Pulmonary Pathology Journal Club (October 2013)
Articles from September 2013
- October 29, 2013 -

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Articles for Discussion
Mellema WW et al. KRAS mutations in advanced nonsquamous non-small-cell lung cancer patients treated with first-line platinum-based chemotherapy have no predictive value. J Thorac Oncol. 2013 Sep;8(9):1190-5.


Articles for Notation

Neoplastic


Eberhardt WE et al. Staging of the mediastinum: are we already there? J Thorac Oncol. 2013 Sep;8(9):1114-5.


*Non-neoplastic*


Case Reports

SUMMARIES - Discussion Articles


**Purpose:**
To evaluate the association of KRAS mutational status with response to chemotherapy, progression-free survival (PFS), and overall survival (OS) in patients with advanced NSCLC treated with platinum-based chemotherapy as first-line treatment

**Methods:**
- Consecutive nonsquamous (p63(-)) NSCLC cases were evaluated from 2 hospitals between 2004-2011.
- Stage IIIb or IV cases, treated with first-line Pt-based chemo, palliative rads was allowed
- Material had to be available for KRAS testing.
- Sex, smoking hx, WHO performance status, histology, stage, chemo courses, response and death were recorded.

**Results:**

- 161 total patients (median age 60 yrs; 79% with stage IV dx, 71.4% had adenocarcinoma, 29.6 were dx with NSCLC NOS, favoring AC)
- KRAS mutations present in 60 patients (37.3%), most having stage IV disease (85%)
- Median PFS in KRAS pts was 4.0 mo vs 4.7 mo (in non-KRAS)
- Median OS in KRAS pts was 7.0 mo vs 9.3 mo (in non-KRAS)

**Take home message:**
- No difference in response to first-line Pt-based chemo treatment in advanced NSCLC with or without KRAS mutation.
- Median OS and 1-year survival rate was worse in KRAS+, it wasn’t statistically significant.
- No apparent differences between different KRAS mutations, but the sample sizes were rather small.

Background:
According to current treatment guidelines, patients with stage 1A NSCLC are treated surgically and observed: adjuvant chemo/radiation is not recommended. Although these patients generally have a favorable prognosis, some experiencing progressive disease and death. Ideally, those patients at high risk would be identified early, and receive more aggressive adjuvant treatment.

Methods:
176 patients who had undergone lobectomy and mediastinal lymph node dissection at a single institution and were determined to be stage 1A (<3 cm, no pleural invasion) from 2000-2006 were classified using the IASCL/ATS/ERS classification. Mean follow up was 73 months (range 10-147).

Results:
- There were approximately 41% papillary predominant, 23% acinar predominant, 9% MIA (16 cases), 8% lepidic predominant, 7% solid predominant, 6% micropapillary predominant, 3% AIS (6 cases).
- Overall five year DFS was 75%, OS was 87%. They divided into three groups based on DFS with significant (p<0.001) difference between the groups: AIS/MIA (100% DFS); lepidic/acinar predominant (85% DFS); and papillary/solid/micropapillary predominant and “variants” including mucinous, colloid, and fetal (63%).
- Women had superior 5 year DFS to men (81% vs. 68%, p=0.01). No impact of age, gross or invasive tumor size was observed.

Discussion:
- It is unclear that the current T stage system accurately reflects the biologic behavior of stage 1A adenocarcinomas. Previous studies have shown that gross size and invasive size were predictive of outcome, but they did not observe that in this study.
- Current staging doesn’t included histologic “grade”/differentiation, although growing evidence exists that this predicts outcome in low stage tumors. Evidence supports that MIA/AIS are good actors, and micropapillary and solid are bad, with acinar and lepidic predominant somewhere in the middle. Previous studies had put papillary in the intermediate group, but this study saw worse survival for these patients, more akin to solid/micropapillary.

Take home message:
Further evidence that pathologic analysis of histologic pattern has something to offer in risk stratifying stage 1 adenocarcinomas. However, I think whether this can reliably be done among observers or if we can agree exactly which patterns correspond to what behavior is yet to be seen.

Purpose:
Combined pulmonary fibrosis and emphysema (CPFE) is a well-recognized clinical syndrome, but most of the available studies on this syndrome have significant limitations, including imprecise definitions, heterogeneous patient populations, and lack of controlling for confounders. The prevalence, clinical features, and prognosis of CPFE still remain poorly understood.

