ARTICLES FOR DISCUSSION


Purpose: To determine if there is a clear relationship between WDPM and malignant mesothelioma, as well as look at the effect of invasive foci on recurrence and survival of WDPM.

Methods: Cases of WDPM were chosen from the authors’ consult files, with 20 cases being accepted for the study. The cases chosen had a predominant papillary architecture, with myxoid-appearing cores and a single layer of bland-appearing mesothelial cells. Invasive foci or areas with higher grade histology were considered, however, areas of solid tumor outside the papillary structures were not included. Clinical finding were recorded. In 5 cases, p16 FISH was performed. Chromosome analysis was performed on the cases.

Results: Women outnumbered men by 16 to 4; ages ranged from 7 to 74. Most cases were from the peritoneal cavity, however a few were from hernia sacs, the pleural cavity and hydrocele sacs. Fifteen cases had multifocal disease with tumor sizes ranging from < 1 to 12 cm. In 6 cases, compressive crowding was noted – “the usual spaced papillae characteristic of WDPM were replaced by back-to-back papillae” (figure 1A, 1B). Keratin staining was performed to r/o invasive tumor. Eighteen cases showed an immunohistochemical pattern of mesothelial cells. Several different patterns of invasion were identified; most were superficial and confined to the polyp. FISH for p16 was negative in 5 available cases. Two cases revealed clonal abnormalities on karyotyping. WDPM recurred in 8 patients; of these 4 had multiple recurrences. One patient had disseminated disease and died, however, there was no histology to confirm the case of death.

Discussion: The lack of p16 deletions suggests that evaluation of this deletion may be helpful in determining if the tumor is malignant mesothelioma, however, the number of cases was small and some malignant mesotheliomas do not have the deletion. The chromosomal abnormalities suggest a potential connection between WDPM and malignant mesothelioma, but this is not diagnostic. The study suggests that WDPM with invasive foci has a tendency to be multifocal and recur. Transformation to malignant mesothelioma is still controversial; compressive crowding further confuses the issue. The morphologic definition of WDPM is problematic with no definitive consensus among pathologists.

Take home message: WDPM with invasive foci is prone to recurrence and multifocality. The authors suggest the use of WDPM with invasive foci as the term of choice for these tumors.

Purpose: To identify the clinicopathologic features of lung adenocarcinoma with morule-like components.

Methods: 904 consecutively resected primary lung ADC were reviewed. Patient clinical information was obtained and recorded. All available slides were reviewed according to IASLC/ATS/ERS lung classification for ADCs. Seventeen cases were identified with morule-like components, defined as “small spindle-cell proliferation buds in the tumor lumens of the glandular carcinoma structures that did not fill the entire lumen (essentially residual airspace).” “The morules consisted of uniform tightly packed spindle- or round-shaped cells with faintly eosinophilic cytoplasm.” The morule-like component was more than 5% of the tumor mass to be in the study. Several ICH studies were performed. Analysis of EGFR, KRAS, BRAF,
HER2, CTNNB1 mutational status and ALK rearrangement were studied. Statistical analyses were performed.

Results: Seventeen cases of ADC with morule-like components were identified. Men and women were fairly equal with median age of 67 years. Never smokers and former/current smokers were fairly equal. Tumor size median was 2.8 cm. LVI was seen in 12 cases. There was no statistical significance with gender, smoking status, lymph node status or pathologic stage in these cases. There was statistical significance with EGFR mutations. Male gender, presence of morule-like component, and papillary-predominant ADC were independent predictive factors of EGFR mutation status. DEL mutation was seen in 8 cases; ALK was seen in 1; no cases had KRAS, BRAF, HER2 or CTNNB1 mutations. Papillary-predominant was the most prevalent ADC variant. Morule-like components and ADC stained with CK7 and TTF-1, and all cases were positive for membranous B-catenin – 9 cases showed focal aberrant expression. MIB showed no significant difference between the morule-like components, the adjacent tumor areas or different variant histologies of ADC. There was a significant difference in survival rate between ADC with morule-like components and lepidic and papillary-predominant ADCs.

Univariate analysis: These were associated with higher risk of death: Presence of ADC with morule-like components, male, age >62, former/present smoker, LVI, tumor size >2.7 cm, LN mets, micropapillary histology, solid-predominant histology, advanced pathologic stage.

Multivariate analysis: Statistically significant independent prognostic factors: ADC with morule-like components, male, age >62, LVI, tumor size >2.7 cm, higher tumor grade, LN mets, advanced pathologic stage.

