PULMONARY PATHOLOGY JOURNAL CLUB
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Discussion articles

Calabrese F et al. International society for heart and lung transplantation scientific statement on pulmonary antibody-mediated rejection and proposed graft, antibody, and pathology (GAP) definition. J Heart Lung Transplant 2026; 45:1357-1374.

Purpose: (1) Update the 2016 ISHLT definition of antibody-mediated rejection (AMR) to improve clinical outcomes, and (2) Propose an alphanumeric classification for AMR

Methods:

- ISHLT advanced lung failure and transplantation interdisciplinary network assembled AMR workgroup comprised of 38 members with expertise in the field (6 pathologists)
- Modified Delphi method – 3 rounds of anonymized questionnaires: exploratory phase → draft statement development and voting using eleven-point Likert scale (-5 = strongly disagree; 5 = strongly agree) → final voting including initial scores with mean ± SD
- Consensus agreement defined as mean score ≥2.5 or ≤ -2.5 with SD not crossing zero

Results:

- GAP definition
    - Graft dysfunction: new or worse respiratory symptoms, >10% decline in spirometry from baseline, new or worsening hypoxemic respiratory failure, or new or worsening imaging abnormalities
    - Antibodies – type and characteristics
    - Pathologic findings: diffuse alveolar damage, acute fibrinous and organizing pneumonia, capillary injury, endothelialitis, microthrombi, septal widening (e.g. edema)
    - AMR can co-exist with other graft injury, including acute cellular rejection (ACR), obliterative bronchiolitis, and infection
- Standardized nomenclature proposed to capture core and non-core (i.e. supplemental information not routinely performed at many centers) elements (see Table 1)
    - Pathology core: **P0**, histologic findings of AMR not present; **P1**, histologic features of AMR present; **P2**, feature of AMR + ACR, chronic rejection, or lymphocytic bronchiolitis also present
    - Pathology *non*-core: Y, p-S6RP immunostain negative; p-S6RP immunostain positive
    - Complement activation *non*-core: C0, C4d immunostain negative; C1, C4d immunostain positive
    - Examples of reporting provided in clinical scenarios
- p-S6RP has been shown to improve diagnostic accuracy of AMR, but it is not yet available at many centers, so this immunostain is a non-core element
- Routine staining for C4d not recommended on surveillance biopsies

Take-home message: The GAP definition for AMR requires a multi-disciplinary approach, so I wonder how this might change our own practices as we implement alphanumeric nomenclature to diagnosis and monitoring of patients with AMR.

Abolfathi H et al. Integrating histologic descriptors into the ninth edition TNM staging improves prognostic stratification of lung adenocarcinoma. J Thorac Oncol 2026; 21:103895.

Purpose: Evaluate the prognostic value and incremental contribution of various histologic parameters to enhance risk stratification within the framework of our current (9th ed) TNM staging system

Methods:

- Study limited to stage I to III invasive nonmucinous adenocarcinomas with R0 resections
  - Discovery cohort: 1139 patients (Institut Universitaire de Cardiologie et De Pneumologie de Quebec-Universite Laval)
  - Validation cohort: 606 patients (National Cancer Center Hospital – Tokyo)
- Histologic parameters evaluated: histologic grade, spread through air spaces (STAS), lymphovascular invasion (LVI), and visceral pleural invasion (VPI)
- Performed univariant and multivariant analysis for recurrence-free survival (RFS) and overall survival (OS), and assessed model performance to determine if their integration individually or in combination improved survival prediction when compared to our current system

Results:

- Prevalence of STAS, LVI, and VPI increased with advancing histologic grade
- Histologic G3 tumors associated with worse OS and RFS, especially in stage I disease
- STAS and LVI had stage-dependent prognostic relevance
  - STAS was associated with worse OS in stages II and III, but not stage I
  - LVI was associated with worse OS in stage I, but not stages II and III tumors
- VPI-negative patients had better OS and RFS
- Prognostic model incorporating histologic grade, STAS, and LVI into TNM demonstrated best performance in predicting OS and RFS compared to TNM alone (see Table 3)

Take-home message: The authors show that the incorporation of histologic grade, LVI, and STAS into our current anatomy-based TNM staging enhances prognostication, but I am left wondering *how* these histologic parameters can be incorporated into the next edition of the TNM staging system and *can* they be applied to other tumor types?

