Nov 2019 Journal Club
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Abstracts – Discussion articles

1. Wright, J. et all. Reproducibility of visual estimation of lung adenocarcinoma subtype proportions. Modern Pathol (2019); 32: 1587-1592. (presented by Simon Walker)

Background: The 2011 IASLC/ATS/ERS recommendations for lung adenocarcinoma suggest that the diagnosis should include a visual estimate of the subtypes of adenocarcinoma, to the nearest 5%.
Aim of the study: To assess the intra and inter-pathologist reproducibility of visual estimates using 5% cut-offs and whether using larger groupings of cut-offs (10% and 25%) would improve reproducibility.
Methods:

- Using 25 invasive non-mucinous adenocarcinoma cases, images were collected at 2x and 10x objective power. The location of the image on the slide was randomly selected.
- Five 'experienced' pathologists were asked to record the percentage of each subtype of adenocarcinoma.
- The pathologists were asked to record the predominant adenocarcinoma subtype.
- The pathologists repeated the tasks after 2 months, with the same images in randomized order.
- One pathologist also completed morphometric analysis for subtyping.
- Intra-pathologist agreement was calculated for 2x and 10x using cut-offs of 5%, 10% and 25%.
- One pathologist was analyzed for morphometric compared to visual assessment.
- Inter-pathologist agreement was reported with percentile histograms (to avoid data skew when using larger cut-offs (10% and 25%)).

Results

- Intra-pathologist agreement was highest for micropapillary and papillary subtypes, but lower for lepidic, acinar and solid using 5% cut-offs, at both 2x and 10 x power.
    - Note: micropapillary and papillary patterns were the predominant pattern in the minority of cases.
- Intra-pathologist agreement appeared to increase using larger cut-offs (10% and 25%).
- Morphometric analysis also showed highest agreement with micropapillary and papillary patterns. Acinar pattern showed the lowest agreement.
- The differences between pathologists (inter-pathologist agreement) was variable. Acinar pattern had large differences, even at 10x power.
- Inter-pathologist agreement of predominant pattern was minimal at both low (kappa 0.35) and high (kappa 0.25) objective powers.

Discussion

- Reproducibility of quantifying lung adenocarcinoma subtypes in this study was variable by pattern and appeared to improve when using larger cut-offs (10% and 25%) when compared to 5% cut-offs.
    - Other studies of lung adenocarcinoma subtype suggested that lepidic and acinar patterns show the best reproducibility, with micropapillary and papillary performing worse after adjusting for amount of cases with predominance of these patterns (Warth et al, 2012).
- Inter-pathologist agreement of predominant subtype was minimal at both 2x and 10x power.

- Visual assessment agreement with morphometric analysis (for one pathologist) was variable by subtype and appeared to improve when using 25% cut-offs.

Discussion points

- Different reproducibility studies used different methods of obtaining study images (i.e. whole slides, random images, selected images etc.). Perhaps these methodological differences can account for some of the differences in reproducibility identified by different studies.
- While reproducibility improved with larger cut-offs, this may be because there are simply less options to choose from (1 in 20 at 5% cut-offs, 1 in 4 at 25% cut-offs).
    - Perhaps using larger cut-offs (10% or 25%) to estimate predominant subtypes would provide more reproducible results for determining the predominant subtype of lung adenocarcinoma.
    - The effect of using larger cut-offs on determining the predominant subtype when there is less than a 25% difference between the predominant subtypes would be an important consideration.
    - The effect of using larger cut-offs on detecting small proportions of important subtypes is not clear.
- It would be interesting to study if inter-pathologist reproducibility increased using morphometric analysis.
- It would be interesting to see if micropapillary and papillary patterns remained the most reproducible patterns when normalizing for how often they occurred in the study set (similar to Warth et al 2012)

2. Emoto, K. et all. Expansion of the Concept of Micropapillary Adenocarcinoma to Include a Newly Recognized Filigree Pattern as Well as the Classical Pattern Based on 1468 Stage I Lung Adenocarcinomas. J Thorac Oncol (2019); 14(11): 1948-1961.

