Pulmonary Journal Club September 2024
Jennifer Boland, MD
Mayo Clinic Rochester

Table of Contents

Articles for Discussion

Articles for Notation

11.....Guillard M, Caumont C, Marcorelles P, et al. Performances of the Idylla GeneFusion Assay: Contribution to a Rapid Diagnosis of Targetable Gene Fusions in Tumour Samples. J Clin Pathol. 2024;77:561-567.

11.....Guler, S. A., Scheschkowski, T., Renner, et al. Interdisciplinary Diagnosis and Management of Patients With Interstitial Lung Disease and Connective Tissue Disease. Chest 2024; 166(2), 352-361.

12.....Kaminuma, Y., Nakai, T., Aokage, et al. Prognostic significance of micronest in cancer stroma in resected lung squamous cell carcinoma. Human Pathology 2024, 150: 20-28.

13.....Lu S, Kato T, Dong X, et al. (2024). Osimertinib after Chemoradiotherapy in Stage III EGFR-Mutated NSCLC. New Engl J Med 2024; 391(7): 585-597.

13.....Maddali MV, Moore AR, Sinha P, et al. Molecular Endotypes of Idiopathic Pulmonary Fibrosis: A Latent Class Analysis of Two Multicenter Observational Cohorts. Am J Respir Crit Care Med. 2024;210(4):455–464.

14.....Malmros K, Lindholm A, Vidarsdottir, et al. Diagnostic gastrointestinal markers in primary lung cancer and pulmonary metastases. Virchows Archiv. 2024;485(3):347–357.

14.....Metintaş M, Ak G, Yildirim H,et al. Image-Assisted Pleural Needle Biopsy or Medical Thoracoscopy: Which Method for Which Patient? A Randomized Controlled Trial. Chest. 2024;166(2):405-412.

15.....Miao J, Tong R, Zhang Y, et al. A Rare Manifestation of Airway Invasion from Pulmonary Artery Liposarcoma. Am J Respir Crit Care Med. 2024;210(3):352-354.

15.....Nambirajan A, Sood R, Khatoon W, et al. Concordance of Immunohistochemistry and Fluorescence In Situ Hybridization in the Detection of Anaplastic Lymphoma Kinase (ALK) and Ros Proto-oncogene 1 (ROS1) Gene Rearrangements in Non–Small Cell Lung Carcinoma: A 4.5-Year Experience Highlighting Challenges and Pitfalls. Arch Pathol Lab Med 2024;148(8):928-937.

16.....Niedermaier B, Kou Y, Tong E, et al. CT-guided needle biopsy is not associated with increased ipsilateral pleural metastasis. Lung Cancer 2024;194:107890.

16.....Puid D N, Cufí Quintana M, Escobedo Rodriguez V, et al. Bilateral mediastinal cysts with müllerian differentiation. Thorax 2024; 2024;79:796-797.

17.....Raidt J, Riepenhausen S, Pennekamp P, et al. Analyses of 1236 genotyped primary ciliary dyskinesia individuals identify regional clusters of distinct DNA variants and significant genotype–phenotype correlations. Eur Respir J 2024; 64:2301769.

17.....Reddy SA, Newman J, Leavy OC, et al. Chronic thromboembolic pulmonary hypertension is an uncommon complication of COVID-19: UK national surveillance and observational screening cohort studies. Eur Respir J 2024;64:2301742.

18.....Sullivan KA, Farrokhya F, Patel YS, et al. Preoperative mediastinal staging in early-stage lung cancer: Targeted nodal sampling is not inferior to systematic nodal sampling. J Thorac Cardiovasc Surg 2024, 168(2), 391-398.

18.....Takahara T, Satou A, Tsuyuki T, et al. (2024). Histology of Bronchiolar Tumor Spread Through Air Spaces. Am J Surg Pathol 2024, 48(8), 1052-1059.

19.....Tuder, RM, Gandjeva A, Williams S, et al. Digital spatial profiling identifies distinct molecular signatures of vascular lesions in pulmonary arterial hypertension. Am J Resp Crit Care Med 2024, 210(3), 329-342.

19.....van Zandwijk N, Frank AL, Reid G, et al. Asbestos-Related Lung Cancer: An Underappreciated Oncological Issue. Lung Cancer 2024; 194: 107861.

20.....Wolf AS, Eisele M, Giroux DJ, et al. The International Association for the Study of Lung Cancer Pleural Mesothelioma Staging Project: Expanded Database to Inform Revisions in the Ninth Edition of the TNM Classification of Pleural Mesothelioma. J Thorac Oncol. 2024;19(8):1242-1252.

20.....Yi L, Wen Y, Xiao M, et al. The proportion of tumour stroma predicts response to treatment of immune checkpoint inhibitor in combination with chemotherapy in patients with stage IIIB-IV non-small cell lung cancer. Histopathol. 2024;85(2):295-309.

21.....Yin X, Wei X, Al Shamsi R, et al. Benign metastasizing fumarate hydratase (FH)-deficient uterine leiomyomas: clinicopathological and molecular study with first documentation of multi-organ metastases. Virchows Archiv. 2024;485(2):223-231.

22.....Zheng Q, Lin X, Qi W, et al. NGS and FISH for MET Amplification Detection in EGFR TKI Resistant Non-Small Cell Lung Cancer (NSCLC) Patients: A Prospective, Multicenter Study in China. Lung Cancer 2024; 194: 107897.

22.....Zhu P, Sun K, Lao IW, et al. Expanding the Spectrum of *NUTM1*-Rearranged Sarcoma: A Clinicopathologic and Molecular Genetic Study of 8 Cases. Am J Surg Pathol 2024; 48(8): 930-941.

Articles for Discussion

Nuclear Protein in Testis (NUT) Carcinoma: A Comprehensive Immunohistochemical Analysis of 57 Cases With Consideration of Interpretation and Pitfall Recognition

Farooq et al, Archives

Background

NUT carcinoma is a highly aggressive cancer with *NUTM1* rearrangement. Initially described as a midline carcinoma (frequent occurrence in mediastinum/thorax and head/neck), it has since been identified in diverse locations. It poses a significant diagnostic challenge, as its morphology overlaps with poorly differentiated squamous cell carcinomas, small cell carcinomas, thoracic SMARA4-deficient undifferentiated tumor, and other undifferentiated or primitive tumors. This study aimed to provide a comprehensive immunohistochemical (IHC) profile of a large cohort of NUT carcinomas and to identify diagnostic pitfalls.

