# Pulmonary Journal Club March 2026 (Articles from February 2026)

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## ARTICLES FOR DISCUSSION

**Mino-Kenudson M, et al. A grading system for resected invasive squamous cell carcinoma of the lung: A multi-institutional study by the IASLC pathology committee. *J Thorac Oncol.* 2026; 21: 294-309.**

### Background

- Lung SqCC = ~25% of lung cancers, but lacks strong molecular targets (immunotherapy imperfect)
- No standardized grading system for lung squamous cell carcinoma (SqCC).
- Traditional grading (keratinization) lacks prognostic value
- Prior proposed systems (budding, nest size, nuclear size) were limited

Key Finding: Tumor budding = only feature consistently associated with both RFS and OS
Proposed System: Low: 0–9 buds vs. High grade: ≥10 buds
Outcome: Strong prognostic separation (e.g., RFS 4.8 vs 1.6 years)
Conclusion: Simple, reproducible, clinically practical grading system

### Methods

- Multi-institutional cohorts (only resections without neoadj. therapy):
  - Training sets: 262 + 427 cases
  - Validation set: 827 cases
- Histologic Features Evaluated
  - Tumor budding, nest size, nuclear size, STAS, mitotic rate, necrosis, invasion patterns

*Tumor Budding Definition*

- Clusters of ≤4 tumor cells at invasive front (hotspot at x200 magn, normalized to 0.785 $mm^2$)
  - Scoring: 3-tier: 0–4, 5–9, ≥10 vs. 2-tier: 0–9 vs ≥10
- Statistics: Kaplan-Meier+Cox for RFS and OS, adjusted for age, sex, stage

### Results

- Training Set 1 (n=262)
  Independent predictors of worse outcomes: Tumor budding, STAS, higher stage, sublobar resection
- Training Set 2 (n=427)
  Independent predictors: Tumor budding, stage, age, pleural invasion
- Only tumor budding was sig. for both RFS and OS and consistent across datasets
- Validation (Test Set, n=827)
  - High grade independently predicts worse RFS (HR ~1.93) and worse OS (HR ~1.97)
  - Strong separation: RFS: 4.8 vs 1.6 years, Stage I: 7.2 vs 3.4 years
- Moderate agreement, with high agreement (>80%) in most cases

### Take Home Message

- Tumor budding is a well-established marker in other cancers (e.g., colorectal), now validated in SqCC
- Advantages of proposed system:
  Simple (single parameter), reproducible, no special stains required
  Outperforms prior multi-parameter systems (better reproducibility, external validation)
- Clinical implications: May guide prognosis and treatment stratification

**Lunardi F, et al. Pathologic assessment of resected stage III non-small cell lung cancer after neoadjuvant chemotherapy: identification of additional prognostic factors.** ***Histopathology.*** **2026;88:710–728.**

**Background**

- 2020 IASLC recommendations for tumor bed assessment
- To assess features of histopathological response to neoadjuvant platinum-based chemotherapy (NACT), focusing on tumour bed stromal components, using more objective and reproducible methodologies such as morphometry and artificial intelligence (AI).

**Methods**

- Retrospective, 70 consecutive stage III NSCLC patients - surgery after NACT (2009–2022), 46% postop radiation, 3 patients (<5%) adjuvant systemic therapy
- Pathology: 2021 WHO, 8th TNM, 2020 IASLC tumor bed recommendations (% necrosis, % viable tumor cells, % stroma = inflammation + fibrosis), inflammation graded based on tissue involvement as mild (<30% of the tissue), moderate (30–60%), marked (>60%)
- Computer-assisted morphometry (Fibrosis – Azan Mallory; inflammation – CD45)
- AI-based immune cell quantification (CD4, CD8, CD68, FoxP3)
- Composite clinico-pathologic scoring (ClinPATH)
  A. MPR, baseline blood lymphocytes, perineural invasion, vascular invasion, proliferative index, fibrosis extension percentage
  B. A + AI-quantified CD4+ cell %
  C. A + AI-quantified FOXP3+ cell %
- No significant p-value provided

**Results**

- 70 patients; 64% adenocarcinoma, MPR: 17%, pCR: 7%
- Tumor bed – median: Necrosis 5%, Viable tumor 55%, Stroma 30%
- Morphometry: Fibrosis extension – median 22%; inflammation 24%
- Inflammatory components (AI), median: CD4+ 11%, CD8+ 13%, CD68+ 15%, FOXP3+ 6%

**Routine Tumor Bed Parameters**

- MPR associated with lower frequency of STAS, vascular and pleural invasion
- MPR associated with higher extension of fibrosis
- MPR associated with lower ClinPATH combined score values (all)
- MPR associated with longer DFS
- pCR – no significant associations - possibly too few cases
- Necrosis and total stroma %, inflammation, %viable tumor cells → not prognostic

