Articles for discussion


**Purpose:**
- The distinction between primary lung adenocarcinoma and squamous cell carcinoma may have important therapeutic considerations.
- p63 is relatively sensitive, but according to the authors suffers from low specificity and may show positivity in some adenocarcinomas and lymphomas.
- To compare the use of p40 (a p63 isoform) vs p63 in the evaluation of a large set of squamous cell carcinomas, adenocarcinomas and large cell lymphomas.

**Methods:**
- Whole tissue sections were selected from two institutions. SCC = 81. Adenocarcinoma = 237.
- The tumor samples were weighted to mostly represent moderately and poorly differentiated carcinomas.
- For these cases p63 was re-analyzed and immunohistochemistry was conducted for p40 on all SCC and 205 adenocarcinomas.
- Lymphomas were evaluated by tissue microarray and included 73 primary mediastinal large B-cell lymphomas, 67 diffuse large B-cell lymphomas not otherwise specified, and 12 anaplastic large cell lymphomas.
- For all markers, both extent (% cells) and intensity (1+, 2+, 3+) of immunoreactivity were recorded.
- H (‘histological’) scores were derived by multiplying percentage of immunoreactive cells by the intensity score.

**Results:**
- Both p63 and p40 were positive in 100% of SCC. Staining was strong and diffuse.
- For adenocarcinoma, the p63 showed a wide range of reactivity. Any reactivity was noted in 31% of cases, including 4% of cases with diffuse reactivity.
- For adenocarcinoma, p40 showed only minimal reactivity in 3% of cases and all such cases exhibited less than 5% staining.
- For lymphoma, p63 showed reactivity in 54% of cases. In contrast, p40 was entirely negative in these cases.

**Take Home Points:**
- p40 has equivalent sensitivity to p63 for the evaluation of SCC.
- p40 is more specific than p63 in the added differential of adenocarcinoma and large cell lymphoma.
- Consideration should be given to routine use of p40 in place of p63.

**Purpose:**
- Some recent studies have demonstrated positivity for Naspsin A in up to 26% of Squamous cell carcinomas.
- To determine the causes of the discrepancies between some recent immunohistochemical studies and previous reports on napsin A expression in squamous cell carcinomas of the lung.

**Methods:**
- Review tissue from 90 SCC from lung (55 whole sections and 35 biopsies), 15 well diff, 43 mod diff, 32 poorly diff
- Review tissue from 64 non-pulmonary squamous carcinomas. Also used normal esophagus, tonsil, cervix and skin.
- Immunohistochemical studies on FFPE sections
- Used was the IP64 mouse anti-napsin A monoclonal antibody

**Results:**
- None of the 90 squamous cell carcinomas of the lung or the 64 extrapulmonary squamous cell carcinomas investigated exhibited napsin A positivity in the neoplastic cells.
- The lung parenchyma adjacent to the tumor often contained Napsin A positive hyperplastic type II pneumocytes and large collections of intra-alveolar macrophages that frequently seemed to be entrapped in areas of desmoplasia adjacent to the tumor.
- In 5 biopsies, these entrapped cells were difficult to distinguish from neoplastic cells.
- In contrast, 2 recent studies, by Fatima et al using cytology specimens and the other by Pereira et al using tissue microarray, reported napsin A positivity in 3 (12%) of 24 and 8 (26%) of 31 squamous cell carcinomas of the lung, respectively.

**Take Home Points:**
- In this study, none of the whole sections or biopsies of the squamous cell carcinomas of the lung showed any napsin A positivity in neoplastic cells, a finding that confirms the similar observation reported by other investigators.
- The napsin A positivity reported in squamous cell carcinomas in some recent studies may have represented entrapped intra-alveolar macrophages and/or type II pneumocytes within the tumor that were difficult to recognize in the type of specimen used.
- In conclusion, pathologists should be aware that the strong napsin A expression in intra-alveolar macrophages and type II pneumocytes can be a pitfall in the interpretation of the immunostaining of lung tumors, especially in tissue microarrays, small lung biopsy specimens, and cytology specimens.