<u>Editorial</u>:
Zhang YZ et al. Incorporation of nonanatomic histologic factors into a staging system for lung cancer: now is the time? J Thorac Oncol 2026; 21:103982.

Take-home message: In this well thought out editorial, the authors attempt to answer these questions and more… The offer multiple suggestions about how these might be included, ranging from upstaging when present – just as we do now for VPI – to introducing multiple staging systems based upon tumor type, or consider parallel reporting similar to the kidney. The authors also question the relative need for improved prognostication and challenges in implementation around the globe.

Piao Z et al. Bronchiolar adenoma and glandular papilloma/mixed squamous cell and glandular papilloma represent a continuous disease spectrum: revelations from combined histological and genetic analysis. Histopathology 2026; 89:467-178.

Purpose: Detail the histologic and molecular characteristic of 20 cases diagnosed as glandular papilloma (GP ≈ ciliated muconodular papilloma), mixed glandular and squamous papilloma (MP), or bronchiolar adenoma (BA) to understand the relationship between these highly overlapping benign lung tumors

Methods:

- Histologic evaluation: tumor location (endobronchiolar vs. peribonchiolar), architecture, and type of epithelium
    - Grouped these tumors as follows (representative images in Figure 1)
        - Group A: Classic GP/MP or GP/MP predominant
        - Group B: Transitional morphology between GP/MP and BA
            - B1 – Both GP/MP and BA components
            - B2 – Glandular predominant BA with "papilloid protrusions"
            - B3 – Papillary-predominant BA (= classic CMPT)
        - Group C: Glandular-predominant BA with absence of papillary formation (distal-type BA / non-classic CMPT?)
- NGS performed on all tumors

Results:

- Table 1 details the pathologic and clinical characteristics
    - Group A was defined by endo<u>bronchiolar</u> location and papillary architecture
        - The description suggests that these tumors were not within cartilaginous airways as we would typically anticipate for papillomas, and "peripheral tumours" was included in the title of this table
- Table 2 details the molecular results
    - *BRAF* mutations were the most common, including all cases in group A, which theoretically differs from groups B and C, of which virtually all (13 of 14) were previously diagnosed as BA/CMPT.
    - Notably, group C lacked *BRAF* mutations in all cases where *EGFR/KRAS* mutations dominated.

Take-home message: This work suggests that these histologically and molecularly diverse tumors represent a spectrum (see Figure 2) that I suspect that at least some of us might group, based upon morphology alone.

Willner J et al. Lung carcinoids with sustentacular cells and low keratin expression: a common yet underrecognized phenomenon with diagnostic and biological implications. Mod Pathol 2026; 39:101037.

Purpose: Determine the reliability of using keratin expression and sustentacular cells to distinguish carcinoid tumors and paragangliomas by comprehensively examining expression of multiple keratins, carcinoid, and paraganglioma immunohistochemical markers, assessing presence of sustentacular cells by immunohistochemistry, and sequencing *n* = 109 carcinoid tumors (85 typical, 24 atypical), and compare these results to *n* = 12 retroperitoneal and intra-abdominal paragangliomas and *n* = 188 enteropancreatic neuroendocrine tumors (NETs)

Methods:

- Tissue microarrays (TMAs) were used for immunohistochemistry and NGS
- For keratins (AE1/AE3, CAM 5.2, CK 18, OSCAR): IHC scored for intensity of staining (1, weak; 2, moderate; 3, strong) and percentage of cells staining to create an H score (intensity x % staining)
- For sustentacular cells: S100 scored as 1+/few (<10% of tumor cell nests or scattered cells), 2+/focal (10 – 75% of nests), 3+/diffuse (>75% of nests); SOX10 scored as present/absent/equivocal
- H scores generated for: OTP, TTF-1, ASCL1, HNF4A (carcinoid markers); GATA-3, PHOX2B (paraganglioma)