Methods:
- Patients with IPF were identified from ongoing IPF cohorts at UCSF and Mayo.
- Two radiologists scored emphysema and fibrosis severity on HRCT.
- CPFE was defined as ≥10% emphysema on HRCT.
- Clinical characteristics and outcomes of IPF patients with and without CPFE were compared before and after adjusting for HRCT fibrosis score.
- Mortality was compared, including time to death (transplantation censored) and time to death or transplant.

Results:
- CPFE criteria were met in 29 of 365 patients with IPF (8%).
- Patients with CPFE had less fibrosis on HRCT and higher FVC, but greater oxygen requirements, even after adjusting for fibrosis severity.
- Inhaled therapies for COPD were used by only 53% of patients with CPFE.
- There was no difference in mortality in IPF with or without CPFE.

Discussion:
- CPFE was identified in 8% of patients with IPF.
- Like previous studies, patients with CPFE in this paper had a heavier smoking history, greater oxygen requirements, higher PA pressure, less restrictive physiology, and lower diffusing capacity; CPFE seems to be a distinct clinical phenotype.
- Inhaled therapies for CPFE remain underutilized.
- Mortality of patients with IPF is similar, with or without CPFE.

Take home message:
Many questions regarding CPFE remain unanswered, but this is the first study to employ rigid definitions in an attempt to control confounders and produce a more homogeneous study population. Obviously, only IPF patients were included, and CPFE occurring in the setting of other, non-IPF fibrotic ILDs will need to be studied in the future. In addition, the histopathology of this condition needs more study. However, this moniker appears to be useful, as it identifies a distinct clinical phenotype in the realm of IPF that seems to be undertreated by pulmonologists. The biggest question of all remains unanswered – is CPFE a distinct disease, or simply a collision of two diseases with similar risk factors in the same patient?
SUMMARIES – Articles for Notation (Neoplastic)


Summary:
Study using expression arrays investigated Ephrin B2 receptor in malignant mesothelioma cell lines vs benign mesothelium. EPHB2 is overexpressed in all MM cell lines, but not in benign mesothelial cells, and is significantly elevated in MM tumor tissue compared with matched normal peritoneum. EPHB2 silencing resulted in a significant increase in apoptotic proteins and activity.

Take home points:
EPHB2 seems to play an important role in MM pathogenesis and these findings indicate that EPHB2 could serve as a potential novel therapeutic target for treatment of the disease.


Take home points:
Review addressing the often conflicting and yet hopelessly intertwined interests of subclassifying all NSCLC to the best of our ability vs. tissue preservation for ancillary genetic testing. In a nutshell, if it looks like lung cancer clinically/radiographically and the morphologic subtype is straightforward, just call it, no stains needed. Stains should be performed to subtype morphologically undifferentiated tumors, to investigate tumors with unusual morphology (i.e. looks like a met morphologically), or cases that are suspicious for met clinically (multiple masses, prior history, etc).


Summary:
As a tissue conserving strategy, they used cocktails of desmoglein 3+CK 5 +napsin, and TTF-1+p40 to test tissue microarrays of 200 lung cancers. Both were sensitive and specific in detection/separation of adeno vs. squamous vs. small cell. Interestingly, the combo DSG3-CK5 antibody showed superior sensitivity than p40 for detection of SQCC (100% vs. 93%, p40 had even lower sensitivity in small biopsies and necrotic specimens), and napsin showed superior sensitivity to TTF1 (86% vs. 77%, although napsin they found harder to read). Therefore, they thought the DSG3-CK5/napsin cocktail was slightly superior to the TTF1/p40 cocktail. They stained lots of other tissue types in their microarray, and as usual, beware, these stains can be positive in tumors from other sites.

Take home points:
I don’t have much experience with cocktail stains, but seems like a valid consideration for tissue preservation- but I always wish studies like this would actually use cases that cannot be classified on morphology alone, the results then would reflect how these stains actually perform in practice.

Summary:
They describe tufting of tumor cells into the alveolar spaces in otherwise lepidic tumors, which they term “low papillary” structures. The found it in 18 of 91 (20%) small (<3cm) invasive adenocarcinomas with a lepidic component (from 10-90% lepidic- I think this would have been a stronger study if they had been more strict and homogeneous about their % lepidic growth), and found significant association with lymph node metastasis, lymphatic invasion and shorter disease free and overall survival. Low papillary areas were often adjacent to non-lepidic components.

