU2007 trial (chemotherapy naïve pt aged 18-75 yrs with histologically verified, inoperable NSCLC, performance status 0-2 and normal organ function) had sufficient bx material for IHC. For molecular study, they used surgically resected samples only that contain at least 90% viable tumor cells in order to perform macrodissection for mRNA extraction and optimal comparison. 33 pts met these criteria for parallel testing with IHC and qRT-PCR. The median values of the biomarker expression dichotomized the population and were correlated to clinical endpoints.

Results: Representative samples from 33 pts showed no significant correlations between mRNA and protein expression. Predictive impact was demonstrated for all four biomarkers by IHC, and reached significance for OS in pts with ERCC-1 negative and TUBB3-negative tumors, but not by RT-PCR.

Conclusions/take home points: IHC is superior to qRT-PCR as methodology for the predictive value of ERCC1, BRCA1, RRM1, and TUBB3 on optimal archival tissue samples from a subgroup of pts in an advanced NSCLC cohort. These findings are further supported by the lack of correlation between transcript and protein.


Purpose: To evaluate sensitivity and specificity of Napsin A as an alternative marker for primary lung adenoca, they compared Napsin A vs. TTF1 in the typing of primary lung ca and dx of primary lung adenoca from ca from other sites.

Methods: IHC on TMA of 1674 cases; 303 lung adenoca, 200 primary squamous ca, 52 lung small cell ca, kidney ca, thyroid ca, biliary ca, bladder ca, breast ca, coln ca, live, ovary, pancreas, prostate, stomach, uterus; negative, weak positive, and strong positive.

Results: In lung adenoca, Napsin A is more sensitive than TTF 1 (87% vs. 64%), and more specific than TTF-1 for primary lung Adeno vs. al; tumors excluding kidney, independent of tumor type (it seems unfair for TTF1 if they did not exclude small cell and thyroid ca in the calculation as they did kidney tumors for Napsin..)

Conclusions/take home points: Napsin might be useful in certain situations and complementary but I am not entirely sure it is any better than TTF1 other than for those TTF-1 negative lung adenoca. Their Table 1 seems to be useful since it includes a lot of cases from all important primary sites as a “immunoquery” type of compiled database. Of note, all TTF-1 positive lung adenoca seems to be also Napsin positive, and thus we need not to do Napsin for TTF1 positive tumors. It seems that what is not reflected in all those numbers is whether the cases that requires IHC, not those straightforward ones that we really do not need any stain, can be helped by Napsin stain.

Purpose: To find the most cost-effective panel to distinguish lung adenoca and sq cell ca

Methods: A total of 291 lung cancers diagnosed as 197 adeno, 66 sq cell, 28 unclassifiable on morphology (these 28 cases were not included) were stained with an IHC panel composed of napsin A, CK5/6, p63, TTF1 on TMA.

Results: Napsin A and p63 combination gave specificity of 94% and a sensitivity of 96% for distinguishing adenoca from sq cell ca

Conclusions/take home points: A combination of p63 and Napsin is the most cost-effective panel for small bx in D.dx of lung adenoca vs. squamous cell ca in this study. Again a factor that all those number may not reflect should be considered: how useful it will when IHC is really needed!

Popat S et al. ALK translocation is associated with ALK immunoreactivity and extensive signet-ring morphology in primary lung adenocarcinoma. Lung Cancer 2012;75:300-5

Purpose: To characterize the predictive utility of tumor morphology and ALK IHC to identify ALK rearrangement as a screening strategy, in a primary lung adenoca enriched for signet ring cell (SRC) morphology

Methods: 7 adenoca with SRC morphology and compared with 11 adenoca without signet ring features over the same time period. ALK IHC (Dako, ALK-1), using detection system Envision™ FLEX/HRP, SM802), IHC scored 0-3+ by two pathologists as for evaluation of adenoca subtype; FISH with vysis probe

Results: 2 excision specimens with pure SRC morphology and solid pattern showed IHC2+ confirmed by FISH. The remaining cases were negative for both IHC and FISH

Conclusions/take home points: ALK rearrangement is strongly associated with ALK IHC and was seen only in tumors with pure SRC morphology, which can be used as good indicators.

Lampen-Sachar K et al. Correlation between tumor measurement on computed tomography and reseted specimen size in lung adenocarcinomas. Lung Cancer 2012;75:332-5

Purpose: to compare preop size of stage I and II lung adenoca as measure by CT and as assessed on gross pathology specimens

Methods: 47 pts included. Tumor contours were delineated using a semiautomated segmentation algorithm and adjusted based on a radiologist’s input. Based on the tumor perimeter, maximal in-
plane tumor diameter was calculated automatically. The largest single diameter from the pathology gross report was used for comparison with CT size.

Results: The mean largest diameter of the tumors at CT and pathology was 29.53 mm and 24.04 mm, respectively. There was a statistically significant difference between the mean CT measurement and mean path measurement of 5.49 mm (SD 9.08 mm, p<0.001 on a paired t test) or 18% (SD 28.2%).

Conclusions/take home points: There is a significant difference between the diameters by two methods. Now, the question is which one is more accurate or appropriate??


Purpose: To clarify the clonality status of multifocal lung adenocarcinomas based on the mutation patterns of EGFR and KRAS.