Discussion: Statistical analysis showed a correlation between ADC with morule-like components and unfavorable outcome. It is associated with higher EGFR mutation rate and DEL mutation. These morule-like components are not squamous metaplasia by IHC. Their MIB-1 rate is similar to adjacent ADC rates. This is a rare variant of pulmonary ADC and should be considered invasive.

Purpose: To determine the significance of the histologic subtype of lung cancer in lobectomy vs wedge resections.
Methods: Reviewed were 85 surgical specimens from patients with NSCLC patients from Mount Sinai Hospital. There were 59 lobectomies, 19 wedge resections and 7 segmentectomies. All tumors were node negative and had negative margins. No patients received chemo or radiation. Histologic type, tumor size, and pleural and LVI were noted. The 2011 IASLC/ATS/ERS guidelines were used for the ADC; the WHO criteria was used for the non-ADC tumors. If the tumor was < 3.0 cm it was entirely submitted, and if > 3 cm one section per cm of tumor was submitted. Patient demographics, staging and post op follow up were compared between the sublobar resections vs the lobectomy resections, and statistically analyzed.

Results: 34 men, 51 women, ave age 79 years, mean follow up time 38 months. Three patients in the wedge resection group died of disease; 18 patients in the lobectomy group died of disease. See Table 2. In ADC, AIS, MIA, and lepidic predominant subtypes had the best prognosis and solid growth pattern had the worst prognosis. Compared to lepidic, solid and squamous subtypes had a significantly poorer prognosis. There was a significantly poor prognosis with increased size of tumor and lymphatic invasion. Pleural or vascular invasion had no association between resection and survival. There was no statistically significant difference in survival between lobectomy and W/S specimens.

Discussion: There are a few limitations to this study – small number of W/S specimens, retrospective review, lack of micropapillary cases. There was decreased survival with increased tumor size, but no cut off size was determined. These results, combined with other studies discussed in the paper, suggest that W/S procedures are appropriate for tumors < or = 2.0 cm. This may be an acceptable procedure for some of the invasive subtypes of lung cancer.
<table>
<thead>
<tr>
<th>Type</th>
<th>Lobectomy (%) (No. = 59)</th>
<th>W/S (%) (No. = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimen type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean tumor size (range), cm</td>
<td>2.7 (1.0-6.0)</td>
<td>1.9 (0.8-5.2)</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIS</td>
<td>2 (3)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>MIA</td>
<td>2 (3)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Lepidic predominant ADC</td>
<td>4 (7)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Adenocarcinoma predominant</td>
<td>9 (15)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Papillary predominant ADC</td>
<td>11 (19)</td>
<td>6 (23)</td>
</tr>
<tr>
<td>Micropapillary predominant</td>
<td>1 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Solid predominant ADC</td>
<td>9 (15)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>13 (22)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Invasive mucinous ADC</td>
<td>8 (14)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Nonpredominant micropapillary component</td>
<td>21 (36)</td>
<td>9 (35)</td>
</tr>
<tr>
<td>Nonpredominant solid component</td>
<td>2 (3)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Necrosis</td>
<td>20 (34)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>Lymphatic invasion</td>
<td>23 (39)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Large vessel invasion</td>
<td>10 (17)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>VPI</td>
<td>11 (19)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Pathologic stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pT1a</td>
<td>22 (37)</td>
<td>17 (65)</td>
</tr>
<tr>
<td>pT1b</td>
<td>16 (27)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>pT2a</td>
<td>14 (24)</td>
<td>4 (15)</td>
</tr>
<tr>
<td>pT2b</td>
<td>7 (12)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

VPI—vascular pleural invasion; W/S—wedge or segmentectomy. See Table 1 legend for expansion of other abbreviations.

Purpose: To determine if there is a way to adequately recognize a tumor in the lung simulating DIP from DIP.

Methods: Mayo Clinic Arizona pathology department files were reviewed for lung tumor cases that had a DIP-like pattern. Seven cases were identified from 1992-2011. One was a transbronchial bx, 1 a needle core bx and 5 were resection specimens. A control group of 4 patients with DIP-reactions was collected. IHC was done on the 7 tumor patients. Detailed morphometric analysis was done on the tumor cells, with average nuclear and cytoplasmic diameters of 100 intra-alveolar cells and compared to the control group. 150 randomly selected lung ADCs were reviewed to understand the incidence of this pattern. N/C ratios were calculated. Statistical analysis was performed.

