ARTICLES FOR DISCUSSION


Background: The authors had a previous study that revealed a strong correlation between nuclear grade and prognosis in pulmonary adenocarcinoma.

Purpose: To examine interobserver variability of the nuclear grading system in pulmonary adenocarcinoma and compare it to histologic class, Noguchi’s classification system and extent of lepidic pattern.

Methods: 122 patients with primary pulmonary adenocarcinoma were selected from the National Cancer Center in Tokyo; 95 were randomly selected and 27 patients who had relapses were selected. 103 patients underwent surgical resection; 5 underwent segmentectomy; 14 had partial resection. None of the patients had received chemo or radiation prior to surgery. All tumors were <2.0 cm. Tumors were classified according to the 2011 IASLC classification, Noguchi’s classification, and assessment of the extent of lepidic pattern by 8 pathologists. Nuclear area (NA) and nuclear dimension (ND) were compared to that of lymphocytes and if the NA and ND of tumor cell nuclei were 5 and 3 times larger respectively, it was considered positive. Slides were reviewed and a field was positive if it contained more than 5 positive cells; the case was positive if it contained 3 or more positive fields. These diagnostic subtypes were given:

- Subtypes of cancer: Acinar, papillary, lepidic, solid, micropapillary
- Noguchi types: A-F
  - A- localized BAC
  - B- localized BAC with foci of alveolar structural collapse
  - C-localized BAC with foci of active fibroblastic proliferation
  - D-poorly differentiated adenocarcinoma
  - E-tubular adenocarcinoma
  - F-papillary adenocarcinoma with a compressive growth pattern
- Nuclear grading: positive vs negative
- Extent of lepidic area: >75%, <75%

Statistical analysis was performed (kappa).

Results: Interobserver agreement (k value) of the histologic grading scheme was then assessed. The k value for the IASLC classification was 0.46 (range 0.24 to 0.61). It rose to 0.66 (range of 0.47 to 0.85) if the classifications were limited to low grade (lepidic, acinar and papillary) and high grade (solid and micropapillary). The k value for the Noguchi classification was 0.48 (range 0.33-0.62), extent of the lepidic pattern 0.45 (range 0.14-0.70) and nuclear grading 0.58 (range 0.43-0.73). The k value for nuclear
grading was significantly higher than that of histology classification and extent of lepidic pattern.

The 5 year disease-free survival rates was found to be statistically significant for nuclear grading, cases diagnosed according to the extent of lepidic component, low vs high grade IASLC classification and types A and B of Noguchi’s classification.

<table>
<thead>
<tr>
<th>Pathologists</th>
<th>Nuclear Grading</th>
<th>Rate of Lepidic Lesion (75%)</th>
<th>Modified 2011 IASLC Classification</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Negative/Positive Case</td>
<td>&gt; 75% / &lt; 75%</td>
<td>Low / High Grade</td>
</tr>
<tr>
<td>1</td>
<td>87.8 / 67.2*</td>
<td>95.0 / 67.5*</td>
<td>81.0 / 47.2*</td>
</tr>
<tr>
<td>2</td>
<td>92.1 / 69.2*</td>
<td>94.3 / 68.4*</td>
<td>80.5 / 39.5*</td>
</tr>
<tr>
<td>3</td>
<td>90.3 / 69.3*</td>
<td>99.5 / 64.3*</td>
<td>79.8 / 51.0*</td>
</tr>
<tr>
<td>4</td>
<td>94.3 / 65.5*</td>
<td>96.1 / 72.6*</td>
<td>80.6 / 42.3*</td>
</tr>
<tr>
<td>5</td>
<td>95.5 / 62.2*</td>
<td>100 / 75.8*</td>
<td>81.1 / 45.4*</td>
</tr>
<tr>
<td>6</td>
<td>89.1 / 71.6*</td>
<td>100 / 74.9*</td>
<td>80.0 / 47.9*</td>
</tr>
<tr>
<td>7</td>
<td>91.5 / 72.3*</td>
<td>100 / 66.7*</td>
<td>81.5 / 37.5*</td>
</tr>
<tr>
<td>8</td>
<td>94.1 / 70.6*</td>
<td>100 / 71.8*</td>
<td>80.5 / 45.2*</td>
</tr>
<tr>
<td>mean/SD</td>
<td>91.8 / 72.7 / 68.6 ± 3.1</td>
<td>97.0 / 73.6 / 70.3 ± 4.1</td>
<td>80.6 / 6.0 / 44.5 ± 4.5</td>
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</table>

*Log-rank p value is 0.05; lepidic lesion, formerly bronchioloalveolar carcinoma.
Modified 2011 IASLC classification; low grade, acinar/papillary/lepidic pattern predominant.
High grade, solid/micropapillary/pattern predominant.
IASLC, International Association for the Study of Lung Cancer.

