Thoracic Pathology Journal Club

July 2026 (articles from June 2026 issues)

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ARTICLES FOR DISCUSSION

1. **Lee J, Han YB, Kim S, Kwon HJ, Kim H, Kim K, Chung JH. Differential prevalence and prognostic significance of spread through air spaces according to oncogenic driver mutations in lung adenocarcinoma. J Thorac Cardiovasc Surg 2026;171(6):1320-1331. PMID: 41520721**

Background:

STAS relationship to oncogenic driver status has been characterized only in small, largely unadjusted series. Whether driver-associated differences in STAS prevalence translate into differences in what STAS actually predicts has been essentially unexplored. This large single-institution cohort addresses both prevalence and prognosis.

Methods:

- Retrospective single-institution cohort (Seoul National University Bundang Hospital), 4027 resected primary nonmucinous lung adenocarcinomas, 2011-2022
- Separate survival cohort of 1117 stage IA patients resected January 2011 to April 2020, after excluding synchronous cancer, prior malignancy, incomplete resection and absent follow-up imaging.
- STAS recorded prospectively as "aerogenous spread" by a single experienced pulmonary pathologist since 2008
- Driver testing was selective rather than universal: EGFR 89.9%, ALK 99.1%, KRAS 29.6%, ROS1 3.1%.
- EGFR classified as E19del, L858R or other.
- Prognostic value of STAS assessed as 5-year cumulative incidence of recurrence, compared according to EGFR mutation status in a smaller subgroup of their cohort, 1117 patients Statistics adjusted for invasive size and LVI.

Results:

- STAS present in 40.2% (1619/4027 with prevalence rising with larger tumor size and higher pathologic stage and highly influenced by architecture.
- Dominated by architecture - STAS in 74.8% of tumors containing any micropapillary pattern versus 10.6% without; 96.4% of micropapillary-predominant and 75.9% of solid-predominant versus 1.3% of lepidic-predominant tumors.
- Prevalence of STAS varied markedly by driver: ROS1-rearranged 100% (16/16), ALK-rearranged 80.0%, versus 38.9% ($P < .001$), KRAS-mutated 56.7% (not significant), EGFR-mutated 36.6% versus wild-type 48.4% ($P < .001$).
- Within EGFR-mutated tumors, STAS was less frequent with L858R (30.7%) than exon 19 deletion (41.2%) or other subtypes (40.7%) ($P < .001$); driver-related differences were most pronounced in stage I and <=2 cm tumors
- Differences concentrated in stage I and ≤2 cm tumors; by stage II–IV, 77.4% had STAS regardless of genotype.

- Survival (stage IA, 1117 patients, 49 recurrences overall 5-year CIR 12.2% for STAS-positive versus 2.3% (P < .001).
- No difference by driver group or by EGFR status alone
- STAS was strongly associated with recurrence in the stage IA EGFR-mutant subgroup (CIR 16.9% vs 1.7%, P < .001) but not in EGFR wild-type cases (5.7% vs 3.2%, P = .239).

Strengths: The largest such series, with STAS recorded prospectively rather than reconstructed from reports. All 4027 cases were scored by a single pulmonary pathologist over more than a decade. That maximizes internal consistency

Limitations:

- No data on blocks per tumor, so part of the size–STAS gradient may be detection rather than biology
- No interobserver data or reproducibility
- AIS was excluded but MIA was not
- Doesn't adjust for the surgical-anatomic context in which STAS becomes a recurrence: margin clearance, resection extent (lobectomy versus segmental and wedge resection), although 73.4% had lobectomy, and location (central vs peripheral)
- 19 metachronous lung cancers censored as second primaries so we don't know if they developed a recurrence or not: 19 censored events against ~38–41 informative ones is not a small pool.
- The narrowing of driver differences in stage II–IV is attributed to reduced confounding, and used to suggest that in early-stage disease the driver differences are "real," and that in advanced disease other factors dominate so the driver stops mattering ("reduced confounding"). More plausibly this could be due to:
    - "No difference" is probably just too few patients, not a true absence, **underpowered.**
    - The **ceiling effect**. In stage II–IV, 77.4% of *all* tumors are STAS-positive regardless of driver. When a rate is already pushed up near the top of the scale, there's simply not much room left to show differences between
    - Stage is partly a ***consequence*** of STAS, so splitting by stage distorts the comparison.

- Molecular testing was selective and very uneven.
- The cohort is 59.7% EGFR-mutant, which is a distinctly East-Asian pattern
- The models adjust for age, sex, smoking and invasive size, but **not for histologic pattern** and pattern is the strongest correlate of STAS in the paper (74.8% versus 10.6% by micropapillary presence alone).

Is this a paper about drivers, or a paper about growth pattern wearing a molecular label?

Do the fusions carry independent prognostic weight, or do they act only through the architecture?

Take home message:

- STAS prevalence is strongly genotype-associated — near-universal in ROS1 and ALK, lowest in L858R in small early tumors.
- In stage IA the recurrence risk carried by STAS was confined to the EGFR-mutant subgroup; roughly a fifth of patients (119/551), whose 5-year recurrence risk approaches that of stage IB.
- However, in EGFR-mutant tumors, mostly lepidic/acinar, STAS may simply be flagging the minority with an unsampled micropapillary or solid component — intratumoral heterogeneity and grade, not a distinct evolutionary event.
- The findings in stage II–IV are more plausibly explained by too few patients, a prevalence ceiling, and the fact that dividing by stage is statistically self-sabotaging when STAS itself drives stage.
- Not established: that STAS is prognostically inert in wild-type disease, that the effect is five-fold, or that any of it is independent of architecture.

