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By Tao Huang, BM, PhD, University of Michigan

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Page 20 Galeano B, et al. Ki-67 Proliferation Index Is Associated With Tumor Grade and Survival in Pleural Epithelioid Mesotheliomas. Am J of Surg Pathol. 2024;48(5):615-622.

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Discussion Article

Naso JR, et al. Prognostic Immunohistochemistry for Ki-67 and OTP on Small Biopsies of Pulmonary Carcinoid Tumors. *Am J Surg Pathol*. 2024;48(6):742-750.

Purpose: This study aimed to investigate the prognostic value of Ki-67 and orthopedia homeobox (OTP) immunohistochemistry on small biopsy and cytology specimens from pulmonary carcinoid tumors. For patients who are not good surgical candidates or treated with tumor ablation with no tissue available for further analysis, it is important to extrapolate prognostic information from the only small biopsy or cytology specimens available.

Methods: The study included 139 small biopsy/cytology specimens of pulmonary carcinoid tumors, collected from the Mayo Clinic archives from 1996 to 2022. Ki-67 labeling index was analyzed using Aperio ImageScope Software via automated image analysis of at least 500 cells by placing 10 or more 107x106 μm (0.11 mm^2) boxes at the hot spot manually identified by an experienced technologist. 10% of cases were reviewed for concordance with manual hot spot Ki-67 counts by a pathologist. OTP immunohistochemistry was performed on 70 cases with sufficient tissue, scored as positive or negative based on staining in less than 20% of tumor nuclei. Clinical data were retrospectively reviewed, and statistical analyses were conducted to evaluate associations with disease-specific progression-free survival (ds-PFS).

Results:

- N=139 (84 TBBX, 37 core needle, 16 FNA, 2 CryoBx); 75% (n=104; 81 typical carcinoid tumor [TC] and 22 atypical carcinoid tumor [AC]) of the cases followed by complete resection and 25% (n=35) of cases with biopsy only; 10 progression events – 6 distant metastasis (3 liver, 1 bone, 1 eye, and 1 with bone and liver metastasis), 2 regional LN metastasis and 2 local recurrence
- **Ki-67 Index**:
    - Median- 2.7%, 13 cases- >10% (with 1 case >20%)
    - The hazard ratio for progression increases as the Ki67 increases and levels off ~ 4-5% (fig 2A)
    - Threshold 3% or 4%, and histology (typical vs atypical) showed similar strong association with ds-PFS (fig 2B-D)
    - 3% threshold was chosen for further analysis given that 3% was chosen in other organ systems.
    - 3-year ds-PFS is 98% for Ki-67 < 3% and 89% for Ki-67 ≥ 3%.
    - For cases with subsequent reactions, TC had a median bx Ki67 of 2.3 % (0%-18.2%) and AC had a median bx Ki67 of 4.4% (0.3%-14%).
    - The positive predictive value of Ki67 >3% for AC is only 36%
    - Ki67 of 3.21% was the optimal threshold to predict TC vs AC with a sensitivity of 77% and specificity of 67% (fig 3B)
- **OTP Expression**:
    - While negative OTP staining was a/w shorter ds-PFS, this finding is not statistically significant.
    - Negative OTP staining was not significantly a/w Ki67 >=3%.
    - Negative OTP staining did not show statistically significant association with AC

Take-home message: Ki-67 immunohistochemistry on small biopsy samples of pulmonary carcinoid tumors is a valuable prognostic tool for pulmonary carcinoid patients who cannot undergo resection, with a 3% threshold predictive of ds-PFS and atypical carcinoid histology. Negative OTP staining may indicate atypical histology, but this conclusion requires additional studies.

Simbolo M, et al. Characterization of two transcriptomic subtypes of marker-null large cell carcinoma of the lung suggests different origin and potential new therapeutic perspectives. *Virchows Arch*. 2024;484:777-788.

Purpose: Pulmonary large cell carcinoma (LCC) is an undifferentiated neoplasm lacking the morphological, histochemical, and immunohistochemical features of neuroendocrine carcinoma, adenocarcinoma (ADC), or squamous cell carcinoma (SCC). Given the rarity of LCC and its diagnosis of exclusion, there is limited molecular information available. Previous studies have identified TP53 as a frequently mutated gene in LCC, but comprehensive genomic and transcriptomic data are sparse. This study aims to provide an integrated molecular overview of LCC, focusing on identifying distinct transcriptomic subtypes and their potential therapeutic implications.

Methods: The study included 16 cases of marker-null LCC, collected from clinical databases of three Italian hospitals between 2010 and 2020. Molecular profiling involved mutational analysis of 409 genes using the Oncomine Tumour Mutational Load panel and transcriptomic analysis of 20,815 genes using RNA sequencing. Immunohistochemistry was performed for specific markers, and gene set enrichment analysis (GSEA) was used to identify biological pathways. Comparative transcriptomic profiling included 17 ADC and 11 large cell neuroendocrine carcinoma (LCNEC) cases. Statistical analyses were conducted to identify significant associations and differences between identified subtypes.

Results:

- **Mutational Analysis**: TP53 was the most frequently mutated gene (93.7%), followed by RB1 (31.3%) and KEAP1 (25%). CRKL and MYB were each amplified in 25% of cases, and MYC in 18.8%.
- **Transcriptomic Subtypes**: Two distinct molecular subtypes were identified:
    - **Pure-LCC**: Characterized by overexpression of POU2F3 and FOXI1, a tuft cell-like profile, and a positive association with DNA repair through homologous recombination mechanisms, including Fanconi, ATM, and ATR pathways.
    - **ADLike-LCC**: Characterized by an alveolar-cell transcriptomic profile and association with inflammatory response pathways, including the AIM2 inflammasome complex signature but not PDL1. PDL1 immunostain is negative in both ADLike-LCC and Pure-LCC. This subtype is a/w a strong leukocyte infiltrate.
- **Gene Expression**: Differential expression of FOXI1, POU2F3, and AIM2 by immunohistochemistry was noted between the subtypes (fig 3A).
- **Biological Pathways**: Pure-LCC was associated with DNA repair and cell proliferation pathways, while ADLike-LCC was linked to inflammatory response pathways.
- **Clinical Features**: Differences in age and mitotic count were observed between the subtypes, with Pure-LCC showing older age, higher mitotic counts and more aggressive behavior.

Take-home message: The study splits marker-null LCC into two transcriptomic subtypes, Pure-LCC and ADLike-LCC, each with distinct molecular and clinical features. Differential markers (POU2F3, FOXI1, AIM2) can aid in diagnosis, and the distinct molecular signatures suggest potential therapeutic targets. Pure-LCC may benefit from therapies targeting replication stress (e.g. Berzosertib, an *ATR* inhibitor), while ADLike-LCC may be responsive to treatments targeting the AIM2 inflammasome complex.

Odintsov, I., et al. Prevalence and Therapeutic Targeting of High-Level ERBB2 Amplification in NSCLC. *J Thorac Oncol*. 2024;19(5), 732-748.

Purpose: HER2, encoded by the ERBB2 gene, is a member of the ERBB/HER family of receptor tyrosine kinases. Overexpression of HER2 due to ERBB2 amplification is a common mechanism in various cancers. While anti-HER2 therapy is established in breast and gastroesophageal cancers, its efficacy in non-small cell lung cancer (NSCLC) with ERBB2 amplification has been less studied. Previous studies showed inconsistent results regarding HER2 overexpression and its correlation with ERBB2 amplification in lung cancer. The study addresses the frequency and therapeutic potential of high-level ERBB2 amplification in NSCLC, with an emphasis on identifying patients who could benefit from HER2-targeted therapies.