The standard deviation for the diagnosis of lepidic pattern was the highest among all the types, as well as the Noguchi pattern C suggesting considerable variation among pathologists. The standard deviation for negative vs positive cases was low, suggesting that the nuclear grading system is better for practical use with better reproducibility. The modified IASLC classification had a good k value, and is better for practical use as well.

Take home message: The nuclear grading system is the most reliable and reproducible of the four tested prognostic factors.


Background: In 1990 the ISHLT introduced a new grading system for standardization of lung transplant rejection reporting.

Purpose: To determine interobserver variability in the ISHLT grading system for lung transplant rejection.

Methods: The AIRSAC study data base was used to find 181 patients from the US who underwent lung transplantation. All patients were between 18 and 65 and had been followed post transplant for at least 3 years. Surveillance bronchoscopies were performed during screening, and at 6 and 12 months post transplant. Clinical bronchoscopies were performed if there were clinical symptoms. Biopsies were reviewed using the ISHLT criteria by a pathologist who was blinded. The search yielded 481 biopsies. Grade A biopsies contained acute rejection (472); grade B biopsies showed
lymphocytic bronchiolitis (412). Reliability of interobserver grading was statistically analyzed using Cohen k coefficients.

Results: The overall concordance rate for grade A biopsies was 74%; for grade B biopsies 89%.

When determining if time of biopsy was a factor, it was found that the highest level of reproducibility was within 6 weeks after transplantation.

<table>
<thead>
<tr>
<th>Table 2—Interobserver Agreement for Grade A Readings</th>
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<tbody>
<tr>
<td>Reader</td>
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<tr>
<td>Site pathologist</td>
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<tr>
<td>Totals</td>
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<table>
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<tr>
<th>Table 3—Interobserver Agreement for Grade B Readings</th>
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<tbody>
<tr>
<td>Reader</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Site pathologist</td>
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<td></td>
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<td></td>
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<tr>
<td>Totals</td>
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</table>

Biopsies were divided between two groups – the presence of rejection or the absence of rejection and statistically evaluated the results of those biopsies on two different immunosuppressants, azathioprine and sirolimus. The concordance rate for grade A and azathioprine group was 82% and for the sirolimus group it was 74%. The grade B and azathioprine group concordance was 88% and the sirolimus group was 91%. The k score for grade A reading was fair to moderate for the Azathioprine group and poor for the Sirolimus groups. The k score for grade B was moderate to poor for both groups.
Transbronchial biopsy specimens with and without clinical symptoms were reviewed. The group A surveillance biopsies had a concordance rate of 82% and clinical group A had a rate of 62%. For group B, the surveillance rate was 91% and clinical group was 81%. When the k score was calculated, the clinical biopsies had the highest value early after transplantation for both groups A and B.

The authors determined if any of the discordance in scoring would have lead to different treatment. 32 grade A2 and 9 grade B2 were downgraded to A0 and B0. Two A0 were upgraded to A2. There were 10% of the total cases that were discordant that would have changed immunosuppressive therapy.

Take home message: There is need for further education of pathologists to improve concordance in grading acute rejection. Reassessment of the current ISHLT criteria for grade A and B might be in order. A novel finding is that there was a time dependent variability with the highest interobserver agreement within 6 weeks of transplant, likely due to confounding factors, such as previous biopsy site changes, rejection and drug effect.
Ha SY et al. Lung parenchymal invasion in pulmonary carcinoid tumor: An important histologic feature suggesting the diagnosis of atypical carcinoid and poor prognosis. Lung Cancer;80: 146-152.

Background: The classification of atypical carcinoid (AC) and typical carcinoids (TC) is made by pathologists on microscopic examination by looking at necrosis and mitotic rate. Other histologic features could be useful diagnostic hints.

Purpose: To determine if there are any histological features that can be used as diagnostic tools in examining ACs and TCs.

Methods: Sixty three cases of surgically resected carcinoid tumors were chosen for the study from the Samsung Medical Center between 1995 and 2011. Clinical information was gathered. All cases were reviewed and NE differentiation was confirmed by positivity of either chromogranin A, synaptophysin or CD56. Mitotic count and necrosis was evaluated using Travis’s method and the cases were divided into AC and TC according to WHO criteria. Histologic features were evaluated including growth pattern, nuclear pleomorphism, presence of nucleoli, presence of intratumoral hemorrhage, vascular or lymphatic invasion, perineural invasion, and the type of cytoplasm. Site of tumor was recorded as central or peripheral. Lung parenchymal invasion was graded as none, minimal (focal with a pushing border), moderate or marked (invasion with an infiltrative border).