Take home points:
I guess the significance of this study depends on your definition of lepidic growth vs. papillary growth- I have to say some of their pictures I would have called papillary pattern and not lepidic…..but this distinction is in the eye of the beholder. It also depends if you believe that papillary formation is a pattern of invasion even without definite desmoplasia, as is put forth in the IASLC/ATS/ERS classification, where it specifies “If a tumor has lepidic growth but the alveolar spaces are filled with papillary structures, the tumor is classified as papillary adenocarcinoma.” I think the point is- if we want AIS/MIA to be a tumor of 100% 5 year survival, we are going to have to be very stringent in the definition, and any about of papillary structure formation is too much to call it lepidic.

5. Eberhardt WE et al. Staging of the mediastinum: are we already there? J Thorac Oncol. 2013 Sep;8(9):1114-5.

Take home points:
Editorial calling for more randomized clinical trials for surgically treated patients so we have more objective evidence for predicting patients at high risk for CT/PET occult N2 disease, since the criteria for invasive mediastinal staging are not standardized and even invasive staging seems to have a high false negative rate.


Summary:
Exosomes are microvesicles of molecules released by cells as a form of long and short range communication with other cells, and their contents are often rich in microRNAs. Since tumor cells produce exosomes/microRNAs very different from benign cells, these could be detected in the serum and used as a screening or diagnostic test. They analyzed micro RNAs from 10 patients with pulmonary adenocarcinoma, 10 with granulomas, and 10 healthy non-smokers, and came up with 4 microRNAs that had potential to discriminate patients with a nodule (granuloma or adenocarcinoma) from those with no nodule (potential screening panel), and 6 microRNAs to discriminate granuloma from adenocarcinoma (potential diagnostic panel). They then used this panel in a validation set of 50 adenocarcinomas, 30 granulomas, and 25 healthy smokers. The screening test was
97.5% sensitive, 72% specific, with an AUC of 90.8%. The diagnostic test was 96% sensitive, 60% specific, and had AUC of 76%.

*Take home points:*
Although this needs to be validated in a large cohort, the concept seems to have promise, especially the screening set which performed better than the diagnostic set, and requires only a blood draw. However, one could argue that especially in locations with endemic fungi, finding patients with any pulmonary nodule including granulomas is going to have an undesirably high false positive rate.


*Summary:*
Surgical resection is the current treatment of choice for stage I NSCLC patients that are good surgical candidates, with SBRT reserved as alternative therapy, mostly used in those patients that are medically inoperable. They used a very complex model and looked at mean cost and quality adjusted life expectancies for SBRT vs. wedge resection for marginal operative candidates, and SBRT vs. lobectomy for clearly operable patients. They found SBRT to be most cost effective for marginal operative candidates, and lobectomy most cost effective in clearly operable patients.

*Take home points:*
They found extra cost and morbidity for wedge resection vs. SBRT with no clear superiority in disease control, making SBRT the cost effective choice (although I can’t say I understood everything about their complex model). If randomized controlled studies show SBRT to be equivalent or superior to wedge resection, this could really lead to a paradigm shift for treating patients with compromised lung function or other comorbidities.


*Take home points:*
Cetuximab therapy may be on the way as an adjunct to traditional chemotherapy for lung cancers showing EGFR expression by immunohistochemistry, and so surgical pathologists may soon be playing a more direct role in predictive biomarker testing (since currently most tests are PCR or FISH based).


*Take home points:*
I don’t think Dr. Moran likes the new classification system 😊. Makes several valid points regarding the flaws with the limited evidence on which the new classification is based, and argues that proper staging still trumps histologic pattern. They refer to their recent article which did not find statistical significance of histologic patterns using the new classification. They argue that any new classification should be rigorously tested before implementation, and worry that the new system may give false sense of security and result in improper staging for patients with AIS/MIA.

Summary:
Aberrant WT1 transcriptional regulatory oncogene expression has been linked to development and progression of NSCLC, although the mechanisms aren’t clear. They looked at WT1 expression in 159 NSCLC samples and adjacent normal tissue. They also developed a WT1 knockdown NSCLC cell line and a WT1 overexpression NSCLC cell line. They found that WT1 mRNA levels were negatively correlated with CDH1 (E-cadherin) expression, and overexpression of WT1 was associated with higher stage, metastases and poor survival in NSCLC. They postulated that WT1 could suppress CDH1 through binding to its promoter, and thought it may enhance invasion in their cell line models.

