

Pulmonary Pathology Journal Club

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Articles for Discussion

1. Lindberg A, Muhl L, Yu H, et al. In situ detection of programmed cell death protein 1 and programmed death ligand 1 interactions as a functional predictor for response to immune checkpoint inhibition in NSCLC. *J Thorac Oncol.* 2025;20(5):625-640.

Background: ICIs have transformed lung cancer treatment, yet their effectiveness seem restricted to certain patient subsets. Current clinical stratification on the basis of PD-L1 expression offers limited predictive value. Given the mechanism of action, directly detecting spatial PD1–PD-L1 interactions might yield more precise insights into immune responses and treatment outcomes.

Methods: The authors applied a second-generation in situ proximity ligation assay (PLA) to detect PD1–PD-L1 interactions in diagnostic tissue samples from 16 different cancer types, a tissue microarray with surgically resected early-stage NSCLC, and diagnostic biopsies from 140 patients with advanced NSCLC with and without ICI treatment. RNA sequencing analysis was used to identify potential resistance mechanisms.

Results:

- In early-stage NSCLC, only half of the cases with detectable PD-L1 and PD1 expression exhibited PD1–PD-L1 interactions, with significantly lower levels in EGFR-mutated tumors.
- Interaction levels varied across cancer types, aligning with reported ICI response rates.
- In ICI-treated patients with NSCLC, higher PD1–PD-L1 interactions were linked to complete responses and longer survival, outperforming standard PD-L1 expression assays.
- Patients who did not respond to ICIs despite high PD1–PD-L1 interactions exhibited additional expression of stromal immune mediators (EOMES, HAVCR1/TIM-1, JAML, FCRL1).

Conclusion: This study proposes a diagnostic shift from static biomarker quantification to assessing active immune pathways, providing more precise ICI treatment. Their results indicate concerted ICI resistance mechanisms, highlighting the need for combination diagnostics and therapies.

Take home message: Assessing the interaction between PD1 and PD-L1 seems to be a better predictor of response to ICI therapy than static assessment of PD-L1 status using the tumor proportion score (TPS), which actually makes a lot of sense. Whether this will translate into clinical practice remains to be seen.

2. Kanaan C, Bani MA, Ducreux M, et al. Diagnostic relevance of p53 and Rb status in neuroendocrine tumors G3 from different organs: an immunohistochemical study of 465 high-grade neuroendocrine neoplasms. *Virchows Archiv*. 2025;486:941-950.

Background: The double inactivation of *TP53* and *RBI* is considered typical of neuroendocrine carcinomas (NECs) but is assumed to be rare in high-grade neuroendocrine tumors (NETs). The immunohistochemical determination of the p53 and Rb status has therefore been proposed as a diagnostic tool.

Methods: The authors studied the p53 and Rb1 status in a large series of high-grade neuroendocrine neoplasms, from multiple origins, in order to (a) assess the patterns observed in the different histopathological categories, (b) compare them among the various anatomic sites, and (c) evaluate their possible diagnostic relevance. 465 cases from 9 organ systems were enrolled in the study, including 142 NETs-Grade3, 162 LCNECs, 144 small cell carcinomas, and 60 cases of NETs-grades1/2.

Results:

- The expression of both proteins was normal in 96.7% of NET-G1/G2, 76.7% of NET-G3, and 5.8% of all NECs.
- p53 expression was abnormal in 12.7% of NET-G3 and 91.5% of NECs.
- Rb expression was lost in 10.6% of NET-G3 and 68.3% of NECs.
- Rb loss was significantly less frequent in LCNEC than in SCNEC (57.3% versus 80.6%); abnormal p53 expression was comparable in the two categories.
- Patterns were comparable between primary sites, except for head and neck NECs.

Conclusions: This study highlights the molecular heterogeneity of NET-G3 and LCNEC, and provides further insight into the diagnostic relevance of p53/Rb immunodetection in high-grade neuroendocrine neoplasms.

Take home message: IHC for p53 and Rb1 may be diagnostically useful to distinguish Grade 3 NET from LCNEC... but it isn't perfect. These findings add to the growing literature suggesting that it may (finally!) be time to separate G3 NET from LCNEC in the next WHO classification of lung tumors, as has been done for the GI tract.