**Quantitative fibrosis (by AI):**

- Intermediate and high fibrosis extension - associated with a longer DFS
- Particularly significant in adenocarcinoma

**ClinPATH Combined Scores**

Score B associated with DFS HR = 6.47 ($P < 0.001$), OS HR = 5.09 ($P < 0.001$)
No multivariate analysis

**Take Home Message**

- MPR – good prognostic parameter (too few events to evaluate pCR)
- MPR combined with other clinical and morphologic parameters and immune cells may correlate better with outcome than MPR alone

**Hélias-Rodzewicz Z et al. ALK ATI Drives Nuclear Anaplastic Lymphoma Kinase (ALK) Expression in Histiocytic Neoplasms Without ALK Fusions. *Mod Pathol.* 2026;39:100956.**

**Background**

- Spectrum of genetic alterations in histiocytoses (MAPK pathway: *BRAFV600E*, *ALK*, other)
- ALK-positive histiocytosis (ALK+H)-WHO entity defined by oncogenic *ALK* fusions, strong cytoplasmic ALK staining, responsive to ALK inhibitors
- Some histiocytoses - ALK protein expression but no detectable *ALK* fusions
- Melanoma - alternative mechanism of ALK activation - Alternative Transcription Initiation (ATI) within ALK intron 19 → truncated isoform ($ALK^{ATI}$)
- To study frequency of ALK expression without *ALK* fusion in histiocytosis

**Methods**

- Retrospective, cases from the French National Histiocytosis Registry
- ALK IHC (clone 1A4; some cases also D5F3)
- Custom RNA-Seq panel targeting histiocytosis-related genes
- Classification of histiocytoses based on ALK expression and oncogenic *ALK* fusion:
  - ALK+H: Expression of ALK / fusion-positive
  - ALK-KP/FN: Expression of ALK / fusion-negative
  - ALK-KN/FN: No expression of ALK / fusion-negative
- *ALK* isoform analysis (targeted PCR) targeting intron 19

**Results**

- See table 2 for included histiocytoses
- N=303
- **RNA ALK expression**: ALK+H: 8%, ALK-KP/FN: 16.5%, ALK-KN/FN: 67%

→ ALK expression without fusion more than twice as frequent as *ALK* fusion–positive histiocytosis

- **Protein expression (IHC)** – studied in 61% of cases (1A4): 96% of ALK+H, 86% of ALK-KP/FN, 9% of ALK-KN/FN samples
  - ALK+H samples – cytoplasmic staining
  - ALK-KP/FN - nuclear staining
  - ALK-KN/FN - mostly negative

→ Fusion-negative cases - nuclear ALK staining, fusion-positive cases - cytoplasmic.

ALK IHC (clone D5F3, n=18) – similar staining but nuclear staining weaker

- High interobserver or intraobserver (not clear) reproducibility for ALK IHC ($\kappa = 0.877$)
- $ALK^{ATI}$ Isoform Analysis in 11 ALK-KP/FN and 10 ALK-KN/FN and control (ALK+H)
- All ALK-KP/FN and ALK+H expressed 3'region encoding the kinase domain but not the 5'region; all ALK-KN/FN lacked both 5' and 3' regions
- Analysis of regions in *ALK* intron 19 that is specifically expression in $ALK^{ATI}$ isoform-regions expression in all ALK-KP/FN but not in ALK-KN/FN → ALK expression in ALK-KP/FN is driven by $ALK^{ATI}$ isoform

**Take Home Message**

- ALK expression in histiocytosis is common and often independent of *ALK* fusions.
- The role of ALK inhibitors in $ALK^{ATI}$ histiocytoses remains to be determined.

**Szalai F, …, Khoor A, et al. GPNMB immunohistochemistry is a useful ancillary tool for the diagnosis of pulmonary lymphangioleiomyomatosis. *Histopathology.* 2026;88:698–709.**

**Background**

- LAM driven by mutations in *TSC1* or *TSC2* genes → mTOR pathway activation
- Typical markers: HMB45, Melan-A, α-SMA, ER, PR, β-catenin (cytoplasmic)
- Glycoprotein non-metastatic melanoma protein B (GPNMB) - transmembrane protein, upregulated by mTOR signaling, expressed in PEComas and TSC-related tumors
- GPNMB – potential predictive biomarker - tumors expressing GPNMB could respond to glembatumumab vedotin (ADC)
- To evaluate GPNMB by IHC as a diagnostic marker for pulmonary LAM and distinguish it from histologic mimickers.