Background: Micropapillary (MIP) adenocarcinoma was formally included in the WHO classification in 2015 and has consistently been shown to be associated with an aggressive clinical course, even when a minor component of ~ 5%. MIP predominant subtype is also reported to benefit from adjuvant therapy (Tsao MS et al. JClin Oncol 2015; 33:3439.)However in many studies (but not the one discussed earlier) concordance is lower for the MIP pattern than for the other major adenocarcinoma patterns. The authors state there is therefore a need for further clarification of the morphologic spectrum of the MIP pattern in lung adenocarcinoma.The classical MIP pattern is defined as *a tumor with cells growing in papillary tufts forming florets that lack fibrovascular cores*. The 'classical' pattern both within airspaces and within stroma:

The authors propose a novel, poorly recognized histologic pattern that they consider to fit best in the spectrum of the MIP pattern - a filigree MIP pattern. Fig 2.

"Filigree" - delicate, lace-like, narrow stacks without fibrovascular cores with attachments to alveolar walls that are frequently visible when cut in cross section. The stacks of tumor cells consist of at least three tumor cells piled above the basal layer of the alveolar wall surface, with a maximum of up to three cells in width. The width of the stacks often consists of a single row of cuboidal tumor cells piled on top of each other. Less often, these filigree lesions have a width of up to three cells along the base. The tumor cells in the filigree pattern usually have a cuboidal shape resembling that of type II pneumocytes A longer vertical direction than horizontal. Presence (classic) or absence (filigree) of floret tufts.

Multiple groups have shown by 3D analyses that most of the classical MIP tufts are attached to alveolar walls and one study showed 4 different cell groups – 1, floating independently in air spaces, 2/ attached to the main tumor 3/ attached to other clusters, and 4/ attached to the normal alveolar wall distant from the tumor.

What about other organs? MIP pattern is recognized by the WHO in tumors of the breast, ovary, and bladder and colorectal adenocarcinomas. MIP pattern in the lung is different due to the air spaces, with discohesive floret and filigree patterns. Only in the ovary, does the MIP concept include the filigree pattern: serous borderline tumor–MIP variant/noninvasive low- grade serous carcinoma and is defined as a serous carcinoma with a myriad of fine micropapillae often arising from the surface of large fibrotic papillae. The micropapillae are usually five times taller than they are wide, with scant or no stromal cores consisting of cuboidal to polygonal tumor cells with scant cytoplasm and small uniform atypical nuclei. It is a more aggressive subtype than the serous borderline tumor/atypical proliferative serous tumor. In the endometrium, the term nonvillous papillae has been used when filigree-like projections occur within endometrioid carcinoma but do not correlate with poor prognosis and have not been recognized as an MIP pattern. No pattern resembling the filigree MIP pattern has been recognized in the breast, bladder, or colon.

The **aim** of this study was to investigate the morphologic spectrum and clinical significance of filigree MIP pattern and present evidence for the expanding the definition of MIP pattern in resected stage I lung adenocarcinoma.

Methods: This was a retrospective study in which all patients with pathologically confirmed stage IA and 1B lung adenocarcinoma who underwent surgical resection at MSKCC between 1995 and 2014 were reviewed. AIS, MIA, and special variants, including mucinous and colloid) excluded. Tumor slides from 1468 patients reviewed by K. E. and W. D. T; Interobserver agreement between the filigree and classical MIP patterns assessed by K.E., N.R., and W.D.T who evaluated 20 selected images of filigree vs classical MIP. Discrepancies were resolved by consensus. The predominant subtype - pattern with the highest percentage. Minor patterns - at least 5%. Pleural invasion, LVI, STAS and necrosis were also evaluated.

When discrimination between the classical and filigree MIP patterns was challenging, the classical pattern was selected. When the distinction between the filigree MIP pattern and cribriform pattern was difficult, the cribriform pattern was selected when the glandular structures had tumor cells surrounding sharply rounded glands in a sieve-like pattern

In addition, the presence of a single-cell pattern, signet ring cell features, and ring-like structures, as well as the presence of psammoma bodies (a clue to presence of MIP) and extracellular mucin were also recorded.

Outcome of interest - cumulative incidence of recurrence (CIR) after surgical resection with curative intent. Patients who did not experience recurrence or die during the study period were censored at the time of the last available follow-up in the CIR analysis. During the study period, 236 patients experienced a recurrence, including 88 patients with only locoregional recurrence and 148 patients with distant metastasis. The median follow-up period for patients who did not experience a recurrence was 4.83 years (range 0.02–17.91 years).

Results: High degree of interobserver agreement in recognizing the filigree MIP pattern among 3 pathologists (all >/= 0.8, $p < 0.001$). The filigree MIP pattern observed in **35%**. After reclassification incidence of total cases with any MIP component (5% or more) increased from 51% to 56% and 4% of cases (n = 57) were reclassified as MIP predominant by including the filigree MIP pattern (increased from 6-10%).

