# Pulmonary Pathology Journal Club – Joanne Yi

**April 25, 2016 (March 2016 Articles)**

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## Articles for discussion

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</table>

## Article for notation

### Neoplastic

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<th>Page</th>
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</tr>
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<tbody>
<tr>
<td>16</td>
<td>Boland JM et al. AIS, MIA, and invasive pulmonary adenocarcinoma-analysis of interobserver agreement, survival, radiographic characteristics and gross pathology in 296 nodules. <em>Hum Pathol</em> 2016;51:41-50</td>
</tr>
</tbody>
</table>

Page 18  Li BT et al. HER2 amplification and HER2 mutation are distinct molecular targets in lung cancers. J Thorac Oncol 2016;11:414-9


Page 19  Steuer CE et al. Role of race in oncogenic driver prevalence and outcomes in lung adenocarcinoma: Results from the lung cancer mutation consortium. Cancer 2016;122:766-72


Non-neoplastic
Grunewals J et al. T-cell receptor-HLA-DRB1 associations suggest specific antigens in pulmonary sarcoidosis. Eur Repir J 2016;47:898-909


Case Reports


PPS 2015 Proceedings/Reviews, Abstracts

Smith ML. Update on pulmonary fibrosis. Not all fibrosis is created equally. Arch Pathol Lab Med 2016;140:221-9


**Articles for discussion**


**Background/ Purpose/ Methods:**

- SCLC used to be staged as either limited or extensive until AJCC 2009 7th edition recommended the TNM system based on analysis of the existing retrospective IASLC database.

- However, not all descriptors could be validated, which prompted the IASLC to launch a call for the collection of new data (Giroux DJ et al. The IASLC lung cancer staging project: data elements for the prospective project. JTO 2009;4:679-83). This call resulted in a new database of 77,156 evaluable patients diagnosed with lung cancer during 1999-2010, which was used to inform the 8th edition of the TNM classification of lung cancers scheduled to be published in 2016.

- This paper reports on the analysis of the clinical and pathological TNM staging for SCLC.

- Survival analyses were performed for clinically and pathologically staged SCLC patients in this database created by IASLC in the revision of 7th edition.

- Prognosis with the proposed changes to the T descriptors in the 8th edition was compared with the prognosis according to the TNM staging in the 7th edition.

**Results:**

Table 1. Source of staging and type of database submissions

<table>
<thead>
<tr>
<th>Type of Database Submission</th>
<th>Available TNM Staging</th>
<th>Geographic Region</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clinical TNM</td>
<td>Pathological TNM</td>
<td>Clinical and Pathological TNM</td>
</tr>
<tr>
<td>Consortium</td>
<td>1688</td>
<td>97</td>
<td>417</td>
</tr>
<tr>
<td>Registry</td>
<td>2645</td>
<td>46</td>
<td>7</td>
</tr>
<tr>
<td>Series</td>
<td>87</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>4420</td>
<td>154</td>
<td>428</td>
</tr>
</tbody>
</table>
Summary of the proposed changes to T categories for NSCLC (and SCLC):

<table>
<thead>
<tr>
<th></th>
<th>7th edition</th>
<th>Changes in 8th edition</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>T1a: ≤ 2 cm</td>
<td>T1a: ≤ 1 cm</td>
</tr>
<tr>
<td></td>
<td>T1b: &gt; 2 - ≤ 3 cm</td>
<td>T1b: &gt; 1 - ≤ 2 cm</td>
</tr>
<tr>
<td></td>
<td>Both without bronchoscopy evidence of invasion more proximal than the lobar bronchus</td>
<td>T1c: &gt; 2 - ≤ 3 cm</td>
</tr>
<tr>
<td></td>
<td>superficial spreading tumor of any size with invasive component limited to the bronchial wall, which may extend proximally to the main bronchus is T1a</td>
<td>(Any end bronchial location becomes T2)</td>
</tr>
<tr>
<td>T2</td>
<td>T2a: &gt; 3 - ≤ 5 cm</td>
<td>Endobronchial location regardless of distance from carina</td>
</tr>
<tr>
<td></td>
<td>T2b: &gt; 5 - ≤ 7 cm</td>
<td>T2a: &gt; 3 - ≤ 4 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T2b: &gt; 4 - ≥ 5 cm</td>
</tr>
<tr>
<td>T3</td>
<td>&gt; 7 cm</td>
<td>&gt; 5 - ≥ 7 cm</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size invading any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body carina, or tumor of any size with separate tumor nodule(s) in a different lobe of ipsilateral lung</td>
<td>&gt; 7 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tumors with diaphragmatic involvement</td>
</tr>
</tbody>
</table>
Figure 4. Survival according to (A) 7th clinical T categories and (B) proposed 8th edition clinical T categories in the subset of cases where tumor descriptor data were sufficient to classify according to the proposed 8th edition. c, clinical; N, number; MST, median survival time