Results: 5 males; 2 females; median age 67 years. Radiology showed lobar consolidation, GGO, and rare nodule formation. None had radiology c/w DIP. The predominant pattern of tumor was intra-alveolar location without pigment. The DIP-like pattern ranged from 80-100% in the 7 tumor cases, and was seen in 18% of the lung ADC cases. IHC was performed on 6 of the cases to confirm the diagnosis. Depending on the type of statistical analysis performed, there was no statistically significant difference in the nuclear or cytoplasmic diameters and only a marginally significant difference in N/C ratio when tumor was compared to control (Wilcoxon rank sum test); however, with generalized estimating equations (GEE) there was a significant difference between the N/C ratio between the two groups, although it showed no difference between the diameters.
Discussion: Detection of DIP-like ADC can be difficult, especially on cytology and when the tumor cells are bland. The radiology may not be helpful, either. These tumors can be primary or metastatic. There was no statistical significance between the diameters of nuclei and cytoplasm between intra-alveolar macrophages and tumor cells and only a small difference was seen in the N/C ratios. The key to the diagnosis is the individual cytology of the cells, with IHC used to confirm the diagnosis. As pulmonary pathologists, we should be aware of this pattern, especially before diagnosing DIP.

| TABLE 3. Statistics Based on the Mean Values From the Patients for Cases and Controls Groups |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                  | Case (n = 7)                   | Control (n = 4)                  |                                  |                                  |                                  |                                  |                                  |                                  |                                  |                                  |                                  |                                  |                                  |                                  |                                  |                                  |                                    |
|                                  | Mean    | SD        | Median  | Mean    | SD        | Median  | P*               | P†               |                                  |                                  |                                  |                                  |                                  |                                  |                                  |                                  |                                    |
| Nuclear                         | 8.30    | 1.50      | 8.49    | 7.80    | 0.43      | 7.71    | 0.3447           | 0.0278           |                                  |                                  |                                  |                                  |                                  |                                  |                                  |                                  |                                    |
| Cytoplasm                       | 15.33   | 3.59      | 17.25   | 16.84   | 2.30      | 15.73   | 0.7055           | 0.3669           |                                  |                                  |                                  |                                  |                                  |                                  |                                  |                                  |                                    |
| N/C ratio                       | 0.56    | 0.07      | 0.50    | 0.48    | 0.07      | 0.50    | 0.0890           | 0.3441           |                                  |                                  |                                  |                                  |                                  |                                  |                                  |                                  |                                    |

*Wilcoxon rank sum test.  
†The Wald test from GEE.

Purpose: To characterize the pathology of pulmonary cysts in DHBS and to try to determine a possible mechanism for their formation.

Methods: 50 patients with BHDS with a total of 229 lung cysts were reviewed. BHDS was diagnosed by genetic testing for the FLCN gene. Lung tissues were obtained by VATS, inflated and then fixed in formalin and routinely prepared. Either trichrome or EVG stains were performed. The amount of chronic inflammation and the amount of fibrous scarring was recorded. The maximum diameter of each cyst was measured. Control tissue was lung tissue from 34 patients who had primary spontaneous pneumothorax (PSP). Statistical analysis was performed.

Results: Most of the BHDS patients had normal lung parenchyma; a few showed centrilobular emphysema, granulomas or fibrosis. The cysts in these patients had very thin and translucent walls, were surrounded by normal lung, and were not at all or minimally affected by inflammation or fibrosis. Half of the cysts were subpleural; the other half were intrapulmonary. Most of the cysts in the PSP patients were subpleural and had inflammatory infiltrates. These differences were statistically significant. Most of the cysts in BHDS patients ranged from 1.0 to 15.7 mm. There was no statistical significance between the median size of intraparenchymal cysts between BHDS patients, smokers and non-smokers. There was a difference between the sizes of the subpleural cysts and for the larger cysts with inflammation than those without inflammation.