Wu Q, Lei T. STAS as a potential indicator of divergent evolutionary trajectories in early-stage lung adenocarcinoma. J Thorac Cardiovasc Surg 2026 [Letter to the Editor]

Correspondence on the Lee et al. study above.

- The authors propose that STAS is not a biologically equivalent event across genotypes - intrinsic and early in ALK/ROS1 tumors, but in otherwise indolent EGFR-mutant tumors a marker of passage through an evolutionary bottleneck from a proliferative to a disseminating state.
- Therefore they propose STAS-positive EGFR-mutant stage I as the subset most likely to benefit from adjuvant TKI.

Limitations: All the above for the main paper

- The letter also asserts that invasive capacity is “undoubtedly a prerequisite” for STAS, which is **not** proven.
- Their proposed single-cell RNA-seq of STAS clusters is not feasible. STAS clusters cannot be dissociated out of archival FFPE, nor prospectively enriched.

Take home: a readable hypothesis-generating commentary, but it is hypothesis only

2. Yang Z, Mino-Kenudson M, Lanuti M, Yang CF, Furlow PW. Extent of resection for spread-through air spaces–positive stage IA1-2 non–small cell lung cancer. J Thorac Cardiovasc Surg 2026;171(6):1310-1319.e3. PMID: 41443465.

Background:

Sublobar resection (segmentectomy or wedge) is now an accepted alternative to lobectomy for small peripheral stage IA NSCLC after noninferiority trials, but those trials did not stratify by spread through air spaces (STAS). STAS is an adverse pathologic feature believed to reflect aerogenous tumor spread beyond the main mass, which raises a specific concern: leaving lung parenchyma behind, as in sublobar resection, could leave STAS foci in situ and increase recurrence. Whether STAS-positive early-stage tumors can be treated safely with sublobar resection is therefore unsettled and practically important.

Methods:

- Retrospective single-institution cohort (Massachusetts General Hospital and affiliated hospitals), 445 patients resected February 2018 to January 2022 for primary pathologic stage IA1-2 NSCLC (≤2 cm)
- STAS scored per the Kadota criteria with institutional artifact-exclusion rules, as a binary variable, by 5 pulmonary pathologists reviewing independently (institutional concordance approximately 80%); no central re-review, no STAS grading, no morphologic subtyping, no distance from the tumor edge. Two consensus conferences were held during the study period.
- Recurrence adjudicated at the discretion of the treating thoracic surgeon or medical oncologist with chart-review verification; no protocolized surveillance schedule.
- Multivariable Fine-Gray competing risk models for recurrence (competing with death) and lung cancer-related death (competing with other-cause death), adjusted a priori for invasive tumor size, LVI and high-grade histology.
- 1:1 nearest-neighbor propensity matching on age, %predicted FEV1, %predicted DLCO, LVI, invasive size and high grade; caliper 0.1; SMD below 0.20 taken as balance; doubly robust multivariable Cox model as sensitivity analysis.
- Exploratory: RFS across lobectomy versus segmentectomy versus wedge and anatomic versus nonanatomic resection; sensitivity analyses restricted to patients with at least one hilar N1 station sampled and to NCCN-concordant 3+1 sampling; margin-to-invasive-tumor-diameter ratio among all sublobar resections.

Results:

- **STAS-positive** in 158 of 445 (**35.5%);** median follow-up 48 months (IQR 39-54).
- **STAS-positive tumors were more often high grade** (28.5% vs 8.7%), **larger** by invasive size (12.0 vs 10.1 mm) and more often **LVI-positive** (12.0% vs 5.9%), with higher recurrence overall (8.9% vs 1.7%, $P < .001$).
- Within the STAS-positive cohort: 81 lobectomy, 77 sublobar (31 segmentectomy, 46 wedge). Sublobar patients were older with lower FEV1 and DLCO, but their tumors were smaller (invasive 10.9 vs 13.0 mm) with equivalent LVI and grade.

- In the **STAS-positive cohort, recurrence was significantly more frequent after sublobar resection** (subdistribution HR 7.60; 95% CI 1.85-31.33; P=.005), **with higher lung cancer-specific mortality** (sHR 5.12; 95% CI 1.03-25.62; P=.047).
- Propensity matching (**40 pairs**): OS was similar (5-year 91.5% lobectomy vs 80.3% sublobar, P=.18), but **RFS was significantly worse after sublobar resection** (5-year 88.8% vs 66.1%, P=.042).
- Exploratory analysis: **inferior RFS with wedge resection (P=.024) but not segmentectomy (P=.324) versus lobectomy.**
- At least one hilar N1 station was sampled in 87.7% of lobectomy versus 44.2% of sublobar cases; NCCN-concordant 3+1 sampling in 39.5% versus 23.4%.
- Margin-to-tumor ratio 1 or more versus less than 1: no difference in STAS-positive tumors (13.7% vs 19.2%, P = .529) but a large difference in STAS-negative tumors (0.8% vs 12.1%, P < .001).

Limitations:

- One reader per case with ~80% concordance means the exposure variable is misclassified in roughly one case in five.
- No extent, no distance from the tumor edge, no morphologic subtype - the features with the best evidence for a prognostic gradient (semiquantitative STAS extent predicts outcome after sublobar resection: Pathobiology, PMID 35947971).
- Hilar N1 sampling was 87.7% in the lobectomy arm versus 44.2% in the sublobar arm.
- The paper asserts a 'stepwise oncologic benefit with increasing extent of resection', singles out wedge resection in its title, and offers segmentectomy as a reasonable intermediate. Crude recurrence after segmentectomy is if anything marginally HIGHER than after wedge.
- RFS counts death from any cause as an event. The sublobar arm was selected for being older, with lower FEV1 and DLCO and more ECOG 1 patients - selected, in other words, for the population that dies of something other than lung cancer.
- The authors float completion lobectomy on the basis of three excluded patients.