Methods

The study included 57 cases of NUT carcinoma seen at Mayo Clinic from 2012 to 2022, 47 of which were consult cases. These cases were confirmed via positive NUT immunostaining (43), *NUTM1* gene rearrangement by FISH (3), or both (11). Anatomical sites included 67% thoracic/mediastinal, 23% head/neck, and 11% other locations (including colorectal, pancreatic, and pelvic soft tissue tumors). A comprehensive immunohistochemical panel was performed including keratins, squamous markers, and neuroendocrine markers.

Results

- Wide age range (2-83), mean 46; no sex predilection (table 1). Morphology ranges from classical (prominent abrupt keratinization) to sheets of small round blue cells (figure 1)
- Fusion partner known in 3 cases: 2 with *MXD4*, 1 with *BRD4*
- **Keratin expression (table 2, figure 2)**: Variable, with CK AE1/AE3, CAM 5.2, and OSCAR keratin showing positivity in 76-88% of cases (CAM most sensitive followed by AE1/AE3, then OSCAR). Notably, 15% of cases were entirely negative for keratin markers, which presents a diagnostic challenge.
- **Squamous cell markers (table 3, figure 3)**: p40 was positive in 65% of cases, significantly less sensitive than p63 (87%) and desmoglein-3 (DSG3, 100%)
- **Neuroendocrine (NE) markers (table 4, figure 4)**: Focal expression of NE markers including synaptophysin (18%) and CD56 (18%) was observed (2 diffuse strong CD56), though chromogranin was negative in all. INSM1 was positive in 54% of cases, indicating a potential diagnostic pitfall. One third showed expression of at least one NE marker.
- **Other markers (table 5)**: TTF-1 showed focal positivity in 26% of cases, particularly in the thoracic region. CD34, CD99, and SALL4 positivity occurred in a subset of cases, which could confuse the diagnosis with entities like sarcoma or germ cell tumors. BRG1 and INI1 were retained in all cases. Ki-67 was high across all cases (median 60%).

Conclusion

NUT carcinoma displays a wide immunohistochemical spectrum in addition to variable morphology, which can complicate its diagnosis. Keratin stains are variably positive, and squamous differentiation markers such as p63 and DSG3 are more reliable than p40. The potential for focal NE marker expression, particularly INSM1, presents a pitfall in distinguishing NUT carcinoma from small cell carcinomas.

Take Home Message: NUT carcinomas are usually keratin positive but may be negative- multiple keratins might be required. Other key markers include NUT, p63, and DSG3. INSM1 positivity and expression of other NE markers may mislead, and a broad panel may be needed to rule out other poorly differentiated malignancies.

Comment: This study highlights the complexity of diagnosing NUT carcinoma. A key strength is the large cohort, which allows for meaningful evaluation of staining patterns. Limitations include the low number of cases stained for some IHC markers, and lack of molecular testing on all cases to understand fusion partners.

Pembrolizumab plus chemotherapy for metastatic NSCLC with programmed cell death ligand 1 tumor proportion score less than 1%: pooled analysis of outcomes after five years of follow-up.

Gadgeel et al, JTO

Introduction: NSCLC is often has metastatic disease at diagnosis, making treatment challenging. Pembrolizumab has been combined with chemotherapy to enhance treatment efficacy in NSCLC patients. Previous studies have shown significant improvements in OS and PFS with this combination, even in patients with <1% PD-L1 expression. However, data shows that patients with PD-L1 <1% are frequently still treated with chemotherapy alone (62.4% in Europe, 32% in the US). This study aims to provide long-term outcomes for metastatic NSCLC patients with PD-L1 TPS less than 1% after five years of treatment with pembrolizumab plus chemotherapy.

Methods: This exploratory pooled analysis includes data from four phase III studies: KEYNOTE-189 (global and Japan extension) for nonsquamous NSCLC, and KEYNOTE-407 (global and China extension) for squamous NSCLC. Patients were randomized to receive either pembrolizumab plus chemotherapy or placebo plus chemotherapy, and patients and investigators were blinded to PD-L1 results. Key endpoints included OS, PFS, and treatment-related adverse events. PD-L1 TPS was assessed using PD-L1 clone 22C3. The analysis included 442 patients with previously untreated metastatic NSCLC with PD-L1 TPS less than 1%.

Results:

- Patients: 442 (255 pembrolizumab + chemotherapy, 187 chemotherapy alone)

- Median Follow-up: 60.7 months

- Overall Survival (OS): Median OS was 18.3 months in the pembrolizumab + chemo group versus 11.4 months in the chemo alone group (HR 0.64, 95% CI: 0.51-0.79; Fig 2A).

- Progression-Free Survival (PFS): Median PFS was 6.5 months versus 5.5 months, respectively (HR 0.66, 95% CI: 0.54-0.81, Fig 2C).

- Five-Year OS Rates: 12.5% for pembrolizumab plus chemo versus 9.3% for chemo alone.

- Adverse Events were similar: Grade 3-5 treatment-related adverse events occurred in 59.1% of patients in the pembrolizumab plus chemo group and 61.3% in the chemo alone group.

Conclusion: The combination of pembrolizumab and chemo offers significant long-term survival benefits compared to chemo alone in patients with metastatic NSCLC with PD-L1 TPS less than 1%. Despite high rates of adverse events, the combination therapy's durable efficacy supports its use as a standard first-line treatment in this patient population.

Take Home Message: Pembrolizumab plus chemo significantly improves survival outcomes in metastatic NSCLC patients with PD-L1 TPS less than 1% compared to chemo alone, establishing it as standard of care.

Discussion/Comment: Hopefully this means we will not be doing PD-L1s forever?

Validation Study for the N Descriptor of the Newly Proposed Ninth Edition of the TNM Staging System Proposed by the International Association for the Study of Lung Cancer.

Kim et al, JTO

Background: Accurate lymph node (LN) metastasis evaluation is critical in lung cancer staging for prognosis, treatment standardization, and clinical trials. The lung TNM staging system's N descriptor was defined in 1987 and has not changed. It has faced criticism for not accounting for metastatic disease burden, a known prognostic factor. New N staging has recently been proposed by the IASLC for the ninth edition, and this study aims to externally validate the ninth edition's N descriptor using a large, independent cohort.