Discussion: BHDS cysts are 1) surrounded by normal lung tissue, 2) abut the interlobular septa, and 3) may have intracystic septa and/or protrusion of venules into the cystic space. Inflammation and cellular proliferation do not play a role in the development of these cysts. The inflammation and fibrosis that are seen in the PSP cysts are likely from the inflammatory process that pneumothorax incites. The authors postulate that the FLCN mutation causes an abnormality in the alveolar-septal junction, which leads to cyst formation.
Table 2. Comparison of the numbers of cysts in lung specimens from patients with Birt-Hogg-Dubé syndrome (BHDS) and primary spontaneous pneumothorax (PSP) [no. (%)]

<table>
<thead>
<tr>
<th>Histological findings</th>
<th>Cysts from BHDS patients (n = 229)</th>
<th>Cysts from PSP patients (n = 117)</th>
<th>$\chi^2$-test</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cysts located in</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subpleural area</td>
<td>116 (50.7)</td>
<td>115 (98.3)</td>
<td></td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Intrapulmonary area</td>
<td>113 (49.3)</td>
<td>2 (1.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cysts abutting on</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interlobular septa</td>
<td>202 (88.2)</td>
<td>16 (13.7)</td>
<td></td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Bronchiole</td>
<td>11 (4.8)</td>
<td>42 (35.9)</td>
<td></td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Intracystic septa</td>
<td>31 (13.6)</td>
<td>0 (0)</td>
<td></td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Venules protruding into the cyst</td>
<td>90 (39.5)</td>
<td>2 (1.7)</td>
<td></td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Cysts without inflammation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>125/229 (54.6)</td>
<td>2/117 (1.7)</td>
<td></td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Subpleural area</td>
<td>37/116 (31.9)</td>
<td>2/115 (1.7)</td>
<td></td>
<td>$P &lt; 0.001$</td>
</tr>
<tr>
<td>Intrapulmonary area</td>
<td>88/113 (77.9)</td>
<td>0/2 (0)</td>
<td></td>
<td>NS ($P = 0.177$)</td>
</tr>
</tbody>
</table>

* $P < 0.001$ for comparison of the numbers of cysts without inflammation between the subpleural and intrapulmonary areas.

NS, not significant.

Purpose: To determine prognostic factors for these tumors.
Methods: 127 AC tumors were collected over a period of 29 years. They were reviewed and classified according to the 1999 WHO classification which included Travis’ new criteria for AC. Clinical behavior, as well as histologic features, were recorded. Survival analysis was performed and local recurrences and mets were recorded. Statistical analysis was performed.

Results: 127 cases of AC were identified that had several different surgical resections for several different stages of tumor. 25% of these patients had recurrence. 23 patients died during the monitoring - 12 of those were because of the tumor. Differentiation grade, tumor pattern, bone metaplasia and IHC staining were not found to be statistically significant for survival influence. There was statistical significant between NO and N+ patients in survival and recurrence. The development of distant recurrence was the main independent factor for survival. The higher the N status, the higher the chance of distant mets. Sublobar resection was an independent prognostic factor to predict locoregional recurrence. There was no statistical significance on survival and recurrence with adjuvant chemotherapy.

Discussion: Nodal status, resection type and recurrence affect the prognosis in these patients. The authors suggest that standard surgical resection with radical lymphadenectomy is essential in these cases.


Purpose: To determine the frequency of preexisting T790M mutations in a tumor, the clinical outcomes of that mutation, and determine the frequency of that mutation when it begins to not respond to TKIs.

Methods: 173 patients with a known NSCLC that were treated with a TKI (gefitinib or erlotinib) were selected. Paraffin embedded tissue was collected for genetic analysis. Direct sequencing of the EGFR gene was performed. Mass spec was performed to determine the detection limit and cut-off value of the T790M mutation. In vitro sensitivity to TKI was performed. Statistical analysis was performed.

Results: The response rate and disease control rate were not different in the two groups, T790M positive and negatives. The median time to disease progression was shorter in the positive patients and the risk to disease progression was significantly higher. The overall survival time was shorter in the positive patients. High frequency of the mutation was also noted to decrease survival time and time to disease progression.

Discussion: The authors believe that resistant subclones before TKI exposure are present, but at undetectable levels by direct sequencing. The presence of this gene has a critical effect on the tumor’s biology and on the clinical outcomes of TKI therapy.

Purpose: To evaluate the expression of the immunohistochemical markers and to see if they have an association with prognosis in neuroendocrine lung tumors.

Methods: The surgical pathology archives were reviewed revealing 109 NE tumors from surgical specimens, 10 tumorlets and 4 normal lung samples for control. Slides were reviewed and diagnosis was confirmed by two pathologists. Microarray of the specimens was made and IHC for KLF4, p21 and p53 were performed. Their expression was graded by two pathologists from negative to strongly positive (+++). Clinical information was collected and statistical analysis was performed.