Take home message:

- The authors conclude that in STAS-positive stage IA1-2 NSCLC, sublobar resection - especially wedge - is associated with substantially worse recurrence-free survival than lobectomy and therefore wedge resection should not be performed
- However the entire signal rests on 14 recurrences and the sublobar arm was staged far less thoroughly, so perhaps STAS marks a tumor needing proper nodal assessment and closer follow-up rather than one that necessarily needs more parenchyma removed.

  Discussion point: should we be doing intraoperative STAS assessment?

Jin H, Zu P, Liu W. Statistical and anatomical refinements for spread-through-air-spaces–positive non–small cell lung cancer resection analysis. J Thorac Cardiovasc Surg 2026;171(6):e149. doi:10.1016/j.jtcvs.2026.01.019. [Letter to the Editor]

Correspondence on the Yang et al. study above. Two objections: that 14 recurrence events cannot support a stable four-covariate Fine-Gray model, and that the propensity model omitted tumor centrality and consolidation-to-tumor ratio, both determinants of resection choice. The authors propose Firth penalized regression for the competing risk analysis and inverse probability weighting incorporating centrality.

Take home: the statistical criticism is correct and but the proposed remedies do not work - Firth penalization cannot create information from 12 events, and centrality was never recorded in the source dataset.

3. Lu J, Zhang L, Zhao S, Ren Y, Wu C, Xie H. The role of rapid IHC in elevating STAS diagnostic accuracy during intraoperative frozen section for lung adenocarcinoma. Histopathology 2026;88(7):1395-1404. PMID: 41652310.

Background: Intraoperatively, STAS is increasingly used to help choose between sublobar resection and lobectomy for small peripheral tumors, which places real weight on a determination made under the time pressure and reduced quality of frozen section. On frozen H&E, small clusters of tumor cells within air spaces are easy to miss or to confuse with alveolar macrophages, reactive pneumocytes, or displaced (knife-carried) cells. This study asks: does adding a rapid cytokeratin (AE1/AE3) immunostain to frozen H&E improve the accuracy and reproducibility of intraoperative STAS assessment?

Methods:

- 153 patients undergoing resection for lung adenocarcinoma.
- Three pathologists of varying experience independently scored STAS on frozen section using (a) H&E alone and (b) H&E combined with rapid AE1/AE3 IHC.
- Postoperative paraffin sections served as the gold standard.
- Endpoints: sensitivity and specificity, intra- and interobserver agreement (kappa), diagnostic time, and causes of misdiagnosis.

Results:

- Mean sensitivity rose from 73.7% to 87.8% and specificity from 85.5% to 89.9% with the addition of rapid IHC, across all experience levels.
- Mean intraobserver agreement improved from kappa 0.644 (83.9%) to 0.907 (95.9%).
- Mean interobserver agreement improved from kappa 0.485 (65.0%) to 0.671 (77.2%).
- Average diagnostic time decreased, without significantly extending overall frozen-section processing; residual misdiagnoses were attributed mainly to sparse STAS clusters, macrophage mimics, and artifact.

Take home message: Adding a rapid keratin stain to frozen H&E meaningfully improves the sensitivity and reproducibility of intraoperative STAS detection at little time cost, which could make intraoperative STAS a more reliable input to the sublobar-versus-lobar decision. The interobserver gains are real but land only at moderate levels, and IHC does not resolve the fundamental problem that keratin also lights up displaced or artefactual clusters; single-center data warrant multicenter validation.

4. Feng L, Liu Q, Liu X, Wang S, Li J, Han Y, Mu X, Wang Y, Jiang J, Wu C, Han X, Zhu S, Zhang F, Tian J, Wang Z, Zhang W, Gong L. NFATC2::NUTM2 Fusion Defines a Novel Primary Pulmonary Epithelial Tumor With a Distinctive Immunophenotype. Am J Surg Pathol 2026;50(6):695-704. PMID: 41821426.

Background: NUT carcinoma (NUTM1) is well established, and a widening group of NUTM2-rearranged epithelial and mesenchymal neoplasms has emerged across anatomic sites. In the lung, a single tumor with an NFATC2::NUTM2B fusion was reported only recently, leaving the morphologic spectrum, immunophenotype, and behavior of NFATC2::NUTM2-driven tumors essentially uncharacterized. Because these tumors are rare, cytologically bland, and lack a signature H&E appearance, they are easily misfiled as adenocarcinoma, sclerosing pneumocytoma, a salivary-type tumor, or a metastasis. This series pairs a small case cohort with integrated genomics to define the entity

Methods:

- Integrated genomic analysis identifying 6 primary pulmonary tumors with recurrent NFATC2::NUTM2A/E fusions; single institution.
- Cohort: 4 females, 2 males; median age 53; all presented as incidentally detected peripheral lung nodules.
- Morphologic review of architecture and cytology.
- Immunohistochemistry panel: CK5/6, GATA3, calponin, EMA, DOG1, p63.
- High-throughput chromosome conformation capture (Hi-C) for structural variants; RNA sequencing for fusion transcripts; electron microscopy in 1 case.