Methods: The study queried an institutional database of 5769 NSCLC samples from 5075 patients for cases with high-level ERBB2 amplification (≥6 copies) using next-generation DNA sequencing data. Clinical and demographic characteristics were extracted from electronic medical records. The efficacy of afatinib (small molecule TKI), anti-HER2 antibody, and HER2 antibody-drug conjugates (ADCs) such as trastuzumab deruxtecan and trastuzumab emtansine was evaluated in preclinical models and patients. HER2 IHC interpretation (0, absent; 1+, weak in <10% tumor cells; 2+ moderate circumferential / basolateral in >10% of tumor cells; 3+, strong circumferential / basolateral in >10% of tumor cells; Negative-score 0 and 1, Positive-score 2 and 3).

Results:

- **Cohort:** N=36 pts; 34 pts have HER2 IHC-26 (76.5%) positive (3+ in 24; 2+ in 2) and 8 (23.5%) negative (1+ in 6; 0 in 2)
- **Prevalence:** High-level ERBB2 amplification was identified in 0.9% (33/3079) of lung adenocarcinomas, reliably predicting HER2 overexpression.
- **Subsets:** Two distinct subsets of NSCLC with ERBB2 amplification were found:
    - **Group A** (n=18; 50%): ERBB2 amplification as the sole driver in patients; enriched in males with a smoking history and higher tumor mutation burden.
    - **Group B** (n=18; 50%): ERBB2 amplification concurrent with other oncogenic drivers; in light or never smokers.
        - **B1** (n=9): concurrent activating single-nucleotide variants or small indels in ERBB2; most had negative HER2 IHC with mutation in ERBB2 tyrosine kinase domain
        - **B2** (n=9): concurrent mutations in other RTKs and MAPK pathway actors (EGFR, MET, RET, KRAS, BRAF) including those with acquired ERBB2 amplification after targeted therapy
- High-level ERBB2 amplification was not limited to lung adenocarcinoma and was also found in 10 non-lung adenocarcinoma (3 SqCC, 3 NSCLC, 2 adenosquamous cell carcinoma, 1 pleomorphic carcinoma, 1 thoracic SMARCA4-deficient undifferentiated tumor)
- **Therapeutic Efficacy:** Preclinical in vitro (cell lines) and in vivo (xenograft) models showed significant sensitivity to HER2-targeted therapies. Clinical cases reported effectiveness of HER2 ADCs in patients acquiring ERBB2 amplification post first-line TKI targeted therapy.

Take-home message: ERBB2 amplification, present in a small percentage (0.9%) of NSCLC cases. This study supports the use of comprehensive genomic profiling to identify patients with ERBB2 amplification who may benefit from HER2-targeted therapies. HER2-ADC showed superior effects than other HER2-targed therapies.

Editorial: Shih JY. ERBB2 Amplification in NSCLC: How Many Faces? *J Thorac Oncol.* 2024;19(5):668-670.

Dacic S, et al. Artificial Intelligence–Powered Assessment of Pathologic Response to Neoadjuvant Atezolizumab in Patients With NSCLC: Results From the LCMC3 Study. *J Thorac Oncol*. 2024;19(5):719-731.

Purpose: The study aimed to evaluate the efficacy and precision of artificial intelligence (AI) in assessing pathologic response to neoadjuvant atezolizumab in patients with resectable non-small cell lung cancer (NSCLC), utilizing data from the Lung Cancer Mutation Consortium 3 (LCMC3) study, which showed 20% major pathologic response (MPR, defined as <=10% viable tumor) rate at the October 15, 2021 clinical cutoff.

Methods: Data were collected from a total of 151 patients with NSCLC who participated in LCMC3 and underwent surgery. Pathologic response was determined using both visual and AI-powered assessments on primary tumor resection specimens. A convolutional neural network (CNN) model was developed to digitally measure the percentage of viable tumor on whole-slide images (WSIs). Concordance was evaluated between visual assessment by local and central pathologists and digital assessment.

Results:

- **Visual Assessment**: High concordance was observed among 4 pathologists (3 central pathologists + 1 local pathologist), with an intraclass correlation coefficient of 0.87 and agreement for MPR at 92.1%. The agreement for visual pathologic complete response (pCR) assessment among 4 reviewers was 98%.
- **Digital Assessment**: Digitally assessed percent viable tumor correlated well with visual assessments (Pearson r = 0.73). The digital model demonstrated outstanding discrimination in predicting MPR (AUROC = 0.98).
- **Survival Outcomes**: Patients with digitally assessed MPR had significantly longer disease-free survival (DFS) and overall survival (OS) compared to those without MPR (DFS HR = 0.30, OS HR = 0.14).

Take-home message: AI-powered digital pathology shows promise in assisting pathologic assessments in neoadjuvant NSCLC clinical trials. Digital assessments of MPR correlate strongly with visual assessments and are associated with improved long-term outcomes, suggesting potential for routine clinical use to enhance precision and efficiency in pathologic evaluations.

Editorial: Ishikawa S. Artificial Intelligence Enhances NSCLC Care by Predicting Treatment Outcomes, Validating Neoadjuvant Therapies, and Improving Precision. *J Thorac Oncol.* 2024;19(5):666-667.

Articles for notation

Neoplastic

Li S, et al. Primary salivary duct carcinoma of the lung: clinicopathological features, diagnosis and practical challenges. *J Clin Pathol.* 2024;77:324-329.

Summary: This study investigates the clinicopathological features, molecular characteristics, and diagnostic criteria of primary salivary duct carcinoma of the lung (LSDC), a rare and aggressive malignancy. The research included five cases from Shanghai Pulmonary Hospital (2020-2022) and reviewed literature on the topic. The study found that all patients were male, aged 49-79 years, with central lung masses averaging 42.6 mm in diameter. Histologically, LSDC exhibited both intraductal and invasive components, with structures such as papillary, micropapillary, cribriform, and solid proliferation. Immunohistochemically, all cases expressed cytokeratin (CK)7 and androgen receptor (AR), with variable expression of HER2, GATA3, and GCDFP15. TP53 mutations and HER2 gene amplification were the most common genetic alterations.

Take-home message: The study underscores the importance of distinguishing LSDC from other lung carcinomas and metastatic salivary gland tumors. The findings highlight potential therapeutic targets, suggesting that AR and HER2 status could guide treatment strategies, thereby improving patient outcomes in this rare lung cancer subtype.

Xu D, et al. BAP1 Deficiency Inflames the Tumor Immune Microenvironment and Is a Candidate Biomarker for Immunotherapy Response in Malignant Pleural Mesothelioma. *JTO Clinical and Research Reports.* 2024;5:100672.

Summary: This study investigates the role of BAP1 deficiency in malignant pleural mesothelioma (MPM) and its potential as a biomarker for immunotherapy response. Researchers performed integrative analyses of data from The Cancer Genome Atlas (TCGA) and the French cohort E-MTAB-1719. They discovered that BAP1 deficiency is associated with enriched immune pathways, increased T-cell inflammation, and a favorable tumor immune microenvironment. Additionally, BAP1-deficient tumors demonstrated higher levels of immune checkpoint receptors and inflammatory macrophages, while showing a reduction in myeloid-derived suppressor cells. The findings suggest that BAP1-deficient MPM could respond better to immune checkpoint inhibitors (ICIs), whereas BAP1-proficient MPM might benefit from MEK inhibitors due to hyperactive MAPK pathways.

Take-home message: BAP1 deficiency in MPM is linked to a more favorable immune microenvironment and enhanced response to ICIs, making it a promising biomarker for predicting immunotherapy outcomes. This study supports the potential of using BAP1 status to guide treatment strategies, offering a step towards personalized medicine in managing MPM.

Blaauwgeers H, et al. Loose Tumor Cells in Pulmonary Arteries of Lung Adenocarcinoma Resection Specimens: No Correlation With Survival, Despite High Prevalence. *Arch Pathol Lab Med.* 2024;148:588-594.

