AUGUST PULMONARY PATHOLOGY JOURNAL CLUB

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I. ARTICLE FOR DISCUSSION

1. **TTF-1 Expression Defines Distinct Clinicopathologic and Molecular Subtypes of Lung Adenocarcinoma and Predicts Outcomes to Immunotherapy and KRASG12C Inhibitors.** Di Federico A, et al. Journal of Thoracic Oncology. 2026;21(7).

Background

- TTF-1 is an important transcription factor for lung development.
- TTF-1 neg LUAD typically mucinous AD with associated factors such as low PD-L1 expression, KRAS mutation and worse prognosis, but little is known about TTF-1 neg non-mucinous AD.

Aim

To perform a comprehensive study to compare patients with TTF-1 pos vs TTF-1 neg AD, in a large cohort of patients

Methods

- Multicenter international study of 3,297 AD (consecutive 2001-2024 from multiple cohorts with clinical and outcome data): pure AD, 85% TTF-1 pos (mostly 8G7G3/1 clone) - data retrospectively collected.
- PD-L1 IHC – 22C3, E1L3N, 28-8, SP263
- Multiplex IF with PD-L1, PD1, CD8, FOXP3, AE1/AE3
- NGS OncoPanel with 277, 302 and 447 genes
- TMB
- Use of publicly available cohorts TCGA, SU2C_mark and POPLAR/OAK

Results

- Compared with TTF-1-pos tumors, TTF-1-neg AD showed:
    - More in smokers, heavy
    - Stage IV presentation
    - More metastatic to bone and adrenals, less brain and liver
    - Even after excluding mucinous AD
- TTF-1 neg AD with:
    - Enrichment for KRAS mutations – G12D, G12V and G13X
    - Enrichment for STK11, KEAP1, SMARCA4, CDKN2A and NKX2-1 alterations.
- TTF-1 neg AD without targets 38.5% vs 25.2 for TTF-1 pos
- TTF-1 neg AD with:
    - Lower PD-L1 expression
    - Lower intratumoral CD8+ T-cells
    - Lower PD1+ and CD8+/PD1+ immune cells

- Distinct transcriptional profiles indicating loss of alveolar lineage differentiation.
- Overall response, mPFS, mOS to ICI, chemotherapy, or targeted therapy was less in TTF-1 neg AD
- Loss of TTF-1 during tumor progression (primary TTF-1-positive tumors becoming TTF-1-negative in metastatic sites), accompanied by acquisition of STK11, KEAP1, or SMARCA4 alterations.

Take Home Message

- TTF-1 negativity identifies an aggressive subtype of lung adenocarcinoma with adverse molecular features, even after excluding mucinous AD.
- This study expands the clinical value of TTF-1 beyond diagnosis, establishing it as a practical prognostic and predictive biomarker in lung adenocarcinoma, beyond and independently of known adverse mutational profile.

2. Lepidic and alveolar subepithelial squamous cell carcinoma: expansion of the concept of peripheral squamous cell carcinoma with proposal for revised terminology based on morphologic, immunophenotypic, and clinical analysis of 22 cases. Fillipello F, Ambrosi F, Blaauwgeers H et al. Virchows Archiv 2026; 489:27-35
**Also refer to article by Sam Yousem* Peripheral squamous cell carcinoma of the lung: patterns of growth with particular focus on airspace filling. Hum Pathol 2009; 49:861-867

Background

- Peripheral Squamous cell carcinoma (SQCC) increasing in incidence and biologically different and diverges clinically and histologically from central SQCC.
- Histologically, 4 patterns described: pushing, infiltrative, pseudoalveolar filling and alveolar filling (see article by Yousem)
- More unusual patterns – "subepithelial" SQCC in which the malignant cells grow on the alveolar walls beneath reactive type II pneumocytes. These can mimic lung AD radiologically with GGO and histologically (also ADSQCC)

Aim

To describe a series of 22 cases of peripheral SQCC with subepithelial growth pattern

Methods

- 2018-2024 in-house and consultation cases from 2 centers (Amsterdam University and Maggiore Hospital) with available clinical and survival information
- All cases reviewed to confirm subepithelial growth defined as layers or nests of tumor cells p40+ growing along alveolar septa and covered by reactive TTF-1 pneumocytes
    - Lepidic if 1 single layer of tumor cells
    - Alveolar if nests of tumor cells
- Other patterns including alveolar and infiltrative noted, and all patterns recorded as %
- IHC performed TTF-1/p40 double staining and p53
- 6 cases NGS covering 27 genes

Results

- 22 cases in 21 patients (13F; med 69 yo) with subepithelial growth pattern; 2 central*
- 11 pT1, 8 pT2 or T3 (4 with PL1) and 2 pN2
- 4 cases with 100% subepithelial pattern, 3 with 90%, 11 with 20-70% and 4 with 10%
- 20 cases with p53 mutation type labeling (0% staining or strong stainin in at least 80%)
- 5 (of 6) with mutation in p53 gene including 1 with wild type IHC – no other mutation
- Lepidic pattern periphery of tumor, the alveolar pattern both center and periphery
- 4 cases only sub-epithelial with no AF or infiltrative. 14 cases with both subepithelial and infiltrative patterns. 8 cases with both AF and subepithelial patterns (infiltrative also in 6 of these).