Results:
Clinical features: 35 males, 28 females, mean age 47 y/o; 2/3 non-smokers
   Incidental tumor findings in 47.6%
   Cough most common symptom
   AC had more smokers than TC
   Mean tumor size 2.8 cm; most were central location (76%)
   Lymph node mets in 11 cases
   Stages of tumors:
      I  - 78%
      II - 16%
      III - 3%
      IV - 3%
   5 year survival rates – TC 100%; AC 83.5%
Histologic features:
   Organoid growth pattern 87% of cases
   Only AC had rosettes – 6 cases
   Intratumoral hemorrhage in 43%
   Nuclear pleomorphism 29%
   Nucleoli 38%
   LVI more in AC than in TC
   Basophilic cytoplasm seen in 10 TC, but not in AC
Parenchymal invasion (more frequent in AC than TC, 39% and 12.5%):
None 52%
Minimal 25%
Moderate 13%
Marked 22%

Spindle cell pattern seem more in tumors with parenchymal invasion
Ossification found exclusively in TC

![Figure](image)

**Fig. 2.** (A) About half of pulmonary carcinoid tumors show well-circumscribed mass with no definite parenchymal invasion. (B) Real minimal parenchymal invasion with pushing border (arrow) is observed in 25.4%. (C and D) Invasion to the adjacent lung parenchyma with an infiltrative border are found in 22.26. According to degree of invasion, cases are classified as moderate (C) or marked (D).

**Survival:**
- Shorts OS and DFS in AC
- Lung parenchymal invasion showed shorter OS and DFS
- AC with mitotic count from 6-10 had shorter OS and DFS than those from 2-5 and TC
- Mitosis > 2/10HPF was the only independent prognostic factor in DFS
Take home message: Several histologic features can be useful diagnostically, including lung parenchymal invasion, basophilic cytoplasm, rosette growth pattern, and ossification. According to the authors, a major finding was that lung parenchymal invasion was more frequent in AC than TC and had a worse prognosis (OS and DFS).


Purpose: The authors previously reported on the impact of the number of involved lymph nodes in NSCLC on survival. However, the anatomic location of the lymph nodes may be even more significant. It has been previously shown that pN1 and pN2 are heterogeneous as a prognostic factor.

Purpose: To determine if anatomic number (nN) or location of the involved lymph nodes (pN) is a better prognostic factor in NSCLC.

Methods: 689 patients were chosen from 2000-2007 who had a surgical resection for primary lung cancer at the Tokyo Medical University. Clinical stages were from IA to IIA including patients with stage cN2 with single-station nodal mets. These patients had dissection of >= 10 hilar and mediastinal lymph nodes. Clinical information was recorded. Slides were reviewed and tumors were staged according to the 6th edition of the TNM staging system. Tumors were typing according to the WHO classification (3rd ed). LN were classified based on anatomic location using the Naruke map. LNs were assessed according to the presence/absence of mets (pN) and the number of LN with mets (nN) using the following: nN0 – no LN mets; nN1-3 - mets in 1-3 LN; nN4- - mets in 4 or more LN. OS and DFS were evaluated. Statistical analysis was performed.
Results:

Patient Characteristics:

417 males, 272 females, median age 64.5 years

Adenos 497
SCCA 140
LCC 42
Others 10

Stages:

<table>
<thead>
<tr>
<th>pN factor</th>
<th>pN0</th>
<th>pN1</th>
<th>pN2</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>480</td>
<td>94</td>
<td>115</td>
</tr>
<tr>
<td>II</td>
<td>510</td>
<td>93</td>
<td>86</td>
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</table>

nN factor:

<table>
<thead>
<tr>
<th>nN factor</th>
<th>nN0</th>
<th>nN1</th>
<th>nN4</th>
</tr>
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<tbody>
<tr>
<td>nN0</td>
<td>510</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nN1-3</td>
<td>101</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nN4-</td>
<td>78</td>
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</table>

Mean LN resected 18.1; mean number of LN involved 4.5

Survival:

There was a clear difference in the OS and DFS of each subgroup of the pN and nN classifications. There was also a significant difference in the OS and DFS for each of the nN categories. There was decline of the OS and DFS from the nN0 to the nN4 subgroup. Patients were then classified into five combinations of the pN and nN status to determine prognostic significance: (see figure 3 below)

1) pN0-nN0
2) pN1-pN1-3
3) pN1-nN4-
4) pN2-nN1-3 Patients had better prognosis than group 3
5) pN2-nN4-
Due to the small number of cases, there were no significant differences between the subgroups. On multivariate analysis, the nN categories and the pN categories were identified as strong prognostic factors for OS and DFS. Based on this, the authors propose a new classification system that will combine the pN and nN categories and may reflect the survival more accurately. (see figure 4 below)

**New categories:**
- **N0**  pN0-nN0
- **N1**  pN1-nN3
- **N2a** pN2-nN1-3 + pN1-nN4- (3 and 4 above combined)
- **N2b** pN2-nN4
Take home message: A combined anatomically based and numerically based classification system is, according to this study, a better prognostic determinant in pN1 and pN2 patients with NSCLC. The IASLC is working on the 8th edition of the stage classification of tumors, so this may be taken into consideration. The editorial comment in this publication that follows the article has relevant pros and cons of this study and is worthwhile reading.