Summary: This multicenter study investigated the presence and prognostic impact of loose tumor cells in the pulmonary arteries of resected non-small cell lung cancer (NSCLC) specimens, specifically lung adenocarcinomas. The researchers found that CK7-positive intravascular tumor cells were present in a high percentage of cases—70% in the pilot study and 58.6% in the validation study. Despite this high prevalence, the presence of these cells did not correlate with worse outcomes. In the pilot study, the 5-year overall survival (OS) was 61% for patients with intravascular tumor cells and 40% for those without (P = .19). In the validation study, the 5-year recurrence-free survival (RFS) was 80.0% for patients with intravascular tumor cells and 80.6% for those without (P = .52), while the 5-year OS was 82.8% and 71.6%, respectively (P = .16). These

findings suggest that loose tumor cells in the pulmonary arteries likely represent an artifact rather than a clinically significant prognostic factor.

Take-home message: Loose tumor cells in the pulmonary arteries of resected lung adenocarcinoma specimens are common but do not correlate with poorer survival outcomes. They are likely artifacts from the specimen preparation process and should be interpreted with caution to avoid misdiagnosis.

Van Schil PE, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revisions of the T-Descriptors in the Forthcoming Ninth Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol.* 2024;19:749-765.

Summary: This article presents the findings and recommendations from the International Association for the Study of Lung Cancer (IASLC) regarding the T-descriptors for the ninth edition of the TNM classification for lung cancer. The study analyzed data from 124,581 patients diagnosed with lung cancer between January 1, 2011, and December 31, 2019. The primary goal was to validate the current eighth edition T-descriptors and determine if any changes were necessary. The comprehensive survival analysis showed that the existing eighth edition T-component criteria performed adequately in the ninth edition dataset. Specifically, pathologic chest wall or parietal pleura involvement (PL3) was associated with worse survival compared to other T3 descriptors, and was similar to the survival of T4 tumors. However, this difference was not observed in clinical chest wall or PL3 tumors. As a result of these findings, the T subcommittee recommended not to reallocate chest wall or PL3 tumors to a different T-category.

Take-home message: The study validates the current eighth edition T-descriptors for lung cancer, suggesting no changes for the ninth edition. The consistent findings in pathologic staging reinforce the existing criteria. The study highlights the importance of continuous evaluation of the TNM classification to ensure accurate staging and prognosis of lung cancer, and sets the groundwork for future editions, especially concerning neoadjuvant cases and more granular data collection for specific tumor types.

Huang J, Osarogiagbon RU, Giroux DJ, et al. The International Association for the Study of Lung Cancer Staging Project for Lung Cancer: Proposals for the Revision of the N Descriptors in the Forthcoming Ninth Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol.* 2024;19(5):766-785.

Summary: This article presents proposals for revising the N descriptors in the ninth edition of the TNM classification for lung cancer. The study aimed to determine whether the current N descriptors should be maintained or revised, based on an analysis of 45,032 clinical and 35,009 pathologic NSCLC cases. The researchers found that the current N0 to N3 descriptors reflect prognostically distinct groups. They propose subdividing N2 into N2a (single-station involvement) and N2b (multiple-station involvement) due to significant prognostic differences. This proposal is supported by consistent findings across resection status, histologic type, T category, and geographic region, and aims to enhance the precision of the N classification in lung cancer staging.

Take-home message: The current N descriptors for lung cancer should be maintained with the addition of new subdescriptors for N2 to distinguish between single-station (N2a) and multiple-station (N2b) involvement. This revision aims to improve the prognostic accuracy and clinical utility of the TNM classification system. he proposed changes to the N descriptors address long-standing limitations in the TNM classification by incorporating a measure of disease burden, which is crucial for prognostic assessment and treatment planning in lung cancer.

Fong KM, et al. The International Association for the Study of Lung Cancer Staging Project for Lung Cancer: Proposals for the Revision of the M Descriptors in the Forthcoming Ninth Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol.* 2024;19:786-802.

Summary: This study by the International Association for the Study of Lung Cancer (IASLC) analyzed metastatic categories in the TNM classification for non-small cell lung cancer (NSCLC) to propose modifications for the ninth edition. The study used data from 124,581 patients, with 14,937 having stages IVA to IVB NSCLC. The analysis aimed to validate and refine the M descriptors of the eighth edition and propose updates based on new findings.

Validation of Eighth Edition M Categories: The current M categories (M1a, M1b, M1c) demonstrated good prognostic discrimination, confirming their utility.

Proposed changes: The study identified two prognostically distinct groups within the M1c category: M**1c1:** Involvement of multiple metastatic lesions within a single extrathoracic organ system; and M1C2: Involvement of multiple extrathoracic organ systems.

Additional findings: Increasing numbers of metastatic lesions and involvement of multiple organ systems were associated with progressively worse prognosis. These findings did not support specific numerical thresholds for stage classification but highlighted a continuum of decreasing survival with increasing metastatic burden.

Take-home message: The proposed revisions for the ninth edition of the TNM classification for lung cancer include subdividing the M1c category into M1c1 (single extrathoracic organ system) and M1c2 (multiple extrathoracic organ systems) to reflect distinct prognostic differences. These changes aim to provide more precise staging and better inform treatment strategies for patients with metastatic NSCLC.

Hwang S, et al. PD-L1 expression in resected lung adenocarcinoma: prevalence and prognostic significance in relation to the IASLC grading system. *Histopathology.* 2024;84:1013-1023.

Summary: This study investigates the prevalence and prognostic significance of PD-L1 expression in lung adenocarcinoma, using the International Association for the Study of Lung Cancer (IASLC) histologic grading system. Researchers analyzed 1233 patients with resected lung adenocarcinoma who underwent PD-L1 immunohistochemistry testing. The study found that PD-L1 positivity rates were 7.0%, 23.5%, and 63.0% for IASLC grade 1 (G1), grade 2 (G2), and grade 3 (G3) tumors, respectively. PD-L1 expression was significantly associated with male sex, smoking, and less sublobar resection among G2 tumors, although these associations were less pronounced in G3 tumors. Importantly, PD-L1 was identified as an independent risk factor for recurrence (adjusted hazard ratio [HR] = 3.25, $P < 0.001$) and death (adjusted HR = 2.69, $P = 0.026$) in the G2 group, but not in the G3 group.

Take-home message: PD-L1 expression varies significantly across IASLC grades and is an independent prognostic factor for worse outcomes in G2 lung adenocarcinoma. This suggests that PD-L1 status should be considered in prognostication and the design of future clinical trials for adjuvant immunotherapy, particularly in G2 tumors.

Gits HC, et al. Sublobar Resection, Stereotactic Body Radiation Therapy, and Percutaneous Ablation Provide Comparable Outcomes for Lung Metastasis-Directed Therapy. *Chest.* 2024;165(5):1247-1259.

Summary: This study compares the outcomes of three different local treatments for lung metastases: sublobar resection (SLR), stereotactic body radiation therapy (SBRT), and percutaneous ablation (PA). The analysis included 511 patients who received a total of 644 treatment courses across these modalities at a single cancer center between 2015 and 2020. The results showed that the two-year overall survival rates were 80.3% for SLR, 63.3% for SBRT, and 83.8% for PA. Local progression rates were 9.6% for SLR, 4.1% for SBRT, and

11.7% for PA. Lesion size per centimeter was significantly associated with worse overall survival (hazard ratio 1.24, P = .003) and local progression (hazard ratio 1.50, P < .001). No significant difference in overall survival was observed among the three modalities after adjusting for patient characteristics. However, SBRT was associated with a decreased risk of local progression compared to SLR (hazard ratio 0.26, P = .023).

Take-home message: Sublobar resection, SBRT, and percutaneous ablation provide comparable outcomes for lung metastasis-directed therapy in terms of overall survival and local control. The choice of treatment should be tailored to the patient's individual clinical scenario, emphasizing the importance of a multidisciplinary approach in managing lung metastases.

Editorial: Arenberg D, et al. Treating Lung Metastases: More Evidence for Equipoise. Chest. 2024;165(5):1037-1038.

Luo J, et al. Initial Chemotherapy for Locally Advanced and Metastatic NUT Carcinoma. *J Thoracic Oncology.* 2024;19:829-838.