- Proposed changes to TNM stage:
  - T1N0M0 subdivided to stage IA1, 2, 3
  - T1a, 1b or 2aN1M0: from IIA to IIB
  - T3N2M0: from IIIA to IIIB
  - T3 or T4N3M0: from IIIB to a new category IIIC
  - stage IV subdivided based on whether or not there is distant disease at multiple sites

- assessment of pathological T2 descriptors- visceral pleural invasion: data show no significant difference between PL0, PL1, or PL2, independent of T category

**Take home points:** This study confirms the prognostic value of clinical and pathological TNM staging in patients with SCLC. Accordingly, the revised TNM staging for lung cancers in the 8th edition will be applied to SCLC as well as to NSCLC

Background: No morphological classifiers have been established for use in routine diagnostic practice of lung SQCC. A previous study by Kadota et al (JTO 2014;9:1126-39) reported that tumor budding and single cell invasion were independent prognostic factors for overall survival in lung SQCC. This study provides a validation of the previous study and proposed a grading system for SQCC using these two parameters.

Methods:

• Study cohort: 541 SQCCs that were completely resected during 2002-10 at the Thoraxklinik Heidelberg (6 wedge resection, 7 segmentectomy, 360 lobectomy, 23 bilobectomy and 145 pneumonectomy). None had neoadjuvant therapy. 442 men, 99 women, mean age at dx 64.8 yrs (range 38.2-82). 112 pts (20.7%) had adjuvant chemo and 68 (12.6%) had radiation. 180 (33.3%) pts died during f/u and 162 (29.9%) relapsed. Mean f/u at the end-point of analysis was 40.8 mos. Mean f/u of pt without recurrence at the end-point was 37.1 mos.

• Histologic evaluation: HE slides were reviewed by two experienced pathologists following the criteria by Kadota et al. SQCCs were subclassified as nonkeratinising, keratinising or basaoid type according to 2015 WHO classification. Tumor budding and the size of the smallest tumor nest were assessed at the areas showing the most extensive budding activity and the maximal number of small tumor nests.

  o tumor budding was defined as small tumor nests composed of <5 cells separately analysed in one HPF (x400) with the highest number of budding and as total budding in 10 HPFs) which "branch" away from larger nests and "bud" into the adjacent parenchyma (supplementary figure S1).

  o tumor cell nest was defined as a cluster of tumor cells surrounded by tumor stroma. the size of the smallest invasive tumor nest was classified as large (>15), intermediate (5-15), small (2-4) and single cell invasion. The size of the smallest tumor nest was assessed in two categories: 1) the smallest tumor nest in the entire sampled tumor area and 2) the smallest tumor nest at the invasion front

  o tumor stromal content was categorized as low (≤25% of whole tumor area, modest (26-50%) or high (>50%).

  o nuclear diameter: tumor areas with the largest nuclei. the average nuclear diameter of at least 100 tumor cells using nearby small lymphocytes as reference. small nuclei were defined as having a diameter of 3 lymphocytes or less, intermediate --~4 and large nuclei as measuring more than 4 lymphocytes.
### Results: (Modified) TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Events: overall survival</th>
<th>Overall survival months</th>
<th>p-value</th>
<th>Events: DFS</th>
<th>DFS months</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects</strong></td>
<td>541</td>
<td>180</td>
<td>69.3±2.4</td>
<td></td>
<td>162</td>
<td>72.5±2.5</td>
<td></td>
</tr>
<tr>
<td><strong>Histological subtype</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonkeratinising</td>
<td>344</td>
<td>102</td>
<td>71.5±3.1</td>
<td>0.037</td>
<td>94</td>
<td>75.1±3.2</td>
<td>0.340</td>
</tr>
<tr>
<td>Keratinising</td>
<td>178</td>
<td>74</td>
<td>62.1±3.8</td>
<td></td>
<td>61</td>
<td>65.8±4.1</td>
<td></td>
</tr>
<tr>
<td>Basaloid</td>
<td>18</td>
<td>4</td>
<td>68.8±6.9</td>
<td></td>
<td>7</td>
<td>55.7±8.5</td>
<td></td>
</tr>
<tr>
<td><strong>Budding (per HPF)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>356</td>
<td>93</td>
<td>77.0±3.1</td>
<td>&lt;0.001</td>
<td>102</td>
<td>73.4±3.1</td>
<td>0.527</td>
</tr>
<tr>
<td>&lt;5</td>
<td>163</td>
<td>72</td>
<td>59.0±4.0</td>
<td></td>
<td>51</td>
<td>68.4±4.4</td>
<td></td>
</tr>
<tr>
<td>≥5</td>
<td>22</td>
<td>15</td>
<td>52.5±8.6</td>
<td></td>
<td>9</td>
<td>60.9±10.0</td>
<td></td>
</tr>
<tr>
<td><strong>Budding (per 10 HPFs)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>356</td>
<td>93</td>
<td>77.0±3.1</td>
<td>&lt;0.001</td>
<td>102</td>
<td>73.7±3.1</td>
<td>0.053</td>
</tr>
<tr>
<td>&lt;15</td>
<td>101</td>
<td>41</td>
<td>63.3±5.0</td>
<td></td>
<td>27</td>
<td>74.1±5.3</td>
<td></td>
</tr>
<tr>
<td>≥15</td>
<td>84</td>
<td>46</td>
<td>50.2±4.8</td>
<td></td>
<td>33</td>
<td>57.8±5.5</td>
<td></td>
</tr>
<tr>
<td><strong>Smallest tumour cell nest (overall)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single cells</td>
<td>92</td>
<td>45</td>
<td>53.5±4.5</td>
<td></td>
<td>32</td>
<td>62.4±4.9</td>
<td></td>
</tr>
<tr>
<td>&lt;5 cells</td>
<td>166</td>
<td>64</td>
<td>62.1±3.8</td>
<td>0.001</td>
<td>55</td>
<td>66.9±4.4</td>
<td>0.383</td>
</tr>
<tr>
<td>5–15 cells</td>
<td>114</td>
<td>33</td>
<td>77.2±4.9</td>
<td></td>
<td>30</td>
<td>77.9±5.0</td>
<td></td>
</tr>
<tr>
<td>&gt;15 cells</td>
<td>166</td>
<td>38</td>
<td>78.0±3.9</td>
<td></td>
<td>45</td>
<td>71.3±4.3</td>
<td></td>
</tr>
<tr>
<td><strong>Smallest tumour cell nest (invasive margin)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single cells</td>
<td>97</td>
<td>48</td>
<td>55.0±4.6</td>
<td></td>
<td>35</td>
<td>61.7±5.0</td>
<td></td>
</tr>
</tbody>
</table>
### Morphologic feature