In the 56% cases with MIP present, the frequencies of the classical MIP pattern only, filigree MIP pattern only, and both MIP patterns were 20%, 13%, and 22%, respectively. Compared with patients with no filigree MIP pattern, those with any filigree MIP pattern were more likely to have: larger total tumor size, larger invasive tumor size, higher pathologic stage, presence of the classical MIP pattern, pleural invasion, LVI, necrosis, STAS.

Of the 57 reclassified MIP predominant cases, 16, 37, and 4 cases were previously diagnosed as acinar, papillary, and solid predominant, respectively.

Clinical Significance: After filigree as predominant component reclassification, CIR curve was similar to that of classical MIP group. Filigree MIP predominant adenocarcinomas were associated with a greater proportion of necrosis and fewer psammoma bodies. There was no clinically significant difference filigree vs classic MIP patterns as a minor component.

Conclusions

- Study supports expansion of the concept of MIP lung adenocarcinoma to include the filigree pattern
- The original definition of MIP was likely too restrictive and hindered recognition
- Morphologic criteria that should be included in the MIP pattern have also been clarified:
  - When lepidic, acinar, or papillary areas are also accompanied by floret/filigree patterns
  - When numerous single tumor cells fill alveolar spaces

Take home message: This study is very convincing and I believe will help in recognition of cases as MIP pattern. The images, both cartoons and microphotographs were a pleasure to look at.

3. Tseng, LH. Et all. Clinical Validation of Discordant Trunk Driver Mutations in Paired Primary and Metastatic Lung Cancer Specimens. Am J Clin Pathol (2019); 152(5): 570-581.

Background: Discerning whether metastatic lesions in patients with lung cancer are originate from the lung lesion are sometimes problematic especially when histology and IHC staining patterns are not concordant. Molecular testing has the potential to solve this problem. The authors compare primary lung lesions to metastatic lesions. They stayed away from multiple lung cancers - multiple primaries or intrapulmonary metastase; a more difficult issue due to the field cancerization effect which increases the the chances of identical driver gene mutations occurring by chance. Driver mutations are categorized into trunk (initiating) drivers and branching drivers. Trunk driver mutations, by definition, are expected to be present in every tumor cell, primary and metastatic cancers. Most hotspot activating mutations in the EGFR, BRAF, and KRAS genes are trunk drivers

Many previous publications have had disappointing results, showing discordant EGFR and/or KRAS mutations between paired primary and metastatic lung cancer specimens. When paired specimens with no mutations in both primary and metastatic tumors were removed from the denominator (ie, including only pairs with one or both specimens positive for the mutation as the denominator), the discordance rate was 30% for EGFR mutations and 62% for KRAS mutations. The discordance rate of KRAS mutations was significantly higher than that for EGFR mutations in each subpopulation analysis. The reasons for this may be lab error or poor sensitivity methods being used.

Methods: Retrospective study, Prior NGS for 7-gene panel AKT1, BRAF, EGFR, ERBB2, KRAS, NRAS and PIK3CA on 1,329 FFPE specimens with a diagnosis of lung adenocarcinoma, adenosquamous carcinoma, or NSCLC. Excluded cases with prior TKI therapy. 15 patients with multiple metastatic tumors and 32 patients with primary and metastatic specimens (tables 2 and 3). A 50-gene panel, including TP53 when there was discordance in the 7-gene panel; H&E-stained slides were reviewed to reevaluate if the tumor cellularity within the designated area(s) for DNA extraction was initially overestimated; reevaluation of clinicopathologic data; tissue identity confirmed using the genotypes of SNPs within the NGS panel.

Results: The specimens taken from 2-3 metastatic sites in 15 patients had concordant results for the 7-gene assay (Table 2). Specimens taken from the primary and metastatic tumors in 32 patients, were concordant in 29 pairs, including 15 pairs with no mutation – the latter doesn't confirm they are the

same tumor (Table 3). In the 3 pairs with discordant results of trunk driver mutations, tissue identity was confirmed to be correct and the entire 50-gene NGS panel was applied.