Summary: This study investigates the effectiveness of chemotherapy regimens for NUT carcinoma (NC), a rare and aggressive cancer, comparing platinum-based and ifosfamide-based treatments. Researchers analyzed data from 118 patients with pathologically confirmed NC who were part of a worldwide registry. Key findings include: 1) 74% of patients received platinum-based chemotherapy, while 26% received ifosfamide-based regimens; 2) In non-metastatic disease, ifosfamide-based therapy showed a higher progression-free survival (PFS) at 12 months compared to platinum-based therapy (59% vs. 37%), though this did not translate into a significant overall survival (OS) benefit. For metastatic disease, ifosfamide had a higher objective response rate (ORR) compared to platinum (75% vs. 31%) but no significant difference in PFS or OS; 3) The 3-year OS for the entire cohort was 19%, with long-term survivors all presenting with non-metastatic and operable disease.

Take-home message: NUT carcinoma presents significant treatment challenges, with an overall poor prognosis. Ifosfamide-based regimens may offer some initial response benefits, particularly in non-metastatic cases, but do not provide a significant survival advantage over platinum-based treatments in metastatic disease. Early diagnosis and aggressive localized treatment appear crucial for improving long-term outcomes. The study underscores the urgent need for the development of more effective therapies and the importance of multidisciplinary management, especially for non-metastatic cases.

Tan AC, et al. Detection of circulating tumor DNA with ultradeep sequencing of plasma cell-free DNA for monitoring minimal residual disease and early detection of recurrence in early-stage lung cancer. *Cancer.* 2024;130:1758-1765.

Summary: This study evaluates the use of circulating tumor DNA (ctDNA) for monitoring minimal residual disease (MRD) and early detection of recurrence in patients with early-stage non-small cell lung cancer (NSCLC). The researchers utilized a personalized, tumor-informed multiplex polymerase chain reaction (mPCR) next-generation sequencing (NGS) assay to track specific mutations in plasma samples. The study included 57 patients with stage I–III NSCLC who underwent standard-of-care management, including surgical resection and adjuvant therapy when indicated. Presurgery ctDNA was detected in 26% of patients and was associated with shorter recurrence-free survival (RFS) (HR, 3.54; p = .009). Postsurgery, ctDNA was detected in seven patients, all of whom experienced radiological recurrence. ctDNA detection preceded radiological findings by a median of 2.8 months. Longitudinally, ctDNA detection at any time point postsurgery was strongly associated with shorter RFS (HR, 16.1; p < .0001)

Take-home message: ctDNA detection before and after surgery is a promising biomarker for identifying patients at high risk of relapse in early-stage NSCLC. The ability of ctDNA to precede radiological detection

of recurrence highlights its potential utility for early intervention and personalized surveillance strategies. Prospective studies are needed to further validate the clinical utility of ctDNA in this setting.

Non-neoplastic

Lim CX, et al. Aberrant Lipid Metabolism in Macrophages Is Associated with Granuloma Formation in Sarcoidosis. *Am J Respir Crit Care Med*. 2024;209(9):1152-1164.

Summary: This study found that macrophages from patients with chronic sarcoidosis exhibit altered lipid metabolism, leading to spontaneous granuloma formation in vitro. Transcriptomic analyses highlighted significant enrichment in lipid metabolic processes in these macrophages. Increased neutral lipid content was observed in granulomas from in vitro experiments, patient skin biopsies, and a sarcoidosis mouse model. Treatment with statins and cholesterol-reducing agents effectively reduced granuloma formation and disease severity in the mouse model.

Take-home message: Aberrant lipid metabolism in macrophages is a crucial factor in granuloma formation in sarcoidosis. Cholesterol-lowering treatments, such as statins, could help reduce granuloma formation and improve clinical outcomes for patients with sarcoidosis.

Editorial: *Hutton, A., & Deshane, J. S. (2024). Aberrant lipid metabolism in sarcoidosis. American Journal of Respiratory and Critical Care Medicine, 209(9), 1064-1066.*

Humphries SM, et al. Deep Learning Classification of Usual Interstitial Pneumonia Predicts Outcomes. *Am J Respir Crit Care Med*. 2024;209(9):1121-1131

Summary: This study developed and validated a deep learning algorithm using multiple instance learning (MIL) to predict usual interstitial pneumonia (UIP) from computed tomography (CT) scans. The algorithm was trained on a large dataset and tested in three independent cohorts. The MIL-based classification demonstrated higher accuracy for predicting histologic UIP compared to visual assessment by radiologists. The study also found that MIL-UIP classifications were significant predictors of mortality and decline in forced vital capacity (FVC), highlighting the algorithm's potential clinical utility.

Take-home message: The deep learning algorithm using MIL enhances the sensitivity and accuracy of UIP classification from CT scans, outperforming traditional visual assessments. Its predictive capability for patient outcomes, such as mortality and FVC decline, underscores its potential to improve diagnostic confidence and patient management in interstitial lung disease.

Editorial: *Lacob, J., & Newton, C. A. (2024). Deep learning classification of UIP on CT predicts outcomes.* American Journal of Respiratory and Critical Care Medicine*, 209(9), 1058-1059.*

Oldham JM, et al. Proteomic Biomarkers of Survival in Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med*. 2024;209(9):1111-1120.

Summary: This study identified 140 protein biomarkers associated with three-year transplant-free survival (TFS) in patients with idiopathic pulmonary fibrosis (IPF). Key proteins with the strongest TFS association included latent-transforming growth factor b-binding protein 2 (LTBP2), collagen a-1(XXIV) chain (COL24A1), and keratin 19 (KRT19). A composite proteomic signature developed in the study demonstrated superior predictive performance for TFS compared to a clinical prediction model.

Take-home message: The identification and validation of 140 proteomic biomarkers associated with TFS in IPF patients provide a valuable prognostic tool that outperforms traditional clinical models. The study

underscores the potential for these biomarkers to improve clinical outcomes by guiding treatment decisions and enabling personalized patient care.

Editorial: *Lee, J. S., & Maher, T. M. (2024). Proteomic biomarkers of survival in IPF. American Journal of Respiratory and Critical Care Medicine, 209(9), 1056-1057.*

O'Dwyer DN, et al. Commensal Oral Microbiota, Disease Severity, and Mortality in Fibrotic Lung Disease. *Am J Respir Crit Care Med*. 2024;209(9):1101-1110.

Summary: This study examined the role of oral microbiota in idiopathic pulmonary fibrosis (IPF) by analyzing buccal swabs from 511 IPF patients. The researchers found that greater buccal microbial diversity was associated with lower baseline forced vital capacity (FVC) and higher mortality risk. Conversely, a higher proportion of the genus Streptococcus, particularly Streptococcus mitis, correlated with higher FVC and reduced mortality risk.

Take-home message: Lower microbial diversity and higher Streptococcus abundance in the oral microbiome are linked to preserved lung function and reduced mortality in IPF patients. These results highlight the potential of targeting the oral microbiome for prognostic and therapeutic purposes in managing fibrotic lung diseases.

Editorial: *Darawshy, F., Molyneaux, P. L., & Segal, L. N. (2024). Commensal oral microbiota and disease in fibrotic lung disease. American Journal of Respiratory and Critical Care Medicine, 209(9), 1054-1055.*

Choi B, et al. Proteomic biomarkers of quantitative interstitial abnormalities in COPDGene and CARDIA Lung Study. *Am J Respir Crit Care Med*. 2024;209(9), 1091-1100.

Summary: This study identified 144 proteomic biomarkers significantly associated with quantitative interstitial abnormalities (QIAs) in two cohorts: COPDGene (older ever-smokers) and CARDIA (younger, healthier individuals). The proteins identified were enriched in pathways related to inflammatory response, cell adhesion, and immune response. Notable biomarkers included lumican, growth differentiation factor 15 (GDF15), and chitin-3-like protein 1 (CHI3L1), which have previously been linked to lung diseases such as pulmonary fibrosis and COPD. These findings suggest that proteomic biomarkers can serve as early indicators of lung injury and disease progression.

