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<u>Non-neoplastic</u>

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Articles for Discussion

Comprehensive Computational Pathological Image Analysis Predicts Lung Cancer Prognosis.

Luo et al. JTO.

Background: Detailed morphologic information including tumor microenvironment is difficult to assess manually. Morphologic features derived from automated computer-based image analysis of tumor histology have been used to predict survival of breast cancer patients. The authors aimed to develop a prognostic model for NSCLC based on computational image analysis of tumor tissue sections.

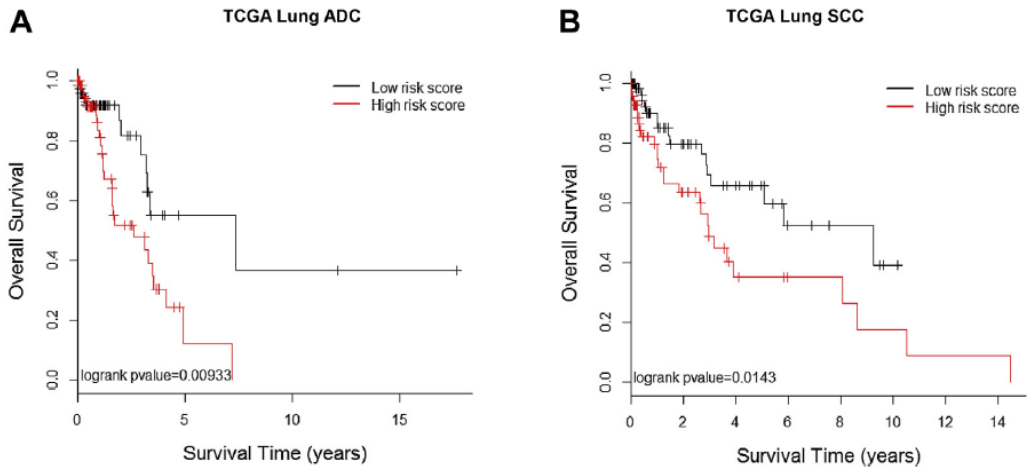
Methods: Cases of adenocarcinoma (ADC, N=523) and squamous cell carcinoma (SCC, N=511) acquired from The Cancer Genome Atlas lung cancer cohorts were analyzed with an open source software CellProfiler, which extracted morphologic features from image tiles of scanned slides. Two-thirds of the patients were used in the training set and one-third used in the testing set to generate statistical model.

Results:

●943 morphologic features of tissue texture, cells, nuclei, and neighboring architecture were extracted. Among those, 18 features enriched by tissue texture–related features in ADC cohort and 12 features enriched by granularity-related features in SCC cohort were significantly associated with overall survival.

●Prediction model based on those 18 features in ADC and 12 features in SCC validated in the testing set showed significant differences in OS between predicted high risk and low risk groups (see figure).

●High level of differentiation, keratinization, and larger areas of stroma were more often represented by images of low risk groups.



Discussion: Systematic analyses of pathological images using computer algorithms enable extraction of quantitative morphologic information for predicative modeling. Some associations between ADC

subtypes (solid, papillary, micropapillary, lepidic, and acinar) and the morphological features were found, but the predictive power of the extracted morphological features could not be solely explained by ADC subtypes. Tumor differentiation seemed to correlate with low risk features, though computer-generated morphologic parameters were not easily translatable to pathologic descriptors.

Take home point: Prediction model based on automated computational image analysis may uncover additional prognostic information independent of tumor stage.

Malignant Peritoneal Mesothelioma and Crohns Disease.

Butnor et al, J Clin Pathol.

Background: While most mesotheliomas occur in patients with asbestos exposure, chronic serosal inflammation has also been associated with mesothelioma in rare cases. The transmural inflammation of Crohns disease is associated with chronic serositis, but association with malignant mesothelioma has not been reported.

Methods: 3800 cases of mesothelioma (1982-present) were searched for coexisting inflammatory bowel disease (IBD).

Results

●The databased included 500 cases of peritoneal mesothelioma. Three patients (0.8%) had a prior diagnosis of IBD, all of which were Crohns disease. There were cases of patients with ulcerative colitis, but all developed pleural mesothelioma with was likely unrelated.

Table 1 Clinicopathological features of patients with CD and peritoneal diffuse MM

Case	Age	Gender	Established diagnosis of CD duration	MM type	Survival	Asbestos exposure
1	60	F	40 years	Epithelial	30 months	Not identified
2	65	F	3 years with antecedent long history of diarrhoea	Biphasic	2 months	Not identified
3	56	M	>20 years	Epithelial	Alive with disease (30 months)	Brake worker

CD, Crohn disease; MM, malignant mesothelioma.

●Diagnosis of Crohns disease was based on typical clinical and radiographic features in 2 cases, with pathologic confirmation in 1 case. All were being treated for Crohns medically with mesalamine alone or in combination with mercaptopurine/prednisone.

●One patient was found to have a 5 cm ileal mesenteric mass and peritoneal nodules at the time of bowel resection (right hemicolectomy, sigmoidectomy, omentectomy and peritoneal biopsies); and 2 had omental/peritoneal studding, and were diagnosed based on laparoscopic peritoneal biopsy and omental needle core biopsy.