Results:

- Uniform morphology: monotonous epithelioid cells arranged in cords, nests, and trabeculae within a prominent desmoplastic stroma.
- Consistent immunophenotype across all tumors: CK5/6+, GATA3+, calponin+, EMA+, DOG1 with a perinuclear dot-like pattern, and p63-.
- Hi-C demonstrated NFATC2::NUTM2E structural variation in all 6 cases.
- RNA-seq detected fusion transcripts in 5 of 6 (NFATC2::NUTM2A n=2; NFATC2::NUTM2E n=3); ultrastructure in the examined case suggested epithelial differentiation.
- All patients remained disease-free after complete resection (median follow-up 24 months; range 9-41).

Limitations:

- Median 24-month follow-up is short for an indolent-appearing tumor - "benign" is premature on this data.
- Only 6 cases from one Chinese institution - enough to define the immunophenotype and fusion spectrum, but far too few for prognostic claims, and incidence/geographic skew is unknown.

Take home message: NFATC2::NUTM2 fusions define a distinct, apparently indolent primary pulmonary epithelial tumor with a reproducible immunophenotype. The most useful practical signature is a bland, monotonous epithelioid peripheral tumor in desmoplastic stroma that is CK5/6+/GATA3+/calponin+/EMA+/p63- with DOG1 perinuclear dot-like staining; when that pattern appears, pursue RNA-based fusion testing rather than defaulting to adenocarcinoma or metastasis.

ARTICLES FOR NOTATION

Neoplastic

Xu K, Tan B, Liang R, Liang J, He Z, He J, Zhong Y, Hu X, Lei K, Lu H, Zhang J, Lin H, Wang M. DNA methylation biomarkers-based method for the differential diagnosis of multiple lung cancers. Lung Cancer 2026;216:109415. doi:10.1016/j.lungcan.2026.109415.

Methylome-seq on 83 specimens from 43 multiple-lung-cancer and 7 pulmonary brain metastasis patients. Rather than diagnose metastasis directly, the authors built a similarity classifier: pulmonary brain metastases were used as a proxy for intrapulmonary metastasis (IPM) and indolent AIS/MIA lesions as a proxy for separate primaries (SPLC). K-means clustering split specimens into a metastasis-like and a primary-like cluster; a 31-region random forest (the DM method) then assigns new specimens, and a patient with any cluster-1 specimen is called DM-IPM. DNMT3B was higher by IHC in the DM-IPM group, and DNMT3A/DNMT3B siRNA knockdown reduced migration and invasion in A549 and H1299.

Limitations: The reference groups carry the whole method and both are questionable. A brain metastasis has completed the full metastatic cascade and adapted to a different organ, so its methylome reflects brain-microenvironment colonization, not intrapulmonary spread. The validation is also partly circular: cluster 1 was defined by containing the brain-met specimens, then 'validated' by showing it tracks with larger size and worse PFS, but those same clinical features helped drive the clustering.

Take home: a genome-wide methylation classifier sorted multiple-lung-cancer lesions by epigenetic resemblance to a brain metastasis versus an indolent nodule.

Saiki M, Inoue T, Takusagawa K, Homma K, Furuya S, Shimamura S, Omori C, Ide S, Hoshino Y, Uchida Y, Yamaguchi Y, Ikemura S, Kondo T, Soejima K. Association of tumor CD73 expression with clinical outcomes in small cell lung cancer treated with first-line chemo-immunotherapy. Lung Cancer 2026;216:109425. doi:10.1016/j.lungcan.2026.109425.

Single-center retrospective series of 36 SCLC patients receiving first-line platinum plus atezolizumab or durvalumab, with CD73 scored by IHC (H-score) and dichotomized as any membranous staining versus none. CD73 was positive in 75%; median PFS was 4.0 versus 7.9 months for CD73-positive versus CD73-negative tumors (p=0.048), with CD73 positivity independent on multivariable analysis (HR 3.19, 95% CI 1.16-8.73). No association with ASCL1/NEUROD1/POU2F3 subtype.

Limitations: Only 9 CD73-negative patients. Note CD73 positivity was defined as an H-score of 1 or more, i.e. any staining at all, which is a permissive threshold that will not reproduce across labs without a defined clone and protocol.

Take home: CD73 IHC may separate patients who will not benefit from ICI-containing regimens. It is a predictive rather than prognostic marker - the ICI-naive public cohort showed no survival difference.

Murata S, Kashima J, Horinouchi H, Kishikawa S, Masuda K, Shinno Y, Okuma Y, Yoshida T, Goto Y, Yamamoto N, Watanabe S, Matsumoto Y, Okuma K, Yatabe Y. Comparative analysis

of therapeutic target protein expression in de novo and transformed small cell lung carcinomas using paired biopsy samples. Lung Cancer 2026;216:109418. doi:10.1016/j.lungcan.2026.109418.

Paired diagnosis and progression biopsies from 15 SCLC patients (9 de novo, 6 transformed), stained for DLL3, TROP2, B7-H3, B7-H4, MET and HER2, with a change of 100 or more H-score points called significant. In transformed SCLC, DLL3 rose in 6/6 while TROP2 and HER2 fell; in de novo SCLC, DLL3 fluctuated in 3/9.

Limitations: The 100-point H-score threshold is arbitrary and very large; several changes the authors call stable (e.g. TROP2 rising in 4/9 de novo cases) would be called real by most other scoring conventions.

Take home: target expression is not stable across a treatment course. If an ADC or bispecific is being considered, the progression biopsy, not the diagnostic block should be used. In transformed SCLC, TROP2 and HER2 might be the wrong targets to pick.

Gallagher TJ, Kokot NC, Lopez J, Rodriguez E, Udelsman BV, Wightman SC, Atay SM, Harano T, Rosenberg GM, Nieva JJ, Kim AW. Association of cannabis use and lung cancer: a retrospective cohort study. Lung Cancer 2026;216:109421. doi:10.1016/j.lungcan.2026.109421.