**Methods**

- 15 LAM cases (8 biopsies, 7 explanted lungs)
- 30 diagnostic mimics: leiomyoma, benign metastasizing leiomyoma, leiomyosarcoma, metastatic leiomyosarcoma
- Other pulmonary lesions: SFT, PLCH, diffuse pulmonary meningotheliomatosis, meningothelial-like nodules, LIP, IMT, emphysema, CPFE, Swyer–James–MacLeod syndrome
- Positive controls: Angiomyolipoma, Subependymal giant cell astrocytoma (SEGA)
- IHC: GPNMB (clone E4D7P)
- H-score: [H-score = intensity (0–3) * % cells expressing GPNMB]
- H-score >= 100 considered high
- Two pulmonary pathologists evaluated slides

**Results**

- GPNMB "considerably" expressed in alveolar macrophages (membranous and cytoplasmic with perinuclear dot=binding to endosomes); no expression in normal lung, bronchial and vascular smooth muscle (Figure 1)
- AML, SEGA = positive control (mean H-score 235, 240, respectively) (Figure 1)
- GPNMB expression in LAM – median H-score 280 (130–290), staining pattern: strong, fine granular cytoplasmic staining, cell membrane accentuation and perinuclear dots (in most cases); expression slightly higher in explants than bxs (Figure 3), not significant
- GPNMB in mimics: all H-scores <100 (benign metastasizing leiomyoma-40, metastatic leiomyosarcoma 75, diffuse pulmonary meningotheliomatosis 70, PLCH 10-20, one CPFE case 10, most others <=5)
- Using H-score ≥100 as cutoff: Sensitivity: 100%, Specificity: 100%, PPV: 100%, NPV: 100%; If any staining counted as positive: Sensitivity: 100%, Specificity 60%, PPV 56%
- Possibly correlation with disease stage (end stage – slightly higher expression)

**Take Home Message**

- GPNMB IHC- highly sensitive and specific ancillary marker for pulmonary LAM.
- Maybe useful specifically in biopsies
- Membrane expression may predict response to GPNMB-targeted therapies.

# ARTICLES FOR NOTATION

## NEOPLASTIC

**Jiang P, et al. Deep learning-based classification of lung adenocarcinoma subtypes in histopathological images using DS-EffNet. *Human Pathology.* 2026;168:106020.**

**Summary**

- Reproducibility of morphologic subtyping of lung adenocarcinoma (LADC) challenging
- Subtyping of LADC is of prognostic importance and important for grading
- Deep learning models—especially convolutional neural networks (CNNs)—have shown promise for automated histologic pattern recognition.
- To develop a deep learning model to classify lung histopathological images, specifically addressing differentiation of LADC subtypes and normal lung tissues; enhance classification accuracy and reduce subjective biases in manual analysis
- Developed a deep learning model (DS-EffNet), built on EfficientNetV2-S, incorporating multiple architectural enhancements (depthwise separable residual blocks, reparameterized convolutions, and attention modules).
- 43 resection specimens with WSI, manually annotated and consensus-reviewed by pathologists, yielding ~12,000 high-confidence patches across key subtypes: acinar, papillary, solid, micropapillary, lepidic, invasive mucinous, and benign lung.
- Histologically relevant features (e.g., papillary structures, mucin pools, acinar formation, lepidic growth along ɯlveolar septa) were effectively captured by the model.
- Performance was strong: Accuracy: 95.1%; F1-score: 0.938; AUC: 0.994
- Model outperformed multiple CNN and transformer baselines while using fewer parameters.
- Interpretability via Grad-CAM showed alignment with known histologic patterns (e.g., mucin in IMA, micropapillary tufts, alveolar lining in lepidic).
- Whole-slide heatmaps demonstrated the ability to map mixed subtype distribution within tumors—clinically relevant given intratumoral heterogeneity.
- Generalization testing on LC25000 showed 100% accuracy, though this dataset lacked subtype granularity, limiting interpretability of that result.

**Take Home Message**

- Deep learning can achieve high-accuracy subtype classification of LADC on histology, with performance approaching expert-level pattern recognition.
- The model demonstrates good interpretability and spatial mapping, aligns with WHO histologic criteria.
- Potential assistance in quantifying and mapping mixed histologic patterns within tumors.

**Fend F, et al. Histiocytoses and reactive proliferations of histiocytes: current state of the art and evolving concepts—a report from the joint CSHP-EA4HP-SH workshop 2024, Hefei, China. *Virchows Archiv.* 2025;488:245–262.**

**Summary**

- Workshop report reviews contemporary concepts in reactive histiocytic proliferations, hemophagocytic lymphohistiocytosis (HLH), and clonal histiocytoses, integrating morphology, immunophenotype, and molecular genetics, with emphasis on diagnostic pitfalls and classification challenges relevant to hematopathologists and surgical pathologists.