Take-home message: The identification of 144 proteomic biomarkers associated with QIAs offers new insights into the early detection and progression of lung diseases. These biomarkers could enhance clinical decision-making and treatment strategies, potentially leading to better outcomes for patients with chronic lung conditions.

Editorial: *Maddali MV, et al. Proteomic Biomarkers of Quantitative Interstitial Abnormalities. American Journal of Respiratory and Critical Care Medicine. 2024;209(9):1052-1054.*

Reviews and Editorial

Hung YP, et al. Molecular and Immunohistochemical Testing in Mesothelioma and Other Mesothelial Lesions. *Arch Pathol Lab Med.* 2024;148(5):e77-e89.

Summary: This review discusses the molecular and immunohistochemical testing used in the evaluation of mesothelioma and other mesothelial lesions. Mesothelioma is an aggressive cancer arising from the serosal lining, influenced by various risk factors including asbestos exposure and genetic factors. The review highlights the genetic diversity within mesothelioma, noting that most cases lack oncogenic kinase mutations and instead exhibit alterations in tumor suppressors and chromatin regulators. It also covers rare genetic alterations such as ALK and ATF1 rearrangements, as well as germline mutations. Immunohistochemical

markers like BAP1, MTAP, and merlin (NF2) are emphasized for their diagnostic utility in distinguishing mesothelioma from reactive mesothelial proliferations and other malignancies.

Take-home message: Molecular and immunohistochemical testing provides critical insights into the diagnosis and characterization of mesothelioma and other mesothelial lesions. These tests enhance diagnostic accuracy, aid in distinguishing mesothelioma from other conditions, and offer prognostic and predictive information that can guide treatment decisions. Continued advancements in molecular testing are essential for improving the management and outcomes of patients with mesothelial lesions.

Chang JC, Rekhtman N. Pathologic Assessment and Staging of Multiple Non-Small Cell Lung Carcinomas: A Paradigm Shift with the Emerging Role of Molecular Methods. *Mod Pathol.* 2024;37:100453.

Summary: This review addresses the challenges and advances in distinguishing separate primary lung carcinomas (SPLCs) from intrapulmonary metastases (IPMs) in patients with multiple non-small cell lung carcinomas (NSCLCs). The advent of genomic sequencing of somatic mutations has significantly improved the ability to discern clonal relationships among multiple NSCLCs, using techniques such as broad-panel next-generation sequencing (NGS). Historically, morphological criteria were used to differentiate SPLCs from IPMs, but these criteria often resulted in inaccuracies. The review highlights the utility of comprehensive molecular profiling, which has emerged as a robust and clinically relevant method for establishing clonal relationships. It proposes a practical approach for integrating molecular testing into the clinical evaluation and staging of multiple NSCLCs, emphasizing the need for collaboration between surgical and molecular pathologists.

Take-home message: The integration of comprehensive molecular profiling, particularly broad-panel NGS, into the assessment of multiple NSCLCs represents a paradigm shift, enhancing diagnostic accuracy and informing staging. This approach addresses the limitations of traditional morphological methods, providing a more reliable basis for clinical decision-making and management of patients with multiple NSCLCs.

Blaauwgeers H, et al. Con: "Is Spread Through Air Spaces an In Vivo Phenomenon or an Inducible Artifact?". *J Thorac Oncol.* 2024;19(5):671-676.

Summary: This editorial argues argue that spread through air spaces (STAS) in non-small cell lung cancer (NSCLC) may be more of an artifact induced by surgical and pathology handling rather than a true biological phenomenon. The authors review the current definition of STAS, which involves loose tumor cells found in air spaces, and highlight several issues complicating its interpretation, including the potential for cells to be dislodged during tissue handling and sectioning. The editorial discusses the lack of reproducibility in identifying STAS, especially in frozen sections, with reported kappa scores indicating only moderate agreement among pathologists. The authors present alternative explanations for the presence of loose tumor cells, such as the physical forces applied during surgery and specimen processing. They suggest that the inclusion of STAS in the WHO classification is premature, citing the need for further investigation into its biological basis and reproducibility.

Take-home message: The editorial raises important questions about the validity of STAS as a diagnostic and prognostic marker in lung cancer. This calls for more rigorous studies to distinguish true biological phenomena from artifacts, which is essential for improving the accuracy of lung cancer staging and treatment planning.

Li Y, et al. STAS is an in vivo phenomenon or artifact: Pro argument. *J Thorac Oncol.* 2024;19(5):677-697.

Summary: The article presents a compelling argument that spread through air spaces (STAS) is a genuine in vivo phenomenon rather than an artifact created during specimen processing. The authors recount the initial

case that led to the development of the STAS concept, describing a patient with nonmucinous lung adenocarcinoma (ADC) whose tumor cells appeared to be floating within alveolar spaces on histologic examination, correlating well with CT findings. The argument emphasizes the clinical significance of STAS, supported by multiple studies demonstrating its presence and prognostic implications in lung ADCs. The review also addresses challenges and skepticism, citing evidence from previous literature and clinical observations to bolster the argument that STAS represents true invasive behavior of the tumor cells, rather than a result of surgical or pathological manipulation.

Take-home message: STAS should be recognized as a true invasive pattern in lung adenocarcinoma, with significant implications for prognosis and treatment strategies. The article encourages pathologists to adopt this paradigm shift in interpreting tumor spread to improve patient outcomes.

STAS	Total pages	Total reference	Reference in common
Con	6	15	12 (below the table are the 3 used in the con paper but not referred in the pro paper)
Pro	21	91	

- Borczuk AC, Cooper WA, Dacic S, et al; WHO Classification of Tumours Editorial Board. Thoracic tumours. In: WHO Classification of Tumours. 5th ed. Lyon, France: IARC; 2021:19–189.
- Radonic T, Dickhoff C, Mino-Kenudson M, Lely R, Paul R, Thunnissen E. Gross handling of pulmonary resection specimen: maintaining the 3-dimensional orientation. J Thorac Dis. 2019;11(suppl 1):S37–S44.
- Thunnissen E, Motoi N, Minami Y, et al. Elastin in pulmonary pathology: relevance in tumours with a lepidic or papillary appearance. A comprehensive understanding from a morphological viewpoint. Histopathology. 2022;80:457–467.

Ito T, et al. Molecular pathology of small cell lung cancer regulated by ASCL1 and Notch signaling. *Pathol Int.* 2024;74:239-251.

Summary: This review investigates the molecular mechanisms regulating neuroendocrine (NE) differentiation in small cell lung cancer (SCLC), focusing on the roles of ASCL1 and Notch signaling. SCLC is a highly aggressive lung cancer characterized by rapid growth, high metastatic potential, and treatment resistance. Researchers found that ASCL1 is crucial for NE differentiation and functions as a lineage-specific oncogene in SCLC. ASCL1 promotes NE traits and is associated with high chemosensitivity. It regulates several downstream targets, including SOX2, INSM1, and components of the Wnt signaling pathway. On the other hand, Notch signaling acts as a repressor of NE differentiation. In SCLC, Notch signaling is typically inactive, but its activation post-chemotherapy can induce intratumor heterogeneity and chemoresistance. Notch1, in particular, suppresses ASCL1 and promotes a switch to non-NE cell fates, contributing to tumor adaptability and resistance to treatment.

Take-home message: The dynamic interplay between ASCL1 and Notch signaling is crucial in determining the NE characteristics and treatment responses of SCLC. Targeting these pathways may offer new therapeutic strategies to combat this aggressive cancer and address treatment resistance.

Woodard GA, Dacic S. Should the TNM Staging of NSCLC Evolve Beyond Anatomical Descriptors? *J Thorac Oncol. 2024*;19(5):663-665.