3. Fanaroff RE, Yang SR, Tan KS, et al. Correlation of Histologic Features with Gene Alterations in Pleural Mesothelioma. *Mod Pathol*. 2025;38:100706.

Background: Histologic features, including architectural patterns, cytologic features, and 2021 WHO nuclear grade have prognostic significance in epithelioid diffuse pleural mesothelioma (DPM). Biphasic and sarcomatoid DPM, regardless of morphology, have worse outcomes. Correlation of architectural patterns, cytologic features, and nuclear grade with genetic alterations has not been well studied.

Methods: To investigate relationships between histologic findings and genomic alterations, 128 treatment-naïve DPM specimens (70% epithelioid, 23% biphasic, and 7% sarcomatoid) with next-generation sequencing data were retrospectively reviewed.

Results:

- Alterations in *BAP1* were the most common genomic alteration (48%), followed by *CDKN2A* (38%) and *NF2* (30%).
- *NF2* alterations were significantly more frequent in biphasic DPM (53% in biphasic vs 25% in sarcomatoid and 22% in epithelioid DPM).
- In epithelioid DPM, *TP53* alterations were associated with the presence of prognostically unfavorable histology, including micropapillary or solid architecture, pleomorphic features, and high nuclear grade.
- Tumors with low tumor-infiltrating lymphocytes (TILs) had a higher rate of *BAP1* alterations than tumors with higher levels of TILs (67% vs 30%).

Conclusions: This study enhances our understanding of the relationships among prognostically significant histologic and molecular features in cases of DPM.

Take home message: There is some correlation between underlying molecular abnormalities and the morphologic features in mesothelioma.

Articles for Notation

1. Hoffman H, Nicholson AG, Detterbeck, et al. The International Association for the Study of Lung Cancer lung cancer staging project: Application and interpretation of the residual tumor classification of lung cancer – results from an international survey among pathologists and thoracic surgeons. *J Thorac Oncol.* 2025;20(5):597-613.

Summary: This study presents results from an international survey assessing how the residual tumor (R) classification is interpreted and applied among thoracic pathologists and surgeons. The survey revealed significant global variability in both the use and interpretation of R categories. As we know, R reporting is routine in Europe and Asia but is infrequently included in pathology reports in North America where the R status is typically assigned by the surgeon. There is also wide variability in handling staple lines, pleural lavage cytology, and lymph node designation. The authors emphasize the need for education, clarification, and possible standardization.

Take home message: More global standardization for reporting of the residual tumor (R) status is needed.

2. Sherman RL, Firth AU, Henley SJ, et al. Annual report to the nation on the status of cancer, featuring state-level statistics after the onset of the COVID-19 epidemic. *Cancer.* 2025;e35833,1-31.

Summary: This 2025 update of the Annual Report to the Nation on the Status of Cancer presents comprehensive U.S. cancer incidence and mortality statistics through 2021 (mortality through 2022), highlighting the effects of the COVID-19 pandemic on cancer diagnosis. Among other statistics, it shows a decline in lung cancer incidence aligning with long-standing anti-smoking efforts, though disparities persist. The pandemic-induced drop in 2020 could delay detection of clinically significant lung cancers, potentially shifting the stage distribution in future reports.

Take home message: Lung cancer rates in the United States continue to decline but might bump up again due to COVID-19-related delays in detection.

3. Rosenlund L, Gundbrandsen K, Ahlborn LB, et al. ctDNA can detect minimal residual disease in curative treated non-small cell lung cancer patients using a tumor agnostic approach. *Lung Cancer*. 2025;203:108528.

Summary: This study evaluates the utility of ctDNA as a biomarker for detecting minimal residual disease (MRD) and predicting recurrence in NSCLC patients post-curative treatment, using a tumor-agnostic approach. Using a commercial NGS panel, ctDNA was assessed in 114 samples. ctDNA detection at the second follow-up (4.5–7.5 months post-treatment) was significantly associated with shorter recurrence-free survival (RFS) and higher recurrence risk. Histologically, adenocarcinoma was the most common subtype (69%), and most recurrences occurred in stage II/III cases. Notably, ctDNA detection showed variable prognostic value depending on the treatment type, being more predictive at 6 months for radiation-treated patients and at both time points for surgical cases.