Take home points:
WT1 overexpression appears to be a bad thing in NSCLC associated with higher stage, metastasis and poor survival, and it may exert its effects at least partially through down regulation of E-cadherin.


Summary:
The study was round robin test to evaluate the interobserver reproducibility of an EGFR IHC scoring system based on staining intensity and percentage staining. The authors note that the efficient testing of tumor tissue for EGFR status has become paramount with the increased usage of cetuximab. The authors claim excellent reproducibility among 3 reviewers.

Take home points:
An author-defined composite score of 200 provides a reliable and feasible threshold to characterize patients with advanced NSCLC into high or low EGFR expression groups.


Summary:
Another study looking at the utility and accuracy of EGFR IHC in adenocarcinoma. This study evaluated a number of mutation specific antibodies against EGFR in a cohort of 204 resected early stage node negative pulmonary adenocarcinoma. Protein expression was compared with DNA analysis from mass spectrometry. L858R IHC (sensitivity, 85.7%; specificity 98.5%), exon 19 deletions (sensitivity, 100%/ specificity, 98%).

Take home points:
Mutant-specific EGFR IHC has a good sensitivity and specificity for identifying targeted activating EGFR mutations. This type of IHC analysis, while inferior to
traditional mutation testing, may have a role when limited tissue is available for analysis.


**Summary:**
Building on previous work where the authors, noted high specificity of EGFR IHC with good mutation-status correlation, the authors expanded to compare results with those for extrapulmonary EGFR+ malignancies. Microarrays containing breast carcinoma, colorectal carcinoma, pancreatic carcinoma and uterine carcinomas were included. IHC with antibodies for exon 19 deletion and L858R were used. The performance statistics of the IHC test in EGFR+ lung cancers were superior to that seen in extrapulmonary EGFR+ malignancies. False positivity was seen in breast carcinoma, but was rare.

**Take home points:**
EGFR mutation-specific antibodies could be an additional tool to help distinguish primary versus metastatic carcinoma in the lung.


**Summary:**
Authors validated five laboratories across Canada using a quality control exercise for EGFR mutation testing using reverse-transcriptase PCR. Patients with nonsquamous histology for EGFR mutation testing using a web-based platform. Mutation testing was performed in 1771 of 2104 requests, with an average TAT of 18 days.

**Take home points:**
Folks seemed very interested in EGFR mutation testing when the funding was covered by the study (pharmaceutical industry support). When the funding was removed, the testing frequency plummeted. The authors close by citing a need to develop a national strategy to ensure resources are in place to implement molecular testing. They suggested more widespread offering of the tests and allowing pathologists to independently order the tests would improve the system. Also, clearly reimbursement strategies are a major impediment to more widespread adoption.


**Summary:**
Authors evaluated whether differences in survival outcomes to first-line TKI in patients with metastatic NSCLC harboring different exon 19/21 EGFR mutations. Evaluated 452 patients with stage IIIB & IV NSCLC. 192 had EGFR mutations. Patients with exon 19 18 nucleotide dels had the shortest median PFS (6.5 mos),
followed by those with 15 nucleotide deletions and mixed insertion/subs (22.3 mos). Patients with exon 19 dels starting on codon E746 had better median PFS (14.2 mos) than those starting on L747 (6.5 mos).

**Take home points:**
Different subtypes of EGFR mutations exhibit different survival statistics and different response to first-line TKI therapy. More detailed surveillance of exon 19 dels may be in order.


**Take home points:**
The authors review the present and future status of lung cancer biomarkers. They note that the advent of predictive biomarker testing on tissue samples for targeted therapy has forever altered the role of the pathologist in the management of patients with lung cancer. The role of the pathologist in biomarker testing, including very direct participation with IHC, has potential to grow. Patients with lung cancer and their families are now more aware of who pathologists are and the critical role that they have in their health care. New tests, new test technologies, and overall advances in precision medicine will likely improve the cost to benefit ratio for biomarker testing which, along with the powerful desire from patients and physicians to improve survival and quality of life, suggest that predictive biomarker testing will expand as a routine component of cancer care.