Take home message

- To be aware of this type of growth pattern in peripheral SQCC and its distinction with bronchiolar adenoma, especially with BA with squamous metaplasia.
- Their discussion on this differential diagnosis was too brief.
- Mention the potential role of p53 vs other mutations for the distinction between SQCC and BA as well as recognizing infiltration/AF pattern as a feature of SQCC as seen in the majority of their cases.

3. Utility of RB1 immunohistochemistry for prognostic subtyping of pulmonary large cell neuroendocrine carcinoma. Minkley M, Ravasia K, Nghiem T et al. Virchow Archiv 2026; 489:135-144

Background

- LCNEC are rare with lacking phase 3 clinical trials and no standard of care
- Molecular studies have shown that a subset of LCNEC has a SCLC-like profile defined by loss of *RB1* and mutation of *p53* and may be best treated as SCLC.

Aim

- Assess prognostic value of RB1 immunohistochemistry alone in LCNEC
- Assess if p53, p16 and cyclin D1 IHC improves prognostic stratification
- Determine if RB1 status predicts benefit from different chemotherapy regimens

Material and Methods

- TMA built from 59 resected pure LCNEC
- IHC for RB 1, P 53, p16 and cyclin D1 performed
- Clinical outcomes assessed for RFS and DSS
- Systematic literature review regarding RB 1 status and chemotherapy response

Results

- RB1 loss common, seen in 58% of cases, 94% of which also show mutant pattern p53 staining
- RB1 loss predicted worse prognosis in advanced stage disease, independently associated with DSS (p=0.0031) but not with RFS.
- As p53 mutation pattern is identified in almost all cases of RB1 loss tumors (94%), it did not add value as a prognostic marker. Incorporating p16 and cyclin D1 did not improve prognostic stratification as p16/cyclin D1 low pattern seen in all but 1 case of RB loss tumors.
- Literature search yielded 176 publications, 5 of which met inclusion criteria (Table 3). The hypothesis is that the LCNEC with SCLC-like profile would respond better to platinum etoposide or pemetrexed therapy like SCLC. Overall studies with small numbers (72 and 54 patients in the 2 largest). Authors added their cases to the literature for a metanalysis. Conflicting results, some suggest better outcome; others showed no difference between subtypes and therapy.

Take home message

- RB loss in “LCNEC” seems to suggest worse prognosis for these tumors, especially in advanced stage.
- The literature remains inconclusive in the use of RB loss to determine chemotherapy.

4. 3D virtual histology demonstrates tumour connectivity in spread through air spaces (STAS) of non-small cell lung cancer. Saccomano G, Brun F, Martellani F, et al. Histopathol 2026; 89:69-80

Background

- WHO definition "as tumor cells within airspaces beyond the edge of the main tumor" and studies on STAS define "...even if it existed within the first alveolar layer from the tumor edge"
- Is STAS truly airspace spread, artefact, other?

Aim

- Determine is STAS cells truly detached from the primary tumor using a form of 3D "virtual histology"

Methods

- Synchrotron-based X-ray phase-contrast microtomography (micro-CT, μCT)
    - Conventional CT measure X-ray ***attenuation*** – Bone absorbs a lot so bright, air absorbs few so dark. This is not enough to visualize tissue like alveolar septa, tumor cells, microscopic architecture thus using
        - "Phase-contrast" which uses x-ray amplitude (intensity) like conventional CT, and phase (position of the wave) as it passes through the tissue which is more sensitive
    - Elettra Syncrhroton produces extremely bright, highly coherent x-rays and tight beam geometry to capture the very tiny phase shifts generated by soft tissue.
- Produced routine FFPE block
    - 1 section used for histoly
    - Block scanned to generate the 3-D images
- Clinical CT scans of the tumors

Results

- From a cohort of 20 cases, 7 with STAS and chose 3 without STAS as control
    - 5 AD and 2 SQCC
    - STAS pattern: 2 MP, 2 Solid nests, 3 Single cells/MP and 1 also solid
- Illustrations comparing H&E, 3-D generated images, and in some conventional CT
    - Images suggest that the tumor cells seen as STAS on H&E are connected to the main tumor – mostly MP and solid patterns of STAT - or attached to alveolar septa or involving vessels - mostly MP and single cells- on the 3-D rendering
    - Conventional CT shows these tumors to have more spiculation, or "tree in bud" growth or tur perilesional nodules (suggesting more T3?).