●The signs and symptoms of mesothelioma (abdominal pain, nausea, vomiting, weigh loss) were mistakenly attributed to Crohns disease at presentation, and treated as such for up to 4 months. While

one case had omental nodules worrisome for carcinomatosis on CT, imaging in the other 2 patients was potentially attributable for Crohns disease as well.

Discussion: Based on the expected incidence of IBD, Crohns disease seems to be more prevalent in patients with peritoneal malignant mesothelioma. Ulcerative colitis does not seem to have the same overrepresentation, which is not surprising given that it does not cause serositis. Unfortunately, the signs and symptoms of peritoneal mesothelioma mimic Crohns disease, and may be treated as such in patients with a history of this disorder, leading to delay in diagnosis. The reactive mesothelial proliferations observed in the setting of serositis also make the diagnosis of malignant mesothelioma more challenging, and one must be careful not to over-diagnose mesothelioma in this setting. Fat invasion was present in all cases in this series.

Take home point: The chronic serositis present in Crohns disease may be a risk factor for peritoneal mesothelioma, which may be quite difficult to diagnose in this setting.

Lung Disease Caused by *ABCA3* mutations

Kroner et al, Thorax.

Background: *ABCA3* is an ATP-binding cassette protein that is mainly expressed in the lung, where it is localized to lamellar body membranes. It is critical for surfactant synthesis and processing. Mutations in *ABCA3* are a classical cause of neonatal surfactant deficiency, and can cause lethal or non-lethal neonatal respiratory distress, as well as pediatric and adult interstitial lung disease.

Methods: All patients (children and adults) from the Kids Lung Register (2001-2015) with homozygous of compound heterozygous *ABCA3* mutations (i.e. 2 disease causing mutations) were included in the study. 29 patients had only a single mutation in *ABCA3*, and were not included. Study group was 40 patients.

Results

●22 were homozygotes (68% male, 82% Caucasian)

-Vast majority were known to have consanguineous parents, and 80% had family history of prior intrauterine deaths or deaths from respiratory issues <1 year**.**

-These patients presented as term babies with immediate respiratory distress requiring mechanical ventilation.

-All babies with null/null mutations died in the postnatal period, while the death rate for those with other types of mutations was 62%.

-Two patients received lung transplants, one of which is still alive (3 years).

-Exogenous surfactant was helpful in about half of patients, while less favorable effects were observed with steroids, hydroxychloroquine, and azathioprine.

●18 were compound heterozygotes (83% female, 94% Caucasian).

-Presentation was more variable: 76% presented with neonatal respiratory distress, but 23% presented later in childhood and 1 presented as an adult.

-The 1 patient with null/null mutations died as a neonate, and the 1 patient with lung transplant died. The death rate for other mutations or null/other was around 60%.

-Exogenous surfactant was helpful in about half of cases, and response to steroids and hydroxychoroquine was variable.

● Biopsies were available in 24 patients, and showed patterns that have traditional been associated with surfactant deficiency syndromes, including patterns resembling DIP, PAP, NSIP and chronic pneumonitis of infancy (CPI).

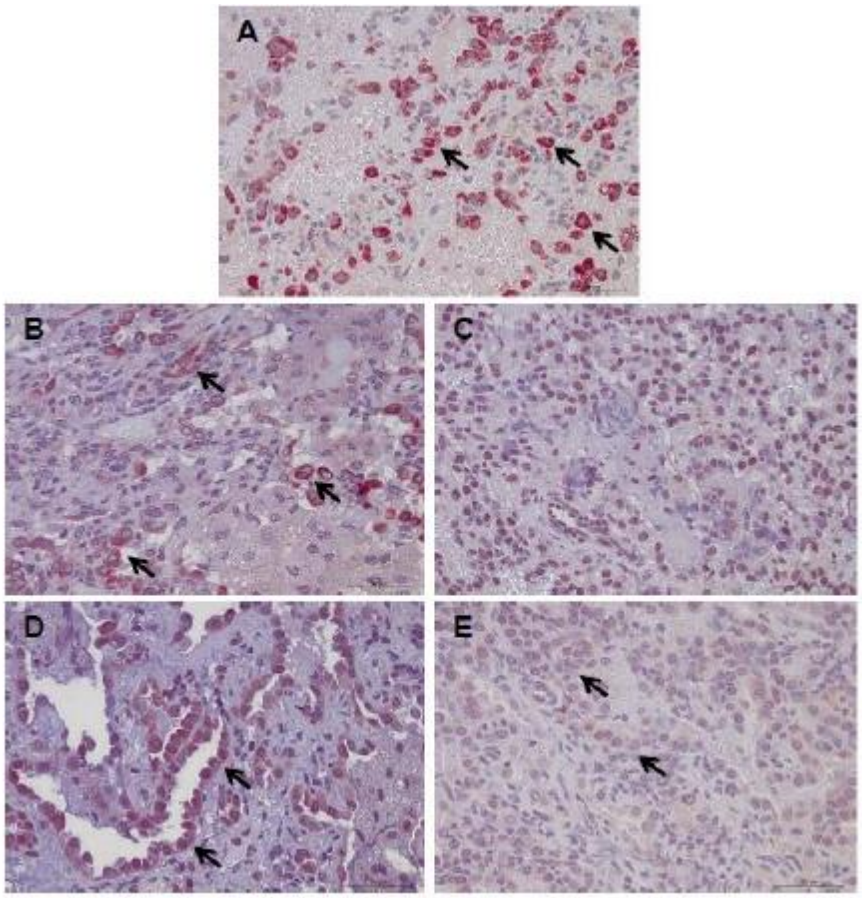
-The CPI pattern was associate with worse outcome, all died <6mos of age

-One patient had pattern resembling UIP (13 years old)

-Type 2 pneumocyte hyperplasia, alveolar macrophage accumulation, and septal thickening were prominent histologic features, with or without mild to moderate chronic inflammation.