Methods: 82 multifocal lung adenocarcinomas (metachronous or synchronous) from 36 pts who underwent surgical resection. D.dx of multiple primary lung cancer (MPLC) vs. pulmonary metastasis (PM) was made by clinicopathologic evaluation according to the Martini and Melamed criteria. Genomic DNA from FFPE analyzed for EGFR and KRAS mutations. Clonality was ruled different if the primary tumor (largest for synchronous or the first for metachronous tumor) has a different pattern of EGFR or KRAS mutation from the secondary (smaller or later tumors), same if those are same, or not determined if there are no mutation in primary and secondary tumors or indefinite mutational status in either tumor. The survival time was estimated and the prognostic factors were evaluated for 31 synchronous tumors.

Results: EGFR and KRAS mutations were detected in 36 (44%) and 19 (23%) of the 82 tumors, respectively. EGFR mutations were random in 20 of 22 (91%) with at least one EGFR mutated tumor. KRAS mutations were random in 14 of 15 (93%). Combining the results for the EGFR and KRAS patterns, the clonality status of multifocal lung adenocarcinomas could be determined in 30 of 36 (83%). However, no statistically significant difference in the actuarial survival of the patient subgroups stratified according to the clonality status based on EGFR and KRAS mutation. In fact, those who had same clonality (i.e. PM) did better than those with different clonality (presumably MPLC) or indetermined groups. In a multivariate analysis, the D.dx of MPLC or PM according to Martini and Melamed’s criteria was the only significant prognostic factor.

Conclusions/take home points: A lot of issues...First of all, it is still not very clear if we can determine the clonality with these mutational status with two genes. It did not appear very sound to state that “combined mutation pattern analyses of EGFR and KRAS may be useful for making decisions regarding treatment strategies for patients with multifocal lung adenocarcinomas” in the Conclusions.

Purpose: To assess genetic abnormalities of EGFR, KRAS and ALK and to examine survival in genotype-specific subsets of never-smokers with non-small cell lung cancers in East Asians (Korean)

Methods: in a cohort of 229 never smokers with NSCLC, direct sequencing of EGFR (exon 18-21) and KRAS (codon 12 and 13) genes and FISH for ALK rearrangement.

Results: the frequency of EGFR mutations, ALK rearrangement, KRAS mutations, no mutations in any of the 3 genes was 48%, 8.3%, 3.5%, and 40.2%, respectively. All genetic abnormalities were mutually exclusive. Median PFS after tx with EGFR TKIs was 12.8 mos, 6.3 mos, 2.1 mos, 1.6 mos in pts with EGFR mutations, no mutations, KRAS mutations, and ALK rearrangement, respectively. OS also differed in each group.

Conclusions/take home points: data on 3 major oncogenic alterations in a cohort of East Asian never-smokers with NSCLC with expected results on the responsiveness to EGFR TKIs


Purpose: comparison of PNA mediated RT-PCR and direct sequencing in EGFR mutational analysis

Methods: 240 NSCLC cases were analysed for EGFR mutations in exons 18-21 using FFPE tissues.

Results: RT-PCR detected 83 and DNA sequencing detected 63 pts. Concordance between the two methods is good. The patients with EGFR mutation detected by RT-PCR alone responded to anti EGFR therapy similarly to those detected by both RT-PCR and DNA sequencing.

Conclusions/take home points: RT-PCR is a simpler and more sensitive method than direct DNA sequencing in clinical setting


Purpose: cost analysis between EGFR testing and first-like therapy with gefitinib for pts with activating mutations vs. conventional chemo without testing for EGFR followed by gefitinib as a second line therapy

Methods: a model using clinical and outcomes data from randomized clinical trials and social costs in Singapore cancer centers. Health effects were expressed as quality-adjusted life-years
Results: EGFR testing and first-line treatment with gefitinib are better with lower costs and greater effectiveness compared with standard care.
Conclusions/take home points: could be a new standard at least in Asia

**Review, Editorials, Case Reports**

A useful review mostly for the clinicians addressing the factors involved in decision thresholds and the probability of cancer for a reasonable balance between observation and surgery

Editorial on the 37-year retrosepecite cohort study of employees from the Chongqing asbestos plant, reminding that the asbestos disease epidemic is not over or decreasing but it has simply moved to other parts of the world like China, lest it is forgotten or overshadowed by other pressing conditions.

An exhaustive review on this disease for who wants an update

Though it was never caught on, Tuder et al has postulated that the endothelial cells in idiopathic pulmonary hypertension are clonal and thus analogous to a neoplasm. Now, he wrote an opinion in the blue journal and claimed abnormal cellular metabolism, notably of aerobic glycolysis and alterations in mitochondrial function are key elements in the pathogenesis, whatever that means…

A case report on presumed chronic sequelae in response to silicone infection for cosmetic reason in HIV patient. They speculate that HIV1 infected patients may be at risk for chronic progressive granulomatous pneumonitis due to silicone injection years after their procedure, likely owing ot shifting levels of cell-mediated immunity

**ter Heine R et al. Fatal interstitial lung disease associate with high erlotinib and metablolite levels. A case report and a review of the literature. Lung Cancer 2012;75:391-7**
A total of 19 cases of erlotinib associated ILD were found in the literature besides this case. Though not entirely clear, they claim that fatal interstitial lung disease may be a dose dependent toxicity of erlotinib therapy.

**Sing et al. Tumor of the heart in a young woman; a rare manifestation of Wegener granulomatosis. Hum Pathol 2012;43:289-92** Rare indeed