- PM03 - same IHC staining patterns (CK7+, CDX2+ napsin-)
  RUL moderately differentiated adenoca - KRAS p.A146V mutation in 3 areas of the tumor
  R paratracheal lymph node- 6 months *before* resection: no mutation
  Unexplained
- PM10
  RUL – KRAS+. Moderately differentiated adenoca with acinar, micropapillary, and lepidic patterns
  R interlobar LN- EGFR+. Poorly differentiated adenoca with signet ring cells
  Imaging studies show a second lung primary near the right hilum (not biopsied)
  Met is from a synchronous primary
- PM26
  RML- BRAF p.V600E. Well- differentiated adenocarcinoma NGS detected a BRAF p.V600E mutation
  Brain – BRAF negative but TP53 p.R158P mutation. Poorly differentiated adenocarcinoma, TTF-1 +. Resected 2 y after the lung.
  A TTF-1–positive poorly differentiated adenocarcinoma of LLL resected 7 y before brain met. TP53 p.R158P mutation but not the BRAF p.V600E mutation.
  Met from a remote lung ca prior to the one in study

Conclusions:

- In the paired metastatic tumors (15 patients) only 3 pairs had no mutations; concordance was 100%.
- In the lung primary and metastatic pairs (32 patients), 15 pairs had no mutations. Concordance was 90.6% (29/32 samples) or 82.3% (14/17 samples) when the pairs with no mutation detected were excluded.
- However, 2 of the 3 'discordant' samples could be argued to have been concordant, making the concordance rate 96.8% (31/32 samples) or 94.1% (16/17 samples).
- Trunk driver mutations are highly concordant between primary and metastatic lung ca *but many of the tumors had no mutation detected therefore cannot confirm that the metastasis is from that particular lung primary.*
- Discordance of activating EGFR, KRAS, and BRAF mutations in paired lung cancer specimens taken from the same patient should raise a concern for laboratory errors.
- Branching driver mutations e.g. in the PIK3CA and TP53 genes or uncommon mutations in the EGFR, KRAS, or BRAF genes may be present in a subpopulation

Take home message:

It seems to be basic commonsense that one should examine H&E slides to see if discordance in trunk mutations is related to inadequate tumor cells for analysis but perhaps this needs to be emphasized. The high sensitivity of NGS used in this study may be one of the reasons why the concordance rate is better than many studies in the literature.

For Notation only:

Neoplastic: original studies

Shih, AR. et all. Problems in the reproducibility of classification of small lung adenocarcinoma: an international interobserver study. Histopathology (2019); 75(5); 649-659.

Differentiating AIS, MIA and small (<2.5 cm) Invasive Adenoca, and estimating area of invasion has poor inter-observer agreement. In this study agreement was excellent in tumours with high-grade cytology and fair with low-grade cytology. Takehome message- nothing new but I found the use of elastic stains to differentiate lepidic vs acinar by Japanese pathologists interesting and might try it in future.

Differentiating lepidic and acinar patterns in multiple foci in a background of fibroelastosis. To illustrate difficulties in identification of small infiltrating glands, A shows a low magnification image of an adenocarcinoma with multiple foci of possible acinar pattern around the periphery of the fibroelastosis. Area 1 (B) shows focal disruption of an elastic framework by a gland associated with collagen deposition (C, elastic stain); area 2 (D) shows lepidic growth with a preserved elastic framework (E, elastic stain); and area 3 (F) shows disruption of an elastic framework by glands and collagen deposition (G, elastic stain). Although no fibroblastic proliferation or classic desmoplastic reaction is seen, the majority of observers classified areas 1 and 3 as acinar pattern.

Samejima, J. et all. Prognostic significance of blood and lymphatic vessel invasion in pathological stage IA lung adenocarcinoma in the 8th edition of the TNM classification. Lung Cancer (2019); 137: 144-148.

The prognostic significance of blood and lymphatic vessel invasion in the 8th edition of the Tumor, Node, Metastasis (TNM) classification remains unclear. Therefore, this study aimed to evaluate the prognostic significance of blood and lymphatic vessel invasion in p-stage IA lung adenocarcinoma in the 8th edition of the TNM classification.Blood and lymphatic vessel invasion were evaluated using hematoxylin-eosin and Elastica van Gieson and hematoxylin-eosin and anti-podoplanin antibody staining, respectively. Combined blood and lymphatic vessel invasion constituted tumor vessel invasion (TVI).

Take home message: TVI is a prognostic factor in patients with p-stage IA1-2 lung adenocarcinoma. P-stage IA1 lung adenocarcinoma without TVI is suggested to be classified as minimally invasive.

La Rosa, S., Volante, M., Uccella, S. et al. ACTH-producing tumorlets and carcinoids of the lung: clinico-pathologic study of 63 cases and review of the literature. Virchows Arch (2019) 475: 587.

Well conducted study that showed that ACTH-producing lung carcinoids are not rare, are not always associated with Cushing syndrome, and do not represent an aggressive variant of lung carcinoid.