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumour budding</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>No budding in 10 HPFs</td>
</tr>
<tr>
<td>2</td>
<td>&lt;15 budding foci per 10 HPFs</td>
</tr>
<tr>
<td>3</td>
<td>≥15 budding foci per 10 HPFs</td>
</tr>
<tr>
<td><strong>Tumour nest size</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>&gt;15 cells (large nest size)</td>
</tr>
<tr>
<td>2</td>
<td>5–15 cells (intermediate nest size)</td>
</tr>
<tr>
<td>3</td>
<td>&lt;5 (or 2–4) cells (small nest size)</td>
</tr>
<tr>
<td>4</td>
<td>Single cell invasion</td>
</tr>
<tr>
<td><strong>Combined score</strong></td>
<td></td>
</tr>
<tr>
<td>2–3</td>
<td>Grade 1 (well differentiated)</td>
</tr>
<tr>
<td>4–6</td>
<td>Grade 2 (moderately differentiated)</td>
</tr>
<tr>
<td>7</td>
<td>Grade 3 (poorly differentiated)</td>
</tr>
</tbody>
</table>

- grading of lung SQCC: a combined grading scheme using the two most significant prognostic markers tumor budding and nest size resulted in an age-, stage, and sex-independent prognosticator for overall survival

- **Take home points:**

Background:

- Although histology and imaging have provided descriptive information, a through morphometric analysis of end-stage CF lung is lacking.

- This study quantified the involvement of small and large airways in end-stage CF. The resolution of current in vivo imaging does not allow the study of the small airways. Recently, the development of micro-CT has allowed high resolution imaging and three-dimensional viewing of the peripheral airways down to the level of the terminal bronchioles and alveoli.

- They used combined techniques of multidetector CT (MDCT) and micro CT to measure, count, and describe the airway and parenchymal abnormalities in end stage CF lungs. The abnormalities detected by these imaging techniques were correlated with histology sections.

Methods:

- Patients: 11 patients with CF who underwent lung transplantation at a university hospital in Belgium during 2010-12. Baseline characteristics from patient clinical files. Last available results of spirometry and plethysmography, preop chest CT scans were evaluated in random order with a CF-CT score, a validated upgraded version of Brody II score and the severely advanced lung ds (SALD) score

- Controls: 7 unused donor lungs

- Preparation of lungs for MDCT and micro-CT: the lungs were air-inflated to total lung capacity, frozen solid in the fumes of liquid nitrogen, and scanned with MDCT according to a previously reported protocol. After MDCT scanning, the lungs were cut in 2 cm thick slices. from each slice, cores with a diameter of 1.4cm were excised and processed for micro-CT scanning

Multidetector computed tomography (MDCT): a form of CT technology for diagnostic imaging. In MDCT, a two-dimensional array of detector elements replaces the linear array of detector elements used in typical conventional and helical CT scanners. The two-dimensional detector array permits CT scanners to acquire multiple slices or sections simultaneously and greatly increase the speed of CT image acquisition. Image reconstruction in MDCT is more complicated than that in single section CT. Nonetheless, the development of MDCT has resulted in the development of high resolution CT. from Wikipedia
- Histology: selected cores with specific features of interest on micro-CT (e.g. obstruction) were processed for histologic analysis

- MDCT scan analysis: The number of airways was calculated from the number of bifurcations. The diameter of each airway segment measured at the level of the most pronounced dilatation. Airway obstructions were defined as complete loss of the airway lumen, with no visible reopening of the lumen downstream of the obstruction

- Micro-CT scan analysis:
  - The numbers of terminal bronchioles (TBs) per mL of tissue were counted and the diameter/cross-sectional area of each TB was measured at their most distal point before evolution to RBs.
  - The parenchyma of CF lung cores and control lungs was compared and described in a qualitative way.
  - The mean linear intercept quantitation: the mean distance between alveolar walls as a measure of emphysema and parenchymal volume (tissue%) as a measure of fibrosis,
  - The patency of TBs and more proximal airways present in the micro-CT core was explored by following their paths through the core. The data were expressed as median (interquartile range).