Summary: This editorial argues for the evolution of the TNM staging system for non-small cell lung cancer (NSCLC) to include biological and molecular factors beyond anatomical descriptors. The authors highlight the historical development and current limitations of the TNM system, which primarily categorizes tumors based on size and anatomical location. They emphasize that tumor biology, including histologic subtype and genetic mutations, significantly impacts prognosis and treatment outcomes. The authors reference the ninth edition of the TNM classification, which largely retains the eighth edition's T-descriptors based on a large dataset analysis. However, they point out discrepancies in survival outcomes based on tumor biology, such as squamous versus non-squamous histology and geographic variations. They argue that integrating factors like

histologic grade, molecular profiling, and radiographic characteristics (e.g., ground-glass opacity) into the TNM system could enhance its prognostic accuracy and clinical relevance.

Take-home message: Integrating biological markers and molecular data into the TNM staging system represents a critical step towards personalized medicine in NSCLC. This approach could provide a more comprehensive understanding of tumor behavior, enabling clinicians to tailor treatments more effectively and improve patient outcomes. Future research and consensus will be essential in developing and validating these enhanced staging criteria.

Wang X, et al. Aggressive Mediastinal Lymphomas. *Semin Diagn Pathol.* 2024;41:125-139.

Summary: This review covers the clinical, histologic, immunophenotypic, and molecular genetic features of the most common and aggressive primary mediastinal lymphomas. These include T-lymphoblastic leukemia/lymphoma (T-ALL/LBL), primary mediastinal (thymic) large B-cell lymphoma (PMBL), primary mediastinal "nonthymic" diffuse large B-cell lymphoma (DLBCL), and mediastinal nodular sclerosis classic Hodgkin lymphoma (NSCHL). Each lymphoma type is associated with unique clinical presentations, histological patterns, and immunophenotypic markers. The review highlights the challenges in accurate diagnosis, particularly with small or crushed biopsy samples, and provides suggested immunohistochemistry panels and differential diagnoses for each entity.

Take-home message: Understanding the distinct clinical, histologic, and molecular features of primary mediastinal lymphomas is crucial for accurate diagnosis and treatment. This review emphasizes the importance of comprehensive immunohistochemical and molecular testing in differentiating these aggressive lymphomas and guiding effective clinical management.

Atabai K, et al. The American Thoracic Society Research Program: Twenty Years of Driving Discovery in Respiratory Medicine. *Am J Respir Crit Care Med*. 2024;209(9):1047-1048.

Summary: This editorial reviews the impact and achievements of the American Thoracic Society Research Program (ATSRP) over the past 20 years. Since its inception in 2004, the ATSRP has awarded $19.5 million to 302 researchers, predominantly early-career investigators. This funding has facilitated significant advancements in various fields, including pulmonary, critical care, and sleep medicine. Notably, researchers initially funded by the ATSRP have subsequently secured $885.4 million in NIH research grants. The program has been instrumental in supporting the development of new diagnostics, treatments, and understanding of diseases such as pulmonary fibrosis, acute lung injury, and sleep disorders.

Take-home message: The ATSRP has significantly contributed to the advancement of respiratory medicine by providing critical early-career funding, resulting in a substantial return on investment in terms of further research funding, scientific discovery, and improved patient care. The program highlights the importance of sustained investment in early-career researchers to drive innovation and progress in the field.

Volkmann ER, et al. Enrichment Strategies for Systemic Sclerosis–Interstitial Lung Disease Trials. *Am J Respir Crit Care Med*. 2024;209(9):1067-1068.

Summary: This editorial examines the increasing use of strict eligibility criteria in clinical trials for systemic sclerosis-associated interstitial lung disease (SSc-ILD) aimed at enriching trial cohorts with patients more likely to develop progressive pulmonary fibrosis (PPF). These criteria often exclude patients with limited cutaneous disease, despite no observed difference in disease progression between cutaneous subtypes in previous trials. The editorial also critiques the focus on inflammatory markers, such as C-reactive protein (CRP), as inclusion criteria, noting limited evidence of their predictive value in patients receiving

mycophenolate mofetil (MMF). The authors argue that these restrictive criteria conflict with FDA guidelines encouraging broader eligibility to enhance trial diversity and better reflect real-world patient populations.

Take-home message: The current restrictive eligibility criteria in SSc-ILD trials may hinder patient accrual and limit the generalizability of findings. Broader criteria could improve trial enrollment and provide valuable data on treatment efficacy and safety across diverse patient subgroups, ultimately benefiting clinical practice and patient care.

Morisset J. Improving Timely Diagnosis for Interstitial Lung Disease. *Chest*. 2024;165(5):1025-1026.

Summary: This review highlights the significant advancements in the diagnosis and treatment of interstitial lung diseases (ILDs) over the past decade. Key developments include the introduction of effective therapies like pirfenidone and nintedanib for idiopathic pulmonary fibrosis (IPF) and the establishment of diagnostic criteria and treatment algorithms. The review also addresses the challenges in diagnosing ILD, such as the nonspecific symptoms that lead to delays in diagnosis and treatment. The collaboration between CHEST and the Council of Medical Specialty Societies aims to promote diagnostic excellence by providing resources that translate recent ILD guidelines into practical, implementable content for clinicians.

Take-home message: The review underscores the importance of timely diagnosis and treatment of ILD to improve patient outcomes. It emphasizes the need for continued efforts to refine diagnostic criteria, enhance clinical guidelines, and educate healthcare providers to ensure early and accurate diagnosis of ILD.

Selman M, et al. Idiopathic Pulmonary Fibrosis: From Common Microscopy to Single-Cell Biology and Precision Medicine. *Am J Respir Crit Care Med*. 2024;209(9):1074-1081.

Summary: This review outlines the historical and recent advancements in understanding and treating idiopathic pulmonary fibrosis (IPF). Starting from early descriptions using common microscopy, the field has evolved significantly with the introduction of high-resolution computed tomography (HRCT) and the identification of usual interstitial pneumonia (UIP) as the key histopathological pattern of IPF. The discovery of antifibrotic drugs, such as pirfenidone and nintedanib, marked a significant milestone, although IPF remains a challenging disease with a high mortality rate. Recent technological advancements, including single-cell RNA sequencing (scRNA-seq) and machine learning, have provided deeper insights into the cellular and molecular mechanisms underlying IPF. These tools have revealed novel cell populations and genetic variants associated with disease progression, highlighting the potential for precision medicine approaches in IPF management.

Take-home message: The review emphasizes the transformation in IPF research and clinical practice, driven by technological advancements and a better understanding of the disease's pathogenesis. These insights pave the way for precision medicine, offering hope for more effective and personalized treatments for patients with IPF.

Correspondence and Case Reports

Devaraj A, et al. e-Lung Computed Tomography Biomarker Stratifies Patients at Risk of Idiopathic Pulmonary Fibrosis Progression in a 52-Week Clinical Trial. *Am J Respir Crit Care Med*. 2024;209(9):1168-1169.

Summary: This correspondence describes a post hoc analysis of a 52-week clinical trial evaluating the e-Lung automated CT processing algorithm, specifically the weighted reticulovascular score (WRVS), as a biomarker for predicting forced vital capacity (FVC) decline in idiopathic pulmonary fibrosis (IPF) patients. The analysis involved 62 patients, stratified into low- and high-risk groups based on WRVS thresholds. Results demonstrated that a WRVS greater than 15% was strongly associated with a significant FVC decline (HR 5.74) over 52 weeks, outperforming traditional measures like baseline FVC and DLCO. The study

suggests that incorporating WRVS in clinical trials can enrich for high-risk patients, potentially reducing sample sizes and improving trial efficiency.

Take-home message: The e-Lung WRVS biomarker shows promise in stratifying IPF patients by risk of disease progression, thereby enhancing the design and efficiency of clinical trials. This tool could help identify patients at higher risk of FVC decline, ensuring well-matched treatment arms and potentially reducing trial sizes. Further validation in additional cohorts is needed to confirm these findings.

Harder EM, et al. Pulmonary Hypertension in Idiopathic Interstitial Pneumonia Is Associated with Small Vessel Pruning. *Am J Respir Crit Care Med*. 2024;209(9):1170-1173.