**Purpose:**
- To compare accuracy of bronchoscopic cytology specimens with biopsy specimens in diagnosing and subclassifying lung carcinoma

**Methods:**
- Identified 467 patients suspected of having lung carcinoma who underwent bronchoscopy in 2007-2008 yielding both cytologic and biopsy specimens.
- No re-review of pathology?
- Bronchoscopy findings classified as 1) visible endoscopic lesion, 2) nonspecific mucosal abnormalities, 3) normal.
- Cytology samples included bronchial brushing, aspirates, and blind TBNA of LNs.
  - brushings = 2 smears
  - aspirates = centrifuge pellets → 3 smears + cell block
  - TBNA = “very few” on-site smears “mainly related to sample collection date”
  - no IHC stains!
- Biopsies included BBx, TBBx, and blind transbronchial core needle bx (ie, 19 gauge histology needle)
  - IHC for CK7, CK20, TTF1, chromogranin, CD56
- Pathology results (both cytologic and histopathologic) classified as 1) non contributive (ie, inadequate), 2) negative, 3) suspicious, and 4) positive.
- Reports for follow-up surgicals in subset (121 – 27%)

**Results:**

<table>
<thead>
<tr>
<th>Histology Dx</th>
<th>Cytology Dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inadequate</td>
<td>Negative</td>
</tr>
<tr>
<td>Inadequate</td>
<td>10</td>
</tr>
<tr>
<td>Negative</td>
<td>42</td>
</tr>
<tr>
<td>Suspicious</td>
<td>0</td>
</tr>
<tr>
<td>Positive</td>
<td>44</td>
</tr>
<tr>
<td>TOTAL</td>
<td>96</td>
</tr>
</tbody>
</table>

- Low rate of agreement between cytology and biopsy (kappa = 0.28)

**Take Home Points:**
- Poorly designed study that does not reflect current standard practices. Observations might have been interesting 10-15 years ago. Now, not so much. Who reviews these things?!
Purpose:
- Report the clinicopathologic and molecular cytogenetic findings in two pediatric cases with NUT carcinoma t(15;19).
- Confirm the presence of NUT Midline carcinoma (NMC) of lung origin and to provide novel information concerning the histogenesis of NMC.

Methods:
- Formalin-fixed paraffin embedded tissues were utilized from the 2 cases. Cases were stained with a variety of immunohistochemical stains, including NUT.
- Additionally ultrastructural examinations were performed, as well as RT-PCR to examine for BRD4-NUT expression.

Results:
- The tumor cells had round-to-oval nuclei with conspicuous nucleoli, relatively fine chromatin, and a slightly basophilic cytoplasm.
- The biopsied specimen of case 2 showed epitheliod tumor cells with overt squamous differentiation in some nests.
- Immunohistochemistry showed both cases to stain for antibodies against p63 and NUT.
- TTF-1 was positive in case 1 but negative in case 2.
- RT-PCR analysis of the biopsied specimens from both case 1 and case 2 confirmed expression of the BRD4-NUT fusion gene.

Take Home Points:
- NMC may occur as an intrapulmonary tumor and may show staining for TTF-1.
- The histopathology of the transitional areas between the tumor cells and bronchioles and diffuse positivity for p63 and TTF-1, leads the authors to suggest that the tumor cells of case 1 were derived from basal cells or have characteristics similar to basal cells of the bronchiolar epithelium.
- The TTF-1 negativity may be related to overt squamous differentiation in tumor cells of case 2.
- NMC may have characteristics similar to basal or progenitor cells of the epithelium.
- Histology and immunohistochemistry may vary by case, even if tumors occur are in the same organ. This may possibly reflect the nature of the tumor, including degree of squamous differentiation.
**Articles for notation**


**Take Home Points:**

5 review articles comprising a special section in the March issue of APLM devoted to conditions of the serosal surfaces, focusing on mesothelioma. There is a fair bit of overlap between the articles, but they’re well written and worth knowing about if you’re looking for the latest summaries of IHC stains of potential value etc.

- Antilla (*Epithelioid lesions of the serosa*) focuses on mesothelioma, touching only briefly on serous papillary carcinoma of the peritoneum and unusual variants of mesothelioma (i.e. localized, well differentiated papillary and adenomatoid tumors) with some nice tables summarizing IHC stains with references.