Results:

- Figure 1 details the results of immunohistochemistry
    - 3 of 109 carcinoids were negative for AE1/AE3
        - 5 additional cases from prospectively identified
        - All (*n* = 8) of the AE1/AE3 negative cases were positive for at least 1 carcinoid marker (see Table 2 for details)
    - All 109 carcinoids were immunoreactive to CAM 5.2, CK18, and OSCAR
    - Cases that showed low/negative labeling for AE1/AE3 also tended to show low labeling for CAM 5.2 ($P < .001$) and lower reactivity for CK 18 and OSCAR
    - OSCAR was the only stain in which there was no low (defined as H score < 50) labeling
- Sustentacular cells were present in the majority (~80%) of carcinoids and in 1/3 of cases diffuse
    - Diffuse sustentacular cells seen in only 2 (1%) of digestive NETs
- GATA-3 and PHOX2B were negative in all carcinoids
- All paragangliomas were negative for all keratins and carcinoid markers tested
- No carcinoid tumors showed mutations typical for paragangliomas

Take-home message: If you think that something is a carcinoid tumor, but it is negative for keratins, try more keratins – CK 18 and OSCAR are your best bets for establishing the diagnosis, and do not be dissuade from the diagnosis by the presence of sustentacular cells

Articles for notation

Neoplastic lung disease

Cortot AB et al. Consistency of c-MET protein overexpression over time in patients with non-squamous non-small cell lung cancer. Histopathology 2026; 89:456-466.

Take-home message: The authors sought to learn if c-Met protein expression by immunohistochemistry varied between pre- and post-treatment biopsies from patients (n = 160) with non-small cell carcinoma (excluding squamous cell carcinoma), who were treated with systemic therapy. c-Met protein overexpression was detected in 14% of initial samples and 21% of post-treatment samples with 81.3% concordance. These results suggest that c-MET status can be evaluated on pre- or post-treatment samples likely with consistent results.

Kawai H et al. AI analysis of elastin staining sections reveals the biological implications of cancer-related fibrosis in small-sized lung adenocarcinomas. Lung Cancer 2026; 219:109542.

Take-home message: An AI diagnostic tool was used to differentiate between non-lepidic patterns of adenocarcinoma and "cancer-related stroma," using elastic stains with the goal of standardizing assessment of invasion. The AI tool was accurate ~90% of the time. Looking at Figure 1, I would like to believe that there would be little disagreement among pathologists or confusion between these areas and I would like to think that our jobs are safe (for today, at least).

Kirmann J et al. Clinicopathological and prognostic validation of pulmonary carcinoid/NET G3: evidence for a distinct subgroup of well-differentiated neuroendocrine neoplasms. Lung Cancer 2026; 219:109545.

Take-home message: Prior to the publication of the IASLC update on pulmonary neuroendocrine neoplasms that we will find in October's J Thorac Oncol (PMID: 42251892), this group worked to describe the clinicopathologic, immunohistochemical features, and outcomes of tumors with carcinoid morphology, but elevated mitotic counts and/or Ki-67 proliferative indices, a group that historically has been classified as large cell neuroendocrine carcinoma, but would now be designated as carcinoid / neuroendocrine tumor grade 3 (NET G3). Unfortunately, for this team, they defined NET G3 using the digestive tract criteria, which differs from that proposed by Beasley et al; nonetheless, these cases certainly still qualify for a diagnosis using the new proposed criteria, which defines lung carcinoid / NET G3 as mitosis > 10 and/or Ki-67 > 20%. Overall, the authors succeed in adding 8 cases to the existing literature, further supporting the concept of NET G3 in the lung.

Nakayama M et al. Negative-pressure pumping fluid as a cytological specimen for bronchoscopic diagnosis and molecular testing in lung cancer. Lung Cancer 2026; 219:109537.

Take-home message: This is a tool that I suppose you could see employed in the future if you are a cytopathologist, since samples obtained by this method showed higher cellularity and improved slide quality compared to convention bronchoalveolar lavage (BAL) fluid samples.