Take home message: Tumor-agnostic ctDNA testing can effectively identify minimal residual disease and predict recurrence after curative treatment in NSCLC. This approach bypasses the need for tumor tissue, increasing its feasibility for routine surveillance.

4. Niesner ICC, Balbi KJ, Poskitt B, et al. Prevalence and breakdown of *KRAS* driver mutations in a large UK non-small cell lung cancer cohort. *J Clin Pathol*. 2025;78:346-350.

Summary: This short report evaluates the prevalence and spectrum of *KRAS* mutations in NSCLC cases in the UK over a 5 year period. *KRAS* mutations were present in 34% of cases, with a female predominance, and most were Class I mutations (notably G12C, G12V, and G12D). Co-mutations were detected in 8.6% of *KRAS*-mutated cases, mainly in *PIK3CA* (5.1%) and *BRAF* (1.6%). In the PD-L1 analysis subset, there was no statistically significant difference in expression between *KRAS* mutant and wild-type tumors.

Take home message: *KRAS* mutations are common (34%) in NSCLC in the UK, and PD-L1 expression does not significantly differ by *KRAS* mutation status.

5. Leung C, Tang M, Finkbeiner WE, et al. Clinical and biological features of a thickened basement membrane zone in asthma. *Am J Respir Crit Care Med*. 2025;211(5):759-769.

Summary: This multicenter study investigated the histologic and immunologic characteristics of a thickened subepithelial basement membrane zone (BMZ) in asthma. Using design-based stereology on endobronchial biopsies from 109 asthmatic patients and 41 healthy controls, the researchers observed that 35% of asthmatics had thickened BMZs per their definition of such. These patients were generally younger, had higher eosinophil counts, elevated FeNO, and elevated total and animal-specific IgE. They also showed significant bronchodilator reversibility despite lower baseline FEV₁, suggesting their airflow limitation is driven by bronchomotor tone rather than fixed obstruction. Molecular findings revealed IL-13-associated gene expression, increased MUC5AC, decreased MUC5B, and high mast cell gene expression, consistent with a type 2 inflammatory endotype.

Take home message: A thickened basement membrane zone in asthma identifies a distinct, type 2-high subgroup of younger, atopic patients with reversible airflow obstruction. This thickening correlates with IL-13-driven epithelial activation and mast cell infiltration, not with non-type 2 inflammation or metabolic dysfunction, which may have implications for anti-IgE or anti-IL-13 therapies.

6. Chiappetta M, Lococo F, Sassorossi C, et al. Tumour dimension is a prognostic factor in thymic epithelial tumours: An update analysis from the ESTS thymic database: Tumour dimension in thymic tumors. *Lung Cancer*. 2025;203:108535.

Summary: This study evaluated the role of tumor size in 2146 patients with thymic epithelial tumors and correlations with overall survival, disease-free survival, and cancer-specific survival. Multivariate analysis confirmed patient age, carcinoma histology, size >5 cm, and tumor infiltration as independent negative prognostic factors for overall survival, advanced TNM stage and carcinoma histology as independent negative prognostic factors for disease-free survival, and tumor infiltration and carcinoma histology as independent negative prognostic factors for cancer-specific survival.

Take-home message: Thymic epithelial tumor size is important and a 5 cm cutoff provides effective prognosis stratification. This data supports the current AJCC 9th Ed. tumor staging criteria.

7. Lin YD, Li HJ, Hong HZ, et al. Genomic profiling of aggressive pathologic features in lung adenocarcinoma. *Lung Cancer*. 2025;203:108460.

Summary: 1559 adenocarcinoma samples were tested for driver mutations and 1306 samples underwent genomic mapping analysis. Results were associated with histologic features including the presence of LVI, STAS, and tumor grade. EGFR mutations were more often associated with no LVI, no STAS, and moderate grade. ALK rearrangements were more often associated with the presence of LVI, STAS, and poor grade. ROS1 rearrangements were more often associated with the presence of STAS and poor grade. KRAS and BRAF-V600E mutations were only associated with poor tumor grade. TP53, CHEK2, KEAP1, PTEN, RB1, and NF1 mutations were significantly enriched in tumors with LVI. TP53, PTEN, CTNNB1, HGF, and NF1 mutations were enriched in tumors with STAS. TP53, LRP1B, and NF1 mutations were enriched in poorly differentiated tumors.