Methods: This is a retrospective analysis of patients who underwent curative surgery for NSCLC at Asan Medical Center in Seoul between January 2004-December 2019. The N descriptor was reclassified according to the ninth edition of the TNM system. The proposal initially included N1a (single station N1 metastasis), N1b (multi-station N1 metastasis), N2a1 (single station N2 metastasis without N1 metastasis), N2a2 (single station N2 metastasis with N1 metastasis), N2b (ipsilateral multiple station N2 metastasis). However, the system accepted for the 9th edition of AJCC includes only N0, N1, N2a (single station N2) or N2b (multi-station N2). Survival analysis used the log-rank test and Cox proportional hazards model to compare adjacent N categories.

Results:

- Study Population: 6649 patients with a median follow-up of 54 months; outlined in Figure 1. Patients with N3 or M1 disease, < 6 LN sampled, or multifocal lung cancer were excluded.

- Pathologic Classification using 9th edition: 4957 (74.6%) N0, 744 (11.2%) N1, 567 (8.5%) N2a, 381 (5.7%) N2b.

- Survival Analysis: Significant prognostic separation between all adjacent clinical and pathologic N categories in terms of overall survival (OS) and recurrence-free survival (RFS). See Figure 3 for KM curves of pathological N stages.

Conclusion: The study validated the clinical utility of the ninth edition's N classification for both clinical and pathologic stages in NSCLC, showing clear prognostic separations between categories (N0, N1, N2a, N2b) in OS and RFS.

Take Home Message: For the ninth edition N classification, expect N2 stage to be divided according to whether there is single station vs. multi-station disease

Discussion/Comment: The study reinforces the importance of considering disease burden in nodal classification and supports the IASLC's approach of dividing N2 based on disease burden.

Autopsy Histopathologic Lung Findings in Patients Treated With Extracorporeal Membrane Oxygenation.

Trejnowska et al, Archives

Background: ECMO is a life-saving intervention increasingly used for severe respiratory and cardiac failure. While technology and subsequently outcomes continue to improve, there is still

significant risk of life-threatening complications; prolonged ECMO is associated with persistent vasoplegia and coagulopathy. Despite its growing use, there is limited data on the histopathologic changes in the lungs of ECMO patients, and histologic findings are confounded by expected changes of DAD in most patients with venovenous (VV) ECMO (who usually have ARDS). This study aimed to evaluate pulmonary histopathologic findings in patients who underwent VV ECMO for pulmonary reasons or venoarterial (VA) ECMO for cardiac indications shortly before death. The goal was to determine if these changes provided insights that could improve therapy and outcomes.

Methods: This retrospective study included lung autopsies from ECMO recipients (n=83; 65 VA ECMO, 18 VV ECMO) and non-ECMO patients with ARDS secondary to pneumonia (n=18), treated between 2008 and 2020 at the Silesian Center for Heart Diseases in Zabrze, Poland. Autopsies included histopathologic examination of lung tissue (sampled from each lobe and areas of gross abnormality), stained with H&E and trichrome, and were reviewed by two blinded pathologists. Clinical data were collected from medical records.

Results:

-The study included 57 men, median age 57 years. Indications for VA ECMO included cardiomyopathy (dilated or hypertrophic), ACS, PE, myocarditis, post-surgery including transplant, valve replacement and CABG. Most (14) VV ECMO patients had ARDS from pneumonia, sepsis/shock, or flu; the remaining 4 needed post-transplant VV ECMO.

-Most common histopathologic findings were (Figure 1) bronchopneumonia (53.0%), interstitial edema (48.2%), DAD [38.6%, more common in VV ECMO vs. VA ECMO (p=0.03)], hemorrhagic infarct with recent organizing thromboembol (33.7%), pulmonary hemorrhage (30.1%).

-DAD was associated with VV ECMO, longer ECMO treatment and hospital stay, but only VV ECMO was significant on multivariate analysis. However, DAD was also observed in 32.3% of VA ECMO patients. The non-ECMO control group showed higher interstitial edema (although I am not sure how they defined this histologic finding) and lower bronchopneumonia prevalence compared to VV ECMO patients.

Conclusion: Not surprisingly, DAD was significantly more common in VV ECMO patients, but one-third of VA ECMO patients also exhibited histopathologic changes characteristic of ARDS, suggesting the need for protective lung ventilation in these patients. Pulmonary hemorrhage was more prevalent in women and associated with shorter ECMO duration, possibly indicating that finding has more to do with the underlying disease than ECMO.

Take Home Message: The most common histologic findings in ECMO patients include bronchopneumonia, DAD, edema, infarction and hemorrhage.

Discussion/Comment: Histologic findings in ECMO patients are not particularly surprising, but are nicely documented. Lack of living patients may limit the generalizability of the findings.

Articles for Notation

Prevalence of pathogenic or likely pathogenic germline variants in cancer predisposition genes among selected patients with lung adenocarcinoma: The GERMLUNG study.

Arrieta et al, Lung Cancer

The GERMLUNG study investigates the prevalence of pathogenic or likely pathogenic germline variants (PGVs) in cancer predisposition genes among lung adenocarcinoma patients. Conducted at the Instituto Nacional de Cancerología in Mexico City, the study includes 201 patients selected based on family history of lung cancer (LC), young-onset LC, minimal smoking history, and the presence of actionable genomic alterations (AGAs). Using the Sophia Hereditary Cancer Solution panel, 43 patients (21.4%) were found to have PGVs, with the majority involving DNA damage repair genes such as ATM (9.3%), TP53 (6.9%), BRCA2 (6.9%), and CHEK2 (6.9%). PGVs were more common in males and showed a trend towards association with AGAs. The study suggests that these selection criteria effectively identify candidates for genetic testing, which is critical for personalized therapeutic strategies in resource-limited settings.

Take home message: The GERMLUNG study highlights a high prevalence of germline variants in lung adenocarcinoma patients, particularly the role of DNA damage repair genes, emphasizing the importance of targeted genetic testing based on specific selection criteria.

Microscopic small airway abnormalities identified in early idiopathic pulmonary fibrosis in vivo using endobronchial optical coherence tomography.