1. Hemophagocytic Lymphohistiocytosis (HLH)
2. Reactive Histiocytic Proliferations
3. Clonal Histiocytoses: MAPK-Driven Myeloid Neoplasms
4. Langerhans Cell Histiocytosis (LCH)
5. Indeterminate Dendritic Cell Histiocytosis (IDCH)
6. Erdheim–Chester Disease (ECD) & Mixed Histiocytosis
7. Juvenile Xanthogranuloma (JXG)
8. Multicentric Reticulohistiocytosis
9. Rosai–Dorfman–Destombes Disease (RDD)
10. ALK-Positive Histiocytosis

- Diagnostic Recommendations from Workshop
  - Always exclude lymphoma in HLH (especially T-cell).
  - Use sensitive molecular testing (<5% VAF detection).
  - Confirm weak BRAFV600E IHC molecularly.
  - Consider mixed histiocytosis when divergent phenotypes coexist.
  - Screen non-LC histiocytoses for ALK rearrangement.
  - Recognize association with clonal hematopoiesis/myeloid neoplasms in adults.

**Take Home Message**

- Histiocytoses are clonal MAPK-driven inflammatory myeloid neoplasms with marked phenotypic plasticity and frequent association with clonal hematopoiesis.
- Distinction between reactive proliferations and true histiocytosis remains a central diagnostic challenge.
- Molecular testing is increasingly essential even in small biopsies.
- Awareness of mixed histiocytosis is critical when discordant histology is seen across sites.

**Louvrier C, et al. De novo SRRM2 variants in neuroendocrine cell hyperplasia of infancy and persistent tachypnoea of infancy. *Eur Respir J.* 2026;67:2500777.**

**Summary**

- Neuroendocrine cell hyperplasia of infancy (NEHI) (pathology diagnosis-high number of neuroendocrine cells in bx) – clinical diagnosis of persistent tachypnoea of infancy (PTI) = major cause of childhood interstitial lung disease (chILD).
- Presents in early infancy with tachypnoea, hypoxemia, crackles, and characteristic CT findings (ground-glass opacities in right middle lobe/lingula with air trapping).
- N=71 patients
- 4 de novo loss-of-function variants in SRRM2 (Prevalence: 5.6%) → supports SRRM2-related disorder as a monogenic cause of a subset of NEHI/PTI.
- All 4 patients had typical NEHI/PTI presentation, Liptzin score >7, characteristic CT pattern, required oxygen, improvement over time
- All 4 patients had mild neurodevelopmental delay → suggests that SRRM2 defines a distinct NEHI subgroup with consistent NDD.

**Take-Home Message**

- SRRM2-related disorder is a monogenic cause of a subset (~5–6%) of NEHI/PTI, particularly in patients with associated neurodevelopmental delay.
- Favorable long-term respiratory outcome.

**Ortiz BA, et al. Diagnostic yield of routine frozen section pathology examination of lymph nodes in lung resections for clinical stage IA non–small cell lung cancer. *J Thorac Cardiovasc Surg.* 2026;171(2):493–499.**

**Summary**

- Retrospective, single-institution study (2018–2023) evaluated the diagnostic performance of routine intraoperative frozen section pathology (FSP) of lymph nodes (LNs) in patients undergoing curative-intent resection for clinical stage IA (≤3 cm, cN0, M0) NSCLC.
- N= 909
- Nodal upstaging (pN+) on final pathology (FP) in 5.1% of patients (pN1: 3.4%, pN2: 1.7%)
- Median LNs sampled: 6; Median nodal stations: 3
- Total LNs examined: 7016, 1.4% positive on FP
- Diagnostic Performance
  - Patient-level performance: Sensitivity: 80.4%; Specificity: 99.9%; PPV: 97.4%; NPV: 99.0%; Accuracy: ~99%
  - Frozen section pathology-correctly identified: 80.7% of patients with pN1 cases, 80% of pN2 cases
  - LN-level performance: Sensitivity: 83.2%; Specificity: 100%; PPV: 98.8%; NPV: 99.8%; only 1 false positive at frozen section (tumor fragment mimicking nodal metastasis).
  - False negatives attributed to: micrometastases, sampling limitations, freezing/cutting artifacts
- Sublobar Resection Subgroup
  - n=565 patients with intended sublobar resection: final pN+ rate: 2.5%; FSP detected 64.3% of these intraoperatively; occult pN+ reduced from 2.5% → 0.9%

**Take Home Message**

- Routine intraoperative frozen section of LNs in clinical stage IA NSCLC – highly specific (~100%) and sensitive (~80%), reducing occult nodal upstaging.
- As sublobar resections become more common following CALGB 140503 and JCOG0802, FSP should be strongly considered as part of multidisciplinary surgical-pathologic management, particularly to minimize unexpected postoperative pN+ disease.
- Study reinforces the central role of pathology in real-time oncologic decision-making
- However: Results reflect a high-expertise center with a unique toluidine blue protocol.