Take home messages

- Novel methodology to suggest, not surprisingly, that we may overestimate STAS i.e. not true airspace, free-floating tumor cells, but truly connected to main tumor or attached to lung structure.
- This methodology does require some "faith" as to what we are seeing i.e. tumor cells vs macrophages etc.

- Lack of data – how many cases had true STAS vs not, within a case, where there some STAS real and some not and could we re-define maybe STAS, if they had done multiple H&E levels would we have eventually seen this connection, how deep

II. ARTICLES FOR NOTATION

Neoplastic

1. **Pathologic response and nodal status guide adjuvant immunotherapy in non–small cell lung cancer after neoadjuvant chemoimmunotherapy: An eastern Asian cohort study.** Pan Y, Sun C, Xu H, et al**.** J Thorac Cardiovasc Surg 2026; 172: 1-11

   The authors aimed at answering the question of which patients benefit from adjuvant immunotherapy, following neoadjuvant chemoimmunotherapy and surgery. Ambitious question to answer with a small number of patients. But these authors did show that MPR and ypN by themselves is insufficient to stratify patients. They devised a practice risk model with 4 groups: MPR ypN0, non-MPR ypN0, MRP ypN+, and non-MPR ypN+. Using this model, they showed that only non-MPR ypN+ patients may benefit from adjuvant immunotherapy. Furthermore, they suggest that patients that are ypN0 have excellent outcomes and show no benefit from adjuvant immunotherapy (and thus avoiding issues of toxicity, financial costs...)

2. **Retrospective Comparison of Operational Metrics Across Diagnostic Approaches for Molecular Testing in Lung and Colon Cancers in a Community-Based Setting.** Tawfik OW, Smith R, Thomason J et al. Arch Pathol Lab Med 2026; 150: 513- 519

   The study compared three molecular testing strategies used in a community hospital setting for non-small cell lung cancer (NSCLC) and colorectal cancer (CRC): 1. Single-gene panel (SGP) performed in-house 2. Oncomine Focus Assay (OFA), a 52-gene targeted NGS panel performed in-house 3. Send-out comprehensive NGS (SO-NGS), a 648-gene external panel. The authors evaluated: 1. Turnaround time (TAT) 2. Quantity-not-sufficient (QNS) rates 3. Detection of NCCN-recommended actionable molecular alterations. For NSCLC, OFS performed the best overall (TAT better than NGS although longer than SGP, but covered all recommended genes vs SGP, low tissue requirement with low QNS. Comprehensive NGS is not always better.

3. **Pulmonary papillary adenoma: Comprehensive clinical pathologic analysis of 10 cases and molecular genetic analysis of 7 cases.** He S, Xie Y, Zhu Y et al. Virchows Archiv 2026; 489:171-178

   Pulmonary papillary adenoma is a rare lung tumor with characteristic papillary morphology and pneumocytic differentiation. This study of 10 cases demonstrates a benign behavior (although no mention of time of FU) and in the 7 cases subjected to NGS, 6 showed at least one gene mutations (MAP2K1, AKT1, NF1, APC, EGFR, NBN, CTNNB1) in Wnt,

RTK/RAS, and PI3K/AKT signaling pathways. These findings contrast with prior studies, mainly case reports, with only one reported case with EGFR mutation.

4. **Thoracic inflammatory myofibroblastic tumors: A decade-long retrospective study integrating clinicopathological and molecular features from a tertiary care centre.** Jacob S, Nambirajan A, Gangule HN, Kumar S, Chandrashekhara SH, Rastogi S, et al. Virchows Archiv. 2026;489:159–170.

   This retrospective study analyzed 30 primary thoracic inflammatory myofibroblastic tumors (IMTs) - one of the largest series - diagnosed over a 10-year period, integrating histopathology with molecular testing. The study demonstrates that thoracic IMTs predominantly affect children and young adults, are usually driven by ALK rearrangements, and have excellent overall outcomes following surgical resection, although local recurrence may occur rarely (3 patients).

   Of note, genomic alterations were seen in only 22 tumors, and while ALK rearrangements accounted for 73% of cases, ROS1 rearrangement was seen in 23% and 1 case with NTRK3 (not detected by immunostaining so need other methods like FISH to detect).

5. **Immunohistochemical profiling of small cell lung cancer reveals subtype heterogeneity and a tuft cell-like subtype characterized by LRMP and TRPM5.** Mahmoud WA, Alorjani MS, Al Bashir SM, et al. Virchows Archiv 2026; 489:123-134.