Results: All normal lung samples were negative for the three IHC markers. All tumorlets were negative for p53 and positive for KLF4, and 6 were positive for p21. Typical carcinoids (TC) were negative for p53; 15 of 47 cases were positive for KLF4. P21 was the same in all TCs. ACs were similar in staining to TCs, with one case positive for p53. LCNEC cases showed 80% positive for p53, 66% positive for KLF4 and 94% positive for p21. 61% of SLCL cases were positive for p53, all were positive for KLF4, and 89% were positive for p21. There were no deaths in the tumorlet group; the other group’s survivals worsened as the histology worsened. Statistically, in the TC group, there were no differences in the T1 and T2 group in relation to KLF4 expression and no correlation was noted between TMN and p21 negativity. There was no difference in survival or mortality for p21 expression in AC. In high grade NEC, there were no differences found in mortality and survival rates for all stages in the surgically resected cases and no differences in the IHC status.

Discussion: Tumorlets did not express p53, but did express KLF4, which may prevent aggressive behavior. TCs did not express p53 or KLF4, and survival was shorter in the KLF4 negative patients. In ACs KLF4 and p21 negative cases were associated with aggressive features. In LCNEC and SCLC most tumors showed positivity for all three markers. In HG NEC p53, KLF4 or p21 expression did not affect patient outcome. The authors suggest that TC and AC are very different from LCNEC and SCLC in IHC staining and survival. It is interesting to note that KLF4 expression is present in tumorlets, not high in TC and AC and highly overexpressed in NEC.


Purpose: To compare the radiological and pathological tumor size of ADC in frozen section using an inflation method and to evaluate the effect of a lepidic component on the size.

Methods: Retrospective review of 59 resected lung specimens that underwent FS diagnosis of lung ADC. All were inflated by saline injection into the lung tissue, and then negative pressure. Then the tissue was frozen for evaluation. Tumor size was measured grossly, microscopically at time of FS, and on paraffin embedded sections microscopically. Chest CT was done to measure the tumors by high resolution CT scans with a 1-2 mm section thickness. Statistical analysis was performed.
Results: Of the 59 specimens, 28 were AIS, 4 were MIA, and 27 were invasive ADC. The FS diagnosis accuracy was 100%. There was significant correlation between CT tumor size and pathological tumor size. Discrepancy rates were higher in air-containing type specimens. The FS and paraffin embedded tumor sizes were smaller than the CT tumor size.

Discussion: The inflation method makes small and medium-sized tumors more apparent at gross examination, easier to cut at frozen section, and made it possible to diagnose minute lesions on FS. The FS tumor size and the paraffin tumor sizes were significantly smaller than the CT tumor size, however the macroscopic tumor size was accurate.

Purpose: To determine if cell-transfer technique can be used for EGFR and KRAS mutation analysis on PCR platforms.

Methods: 32 FNA cases with corresponding paraffin embedded tissue that were done over a 48 month period were chosen. EGFR and KRAS mutation analysis were performed on ethanol fixed, air dried, and paraffin embedded samples of the same tumor. The cell transfer technique was performed to obtain DNA and PCR was performed.

Results: All of the cytological samples had more than 50 tumor cells. In all of the ethanol fixed samples and in all but one of the air dried samples, EGFR and KRAS were successfully performed. For KRAS all but one case correlated with the paraffin embedded sample. For EGFR, all cases showed correlation with the paraffin embedded tissue. When molecular tests were successfully performed, the cell transfer technique showed 100% correlation between ethanol fixed and air dried specimens, and nearly 100% correlation between cell transfer technique and paraffin embedded tissue, with a sensitivity of 95% and a specificity of 100%.

Discussion: Cell transfer technique can be used for FNA smears, however, there needs to be adequate numbers of tumor cells selected. One needs at least 30 tumor cells and more than 50% of the cells submitted must be tumor cells.


Purpose: To investigate the incidence of ALK in a large cohort of Chinese patients, comparing clinicopathological features, treatment response, and survival as compared to ALK negative patients.

Methods: 793 lung adenocarcinoma cases over a 2 year period were reviewed, including clinical information, treatment and follow up. All slides were reviewed by 2 pathologists and morphologic features were recorded. IHC and FISH analysis were performed for ALK. If > 10% of cells were positive it was considered positive (1-3+ depending on the number of cells positive). FISH was performed on all cases that were ALK IHC positive. EGFR mutation analysis was performed. Randomly collected ALK translocation negative cases were selected and their histology was recorded. Statistical analysis was performed.