Results:

- Pretransplant lung function in CF patients showed very severe airway obstruction (low FEV1 and FEV1/FVC) and air trapping as indicated by high residual volume

- CF lungs had smaller volumes but heavier (i.e. higher density)

- MDCT: CF lungs showed an increased median number (631[511-710] vs. 344 [277-349]; p=0.003) and size of visible airways (cumulative airway diameter 217cm [209-250] vs. 91cm [80-15]; p < 0.001) than control lungs. Airway obstruction started from generation 6 and increased to 40-50% of airway from generation 9 onward.

- Micro-CT: ~9 cores/lung were analyzed, 100 cores from CF and 67 cores from control
  - Decreased total number of TBs (2.9/ml [2.6-4.4] vs. 5.3 /ml [4.8-5.7]; p < 0.001)
  - 49% with obstruction and reduced cross-sectional area of the open TBs (0.093 mm2 [0.084-0.123] vs. 0.179 mm2 [0.140-0.196]; p < 0.001)
41% of obstructed airway reopened more distally; median length of obstructed segment was 1.81 mm.

- Matched histologic examination showed airway wall thickening and mucus plugging. Neoangiogenesis in the destroyed airway wall and replacement of obstructed lumen by granulation tissue. CF lungs show emphysema with fibrosis around bronchiecatic lesions, zones of scarring and atelectasis around bronchioles.

Discussion:
- There is a wide variability between patients in the findings on HRCT, reflecting the predominance of large bronchiectasis with pronounced destruction in some patients, and hyperinflation with small airways obstruction in other patients. Micro-CT allowed the study of the TBs, where dramatic reduction of the number of TBs and especially open TBs; the gateways to the lung acini where oxygenation takes place was more than halved compared with control lungs.

Take home points: In end stage CF lung, a marked reduction in the number and size of TBs as well as the extensive airway dilatation and obstruction involving the larger airways.


Background:
- PCD: an autosomal recessive disorder of dysfunctional respiratory cilia with a broad spectrum of ciliary defects.
- > 250 proteins involved in cilia structure alone with additional proteins in assembly and transport.
- Current diagnostic modalities individually examine specific aspects of ciliary structure or function. The sensitivity, specificity and accuracy inherent to each test vary widely and testing in multimodal fashion is often required.
- Currently used modalities: transmission electron microscopy (TEM) of cilia, nasal nitric oxide (nNO) measurement, IF testing for certain protein, genetic testing and high-speed video microscopy analysis (HSVMA).
- HSVMA protocols for PCD dx have been established at specialized centers in Europe but not in routine use in North America. Currently, dx of PCD lacks a gold standard test and is
therefore based on combinations of TEM, nNO, HSVMA and other tests. There are few published data on the accuracy of this approach.

Methods:

- Prospectively collected data from 654 patients referred for PCD diagnostics were analyzed for sensitivity and specificity for individual and combination testing strategies. Not all patients underwent all tests.

- Data were reviewed a multidisciplinary team meetings, attended by a clinician, an HSVMA microscopist, and a TEM microscopist. All clinical and diagnostic data were considered when agreeing the diagnostic outcome as PCD-positive, PCD-negative or inconclusive.

- Positive dx: typical clinical hx, usually with at least two abnormal diagnostic tests (TEM, HSVMA and nNO), but in patients with a strong hx (e.g. sibling with PCD or full clinical phenotype, such as neonatal respiratory distress at term followed by daily wet cough, persistent rhinitis and glue ear, often associated with episodes of upper and lower resp tract infection). Occasionally, positive dx was based on "hallmark" TEM or repeated HSVMA consistent with PCD. Ciliary beat pattern (CBP) was considered positive if the pattern was typical of PCD rather than secondary ciliary dyskinesia, determined either from two brushing biopsies or from one brushing with reanalysis following air liquid interface (ALI) culture.

- Negative dx: (1) HSVMA with or without TEM was normal or (2) HSVMA and TEM abnormalities were consistent with secondary rather than primary dyskinesia and normal nNO (if available)

- Valid-inconclusive dx: on repeated testing, adequate samples had subtle abnormalities not "classical" for PCD but outside the range of their experience of secondary defects; these patients might have subtle or rare variants of ciliary phenotype. Patients were therefore told that the dx was equivocal, with the recommendation that they received appropriate treatment (e.g. airway clearance or tx of exacerbations). They were investigated for other causes of their symptoms (e.g. CF genotype and immunology) and were kept under review for further testing as new tests become available (e.g. new PCD-associated mutations).