   In this study, the authors aim to further define fine the four major subtypes of SCLC, with a particular emphasis on POU2F3 SCLC, representing a tuft cell-like variant. The results confirm already known data about these subtypes. The novel finding is the identification of overexpressed LRMP. TRPM5, AVIL, ASCL2, COCA2, in the transcriptomic data in POU3F3 SCLC, all genes associated with tuft-cell biology. Additionally, the POU2F3 SCLC did express LRMP and TRPM5 using immunohistochemistry, further defining these SCLC.

6. **Clinically actionable molecular alterations in Rb-retained small cell lung carcinoma variants.** Zacharias M, John N, Kashover K, Popper H. Virchows Archiv 2026; 489:219-24.

   Report of 2 cases of SCLC with retained RB showing in one case KRAS G12C mutation and in the other a novel fusion IKZF2::ERBB4 fusion, with TP53 mutation, STK11 inactivation. The authors conclude that RB retained SCLC are molecularly distinct from RB lost SCLC and that RB showed be done routinely in SCLC to detect RB intact SCLC, to further perform genomics in search of actionable mutations. But are these 2 cases really SCLCL?

7. **FigATree: a novel framework for histological subtyping and grading of lung adenocarcinoma.** Huang Q, Zhang J, He Q et al. Virchows Archiv 2026; 489:37-47

   FigATree (fine-graines Adaptive Tree) is a highly interpretable AI system that combines a pathology foundation model with an XGBoost decision tree framework to classify lung

adenocarcinoma using 1,100 WSI. It achieved 95% region-level accuracy – Histologic patterns [Struggled with papillary and cribriform/complex glands], 89% slide-level subtype accuracy – AIS-MIA-IA, and 84% differentiation grading accuracy – Well, mod and poorly diff, substantially outperforming conventional pathology-AI approaches while retaining explainability (mirror pathology workflows and grading rules). The strong external validation - validated on TCGA data, suggests that FigATree may represent a practical next-generation computational pathology tool for LUAD diagnosis and grading.

8. **Hepatoid adenocarcinoma of the lung: clinicopathologic and molecular analysis of 17 cases.** Nezami BG, Fridland S, dos Santos LC et al. Virchows Archiv 2026; 489:91-101.

   This study had 3 goals: 1- routine morphology and immunophenotype, 2- quantification of metastatic disease and 3- genomic architecture. In this cohort of 17 cases, the tumors were predominantly high-grade, solid, or with complex glandular architecture. By definition, HepPar 1 was positive in all cases and PD-L1 TC score of 50% + seen in only 2 cases. The genomic profile showed a predominance of STK11 alteration (53%), followed by TP53 (41.2%) and KRAS (35.3% - G12C, G12 D and G12V). SMARAC4 alterations were seen in 18% of cases. In this study, the authors argue that the poorer prognosis of these tumors is due to high stage at presentation compared to non-hepatoid type AD (SEER data). Their emphasis on molecular alterations as landscape for aggressiveness is also mentioned.

9. **Clinicopathologic features of KRAS G12C-mutated non-small cell lung carcinomas: insights from 279 retrospective cases.** Bradova M, Slavik P, Vanecek T, et al. Virchows Archiv 2026; 489:49-63.

   The authors studied 279 patients with KRAS G12C-mutated NSCLC. As in other studies, the patients were predominantly smokers, with advanced stage presentation, and poor survival. The authors emphasized the morphology of these tumors, typically high grade and occasionally mimicking SQCC including by IHC with p40/p63 and CK5/6 focal immunoreactivity in a small subset which could lead to a misdiagnosis of SQCC and a missed opportunity for molecular testing with appropriate targeted therapy. These tumors were commonly positive for PD-L1, with co-mutations in 21% (TP53 and STK11 most common – as reported in other studies – but other genes as well, like BRAF, MET etc)

10. **The clinicopathologic characteristics and outcomes of uncommon KRAS mutations in patients with non-small cell lung cancer.** Zhang Y, Zhao J, Gao Q, Kong M. Virchows Archiv 2026; 489:113–122.

    This retrospective study evaluated the clinicopathologic characteristics and clinical outcomes of patients with NSCLC containing uncommon KRAS mutations. Among 4,661 patients who underwent molecular testing, 378 (8.1%) had KRAS mutations, and 14 of those cases (6.7%) harbored uncommon KRAS variants- most common G12F followed by G12S and G12R, and novel variants G12Y and G13R. There was no difference between cases of NSCLC with common and rare mutations except PFS and OS were shorter in patients with NSCLC with uncommon mutations.