Results: ALK was detected in 18.7% (148) of the cases. 54 of these cases (6.8%) had ALK translocation by FISH. The ALK positive patients were younger, more women, nonsmokers, advanced stage of tumor, and no well-differentiated histology. Growth pattern was predominantly solid, with few papillary or lepidic patterns. No statistical significant was observed in overall survival between ALK + and ALK – cases. Signet ring cell histology was seen in 30% of the ALK+ cases, and mucinous cribriform structure in 50% of the cases. One third of EGFR wild type patients had an ALK translocation.
Discussion: The authors suggest that FISH detection for ALK should be performed on ADC with signet ring cell component or EGFR wild type status. FISH for ALK should be performed in IHC + cases because the IHC can have false positives, depending on the clone used. I don’t think there was much else that was new information about ALK + cases.


Purpose: To evaluate the accuracy of FNA and core biopsy in the setting of mucinous ADC.

Methods: Review of the hospital’s cancer registry revealed 105 patients with MA who underwent preoperative FNA or CNB , 8 of which had both for the same tumor. 54 of these were subtyped as MA. Surgical specimens were reviewed and subtyped. Cytology cases were reviewed and subtyped. IHC was done to confirm the diagnosis. CT scans were evaluated for tumor size and characteristics. Statistical analysis was performed.

Results: 87% of biopsy specimens and 67% of aspirates were adequate for determining malignancy, and of those 68% and 30% were successfully diagnosed as MA, respectively.

Discussion: The authors conclude that CNB has high accuracy in diagnosing MA. They warn that lepidic-predominant pattern of growth may be adjacent to a well-differentiated ADC, making the diagnosis difficult in those cases.


Purpose: To determine if laser capture micro-dissection (LCM) combined with FFPE RNA-Seq could identify novel alterations in the continuum of normal-AIS-invasive ADC in lung cancer.
Methods: FFPE blocks of normal lung, AIS and lung ADC were reviewed. LCM was performed on all blocks and RNA was isolated and analyzed against RNA sequencing libraries.

Results: Several RNAs were found to be up or down-regulated in the sequence from normal to ADC.

Discussion: The authors are hoping that their work with these RNAs will lead to future experiments that will identify their functional roles in lung cancer.


Purpose: To determine if molecular profiling of lung cancer can adequately be performed on pleural effusion.

Methods: 102 pleural effusion samples were used from 84 patients with available paraffin embedded tissue. Cell isolation was performed on the effusions and they were analyzed for multiple genes using PCR. Results were compared to the paraffin embedded tissue results.

Results: Among the 63 pathologically positive samples, 30 had genetic abnormalities, the most frequent of which was EGFR mutation. Among 17 samples that were pathologically negative, 3 had genetic abnormalities. This was a significant difference. The concordance rate between pleural effusion and paraffin embedded samples was 88%.

Discussion: In some instances, molecular profiles could be monitored with pleural effusion.


Purpose: To investigate the impact of the ambiguities in classification of multiple foci of lung cancer.

Methods: A questionnaire with four different cases was created and sent to ACCP panel, the ESTS members, and members of the Thoracic Oncology Network of the ACCP. Surveymonkey was used. Data was analyzed. See attached Appendix A.

Results: 360 surveys were completed; 74% were thoracic surgeons, 23% were pulmonologists and 3% were cardiac or cardiothoracic surgeons. All of the different ways to classify the tumors were answered, with no single classification that was used more than another. There was no difference in how the scenarios were classified according to the group surveyed, or according to specialization by multivariate analysis.

Discussion: There is significant inconsistency in how patients are classified. A clear definition of what constitutes a primary lung cancer, multifocal disease and an additional nodule is needed.
Appendix A. Appendix

This is a brief survey (four cases) to see how people interpret IASLC/AJCC/UICC stage classification rules. All answers are in accordance with the official rules; they differ only by how the rules are interpreted. There are no right or wrong answers; this is merely an assessment of how we use the system in certain situations.

What T, N, M would you use to classify the following patients?

(1) A 60 year old man with a RUL 4 cm adenocarcinoma (bronchoscop biopsy proven), adenocarcinoma in an R4 node by EBUS, and an enhancing classic metastatic lesion in the brain (not biopsied) as well as an endobronchial squamous cell cancer (bronchoscop biopsy proven) in the LLL basilar bronchus (8 mm) with no left segmental/hilar/mediastinal abnormal nodes? (No other suspicious areas by PET or CT).