- Invalid-inconclusive dx: If TEM and HSVMA were inconclusive due to inadequate samples, (e.g. sparse cilia) and repeat testing was done. Patients with normal TEM in isolation were considered invalid-inconclusive, since TEM misses 20-30% of PCD cases. Patients with nNO < 30 nL/min were deemed likely to have PCD but it was not accepted as a lone diagnostic test.
Results:

- HSVMA has excellent sensitivity and specificity at 100% and 93%, respectively.
- TEM was 100% specific but 21% of PCD pts had normal ultrastructure.
- nNO with 30 nL/min as cut-off had 91% sensitivity and 96% specificity.
- Simultaneous testing using HSVMA and TEM was 100% sensitive and 92% specific.

Discussion: This is a large cross-sectional study with a prospectively collected outcome data following a comprehensive range of PCD diagnostic tests. The lack of a gold reference standard was the major limitation and they had to use a surrogate standard of expert multidisciplinary consensus.

Take home points: Combination testing is a better approach for diagnosing PCD.

Article for notation

Neoplastic
AIS, MIA, and invasive pulmonary adenocarcinoma—analysis of interobserver agreement, survival, radiographic characteristics and gross pathology in 296 nodules. Boland JM et al. Hum Pathol 2016;51:41-50

Summary: 296 surgically resected pulmonary ADCs from 254 patients during 1997 - 2009 were independently reviewed by 2 observers. Each tumor was categorized as AIS, MIA or IA. Of 296 nodules, 244 (82.4%) were agreed upon by both observers: 10 AIS, 61 MIA, and 173 IA ($\kappa = 0.63$, good agreement). However, there was disagreement between AIS and MIA in 6 cases (2%), between MIA and IA in 45 cases (15%), and between AIS and IA in 1 case. OS was significantly different among categories as determined by both observers. Cases with disagreement between MIA and IA had similar survival to agreed MIA. DSS at 10 years was 100% for AIS in both observers, 97.3 and 97.6% for MIA, although this did not reach statistical significance compared to IA for either observer.

Take home points: Good agreement was present between observers when classifying tumors as AIS, MIA and IA. However, there was still interobserver variability. Tumors with disagreement between MIA and IA had survival similar to agreed MIA, and thus, borderline cases can be confidently classified as MIA. Patients with AIS and MIA underwent excellent DSS, although the significance of this improved DSS compared to IA could not be definitely established.


Summary: From a database of ~3800 patients with diffuse malignant mesothelioma (DMM), 18 pts (0.5%) were found to have synchronous lung cancer (LC). The clinical features, occupational exposure hx and fiber burden analysis data were reviewed in these patients. Among the 18 pts (14M/4F; median age 68y, range 58-84), 11 (61%) had epithelioid, 5 (28%) biphasic, and 2 (11%) sarcomatoid DMM; 16 pleural, 2 peritoneal DMM. 12 (67%) cases had ADC, 5 SQCC, and 1 small cell ca. 3 of 18 had a hx of prior malignancy (1 with testicular seminoma and bladder ca; 2 with prostate ca). 15 had a smoking hx, 15 had documented asbestos exposure with histologic features of asbestosis in 3. Mineral analysis done in 8 patients, 4 of whom showed an elevated asbestos fiber burden; amosite in 4, crocidolite in 3, and non-commercial amphiboles in 5.

Take home points: The simultaneous occurrence of LC and DMM is rare (0.5%) in this large series of DMM and mostly as ADC and epithelial DMM, which can pose as a diagnostic challenge.

Summary: This study tested a new ALK antibody 1A4 (Origene, MD, USA) along with D5F3 (Ventana Medical Systems, Inc., AZ, USA) for the screening of 595 lung ADC cases via routine IHC system using FFPE tissues. Ventana detection system and FISH were used as reference methods. Among 595 cases, 1A4 was 3+ in 18, 2+ in 50, 1+ in 153 and 0 in 374 cases, while D5F3 was 3+ in 17, 2+ in 18, 1+ in 20, and 0 in 540 cases. A fully automated Ventana Benchmark XT System with the D5F3 antibody, the Obtiview DAB detection Kit, and the Optiview Amplification Kit, was used for Ventana detection system. 298 1A4 showed 100% concordance with ALK FISH. All 58 FISH+ cases were identified by 1A4 Ab. 14 and 5 cases were missed by D5F3 with routine IHC and Ventana system, respectively. Sensitivity was 100%, 75.9% and 91.4% by 1A4, D5F3 with routine IHC, and D5F3 with Ventana, respectively; Specificity was 70.3%, 99.8% and 100%.

Take home points: 1A4 Ab is more sensitive but less specific than the other two methods.


