# Articles for Discussion

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# Articles for Notation

## Original Articles

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## Review Articles

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<td>Bremnes RM et al.</td>
<td>The role of tumor-infiltrating immune cells and chronic inflammation at the tumor site on cancer development, progression, and</td>
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Case Reports
I. Articles for Discussion


Purpose: To compare the utility of p16 FISH and GLUT-1 immunohistochemistry in distinguishing benign and malignant mesothelial proliferations.

Methods: A total of 158 cases (70 benign/reactive, 16 atypical, 68 malignant mesothelioma) were subjected to GLUT-1 immunohistochemical analysis and dual-color FISH analysis for the p16 deletion. GLUT-1 staining was scored semiquantitatively. A majority of the specimens were biopsies/resections and the remaining 30% were cytologic specimens with cell blocks. Of the mesotheliomas, 40% were pleural and 60% were peritoneal.

Results: GLUT-1 staining was observed in 7% of benign cases, 19% of atypical cases, and 40% of mesotheliomas (56% of pleural and 29% of peritoneal mesotheliomas). In the diagnosis of mesothelioma, overall GLUT-1 sensitivity was 40% and specificity was 93%. GLUT-1 sensitivity was higher for pleural mesothelioma, while specificity was higher for peritoneal mesothelioma. p16 deletion was identified in 59% of mesotheliomas (59% sensitivity and 100% specificity) with sensitivity being better in pleural (70%) than peritoneal (51%) mesotheliomas. None of the benign/reactive cases had a p16 deletion, while 44% of atypical cases were positive for p16 deletion. Of the atypical cases with follow-up, p16 FISH correlated better than GLUT-1 with the follow-up histologic findings, being positive in 50% of subsequently histologically confirmed mesotheliomas and negative in all cases confirmed as benign/reactive on follow-up.

Discussion: p16 FISH has higher sensitivity and specificity as compared with GLUT-1 immunostaining in the distinction of malignant mesothelioma from benign mesothelial proliferations, particularly in pleural cases.

Take Home Message: GLUT-1 staining can be difficult to interpret as staining is often weak and/or heterogeneous and because it also stains red blood cells. In the management of atypical mesothelial proliferations, p16 FISH appears to be a useful tool for guiding follow-up.

Tsuta K et al. Oncocytic neuroendocrine tumors of the lung: histopathologic spectrum and immunohistochemical analysis of 15 cases. Human Pathol 2011;42:578-85

Purpose: To describe the clinicopathologic features of oncocytic neuroendocrine tumors of the lung.

Methods: Cases of neuroendocrine carcinoma of the lung were retrospectively reviewed for the presence of 50% or more of cells showing oncocytic cytoplasmic change.

Results: There were 15 cases (11 typical carcinoid, 3 atypical carcinoid, and 1 large cell neuroendocrine tumor. While the oncocytic cells in most cases showed ample granular cytoplasm, 2 cases were composed of mainly small to medium-sized cells with eccentric nuclei and eosinophilic cytoplasm resembling plasma cells. In 8 of the 15 cases, giant cells with bizarre
nuclei were seen. Most of the oncocytic cells stained for antimitochondrial antibody. There were no statistical difference between the clinical features and 5-year recurrence-free survival in oncocytic and nononcocytic cases. Bone formation, giant tumor cells, and conspicuous nucleoli were statistically more frequent in oncocytic than non-oncocytic tumors.

Discussion: In the authors’ experience, the overall incidence of oncocytic carcinoid tumor is about 8.8%. Oncocytic change can be seen across the spectrum of neuroendocrine tumors, including large cell neuroendocrine carcinoma.

Take Home Message: Although distinguishing oncocytic neuroendocrine carcinoma from nononcocytic neuroendocrine carcinoma does not have prognostic implications, the former may be mistaken for squamous cell carcinoma or the recently described oncocytic primary adenocarcinoma of the lung. Utilization of neuroendocrine markers in the evaluation of oncocytic lesions and an awareness of the histologic features that may be seen in oncocytic neuroendocrine carcinoma, including giant cells and plasmacytoid cells, can prevent misdiagnosis.