Berigei et al, AJRCCM

This study uses endobronchial optical coherence tomography (EB-OCT) to examine small airway involvement in early idiopathic pulmonary fibrosis (IPF), a condition traditionally thought to spare small airways. The authors performed EB-OCT on 12 patients with early IPF and 5 control subjects to evaluate bronchiole counts and small airway metric. They found significant bronchiole reduction (42% loss overall) in IPF patients, including both IPF-affected (48% loss) and less affected (33% loss) sites compared to controls. IPF-affected airways were larger, more distorted, and irregular, whereas less affected airways were similar to controls. This suggests small airway disease is an early pathologic feature of IPF, occurring before overt fibrotic changes. These results challenge the assumption that IPF spares the small airways.

Take Home Message: Small airway abnormalities are present early in IPF, with significant bronchiolar loss (up to 50%) even in less affected areas. This study adds a new twist to the concept of IPF pathogenesis, suggesting that small airway changes occur early in the disease course.

The role of pathologists in the diagnosis of occupational lung diseases: an expert opinion of the European Society of Pathology Pulmonary Pathology Working Group.

Calabrese et al, Virchows Archiv

This review article highlights the crucial role of pathologists in diagnosing occupational lung diseases (OLD), which continue to be a significant global public health concern. These diseases stem from workplace exposure to harmful dusts, fumes, and organic materials, often leading to irreversible lung damage. The authors emphasize the complexity of diagnosing OLD due to overlapping clinical features with other respiratory diseases, latency periods, and insufficient reporting. Key diseases discussed include silicosis, asbestosis, coal workers' pneumoconiosis, and hypersensitivity pneumonitis, among others. Pathological diagnosis often requires lung biopsy, particularly when imaging is inconclusive or a patient has an atypical exposure history. The article stresses the importance of multidisciplinary collaboration, involving not only pathologists but also radiologists, clinicians, and occupational health experts, to enhance diagnostic accuracy. The review also covers modern diagnostic tools such as cryobiopsy, liquid biopsy, and bronchoalveolar lavage (BAL), which are increasingly used to detect inhaled particles and guide diagnosis. Pathologists' input is vital for identifying fibrotic changes, dust deposits, and specific disease-related features in biopsy samples. New biomarkers and advanced imaging techniques continue to enhance diagnostic precision, especially in complex cases like mesothelioma and hard-metal lung disease.

Take Home Message: Nice review on occupational lung disease.

Real-World Evidence of Intra-institutional Performance Variation in Indefinite Diagnosis of Pleural Effusion Cytology.

Chen et al, Archives

This study explores the variation in the use of indefinite diagnostic categories, specifically "atypia of uncertain significance" (AUS) and "suspicious for malignancy" (SFM), in pleural effusion cytology within a single institution. A retrospective analysis of 51,675 pleural effusion cytology reports from a 20-year period (2002-2021) at Linkou Chang Gung Memorial Hospital, Taiwan, was conducted. The findings revealed that 7.86% of cases were diagnosed as AUS and 3.01% as SFM, with significant variation (up to threefold) among the 11 pathologists involved.

The study found no correlation between pathologists' years of experience or case volume and the rates of indefinite diagnoses. The data suggest that personal diagnostic tendencies significantly influence the use of indefinite categories, indicating a need for standardized criteria and continuous monitoring to ensure diagnostic consistency.

Take Home Message: Significant intra-institutional variation exists in the use of indefinite diagnostic categories in pleural effusion cytology, driven more by individual pathologists' tendencies than by their experience or case volume.

Performances of the Idylla GeneFusion Assay: Contribution to a Rapid Diagnosis of Targetable Gene Fusions in Tumour Samples.

Guillard et al, J Clin Pathol

This study aimed to evaluate the Idylla GeneFusion Assay (IGFA) for its effectiveness in rapidly detecting targetable gene fusions and *MET* exon 14 skipping in cancer samples. The IGFA is a fully automated assay designed to detect *ALK, ROS1, RET, NTRK1, NTRK2, NTRK3* gene fusions, and *MET* exon 14 skipping. The assay was tested on 68 tumor samples, including 49 known to have gene fusions or *MET* exon 14 skipping and 19 negative controls. A total of 128 IGFA tests were performed, and the results were compared with IHC, FISH, and NGS methods. The global sensitivity and specificity of the IGFA were 62.82% and 99.2%, respectively. Sensitivity was higher (72.5%) in tissue samples meeting the manufacturer's criteria (>20 mm^2 and >10% tumor cells). However, the sensitivity varied across different molecular targets and was lower for small samples with low tumor cell content. Specificity remained high across all sample types. The study suggests that while the IGFA offers rapid and specific results, it may not be suitable as a standalone diagnostic tool due to variability in sensitivity and the occurrence of false positives and negatives.

Take Home Message: The Idylla GeneFusion Assay provides a rapid and automated method for detecting targetable gene fusions and MET exon 14 skipping in cancer samples, with high specificity but variable sensitivity. While useful for urgent therapeutic decisions, it should be used in conjunction with other diagnostic methods like IHC, FISH, and NGS to ensure accuracy and reliability in clinical practice. The IGFA can significantly expedite the molecular diagnosis of gene fusions and mutations, particularly in rapidly progressing cancers where timely therapeutic decisions are critical.

Interdisciplinary Diagnosis and Management of Patients With Interstitial Lung Disease and Connective Tissue Disease.

Guler et al, Chest

This article discusses the complexities of diagnosing and managing patients with ILD associated with connective tissue disease (CTD), emphasizing the need for interdisciplinary collaboration between pulmonologists and rheumatologists. ILD, which can manifest in up to 85% of CTD patients, significantly impacts morbidity and mortality, particularly in diseases like systemic sclerosis (SSc) and rheumatoid arthritis (RA). The study highlights the challenges posed by delayed diagnosis and fragmented care, advocating for a structured interdisciplinary approach. The article outlines a formal joint consultation model between pulmonology and rheumatology, which was piloted in 2021. The process includes comprehensive diagnostics such as pulmonary function tests, chest CT scans, and rheumatological evaluations. In the study, 170 patients were evaluated, leading to diagnoses such as systemic sclerosis, idiopathic inflammatory myopathy, and Sjögren's syndrome, among others. Immunosuppressive and antifibrotic treatments were adjusted based on the joint consultations. The authors emphasize the importance of multidisciplinary team discussions (MDD) in diagnosing ILD, which improves diagnostic accuracy and treatment decisions. The benefits of this interdisciplinary care model include more coordinated care, a holistic approach to management, and improved patient outcomes, though logistical and resource challenges are acknowledged.