Fiset, PO. et al. Anaplastic lymphoma kinase 5A4 immunohistochemistry as a diagnostic assay in lung cancer: A Canadian reference testing center's results in population-based reflex testing. Cancer. 2019 Nov 15;125(22):4043-4051.

Take home message: ALK 5A4 IHC validated as a diagnostic test for ALK-rearranged lung cancer and is associated with treatment response and survival. One of the conclusions, that FISH testing is not needed for ALK IHC+ cases with a validated protocol is already widely accepted. Interestingly, five cases (1.7%) had concurrent EGFR mutation and ALK IHC positivity; 4 were confirmed as ALK FISH+, but one did not have FISH performed.

Kawai, T. et al. Clinicopathologic study of deciduoid mesothelioma using SMARCB1/INI1 immunohistochemistry and fluorescence in situ hybridization. Human Pathology (2019) 93, 23-29.

Deciduoid mesothelioma is a rare variant of epithelioid mesothelioma ? is it even accepted as a variant now? Malignant rhabdoid tumors, renal medullary carcinoma, and some synovial sarcomas show a loss of SMARCB1/INI1 protein. Some mesothelioma cases, such as those of the deciduoid type, have been reported to have rhabdoid features. Since this topic has not been studied in malignant mesothelioma, we analyzed the ReducedSMARCB1/INI1 expression was more frequent in the deciduoid type (although authors admit there were very few cases) than in either the epithelioid type (14%) or biphasic type (8%), whether or not rhabdoid cells were present. **Take home message**: cases with reduced SMARCB1/INI1 protein expression should not be excluded from a diagnosis of malignant mesothelioma.

Zhang, C. et all. Genomic Landscape and Immune Microenvironment Features of Preinvasive and Early Invasive Lung Adenocarcinoma. J Thorac Oncol (2019); 14(11): 1912-1923.

80 tumor tissue samples and 30 paired histologically normal lung tissue samples from 30 patients with adenocarcinoma in situ (AIS) (n = 8), minimally invasive adenocarcinoma (MIA) (n = 8), and invasive adenocarcinoma (IAC) (n = 14) were subjected to multiregion whole exome sequencing and immunohistochemistry staining for CD8 and programmed death ligand 1 (PD-L1). All tumors, including AIS, exhibited evidence of genomic intratumor heterogeneity. Canonical cancer gene mutations in EGFR, erb-b2 receptor tyrosine kinase 2 gene (ERBB2), NRAS, and BRAF were exclusively trunk mutations detected in all regions within each tumor, whereas genes associated with cell mobility, gap junction, and metastasis were all subclonal mutations. EGFR mutation represented the most common driver alterations across AIS, MIA, and IAC, whereas tumor protein p53 gene (TP53) was identified in MIA and IAC but not in AIS. There was no difference in PD-L1 expression among AIS, MIA, and IAC, but the CD8 positivity

rate was higher in IAC. Genomic intratumor heterogeneity and immunoediting are common and early phenomena that may have occurred before the acquisition of invasion.
Take home message: Findings very much as expected except that Interesting in that AIS shows many of the changes seen in invasive adenoca

Hellmann, MD. Et all. Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer. N Engl J Med (2019); 38(21): 2020-2031.

First-line treatment with nivolumab plus ipilimumab resulted in a longer duration of overall survival than did chemotherapy in patients with NSCLC, independent of the PD-L1 expression level. No new safety concerns emerged with longer follow-up.
Included this in an attempt to keep up with the fast changing treatment landscape!

Huang, RSP. Et all. Delta-like Protein 3 Prevalence in Small Cell Lung Cancer and DLL3 (SP347) Assay Characteristics. Arch Pathol Lab Medicine (2019); 143(11): 1373-1377.

Delta-like protein 3 (DLL3) is a protein that is elevated in neuroendocrine tumors, including SCLC, whereas it is low in the majority of normal tissue. This presents an opportunity to target and selectively deliver drugs to tumor cells highly expressing the DLL3 antigen by using antibody drug conjugates specific to the DLL3 antigen. Study findings provided the profile of DLL3 staining characteristics that can be used for determining the level of DLL3 expression in small cell lung cancer.

Iams, WT. et all. Improved Prognosis and Increased Tumor-Infiltrating Lymphocytes in Patients Who Have SCLC With Neurologic Paraneoplastic Syndromes. J Thorac Oncol (2019): 14(11): 1970-1981.