Purpose: To identify poor prognostic factors in patients with stage I NSCLC based on the sixth edition TNM classification who would be reclassified as stage IB according to the seventh edition.

Methods: A total of 1204 consecutive patients with pathologic stage I NSCLC according to the sixth edition TNM classification who underwent complete resection with systematic node dissection between 1992 and 2004 at a single institution in Japan and did not receive neoadjuvant or adjuvant therapy were included. Of these, 434 were reclassified as stage IB according to the seventh edition TNM classification.

Results: On multivariate analysis, intratumoral vascular invasion and visceral pleural invasion, as determined either by H&E or on elastic staining, were independent significant adverse prognostic factors. The 5-year survival among patients without these factors of 93% did not differ from stage IA patients. Patients with one or two of these factors had a 5-year survival of 83 and 73%, respectively. The 5-year disease-specific survival curve of patients with both factors did not differ from that of patients with T2b or T3N0M0 (stage II) disease.

Discussion: Both intratumoral vascular invasion and visceral pleural invasion are poor prognostic factors in patients with stage IB NSCLC, but intratumoral vascular invasion is the most powerful prognostic factor. Further studies are required to determine if patients with these risk factors benefit from adjuvant chemotherapy.

Take Home Message: It appears likely that vascular invasion will be a staging parameter in future TNM classifications. Consider using elastic stains for evaluating not only visceral pleural invasion, but also vascular invasion.


Purpose: To evaluate whether involvement of a higher number of N1 lymph nodes is associated with worse survival independent of known prognostic factors in patients with NSCLC.

Methods: The SEER database was used to identify 1682 resected patients with N1 NSCLC diagnosed between 1992 and 2005. To account for the number of positive lymph nodes being confounded by the total number of nodes sampled, cases were classified into three groups based on the ratio of positive to total number of lymph nodes removed (lymph node ration (LNR)): less than or equal to 0.15, 0.16-0.5, > 0.5. Survival was compared between the groups using standard statistical methods.

Results: Survival was lower among patients with a high LNR with median lung cancer-specific survival being 47, 37, and 21 months for the less than or equal to 0.15, 0.16-0.5, > 0.5 LNR groups, respectively.
Discussion: In patients with N1 NSCLC, the extent of nodal involvement provides independent prognostic information that may allow for identifying patients that could potentially benefit from adjuvant therapy.

Take Home Message: While this paper provides some compelling data, it is not without its limitations. The patients were treated by different providers at multiple institutions and there was no uniform process for nodal sampling or to establish the absence of N2 disease. Although some studies have suggested at least 11 nodes be removed for optimal staging, there are no established guidelines. Additionally, the perennial issue of whether a fragmented specimen represents multiple nodes or pieces of a single node was not clearly addressed in this study.

II. Articles for Notation

Original Articles


Purpose: To better understand the relationship between pulmonary sarcoid granulomas and the blood vessels and capillaries that supply them.

Methods: A morphometric study of surgical lung biopsies from six cases of sarcoidosis stained for D2-40, CD34 and CD31 in which the distance from granulomas to lymphatics and the distribution of blood vessels associated with granulomas was evaluated.

Results: Intralobular granulomas were closely associated with lymphatics, while granulomas were very poorly supplied by capillaries. Capillaries stopped at the outer border of the fibrous ring surrounding granulomas. Lymphatic vessels were not seen within granulomas.

Take Home Message: Lymphatics, but not blood vessels, appear to play a critical role in the development (or at least sustenance) of pulmonary granulomas. The relatively avascular nature of sarcoid granulomas suggests blood-borne therapeutic agents may not be effective.


Purpose: To examine the associated between cigarette smoking and histologic subtypes of pulmonary adenocarcinoma.

Methods: A total of 320 consecutive Japanese patients with completely resected stage I adenocarcinoma were reviewed.

Results: Adenocarcinoma with a solid component was significantly more frequent in ever smokers than in never smokers. Adenocarcinomas with a solid component had significantly more lymph-vascular and visceral pleural invasion. A greater smoking extent was associated
with the presence of a solid component. Ever smokers had significantly lower recurrence-free probability than never smokers.