Take Home Message: The integration of pulmonology and rheumatology in the diagnosis and management of ILD-CTD patients is essential for improving diagnostic accuracy and treatment outcomes.

Prognostic significance of micronest in cancer stroma in resected lung squamous cell carcinoma.

Kaminuma et al, Human Pathology

This study explores the clinical significance of micronests in cancer stroma (MICS) in lung squamous cell carcinoma (LSqCC). Micronests are defined as clusters of 5–200 tumor cells, distinct from the main tumor, and larger than tumor budding. Out of 198 patients with resected LSqCC, 28.8% had MICS, and the presence of these nests was associated with significantly worse overall survival (OS) and recurrence-free survival (RFS). The presence of MICS was an independent poor prognostic factor, with lower E-cadherin and GLUT-1 expression in MICS compared to the rest of the tumor, indicating a possible association with epithelial-mesenchymal transition (EMT) and hypoxia.

Take Home Message: The presence of MICS in lung squamous cell carcinoma is a strong independent indicator of poor prognosis. MICS may play a role in cancer progression via EMT, suggesting that recognizing these structures could be critical for predicting outcomes and tailoring treatment strategies.

Osimertinib after Chemoradiotherapy in Stage III EGFR-Mutated NSCLC.

Lu et al, NEJM

This phase 3, double-blind, placebo-controlled trial (LAURA study) examined the efficacy and safety of osimertinib as maintenance therapy following chemoradiotherapy in patients with unresectable, EGFR-mutated stage III non-small-cell lung cancer (NSCLC). A total of 216 patients were randomized to receive osimertinib or placebo after completing chemoradiotherapy. The primary endpoint was progression-free survival (PFS). Patients receiving osimertinib demonstrated a significant improvement in PFS, with a median of 39.1 months compared to 5.6 months in the placebo group (hazard ratio for progression or death, 0.16; P<0.001). At 12 months, 74% of patients on osimertinib were alive and progression-free, versus 22% with placebo. Safety outcomes showed an increased incidence of adverse events in the osimertinib group, particularly grade 3 or higher events (35% vs. 12%). The most common adverse effects included radiation pneumonitis and diarrhea, but no new safety concerns were observed.

Take Home Message: Osimertinib significantly prolongs progression-free survival when used as maintenance therapy in patients with unresectable stage III EGFR-mutated NSCLC after chemoradiotherapy, making it a promising option for extending disease control in this setting. However, careful monitoring for adverse events such as pneumonitis is essential.

Molecular Endotypes of Idiopathic Pulmonary Fibrosis: A Latent Class Analysis of Two Multicenter Observational Cohorts.

Maddali et al, AJRCCM

This study aimed to define molecular endotypes in idiopathic pulmonary fibrosis (IPF) through latent class analysis (LCA) based on 25 plasma biomarkers involved in IPF-related pathways. The study analyzed data from a large discovery cohort (n=875) and a validation cohort (n=347) to assess these endotypes and their clinical relevance. Two molecular endotypes were identified. Endotype 2 was associated with elevated biomarkers such as WFDC2 and GDF15 and demonstrated worse 4-year transplant-free survival compared to Endotype 1. Patients in Endotype 2 had a hazard ratio (HR) of 2.02 for death or lung transplant in the discovery cohort and 1.95 in the validation cohort. Interestingly, Endotype 2 also showed a significantly better response to antifibrotic therapies, such as pirfenidone and nintedanib, with a reduced risk of death or transplant (HR = 0.64), while Endotype 1 did not benefit from such treatments (HR = 1.19).

Take Home Message: The study provides evidence of two molecular endotypes in IPF, which exhibit distinct clinical outcomes and differential responses to antifibrotic therapy. The

identification of molecular endotypes offers valuable insights into the biological heterogeneity of IPF.

Diagnostic gastrointestinal markers in primary lung cancer and pulmonary metastases.

Malmros et al, Virchows Archiv

This study focuses on the use of gastrointestinal (GI) immunohistochemical markers to differentiate between primary lung adenocarcinomas (AC) and pulmonary metastases from GI adenocarcinomas. The challenge arises because common markers like CK20 and CDX2, often used for GI cancers, may be positive in mucinous primary lung cancers. The study examined tissue microarrays from 629 primary lung cancers and 422 pulmonary metastases to evaluate the diagnostic value of six GI markers: CDH17, GPA33, MUC2, MUC6, SATB2, and SMAD4, in comparison with traditional markers like CDX2, CK20, CK7, and TTF-1. The results demonstrated that GPA33, CDX2, and CDH17 had high sensitivity for detecting pulmonary metastases from GI tract adenocarcinomas, particularly colorectal and pancreatic cancers. However, no single marker or combination was able to perfectly distinguish between primary lung cancers and GI metastases, especially in mucinous subtypes. SATB2 and CK20 exhibited higher specificity, being rarely expressed in primary lung adenocarcinomas.

Take Home Message: CDH17, GPA33, and SATB2, along with CDX2 and CK20, are valuable markers in distinguishing pulmonary metastases from GI origins, though no panel of markers provides complete accuracy.

Image-Assisted Pleural Needle Biopsy or Medical Thoracoscopy: Which Method for Which Patient? A Randomized Controlled Trial.

Metintas et al, Chest

This randomized controlled trial compared the diagnostic efficacy, reliability, and safety of image-assisted Abrams needle pleural biopsy (IA-ANPB) versus medical thoracoscopy (MT) in diagnosing pleural effusion. A total of 228 patients with undiagnosed exudative pleural effusion were divided into two groups based on thoracic CT findings: Group 1 included patients with pleural effusion only, while Group 2 included patients with pleural effusion and pleural thickening or lesions. Each group was then randomized to either IA-ANPB or MT. In patients with pleural effusion alone (Group 1), MT was significantly more sensitive (96.9%) compared to IA-ANPB (69.7%), with a much lower false-negative rate (3.1% vs 30.3%). However, for patients with pleural thickening or lesions (Group 2), the diagnostic sensitivity of IA-ANPB (88.1%) was similar to MT (95.4%).