**Summary:**
Authors evaluate ROS1 IHC in the analysis of pulmonary adenocarcinomas, compared with FISH. IHC was compared with ROS1 break-apart FISH in 53 cases of lung adenocarcinoma as part of a validation cohort. The same methodology was then applied to a screening cohort of 167 consecutive cases. The validation cohort contained 6 (11%) FISH+ and IHC+ cases. One FISH- case was strongly IHC+. The screening cohort had 2 (1.2%) FISH+ and IHC+ cases.

**Take home points:**
ROS1 protein expression in tumor cells is 100% sensitive and 92% specific for ROS1 rearrangements by FISH. ROS1 IHC appears to be an effective screening tool for this subset of lung adenocarcinomas.


**Summary:**
The authors were concerned about the relatively high rate of EGFR mutations recently reported by several investigators and cited inconsistency with other reports. They noted that these studies were on FFPE tissue (not frozen tissue) and hypothesized that there may be artifactual false+ results from tissue processing. They collective 36 TKI-naïve NSCLC tumor cases carrying EGFR mutations, including 19-del, L858R and other mutations along with adjacent normal lung tissue
(both frozen and FFPE). They noted a T790M in 15/36 (41.7%) in FFPE samples, but in only 1 (2.8%) of the frozen samples. Surprisingly, 48.5% of the T790M were identified in adjacent normal FFPE tissues as well (none in the frozen).

**Take home points:**
It is possible that the high T790M positivity detected in TKI-naive NSCLCs using highly sensitive methods may actually be the FFPE-derived artifacts.


**Summary:**
Patients with multiple primary lung cancers are often a conundrum, since surgical treatment is often not possible for all lesions. SBRT (a.k.a. SABR) is effective treatment for stage I NSCLC that occur in patients that are not operative candidates, so it seems logical to extend this patient base to include those with multiple tumors not amenable to surgery. They looked at 101 patients with multiple tumors, including metachronous and synchronous tumors. Of note, in most patients, the initial “index” tumor was treated conventionally (surgery, conventional radiotherapy, adjuvant chemo, etc), and not all the “index” tumors were stage I. The secondary tumors were all stage I, and were all treated with SBRT. 93% of tumors were NSCLC, while the remaining were a range of neuroendocrine carcinomas (small cells were not treated primarily with SBRT, but if they got a secondary NSCLC that tumor was eligible). 67% had similar histology between tumors, and 76% were contralateral. Survival was better for those with metachronous tumors than synchronous. SBRT showed very good local control (97.4% at 2 years, 95.7% at 4 years). Complications including radiation pneumonitis were more common in patients with prior surgery or particularly prior conventional radiotherapy. The 4 year overall and progression free survival rates were 47.5% and 58% for all patients, and even better in the metachronous group, indicating that this treatment may be curative for some patients.

**Take home points:**
Optimally this study will be repeated in a prospective trial with more standardized initial therapy, but promising results for SBRT in patients with multiple lung cancers.

   Take home points:
   A concise and fairly superficial review of the numerous emerging biomarkers for monitoring disease severity and response to therapy. Markers discussed include those related to heart failure, inflammation, hemostasis, remodeling, endothelial-smooth muscle cell interaction, as well as circulating endothelial and progenitor cells, many of which remain controversial and none of which have been validated by large prospective clinical studies. With the exception of BNP and NT-proBNP in patients with secondary PH due to left sided cardiac disease, no large prospective studies are available to support routine clinical use of any of the new biomarkers. Only time will tell whether any of these will turn out to be useful.


   Take home points:
   Thorough familiarity with this one is (obviously) obligatory for all of us. We now have a new category of “Rare IIPs.” LIP has been relegated to this category, and PPFE has been officially recognized. Multidisciplinary discussion continues to be emphasized. Know the following 2 tables by heart:

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   **TABLE 1. REVISED AMERICAN THORACIC SOCIETY/EUROPEAN RESPIRATORY SOCIETY CLASSIFICATION OF IDIOPATHIC INTERSTITIAL PNEUMONIAS: MULTIDISCIPLINARY DIAGNOSES**
   
   **Major idiopathic interstitial pneumonias**
   - Idiopathic pulmonary fibrosis
   - Idiopathic nonspecific interstitial pneumonia
   - Respiratory bronchiolitis–interstitial lung disease
   - Desquamative interstitial pneumonia
   - Cryptogenic organizing pneumonia
   - Acute interstitial pneumonia
   