**Pecci F, et al. Brief Report: Critical Role for DNA-Based Sequencing in Discriminating Distinct Primary Lung Cancers With Different MET Exon 14 Skipping Mutations. *J Thorac Oncol.* 2026;21(2):310–317.**

**Summary**

- Multi-institutional study (DFCI and MSKCC)
- Highlights critical role of DNA-based NGS in distinguishing separate primary lung cancers from metastatic disease in patients with *MET exon 14* (METex14)–mutant NSCLC.
- *METex14* skipping occurs in ~3–4% of NSCLC and can be detected by either:
  - RNA-based sequencing (detects exon 14 skipping event), or
  - DNA-based sequencing (identifies precise underlying splice-site mutation or deletion).
- RNA sequencing confirms exon 14 skipping but does not define specific DNA alteration, limiting its ability to determine tumor clonality.

- 589 patients with *METex14*-mutant NSCLC identified by DNA NGS.
- 112 had ≥2 tumor samples with *METex14* mutations.
- 8 patients -distinct primary lung cancers, each harboring different *METex14* DNA alterations: 4 synchronous (≤12 months), 4 metachronous (>12 months)
- Each case demonstrated different *METex14* splice-site mutations/deletions at the DNA level, distinct co-mutation profiles, genomic patterns incompatible with clonal relatedness
- Control cohort of clonally related metastatic tumors showed (n=20): Identical *METex14* mutations, shared co-mutations across sites

**Take Home Message**

- In patients with multiple lung tumors harboring *MET exon 14* skipping:
  - RNA-based testing alone is insufficient to determine clonality.
  - DNA-based NGS is essential to identify distinct splice-site mutations.
  - Different *METex14* DNA alterations strongly support separate primary lung cancers.
- Compare co-mutation and copy number profiles when multiple tumors are present.
- Driver mutation presence alone does not prove clonality — molecular granularity matters.

**Toussieng T, et al. Pulmonary immunohistochemical markers may be positive in gastric adenocarcinomas associated with autoimmune metaplastic atrophic gastritis.**
***Histopathology.*** **2026;88:729–735.**

**Summary**

- Autoimmune metaplastic atrophic gastritis (AMAG) - autoimmune condition affecting the gastric body (destruction of parietal cells, oxyntic gland atrophy, metaplasia); associated with increased risk of gastric adenocarcinoma, type I gastric neuroendocrine tumors, pernicious anemia.
- AMAG can induce pulmonary-type trans-differentiation of gastric mucosa - may lead to expression of pulmonary markers (TTF-1, Napsin A). Expression in gastric tumors may create a diagnostic pitfall.
- 18 gastric adenocarcinomas associated with AMAG were compared with 36 gastric adenocarcinomas without AMAG.
- IHC: TTF-1 (clones SP141, 8G7G3/1), Napsin A (clone 1P64)
- Tumor component:
  - TTF-1 positivity: AMAG-associated: 39% (SP141) and 22% (8G7G3/1)
    Controls: 11% and 6%, respectively.
  - Napsin A positivity: AMAG-associated: 28%
    Controls: 0% (statistically significant).
  - Staining always patchy, involving 1–20% of tumor cells; Intensity 1+–3+.
  - Only intestinal-type gastric adenocarcinomas showed positivity.

**Take Home Message**

- TTF-1 and Napsin A can be positive in primary gastric adenocarcinomas associated with AMAG but staining is patchy and limited to a minority of tumor cells

**Zhou DD-X, et al. Clinical impact of TP53 classifications in previously treated advanced driver-negative non-small cell lung cancer: A biomarker analysis of the OAK and POPLAR randomized clinical trials. *Lung Cancer.* 2026;212:108891.**

**Summary**

- *TP53* mutations ~50% of lung adenocarcinoma, up to 85% of squamous cell carcinoma.
- *TP53* alterations - biologically heterogeneous; mutant vs wild-type may not adequately reflect their clinical impact.
- To evaluate whether more refined *TP53* mutation classifications provide better prognostic information in advanced driver-negative NSCLC.
- Use cfDNA; analyzed using the FoundationOne Liquid CDx NGS assay.
- N=762 with advanced NSCLC (*EGFR/ALK/ROS1* negative).
- 49% with *TP53* mutations.
- Binary *TP53* mutant vs wild-type status was not independently prognostic after adjusting for clinical variables (adjusted HR 1.15).
- Certain mutation subtypes were associated with significantly worse overall survival (OS): Nonsense mutations (adjusted HR ~1.7), non-missense mutations (Olivier classification), disruptive mutations (Poeta classification).
- Median OS: wt *TP53*: ~11.8 months; missense mutations: ~8.4 months; nonsense mutations: ~6.0 months.
- *TP53* status or subtype did not predict benefit from immunotherapy compared with chemo.

**Take Home Message**

- Refined *TP53* mutation classifications provide better prognostic information than simple mutant vs wild-type categorization in advanced NSCLC.
- Nonsense, non-missense, and disruptive *TP53* mutations are associated with poorer survival.
- *TP53* mutation status does not predict differential response to immune checkpoint inhibitors.