Take Home Message: MT is superior in patients with pleural effusion only, offering higher diagnostic accuracy. IA-ANPB is a viable alternative in patients with pleural thickening or lesions, achieving similar diagnostic outcomes as MT.

A Rare Manifestation of Airway Invasion from Pulmonary Artery Liposarcoma.

Miao et al, Am J Respir Crit Care Med

Case of a 45-year-old female with airway invasion resulting from pulmonary artery liposarcoma- I am not at all sure how it was subclassified as liposarc, I see no clear evlidence of that. The patient experienced chest tightness and exertional dyspnea for 14 months, which worsened with a productive cough for one month. A history of pulmonary artery liposarcoma was noted, treated with tumor resection, pulmonary arterioplasty, and valve replacement a year prior. Postoperative imaging revealed a nodule in the left bronchus and atelectasis in the left lower lobe. PET/CT indicated increased uptake in the mass, suggesting malignancy. Bronchoscopy identified and removed the tumor obstructing the left main bronchus. Histopathological examination confirmed bronchial metastasis originating from pulmonary artery liposarcoma with “retrodifferentiation”- no idea what that actually means. The patient's respiratory symptoms and exercise tolerance improved following tumor removal.

Take Home Message: Pulmonary artery sarcomas are exceptionally rare and aggressive tumors. This case highlights the unusual occurrence of bronchial metastasis from a pulmonary artery sarcoma, emphasizing the need for awareness of potential airway involvement in such malignancies. But I am not sure it is actually a liposarcoma 😊.

Concordance of Immunohistochemistry and Fluorescence In Situ Hybridization in the Detection of Anaplastic Lymphoma Kinase (*ALK*) and Ros Proto-oncogene 1 (*ROS1*) Gene Rearrangements in Non–Small Cell Lung Carcinoma: A 4.5-Year Experience Highlighting Challenges and Pitfalls.

Nambirajan et al, Archives

This study evaluates the concordance between IHC and FISH in detecting *ALK* and *ROS1* rearrangements in non-small cell lung carcinoma (NSCLC). Over a span of 4.5 years, 1,874 lung adenocarcinoma samples were analyzed for *EGFR* mutations using real-time PCR and for *ALK/ROS1* rearrangements using IHC, with FISH confirmation in equivocal cases. The study found a 27% prevalence of *EGFR* mutations and 10% positivity for *ALK* rearrangements by IHC, with an 81% concordance between ALK IHC and FISH. ROS1 IHC showed a 13% positivity rate, with 19.3% confirmed by FISH. The study highlights the robustness of IHC for initial screening of *ALK* and *ROS1* rearrangements, recommending FISH for confirmation in equivocal cases or when tissue samples are limited.

Take Home Message: Immunohistochemistry is a reliable initial screening method for detecting *ALK* rearrangements in NSCLC, with FISH providing additional confirmation in equivocal cases. For *ROS1* rearrangements, a combination of IHC followed by FISH may be effective and cost-efficient, particularly after excluding *EGFR* and *ALK* mutations.

CT-guided needle biopsy is not associated with increased ipsilateral pleural metastasis.

Niedermaier et al, Lung Cancer

This retrospective study investigates whether CT-guided needle biopsy (CTGNB) increases the risk of ipsilateral pleural recurrence (IPR) in patients with early-stage lung cancer. A total of 844 patients who underwent curative resection between 2010 and 2020 were included. The study compared the outcomes of patients diagnosed via CTGNB and bronchoscopy. The median follow-up was 47.5 months. The primary finding was that CTGNB did not significantly affect the rate of IPR. The study identified microscopic pleural invasion and tumor location in the lower lobe as significant risk factors for IPR. Notably, tumors diagnosed by CTGNB were significantly closer to the pleura than those diagnosed by bronchoscopy.

Take Home Message: CT-guided needle biopsy is a safe diagnostic tool for early-stage lung cancer and does not increase the risk of ipsilateral pleural metastasis. The presence of microscopic pleural invasion and tumors in the lower lobe are more critical factors for pleural recurrence.

Bilateral mediastinal cysts with müllerian differentiation.

Puig et al, Thorax

This case report describes a 40-year-old woman who presented with bilateral mediastinal cysts that were discovered incidentally during imaging for an unrelated acute cough. The cysts, located in the posterior mediastinum, were identified as Müllerian differentiation cysts based on histological findings and immunohistochemical positivity for estrogen receptors. The almost look like adenofibromas, based on very limited photos. Müllerian cysts, though typically found in the abdomen or retroperitoneum, are rare in the posterior mediastinum. These lesions were initially mistaken for bronchogenic cysts but were ultimately diagnosed as Müllerian differentiation cysts, a rare entity with only about 40 cases reported worldwide. The patient's history included hormonal contraception use, and the cysts showed slow growth over five years, necessitating surgical excision.

Take Home Message: Müllerian differentiation cysts should be considered in the differential diagnosis of posterior mediastinal cystic lesions, especially in middle-aged women with obesity or a history of hormone treatment. Surgical excision is recommended due to the potential risk of malignant transformation. I have never seen one.

Analyses of 1236 genotyped primary ciliary dyskinesia individuals identify regional clusters of distinct DNA variants and significant genotype–phenotype correlations.

Raidt et al, Eur Respir J

This study investigates the genetic and phenotypic characteristics of 1,236 individuals with genetically confirmed primary ciliary dyskinesia (PCD) across 19 countries. The research identified 908 distinct pathogenic variants across 46 PCD-related genes, highlighting significant regional differences in gene variants and genotype–phenotype correlations. For example, the study found that variants in the genes *DNAH5, CCDC39*, and *CCDC40* were more prevalent in certain regions. These genes are associated with more severe lung function decline, as indicated by lower median FEV1 z-scores. In contrast, milder lung function impairment was observed in individuals with variants in *DNAH11* and *ODAD1*. Additionally, laterality defects were more common in PCD patients with variants causing pathognomonic ciliary ultrastructure defects, while patients without these defects were less likely to present with laterality abnormalities.

Take Home Message: The study underscores the importance of understanding regional genetic differences in PCD for accurate diagnosis and management. Genotype-specific patterns, such as the impact on lung function and the presence of laterality defects, can guide more personalized approaches to patient care, particularly in predicting disease progression and tailoring treatment strategies.

Chronic thromboembolic pulmonary hypertension is an uncommon complication of COVID-19: UK national surveillance and observational screening cohort studies.