Summary: They compared two strategies for selecting neoantigens as targets for non-small cell lung cancer vaccines: (1) an “off-the-shelf” approach starting with shared mutations extracted from global database (2) a personalized pipeline using whole-exome sequencing data on each patient’s tumor. The Catalogue of somatic Mutations in Cancer database was used to create a list of shared missense mutation were compared: They assessed for predicted binding affinity to HLA alleles of 15 lung cancer patients and selected potential neoantigens for each patient. In the second approach, potential neoantigens were selected from missense mutations detected by whole-exome sequencing of the patient’s own samples. They found that only one or two off-the-shelf potential neoantigens were included in the set of personalized potential neoantigens, in only three patients. In the remaining 12 patients, there was no overlap.

Take home points: Use of an off-the-shelf pipeline is feasible but may not be satisfactory for most patients with NSCLC. They recommended identifying personal mutations by comprehensive genome sequencing for developing neoantigen-targeted cancer immunotherapies.

Summary: 13 SCLC cases with EGFR mutation have been documented in the literature; 7 never smokers, 5 smokers (2.5-67.5 pack years), 1 unknown. This paper reported additional 2 SCLC cases with EGFR mutation.

Case 1: 82M, 35 pack year smoker with combined small cell ca (adenoca + small cell). microdissected tumor from each component revealed a novel mutation in exon 21 resulting in an aspartate to histidine missense mutation in amino acid 855 (p.D855H) in both components, but not in the non-neoplastic lung tissue (i.e. not germ line). treated with cisplatin and etoposide chemotherapy, lost to clinical follow up

Case 2: 68F, never smoker. pure small cell ca with L858R EGFR mutation in exon 21. treated with several chemotherapy, eventually died with progression despite chemotherapy before the final results of molecular testing became available.

Take home points: Rarely, EGFR mutation occurs in SCLC and molecular testing might be justifiable in selected clinical situations.

**HER2 amplification and HER2 mutation are distinct molecular targets in lung cancers.** Li BT et al. J Thorac Oncol 2016;11:414-9

Summary: They studied HER2 gene amplification, HER2 mutation and HER2 protein overexpression in 175 cases of lung ADCs without prior targeted therapy from MSKCC and Univ of Colorado, by HER2 FISH for amplification, fragment analysis, mass spectrometry genotyping and Sanger sequencing for mutation and IHC for HER2 overexpression. HER2 amplification was detected in 5 of 175 (3%), HER2 mutation in 4 of 148 (3%); none of the HER2-mutant cases was amplified. HER2 overexpression (2+ or 3+) on IHC staining was not detected in the 25 specimens tested. Negative IHC correlated with negative amplification by FISH but no case tested for both HER2 IHC and HER2 mutation testing.

Take home points: HER2 mutation or amplification is a rare event in lung ADCs.

**Estimation of the pathological invasive size of pulmonary adenocarcinoma using high-resolution computed tomography of the chest: A consideration based on lung and mediastinal window settings.** Sakakura N et al. Lung Cancer 2016;95:51-6

Summary: The aim of this study was to determine whether HRCT could be used to preoperatively evaluate the invasive size of lung ADC. 360 resected cT1a, 1b, 2aN0 lung ADCs were examined for the correlation of pathological invasive size with 3 parameters including whole tumor dimension in the lung window (LD), consolidation dimension in the lung window
HRCT prediction of an invasive size of ≤ 5mm was determined using receiver operating characteristic curve analysis. Pathologic invasive size correlated well with both CD ($r^2=0.710$) and MD ($r^2=0.743$) comparably, and moderately with LD ($r^2=0.514$). CD and MD tend to be slightly larger and smaller, respectively, than the actual invasive size by pathological examination. Invasive size roughly approximated to MD + 3, and an invasive size of ≤ 5mm was best predicted by MD, followed by CD. MD of ≤ 2mm and 0mm predicted an invasive size of ≤ 5mm with 64.1 and 47.4% sensitivity and 96.5% and 98.9% specificity, respectively.

Take home points: Preoperative estimation of the invasive size of lung ADC was possible by MD. This approach parallels another study using radiology based technique Computer-Aided Nodule Assessment and Risk Yield (CANARY) developed at Mayo (Maldonado F et al. Am J Respir Crit Care Med 2015;192:737-44)

Role of race in oncogenic driver prevalence and outcomes in lung adenocarcinoma: Results from the lung cancer mutation consortium. Steuer CE et al. Cancer 2016;122:766-72

Summary: The lung Cancer Mutation Consortium 1 (LVMC1) database was investigated to evaluate the frequency and impact of oncogenic drivers in lung ADCs in the racial/ethnic minority patient population. Patients with metastatic lung ADCs from 14 US sites were enrolled in the LCMC1. Tumor samples were collected from 2009 to 2012 with multiplex genotyping performed on 10 oncogenic drivers (Kras, EGFR, ALK rearrangement, ERBB2, BRAF, PIK3CA, MET amplification, NRAS, MEK1 and AKT1). Patients were classified as white (n=838), Asian (n=48), African American (AA) (n=60), or Latinos (n=28). Asian patients had the highest rate of oncogenic drivers with 81% (n=39), followed by Latinos with 68% (n=19), white with 61% (n=511), and AA with 53% (n=32). There were no significant differences in overall survival.