- Betta et al (Immunohistochemistry and molecular diagnostics of pleural malignant mesothelioma) expands on review by Antilla and includes new knowledge developed from interrogation of 2003-2009 database entries from a hospital in a region of Italy with high levels of asbestos exposure. Important observations are performance of **3-antibody** (calretinin, Ber-EP4, MOC31) and **2-antibody** (calretinin and Ber-EP4) panels to distinguish MM from adca, with sensitivities of 98% and 93% and specificities of 90% and 97%, respectively. In addition nice summary of emerging tools (9p21 deletion, CGH, DNA methylation and miRNA expression profiling) potentially useful in distinguishing benign from malignant mesothelial proliferations.

- Jasani et al (Mesothelioma not associated with asbestos exposure) review known causes of mesothelioma other than asbestosis, focusing on erionite (non-asbestos fibrous metal reported as cause of MM in Turkey), irradiation and thorium dioxide (Thoratrast) administratin. Finishes with nice review of the still controversial literature regarding potential carcinogenic role of SV40 virus.

- Attanoos (Lymphoproliferative conditions of the serosa) briefly reviews both neoplastic and non-neoplastic lymphoproliferative disorders involving serosal surfaces, including synopsis of HHV-8 positive primary effusion lymphomas and pyothorax-associated B-cell lymphomas.

- Jean et al (Molecular changes in mesothelioma with an impact on prognosis and treatment) have produced a well written review that is the largest and most cutting edge of the bunch. A comprehensive overview of current understanding of molecular events in MM. Tried hard to read it but confess that after awhile all of the chromosomal losses and gains, tumor suppressor genes, oncogenes, miRNAs, CpG islands, and affected pathways triggered my circuit breaker. But at least I’ll remember this reference should knowing the answers to these questions seem useful! At this point enough to know that there are some unique molecular profiles that have potential value in both diagnosis and prognosis, and that while no consistent targetable mutations have yet reached the stage of being tested in clinical trials that will no doubt change, as demonstrated in the notation article published by the same group elsewhere (Levallet et al. JTO 2012; 7: 599).

Purpose:
- To investigate prognostic significance of mesenchymal-epithelial transition (c-MET) and phospho-c-MET (activated form) expression on prognosis in mesothelioma

Methods:
- IHC staining of 157 cases sent to MESOPATH group (French mesothelioma study group)
- Staining score (“H-score”) = intensity (0-3) x percentage of positively staining cells (0-100%)
- Localization: cytoplasmic, cytoplasmic + cell membrane, cell membrane
- Confocal microscopy on human bronchial epithelial cell line stimulated to express c-MET

Results:
- Epithelioid 76% (119/157), sarcomatoid 12% (19/157), biphasic 10% (15/157), desmoplastic 2% (4/157)
- 119 (76%) were c-MET positive, primarily of epithelioid type (87%)
- Increasing intensity of staining was associated with localization to cell membranes
- 77 (65%) of c-MET positive tumors also expressed phospho-c-MET
- In vitro model showed same relationship between intensity of c-MET expression and localization to cell membrane
- ↑c-MET expression associated with longer survival; for those with staining intensity ≥ 2 median OS 25 months versus 13 months for others
- c-MET localization to cell membrane associated with longer survival; for those with membrane staining only median OS was 25 months compared to 11 months for cytoplasmic staining and 13 months for cytoplasmic + cell membrane staining

Take Home Points:
- c-MET may be useful prognostic marker, and more importantly might represent a novel therapeutic target, but methods not yet ready for prime time!

**Purpose:**
- One of a pair of articles using 250 surgically resected cases to evaluate, in the case of this paper, the WHO histologic classification scheme and, in the next paper, a new proposed staging system.

**Methods:**
- Tumors resected at MD Anderson from 1980-2009 characterized by, 1) slides available for review, and 2) ≥ 5 histologic sections, and 3) complete surgical excision (no biopsies included)
- Any histology comprising ≥ 5% of the examined surface area resulted in “mixed” histology

**Results:**
- type A – 54 (21.6%)
  - A+B – 38 (15.2%)
- type B1 – 33 (13.2%)
- type B2 – 8 (3.2%)
- type B3 – 23 (9.2%)
  - B1 + B2/B3 – 79 (31.6%)
  - B2 + B3 – 15 (6.0%)
- 52.8% showed mixed histology; majority (158; 63.2%) were B-type thymomas
- the more slides examined the more likely to be mixed
- no significant difference in overall survival, although trend toward decreased recurrence free survival for tumors lacking A-type histology

**Take Home Points:** Boy that WHO nomenclature sucks, and just might have very limited value exactly as we’d hoped!

**Purpose:**
- Second of two article using same single institution experience with resected thymomas, this one to propose a new staging system that performs better than the currently used Masaoka system.