Background: Confocal laser endomicroscopy is used in the GI tract and predicts neoplasia in the GI tract.

Purpose: To evaluate central airway lesions with confocal laser endomicroscopy (CLE) using acriflavine as a contrast agent.

Methods: Bronchoscopy and CLE were performed on 32 consecutively recruited patients that had nodular lesions in their airways (9 women, 23 men, mean age 65). Biopsies were taken and evaluated histologically; findings were compared to the CLE analysis results. An acriflavine solution was used to visualize the trachea and bronchi. Multiple confocal images were taken and compared to the histological findings, and to allow for identification of normal vs. neoplastic tissue.
Results:
A homogeneous staining pattern was identified in normal bronchial mucosa. A loss of homogeneity was seen in exophytic and infiltrative lesions, with a bright nucleus and dark cytoplasm. Squamous metaplasia contained large cells with small nuclei and a “fried-egg”-like structure of the cells with abundant cytoplasm. In NSCLC dark neoplastic cells were visualized with large nuclei and weaker acriflavine uptake and a wide and dark cytoplasm. In SCLC there was a homogeneous pattern with weak acriflavine uptake and small dark round cells with very little cytoplasm. Three different tissue types could be identified by confocal microscopy – normal tissue, inflammation/regeneration, and neoplasia. Comparison of histology and CLE showed a sensitivity of 96% and specificity of 87% for detection of malignant lesions. PPV was 86% and NPV was 96% and CLE correctly classified all sites 91% of the time.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Confocal pattern classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confocal diagnosis</td>
<td>Cell structure</td>
</tr>
<tr>
<td>Normal mucosa</td>
<td>Bright nuclei</td>
</tr>
<tr>
<td>Inflammation/ regeneration</td>
<td>No overlapping Moderately enlarged cytoplasm</td>
</tr>
<tr>
<td>Neoplastic lesion</td>
<td>No overlapping Chaotic cell distribution Heterogeneous size of nuclei Variable distances between nuclei</td>
</tr>
</tbody>
</table>
Take home messages:
CLE may aid in evaluation of tumor spread prior to surgery.
May be helpful in research applications.
Can distinguish between neoplastic and non-neoplastic lesions.
May reduce the number of biopsies and help to target biopsies.
Is very expensive (microscope cost 120,00 euros; procedure 250 euros).
Still a need for tissue for tumor subtyping and molecular markers.

ARTICLES FOR NOTATION

NEOPLASTIC


Background: Human Papilloma Virus has been linked to cervical, anogenital, and oropharyngeal cancers.

Purpose: To determine if HPV is involved in the development of lung cancer.

Methods: Lung cancer specimens from 223 patients were evaluated for GP5+/6+ PCR (a cocktail probe for 14 different HPV types) and p16 IHC. The tumors were a mix of primary lung tumors (211) and tumors in patients with a history of another primary (possible metastatic disease)(12). The tumor type was not delineated. Analysis of allelic loss with 12 satellite markers was done by PCR. Array comparative genomic hybridization was performed, along with RT-PCR to detect HPVE7 mRNA.

Results: All of the primary lung cancers were negative for HPV. Three of the equivocal cases were positive; two of the cases were from women with a history of cervical carcinoma and one case was from a man who had a history of tonsillar cancer. One lung SCC had low risk HPV type 11 in a patient with a history of juvenile laryngeal papillomatosis. Two of three of these cases had similar patterns of allelic imbalance between the lung tumor and the original tumor.
Take home message: There was no support for HPV being a causative factor in primary lung cancer in this population.

**Watanabe S et al. Results of T4 Surgical Cases in the Japanese Lung Cancer Registry Study. Should Mediastinal Fat Tissue Invasion Really be Included in the T4 Category? J Thorac Oncol 2013;8: 759-765.**

Background: T4 lung cancer includes invasion of the mediastinal fat, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body and carina, and nodules in ipsilateral different lobes.

Purpose: To determine if T4 lung cancer patients have a better prognosis if only mediastinal fat is involved without invasion of other organs or ipsilateral nonprimary lobe pulmonary mets.

Methods: The Japanese Joint Committee of Lung Cancer Registry did a retrospective study of primary lung cancers in 2004. Of these, 215 surgical cases had a T4 stage. The cancers were adenos, SCCA and others. R status and N status were recorded. The outcomes of the patients were recorded.