-Interstitial fibrosis appeared to increase with age

-They used ABCA3 immunostaining and claimed strong diffuse "ring-like" cytoplasmic staining in controls, with weak staining in mutants. Seem like it might be a little difficult to interpret, see below with A as a control and B-C with mutations. Not very good quality in supplemental images.



●Radiology most commonly showed GGOs and reticular opacities. Other less common observations included: bronchial wall thickening, cysts, honeycombing, paraseptal emphysema, crazy paving, nodules traction bronchiectasis, and consolidation

Discussion: *ABCA3* mutations can be divided into 2 phenotypes, those with early lethal mutations (further subdivided into those with death within 6 months and those with death between 6 months and 5 years), and those with prolonged survival into childhood, adolescence and adulthood. Those with

early lethal mutations usually present as a term baby with immediate severe respiratory distress, while the second group presents with symptoms of chronic interstitial lung disease. Patients with homozygous null mutations have early severe and fatal disease. Other mutations seem to have variable severity and penetrance.

Take home point: *ABCA3* mutations can have variable age at presentation and variable histology, depending on the severity of the mutations present and duration of disease. It should be noted that patients can present as older children, teenagers, and even adults. Classic histologic patterns range from DIP/PAP/CPI to patterns of fibrotic ILD, such as NSIP and UIP.

Quantitative and Pathologist-Read Comparison of the Heterogeneity of Programmed Death Ligand-1 (PDL-1) Expression in Non-Small Cell Lung Cancer.

Rehman et al, Modern Pathol.

Background: While increased response rates have been reported for PDL1 targeted therapy in patients with tumors showing high level PDL1 expression, there have also been responses in "PDL1 negative" tumors, which indicate that PDL1 expression by IHC is not a perfect biomarker, or could be because of sampling or interpretation issues. There are also all kinds of issues that we are aware of, regarding the antibody clones and different cutoffs proposed for different drugs.

Methods: They used 35 resected non-small cell lung cancers (half squam, half adeno) stained with the SP142 clone (Spring Bioscience) that had at least 1 cm^2 of tissue in each of 3 blocks. They used regular chromogenic immunohistochemistry on 3 blocks from each case, as well as quantitative immunofluorescence (tumor staining vs. stromal staining counting as immune cell staining, 29-70 field of view read including manually detected hot-spot targeting). The immunostains were read independently by 5 different pathologists.

Results

●Good concordance was observed between the 5 pathologists regarding percentage of PDL1 positive tumor cells (ICC 94% using the single highest rating by each pathologist among the 3 blocks)

●The reading of stromal/immune cells was substantially discordant (ICC 27% using single highest percentage), with wide variation among pathologists

●Generally pathologists scored the tumor expression similarly across 3 blocks (ICC 94%), with more variability among stromal/immune cells (ICC 75%)

Table 2a PD-L1 heterogeneity summary chromogenic immunohistochemistry (diaminobenzidine): programmed death-ligand 1 heterogeneity among pathologists and blocks

Table 2a	*Intraclass correlation coefficient among pathologists*	*Intraclass correlation coefficient among blocks*
Tumor	94%	94%
Stroma	27%	75%

Table 2b PD-L1 heterogeneity summary quantitative immunofluorescence: programmed death-ligand 1 heterogeneity among blocks

Table 2b	*Intraclass correlation coefficient among blocks (mean quantitative immunofluorescence score per block)*	*Intraclass correlation coefficient among blocks (maximum quantitative immunofluorescence score per block)*
Tumor	95%	88%
Stroma	88%	79%

●Quantitative IF uses a combination of number of cells staining and intensity to generate a score, which generally agreed with pathologists' interpretation of tumor cell staining. ICC between blocks for tumor was 95%, and for stroma was 88%.

●Most heterogeneity was observed between areas of view on a single slide, and not between the blocks

Table 2c PD-L1 heterogeneity summary quantitative immunofluorescence: variance of fields of view among 3 blocks and within a block

Table 2c	*Variance of fields of view among 3 blocks*	*Variance of fields of view within a block*
Tumor	9%	91%
Stroma	4%	96%

●Concordance between pathologists' read and digital read was 94% for tumor and 68% for stromal/immune cells. Regression analysis showed better agreement between pathologists' and digital scores in the tumor compared to stroma/immune cells, and also showed better agreement with the pathologists' scores when the maximum IF value was used compared to the mean IF value.

Discussion: Pathologists are actually quite concordant in scoring tumor PDL1 expression, but not so much for the stromal/immune cell expression. The pathologists' read of stroma/immune cells is also not as concordant with the digital read compared to tumor expression. Expression among whole tissue blocks seems quite concordant, as most of the variability observed in observed within a single whole section (variability at the mm level and not the cm level). However, this does not answer the question about how small the tissue fragment can be in order to accurately score PDL1, since we know most of these patients only get a small biopsy.