**Methods:**
- Same 250 resected thymomas used in previous paper reporting on histology
- Unclear how definitions were devised, but used these stage categories to predictive value

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>encapsulated</td>
</tr>
<tr>
<td>I</td>
<td>invasive into perithymic adipose tissue</td>
</tr>
<tr>
<td>II</td>
<td>direct invasion</td>
</tr>
<tr>
<td>II A</td>
<td>innominate vein, mediastinal pleura, lung</td>
</tr>
<tr>
<td>II B</td>
<td>pericardium</td>
</tr>
<tr>
<td>II C</td>
<td>great vessels (aorta, SVC), heart</td>
</tr>
<tr>
<td>III</td>
<td>metastatic</td>
</tr>
<tr>
<td>III A</td>
<td>intrathoracic (i.e., diaphragm, lymph nodes)</td>
</tr>
<tr>
<td>III B</td>
<td>extrathoracic</td>
</tr>
</tbody>
</table>

**Results:**
- majority of thymomas invasive

<table>
<thead>
<tr>
<th>Stage</th>
<th>N (%)</th>
<th>Recurrence</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>31 (12.4%)</td>
<td>0</td>
<td>alive (mean 3.5 yrs, range 1-10 yrs)</td>
</tr>
<tr>
<td>I</td>
<td>128 (51.2%)</td>
<td>7 (6.1%)</td>
<td>alive (mean 3.5 yrs, range 1-16 yrs)</td>
</tr>
<tr>
<td>II</td>
<td>70 (28.0%)</td>
<td>15 (22.7%)</td>
<td>alive (mean 3.5 yrs, range 1-16 yrs)</td>
</tr>
<tr>
<td>III</td>
<td>20 (8.0%)</td>
<td>4 (20%)</td>
<td>9 dead (mean 3.5 yrs, range 1-12 yrs)</td>
</tr>
</tbody>
</table>

- follow-up in 231 patients
  - 185 (80.1%) alive
  - 22 (9.5%) recurrent and/or metastatic disease
  - 46 (19.9%) dead

**Take Home Points:**
- Nice table in Discussion comparing previous/current staging systems, and a summary of studies showing outcome for Masaoka Stage I and II tumors
- Seems straightforward and makes more sense to me than Masaoka system given anecdotal experience that if you look hard enough capsular “invasion” into fat is a common finding that has little impact on outcome.

**Purpose:**
- This study describes a series of 35 cases of histologically documented metastatic thymic tumors at extrathoracic sites, classifies them according to latest WHO classification criteria, compares different clinical data, and discusses the differential diagnoses of these lesions. It documents that all types of thymic tumors can be associated with extrathoracic metastases.

**Methods:**
- A search of their database identified all cases of thymic tumors with metastases.
- All cases with only intrathoracic metastases were excluded
- slides from 35 cases were available for review
- The variables of interest obtained were age, sex, date of initial diagnosis, clinical features at time of presentation, type of primary tumor, and site of extrathoracic metastases.
- WHO (2004) thymoma classification was used to identify the histology type of the metastatic lesion on hematoxylin and eosin-stained slides.
- Where possible, the histological features of the primary and metastatic lesions were compared.

**Results:**
- Histologically, the tumors were classified as thymoma type A (n=1) type B1 (n=3), type B2 (n=3) (Figure 2), type B3 (n=6), and thymic carcinoma (n=22)
- The primary tumor was available for review in only 8 of the 35 cases. In all of the cases, the histology of the metastatic tumor was very similar to that of the primary tumor. However, in one case, relative depletion of the lymphoid population was noted.
- Among the extrathoracic sites, lymph nodes were the most common site biopsied, with nine cases metastasizing to this site, followed by liver (eight cases) and soft tissue/skeletal muscles (four cases).