11. **Prevalence and clinico-morphological correlates of STK11 mutations in a large cohort of NSCLC lung adenocarcinomas.** Rustamov R, Fuzesi L, Lesser T et al. Virchows Archiv 2026; 489:65–77

    Single institution study that found STK11 in 3% of 473 AD, mostly in smokers, and with aggressive histology and poor overall survival, if co-mutated with KTAS and TP53. The main novel finding was to explore morphologic differences (as well as clinical) in STK11 only, STK11+ KRAS, STK11+P53, and STK11+KRAS+P53, noting progressive undifferentiation and poor outcome with additional mutations (P53 worse than KRAS, triple mutation the worst).

12. **NTRK Fusion Landscape in 195 Positive Cases of 17 Tumors: A Chinese Multicenter Retrospective Study With Optimized Pan-TRK Immunohistochemistry (IHC) Screening.** Wu S, Wang J, Yang W et al. Mod Pathol 2026; 39

    In this study, the authors optimized the standard pan-TRK assay, adding OptiView Amplification kit, which leads to a very high sensitivity for NTRK3 cancers, and overall improved specificity up to 80% (from 60%). Specifically, for NSCLC, all were TRK1 in this study, all with cytoplasmic staining alone, and were the major source of false + cases, which decreased with the optimization. Still, a positive IHC in NSCLC needs confirmation of NTRK fusion by other method (FISH/NGS).

13. **SMARCA4-deficient thoracic tumors exhibit an immunosuppressive microenvironment and respond to combined antiangiogenic and immune checkpoint inhibitor therapy.** Zhang P, Kuang Y, Jia B et al. Lung Cancer 2026

    This retrospective study compared clinical outcomes and spatially resolved tumor immune microenvironment using multiplex immunohistochemistry (Panel 1: CD4, PD-1, CD8, PD-L1, TIM3, FOXP3, PANCK; Panel 2: CD68, CD20, CD163, TIM3, CD3, PANCK) between SDTT (n=121) and non-SDTT (n=132). Basically, no new data is provided. The study confirms inferior survival of SDTT, SMARAC4 being an independent risk factor. Compared to non-treated SDTT, SDTT treated with ICI had a better outcome. SDTT has low PD-L1 expression with common co-mutations in TP53, KRAS, STK11 and KEAP1. No significant difference in the microenvironment between SDTT and non-SDTT. And a spurious observation that combining antiangiogenic therapy to ICI may improve PFS in SDTT.

14. **Clinical outcomes and tumor immune microenvironment in SMARCA4-Deficient NSCLC: A Real-World retrospective study.** Zhao W, Guan M, Zhang H, et al. Lung Cancer 2026.

    This retrospective study of 221 patients with stage III and IV NSCLC (59 SMARCA4-deficient and 162 SMARCA-4 intact) aimed at studying the prognostic significance of SMARCA4 loss, comparing clinical characteristic with pathological and immunological features of these tumors.

Very similar study to the one above with similar results and conclusions. The main difference was in the immunostudy which used a multiplex immunofluorescence platform with CD4, CD8, FOXP 3, CD11c, and GZMB (granzyme B). Their study shows that among patients with SMARCA4- deficient tumors, those having received immunotherapy, with or without chemotherapy, had an improved PFS versus patient receiving chemotherapy alone (although response not as good as SMARCA4 intact tumors). The microenvironment profile suggested that responders had a higher prevalence of CD4/ CD11c and reduced FOXP3 levels, while elevated CD8/GZMB levels were higher in non-responders.

15. **Molecular co-alteration patterns of RICTOR-mutant metastatic lung adenocarcinomas: a single-center cohort study.** Ozata MB, Aytac A, Erdogdu IH, et al. Virchows Archiv 2026; 489:103-112

    This study investigated the molecular landscape of RICTOR-mutant metastatic lung adenocarcinoma and examined which genetic alterations commonly occur alongside RICTOR mutations. 20 (15%) of 137 metastatic AD harbored a RICTOR mutation, 65% of which had EGFR mutation, 22% with KRAS and 45% with p53, and a list of others. RICOTR is a critical component of the mTORC2 complex and likely does not act in isolation but more as a facilitator of more complex genomic signaling and a potential therapeutic target.

16. **Prognostic significance of RICTOR mutations in EGFR-mutant metastatic lung adenocarcinoma: a retrospective cohort study.** Aytac A, Ozata MB, Erdogdu IH et al. Virchows Archiv 2026; 489:79–90

    This retrospective study studied the role of RICTOR mutations in outcome of patients with EGFR mutated metastatic lung AD. The premise is that RICTOR mutations have been implicated in cancer progression and resistance to targeted therapy. Small cohort of 39 patients with EGFR mutated AD, 15 of which carried RICTOR mutations. Patients with RICTOR mutation had a shorter overall survival (8 vs 14 months), independent of other risk variables.