Retrospective cohort using 20 years of de-identified electronic medical record data from 67 U.S. healthcare organisations, comparing adults with cannabis use disorder to a matched comparison group after propensity-score matching on demographics and lung-cancer risk factors (n=149,632 per group). Cannabis use disorder was associated with a higher risk of subsequent lung and/or bronchus cancer (RR 3.87, 95% CI 3.43–4.38), with the elevation persisting at 1 and 5 years and seen across histologies — small cell RR 2.70, adenocarcinoma RR 2.54, squamous RR 2.90.

Limitations: Paired with the Topkan and Selek letter under Commentaries and Letters — read the two together. The exposure is a coded diagnosis of cannabis use disorder, not measured cannabis or tobacco dose, so despite propensity matching the residual confounding by smoking is severe; the effect size is far below tobacco's and rises with co-use, which is what you would expect if tobacco were doing the work. The cross-histology RRs (adenocarcinoma included) argue mildly against a purely smoking-mediated effect but do not settle it.

Take home: a large administrative-data signal linking cannabis use disorder to lung cancer, but the exposure is an ICD code for use disorder, not quantified smoking, and residual tobacco confounding is the obvious alternative explanation.

Topkan E, Selek U. Cannabis use disorder and lung cancer risk: methodological considerations in interpretation. Lung Cancer 2026;218:109497. doi:10.1016/j.lungcan.2026.109497.

Letter to the Editor on the Gallagher et al. cohort. Three objections: the exposure is an ICD-coded diagnosis of cannabis use disorder rather than measured cannabis exposure; residual tobacco confounding is likely severe, since the cannabis effect size is far below tobacco's within the same data and rises with co-use; and defining the index date as the first coded diagnosis of use disorder rather than the onset of exposure introduces time-anchoring bias.

Take home: a well-aimed methodological critique. The association is real in the data but probably inflated by unmeasured smoking and by how exposure and follow-up time were defined. The authors call for dose-response and tobacco-adjusted analyses before any causal reading.

Ghani A, Seyoum N, Eaton DB Jr, Malone S, Chang SH, Yan Y, Baumann AA, Thomas TS, Schoen MW, Tokaz MC, Tohmasi S, Rossetti N, Patel MR, Brandt WS, Kreisel D, Nava RG, Meyers BF, Kozower BD, Puri V, Heiden BT. Characterizing phantom lymph node collection during curative-intent resection of non-small cell lung cancer. J Thorac Cardiovasc Surg 2026;171(6):1332-1338.e3. doi:10.1016/j.jtcvs.2026.01.013.

Retrospective Veterans Health Administration cohort of 2972 patients resected for clinical stage I NSCLC between 2018 and 2024, with manual review of a randomly selected 50% of pathology reports, quantifying phantom lymph node collection — tissue submitted intraoperatively as nodal that proves non-nodal on microscopic examination. Phantom collection occurred in 327 patients (11.0%), usually at a single station (85.3%) and most often at station 9 (27.1% of phantom specimens). It was more likely with lower-lobe tumors (aOR 1.45, 95% CI 1.13-1.88) and less likely with NCCN-concordant sampling (aOR 0.56, 95% CI 0.43-0.74), but was not independently associated with overall survival (aHR 0.96, 95% CI 0.77-1.19) or recurrence (aHR 0.86, 95% CI 0.68-1.08). Only 40.7% of the cohort met the NCCN standard of at least three N2 and one N1 station.

Limitations: A phantom collection is defined by what we sign out, which makes this partly a pathology metric. A station submitted as nodal and reported as fibroadipose tissue counts as a phantom, but that outcome conflates surgeon sampling error with failure to find a small node during grossing - the authors concede as much and cite Osarogiagbon et al. (Ann Diagn Pathol 2014;18:136-9), who recovered nodal material from tissue discarded after routine examination. Station 9 accounts for 27.1% of phantom specimens, which is precisely the pulmonary ligament fat in which a 2 mm node is easiest to miss on a single section, and stations 8 and 9 together account for a further large share.

Take home: an outcome defined entirely by the pathology report. It carries no prognostic weight in stage I disease, but it accounts for a measurable share of guideline discordance — had the phantom specimens contained nodal tissue, 5.7% of the NCCN-discordant cases would have met the standard.

Raymond DP. Commentary: is this phantom a menace or meaningless? J Thorac Cardiovasc Surg 2026;171(6):1339-1340. doi:10.1016/j.jtcvs.2026.02.002. [Invited commentary]

Invited commentary on the Ghani et al. phantom lymph node study. Raymond is unsurprised that phantom collection carried no survival penalty in a predominantly stage I cohort, and redirects attention to the 40.7% NCCN sampling concordance, adding inadequate systems and culture as a third driver of guideline discordance alongside technical failure and simple non-attempt. He describes a program reaching over 90% compliance through a surgeon champion, a quality database that tracks the metric, and review of every failed case at monthly morbidity and mortality rounds.

Take home: quality-improvement audit

Barlesi F, Ahn JS, Solomon BJ, Nishio M, Dziadziuszko R, Lee DH, Lee JS, Zhong W, Horinouchi H, Mao W, Hochmair M, de Marinis F, Migliorino MR, Bondarenko I, Xu T, Bara I, Ding B, Ngiam C, Petric P, Wu YL. Disease characteristics and treatment outcomes in patients with resected early-stage ALK-positive non-small cell lung cancer from the randomized ALINA trial. Lung Cancer 2026;216:109385. doi:10.1016/j.lungcan.2026.109385.