Take home point: PDL1 concordance between pathologists is pretty good for tumor, but not for immune cells. Likewise, pathologists' reads are concordant with digital reads for tumor, but not for immune cells. Thus it seems immune cell scoring might be better with a digital platform. Heterogeneity also seems to be well represented within a single whole tissue section, but this report did not look at biopsy interpretation and under/over estimating PDL1 expression.

The Pathological Features of Idiopathic Interstitial Pneumonia-Associated Pulmonary Adenocarcinomas

Kojima et al, Histopathology

Background: Idiopathic interstitial pneumonias (IIP) increase the risk for lung cancer. Reported risk for patients with IPF is 15% in 5 years and 55% in 10 years. Most studies of lung cancer in UIP have focused on squamous cell carcinoma, but this one focuses on adenocarcinoma.

Methods: They studied lung cancers which were resected in 199 patients with IIP compared to 971 cases without IIP. They classified adenocarcinomas as TRU-type (cuboidal/low columnar cells resembling type 2 cells), non-TRU type (columnar-shaped cells resembling bronchial epithelium), and others (poorly diff, etc). IIPs were categorized using ATS criteria; they excluded collagen vascular disease, occupational lung disease, radiation-associated lung disease, and mets. They included 88 IPF, 23 NSIP, 66 RB-ILD, 1 AIP, 1 PPFE, and 20 unclassifiable IIP. They searched for KRAS and EGFR mutations, and did IHC for TTF1 (often expressed in TRU-type), HNF4α (often expressed in non-TRU type), ALK and Ki67.

Results:

Table 1. Clinicopathological characteristics [idiopathic interstitial pneumonia (IIP) group versus non-IIP group]

	Subjects		
	IIP group (N = 199)	Non-IIP group (N = 971)	P-value
Age (years)			
Range	47–84	28–89	<0.0001
Median ± quartile deviation	71.0 ± 4.5	68.0 ± 6.5	
Gender, n (%)			
Female	15 (7.54)	368 (37.90)	<0.0001
Male	184 (92.46)	603 (62.10)	
Smoking status, n (%)			
Never smoked	26 (13.07)	325 (33.47)	<0.0001
Smoker	173 (86.93)	645 (66.43)	
NA	0 (0.00)	1 (0.10)	
PYI			
Range	0–270	0–245	<0.0001
Median ± quartile deviation	49.5 ± 19.0	29.75 ± 25.0	
Tumour location, n (%)			
Upper or middle lobe	103 (51.76)	650 (66.94)	<0.0001
Lower lobe	96 (48.24)	320 (32.96)	
Other	0 (0.00)	1 (0.10)	
Surgical procedure, n (%)			
Wedge resection	21 (10.55)	70 (7.21)	0.0008
Segmentectomy	15 (7.54)	45 (4.63)	
Lobectomy	159 (79.90)	793 (81.67)	
Bilobectomy/ pneumonectomy	3 (1.51)	63 (6.49)	
NA	1 (0.50)	0 (0.00)	
Histological diagnosis, n (%)			
Adenocarcinoma	89 (44.72)	648 (66.74)	<0.0001
Squamous cell carcinoma	80 (40.20)	220 (22.66)	
Small-cell carcinoma	7 (3.52)	14 (1.44)	
Large-cell carcinoma	10 (5.03)	45 (4.63)	
Others	13 (6.53)	44 (4.53)	

●IIP patients had shorter PFS (HR for recurrence 1.6), which seemed to be mostly due to a difference in PFS in the adenocarcinoma patients (HR 2.1) which was not found in SQCC.

●Adenocarcinomas in the IIP group were more likely to be of the non-TRU type, comparted to more common TRU-type in the non-IIP group. IIP adenocarcinomas also had higher Ki67 proliferative activity, heavier smoking history, and were more likely to be men.

●When specifically considering adenocarcinomas that arose in honeycomb lesions, acinar and mucinous tumors were more common, with non-TRU morphology.

●Most of the tumors arising in honeycomb areas were TTF-/ HNF4α +, while those arising away from honeycomb change were TTF1/ HNF4α -, similar to those arising outside the setting of IIP.

●EGFR mutations were less common in tumors arising in honeycomb areas, while KRAS mutations were similar among groups. No ALK mutations were found in the adenocarcinomas arising in honeycomb areas.

Discussion: This study supports prior studies that IIP-associated lung cancer has a poor prognosis, is most often observed in male smokers, and has a preponderance of SQCC. However, adenocarcinoma was still the most common lung cancer type observed in the setting of IIP in this study. The tumors that arise in honeycomb change appear to be the most distinct, often with non-TRU morphology and TTF negativity. The tumor arising away for honeycomb change seemed to have more in common with pulmonary adenocarcinomas in the non-IIP setting.

Take home point: Adenocarcinoma is the most common type of lung cancer to be observed in IIP, although SQCC is over-represented in this group. Adenocarcinomas arising in areas of honeycomb change seem to be distinct, and are often non-TRU type tumors and are often TTF negative.