Take-home message: Some pathologic features of tumor aggressiveness (LVI, STAS, and poor tumor grade) are more commonly seen with some mutations and less commonly seen with others. If you get excited by data like this, look at the list above, or read the paper. If you suffer from insomnia and aren't stimulated by molecular studies, you might also choose to read this paper.

Case Reports, Reviews, Editorials, and Miscellaneous.

1. Jiang J, Rao Y, Liu C, Chang S-J, Qiu Y, Lin X. A 7-year-old girl with multiple pulmonary nodules. *Chest*. 2025;167(5):e161–e165.

Summary: An interesting report of a rare presentation of multiple infantile hemangiomas in the lung of a young child.

2. Hornick DB, Meyerholz DK. Primary ciliary dyskinesia with broncholithiasis. *Am J Respir Crit Care Med*. 2025;211(5):866–867.

Summary: An interesting case report of broncholithiasis occurring in a middle-aged man with primary ciliary dyskinesia. The images are worth a quick glance and show something that you don't see every day!

3. Schoedel K, Hegazy S, Zilla ML, Chang J, Nacev BA. Novel dual gene fusions identified in a late pulmonary metastasis of an infantile fibrosarcoma-like tumor. *Virchows Archiv*. 2025;486:1069–1072.

Summary: A case report of a middle-aged woman who developed late pulmonary metastasis from a spindle cell sarcoma resembling infantile fibrosarcoma and harboring dual *FKBP5::PRKCA* and *SEPT7::RAF1* gene fusions, adding to the ever-expanding list of fusion-associated spindle cell neoplasms. This will be of interest to those who also do bone and soft tissue pathology.

4. Mremi A, Ndumbalo J, Chuwa H, Henke O, Rost M. Lung cancer in Tanzania. *J Thorac Oncol*. 2025;20(5):560–564.

Summary: An editorial describing the numerous challenges in the healthcare system of Tanzania as they relate to diagnosing and caring for patients with lung cancer.

5. San José Estépar R, Barr RG, Fain SB, Grenier PA, Hoffman EA, Humphries SM, et al. The use of computed tomography densitometry for the assessment of emphysema in clinical trials: A position paper from the Fleischner Society. *Am J Respir Crit Care Med*. 2025 May;211(5):709–728.

Summary: This Fleischner Society position paper provides a comprehensive review and guideline for using CT densitometry as a biomarker in emphysema assessment, particularly for clinical trials. The authors propose that CT densitometry provides reliable, noninvasive measurements that correlate with histologic emphysema, clinical outcomes, and disease progression.

6. Dennehy, C., Conroy, M. R., & Forde, P. M. Immunotherapy for resectable lung cancer. *Cancer*. 2025; 131: e35849.

Summary: This comprehensive review evaluates the evolving role of immunotherapy in resectable NSCLC focusing on neoadjuvant and perioperative approaches. This review also highlights the growing relevance of pathologic response evaluation as a surrogate marker of treatment efficacy.

7. Morena D, Scopetti M, Padovano M, Turillazzi E, Fineschi V. Fat embolism: a systematic review to facilitate the development of standardized procedures in pathology. *Histopathology*. 2025;86(6):845–861.

Summary: A systematic review of the literature on diagnosis of fat embolism and fat embolism syndrome in the autopsy setting for forensic pathologists, describing the various methods utilized and diagnostic challenges.

8. Hanzal N, Mhapankar GS, Sell E, et al. Lipoid pneumonia following chronic aspiration of cannabis oil used for the treatment of seizures. *Chest*. 2025;167(5):e149-e154.

Summary: The title says it all. A lovely case with some good images.

9. Abstracts from the Pulmonary Pathology Society 2024 Biennial Meeting. *Arch Pathol Lab Med*. 2025;149:e100-e114.

Summary: As the title says, here are the abstracts from last year's PPS meeting. Enjoy.