Interestingly, however, the specimen is prepared using a forceps biopsy sample, so perhaps not surprisingly, there was higher concordance between forceps biopsy using this method compared to BAL. Having said that, it is still unclear to me how this method is superior to our usual histopathologic examination of the biopsy without the added step of making a single tissue fragment into a cytology preparation as well.

Nishimura T et al. Prediction of spread through air spaces with biopsy specimens in early-stage adenocarcinoma of the lung. Lung Cancer 2026; 219:109546.

Take-home message: The investigators worked to identify predictive factors for spread through air spaces (STAS) in clinical stage I adenocarcinomas (n = 142) and developed a scoring system to incorporate into reporting with the goal of aiding preoperative planning for the extent of the resection. Grade 3 histologic patterns (micropapillary, solid, fused glandular / cribriform) in biopsies, SUVmax of 1.36, and consolidation-to-tumor ratio of 1 predicted for the presence of STAS in the resection specimen. Patients were stratified into low (0-1), intermediate (2-3), and high (4) risk based upon the presence or absence of these features with grade 3 component given 2 points, while the other 2 parameters were weighted less heavily with 1 point each.

Noberini R et al. Epiproteomic profiling identifies histone H4 hyperacetylation as a prognostic marker in pleural mesothelioma. Lung Cancer 2026; 219:109544.

Take-home message: Mass spectrometry-based epiproteomics was employed to demonstrate that hyper-acetylation of the histone H4 tail is an independent predictor of worse prognosis. Somewhat disappointingly, no information was provided about mesothelioma subtype, which makes me wonder if this tool is superior to histology alone for predicting survival. Finally, formalin-fixed paraffin-embedded tissue was used for this testing, so I suppose this might be of clinical interest in the future as biopsies are often obtained for the diagnosis of mesothelioma.

Onozato Y et al. Deep learning for differentiating pulmonary metastases from primary lung cancer constructed on frozen sections for intraoperative diagnosis. Mod Pathol 2026; 39:101035.

Take-home message: In this study, a large number (n = 1668) of frozen section slides from 1468 patients were used to develop a deep learning model to differentiate primary lung cancer from metastatic tumors. The model was accurate 80% of the time, but accuracy varied considerably with the model particularly struggling with squamous cell carcinomas and neuroendocrine neoplasms, and the accuracy was not as good as the pathologists' when cases categorized as "undetermined" cases were excluded. Again, we are likely "safe" from being pushed out of our jobs by AI (today), but as the authors allude to, this technology may have value in centers that do not have pathologists available for intra-operative assessment.

Scattolin D et al. Analysis of SLFN11 expression in small cell lung cancer, carcinoids and large cell neuroendocrine carcinomas: insights into lung neuroendocrine neoplasms. Lung Cancer 2026; 219:109539.

Take-home message: Schlafen11 (SLFN11) is a biomarker expressed in small cell carcinomas that has been shown to predict sensitivity to DNA-damaging agents. The authors now assess immunohistochemical expression in various pulmonary neuroendocrine neoplasms, including 47 small cell carcinomas (SCLC), 152 large cell neuroendocrine carcinomas (LCNC), 35 atypical carcinoids, and 127 typical carcinoids. SLFN11 expression correlated with Ki-67 proliferative indices with H score ≥ 10 in 1.6% typical carcinoids, 17.1% of atypical carcinoids, 42.8% LCNCs, and 66% of SCLCs.

Torchiat A et al. Low baseline cGAS expression is associated with longer progression-free survival in patients with pleural mesothelioma. Lung Cancer 2026; 219:109553.

Take-home message: The authors investigated cGAS/STING expression by multiplex immunofluorescence in tissue microarrays from 190 patients with mesothelioma. High cGAS was associated with shorter overall survival, while STING had no association with overall survival. Expression increased in both epithelioid and biphasic subtypes following chemotherapy in patients with paired specimens.