Results:
Univariate analysis showed age, tumor size and nodal status to be significant prognostic factors.
Multivariate analysis showed that 70 year of age and older and nodal status were significant prognostic factors. Patients over 70 with any nodal involvement did worse, while patients under 70 without nodal involvement had a better prognosis. There was no significant difference in survival in the three groups with T4 disease.

Take home message: The current TNM staging system has an appropriate definition.


Background: EGFR has been found to be more likely positive in East Asians, women, never-smokers, and adenocarcinoma.

Purpose: To determine the frequency of EGFR in Malaysian patients with lung adenocarcinoma.

Methods: Records from patients who had EGFR testing at the Sime Darby Medical Center were reviewed and 812 adenocarcinomas were chosen to be evaluated. Tissue samples were obtained and mutation analysis was performed for EGFR.

Results:
The highest prevalence of lung cancer in the Malaysian patients was in the Chinese (63.7%).
EGFR mutations were detected in 40% of patients, most commonly exon 19 and next common exon 21. Eleven cases had more than one mutation (1%). There was no statistical significance between age of patients with and without EGFR mutations. Mutations were seen in more men than women, and in more never-smokers than ever-smokers.

Take home message: The Asian pathologist and clinicians advisory board recommends reflex testing for EGFR on lung adenocarcinomas, which has been justified by this study.


Background: It is no uncommon for tissue to be insufficient for a cell block after FNA.

Purpose: To evaluate the results of immunostaining cell-transferred FNA cytologic smear results with FFPE tissue.

Methods: Forty two FNA specimens were obtained from Indiana University in which there was enough material for direct smears and tissue block. These tumors included 6 adenos, 12 SCCA, 6 small cell CA, 13 metastatic urothelial cell CA and 5 metastatic ductal adenoca of the breast. IHC on the adenos and SCCA were performed – CK7, CK20, TTF1, CDX2, p63, and AE1/3. Small cell CA panel included TTF1, chromogranin, synaptophysin, and CKAE1/CAM5.2. IHC for the urothelial CA were CK7, CK20, and p63. The ductal CA has ER, PR and her2. A cell transfer technique was used on Pap stained slides – the areas on interest were transferred onto charged glass slides, then IHC was performed. IHC was recorded as 0 (no staining), 1+ (1-33% staining), 2+ (34-66% staining), and 3+ (>66% staining).

Results: Ninety seven percent of the cases showed staining results that agreed with the FFPE results, which included 78/81 positive cases and 75/76 negative cases. Two cases of urothelial CA showed discrepancies on CK20. Overall there was a 97.5% concordance rate between the cell transfer slides and the FFPE slides. Limitations include: only alcohol-fixed direct smears can be used for the cell transfer. The cell transfer itself takes 5-7 hours to complete.

Take home message: IHC performed on cell-transferred FNA smears is accurate and comparable to the FFPE tissue and may be helpful when no tissue is available for cell block.

Background: The histology of lung cancer has been considered a predictive factor for the effectiveness of chemotherapy on NSCLC, but there has not been evaluation of the histology as a prognostic factor.

Purpose: To determine if adenocarcinoma of the lung and lower smoking status results in better overall survival in advanced NSCLC.

Methods: Case report forms were sent to 40 institutions affiliated with the West Japan Oncology Group, requesting information on their patients with Stage IIIB or IV NSCLC who were on chemotherapy during a two year period of time. These reports yielded 1731 adenocarcinoma patients and 740 non-adenocarcinoma patients. Demographic and clinical variables were recorded.

Results: The case reports showed 1346 deaths in the adeno group and 599 deaths in the non-adenoc group. There were more women and non-smokers in the adeno group than in the non-adenoc group. Adeno had a significantly better survival than SCCA and large cell CA. Non-smokers had a significantly longer survival than smokers, in both adeno and SCCA. Sex, age, smoking status, disease stage, histology and chemotherapy showed a statistically significant impact on survival.

Take home message: Adenocarcinoma histology has a better prognosis than the other histologies. Smoking status has a prognostic impact only on patients with adenocarcinoma.


Background: Up-regulation of PD-L1 allows tumors to escape the effector-immune responses. Monoclonal antibodies against PD-L1 show antitumor activity in lung adenocarcinomas. However, sarcomatoid carcinomas have not been studied in this light.

Purpose: To determine if anti-PD-L1 therapy would be useful in sarcomatoid carcinomas (SC) of the lung.