   **Rare idiopathic interstitial pneumonias**
   - Idiopathic lymphoid interstitial pneumonia
   - Idiopathic pleuroparenchymal fibroelastosis
   
   **Unclassifiable idiopathic interstitial pneumonias**
   
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   **TABLE 2. CATEGORIZATION OF MAJOR IDIOPATHIC INTERSTITIAL PNEUMONIAS**
   
   **Category**
   - Chronic fibrosing IP
   - Idiopathic nonspecific interstitial pneumonia
   
   **Clinical–Radiologic–Pathologic Diagnoses**
   - Idiopathic pulmonary fibrosis
   - Nonspecific interstitial pneumonia
   
   **Associated Radiologic and/or Pathologic–Morphologic Patterns**
   - Usual
   - Nonspecific interstitial pneumonia

Take home points:
A brief overview of IgG4-RD, for the uninitiated, with some historical perspective. Nothing new here, but may be good for trainees who are first encountering this entity and need a quick overview of the essentials.


Take home points:
A very nice and detailed contemporary clinical review of bronchiectasis in patients without CF, including epidemiology, pathogenesis, etiology, diagnosis, microbiology, medical management, and surgery. The major focus of the review is medical management of these patients, but it also includes some nice historical perspective and a long "laundry list" table of the various non-CF causes of bronchiectasis, a list that may prove beneficial when listing potential etiologies for bronchiectasis in a consult letter (how often do we forget to include yellow nail syndrome in our list?).


Take home points:
A very long and detailed review of the various research methodologies available for biomarker discovery, including methods for interrogation of all of the major ‘omics – transcriptomics, proteomics, lipidomics, and metabolomics, in particular as they relate to lung disease. Although the article is dense and long, it includes a very nice reference table highlighting the analytical advantages and disadvantages of particular respiratory specimen types for biomarker discovery, e.g. BAL, exhaled breath condensate, exhaled air volatiles, and sputum, as well as more conventional specimens like blood, urine, and tissue. It also includes an extensive glossary of terms for those of us who do not routinely use terms like “breathomics.”


Summary:
Using high-throughput next-generation sequencing of RNA (RNA-Seq), the authors compared the gene expression profiles in endobronchial biopsies obtained from 4 steroid-naïve patients with asthma and 5 control patients. This approach identified 46 genes that were differentially expressed between the cohorts, corresponding to
10 gene networks involved in cellular morphology, movement, and development, including BCL2, TGF-β, NF-κB, and p38 MAPK, among many other less familiar genes.

**Take home points:**
The authors claim that this very small study demonstrates the feasibility of performing RNA-Seq on bronchial tissue obtained by endobronchial biopsy for gene expression profiling purposes. In theory, this approach has the advantage of being unbiased, unlike tissue microarrays, but this “shotgun approach” yields a tremendous amount of data that is difficult to sort out in the end. Not surprisingly, numerous genes were differentially expressed, but the clinical relevance of these findings remains unknown, as with many studies like this one.


**Take home points:**
A brief editorial discussing the merits of the unclassifiable category of ILD. Unfortunately, no good answer to the question is offered, and it remains both a helpful and confusing category, as we well know.


**Take home points:**
A comprehensive review of pulmonary AVMs from a clinical perspective, including epidemiology, pathophysiology, etiology, clinical manifestations and complications, diagnostic testing, and treatment and management approaches. This paper includes a detailed review of HHT, including a discussion of genetics and some nice tables and diagrams. Also includes some very nice CT and angiographic images. Although histopathology is not included, this is a nice clinical reference on the topic.

**SUMMARIES – Case Reports for Notation**


**Take home points:**
71 year old woman with recurrent spontaneous pneumothorax, impressive CT showing numerous cysts and infiltrates. Autopsy showed metastatic angiosarc, although they never said where the primary site was. The CT and gross images are nice; I didn’t find the photomicrographs very helpful.

Take home points:
62-year-old woman presented with SOB and high PA pressure with apparent co pulmonale. Endarterectomy was performed with concern for thromboembolic disease. Histologic examination disclosed a malignant proliferation. They cite PA sarcoma with rare and unusual presentation (primarily right-sided heart failure).