Reddy et al, Eur Respir J

This study explored the incidence of chronic thromboembolic pulmonary hypertension (CTEPH) as a complication of COVID-19 in the UK. Using two national datasets, the study found that CTEPH following COVID-19-related pulmonary embolism (PE) is rare. Over a one-year period, only 1.4% of newly diagnosed CTEPH cases were potentially attributable to COVID-19-associated PE. A second cohort of 1,094 COVID-19 survivors was screened for CTEPH risk using a combination of clinical assessment, ECG, and NT-proBNP levels, identifying just 1% of patients at high risk. The study concluded that although COVID-19 can lead to PE, the progression to CTEPH is uncommon.

Take Home Message: CTEPH is a rare complication following COVID-19, with the majority of patients recovering without developing this severe condition.

Preoperative mediastinal staging in early-stage lung cancer: Targeted nodal sampling is not inferior to systematic nodal sampling.

Sullivan et al, JTO

This study evaluates whether targeted sampling (TS) is noninferior to systematic sampling (SS) for preoperative mediastinal staging in early-stage NSCLC. Conducted at six Canadian tertiary care centers, the prospective, multicenter trial involved 91 patients who underwent both TS and SS during endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). The noninferiority margin for missed nodal metastasis (MNM) was set at 6%.

- TS identified 255 out of 256 lymph nodes (LNs) as benign and 1 as malignant.
- SS found 247 LNs as benign and 8 as malignant, with a higher incidence of nondiagnostic samples compared to TS.
- The MNM incidence was 0.78% for SS and 2.34% for TS, with an absolute difference of 1.56%, falling within the noninferiority margin.
- No major complications were reported for either method, and TS significantly reduced procedure time compared to SS.

Take Home Message: Targeted nodal sampling is a viable and noninferior alternative to systematic sampling for mediastinal staging in early-stage NSCLC when performed by experienced endoscopists at high-volume centers. TS can streamline the staging process, reducing procedure time and maintaining diagnostic accuracy.

Histology of Bronchiolar Tumor Spread Through Air Spaces.

Takahara et al, AJSP

This study investigates the clinical significance of bronchiolar STAS in lung adenocarcinoma. Unlike previous studies focusing on alveolar STAS, this research examines the presence and implications of bronchiolar STAS.

- Bronchiolar STAS was identified in 18% of the 306 cases of primary lung adenocarcinoma.
- Bronchiolar STAS was associated with an inferior prognosis, advanced stage, and higher histologic grade.
- No significant difference was observed in clinicopathological factors or prognosis between cases with bronchiolar STAS and those with alveolar STAS alone.
- Bronchiolar STAS often co-occurred with alveolar STAS and endobronchial spread of adenocarcinoma (EBSA), especially when bronchiolar STAS was found outside the main tumor.

- The presence of bronchiolar STAS was significantly associated with poor relapse-free survival (RFS) and cancer-specific survival (CSS).

Take Home Message: Bronchiolar STAS, like alveolar STAS, is associated with a poor prognosis.

Digital spatial profiling identifies distinct molecular signatures of vascular lesions in pulmonary arterial hypertension.

Tuder et al, AJRCCM

This study explores the molecular profiles of microscopic vascular lesions in idiopathic pulmonary arterial hypertension (IPAH) using digital spatial transcriptomics. The aim was to identify unique gene expression signatures across different types of vascular lesions, which include plexiform lesions (Plxs), obliterative lesions (Oblits), intima-media hypertrophy (IMH), and changes in adventitia (Adv).
-Gene Detection and Expression: A total of 8,273 transcripts were identified across IPAH lesions and control lung pulmonary arteries. Plexiform lesions and IPAH adventitia exhibited the most differentially expressed genes compared to intima-media hypertrophy and obliterative lesions.
-Plexiform Lesions: Enriched for genes associated with transforming growth factor-beta (TGF-β) signaling, extracellular matrix mutations, and endothelial-mesenchymal transformation. Showed upregulation in immune and interferon signaling, coagulation, and complement pathways.
-Adventitia: Displayed significant gene expression changes, particularly in inflammatory pathways and complement activation, highlighting its role in immune mechanisms in IPAH.
-Differential Pathway Enrichment: Pathways involved in inflammation, hypoxia signaling, apoptosis, and oxidative stress were significantly enriched in IPAH lesions compared to controls.
-Cellular Composition: Digital spatial profiling revealed variability in the cellular makeup of IPAH lesions, emphasizing the presence of vascular and inflammatory cells.

Take Home Message: The study demonstrates that distinct molecular signatures characterize various vascular lesions in IPAH, with plexiform lesions and adventitia showing significant enrichment in pathogenic pathways. These findings provide a framework for identifying new biomarkers and therapeutic targets for pulmonary arterial hypertension.

Asbestos-Related Lung Cancer: An Underappreciated Oncological Issue.

Van Zandwijk et al, Lung Cancer

This paper highlights asbestos as a major cause of mesothelioma and an underappreciated cause of lung cancer, termed asbestos-related lung cancer (ARLC). It emphasizes that ARLC

incidence is estimated to be significantly higher than mesothelioma. It explores the synergistic effect of asbestos exposure combined with other carcinogens such as tobacco smoke, radon, and PM2.5 air pollution. The combination of these factors significantly increases the risk of developing lung cancer. The study underlines the importance of accurate historical data on asbestos exposure, which can often be challenging due to various sources including occupational, environmental, and even household exposures. There is a particular focus on the potential role of asbestos in lung cancer in never-smokers (LCINS), suggesting that historic and current asbestos exposure along with air pollution may account for a significant proportion of these cases. The research calls for improved surveillance and prevention measures, particularly in documenting occupational and environmental exposure histories. The study also notes the importance of combining these histories with molecular tumor signatures to better understand carcinogenesis pathways.

Take Home Message: Asbestos exposure remains a significant but underappreciated cause of lung cancer.

The International Association for the Study of Lung Cancer Pleural Mesothelioma Staging Project: Expanded Database to Inform Revisions in the Ninth Edition of the TNM Classification of Pleural Mesothelioma.