17. **The International Association for the Study of Lung Cancer Pleural Mesothelioma Staging Project: Impact of Common Molecular Alterations and Programmed Death-Ligand 1 Expression on Overall Survival in a Select Cohort From the International Association for the Study of Lung Cancer Ninth Edition Staging Database.** Yang ST, Tjota MY, Goren E, Girous D et al. JTO 2026; 21

    A large multi-institutional (MSK, U of Chicago, French Mesobank) study of 556 pleural mesotheliomas evaluated whether common molecular alterations improve prognostic assessment beyond traditional factors such as stage and histology. The major finding was that CDKN2A, NF2, and TP53 alterations predict worse survival, whereas BAP1 alterations or BAP1 protein loss predict better survival, which remained independent in multivariate analysis. In contrast, PD-L1 expression was not associated with overall survival (OS) in this cohort. Molecular alterations performed almost equally to clinical co-variates, and adding molecular alterations to a prognostic model, improved prediction of outcome and survival.

18. **Clinical utility and prognostic value of GATA3 in epithelioid malignant mesothelioma: a practical and cost-effective approach for resource- limited settings.** Thabit DM, Thabet DM. J Clin Pathol 2026; 79:475-485

The purpose of this study was to evaluate the role of GATA3 as a diagnostic and prognostic marker in epithelioid mesothelioma, including correlation with tumor infiltrating lymphocytes (TILs). The study comprised 115 patients, 55 with epithelioid mesothelioma and 60 with poorly differentiated lung adenocarcinoma. Almost 80% of epithelial mesothelioma were positive for GATA3 compared to 7% poorly differentiated lung adenocarcinoma- higher than other studies. The sensitivity and specificity of the diagnosis of epithelial mesothelioma increased when adding calretinin and WT1 immunostains. GATA3 positivity correlated with indicators of advanced disease and stage, and shorter overall survival - similar observation to other studies but not confounded by sarcomatoid subtype. GATA3 expression was shown to be an independent prognostic factor in a multivariate analysis. The tumor microenvironment analysis shows that the GATA3 negative tumors had stromal TILs that expressed GATA3, in contrast to the GATA3 positive tumor cases, suggesting that it was not the density of TILS that matter but their expression of GATA3- observation which would remain to be observed by other investigators in the future.

19. **Gene expression and immunohistochemical phenotypes of high-grade epithelioid mesothelioma.** Gagnon MF, Rozenova K, Lu C et al. Hum Pathol 2026

The main goal of this study is to compare the RNA expression, using NanoString PanCancer Pathways (770 genes), of high-grade EM to low-grade EM and biphasic/ sarcomatoid mesothelioma (SM/BM). The cohort was comprised of 35 EM – 21 LG and 14 HG, 6 BM and 6 SM. The study confirmed typical findings such as a male predominance, common history of asbestos exposure and preponderance of surgical treatment in EM. Also demonstrated was a clear prognostic separation with EM-LG having the best median OS, the SM/BM lowest and EM-HG in between. The RNA expression data showed clustering of EM-HG closer to the SM/BM than the EM-LG with a smaller number of differentially expressed genes, suggesting EM-HG are biologically distinct from EM-LG. In EM-HG, BAP1 was less often lost, PD-L1 with low scores (like EM-LG), and EZH2 H-Score was intermediate between EM-LG and SM/BM therefore supporting EZH2 as a potential biomarker and therapeutic target.

20. **Immune-related markers define clinically relevant prognostic subgroups in thymic epithelial tumors.** Megyesfalvi E, Teglas V, Ferencz B et al Virchows Archiv 2026; 489

The authors sought to identify biomarkers that would potentially identify biologically distinct and clinically meaningful TET. As TET are commonly associate with immune related disorders, the focus was on immune biomarkers, 5 (somewhat random) evaluated by IHC on TMA from 119 thymomas and 18 carcinomas This study demonstrates that TIM3, GTF2I, and XPO1 are highly expressed in all types of thymic epithelial tumors. The particularly poor-prognosis subgroup is characterized by high expression of TIM3, GTF2I, and XPO1, while OX40L is strongly associated with myasthenia gravis. More interesting is the potential of using targeted therapies like TIM3 and XPO1 inhibitors.