Articles for Notation

Neoplastic

Radiomic-Based Pathological Response Prediction from Primary Tumors and Lymph Nodes in NSCLC

Coroller et al, JTO

Background: They sought to use radiomic data based on CT scans to predict pathological response of the tumor and nodal metastasis after neoadjuvant therapy. This could be helpful to determine which patients may benefit from further chemo, vs. those that might benefit from proceeding with surgical intervention.

Methods: They studied 85 patients with locally advanced NSCLC treated with neoadjuvant therapy (85 primary tumors and 178 nodes), and tried to differentiated pathological complete response from gross residual disease. At the time of surgery, pathological response was qualified as complete, microscopic residual, or gross residual.

Results: They found 3 radiomic features describing primary tumor "sphereicity" and lymph node homogeneity that were predictive of pathologic complete response, and 2 features describing lymph node homogeneity that were predictive of gross residual disease. The features of the lymph nodes out performed the features of the primary tumor.

Take home point: As we get better at designing computer systems to digest all the available data in CT scans, it seems we will have more power to predict important information, like response to therapy, by non-invasive means.

Impact of Tumor Thickness on Survival after Radical Radiation and Surgery in Malignant Pleural Mesothelioma

De Perrot, et al. Eur Respir J

Background: They have a hard time choosing patients for SMART protocol, since they clinically underestimate the number of patients with N2 disease and biphasic morphology based on biopsy and clinical staging. They are looking for better clinical staging parameters.

Methods: They reviewed 65 patients undergoing extrapleural pneumonectomy for mesothelioma after radiation (SMART protocol). Tumor thickness was determined by measuring maximal thickness of 9 predetermined regions of the chest wall, mediastinum and diaphragm based on pretreatment CT scans. The thickness of all 9 sites was then summed together to determine total tumor thickness.

Results: During their follow-up period, 62% of patients recurred and 55% died. Total tumor thickness spanned from 2.4 cm to 21 cm (median 9.9 cm), and correlated with tumor volume and SUV max. Total tumor thickness predicted OS and PFS on multivariable analysis. Other significant variables included

epithelioid histology and N2 nodal status. Interestingly, 30% of the patients were found to be biphasic upon resection, and 50% had N2 disease. 7 cm seemed to be a significant cut-off, with patients with total tumor thickness <7 cm having better outcome than those with thickness > 7cm. Diaphragmatic tumor thickness correlated most strongly with time to recurrence and death.

Take home point: Total tumor thickness in mesothelioma determined by CT analysis holds promise as a clinical staging tool, as it is associated with poor overall and progression-free survival. A significant number of patients have unsuspected biphasic morphology or N2 disease when only biopsy and clinical parameters are used.

Prognostic and Predictive Value of Nuclear RAD51 Immunoreactivity in Non-Small Cell Lung Cancer Patients.

Gachechiladze et al, Lung Cancer.

Background: RAD51 is a DNA repair protein important in homologous recombination. While defective DNA repair may lead to more aggressive tumor phenotype, tumors that harbor defective DNA repair are often very sensitive to chemotherapy and radiation, which could be considered in therapy decisions. The authors explore loss of nuclear RAD51 expression as a possible prognostic marker.

Methods: They studied 69 NSCLC patients in a discovery set and 845 NSCLC patients in a validation set. All underwent surgical resection. RAD51 loss was defined as less than 20% of cells staining.

Results: RAD51 loss was observed in a little over half of cases in both the discovery and validation cohorts, and was a bit more common in adenocarcinoma compared to SQCC. RAD51 loss was more common in higher stage tumors, and in patients with a history of smoking. In patients not receiving perioperative chemo or radiation, RAD51 loss was associated with shorter OS and PFS on multivariable analysis. This was true for both adenocarcinoma and SQCC. Interestingly, this was not seen in patients with perioperative chemo or radiation, possibly due to increased sensitivity to these modalities secondary to impaired DNA repair.

Take home point: Yet to be seen if this will amount to anything, but NSCLC with RAD51 loss seems to have a poor prognosis but increased sensitivity to chemo and radiation.

DNA Hypermethylation Analysis in Sputum of Asymptomatic Subjects at Risk for Lung Cancer Participating in the NELSON Trial: Argument for Maximal Screening Interval of 2 Years.

Hubers et al, J Clin Pathol

Background: A non-invasive and simple screening test for lung cancer with low false positive rate would be idea. This group investigated hypermethylation in sputum as a possible screening test that would fit this bill.

Methods: They tested sputum for hypermethylation from a subgroup of patients enrolled in the Dutch-Belgian Lung Cancer Screening Trial (NELSON trial). Sputum was self-collected at home for 3 days in a jar with fixative, and then mailed to the pathology lab.

Results: They studied 65 patients who developed lung cancer, comparted to a control group of 219 that did not. Hypermethylation of *RASSF1A* was promising, with an optimal discriminating capacity at 2 years (sensitivity 17%, specificity 93%). When combined with 2 other markers (*3OST2* and *PRDM14*), there was a 28% sensitivity and 90% specificity. Longer time spans lead to decreased sensitivity and specificity.

Take home point: While it doesn't seem ready for prime time, sputum-based screening via molecular testing is very appealing for lung cancer if an appropriate panel of markers can be found.

Preferential Localization of MET Expression at the Invasion Front and in Spreading Cells Through Alveolar Spaces in Non-Small Cell Lung Carcinomas

Lapere et al, AJSP

Background: Identification of an effective biomarker to predict which patients will respond to MET inhibitor therapy has been a challenge. This may be partly due to intratumoral heterogeneity, so this group sought to study that phenomenon in NSCLC.