Exploratory subgroup analysis of the phase III ALINA trial (NCT03456076), which randomized patients with resected stage IB (≥4 cm)–IIIA ALK-positive NSCLC to adjuvant alectinib 600 mg twice daily for 24 months versus four cycles of platinum-based chemotherapy. Most patients had tumours ≤3 cm (57.4%), stage IIIA disease (52.1%) and N2 nodal status (50.6%). The disease-free survival benefit of alectinib over chemotherapy was maintained across every surgical and staging subgroup examined — by AJCC/UICC 8th-edition stage, nodal status, tumour size and other surgical characteristics — consistent with the primary result and the reported CNS-DFS benefit (HR 0.22, 95% CI 0.08–0.58).

Take home: the adjuvant alectinib benefit in resected ALK-positive NSCLC holds regardless of stage, nodal burden or tumour size. Reliable ALK testing on every resected non-squamous NSCLC is now what gates access to an adjuvant therapy with a large DFS effect. A missed ALK rearrangement on a resection specimen is no longer only a metastatic-setting problem.

Pasello G, Pigato G, Mulargiu C, Ferrarini F, Pezzuto F, Schiavon M, Ferro A, Scattolin D, Dal Maso A, Frega S, Bonanno L, Calabrese F, Dell'Amore A, Guarneri V, Indraccolo S. Dissecting the prognostic role of metabolic markers in lung neuroendocrine tumors: the MONET study. Lung Cancer 2026;216:109404. doi:10.1016/j.lungcan.2026.109404.

Single-centre translational study of 49 resected lung neuroendocrine tumours (11 typical carcinoid, 19 atypical carcinoid, 19 LCNEC) profiled by standardized IHC and quantitative digital image analysis for glycolysis (MCT1, MCT4, CD147), amino-acid transport (SLC1A5, SLC7A5, GLS) and fatty-acid synthesis (FAS, ACC) markers, scored by H-score and dichotomized. LCNEC showed marked upregulation of glycolytic and amino-acid transport markers versus carcinoids; fatty-acid markers were uniformly low. High MCT1 and SLC7A5 predicted shorter OS, and high MCT1 and CD147 shorter RFS, with MCT1 independently prognostic for RFS on multivariable analysis. A subset of atypical carcinoids with elevated glycolytic/amino-acid markers showed LCNEC-like outcomes independent of Ki-67.

Limitations: 49 tumours across three grades leaves roughly 11–19 per subtype, enough for a signal, not for the multivariable RFS claim on MCT1.

Take home: a metabolic immunophenotype, mostly MCT1, stratifies lung neuroendocrine tumours and flags a high-risk, LCNEC-like subgroup of atypical carcinoids that Ki-67 alone misses. Exploratory and small, but it points at an add-on stain that could sharpen a notoriously reproducibility-limited grading problem, and at druggable metabolic axes (MCT1, SLC7A5).

de Jager VD, van der Ree M, Cajiao Garcia B, Kuijpers C, van der Wekken AJ, van Kempen LC, Schuuring E, Willems SM. Large language model-based approach for low-cost, rapid and accurate automated extraction of predictive biomarker testing results from Dutch pathology reports. Virchows Arch 2026;488(6):1283–1291. doi:10.1007/s00428-025-04337-6.

Development and validation of a large language model to extract EGFR and KRAS testing status, NGS use and specific mutations from free-text NSCLC pathology reports drawn from the Netherlands Cancer Registry and the nationwide pathology databank (Palga). Trained and tested on 3887 metastatic NSCLC patients diagnosed in 2019 (test-set micro-F1 ≥0.98 for all variables), then applied to 4122 patients diagnosed 2022–2023 with manual annotation of 410 cases (micro-F1 ≥0.95). No manually annotated positive molecular result was missed, and standardized mutation notation was correct in 98.7% (KRAS) and 100% (EGFR). Across the 2022–2023 cohort the model estimated testing rates of 88.1% (KRAS) and 86.4% (EGFR), with positive results in 40.5% and 11.5% of those tested.

Limitations: The pathology-facing message is about report structure, not the model: extraction accuracy is a downstream measure of how consistently we phrase biomarker results. Two caveats for the table - this is EGFR/KRAS only (categorical, well-templated variables) and single-country, so F1 >=0.95 will not transfer to messier free text or to markers reported as continuous scores; and 'no positive result missed' is reassuring but the denominator that matters clinically is the rare, awkwardly-worded positive, which 410 annotated cases may under-sample.

Take home: an LLM can read free-text biomarker reports at near-perfect accuracy and turn them into structured registry data - useful for auditing guideline adherence and building retrospective cohorts without manual curation (but see limitations)

Takata S, Horie M, Miyabe K, Ito Y, Nakatani Y, Kudo-Asabe Y, Ishida H, Yamada S, Goto A, Kumanogoh A, Shintani Y, Morii E, Yachida S, Maeda D. Thymic cyst: a clinicopathological, immunohistochemical, and molecular study of 36 cases focusing on squamous- and ciliated-type epithelium. Hum Pathol 2026;172:106109. doi:10.1016/j.humpath.2026.106109.

Clinicopathologic, immunohistochemical and targeted-NGS study of 36 resected primary thymic cysts, plus 15 occult cystic lesions (OCLs) associated with thymic epithelial tumours. Morphology separated two dominant types: squamous/cuboidal (SC-type, n=18) and ciliated columnar (CC-type, n=15), with rare mucinous and mixed cysts. All were CK7-positive; SC-type showed linear-luminal CK7 (100% vs 40%), full-layer HMWCK (CK34βE12; 78% vs 6.7%) and CK13 (70.6% vs 21.4%) more often than CC-type, and was more frequently multilocular (55.6% vs 6.7%), larger, and of lower CT attenuation. BRAF VE1 immunostaining highlighted ciliated cells (a known cross-reactivity with axonemal dyneins). Targeted sequencing of 161 genes found no pathogenic somatic mutations, including no TP53. Most OCLs were SC-type (13/15).