Non-neoplastic

1. **Morphological artifacts in pulmonary pathology and literature review.** Filipello F, Timens W, Blauuwgeers H et al. Virchows Archiv 2026; 489:15-26

   This review article provides a comprehensive overview of **iatrogenic and pre-analytic artifacts in pulmonary pathology** that can alter lung morphology and potentially lead to diagnostic errors. The authors emphasize that the lung is particularly susceptible to artifacts because its structure changes dramatically after removal from the body and during surgical handling (a new one: Hook-wire localization artifact with STAS-like changes), fixation, and pathology processing. Awareness of these artifacts is essential to avoid overdiagnosis of malignancy, invasion, STAS, edema, vasculitis, or interstitial lung disease. Very nice review!

2. **Idiopathic pulmonary fibrosis risk loci in East Asian populations mirror those of European populations.** Peljto AL, Furusawa H, Puthenvedu D, et al. Am J Respir Crit Care Med 2026; 212: 1522- 12532

   Accompanying Editorial **Moving towards a global perspective of the genetics of idiopathic pulmonary fibrosis** by Nabunje R and Allen RJ

   Largest GWAS study of IPF in East Asian population (1,026 IPF patients – 359 Japanese, 667 Korean, and 1,723 controls) showed that the major IPF susceptibility genes are similar between East Asian and European populations. In this study, MUC5B was the strongest genetic risk factor (OR 14.36), IPF shared similar pathways - mucociliary dysfunction (MUC5B), telomere biology (TERT), epithelial integrity (DSP), and airway epithelial function (FAM13A). This has significant implications for treatment as the therapeutic targets derived from European studies, likely relevant to East Asian patients.

3. **Antifibrotic therapy and lung cancer risk in patients with idiopathic pulmonary fibrosis: a large retrospective propensity-weighted cohort study.** Kijlertsuphasri S, Petnak T and Moua T. Thorax 2026; 81:672-678

   This retrospective study of 3313 IPF patients (1161 treated and 2152 untreated) aimed at assessing the association between anti-fibrotic therapy and lung cancer risk. The authors used propensity weighing to control for variables, such as smoking, age at diagnosis and on treatment, sex, era in which they were followed (cohort ranging from 2005-2022). Lung occurred in 10 (0.86%) patients of the treated group and 56 (2.6%) in the non-treated. No differences between cancers. Calculated incidence was statistically lower.

   The findings in this study corroborate others that antifibrotic therapy is associated with a significantly lower risk of developing lung cancer in patients with IPF, even after adjusting for baseline differences in accounting for death as a competing risk. The authors hypothesize potential mechanisms such as reduced fibroblast activity, altered tumor –stromal interactions, effects on immune cell population and the anti-angiogenic activity of nintedanib.

Case Report/Correspondence/Editorial

1. **YAP1::TFE3–rearranged inflammatory spindle cell PEComa of the anterior mediastinum in a 5-year-old child: first pediatric case.** Ali RH, Hamdy D, Nasr A, Khalifa N, Agaimy A. Virchows Archiv. 2026;489:225–231.

   This report describes the first pediatric case of YAP1::TFE3-rearranged inflammatory spindle cell PEComa in the mediastinum. This is an emerging molecular subtype of PEComa that has previously been reported predominantly in the lungs and soft tissues of adults.

   Morphologically, it does not look like a PEComa and raises a broad differential diagnosis including IMT, AFH and mostly **clear cell stromal tumor of the lung (CCST-L)** as it also shares the SAME molecular abnormality. Immunostains are helpful for the differential diagnosis, as even this subtype demonstrates myomelanocytic differentiation.

2. **Pulmonary mesenchymal cystic hamartoma with EWSR1::CREM fusion: molecular redefinition and diagnostic implications.** Lei H, Zhang H, Hu J et al. Virchows Archiv. 2026;489: 205–218.

   The authors describe a case of so-called pulmonary mesenchymal cystic hamartoma with an EWSR1::CREM fusion. Their workup was extensive, ruling out several mimickers. Nice review of the literature and thorough discussion on differential diagnosis. However, considering the number of tumors that carry this fusion, not always with a distinctive immunophenotype, the controversy as to the existence of this entity continues.

3. **Meningioma-like infammatory myofbroblastic tumor of the lung with TPM3::ALK fusion.** Akin AE, Durmaz CD, Yilmaz AN et al. Virchows Archiv 2026; 489:233-237

   Case report of a 45-year-old woman with a lung nodule which had an unusual morphology which the authors described as meningothelial like whorls (or what could be described as neural or perineurioma-like). The EMA and PR were negative (SSTR2A was not performed). ALK 5A4 clone and break apart FISH for ALK were negative. ALK 1 clone was positive, and confirmation of ALK rearrangement required RNA based NGS.