Approximately 10% of patients with SCLC develop a paraneoplastic syndrome (PNS). Neurologic PNS are thought to improve prognosis, which was hypothesized to be related to increased tumor-infiltrating lymphocytes and immune recognition. Authors evaluated 145 SCLC patients: 55 with PNS (25 neurologic and 30 endocrinologic) and 90 controls. Patients with neurologic PNS experienced improved overall survival compared to patients with endocrinologic PNS and controls (median overall survival of 24 months versus 12 months versus 13 months, respectively).

Take home message: Fascinating study in which tumor tissue from patients with SCLC with neurologic PNS showed increased tumor-infiltrating lymphocytes and PD-1/PD-L1 interaction consistent with an inflamed tumor microenvironment. Keeping in mind the more favorable prognosis of patients with SCLC with neurologic PNS, the use of immunoncology compounds has to be carefully evaluated given the potential risk of higher frequencies of immune-related adverse events.

Sebastian, M. et all. SCLC, Paraneoplastic Syndromes, and the Immune System. J Thorac Oncol (2019): 14(11); 1878-1880. Editorial

Krencz, I. et all. Correlation between immunohistochemistry and RICTOR fluorescence in situ hybridization amplification in small cell lung carcinoma. Hum Pathol (2019); 93: 74-80

The *RICTOR* gene (rapamycin-insensitive companion of mTOR [mammalian target of rapamycin]), which encodes a key structural (scaffold) protein of mTOR complex 2), has recently been identified as one of the most frequently amplified genes and a potential therapeutic target in SCLC. The aim of this study was to compare immunohistochemical (IHC) expression of Rictor and phospho-Akt (a downstream target of mTOR complex 2) with *RICTOR* amplification as detected by fluorescence in situ hybridization (FISH) in SCLC. In conclusion, IHC expression of Rictor correlates highly with *RICTOR* amplification. Therefore, Rictor IHC can be used as a cost-effective method to select patients for *RICTOR* FISH and, potentially, for mTORC1/2 inhibitor therapy.

Xie, H. et all. Use of Autofluorescence to Intraoperatively Diagnose Visceral Pleural Invasion From Frozen Sections in Patients With Lung Adenocarcinoma 2 cm or Less. Am J Clin Pathol (2019); 152(5): 608-615.

Prospectively study to investigate the accuracy of frozen sections for diagnosing visceral pleural invasion (VPI) by autofluorescence using a fluorescence microscope. A total of 112 patients were enrolled.

Take home message: Not clear if the small increase in accuracy using autofluorescence in frozen sections to diagnose VPI is worth the extra trouble and time.

Neoplastic: Reviews

Broderick, SR. et all. Neoadjuvant immunotherapy in patients with resectable non–small cell lung cancer. J Thorac Cardiovasc Surg (2019); 158(5): 1471-1474.
Essential reading to keep up with the rapidly changing treatments.

Regzedmss, O. et all. Immune checkpoint blockade in small cell lung cancer. Onco Targets Ther (2019); 12: 4605-4620.
This review discusses the discovery of new immune inhibitory and stimulatory pathways and rational combination strategies to explain the role of immunotherapy in SCLC and its future opportunities and challenges.

Pritzker, KPH. Et all. Needle Biopsy Adequacy in the Era of Precision Medicine and Value-Based Health Care. Arch Pathol Lab Med (2019); 143(11): 1399-1415.
Well written and comprehensive discussion on needle biopsy adequacy – not focused only on the lung but still very relevant read for pulmonary pathologists.

Gelatti, ACZ. Et all. Optimizing the sequencing of tyrosine kinase inhibitors (TKIs) in epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC). Lung Cancer (2019); 137: 113-122.

Epidermal growth factor receptor (EGFR) mutations are observed in approximately 40% and 20% of patients with NSCLC in Asian and non-Asian populations, respectively. First-generation (gefitinib, erlotinib) and second-generation (afatinib, dacomitinib) EGFR-tyrosine kinase inhibitors (TKIs) have been standard-of-care (SoC) first-line treatment for patients with sensitizing EGFR mutation positive advanced NSCLC following Phase III trials versus platinum-based doublet chemotherapy. However, most patients treated with first-line first- or second-generation EGFR-TKIs develop resistance. Osimertinib, a third-generation, central nervous system active EGFR-TKI which potently and selectively inhibits both EGFR-TKI sensitizing (EGFRm) and the most common EGFR T790 M resistance mutations, has shown superior efficacy versus first-generation EGFR-TKIs (gefitinib / erlotinib). Osimertinib is now a treatment option for patients with advanced NSCLC harboring EGFRm in the first-line setting, and treatment of choice for patients with T790 M positive NSCLC following disease progression on first-line EGFR-TKIs. The second-generation EGFR-TKI dacomitinib has also recently been approved for the first-line treatment of EGFRm positive metastatic NSCLC. There remains a need to determine appropriate sequencing of EGFR-TKIs in this setting, including EGFR-TKIs as monotherapy or in combination with other TKIs / signaling pathway inhibitors. This review considers the evolving role of sequencing treatments to maximize benefits for patients with EGFRm positive advanced NSCLC.