Wolf et al, JTO

This article describes the work of the IASLC in updating the TNM classification system for pleural mesothelioma in the ninth edition. The study significantly expands on the previous staging databases by incorporating data from 3,598 cases diagnosed between 2013 and 2022. The new database includes a broader geographic representation and a higher proportion of patients treated nonsurgically, reflecting shifts in clinical practice. The article details the evolution of the pleural mesothelioma staging systems, starting with early systems and moving to the current iteration, which emphasizes a more accurate staging for both surgically and nonsurgically treated patients. Key updates include refined T and N descriptors based on pleural thickness and lymph node involvement, respectively, and the potential inclusion of mesothelioma in situ in future staging systems.

Take Home Message: The ninth edition of the TNM classification system for pleural mesothelioma will provide a more accurate staging framework, informed by a large, geographically diverse database that better reflects current clinical practices. These updates aim to improve prognostication and treatment strategies for mesothelioma patients.

The proportion of tumour stroma predicts response to treatment of immune checkpoint inhibitor in combination with chemotherapy in patients with stage IIIB-IV non-small cell lung cancer.

Yi et al, Histopathol.

This study investigates the predictive value of intratumour stroma proportion (iTSP) for the effectiveness of immune checkpoint inhibitors (ICIs) combined with chemotherapy in patients with stage IIIB-IV non-small cell lung cancer (NSCLC). The researchers analyzed 102 biopsy samples from patients who received ICIs plus chemotherapy. The study found that patients with lower iTSP (less than 50%, categorized as stroma-L) had significantly better clinical outcomes compared to those with higher iTSP (greater than 50%, categorized as stroma-H). Specifically, the stroma-L group exhibited higher objective response rates, greater depth of response, and longer median progression-free survival and overall survival. Multivariate analysis confirmed iTSP as an independent prognostic factor for both progression-free survival and overall survival.

Take Home Message: The proportion of tumour stroma (iTSP) serves as a significant predictive biomarker for the response to ICIs combined with chemotherapy in advanced NSCLC. Patients with lower iTSP show better treatment outcomes.

Benign metastasizing fumarate hydratase (FH)-deficient uterine leiomyomas: clinicopathological and molecular study with first documentation of multi-organ metastases.

Yin et al, Virchows Archiv

This study presents two cases of benign metastasizing fumarate hydratase-deficient (FH-d) uterine leiomyomas (BML), a rare occurrence wherein benign uterine tumors metastasize to distant organs. Both patients, aged 21 and 34, developed multiple metastases, primarily in the lungs, with one case involving multi-organ metastases including the kidney, lymph nodes, and other sites. Histological analysis confirmed the benign nature of the primary and metastatic tumors, characterized by FH deficiency, and genetic testing revealed pathogenic germline FH mutations in both cases, linking them to hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome.

Take Home Message: FH-deficient uterine leiomyomas can metastasize to multiple organs while retaining benign histological features. These cases underscore the importance of recognizing FH deficiency and its association with HLRCC syndrome, which may have significant implications for the management and genetic counseling of affected patients.

NGS and FISH for MET Amplification Detection in EGFR TKI Resistant Non-Small Cell Lung Cancer (NSCLC) Patients: A Prospective, Multicenter Study in China.

Zheng et al, Lung Cancer

This study evaluates the use of NGS and FISH for detecting *MET* amplification in Chinese patients with NSCLC who have developed resistance to EGFR TKIs. A total of 116 patients with EGFR TKI-resistant NSCLC were included, with tissue and paired plasma samples analyzed using NGS and FISH to determine *MET* amplification. *MET* amplification was found in 37.1% of patients by FISH, and the study further differentiated between polysomy and focal amplification. The sensitivity, specificity, and agreement of NGS in detecting MET amplification in tissue samples were 39.5%, 98.6%, and 76.7%, respectively. For plasma samples, the sensitivity was lower, indicating the need for improvement in plasma-based NGS. The research identified optimal threshold values for NGS in detecting *MET* amplification to enhance its sensitivity while maintaining high specificity. The study emphasizes the clinical significance of *MET* amplification as a mechanism of resistance to EGFR TKIs and highlights the importance of accurate detection methods for guiding treatment decisions.

Take Home Message: NGS can be a viable alternative to FISH for detecting *MET* amplification in tissue samples, although its sensitivity in plasma samples needs improvement. Accurate detection of MET amplification is crucial for managing NSCLC patients who have developed resistance to EGFR TKIs, as it can inform potential dual-targeted therapies.

Expanding the Spectrum of *NUTM1*-Rearranged Sarcoma: A Clinicopathologic and Molecular Genetic Study of 8 Cases.

Zhu et al, AJSP

This study characterizes the clinicopathologic and molecular features of *NUTM1*-rearranged sarcomas through an analysis of 8 cases, aiming to expand the understanding of this rare tumor entity. *NUTM1*-rearranged sarcomas are a diverse group of tumors involving *NUTM1* translocation, commonly associated with poor differentiation and aggressive behavior. These sarcomas manifest in various anatomic locations, including the gastrointestinal tract, thoracic cavity, and soft tissues. The cohort consisted of 2 males and 6 females, with ages ranging from 24 to 64 years. Tumors were found in the colon, abdomen, jejunum, esophagus, lung, and infraorbital region, with 6 out of 8 patients presenting with metastatic disease at diagnosis. Histologically, the tumors exhibited a range of morphologies, from small round cells to epithelioid and spindle cells, with frequent presence of rhabdoid features, pronounced nuclear

convolutions, and varied stroma including hyalinized and myxoid regions. Immunohistochemically, all tumors showed strong nuclear staining for NUT protein, with variable expression of other markers such as pancytokeratin, CD99, NKX2.2, cyclin D1, desmin, and BCOR. Molecular analysis revealed various *NUTM1* fusions, including *MXD4::NUTM1*, *MXI1::NUTM1*, and *MGA::NUTM1*. DNA methylation profiling in two cases showed distinct epigenetic signatures, differentiating these tumors from other sarcomas and NUT carcinomas. The clinical course of *NUTM1*-rearranged sarcomas varied, with some patients experiencing recurrence and others remaining well without signs of disease over follow-up periods ranging from 4 to 24 months.

Take Home Message: *NUTM1*-rearranged sarcomas represent a heterogeneous group of aggressive tumors that should be considered in the differential diagnosis of undifferentiated small round cell, epithelioid, and spindle cell malignancies. Accurate identification using NUT immunohistochemistry and molecular genetic testing is crucial for appropriate diagnosis and management.