4. **Primary pulmonary NFATC2::NUTM2-associated myoepithelial-like neoplasms: two hi-C-detected cases beyond routine targeted NGS and review of the literature**

   Recently described tumor in the lung – see article from July JC by Feng et al in Am J Surg Pathol 2026;50:695–704. Morphologically these tumors do share features of myoepithelial tumors and an immunophenotype charaterized by CK5/6, GATA3, calponin, DOG1 positivity, and negative CK7 and p63, and distinct fusion NFATC2::NUTM2, fusion previously described in salivary gland myoepithelial carcinoma. The authors add another 2 cases to the existing literature, to further argue that these tumors represent a distinct entity in the lung.

5. **Primary adenoid cystic carcinoma of the trachea.** Ooi SH, Wilson A, Clarke L, Rynne M, Chew V. Thorax 2026; 705-706

Case report of a 72-year-old woman found to have a fixed large airway obstruction due to a primary adenoid cystic carcinoma of the trachea. Although this type of tumor is rare, it is the 2nd most common in trachea after squamous cell carcinoma.

6. **Somatic mutation analysis of mucin genes and pathways in idiopathic pulmonary fibrosis.** Letter to the Editor. Seo MK et al. Am J Respir Crit Care Med. 2026; 212: 1628-1630

   The pathogenesis of IPF involves interactions between genetic susceptibility and various exposures and aging-related processes. In this small study of 10 patients of IPF, all never smokers, with matched blood and tissue, the authors describe the potential role of somatic mutations in the *MUC5B* gene in the pathogenesis of IPF.

7. **Cyst-predominant nonfibrotic hypersensitivity pneumonitis mimicking Birt–Hogg–Dubé syndrome.** Shimizu K, Furuya M, Uehara H et al. Virchows Archiv 2026; 489:239-243

   The authors case for HP is slim: childhood exposure to birds, only cysts on imaging, IgG seroly which is not reliable was labeled as borderline and the histology shows mild bronchiolitis with poorly formed granulomas, which appear scant and in one image looks more like airspace foamy histiocytes. And the cysts are simple cysts as seen in BHD syndrome, but the patient had no other stigmata.

Review articles/ Position paper

1. **Pleural Epithelioid Mesothelioma: Pathology and Molecular Update—IASLC Consensus Statement.** Galateau-Sallé F, Beasley MB, Brcic L, Cooper W, Dacic S, Tsao MS, et al. Journal of Thoracic Oncology. 2026;21(7).

   This International Association for the Study of Lung Cancer (IASLC) consensus statement provides an updated review of the histopathology, immunohistochemistry, molecular pathology, cytology, and emerging diagnostic technologies for pleural epithelioid mesothelioma (PEM). The document emphasizes standardized pathologic reporting and the integration of molecular testing into routine diagnostic practice. Not much new....

   Re-emphasizes the current content in the WHO in regard to histology and grading, the use of IHC for the distinction between benign and malignant mesothelial proliferation, with emphasis on HEG1 and Claudin-4 as the most sensitive and specific stains for the distinction between mesothelioma and carcinoma (nice algorithm in Figure 4), discuss rarer gene rearrangements (ALK, EWSR1, MAP3K8), epigenetic alterations as targets (EZH2), and role of AI.

2. **Lung Cancer in Never Smokers: Genetics, Epidemiology, Environmental Exposures, and Distinct Immune Landscape.** Lu J, Shum E, Samstein M et al. JTO 2026; 21

   Excellent review of lung cancer in never smokers. Authors make a great argument on this being a distinct disease entity with unique epidemiology, genetic susceptibility, molecular

drivers, environmental risk factor and immune biology. As the incidence is increasing, particularly among woman in younger patients, representing 10-20% of lung cancers in the United States and 30-40% in East Asia, the current screening strategies which is based solely on smoking history will continue to fail identifying this growing population at risk.

3. **Pulmonary carcinoid tumors and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: Surgical perspectives on a rare and evolving spectrum of lung neuroendocrine disease.** Gawdi R, Furlow P, Colson YL, McNamee CJ. J Thorac Cardiovasc Surg 2026;172:24-31

   Review of DIPNECH from a surgical perspective. The review is exhaustive, covering the progression of DIPNECH spectrum lesions, diagnostic challenges, differences in surgical decision making for carcinoid tumors with or without DIPNECH, nonoperative therapies, follow-up in prognosis, in brief insight into the emerging molecular landscape of DIPNECH.

4. **Pulmonary hypertension associated with interstitial lung disease: a state-of-the-art review.** Raghu G, Shahay S, Price LC et al. Eur Respir J 2026; 68.

   Great review article on pulmonary hypertension secondary to ILD, covering clinical characteristics, detection and diagnostic challenges, prognosis, impact of comorbidities, known pathogenesis and treatment options. Pulmonary hypertension associated with ILD is common, serious, and often under recognized, and early detection is essential. Of note, it is very nicely illustrated with graphs and schematic, useful for presentations.