(a) T2a N2 M1b adenocarcinoma and T1 N0 M0 squamous carcinoma.
(b) T2a(2) N2 M1b NSCLC.

(2) A 60 year old man with a RUL 4 cm solid adenocarcinoma, primarily acinar (bronchoscop biopsy proven), adenocarcinoma in an R4 node by EBUS as well as a 1.5 cm solid RLL adenocarcinoma, primarily papillary (bronchoscop biopsy proven)? (No other suspicious areas by PET or CT).

(a) T2a N2 M0 adenocarcinoma and T1a N0 M0 adenocarcinoma.
(b) T2a(2) N2 M0 adenocarcinoma.
(c) T4 N2 M0 adenocarcinoma.
(d) T2a N2 M1b adenocarcinoma.

(3) A 60 year old man with a RUL 2.1 cm >50% ground glass opacity (GGO) lesion with a definite solid component, bronchoscop biopsy proven adenocarcinoma, primarily lepidic, mediastinum negative by CT, PET and EBUS as well as a RLL 11 mm pure GGO, also lepidic adenocarcinoma by bronchoscopic biopsy? (No other suspicious areas by PET or CT).

(a) T1b N0 M0 adenocarcinoma and T1a N0 M0 adenocarcinoma.
(b) T1b(2) N0 M0 adenocarcinoma.
(c) T4 N0 M0 adenocarcinoma.

(4) A 60 year old man with a RUL 2.1 cm >50% GGO lesion, two additional 10 mm RUL pure GGOs as well as 2 RUL 6–8 mm GGOs.

He undergoes RUL resection, has lepidic adenocarcinoma in all three right-sided lesions, similar appearance although perhaps slight difference (<10%) in an acinar component?

(No other suspicious areas by PET or CT, N1, two nodes sampled and all negative).

(a) T1b N0 M0 adenocarcinoma and two additional T1a N0 M0 adenocarcinomas.
(b) T1b(3) N0 M0 adenocarcinoma.
(c) T1b(5) N0 M0 adenocarcinoma.
(d) T3 N0 M0 adenocarcinoma.
(e) T3 N0 M1a adenocarcinoma.

Background: PRMT5 overexpression has been noted in various cancers, including lung cancer. It plays multiple roles in cellular processes, like differentiation, proliferation, apoptosis and ribosome biogenesis.

Purpose: To describe the expression pattern of PRMT5 in different cells lines and its significance in malignant progression.

Methods: 40 NSCLC cell lines of patients with lung cancer were used in microarray as well as other cell lines depicting bronchial epithelial phenotypes and mesenchymal phenotypes. IHC for PRMT5, E-cadherin, CK7, MUC1 and TTF-1 were performed on paraffin embedded tissue. Gene expression profiling was performed on the 40 cell lines. Statistical analysis was performed.

Results: PRMT5 was correlated with expression of vimentin genes and low levels of the IHC marker genes. EGFR mutations were frequently seen in the low PRMT5 cell lines, and KRAS appeared in low and high PRMT5 expression. The PRMT5 expression was higher in mesenchymal lines and prominent in the cytoplasm, whereas it was more prominent in the nuclei in the epithelial phenotype. Normal bronchial epithelium was negative for PRMT5, and there was positive nuclear expression in ADC, with cytoplasmic expression in poorly differentiated ADC. Cases that had cytoplasmic positivity had significantly poorer survival rates than nuclear expression.

Discussion: The authors suggest that nuclear PRMT5 expression may be the first step in malignant transformation and then localization to the cytoplasm may occur in epithelial-mesenchymal transition.

Purpose: To determine if there is a marker in fatty acid profiles of total lipids in erythrocytes of patients with different kinds of lung cancer.

Methods: Cohort consisted of 65 current smokers with NSCLC (30 with SCC and 20 with ADC) and 15 with SLCL, 17 smokers with COPD, 19 patients with asthma and 55 health controls. Patients with cancer had no received treatment and had no known brain mets, and were otherwise healthy except for their cancer, ranging from stage IIIA to IV. CT of the chest was performed. Two blood samples were taken from each patient – one was allowed to coagulate at room temp and one was heparinized. B-TG and PF4 were measured in serum and plasma. Several sialic acids and cytokeratins were measured in serum. Total lipids were extracted and cholesterol and phospholipids were measured. Mass spec was done to analyze the fatty acids. Statistical analysis was done.