## ARTICLES FOR NOTATION

## NON-NEOPLASTIC

**Kennedy A, Maldonado F, Leonard K, et al. Clinical and Research Implications of Nonspecific Necrosis on Peripheral Pulmonary Lesion Biopsies. *CHEST.* 2026;169(2):562–565.**

**Summary**

- To evaluate the diagnostic significance of necrosis identified in peripheral pulmonary lesion (PPL) biopsies, which is currently classified as a nonspecific (nondiagnostic) finding in the ATS/CHEST consensus definition of diagnostic yield for advanced bronchoscopy studies.
- Retrospective, navigational bronchoscopy, transthoracic needle biopsy.
- Lesions were categorized as: malignant, specific benign, nonspecific benign, according to ATS/CHEST definitions.
- All nodules were followed ≥1 year to determine final diagnosis.
- 1,519 biopsies from 1,327 patients analyzed, necrosis in 10% of biopsies.
- Among necrotic lesions:
  - Specific diagnoses present (108 cases): Malignancy: 21.9%, granulomatous inflammation: 33.8%; mycobacterial or fungal infection: 10.6%; bacterial infection: 5.3%

  - Nonspecific necrosis (43 cases): 40 benign, 3 malignant (7%) (2 of the 3 malignant cases showed atypical cells suspicious for malignancy on the original biopsy). Only 1 case with pure nonspecific necrosis (no atypia) was later found malignant.
  - Diagnostic Performance: NPV of nonspecific necrosis for benign disease: 93%.
- Radiographically: Malignant necrotic lesions were larger than benign ones; 28.3 mm vs 21.6 mm ($P < .03$).

**Take Home Message**
- Necrosis is present in ~10% of PPL biopsies.
- Isolated nonspecific necrosis without atypia has a high likelihood of being benign (NPV ~93–98%).
- Follow-up or repeat biopsy is recommended, especially for larger lesions or those with persistent suspicion for malignancy.

**Roden AC, et al. A Prospective Video-Reflexive Ethnographic Study of Direct Patient-Pathologist Interactions With Heart and Lung Allograft Recipients. *Arch Pathol Lab Med.* 2026;150(2):129–135.**

**Summary**
- Prospective study evaluating a novel pathologist-led clinic ("On My Path") in which heart and lung transplant recipients review their explanted organs directly with a pathologist, using video-reflexive ethnography (VRE) to assess impact and improve practice.
- N=143 patients participated in organ viewing, 21 consented; 17 videotaped sessions; 20 postviewing interviews
- 5 pathologists participated in reflexive sessions
- During the session: Explanted organs were reviewed grossly; patients could touch/hold the specimen; pathology findings were discussed; a 3D-printed replica of the explant was provided.
- VRE involved reviewing recorded sessions to identify communication patterns, emotional responses, and opportunities for improvement.
- Patient Perspective: Highly positive experience, multiple benefits, 3D-printed model especially impactful, few concerns
- All patients were accompanied by family/friends, highlighting the relational importance of the experience.
- Pathologist Perspective: Increased job satisfaction among other benefits, few challenges
- Results led to practice improvements

**Take Home Message**
- A structured patient–pathologist explant viewing clinic is feasible, deeply valued by transplant recipients, and professionally meaningful for pathologists.
- VRE is an effective tool for iterative clinical practice improvement.
- Evolving role of the pathologist from diagnostician to direct patient educator and care participant, particularly in transplant pathology.
- Institutional sustainability will require reimbursement pathways.

## REVIEW

**Courtwright AM, et al. ISHLT Consensus Statement on Short Telomere Syndrome and Lung Transplantation. *J Heart Lung Transplant.* 2026;45:e83–e103.**

**Summary**

- Recommendations for the evaluation and management of patients with short telomere syndrome (STS) in lung transplantation, addressing screening, transplant candidacy, and post-transplant complications.
- Developed by an international expert panel through literature review and Delphi consensus methods.
- Telomeres = repetitive DNA sequences (TTAGGG repeats with shelterin proteins) that protect chromosome ends and maintain genomic stability. Progressive telomere shortening limits cellular replicative capacity and can trigger cellular senescence or apoptosis once a critical threshold is reached.
- Mutations in telomere maintenance genes (e.g., *TERT, TERC, RTEL1, PARN, DKC1, TINF2*) lead to short telomere syndrome, a telomere biology disorder with multisystem manifestations.
- Clinical manifestations vary across the lifespan and include: Pulmonary fibrosis (most common adult manifestation), bone marrow failure / cytopenias, liver disease, dyskeratosis congenita features, early hair graying and increased malignancy risk.
- Short telomeres are common in fibrotic lung disease:
- Cutoff currently-Peripheral blood telomere length ≤10th age-adjusted percentile - <1$^{st}$ percentile – ultrashort; by Flow-FISH

**Take Home Message**

- STS-common and underrecognized cause of pulmonary fibrosis
- STS may predict distinct complications, particularly hematologic toxicity, CMV infection, liver disease, and malignancy.