**Take Home Points:**
- Metastases from a type A thymoma can be confused with spindle cell carcinomas.
- Types B1 and B2 thymomas may be mistaken for a ‘small blue cell tumor,’ particularly in a limited biopsy specimen collected from a metastatic tumor. The presence of keratin-positive cells admixed with lymphoid cells that express CD3 is useful in the distinction.
- The most common metastatic sites biopsied were lymph node, followed by liver and soft tissue (skeletal muscle, retroperitoneal fat). Metastases morphologically closely resembled the primary tumor.

Purpose:
- Focal adhesion Kinase (FAK) is a non-receptor tyrosine kinase linked to tumor growth, invasion and metastasis. FAK has been found to be overexpressed with prognostic implications in many cancers, however the role in SCLC is unknown.

Methods:
- Total FAK expression was analyzed via immunohistochemistry in tissue microarrays consisting of formalin-fixed, paraffin-embedded SCLC specimens from 85 patients.
- FAK staining scores were tested for correlations with pathological characteristics and clinical outcomes.

Results
- FAK expression was scored low in 11 (13%), moderate in 17 (20%), and high in 50 (59%) SCLCs.
- FAK staining scores treated as continuous variables did not correlate with SCLC disease stage, response to therapy, recurrence/progression-free survival, or overall survival.

Take Home Points:
- Total FAK is strongly expressed in a majority of SCLC tumors. However, the expression evaluated via immunohistochemistry is not a prognostic factor in patients with SCLC.

Purpose:
- This study investigated the association between the number of circulating endothelial progenitor cells (EPCs), intratumoral microvessel density (MVD), and lung cancer histological types, with particular emphasis on adenocarcinoma subtypes.
- Discuss markers of angiogenesis in various histological types of NSCLC.

Methods:
- Tumors from 83 Japanese patients with NSCLC stage I, who underwent lobectomy or more extensive surgery were evaluated. Sixty-three patients had adenocarcinoma, 15 had squamous cell carcinoma, and 5 had other histological subtypes.
- The number of EPCs from the pulmonary artery of the resected lungs was measured by flow cytometry assaying CD34+/vascular endothelial growth factor receptor 2 positive cells.
- Immunohistochemistry was performed for antibodies against CD34 on FFPE tissue.

Results
- The high-MVD group included a significantly higher number of solid adenocarcinoma patients than those with nonsolid adenocarcinoma.
- There was a statistically significant correlation between the number of EPCs from pulmonary artery and intratumoral MVD.
- No statistically significant differences in the number of EPCs and the MVD were observed between adenocarcinomas and squamous cell carcinomas

Take Home Points:
- solid adenocarcinoma may be the best candidate for anti-angiogenic therapies against VEGF

**Purpose:**
- To analyze various factors which may have prognostic significance in non-small cell lung cancer.

**Methods:**
- 383 surgically resected NSCLC were analyzed by tissue microarray using immunohistochemistry with various stains. These included CD4, CD8, forkhead box protein P3, transforming growth factor β, Casitas B-cell lymphoma-b, programed death 1, T-cell–restricted intracellular antigen 1, granzyme B, mast cell tryptase, and stromal cell–derived factor 1.
- A post-operative follow-up period of 15 years was available.

**Results**
- Among the immunologic variables focused on, transforming growth factor β expression was the only prognostically relevant factor.
- Transforming growth factor β was more frequently expressed in adenocarcinoma as compared with other histologic subtypes.
- Expression of transforming growth factor β in tumor-infiltrating lymphocytes or in tumor cells was associated with significantly reduced postoperative survival time especially in patients with squamous cell carcinoma.

**Take Home Points:**
- TGF-β is an adverse prognostic factor for patients with NSCLC, which might be due not only to its potent immune-suppressive functions but also to its direct effects on other tumor stromal cells.
- This effect was most prominent in patients with SCC.
- Trials are underway evaluating TGF-β as a potential target in molecular based treatments.

**Purpose:**
- To determine the relationship between the diagnosis of undifferentiated connective tissue disease (UCTD) and NSIP histology in a large cohort of patients with biopsy-proven idiopathic NSIP and IPF.
- They also studied the clinical and prognostic utility of a diagnosis of UCTD in patients with biopsy proven idiopathic interstitial pneumonia (IIP).