Methods: Between Yale University and a hospital in Greece, 13 SC were selected from 458 patients with lung cancer for PD-L1 measurement using a TMA format. Of the 13 SC, 10 were giant cell carcinomas, 1 was a carcinosarcoma and one was a pleomorphic carcinoma. Human placenta and tonsil was used as controls. All 458 samples were measure for PD-L1. PD-L1 was measured using quantitative fluorescence analysis.
Results: In the giant cell carcinomas, PD-L1 positivity was seen in both tumor and stromal cells. Of the 13 SC, 9 were positive for PD-L1 and levels were 40% higher than in NSCLC. Only 122 of the 445 NSCLC were positive for PD-L1.

Take home message: Anti-PD-L1 targeted therapy might be useful in sarcomatoid carcinomas of the lung.


Background: IGF is a growth factor that regulates fetal development, growth and metabolism; the central component of this regulator is IGF-1 receptor (IGF-1R). It has been suggested that IGF-1R activation may enhance proliferative and metastatic potential in tumors, suggesting that this may be a pathway that would be potential therapy.

Purpose: To study the expression of IGF-1R in NSCLC, the correlations between that and gene copy number alternations. To determine the status of EGFR, K-ras mutations and ALK rearrangements in these cases.

Methods: From the National Care Center Hospital in Tokyo, 379 patients who underwent lung resection for lung cancer between 1997 and 2007 were chosen. Diagnoses were made based on the WHO classification and the newly proposed ADC classification. There were 179 adenos (69 well-diff, 52 mod dif, 58 poorly diff), 150 SCCAs (53 well diff, 51 mod diff, 46 poorly diff), 9 large cell CAs and 41 sarcomatoid carcinomas. They were reclassified using 10 antibodies and divided into 3 grades. Microarrays were constructed and IHC was performed. Gene copy number was done by BISH analysis. EGFR, K-Ras and ALK mutations/gene rearrangement were analyzed.

Results: EGFR mutation was detected in 33% of 218 cases, K-ras mutation was detected in 20% of 216 cases and ALK rearrangement was detected in 3% of 223 cases. IGF-1R expression was seen in 41% of 379 NSCLC (25% of adenos, 70% of SCCAs, 33% of large cell CAs and 12% of sarcomatoid CAs). Seventy five percent of invasive mucinous adenos were positive for IGF-1R. No expression was seen in normal or hyperplastic lung tissues. IGF-1R was seen more frequently in smokers than non-smokers, older patients, males, and K-ras mutation status. A positive gene copy number of IGF-1R BISH did not confer gene amplification. IGF-1R expression was not correlated with overall survival.

Take home message: No prognostic value of IGF-1R expression in NSCLC was revealed in this study.

Background: The pathogenic features of ILD are similar to those of carcinogenesis related to cigarette smoking as well as COPD and IPF.

Purpose: To determine if there is a negative correlation between tumors with EGFR mutations and preexisting ILD, which is independent of other predictive factors.

Methods: Between Jan 2008 and April 2012, 555 patients with lung adenocarcinoma at Kobe City Medical Center were analyzed. Records on the cases and radiographs were reviewed. Smoking status was obtained. EGFR, KRAS and ALK rearrangements were tested for. Preexisting ILD was evaluated using HRCT and/or tissue review. Patients with ILD and adeno were categorized into two areas: those in which the tumor was located in the ILD and those in which the tumor was in a non-ILD area.

Results: Six percent of the 555 patients had preexisting ILD. The frequency of EGFR mutations was very low in patients with ILD. None of the adenos were ALK positive. None of the tumors in the non-ILD area were EGFR positive. Kras mutation positivity was similar to that seen in previous reports.

Results: There is an inverse relationship between ILD and tumors with EGFR mutations in lung adenos. This suggests that patients with underlying ILD and tumor may not need EGFR studies.


Background: Smoking exposure (nicotine) has been shown to have a negative effect on EGFR-TKI therapy in lung cancer reportedly by activating survival pathways as well as changing expression of nAChR subunits in the lungs.

Purpose: To study the expression of the nAChR mRNA and protein in NSCLC cell lines and human tissues. To study the role of nicotine in activation of ERK and Akt pathways through the nAChR cells. To study the ability of nicotine nAChR signaling to inhibit treatment by EGFR-TKI.

Methods: Forty three paraffin embedded lung cancer specimens were obtained from Kyushu University Hospital to include 32 adenos, 7 SCCA, 2 large cell adenos, and 2 small cell CAs. These were stained with IHC for nAChR and scored according to the amount and intensity of membrane staining. Comparisons of these results were made with results from three NSCLC cell lines that were purchased. Using Western blot analysis, the pathways induced by nicotine were examined in purchased cell lines. The purchased cell lines were pretreated with nicotine and then treated with various
concentrations of EGFR TKI, after which survival was determined by absorbance testing and comparison with control.