## EDITORIALS / LETTERS

**Schirmacher P. Artificial intelligence and the process of publishing scientific manuscripts. *Virchows Archiv.* 2025;488:213–214.**

- Discussion of the growing role of artificial intelligence (AI) in scientific publishing, highlighting both its potential benefits and significant risks.
- Scientific publications function as "ground truth" for future research, clinical decision-making, funding decisions, and academic careers. Therefore, errors introduced by AI—especially fabricated references or incorrect information—can propagate widely and become difficult to correct once published.
- Evidence cited - when ChatGPT was used for pathology-related diagnostic questions, 30% of references were incorrect and 60% of those did not exist, highlighting the risk of misinformation entering the literature.
- Author proposes several policy recommendations for journals:
  - Transparency: Authors must clearly disclose any AI assistance used in manuscript preparation.
  - Author responsibility: AI should not write manuscripts

- Reviewer integrity: Generative AI should not be used to write peer reviews.
- Editorial independence: AI should not be involved in critical editorial decisions such as manuscript acceptance.
- Governance policies: Journals should develop formal codes of conduct regulating AI use in publishing.

**Vermaut A, et al. Large and small airway remodelling in human end-stage primary ciliary dyskinesia lungs. *European Respiratory Journal.* 2026;67:2501744.**

- Primary ciliary dyskinesia (PCD) and cystic fibrosis (CF) share similar clinical manifestations (chronic infection, inflammation, airflow obstruction, and bronchiectasis), but their underlying pathophysiology differs.
- To investigate airway remodelling in end-stage PCD lungs and compared them with CF and control lungs using ex vivo HRCT, micro-CT, and histological analysis.
- 4 PCD lungs, 8 CF lungs, 4 control lungs.
- Severe loss of small airways: Number of terminal bronchioles in PCD was reduced by ~80% compared with controls, indicating substantial small airway destruction; comparable with CF.
- Mucus plugs - more frequent in PCD than in CF
- Irregular airway walls, lymphocytic inflammation, and peribronchiolar fibrosis, with focal airway collapse in PCD
- Extent of small airway loss was comparable between PCD and CF, bronchiectasis was more homogeneous affecting middle and lower lobes. Airway dilatation in PCD was less distally than in CF.
- Unlike CF, where constrictive bronchiolitis and fibrosis are major drivers of airway loss, PCD airway obliteration appears more strongly linked to mucus plugging and chronic inflammation.

**Take Home Message**

- End-stage PCD demonstrates severe and irreversible small airway loss, with >80% loss of terminal bronchioles.
- Airway obstruction in PCD is not purely functional or mucus-related but includes structural airway remodelling and collapse.
- PCD airway remodelling is more mucus-driven and less fibrotic, with bronchiectasis predominantly in proximal/mid airways.

## Case Reports

**Admire K, et al. Right Atrial Mass in a 63-Year-Old Woman. *Chest.* 2026;169(2):e67-e71.**

**Summary**

- 63-year-old woman with history of breast intraductal carcinoma who presented with sudden abdominal pain and vomiting.
- CT angiography performed for abdominal symptoms incidentally revealed sigmoid diverticulitis, pulmonary emboli, and a large heterogeneous right atrial mass.
- Surgical excision of the right atrial mass, reconstruction of the right atrium and vena cavae, and bypass grafting due to coronary invasion.

- Primary cardiac angiosarcoma is the most common malignant primary cardiac tumor, typically arising in the right atrium.

**Churg A, et al. Mesothelioma in Situ With a TP53 Mutation. *Am J Surg Pathol.* 2026;50(2):267–271.**

**Summary**

- 55-year-old man underwent a cholecystectomy and repair of an umbilical hernia. Microscopy of the hernial tissues revealed epithelioid mesothelioma.
- Subsequent laparotomy showed small tumor nodules (usually < 3 mm in size) in the pelvis, bladder, rectovesical space, mesorectum, appendix, cecum, small bowel mesentery, and terminal ileum.
- Peritoneal lesions demonstrated three components: 1. Papillary mesothelioma in situ; 2. papillary proliferations mimicking well-differentiated papillary mesothelial tumor (WDPMT); 3. Early invasive mesothelioma
- BAP1, MTAP, NF2/Merlin: retained
- p53 - diffuse overexpression in flat MIS, papillary MIS, and invasive areas
- NGS: TP53 in-frame deletion: c.1012_1047del (p.F338_E349del); Variant allele frequency: ~5%
- The authors conclude that this represents the first reported case of mesothelioma in situ associated with a TP53 mutation

**Lérias S, et al. Molecular characterization of a thymic neuroblastoma in an adult associated with inappropriate antidiuretic hormone secretion syndrome. *Virchows Archiv.* 2025;488:421–427.**