**Methods:**
- Retrospective study of 101 total patients with lung biopsy and chest CT (IPF = 56, NSIP = 45)
- No patients met criteria for a specific connective tissue disorder.
- Lung biopsies were reviewed by two pathologists
- Other evaluated data included PFT’s, antibodies, and clinical symptoms

**Results**
- UCTD was present in 14 (31%) NSIP and seven (13%) IPF patients.
- Generated algorithm to predict NSIP based on imaging findings and clinical characteristics (Female < age 50) or Raynaud’s.

**Take Home Points:**
- in IIP, the diagnosis of UCTD is associated with NSIP histology, but is neither sensitive nor specific for NSIP.

Purpose:
- The purpose of the current study was to analyze in situ the histologically normal, active, and fibrotic regions of idiopathic pulmonary fibrosis lung to characterize the inflammatory cells and mediators present, and to provide a novel description of the cellular cytokine production associated with the disease process.

Methods:
- Analyzed lung tissue from 21 cases of idiopathic pulmonary fibrosis and 21 (non-fibrotic, non-cancerous) controls for immune cell and inflammation-related markers.
- The histological features of the lungs from patients with Usual interstitial pneumonia were divided into three categories; normal, alveolar damage, fibrosis only.
- Correlated the histological features of 21 samples and 21 controls with the immunohistochemical detection of the following: CD1a, CD3, CD4, CD8, CD20, CD34, CD45, CD45RO, CD56, CD68, CD80, retinoic acid-related orphan receptor (ROR)-a, ROR-b, ROR-g, forkhead box p3 (Foxp3), chemokine receptor 6 (CCR6), S100, IL-17, and tumor necrosis factor (TNF)-a.

Results
- Within zones of active disease, characterized by epithelial cell regeneration and fibrosis, there were significantly more cells expressing CD4, CD8, CD20, CD68, CD80, chemokine receptor 6(CCR6), S100, IL-17, tumor necrosis factor-a, and retinoic acid-related orphan receptors compared with histologically normal lung areas from idiopathic pulmonary fibrosis patients.
- Inflammation was implicated in active regions by the cells that expressed retinoid orphan receptor-a, -b, and -c, CCR6, and IL-17.

Take Home Points:
- Demonstrated the cell-specific expression of IL-17 in the lungs of idiopathic pulmonary fibrosis patients, unexpectedly localized to regenerating epithelial cells, as well as alveolar macrophages and T-cells.
- This could be an indication that autoimmune reactivity is present in the disease as suggested by others, or this could be another disease in which IL-17 has a role.
Mura et al. Gene Expression Profiling in the Lungs of Associated with Pulmonary Fibrosis Patients With Pulmonary Hypertension. *Chest* 2012;141;661-673.

**Purpose:**
- It is unknown whether patients with pulmonary fibrosis (PF) with associated PH (APH) represents a distinct phenotype of the disease
- determine if different gene expression signatures in PF could be determined based on pulmonary arterial pressures (PAPs) and to provide new insights into the pathobiology of APH.

**Methods:**
- Microarray analysis
- 116 consecutive patients with PF (development set, n = 84; validation set, n = 32) and seven subjects with idiopathic pulmonary arterial hypertension undergoing lung transplant (LTx).
- PAP were recorded intraoperatively immediately before starting LTx. The development set was divided into three groups according to mean PAP (mPAP).

**Results**
- Distinct gene signatures were observed. Patients in the severe PH group showed increased expression of genes, gene sets, and networks related to myofibroblast proliferation and vascular remodeling, whereas patients in the No PH group strongly expressed proinflammatory genes.

**Take Home Points:**
- Gene expression profiles distinguish PF phenotypes with and without APH
**Current Topics/Review Articles:**


Purpose:
- Review article focusing on molecular aspects of EGFR mutation as well as EML4-ALK.
- Additional focus of the article is on mechanisms of resistance to targeted therapies.
- Rather lengthy review, with a bit cumbersome pace and flow.
- Many elements are repeated throughout and seems like this should have been a bit more concise with less repetition.


Purpose:
- Review article focused on new molecular developments in lung cancer. The article is good in that it addresses issues sometimes not found in other similar reviews. Issues covered including NOS nomenclature, sampling, approach to small biopsy specimens and review of common mutations. It is written from a working pathologist perspective and addresses issues that may arise with these specimens. The article is not overburdened by excessive technical developments or excessive lists of various mutations. In summary, a very practical review. Concise and hits on the high points of interest to pathologists.