Results: Nicotine caused phosphorylation of EGFR within 5 minutes and peaked within 30 minutes (in a time dependent manner). Nicotine likely acts through a pathway from nAChR to EGFR thereby inducing EGFR-signaling pathways. The study proved that the alpha-1 subunit is responsible for the EGFR release.

Take home message: Continued or chronic nicotine exposure increases resistance to EGFR-TKI. Targeted inhibition of nAChR might be a treatment in NSCLC.


Background: The molecular basis for this disease process is unknown.

Purpose: To analyze multiple PLCH nodules in a single individual for the presence of BRAF V600E mutations.

Methods: Five cases of PLCH were identified from UPMC. The diagnoses were confirmed by S100 and CD1a positivity. In these cases, 22 nodules were microdissected and DNA was isolated for next-generation sequencing.

Results: There was concordance of the BRAF mutation. If BRAF mutation was found in one nodule in a patient, all of that patient’s nodules were positive, and if it was not present in one, it was not present in any in the same patient, suggesting a clonal process.

Take home message: Targeted therapy against BRAF mutations is currently used in other tumors, and may be successful in PLCH in patients positive for that mutation.


Background: Crystal-storing Histiocytosis (CSH) is a rare disorder which may involve several organs, including the lungs. There are rare reports in the literature with no previous series reported.

Purpose: To report a series of 5 cases of CSH with a review of clinicopathologic conditions and differential diagnosis.

Methods: Five cases of CSH from 2007 and 2011 involving the lung were reviewed. One of these cases was pleural based. IHC was performed on the paraffin embedded tissue for CD68, CD1a, CD3, CD20, CD79a, CD138, Ki67 and pancytokeratin. CXR and CTs were
performed and reviewed on all patients. Heavy chain clonality was assessed on all cases using PCR. Histology was reviewed in all cases.

Results: All cases had an underlying hematopoietic disorder. Three patients underwent chemo; 1 had steroids, and 1 had no treatment. Two patients died – one of lung disease and one of an MI. Imaging showed different results from cystic nodules to calcified nodules to pleural plaque. Histology was typical for CSH with CD68 positivity. Intracytoplasmic crystals were kappa positive. Kappa light chain restriction was identified. All cases had a clonal restriction of the lymphoproliferative and plasma cell disorders, confirmed by PCR. Discussion of the differential diagnosis was included.

Take home message: The clinical presentation of CSH is variable, as well as the background disease that sustains CSH. The differential diagnosis may be challenging.

NON-NEOPLASTIC


Background: The inhalation of flocked nylon fragments which can take place in nylon flocking plants in the world has been linked to a recognized occupational lung disease.

Purpose: To study the natural history of Flock Worker’s Lung Disease (FWL) and to examine the long term effects of exposure to worker’s who don’t have the disease process.

Methods: Baseline surveys were given to 86 people who worked in this field in the years 1991-1992. FWL was diagnosed in 9; 30 were exposures. Several were lost to follow up. Data reviewed included symptoms, spirometry, chest radiographs, PFTs, plethysmographic lung volumes and DLCO.

Results: The natural history of FWL has several patterns from complete resolution of symptoms after leaving the workplace to progressive decline in lung function with resultant respiratory failure, pulmonary hypertension and death.

Take home message: FWL can be a serious occupational health disease which can result in death. Further work needs to be done to determine the effect of cigarette smoking on these patients and the risk of lung cancer development, if any.


Background: Glut-1 is the predominant glucose transporter in the lung and is responsible for FDG uptake in PET scans.
Purpose: To determine the cause of increased FDG uptake in lung with pulmonary fibrosis.

Methods: Patients with IPF, Hermansky-Pudlak syndrome (HPS) and health volunteers had BAL performed. Lung tissue was obtained from clinically indicated procedures. An array of normal lung tissue and 19 different lung tumors was purchased. Anti-Glut-1 antibody was placed on the lung sections and confocal microscopy was performed with comparison to H&E stained slides.

Results: Increased Glut-1 staining was seen in erythrocytes and inflammatory cells in IPF. In normal lung tissue, staining was seen in erythrocytes but no other cells. In HPS, increased staining was similar to that of IPF. The same findings were seen in BAL fluids. In tumors, pronounced positivity with anti-Glut-1 antibody was seen, even in BAC which usually does not show increased uptake on PET.

Take home message: Glut-1 uptake is seen in erythrocytes and inflammatory cells in fibrotic lung disease and not in the fibrotic tissue. This suggests that changes in vascular development and increased erythrocytes may explain the Glut-1 expression in fibrotic lung disease. It does not appear that increased metabolic rate of epithelial cells is responsible for the Glut-1 uptake on PET scans.


Background: Chronic lung allograft dysfunction (CLAD) has been previously linked to obliterative bronchiolitis (OB). Recent studies suggest that this is actually a heterogeneous group of conditions.