**Summary**

- 72-year-old man presenting with SIADH.
- CT scan revealed an anterior mediastinal mass (5 × 3.8 × 2.5 cm)
- Thymectomy: well-circumscribed lobulated mass (~5.5 cm)
- Microscopy: Lobular architecture separated by fibrovascular septa, small round blue tumor cells, fine fibrillary eosinophilic neuropil, Homer-Wright pseudorosettes, foci of necrosis and hemorrhage, capsular invasion into adjacent fat, mitotic-karyorrhexis index <1%, no ganglion cells or Schwannian stroma.
- IHC+: Synaptophysin, Chromogranin (patchy), CD56, NSE, TdT (focal), PAX8 (focal)
- IHC-: Cytokeratins (AE1/AE3, CK8/18), EMA, TTF-1, and others
- No MYCN amplification, no ALK alterations
- Loss: chromosome 3p, 6q, 11q regions; Gain: 3q26.3–q29; copy number gain of PIK3CA
- No gene fusions detected.
- Diagnosis: poorly differentiated thymic neuroblastoma associated with SIADH
- No evidence of disease at 12-month follow-up.

**Lötscher J, et al. Pulmonary Mucormycosis. *NEJM.* 2026;394(7):699.**

**Summary**

- 49-year-old man with acute myeloid leukemia (AML) who developed prolonged neutropenic fever during induction chemotherapy.

- CT: Rounded pulmonary opacities, central ground-glass attenuation, peripheral ring-like consolidation (reversed halo sign)
- Lung tissue showed: central necrosis, surrounding organizing pneumonia; GMS: intravascular fungal hyphae
- PCR of the resected tissue: Rhizomucor pusillus
- Diagnosis: Pulmonary mucormycosis.

**Sasaki E, et al. Aerogenous Dissemination of DEK::AFF2 Carcinoma: A Prototype of a Previously Underrecognized Pattern of Endobronchial Metastasis From Extrathoracic Malignancies. *Am J Surg Pathol.* 2026;50(2):189–193.**

**Summary**

- 2 cases of sinonasal *DEK::AFF2* carcinoma demonstrating an unusual pattern of recurrent tracheobronchial metastases, suggesting aerogenous dissemination rather than the conventional hematogenous or lymphatic spread.
- Tumors had multiple local recurrences (7 in case 1; 4 in case 2).
- Tracheal and bronchial nodules appeared ~8 years after initial diagnosis.
- Metastatic lesions were repeatedly treated by endoscopic resection.
- No lymph node metastases or distant metastases outside the tracheobronchial tree were identified.
- Patients remained alive 10 and 18 years after diagnosis.
- Histology: Papillary and inverted growth patterns, basaloid to nonkeratinizing squamous cells, uniform cytology, loss of cellular cohesion resembling STAS-like changes.
- IHC+: p40, AFF2 (nuclear)
- IHC-: NUT
- DEK rearrangement confirmed by FISH
- DEK::AFF2 carcinoma is a newly recognized molecularly defined sinonasal carcinoma with deceptively bland histology.
- This tumor may show a unique metastatic pattern via aerogenous spread along the respiratory tract.
- Key features suggesting aerogenous dissemination:
- Primary tumor in upper aerodigestive tract

**Zhang Y, et al. Bronchial mucoacinar carcinoma: a newly proposed subtype of mucoepidermoid carcinoma in the bronchus. *J Clin Pathol.* 2026;79:128–131.**

**Summary**

- Salivary gland variant termed mucoacinar carcinoma (MAC) described, showing dual mucoepidermoid and serous acinar differentiation, and demonstrating MAML2 rearrangement.
- Juvenile patient with recurrent pneumonia, chronic cough, hypoxia.
- CT: 2.7 × 2.0 cm mass obstructing bronchus intermedius.
- Bronchoscopy: friable fungating mass; endoscopic removal followed by lobectomy
- Histopathology: endobronchial epithelial neoplasm with glandular, solid, and cystic architecture, bland round nuclei, eosinophilic granular to foamy cytoplasm, intracellular and extracellular mucin (mucicarmine+), no necrosis, low mitotic rate, Ki-67 ~5%
- IHC+: CK7, SOX10, NR4A3, LMO2 (focal), DOG1 (focal), CK5/6 (focal), p63 (focal), CD56 (focal)

- IHC-: TTF-1, Napsin A, S100, Mammaglobin, GATA3, Chromogranin, Synaptophysin, HMB45, MART1, Smooth muscle myosin
- FISH negative for *MAML2, NR4A3, EWSR1, ETV6*
- RNA-based NGS (ArcherDx Fusion Panel): *CRTC3* exon 2 :: *MAML2* exon 2 fusion; *PIK3CA* p.Glu545Ala mutation (13% VAF); *PIK3CA* mutation identified (potential therapeutic implication)
- No recurrence at 6 months, no LN met