Summary: This correspondence investigates the relationship between pulmonary hypertension (PH) and small vessel pruning in idiopathic interstitial pneumonia (IIP). The study included 12 patients who underwent right heart catheterization and noncontrast CT imaging. It compared those with severe PH (PF-PH) to those without PH (PF-NPH). Results showed that patients with PF-PH had significant reductions in small arterial volume and compensatory pre-acinar arterial dilation compared to PF-NPH patients. These differences were most notable in lung regions with minimal interstitial lung disease (ILD). Whole lung aBV5/TBV (small arterial volume normalized by total blood volume) was inversely associated with mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR), highlighting the potential of using quantitative CT imaging to assess vascular changes in PH associated with IIP.

Take-home message: Quantitative CT imaging can effectively quantify small vessel loss in PH associated with IIP, especially in lung regions with minimal ILD. This method could provide a valuable tool for distinguishing patients with severe PH from those without PH, potentially aiding in the diagnosis and management of PH in the context of IIP. Further studies with larger cohorts are needed to validate these findings.

Montgomery AB. Question: Is Idiopathic Pulmonary Fibrosis Driven by an Abnormality in the Interstitium? *Am J Respir Crit Care Med*. 2024;209(9):1173-1174.

Summary: This correspondence challenges the characterization of idiopathic pulmonary fibrosis (IPF) as an "interstitial" lung disease. The author argues that surfactant mutations, a known risk factor for IPF, do not occur in interstitial cells, and evidence from animal and clinical studies suggests that the interstitium might not be the primary site of disease. For instance, aerosolized pirfenidone showed therapeutic efficacy in IPF patients despite low interstitial concentrations. The author posits that the alveolar epithelium, rather than the interstitium, may be the critical tissue in IPF, highlighting the failure of large-molecule protein therapies that poorly penetrate the alveolar capillary membrane. The correspondence suggests renaming the disease "fibrosing alveolitis" to better reflect its pathology and direct appropriate therapeutic strategies.

Take-home message: The correspondence argues for a reevaluation of IPF's classification and suggests focusing on the alveolar epithelium rather than the interstitium. This perspective could shift therapeutic development towards more effective treatments targeting the correct tissue.

Lee J, et al. Separation of Benign From Malignant Mesothelial Proliferations Using YAP-TAZ Immunohistochemistry. *Mod Pathol.* 2024;37:100473.

Summary: This correspondence addresses the effectiveness of using YAP-TAZ immunohistochemistry (IHC) in distinguishing between benign and malignant mesothelial proliferations. The study builds on previous work by Li et al., who used H-scores to separate normal from abnormal mesothelial cells based on Merlin and YAP-TAZ staining. The authors attempted to simplify this method by using two YAP-TAZ antibody clones, D24E4 and E9M8G, on tissue microarrays of mesotheliomas and reactive mesothelial processes. The results showed that YAP-TAZ staining was inconsistent, with nuclear staining varying

regardless of Merlin status. Cytoplasmic YAP-TAZ staining was present in all tumor cells. This variability suggests that simple yes/no staining for YAP-TAZ is not reliable for distinguishing benign from malignant mesothelial proliferations.

Take-home message: While YAP-TAZ IHC has potential, its variability and the lack of a consistent correlation with Merlin status indicate that it may not be straightforward or reliable for differentiating benign from malignant mesothelial proliferations. More complex or dual-staining approaches may be necessary to improve diagnostic accuracy.

Varone F, et al. Case of a 33-Year-Old Woman With Hemoptysis and Migrant Nodular Cavitary Lesions. *Chest*. 2024;165(5).

Summary: This case report describes a 33-year-old woman presenting with progressive dyspnea, hemoptysis, and migrant nodular cavitary lesions observed on CT scans. Physical examination revealed features suggestive of vascular Ehlers-Danlos syndrome (vEDS), such as translucent and thin skin, evident venous vascular pattern, thin vermilion of the lip, micrognathia, thin nose, and occasional Raynaud phenomenon. Initial investigations, including bronchoscopy, were non-diagnostic. Surgical lung biopsy showed irregularly shaped foci of ossification with bone marrow, tendinous-like fibrous tissue, desmoid-like fibrosis, and intraalveolar hemorrhage. Genetic testing revealed a heterozygous de novo missense mutation in the COL3A1 gene, confirming the diagnosis of vEDS.

Take-home message: This case highlights the importance of considering vEDS in young patients with unexplained pulmonary symptoms and characteristic physical features. Multidisciplinary evaluation and genetic testing are crucial for accurate diagnosis and management. Histologic findings, such as ossification and fibrosis, can provide important diagnostic clues.

Kerper AL, et al. Primary Pulmonary Myxoid Sarcoma and Thoracic Angiomatoid Fibrous Histiocytoma: Two Sides of the Same Coin? *Am J of Surg Pathol*. 2024;48(5):562-569.

Purpose: Primary pulmonary myxoid sarcoma (PPMS) and thoracic angiomatoid fibrous histiocytoma (AFH) are rare neoplasms with overlapping morphological features and EWSR1 fusions. PPMS is a rare, low-grade malignancy typically found in middle-aged women, characterized by nodules of spindled to epithelioid cells with myxoid stroma and reticular architecture. AFH, primarily a soft tissue tumor, also appears in visceral sites like the lung and mediastinum and is marked by nodules of epithelioid to spindled cells with pseudoangiomatous spaces and a lymphoid rim. This study aims to evaluate the morphologic and immunophenotypic overlap between PPMS and AFH, suggesting they may represent variations of the same entity.

Methods: A retrospective review was conducted on 16 molecularly confirmed cases of PPMS (n=5) and thoracic AFH (n=11) diagnosed from 2010 to 2023 at the Mayo Clinic. The cases were assessed for clinical presentation, tumor location, histologic characteristics, and immunohistochemical (IHC) staining patterns. Histopathologic features evaluated included the presence of fibrous pseudocapsules, lymphoid rims, myxoid stroma, reticular growth patterns, pseudoangiomatous spaces, and syncytial growth. Molecular confirmation involved detecting EWSR1 rearrangements via fluorescence in situ hybridization (FISH) or next-generation sequencing (NGS).

Results:

- **Clinical features:**
  - Mean age at diagnosis: 49 years (AFH), 47 years (PPMS).
  - Sex distribution: AFH had a male predominance (8M/3F), while PPMS had a female predominance (1M/4F).
  - Most patients presented with incidentally discovered masses; symptomatic presentations included shortness of breath and chest pain.
- **Histopathologic and Immunohistochemical Findings**:
  - Fibrous pseudocapsule and lymphoid rim: Present in 10/11 AFH (91%) and all 5 PPMS (100%).
  - Myxoid stroma: Found in 7/11 AFH (64%) and all 5 PPMS (100%).
  - Reticular growth pattern: Seen in 5/11 AFH (45%) and all 5 PPMS (100%).
  - Pseudoangiomatous spaces and hemosiderosis: More common in AFH (4/11, 36%) but also present in PPMS (1/5, 20%).
  - Syncytial growth: Observed in 8/11 AFH (73%) and 2/5 PPMS (40%).
  - Immunohistochemical staining:
    - EMA: Positive in 7/10 AFH and 1/3 PPMS.
    - Desmin: Positive in 4/10 AFH, negative in all PPMS.
    - ALK: Positive in 4/10 AFH and 1/5 PPMS.
    - Synaptophysin: Positive in 6/11 AFH and 1/5 PPMS, with some cases showing coexpression with ALK.
    - All cases were negative for chromogranin.

Take-home message: This study supports the hypothesis that PPMS and thoracic AFH may be morphologic variants of the same clinicopathologic entity, given their significant overlap in histopathologic and immunophenotypic features. The presence of myxoid stroma and reticular growth patterns in both entities, along with shared EWSR1 fusions, suggests a continuum rather than distinct categories. These findings advocate for potentially unifying the classification of these tumors under the term "myxoid angiomatoid fibrous histiocytoma," which could simplify diagnosis and treatment. Further research is needed to confirm these findings and refine the diagnostic criteria, potentially incorporating Ki-67 and other molecular markers to better predict prognosis.