Compton, CC. et all. Pathology Practices to Ensure Molecular Integrity of Cancer Patient Biospecimens for Precision Medicine. Arch Pathol Lab Med (2019); 143(11): 1346-1363.

Biospecimens acquired during routine medical practice are the primary sources of molecular information about patients and their diseases that underlies precision medicine and translational research. In cancer care, molecular analysis of biospecimens is especially common because it often determines treatment choices and may be used to monitor therapy in real time. However, patient specimens are collected, handled, and processed according to routine clinical procedures during which they are subjected to factors that may alter their molecular quality and composition. Such artefactual alteration may skew data from molecular analyses, render analysis data uninterpretable, or even preclude analysis altogether if the integrity of a specimen is severely compromised. As a result, patient care and safety may be affected, and medical research dependent on patient samples may be compromised. Despite these issues, there is currently no requirement to control or record preanalytical variables in clinical practice with the single exception of breast cancer tissue handled according to the guideline jointly developed by the American Society of Clinical Oncology and College of American Pathologists (CAP) and enforced through the CAP Laboratory Accreditation Program. Recognizing the importance of molecular data derived from patient specimens, the CAP Personalized Healthcare Committee established the Preanalytics for Precision Medicine Project Team to develop a basic

set of evidence-based recommendations for key preanalytics for tissue and blood specimens. If used for biospecimens from patients, these preanalytical recommendations would ensure the fitness of those specimens for molecular analysis and help to assure the quality and reliability of the analysis data.
Take home message: excellent article that spells out all pathologists need to know about integrity of specimens for molecular testing

Nangalia, J. et all. Genome Sequencing during a Patient's Journey through Cancer. N Engl J Med (2019); 38(22): 2145-2156.

Fascinating review which explores what is known about systematic sequencing of cancer genomes and discusses the current and potential future clinical applications of genome sequencing.

Pina-Oviedo, S. et all. Primary Mediastinal Nodal and Extranodal Non-Hodgkin Lymphomas: Current Concepts, Historical Evolution, and Useful Diagnostic Approach: Part 1. Adv Anat Pathol (2019); 26(6): 346-370.
Pina-Oviedo, S. et all. Primary Mediastinal Nodal and Extranodal Non-Hodgkin Lymphomas: Current Concepts, Historical Evolution, and Useful Diagnostic Approach: Part 2. Adv Anat Pathol (2019); 26(6): 371-389.

Primary mediastinal non-Hodgkin lymphomas (PM-NHLs) represent ~5% of all NHLs and comprise lymphomas of B-cell and T-cell origin. PM-NHLs are defined as involvement of mediastinal lymph nodes, thymus, and/or mediastinal organs (heart, lung, pleura, pericardium) by NHL without evidence of systemic disease at presentation. The clinical scenario is variable and depends on the lymphoma subtype. The radiologic presentation is also variable ranging from a mediastinal mass with or without superior vena cava syndrome, a pleural or a cardiac mass associated with an effusion, or as an effusion only. The diagnosis of PM-NHLs can only be established by microscopic evaluation, and therefore, general pathologists should be aware of these tumors and familiar with their diagnostic approach. The most common anterior mediastinal NHLs (90% to 95%) are primary mediastinal large B-cell lymphoma and T lymphoblastic lymphoma. Thymic marginal zone lymphoma and mediastinal gray zone lymphoma are very rare. The remainder PM-NHLs involving middle or posterior mediastinum include diffuse large B-cell lymphoma (DLBCL) and rare cases of T-cell lymphoma, including anaplastic large cell lymphoma and breast implant-associated anaplastic large cell lymphoma extending to the anterior mediastinum. Primary pleural and cardiac NHLs are mostly DLBCLs. Other rare subtypes of PM-NHLs include DLBCL associated with chronic inflammation/pyothorax-associated lymphoma, fibrin-associated DLBCL (both EBV), and pleural and/or pericardial primary effusion lymphoma (HHV-8/EBV). The historical aspects, epidemiology, clinico-radiologic features, histopathology, immunohistochemistry, differential