Methods: They studied 62 resected NSCLC for MET expression by IHC (SP44 clone, Ventana) and phosphoMET (clone D26, Cell Signaling), and copy number was assessed by CISH.

Results: MET positivity (2+ or 3+ staining) was observed in 52% of adenocarcinomas, compared to only 16% of SQCC. PhosphoMET positivity was seen in 30% of adenocarcinomas, but it was always present in only a minority of cells, and it was positive in scattered cells in <5% of SQCC. There was some association between MET and phosphoMET staining. They observed 2 patterns of heterogeneity: regional (localized to specific areas) and mosaic (more random and intermingled). MET expression was less intense at the center of the squamous nests where differentiation was occurring in MET-positive SQCCs. Heterogeneity was considered "high" in 30-40% of NSCLCs, and was present in some degree in 75% of cases. Only around 10% of cases showed significant heterogeneity between different slides, thus in most cases, the heterogeneity was well represented on a single slide. MET expression seemed to be particularly prominent at the interface between the tumor and the benign lung, and in regions of STAS: this was observed in 50% of adenocarcinomas and 20% of SQCC. They could show no association between high MET copy number and MET expression by IHC.

Take home point: MET expression by IHC is heterogeneous within NSCLC tumors, and seems to be prominent at the invasive front and in areas of STAS. This may indicate an important role in tumor motility and invasion.

Dataset for the Reporting of Thymic Epithelial Tumors: Recommendations from the International Collaboration on Cancer Reporting (ICCR)

Nicholson et al, Histopathology

Background: The ICCR has been putting together datasets to standardize cancer reporting around the world, and has recently done this for thymic epithelial tumors after the 2015 WHO was released.

Methods: The dataset was assembled to include required and recommended reporting elements, with appropriate stakeholder involvement. Required elements were unanimously agreed to be critical for staging, management, histological diagnosis, or prognosis.

Results: Tumors included in these recommendations are thymoma, neuroendocrine tumors, and thymic carcinomas. Required elements include type of specimen submitted, histological tumor type, extrathymic tumor nodes/metastases, margin status, lymph node status, and stage. Recommended elements include clinical information, operative procedure, specimen integrity, macroscopic site of primary tumor, block identification key, thymoma subtype, response to neoadjuvant therapy, coexistent pathology, lymph node details, and ancillary studies.

Take home point: This is a good reference when putting together reporting protocols for thymic epithelial tumors.

Her2 Transmembrane Domain (TMD) Mutations (V659/G660) that Stabilize Homo- and Heterodimerization are Rare Oncogenic Drivers in Lung Adenocarcinomas that Respond to Afatinib

Ou et al, JTO

Background: HER2 kinase domain mutations occur in 1-3% of pulmonary adenocarcinomas. HER2 TMD mutations have rarely been described in lung adenocarcinomas, but their incidence and clinical significance is not as well characterized.

Methods: They studied 8551 adenocarcinoma cases via Foundation One testing.

Results: 15 of 8551 cases (0.18%) of lung adenocarcinomas had HER2 TMD mutations at residues 659 or 660 (11 V659, 2 with G660, 1 with V659 and G660, and one with an insertion in this region; 4 had non-659/660 mutations). 79% of patients with TMD mutations were women, and 8 or 9 had light or never-smoking history, and they were younger than those with tumors showing other mutations. They were mutually exclusive with HER2 kinase domain mutations and other oncogenic drivers, and the overall mutational burden was lower in those with TMD mutations comparted to those without. 13% had coexisting HER2 amplification. Interestingly, about a third of tumors with HER2 TMD mutations were invasive mucinous adenocarcinomas. They modeled the V659 and G6660 mutations and found that they are predicted to stabilize HER2 homodimers and heterodimers in the activated position. Three of

the 4 patients with HER2 TMD mutation treated with the HER2 inhibitor Afatinib had a durable clinical response.

Take home point: HER2 TMD mutations appear to be a very rare (0.18%) oncogenic driver in lung adenocarcinomas, and have a propensity of mucinous tumors. These mutations appear to respond favorable to Afatinib.

Improving Adequacy of Small Biopsy and Fine Needle Aspiration Specimens for Molecular Testing by Next-Generation Sequencing in Patients with Lung Cancer

Padmanabhan et al, Archives of Lab Medicine and Pathol

Background: Adequacy of small biopsies for more extended molecular genetic testing is a challenge for us all. When this institution went to a 50 gene panel, their success rate from small biopsies and FNAs fell to 68%.

Methods: They implemented 2 changes to see if they could increase adequacy: first they incorporated all tissue in one block. When that did not work, they cut unstained for molecular testing up front (23 total slides!) so they only had to face the block once.

Results: Implementing the first change alone actually led to a decrease in adequacy. They were able to increase their adequacy rate to 90% with on site adequacy assessment for CT-guided cores and FNAs. By combining all tissue in one block and cutting all unstained up front.

Take home point: They argue that cutting unstained up front for molecular testing and concentrating all cores in one block increases adequacy of small biopsies for advanced molecular testing. This is contrary to the strategy taken by some, to split into 2 blocks, one used to diagnostic IHC if needed, and one reserved for molecular testing. Not sure which method is best.