Galeano B, et al. Ki-67 Proliferation Index Is Associated With Tumor Grade and Survival in Pleural Epithelioid Mesotheliomas. *Am J of Surg Pathol*. 2024;48(5):615-622.

Purpose: Pleural epithelioid mesothelioma (PEM) is classified into low and high grades based on nuclear atypia, mitotic count, and necrosis. However, assessing these features is labor-intensive and has limited reproducibility. The Ki-67 proliferation index has been shown to be a prognostic factor in PEM but has not been directly correlated with tumor grade or mitotic score. This study evaluates the potential of the Ki-67 index as a surrogate marker for tumor grade and compares its predictability for overall survival (OS) with that of the mitotic count.

Methods: The study reviewed 96 PEM samples from 85 patients diagnosed between 2000 and 2021. Two pulmonary pathologists confirmed the diagnoses and assigned tumor grades based on WHO criteria. Digital image analysis (DIA) was used to evaluate the Ki-67 index. Clinical data, including patient demographics, treatment history, and survival data, were collected. The correlation between Ki-67 index and mitotic count, as well as their association with OS, was analyzed using statistical methods including kappa statistics for interobserver agreement and Cox proportional hazards regression for survival analysis.

Results:

- **Demographics:** Mean age of 67.2 years; 77.6% male.
- **Pathologic findings**:
    - Moderate agreement between pathologists for mitotic count (κ=0.53), nuclear grade (κ=0.49), and tumor grade (κ=0.47).
    - Ki-67 index correlated with mitotic count (Spearman correlation=0.65).
    - Area under the curve (AUC) for predicting tumor grade:
        - Mitotic count: 0.84 (reviewer 1), 0.85 (reviewer 2).
        - Ki-67 index: 0.74 (reviewer 1), 0.81 (reviewer 2).
    - High Ki-67 index (≥30%) and high mitotic count (≥10 per 2 mm^2) associated with poor OS.
    - Median OS for high mitotic count: 43.8% 1-year OS, no 3-year survivors (HR=3.21, P=0.0005).
    - Median OS for high Ki-67 index: 60.0% 1-year OS, 5.3% 3-year OS (HR=1.79, P=0.03).

Take-home message: The Ki-67 proliferation index, assessed via DIA, strongly correlates with traditional histopathologic grading parameters and demonstrates comparable predictive value for OS in PEM. Given the moderate interobserver agreement and its objectivity, Ki-67 index could serve as a viable surrogate for tumor grading. The findings suggest potential revisions to the current WHO grading system to incorporate Ki-67 index and alternative mitotic count ranges for improved prognostic accuracy. Further studies are warranted to validate these findings and explore their integration into clinical practice for PEM management.

Nicotra S, et al. STAS does not impact survival but vascular invasion has adverse prognosis in early stage lung adenocarcinoma. *Am J Surg Pathol.* 2024;48(5):605-614.

Purpose: Lung cancer is a leading cause of global mortality, with surgical resection being a key treatment for early and locally advanced non-small cell lung cancer (NSCLC). Spread through air spaces (STAS) is a novel invasive pattern associated with poor prognosis in NSCLC. This study investigates the incidence and impact of STAS and vascular invasion (VI) on survival and recurrence in early-stage lung adenocarcinoma (ADC). Previous research suggests mixed results regarding the prognostic significance of STAS, while VI is a well-established adverse prognostic factor.

Methods: This study is a retrospective analysis of 427 patients with stage cT1a-cT2b ADC who underwent surgical resection between 2016 and 2022 at the Thoracic Surgery Unit of Padua University Hospital. Comprehensive pathologic reports included histotype, mitoses, pleural invasion, fibrosis, tumor-infiltrating lymphocytes (TILs), necrosis, inflammation, VI, perineural invasion, and STAS. PD-L1 expression was also examined. Kaplan-Meier method is used for survival and recurrence probabilities, and Cox Proportional Hazard Model is used for multivariable analysis. Significance level is set at $P \leq 0.05$.

Results:

- **Demographics:** Median age 70, 51% female, 70% smokers, and 11% with COPD
- **Pathologic findings**: 57% were STAS positive, 25% had VI. Acinar ADC was the predominant type (74%), and G2 was the most common grade (70%).
- **Survival analysis**: No significant difference in overall survival (OS) between STAS+ and STAS- groups (P=0.44). VI was associated with poorer survival (P=0.018).
- **Recurrence analysis**: No significant difference in recurrence rates between STAS+ and STAS- groups (P=0.2). VI was significantly linked to elevated recurrence risk (P=0.0048).
- **Multivariable analysis**: IS activation (TILs >10% and PD-L1 ≥1%) significantly increased OS. VI remained a significant adverse predictor for both survival and recurrence.

Take-home message: This study demonstrates that STAS does not significantly impact survival or recurrence in early-stage resected ADCs. In contrast, VI is a critical adverse prognostic factor for both survival and recurrence. The findings underscore the importance of vascular assessment in pathology reports and suggest that VI should potentially be considered for upstaging lung adenocarcinomas, similar to pleural invasion. Moreover, the presence of immune activation markers like TILs and PD-L1 expression correlates with better outcomes, indicating that immunotherapeutic approaches could benefit patients with early-stage ADC. Further research is needed to explore the mechanisms by which VI contributes to metastasis and to evaluate its role in treatment strategies.

Laville D, et al. STAS has negative impact on survival and may justify upstaging. *Am J Surg Pathol.* 2024;48(5):596-604.

Purpose: The concept of spread through air spaces (STAS) has been discussed as an adverse prognostic factor for lung cancer. STAS refers to the presence of tumor cells within the air spaces of the lung parenchyma beyond the tumor boundaries. Previous studies, mainly conducted in Asian cohorts, have suggested that STAS is associated with poor prognosis in various types of lung cancer, including adenocarcinoma. This study aims to clarify the prognostic role of STAS in a European cohort of patients with stages I to III lung adenocarcinoma who underwent surgical resection, comparing it to established prognostic factors.

Methods: The study is a retrospective cohort analysis of 330 patients with stages I to III lung adenocarcinoma who underwent resection between 2012 and 2020 at the University Hospital of Saint Etienne, France. Invasive mucinous adenocarcinoma cases were excluded. Pathologic staging was reclassified according to the eighth edition of the AJCC staging manual. STAS was assessed according to the WHO definition, and its presence was recorded by two independent observers. Molecular analysis for EGFR, KRAS mutations, and ALK rearrangement was performed on available samples. Statistical analyses included Kaplan-Meier survival estimates, univariate and multivariate Cox proportional hazards regression models, and concordance studies using Cohen's kappa.

Results:

- STAS was observed in 56.1% of the patients.

- Presence of STAS significantly correlated with lower progression-free survival (PFS) and overall survival (OS).
    - Median PFS: 43.6 months in STAS-positive patients vs. not reached (NR) in STAS-negative patients (P=0.018).
    - Median OS: 87.7 months in STAS-positive patients vs. NR in STAS-negative patients (P=0.036).
- Multivariate analysis showed:
    - STAS was an independent prognostic factor for PFS (HR: 1.51; P=0.050).
    - STAS was an independent prognostic factor for OS (HR: 1.67; P=0.050).
- Presence of STAS in T3 stage tumors reduced median PFS from 62.8 months to 15.7 months, making it comparable to T4 stage tumors.

Take-home message: This study confirms that STAS is an independent adverse prognostic factor for both PFS and OS in stages I to III lung adenocarcinoma in a European cohort. The findings suggest that the presence of STAS significantly worsens prognosis, similar to the next higher pathologic T stage. Consequently, the study proposes that the presence of STAS should be considered for upstaging lung adenocarcinomas, akin to the handling of pleural invasion. These results underscore the need for further studies and potential adjustments to lung cancer staging guidelines to incorporate STAS as a critical prognostic factor.