Results: No differences in cholesterol, HDL cholesterol or triacylglycerol were seen between patients and controls. Cytokeratins were increased in patients with SCC. 18.0 and 18:in9 fatty acids were significantly increased in patients with NSCLC but not in SCLC. 18:2n6 fatty acid was decreased in SCLC. 20:4n6 and 22:4n6 fatty acids were decreased in all lung cancers with 20:4n6 significantly decreased in ADC. Sialic acids were increased in ADC.

Discussion: At least one major fatty acid had a high diagnostic accuracy in every type of lung cancer analyzed. These are potential biomarkers for different types of lung cancer.

ARTICLES FOR NOTATION – NON-NEOPLASTIC LUNG DISEASE


Purpose: To evaluate the vascular remodeling in these two disease processes to see if they share similar or divergent molecular changes.

Methods: Lung tissue was obtained from 10 patients with PH-IPF, 10 with PH-COPD, and 8 with COPD (no PH) who underwent lung transplantation. Microarray analysis was performed for genome-wide expression profiling. IHC was performed (details were in the online supplement). Findings were compared with those of healthy control subjects.

Results: Quantification of remodeling in pulmonary vessels revealed a significant reduction in lumen size in both PH-COPD and PH-IPF lungs, mainly seen in the intima. The smaller vessels were more affected than the larger vessels in PH-COPD, whereas the lumen reduction was similar in large and small vessels in PH-IPF. COPD patients with and without PH had no difference in larger vessels, however, the smaller vessels showed an intimal increase in PH-COPD. Gene expression showed slightly more regulated genes.
in PH-IPF vs. donor than in PH-COPD vs. donor. No significant difference was seen in gene expression between the COPD group, with or without PH.

Discussion: Various degrees of vascular remodeling were seen in each of the disease groups, with medial and especially intimal thickening. Those with severe COPD showed significant intimal hyperplasia and medial thickening of small pulmonary arteries. The gene signature in patients with IPF were similar with or without PH. There was no significant difference in the COPD patients with or without PH in gene expression. There was a small overlap in genes between PH-COPD and PH-IPF which, according to the authors, suggests different mechanisms and pathways involved in vascular remodeling.

Figure 1. Characterization of human donor, pulmonary hypertension (PH), chronic obstructive pulmonary disease (COPD), and idiopathic pulmonary fibrosis (IPF) lungs. (A) Representative computed tomography images of PH-COPD and PH-IPF lungs. (B-D) Representative stainings of donor, COPD, and IPF lungs (n = 10 each) with (B) hematoxylin and eosin, (C) w-smooth muscle actin (pink), and (D) von Willebrand factor (brown)/w-smooth muscle actin (purple).


Summary: Review of changes during 2013 that occurred in lung transplantation. There was a growth in lung transplant volumes, with older patients being transplanted. Three month and one year survivals are improving, however long-term survival is about the same. DCDD donors may become more promising. There is discussion about graft dysfunction, rejection, infections and chronic lung allograft dysfunction.

CASE REPORTS


Summary: Case report of a young man who had several pneumothoraces despite bullectomy and pleurectomy with a history of scleroderma.

Purpose: To report a CMPT case and point out the diagnostic pitfalls in frozen section.

Summary: Presentation of a 68 year old male with a solitary 7 mm GG nodule in the periphery of the lung. At time of surgery the tumor was called ADC on FS, mimicking colloid ADC. On histology, the tumor was nodular and papillary, with ciliated and nonciliated columnar cells, goblet cells, and basaloid cells in a pool of mucin. The cells were focally positive for CEA, TTF-1, EMA, and CK7. They were negative for CK20. Basaloid cells stained with p63. Ki67 ad p53 staining was low. EGFR and KRAS were negative.

Discussion: The authors suggest that the presence of ciliated cells and basaloid cells distinguish this tumor as CMPT, which has been previously described. We have reviewed the previous paper in 2012 and did not feel that this entity existed. There have only been 6 cases reported in the literature and seems to be limited to East Asia.

CORRESPONDENCE


Summary: Letter to the editor describing three new cases of PPMS with overlap with AFH. It seems that these unusual lesions have a spectrum of histology from PPMS to AFH and may represent an overlapping morphological and biological spectrum.


Summary: Letter to the editor about MPM mimicking EHE with hyalinized stroma that was WT-1 and D2-40 positive and negative for endothelial markers. CT findings suggested ADC, and was not diagnostic.