Take home points: Differences were observed in the prevalence of oncogenic drivers in lung ADC and subsequent treatment among racial groups. The lowest frequency of drivers was seen for African American patients. However, more than half of AA patients still had a driver and those treated with targeted therapy had outcomes similar to those of other races.


Summary: SCLC is extremely rare in never-smokers; ~2.5% of SLCL cases were never-smokers according to a USA study. Risk factors for SCLC in never-smokers are completely unknown. Also, little is known about age at onset, gender distribution, and stage at diagnosis (limited or extended disease) in these patients. Information is scarce on the role that residential
radon might play in the genesis of SCLC in never-smokers. This study aimed to describe the characteristics of a case-series of never-smoking SCLC patients from the Lung Cancer Risk in Never Smokers Study (LCRINS study), a study performed in the northwest of Spain, which is a radon-prone area. This is a prospective, multicenter, hospital-based case-control study performed in Spain. Participants were never smokers older than 30 years with a confirmed dx of primary lung cancer. Clinical and epidemiological variables were collected according to the study’s protocol. 19 SCLC cases were recruited from a total of 322 never-smoking lung cancer cases (5.9%). 18 women (93.7%), median age 75 yrs, were identified. 10 cases had limited disease (confined to the thorax) and 9 had extended ds. Only 4 lived with a smoker during the last 20 yrs in the same dwelling. Most of the participants were housewives or performed agricultural activities. 4 had worked as cleaners. Median residential radon was 195 Bqm$^{-3}$ (as compared to 149 Bqm$^{-3}$ in never-smoking controls of the LCRINS study). Median survival was 242 days; 1- and 2-yr survivals were 36.8% and 17.6%, respectively.

**Take home points:** SCLC in never-smokers is infrequent, highly aggressive ds. Survival is poor, even for limited disease. Age at dx in SLCL is higher than that observed for never-smokers with ADC. Residential radon exposure is higher than the levels recommended by the WHO.

**Thymic epithelial tumor-associated cytopenia: A 10-year observational study in France.**

**Summary:** A multicenter, retrospective study of TET and associated forms of cytopenia from France. Cases collected by the French National Reference Center for Autoimmune Cytopenia and the French National Thymic Malignancy Interest Group and through a call for cases by the French Society of Internal Medicine. 36 cases were recorded during 2002-14 with a median f/u of 38 months. 32 had surgery for TET, 14 were in complete remission at last f/u. Cytopenia can occur before, simultaneously, or after dx of TET. Pure red cell aplasia and Good syndrome were the most common types, both at 30%. Good syndrome is seen in ~5% of TET and comprised of B lymphopenia, variable CD8 and CD4 T-cell counts, hypogammaglobulinemia, and susceptibility to infections. 11 had 2 or more bouts of cytopenia. 18 received steroid, with a complete response in 9. Infection developed in 84% of pts with Good syndrome, without apparent relation to immunosuppressive tx or chemotherapy. 8 died during the f/u period due to cytopenia in 2 and infections in 5.

**Take home points:** Optimal tx for cytopenia associated TET has not been established and the outcome did not correlate with TET progression in Good syndrome.

Summary: This study was to review the literature on 5 yr survival rates after lobectomy (L), the historic standard tx, and sublobar resection (SL) for patients with early-stage LC. The inclusion criteria include: 1) observational studies, 2) L compared to SL for early stage lung cancers, 3) radiographic staging by CT scan and 4) 5 year survival reported. A Medline search through Jan 2015 yielded 31 studies representing 23 distinct datasets. The absolute difference in 5 yr survival was calculated and plotted for each study. These studies comparing 5 ear survival rates of SL to L were too heterogeneous to carry out traditional meta-analysis.

Take home points: We still don’t know how SL does when compared against L and new approaches are needed.

Non-neoplastic


Summary: There have been many reports of resurgent progressive massive fibrosis and rapidly progressive pneumoconiosis (RPP) in US coal miners. The causes of this disease are not well understood. There have been no studies performed in which researchers evaluated the pathology underlying this severe and aggressive form of the ds. There are only reports of radiographic findings. Based on chest radiographs of miners from certain geographic regions with a high prevalence of RPP, these reports have shown a rising proportion of r-type pneumoconiotic opacities, suggesting increasing exposure to silica and silicates. However, this has not been confirmed pathologically. This study is the first in which lung pathology specimens were obtained from US coal miners with RPP. Three expert occupational pulmonary pathologists systematically evaluated the lung pathology, patterns of inflammation, fibrosis and retained mineral particles and compared findings with those from corresponding chest radiographs. They found that the lung pathology observed in these well-characterized cases of RPP in US coal miners had features of accelerated silicosis, mixed dust pneumoconiosis, and progressive massive fibrosis. Their findings suggest that exposures to respirable silica and silicate minerals play an important role in the pathogenesis of RPP. This evidence is consistent with prior reports of radiologic patterns associated with heavy exposure to silica. Prevention of this disease likely requires more stringent efforts to monitor and control exposure to coal mine dust that may contain high quantities of respirable silica and silicates.