Take home: BRAF VE1 is not showing a BRAF mutation here, it cross-reacts with axonemal dyneins and simply marks ciliated cells. Thymic cysts sort into two reproducible immunophenotypes, a squamous/cuboidal type that is larger, multilocular and low-attenuation, and a smaller ciliated type, and the absence of any driver mutation on NGS (no TP53) supports treating them as non-neoplastic rather than as low-grade thymic neoplasia. Practically,

CK7/HMWCK/CK13 plus BRAF VE1 help type the lining, and SC-type predominance among occult cystic lesions is worth remembering when a cyst accompanies a thymic epithelial tumour.

Case reports and clinical images

McGann KC, Holmes HM, Pinkerman R, Hartzell C, James SD, Grogan EL, Demarest CT. Head and neck dystonia with a posterior mediastinal mass. Chest 2026;169(6):e193-e198. doi:10.1016/j.chest.2025.12.042.

A 65-year-old man with years of stable right apical paraspinal mass and progressive blepharospasm, ptosis and cervical dystonia, managed for presumed idiopathic Parkinson syndrome. Robot-assisted thoracoscopic resection showed a mass arising from the T1 sympathetic chain; histology showed Schwannian stroma with intermixed mature ganglion cells, diagnostic of ganglioneuroma. Symptoms improved markedly after resection.

Take home: a benign posterior mediastinal neuroblastic tumor abutting the sympathetic chain can produce a florid neurologic syndrome

Qin X, Zeng L, Huang S, Zhao J, Deng Y, Sun L. A 13-year-old boy with dyspnea, pleural effusion, and bone lesions. Chest 2026;169(6):e181-e185. doi:10.1016/j.chest.2025.12.014.

Hemorrhagic chylothorax with sternal and vertebral lytic lesions in a 13-year-old, diagnosed as kaposiform lymphangiomatosis on ultrasound-guided biopsy of a superficial inguinal lesion. Histology showed clusters of bland spindled cells adjacent to irregularly dilated D2-40-positive lymphatic channels with Ki-67 under 1%. Kaposiform lymphangiomatosis (KLA) is a rare, infiltrative lymphatic anomaly often involving the mediastinum, pleura, spleen, and bone. This process disrupts normal lymphatic architecture, leading to severe hemorrhagic effusions and a complex coagulopathy. The differential diagnosis includes generalized lymphatic anomaly and malignancies such as lymphoma. Managed supportively with prophylactic low-molecular-weight heparin; family declined sirolimus and NRAS testing. Well at nearly 3 years despite persistent imaging abnormalities.

Take home: the diagnostic features of KLA are focal, so a small biopsy can read as negative. Thromboelastography showed marked hypercoagulability with fibrinolysis shutdown despite an overtly hemorrhagic effusion, inverting the usual reading of a prolonged PT and aPTT and important diagnostic clue. Note also that the pleural fluid NGS detected EBV sequences with a negative plasma EBV.

Dubey I, Wadhwa N. Dysphagia lusoria. N Engl J Med 2026;394(21):e50. doi:10.1056/NEJMicm2600585.

Images in Clinical Medicine. A 44-year-old man with cerebral palsy and a 4-year history of choking on solids, unresponsive to a proton-pump inhibitor and texture modification. Endoscopy showed a pulsating cordlike structure narrowing the upper oesophagus; CT

demonstrated an aberrant right subclavian artery arising as the fourth branch of the aortic arch and coursing behind the oesophagus. Diagnosis: dysphagia lusoria, managed non-surgically with continued swallowing therapy.

Take home: The aberrant right subclavian artery (arteria lusoria) is a vascular anomaly and a retro-oesophageal, posterior-mediastinal structure that can mimic a mass on imaging.

Luo Y, Dai L, Wang X, Xie J, Wang G, Zhang R, Guo S. An unusual etiology of hemoptysis in an infertile female. Am J Respir Crit Care Med 2026;212(6):1334–1336. doi:10.1093/ajrccm/aamaf130.

Images in Pulmonary Medicine. A 44-year-old infertile woman with isolated haemoptysis. CT angiography showed right lung hypoplasia with anomalous right pulmonary venous drainage into the inferior vena cava (scimitar vein) and an aberrant systemic artery from the celiac axis supplying the right lower lobe, which formed the pathologic vascular network responsible for the bleeding; gynaecological ultrasound showed congenital absence of the uterus. Embolisation stopped the bleeding with no recurrence at >1 year. Whole-genome sequencing found no MYRF mutation but two candidate variants (TAGLN, KISS1). Non-bronchial systemic supply that bronchial-artery embolisation alone would miss.

Take home: systemic (non-bronchial) arterial supply to the lung is a treatable, embolisable cause of haemoptysis, and scimitar syndrome is the anatomic setting here

Lin JX, Yin K, Yan LX, Zhu Y, Xu BF, Sun YL, Wu YL, Tu HY. First case report of transformation of adenocarcinoma to adenosquamous carcinoma with giant-cell carcinoma harboring HER2 mutation after zongertinib (BI 1810631) resistance. Lung Cancer 2026;216:108912. doi:10.1016/j.lungcan.2026.108912.