**Take Home Message:** Smoking-related lung adenocarcinomas appear to behave more aggressively than tumors in never smokers

**Raad D et al. Effects of water-pipe smoking on lung function: a systematic review and meta-analysis.** Chest 2011;139:764-74

**Purpose:** To systematically review the effects of water pipe smoking, which is becoming increasingly popular in Western cultures, on lung function and compare its effects to those of cigarette smoking on lung function.

**Methods:** A meta-analysis of six systematically identified studies was conducted, which compared spirometric measurements among nonsmokers, water pipe smokers, and cigarette smokers.

**Results:** Water pipe smoking was associated with a statistically significant reduction in FEV1 and FEV1/FVC as compared to no smoking. There was no significant difference in FEV1, FVC, and FEV1/FVC between water pipe smokers and cigarette smokers.
Take Home Message: Water pipe smoking adversely affects lung function and may be as harmful as cigarette smoking.

*Sterlacci W et al. The prognostic impact of sex on surgically resected non-small cell lung cancer depends on clinicopathologic characteristics. Am J Clin Pathol 2011;135:611-18*

**Purpose:** To analyze the impact of gender on survival in patients with surgically resected NSCLC.

**Methods:** Clinicopathologic features of 405 surgically resected NSCLC at a single institution from 1992 to 2004 in Austria were analyzed using tissue microarray.

**Results:** Female gender, which was significantly associated with favorable factors, including adenocarcinoma histology and well to moderate differentiation, predicted increased survival only by univariate analysis.
Take Home Message: Gender is not itself an independent prognostic parameter in patients with surgically resected NSCLC but is rather associated with other favorable factors, thus simulating a prognostic impact of gender.


Purpose: To compare the immunohistochemical expression profiles of the neurotrophic tyrosine kinase receptors NTRK1 and NTRK2 in various histologic subtypes of lung carcinoma and correlate with patient outcome.

Methods: A tissue microarray of 680 lung cancers (271 squamous cell, 226 adenocarcinoma, 94 carcinoid, 21 NSCLC NOS, 53 large cell, 21 other) was subjected to immunostaining using commercially available antibodies. Only cases with circumferential membranous staining in 1 or more tumor cells regardless of staining intensity were considered positive.

Results: Expression of NTRK1 and NTRK2 correlates strongly with squamous histology and is highly specific (92.8 and 96.4%, respectively), but only moderately sensitive (71.6 and 51.3%, respectively). Positive NTRK2 staining in squamous cell carcinoma correlates with improved disease-specific and overall survival.

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Total Cases</th>
<th>NTRK1</th>
<th></th>
<th>NTRK2</th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive</td>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>Squamous</td>
<td>271</td>
<td>194</td>
<td>77</td>
<td>72</td>
<td>139</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>226</td>
<td>19</td>
<td>207</td>
<td>6.4</td>
<td>6</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>94</td>
<td>1</td>
<td>93</td>
<td>1.1</td>
<td>1</td>
</tr>
<tr>
<td>Non-small cell NOS</td>
<td>21</td>
<td>5</td>
<td>16</td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Large cell</td>
<td>53</td>
<td>3</td>
<td>50</td>
<td>5.7</td>
<td>7</td>
</tr>
<tr>
<td>Other</td>
<td>21</td>
<td>2</td>
<td>19</td>
<td>9.5</td>
<td>0</td>
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</table>

Take Home Message: Although the authors conclude that NTRK1 and 2 are potentially useful in separating squamous cell carcinoma from adenocarcinoma, they concede that the specificity of these markers is comparable to other markers (e.g. p63, CK 5/6, TTF-1) commonly used in this distinction and their sensitivity is lower. While not emphasized in this paper, it is also important to note that NTRK1 is unlikely to aid in the distinction from primary lung and metastatic squamous cell carcinoma, as expression was seen in normal oral mucosa and squamous cell carcinoma of the skin. Interestingly, NTRK2 expression was not observed in extra-pulmonary sites, suggesting further studies of this marker might be warranted.
Review Articles