Prognostic Impact of Newly Proposed M Descriptors in TNM Classification of Non-Small Cell Lung Cancer

Shin et al, JTO

Background: M1a currently indicates pleural dissemination, and M1b indicates extrathoracic metastases. IASLC recently proposed diving the current M1b into two groups. The new proposed M1b would include solitary extrathoracic metastasis in a single organ, while M1c would be multiple extrathoracic metastases.

Methods: They studied the power of this new proposed M stage to predict survival in 1024 stage IV NSCLC patients.

Results: About 25% of patients were M1a, 15% M1b, and 60% M1c. Median OS was 22.5 vs 17.8 vs 13.6 months, respectively, which was prognostically significant on univariable and multivariable analysis.

Take home point: The new M descriptors seem to have prognostic significance.

Significance of Immune Checkpoint Proteins in *EGFR*-mutant Non-Small Cell Lung Cancer

Soo et al, Lung cancer

Background: There is some evidence that EGFR mutated NSCLC have a high degree of PDL1 expression, which this group sought to further study.

Methods: They evaluated 90 cases of EGFR mutant NSCLC treated with first like EGFR TKI, for expression of PDL1 (SP142), PD1, TIM3, CD3, and CTLA-4.

Results: They observed the expected preponderance of women and never smokers. All cases showed adenocarcinoma histology (so I don't know why they did not specify that in their title ☺). 48% had exon 19 deletions, 46% had L858R, the remainder had other mutations. Initial response/stability rate to EGFR TKI was 90%. 59% percent of tumors had tumor cell staining >1%, and 44% had immune cell staining >1%. Shorter progression-free survival was observed in patients whose tumors had a higher number of CD3 positive T-cells and higher PDL1 expression by tumor cells (and these two variables often occurred together).

Take home point: EGFR mutated lung adenocarcinomas have a high rate of PDL1 expression, which may be an attractive therapeutic target in the face of EGFR TKI resistance. EGFR mutant tumors with PDL1 expression appear to have more tumor infiltrating T-cells, and to behave more aggressively.

Programed Cell Death Ligand-1 (PD-L1) Expression in Stage II and III Lung Adenocarcinomas and Nodal Metastases

Uruga et al, JTO

Background: There is still much to learn about PDL1 expression heterogeneity in tumors and their metastases.

Methods: They studied 109 stage II and stage III tumors for PDL1 expression (clone E1L3N, Cell Signaling). Nodal mets were available to stain in 66 cases.

Results: They observed over 50% of tumor cells staining in 17%, over 5% of tumor cells staining in 39%, and over 1% of tumor cells staining in 51%. Tumors with >1% PLD1 expression were more likely to have higher N stage, solid-dominant histology, high nuclear grade, necrosis, and vascular invasion. Tumors with PLD1 expression were more likely to have abundant tumor infiltrating T-cells. PDL1 expression was discrepant between the primary tumor and nodal mets is up to 38%, depending on N stage and cutoffs

used. They did not observe a survival difference between patients with PDL1 expression and those without, regardless of cutoff used.

Take home point: PDL1 expression can be variable between nodes and primary tumor, although the majority of cases are concordant.

A Histologic Basis for the Efficacy of SBRT to the Lung

Woody et al, JTO

Background: The impact of different histological subtypes on the efficacy of SBRT has not been established.

Methods: They studied 740 patients who received definitive SBRT for early stage NSCLC.

Results: Local failure rate at 3 years was about 12%. Factors associated with local failure on univariable analysis included SQCC histology, young age, fewer comorbidities, high BMI, high SUV max, central tumor location, and lower radiation dose. Squamous histology was the most significant factor predicting local recurrence on multivariable analysis (HR=2.4). Rate of failure at 3 years was about 19% in SQCC compared to 9% in ADCA and 4% in NSCLC, NOS.

Take home point: This study indicates the SBRT has a higher rate of failure in SQCC compared to adenocarcinoma and NSCLC, NOS.

The Prognostic Value of Lymph Node Ratio and Log Odds of Positive Lymph Nodes in Patients with Lung Adenocarcinoma.

Zhao et al, J Thorac CV Surg

Background: The current TNM staging system for lung cancer takes into account the location of positive nodes, but not the number of positive nodes. There is some data that a higher number of positive nodes is associated with poor outcome, which can be assessed by lymph node ratio (defined as number of positive lymph nodes/total lymph nodes) or log odds ratio (log[positive lymph nodes +0.5/total lymph nodes + 0.5]).

Methods: They looked at outcome for 1097 patients with pulmonary adenocarcinoma that were resected with lymph node dissection.

Results: Median number of nodes was 16, from a median of 6 stations. Poor prognostic factors include stage, male sex, increased smoking history, LVI, more positive nodes, more nodes dissected, higher comorbidity index, more invasive surgery, and adjuvant chemo. Lymph node ratio and log odds ratio also correlated with poor OS and RFS. The log odds ratio provided the best prognostic information.

Take home point: Lymph node ratio and log odds ratio of positive lymph nodes predict survival in adenocarcinoma. However, practically speaking, it seems like this is easier said than done as we get many thoracic nodes fragmented, and precise count can actually be quite difficult.