Purpose: To follow the postoperative course of lung transplant recipients using FEV1 and FVC, CT to evaluate BOS/BO, and to review the pathology to determine the causative factors.

Methods: 194 lung transplant recipients were selected. CTs and pathology were reviewed to determine the cause for CLAD. PFTs were done serially, as well as monthly spirometry.

Results: Two distince forms of CLAD emerged during this process. Only 45% of patients with CLAD fit the criteria for BOS/OB. Twenty five percent were categorized as AFOP. The remaining patients were a heterogeneous group and a cause couldn’t be determined. Survival was worse in the AFOP group.

Take home message: I am not sure what the message is – I had a hard time with this paper that still calls AFOP a disease process, when we think of it as non-specific changes.
Watanabe M et al. Micropapillary components in a lung adenocarcinoma predict stump recurrence 8 years after resection: A case report.

Case Summary: A 50-some year old woman with an abnormal CXR had a CT showing a tumor in the right middle lobe invading into the right upper lobe. A right middle lobectomy was performed revealing an invasive adenocarcinoma with a 10% micropapillary component. Two years later, another tumor was seen on CT and she had a right upper lobectomy which revealed an invasive adeno with 20% micropapillary component with LVI. Both tumors were histologically and immunohistochemically similar, as well as shared the same genetic deletions. Upon further review of the original surgery, clusters of micropapillary adeno were found in alveoli 2.5 mm from the margin, suggesting this is a stump recurrence.

Take Home Message: Adeno with a micropapillary component can spread further from the main tumor through aerogenous dissemination and if seen near the surgical margin closer follow up is suggested.


Case Summary: A 70-year-old former smoker and current marathon runner (male) was diagnosed with a probably SCCA of the RUL with possible satellite lesions in the RML and LUL on CT, and was considered to have a primary lung CA with intrapulmonary mets. He received chemotherapy and 11 months later the RUL lesion increased in size. At that time, the possibility of multiple primary tumors was entertained. The three lesions were biopsied and showed two papillary adenos and a mixed papillary adeno/adeno CA in situ. Genomic hybridization analysis showed all three lesions to have different patterns of gains and losses, c/w 3 different primary tumors.

Take Home Message: Because the treatment is different, intrapulmonary lung mets and multiple synchronous primary lung cancers need to be differentiated. This requires histology and imaging, and array-comparative genomic hybridization analysis may be helpful.


Case Summary. A 40-year-old woman with chronic kidney disease requiring dialysis and a remote history of leiomyoma requiring hysterectomy was found to have multiple lung nodules on CXR. VATS was performed and a nodular protrusion was seen on the pleural surface. Sections revealed a cyst filled with brown fluid, lined by TTF-1 positive pneumocytes and focal micropapillary pneumocyte hyperplasia. The wall of the cyst resembled smooth muscle and was positive for ER, PR, Bcl-2, CD10 and SMA. The
diagnosis of benign metastasizing leiomyoma was made. Further discussion of the clinical, radiologic and pathologic findings followed.

Take Home Message: The most common metastatic site for leiomyoma is the lung and this needs to be part of the differential diagnosis of a woman with lung nodules.


Case Summary: A 31-year-old Japanese male was found to have a pleural mass on CT. VATS revealed disseminated plaque-like nodules over the left parietal and visceral pleura, as well as the diaphragm and pericardium. Histology showed the tumors to be multiple/disseminated calcifying tumor of the pleura.

Take Home Message: Multiple/disseminated calcifying tumor of the pleura is a rare lesion that needs to be differentiated from desmoplastic mesothelioma and IgG-4 sclerosing disease.


Case Summary: A 60-year-old man presented with weakness, LE swelling and SOB. His BP was elevated, serum potassium was low and bicarb was low. Renin activity and aldosterone were low. ACTH was high on two consecutive days. CT revealed a soft tissue mass to the left of the main pulmonary artery. Resection revealed a typical thymic neuroendocrine tumor. Postoperatively, his potassium levels normalized, as well as his ACTH level.

Take Home Message: Thymic NETs comprise 4-6% of anterior mediastinal tumors and commonly cause endocrinopathies and paraneoplastic syndromes.

REVIEW ARTICLES


A review of Coal Mine Dust Lung Disease with discussion of recent advances made in coal mining in lieu of the lung diseases that can be seen in these workers. The radiology, diagnosis, histology and management of this disease process is reviewed. The article is more clinically based that pathology based.

A guideline from the CAP, IASLC, and AMP that establishes evidence-based recommendations for choosing which patients and samples should be tested for EGFR and ALK directed therapies, answering such questions as when should testing be performed, which tests should be ordered, how long should results take to come back, how should EGFR testing be performed, what is the role of KRAS analysis, how should ALK be performed, what other testing should be done, and others.