Zhang Y et al. Correlative assessment of p53 immunostaining patterns and TP53 mutation status by next-generation sequencing in lung adenocarcinoma (LUAD). Histopathology 2026; 89:522-532.

Take-home message: *TP53* mutation status by next-generation sequencing (NGS) and p53 immunohistochemistry (IHC) were assessed in cohort of 221 pulmonary adenocarcinomas with the goal of determining if IHC is a good surrogate for NGS. Using a cutoff of ≥40% nuclear staining with 3+ intensity for IHC, there was ~95% accuracy for predicting *TP53* mutations. A complete absence of staining (null mutant) or cytoplasmic expression were also relevant and correlated with truncating mutations (~92% concordance).

Zhu J-X et al. An innovative diagnostic strategy for malignant pleural effusion using discontinuous gradient centrifugation. Arch Pathol Lab Med 2026; 150:736-741.

Take-home message: This study used pleural effusion samples, 24 benign and 31 malignant, to show that discontinuous gradient centrifugation is superior to liquid-based cytology. This method was more sensitive (90% vs. 71%) and had better diagnostic accuracy (93% vs. 80%) than liquid-based cytology.

Non-neoplastic lung disease

Bintalib HM et al. Clinical practice guideline for the diagnosis of granulomatous-lymphocytic interstitial lung disease in patients with common variable immunodeficiency disorders: an ERS clinical research collaboration. Eur Respir J 2026; 68:2502224.

Take-home message: This clinical practice guideline is relevant pathologists in understanding where we enter the diagnostic approach for patients with CVID who develop clinical features of GLILD. Lung biopsy is reserved for patients with outstanding uncertainly following multidisciplinary discussion. This is a conditional recommendation is based upon "very low-certainty evidence."

Case Reports

Wu T-Y et al. A novel MYO5C-ALK fusion in lung adenocarcinoma: limited alectinib response and durable lorlatinib benefit. Lung Cancer 2026; 219:109548.

Take-home message: The title pretty much says it all… The patient was a never-smoker with stage IVB disease, who progressed on alectinib, but achieved partial response to lorlatinib. The adenocarcinoma had micropapillary features on biopsy.

Letters to the Editor

Saluja P et al. Diffuse alveolar hemorrhage in lymphangioleiomyomatosis. Chest 2026; 170:806-809.

Take-home message: The authors describe 4 patients with lymphangioleiomyomatosis (LAM) who presented with hemoptysis and were diagnosed with diffuse alveolar hemorrhage (DAH). In 3 of 4 patients, DAH was the presenting manifestation of LAM, and all 3 of those patients were diagnosed with LAM by surgical lung biopsy. For pathologists, it is worth remembering that you might be the 1st to recognize and diagnose LAM in lung wedge biopsies performed during evaluation of DAH.

Xiang M et al. Primary pseudomyogenic haemangioendothelioma of the lung with a novel ACTG1::FOSB gene fusion. Histopathology 2026; 89: 565-567.

Take-home message: A 13-years-old patient presented with multiple, bilateral lung nodules. While pseudomyogenic haemangioendotheliomas typically occur in the lower extremities, no disease was discovered outside of the chest and the authors, therefore, concluded the tumor to be of primary lung origin. *SERPINE1::FOSB* and *ACTB::FOSB* gene fusions are the most common molecular alterations, but this tumor showed a novel *ACTG1::FOSB* fusion.

Review Articles

Nicholson AG et al. The 2025 ATS/ERS update of the international multidisciplinary classification of the interstitial pneumonias: implications for the pathologist. Histopathology 2026; 89:403-425.

Take-home message: A subset of the authors from the 2025 ATS/ERS consensus statement team up to rehash some of what was already presented in that document published in the *European Respiratory Journal*, but now, elaborate on the pathologic findings, continuing the emphasis on secondary causes/associations and combined patterns. I must admit that even as a trained thoracic pathologist, I find the tables dizzyingly complex as well as the suggested approach to reporting (page 408). It is difficult for me to imagine that a pathologist without expertise in the field would gain any greater clarity of this complex topic from reading this daunting review.