Non-Neoplastic

Abnormal Pulmonary Endothelial Cells may Underlie the Enigmatic Pathogenesis of Chronic Thromboembolic Pulmonary Hypertension

Mercier et al, JHLT

Background: How an unresolved thrombus develops into fibrotic intimal remodeling in CTED is not clear, but endothelial cells may play a role. CTED arises in about 0.1-9.1% of patients who suffer from an acute PE.

Methods: Pulmonary arteries were harvested for 109 pulmonary endarterectomy specimens, and 94 pulmonary arteries harvested from lung cancer controls without preoperative evidence of pulmonary hypertension. They studies preoperative cytokine levels, and endothelial adhesion molecule/growth factor expression. They cultured endothelial cells from 10 patients with CTED and 10 controls in vitro, and studied levels of cytokines produced along with detailed antigen expression analysis.

Results: Plasma concentrations of several cytokines were higher in patients with CTED compared to controls, including MCP-1, IL-6, TGF-B1, and IL-1B, as well as adhesion molecules VCAM-1 and ICAM. The culture media from endothelial cells from patients with CTED lead to increased proliferative activity of pulmonary artery smooth muscle cells from both controls and CTED patients, and also lead to increased monocyte migration. This culture media from endothelial cells of CTED patients also showed increased levels of growth factors, inflammatory cytokines, and ICAM-1.

Take home point: Basic science paper that shows endothelial cells from patients with CTED have a different profile of cytokine and growth factor production, and thus may play a role in disease pathogenesis through regulation of artery smooth muscle and monocyte activity, as well as promoting inflammation.

Reviews, Editorials, Etc.

Histologists' Original Opinion Compared with Multidisciplinary Team in Determining Diagnosis in Interstitial Lung Disease.

Burge et al, Thorax

In this letter, they present data on 71 biopsies, and conclude that multidisciplinary approach is better than histology interpretation in isolation, with change in diagnosis in 30% of cases and change in level of confidence from probable to confident in an additional 17%.

Integrin β4 is a Controversial Target for Non-Small Cell Lung Cancer

Cao et al and reply by Stewart et al, Human Pathol

The title speaks for itself ☺

Large and Small Airway Disease Related to Inflammatory Bowel Disease

Chiu et al, Arch Lab Med Pathol

Nice concise review of typical findings and differential diagnosis

Patents with Lung Cancer: Are Electronic Cigarettes Harmful of Useful?

Dautzenberg et al, Lung Cancer

Although not advised for non-smokers, for patients that smoke, e-cigarettes are at least 20 times less dangerous than regular cigarettes, estimated to be 95% less toxic.

Neuroendocrine Tumors of the Lung: Current Challenges and Advancements in the Diagnosis and Management of Well-Differentiated Disease.

Hendifar et al, JTO

Clinically oriented review, most extensive discussion is surrounding therapy and lack of therapeutic consensus in lower grade tumors.

Are Transbronchial Biopsies Living up to the Expectations?

Maldonado F; and response by Ussavarungsi K, ES Edell, and JH Ryu. Chest

While cryobiopsies are promising, their role in diagnosis of diffuse parenchymal lung disease remains to be seen. This references a Mayo Clinic paper from February 2017.

The Clinical Implications and Thoughts on Different Patterns in Resected Lung Adenocarcinoma

Mao et al, and response by Yanagawa et al, JTO

Entertaining back and forth regarding study design for work on invasive patterns in lung adeno.

Her2 Transmembrane Domain Mutations: Rare New Target for Non-Small Cell Lung Cancer Therapy.

Notsuda et al, JTO

Editorial discussing the significance of this apparently very rare driver mutation in lung adenocarcinoma.

Diagnosis of Acute Cellular Rejection and Antibody-Mediated Rejection on Lung Transplant Biopsies- A Perspective From Members of the Pulmonary Pathology Society

Roden and Yi et al, Archives Lab Med Pathol

Great overview with lovely photos. Great job ladies!

BCL-2 Family in Non-Small Cell Lung Cancer: Its Prognostic and Therapeutic Implications

Sun et al, Pathology International

Discusses significance of apoptotic proteins in the BCL2 family, which contains a lot of proteins which I am not very familiar with. This family of proteins contains members that have both anti-apoptotic and pro-apoptotic effects. Very in depth review.

Dendritic Cells in Human Lung Disease

Upham JW et al, Chest

Summary of what we know about dendritic cell function in asthma, COPD, lung cancer, and infection. Dendtric cell function could potentially be the target of therapy in the future, intended to modify pulmonary immune responses.

Biological Therapies in Non-Small Cell Lung Cancer

Zugazagoitia et al, Eur Resp J

Nice review of the current state of targeted therapy for NSCLC, with nice complete tables.

Case Reports

Placental transmogrification of the Lung Presenting as Progressive Symptomatic Bullous Emphysema

Brustle et al, Thorax

Ciliated Muconodular Papillary Tumor of the Lung Harboring *ALK* Gene Rearrangement: Case Report and Review of the Literature

Jin et al, Pathology International

Histologic Transformation of *EGFR* Mutant Lung Adenocarcinoma without Exposure to EGFR Inhibition

Le et al, Lung Cancer

Adenocarcinoma at the time of excision, recurred as SQCC with identical *EGFR* mutation

Metastatic Cancer Mimicking a Mycetoma

Ong et al, Am J Resp Critical Care Med