Single case. A 52-year-old female never-smoker with stage IV lung adenocarcinoma harbouring an HER2 exon 20 Y772_A775dup mutation (with concurrent NF1, RB1 and TP53 mutations and AKT2 copy gain). After first-line chemo-immunotherapy she achieved a confirmed partial response to the covalent HER2 inhibitor zongertinib (Beamion LUNG-1) lasting 20 months. At progression, rebiopsy showed histologic transformation to adenosquamous carcinoma with giant-cell features and a PD-L1 switch from undetectable to 80%; genomic profiling retained the original mutations and added a MAP3K1 mutation, HER2 amplification and TERT amplification. Third-line BC3195, a CDH3-targeted antibody-drug conjugate, produced a partial response at reporting.

Take home: the first described zongertinib-resistance mechanism in HER2-mutant NSCLC couples histologic transformation (adenosquamous with giant-cell change) to acquired HER2 amplification and a striking PD-L1 switch — a reminder that HER2-TKI resistance can be morphologic, not just mutational. Post-progression tissue, not liquid biopsy alone, is what catches this. illustration of why morphology still matters at progression: transformation to adenosquamous/giant-cell histology would be invisible on ctDNA, and the PD-L1 0%→80% switch changes downstream options. Note the baseline TP53/RB1 co-mutation, the same high-risk background tied to small-cell and squamous transformation on EGFR TKIs; whether HER2-TKIs share that transformation biology is the open question this raises.

Kashizaki F, Oouchi M, Watanabe S, Shonai S, Orii R, Takeuchi K, Konishi K, Suematsu N. Lung cancer with MET exon 14 skipping mutation presenting with a crazy-paving appearance. Am J Respir Crit Care Med 2026;212(6):1156–1157. doi:10.1093/ajrccm/aamag036.

Images in Pulmonary Medicine. An 88-year-old man with minimal smoking history and an incidental left upper lobe ground-glass opacity, a 35 mm ill-defined lesion with a crazy-paving appearance in S3a that grew slightly over six months, with only mild FDG uptake distributed along the pulmonary veins. Left upper lobectomy showed papillary proliferation of atypical epithelial cells along thickened alveolar septa, with intra-alveolar haemorrhage, hemosiderin-laden macrophages and fibrous intimal thickening of pulmonary vessels; IHC was CK7- and TTF-1-positive with PD-L1 TPS ~10%, and a MET exon 14 skipping mutation. Staged pT2aN0M0 (IB); no adjuvant therapy and no recurrence at 6 months.

Take home: MET exon 14-skipping NSCLC usually presents as a rapidly growing solid mass, so this crazy-paving/ground-glass presentation is atypical. The radiographic crazy-paving corresponds histologically to lepidic/papillary tumour along septa plus intra-alveolar haemorrhage, a reminder that the pattern is non-specific and that even a low-grade-looking GGO can be a targetable-driver NSCLC warranting molecular testing.

Reviews

Lieu A, Mah JK, Vinh DC, Qureshi ST. Pulmonary fungal infections in the immunocompetent host. Chest 2026;169(6):1506-1523. doi:10.1016/j.chest.2025.12.041. [Review. PMID not confirmed at time of writing.]

Timely article due to the changing epidemiology attributed to climate-driven range expansion of the dimorphic fungi, post-influenza and post-COVID aspergillosis, and modern ICU practice. Covers Aspergillus (invasive, chronic and allergic bronchopulmonary), Mucorales, Scedosporium after near-drowning, Histoplasma, Blastomyces, Coccidioides and Cryptococcus, with a table of clinical syndromes, exposures and imaging findings and a figure setting out the noninvasive and invasive diagnostic options for each organism.

Septate acute-angle hyphae are indistinguishable across Aspergillus, Fusarium, Scedosporium and the other hyalohyphomycetes - speciation depends on MALDI-TOF or ITS/28S sequencing. Mucorales hyphae are fragile and are destroyed by grinding or homogenisation, so tissue for fungal culture should be minced. And the laboratory must be told when a dimorphic fungus is in the differential, because culture of Histoplasma, Blastomyces and Coccidioides carries a real laboratory-acquired infection risk and MALDI-TOF is explicitly not recommended outside containment.

Take home: the noninvasive assays perform poorly in this population — serum galactomannan is 22.6% sensitive for chronic pulmonary aspergillosis against 85.7% for BAL, serum Aspergillus PCR is 63% sensitive in nonneutropenic patients, and neither galactomannan nor beta-D-glucan detects Mucorales at all. Tissue therefore remains the reference standard, and the histologic call carries more weight here than it does in the classically immunocompromised host.

Baker JR, Beaulieu D, Avci E, Huang E, Eickelberg O, Meiners S, Savai R, Lehmann M, Königshoff M. Hallmarks of the ageing lung: 10 years later. Eur Respir J 2026;67(6):2501272. doi:10.1183/13993003.01272-2025.

Invited review marking the 10th anniversary of the original 'hallmarks of the ageing lung', updating how cellular and molecular ageing drives COPD, idiopathic pulmonary fibrosis and lung cancer. Nearly all recognised ageing hallmarks are now implicated, with extracellular-matrix dysregulation — first proposed as a lung-specific hallmark in 2015 — now central. Environmental exposures (cigarette and wildfire smoke) accelerate change through oxidative stress and cellular senescence. In lung cancer, ageing contributes genomic and epigenetic alterations, immune evasion and therapeutic resistance; extracellular vesicles and the microbiome are emerging themes, and early trials are testing senolytics.

Take home: a synthesis review, useful as background on why age is the dominant risk factor across COPD, IPF and lung cancer, and on senescence as an emerging therapeutic target.