Take home points: The lung pathology observed in 13 well characterized cases of RPP in US coal miners had features of accelerated silicosis, mixed dust pneumoconiosis, and PMF. RPP in
in US coal miners was associated with exposure to coal mine dust containing high concentrations of respirable silica and silicates.

**T-cell receptor-HLA-DRB1 associations suggest specific antigens in pulmonary sarcoidosis.**

**Summary:** Pulmonary sarcoidosis patients (n=43) underwent bronchoscopy with BAL. T-cell receptor α and β chains of CD4+ T-cells were analyzed by flow cytometry, DNA sequenced and 3-dimensional molecular models of T-cell receptor –HLA-DRB*03 complexes were generated. Accumulation of large clonal populations of specific Vα2.3/vβ22 T-cell receptor-expressing CD4+ T-cells in the lungs of HLA-DRB1*03+ sarcoidosis patients with several distinct points between Vα2.3/vβ22 T-cell receptor and HLA-DRB1*03+ molecules suggest presentation of prototypic vimentin-derived peptides.

**Take home points:** This study introduces a new concept in sarcoidosis as a mimicry-driven autoaggressive disorder.

**Intrapulmonary bronchopulmonary anastomoses and plexiform lesions in idiopathic pulmonary arterial hypertension.** Galambos C et al. Am J Respir Crit Care Med 2016;193:574-6

**Summary:** New thoughts about the origin of plexiform lesions. They say that a plexiform lesion is connected to the bronchial circulation and is in close proximity to an open bronchial artery-pulmonary artery anastomotic connection. Here are their fancy illustrations!
Case Reports


Summary: Germline DICER1 mutations predispose to a distinctive tumor predisposition syndrome, the DICER1 syndrome, which is associated with a spectrum of rare mainly childhood onset tumors, but later also included well differentiated fetal adenocarcinoma (WDFA). This is a case of 16-year-old girl who has WDFA with somatic DICER1 RNAse IIIb missense mutation. She also has a personal history consistent with the DICER1 syndrome: multinodular goiter at age 14, an ovarian Sertoli-Leydig cell tumor at age 16, each of which were found to harbor somatic DICER1 RNAse IIIb missense mutation. This case highlights two DICER1 “hits” in WDFA, a rare, previously-unrecognized manifestation of DICER 1 syndrome.
Organizing pneumonia induced by nivolumab in a patient with metastatic melanoma.

**Take home points:** GGO developed after use of 4 doses of nivolumab for metastatic melanoma and transbronchial bx with clinical correlation led to the dx of nivolumab induced organizing pneumonia. The clinical sx and radiographic abnormalities rapidly resolved after discontinuation of nivolumab. With the increasing use of immune checkpoint inhibitors will necessitate the establishment of a standard algorithm for early detection and intervention against common immune-related adverse events.


**Take home points:** Classification of NET with an intermediate grade may be difficult and may lead to different dx over time with different therapeutic tx implications. This study highlighted the potential pitfalls in the current WHO classification for pulmonary neuroendocrine cancers. Distinction between borderline cases for high-grade NET and atypical carcinoid can be extremely difficult as shown in their case.


**Take home points:** This case documented a pulmonary MALT lymphoma associated with pulmonary sarcoidosis in exactly the same location, as proven by IHC and Ig heavy-chain gene rearrangements for lymphoma dx and propionibacterium acnes-specific antibody reactions for sarcoidosis (though I am not sure it can prove the dx of sarcoidosis; this is in contrast to a study reviewed earlier that claimed it as a “mimicry-driven autoaggressive disorder” Grunewals J et al. Eur Repir J 2016;47:898-909). Anyhow, they also listed 8 previous cases of MALT lymphoma with sarcoidosis on literature review, though none of these cases had MALT lymphoma and sarcoidosis in the same location, unlike the current case that they reported.

PPS 2015 Proceedings: Excellent reviews and interesting abstracts
Update on pulmonary fibrosis. Not all fibrosis is created equally. Smith ML. Arch Pathol Lab Med 2016;140:221-9
Pulmonary Langerhans cell histiocytosis. An update from the pathologists’ point of view. Roden AC and Yi ES. Arch Pathol Lab Med 2016;140:230-40

Ex vivo artifacts and histopathologic pitfalls in the lung. Thunnissen E et al. Arch Pathol Lab Med 2016;140:212-20

Next-generation sequencing and immunotherapy biomarkers. A medical oncology perspective. Bernicker E. Arch Pathol Lab Med 2016;140:245-8

Lung transplantation. The state of the airways. Husain AN and Garrity ER. Arch Pathol Lab Med 2016;140:241-4

Abstracts from the PPS 2015 biennial meeting. Arch Pathol Lab Med 2016;140:255-66