Bremnes RM et al. The role of tumor-infiltrating immune cells and chronic inflammation at the tumor site on cancer development, progression, and prognosis: emphasis on nonsmall cell lung cancer. J Thorac Oncol 2011;6:824-33

This report presents a review of the literature on the role of tumor-infiltrating inflammatory cells in tumor progression and survival. In short, increased numbers of stromal dendritic cells, T-cells, and NK cells, as well as peritumoral B-cells are significantly associated with increased disease-specific survival, while macrophages do not appear to play a role. Survival data on mast cell infiltration has been mixed. The findings support investigating combined treatment strategies that attack the tumor microenvironment as well as the neoplastic cells.

Case Reports


Case Summary: A 19-year-old male with a history of asthma presented with SOB and right-sided pleuritic pain. Imaging showed mediastinal shift with right volume loss, prominent right interstitial markings, and an extraneous left atrial septum. Endobronchial biopsy disclosed prominent submucosal capillaries. A diagnosis of cor triatriatum sinistrum with secondary unilateral pulmonary venous hypertension and right lung hypoplasia was made.
Take Home Message: In this unusual case, a membrane in the left atrium preferentially obstructed right pulmonary venous inflow. In classic cor triatriatum sinistrum, the anomaly is situated such that bilateral pulmonary venous hypertension results, clinically resembling congenital mitral stenosis. This case illustrates the importance of considering a cardiac etiology in patients with unilateral pathologic features of pulmonary hypertension.


Case Summary: Two cases of nodular pulmonary ossification manifesting radiographically as a solitary nodule are presented. One was a 68-year-old male with a PET-positive right hilar nodularity. Wedge resection of the RML disclosed an area of diffuse nodular pulmonary ossification (NPO) and features of pulmonary hypertension. The other case was a 71-year-old male status post chemotherapy for pT4N2M1 rectal carcinoma with two lung nodules suspicious for metastatic disease. Wedge resections disclosed one of the nodules was a metastasis with the other showing features of NPO.
Take Home Message: Pulmonary ossifications are regularly misinterpreted on imaging, often being mistaken for bronchiectasis, hamartomas, or silicotic nodules. A nice table for distinguishing nodular and dendritic pulmonary ossification is presented in this report.

<table>
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<tr>
<th>Feature</th>
<th>DPO</th>
<th>NPO</th>
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<tr>
<td>Radiographic</td>
<td>Branching, dendritic, coral-like</td>
<td>Round with smooth contours, lobulated</td>
</tr>
<tr>
<td>Histological</td>
<td>In alveolar septa, tubular shape of bone</td>
<td>Within alveolar spaces, lobulated bone</td>
</tr>
<tr>
<td>Marrow</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Clinic</td>
<td>Associated with chronic obstructive lung disease and interstitial fibrosis</td>
<td>History of passive congestion and cardiac problems</td>
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Case Summary: A 77-year-old male presented with a 6-month history of progressive dyspnea, weight loss, low grade fever, dry cough and dry mouth. Imaging showed mediastinal and hilar adenopathy and diffuse linear and nodular pulmonary opacities with patchy ground glass attenuation. Lung biopsy showed interstitial plasmacytic infiltration with alveolar septal thickening and architectural distortion. Results of staining for IgG4 and IgG serum levels were consistent with IgG4-related systemic sclerosing disease. The patient became asymptomatic following lung biopsy.

Take Home Message: Spontaneous remission of IgG4-related systemic sclerosing disease is exceedingly rare, but has now been reported in two instances.


Case Summary: A 73-year-old female with pulmonary veno-occlusive disease, who was treated with imatinib (Gleevec) on the basis of a prior case report demonstrating marked improvement in functional capacity in a patient with PVOD treated with this agent, showed no favorable response to the drug.

Take Home Message: While imatinib has been effective in treating at least one case of PVOD and some patients with advanced pulmonary arterial hypertension, much remains to be learned about the role of PDGF and other cell signalling molecules that are in the pathway affected by tyrosine kinase inhibitors in the development of PVOD.