diagnosis, and relevant cytogenetic and molecular features of PM (thymic) LBCL, PM "nonthymic" DLBCL, BCL, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma (mediastinal gray zone lymphoma), DLBCL associated with chronic inflammation (pyothorax-associated lymphoma), fibrin-associated DLBCL, primary effusion lymphoma, remaining mediastinal B-cell lymphomas, including primary thymic marginal zone lymphoma of the mucosa-associated lymphoid tissue type, other PM small B-cell lymphomas, PM plasmacytoma, and the most relevant PM T-cell lymphomas are reviewed.

Superb reviews in two parts covering PM-NHLs.

Hamza, A. et all. Thymic Mucoepidermoid Carcinoma: A Systematic Review and Meta-analysis. Adv Anat Pathol (2019); 26(6): 341-345.

Thymic mucoepidermoid carcinoma is a rare tumor that remains poorly characterized and a diagnostic challenge. There is limited data regarding the utility of MAML2 gene rearrangement in the thymic location. Histologic grade and tumor stage/resectability are the main prognostic factors.

Non-neoplastic: original articles

Walsh, SLF. Et all. Diagnostic Likelihood Thresholds That Define a Working Diagnosis of Idiopathic Pulmonary Fibrosis. Am J Crit Care Med (2019); 200(9): 1146-1153.

The level of diagnostic likelihood at which physicians prescribe antifibrotic therapy without requesting surgical lung biopsy (SLB) in patients suspected of idiopathic pulmonary fibrosis (IPF) is unknown. An international cohort of respiratory physicians evaluated 60 cases of interstitial lung disease, giving: *1*) differential diagnoses with diagnostic likelihood; *2*) a decision on the need for SLB; and *3*) initial management. Diagnoses were stratified according to diagnostic likelihood bands described by Ryerson and colleagues.
Conclusions: Most respiratory physicians prescribe antifibrotic therapy without requesting an SLB if a provisional high-confidence diagnosis or "working diagnosis" of IPF can be made (likelihood ≥ 70%).

Editorial Limper, AH. The Role of Surgical Lung Biopsy in Antifibrotic Therapy for Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med (2019); 200: 1084-1085.

Raghu, G. et all. The 2018 Diagnosis of Idiopathic Pulmonary Fibrosis Guidelines: Surgical Lung Biopsy for Radiological Pattern of Probable Usual Interstitial Pneumonia Is Not Mandatory. Am J Respir Crit Care Med (2019); 200: 1089-1092.

Take home message of articles on SLB in IPF**:** ***SLB is recommended in only a minority of patients with suspected, but not definite, IPF.***

Monzonis, X. et all. Early Onset Pulmonary Toxicity With Lorlatinib in a Patient With Previous Pulmonary Toxicity From Brigatinib. J Thorac Oncol (2019); 14(11): e247-e248. Letter to the Editor.

Describes a case with apparent cross-reactivity involving lung toxicity between different ALK inhibitors. This calls for caution after a respiratory episode with one agent when deciding treatment with subsequent ALK inhibitors.

Take home message: more evidence that pulmonary pathologists need to be hyperaware of these increasing lung toxicities

Oh, JY. Et all. Invasive Endobronchial Mycobacterium kansasii Infection. Am J Respir Crit Care Med (2019): 200(10): e143-e144.

Non-neoplastic: Reviews

Deterding, RR. Et all. Approaching Clinical Trials in Childhood Interstitial Lung Disease and Pediatric Pulmonary Fibrosis. Am J Respir Crit Care Med (2019); 200(10): 1219-1227.

Childhood interstitial lung disease (chILD) comprises a spectrum of rare diffuse lung disorders. chILD is heterogeneous in origin, with different disease manifestations occurring in the context of ongoing lung development. The large number of disorders in chILD, in combination with the rarity of each diagnosis, has hampered scientific and clinical progress within the field. Epidemiologic and natural history data are limited. No clinical trials have been conducted in a pediatric population using agents designed to treat lung fibrosis. This review focuses on progressive chILD disorders and on the urgent need for meaningful objective outcome measures to define, detect, and monitor fibrosis in children.

Formanek, PE. Et all. Advances in the Diagnosis and Management of Invasive Fungal Disease. Chest (2019); 156(5): 834-842

Good update on diagnosis of iInvasive fungal disease