PULMONARY PATHOLOGY JOURNAL CLUB – JULY 2024*
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Summaries prepared with the help of ChatGPT and Matt Cecchini's Journal Club Assistant; any critical thinking was done by the presenter.

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Discussion articles

Abdulfatah et al. (2024). Extragonadal germ cell tumors: A clinicopathologic study with emphasis on molecular features, clinical outcomes and associated secondary malignancies. Hum Pathol 2024; 148: 41-50.

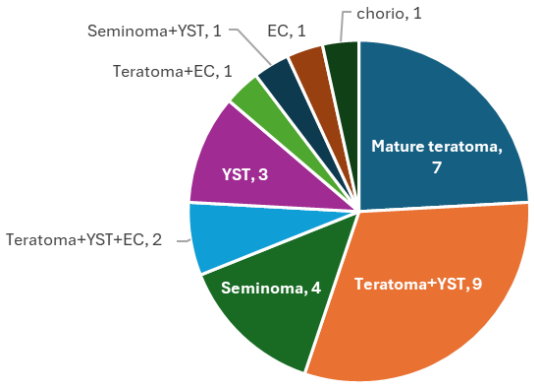
Purpose: Extragonadal germ cell tumors (EGCTs) are rare, accounting for less than 5% of all germ cell tumors (GCTs). They tend to be more aggressive than gonadal counterparts and more frequently associated with secondary somatic malignancies. Mediastinum is a frequently affected site and is the focus of this summary. This study aims to evaluate the clinical, morphological, and immunohistochemical features of EGCTs and analyze chromosomal abnormalities, particularly of 12p, in these tumors.

Methods:

- Retrospective review of EGCT cases (in-house and consultation cases) diagnosed between 2001 and 2020 at a single tertiary institution (UMich).
- 77 patients with EGCTs → **29 mediastinal (focus of this review)** confirmed by histological review.
- Clinical records reviewed for patient demographics, tumor characteristics, treatment, and outcomes.
- Histological and immunohistochemical features evaluated using with SALL4, CD117, PLAP, OCT4, CD30, AFP, Glypican-3, HCG, and AE1/AE3.
- Whole genome SNP array analysis was performed on a subset of cases (8 of 29) to determine isochromosome 12p status and other copy number alterations using the Oncoscan FFPE Assay Kit.

Results:

- 25 males (86%) and 4 females (14%), with a median and mean (± STD) age of 26 and 28.7 (± 18.8) years, respectively. 3 of 5 prepubertal (2 prenatal; 1, 4, 7 years) patients were female.
- 2.5 – 21.5 cm; median and mean (± STD) 9.8 and 10.3 (± 5.2 cms)
- GCT components:



- IHC results as per gonadal tumors (Tble 2: OCT4+ = seminoma & EC ≠ YST; CD30+ = EC; glypican-3 & AFP = YST; CD117+ = seminoma)
- Cytogenetics in 7 (Tble 3): 1-isochromosome 12p; 4-trisomy 21; 1-trisomy 4, gain 6p.
- Somatic malignancies *only* in mediastinal EGCT (6/29; 21%): adenoca (1), MPNST (2), RMS (2), undiff round cell sarc (1).
- 4 DOD (prenatal, 7, 14, 15 yrs; 2 MPNST, 1 undiff round cell sarc); 17 ANED (1 RMS)

Take-home message: Mediastinum is a common site for rare EGCTs that present in a broad age range. "Pure" tumors (mature teratoma, seminoma, YST) ≈ mixed GCTs (teratoma + YST). Young age and somatic malignancies affiliated with more aggressive course.

Lee, Y. et al. Clinicopathologic and Molecular Characteristics of HER2 (ERBB2)-Altered Non-Small Cell Lung Cancer: Implications for Precision Medicine. Mod Pathol 2024; 37:100490

Purpose: HER2 (ERBB2) alterations, including mutations and amplifications, have been identified in various cancers, including NSCLC. A recent trial investigating an antibody-drug conjugate, trastuzumab deruxtecan (T-DXd), demonstrated a 55% response rate in 91 patients with metastatic HER2-mutated NSCLC (84% IHC positive). Current study aims to 1) elucidate clinicopathologic and molecular characteristics of HER2-altered NSCLC, and 2) identify approaches for identifying patients likely to benefit from targeted therapy.

Methods

- Retrospective cohort study: 1680 NSCLC+NGS±SISH → 105 HER2 amplified (43) or mutated (62).
  - 12 excluded (6 – inadequate IHC; 6 – amplification the results of acquired TKI resistance)
  - control group: 165 NSCLC+NGS → NO HER2 amplification/mutation
    - 97 consecutive surgically resected adenocarcinomas (68 w HER2 IHC)
- NGS: TruSight Oncology 500 (Illumina Inc) and CancerSCAN (Geninus)
- Clinicopathologic data and tissue slides reviewed, including immunohistochemistry (IHC) and silver in situ hybridization (SISH) scored according to ASCO/CAP guidelines for breast and gastric.
- Comparison of 89 patients with HER2-altered NSCLC to 165 controls without HER2 alterations.

Results

- HER2 alterations in 89 (5.3%): 30 (1.8%) amplifications & 59 (3.5%) mutations.
- Nearly 97% of patients had stage III-IV disease; no difference between HER2 altered and controls
- Majority of mutations (81.4%) were exon 20 insertions; 52 TKD and 7 non-TKD mutations; 4/11 point mutations in TKD
  - TKD younger age, female sex, never smoker, adenocarcinoma histology.
- 61.07% of HER2-mutated cases showed incomplete or complete membranous HER2 immunoreactivity (1+ and 2+). Some amplified cases had high copy numbers but low IHC scores.
- Frequent co-alterations included TP53 mutations (67.4%) and were more common in those with HER2 amplification (71%) and non-TKD mutations (80%) than those with TKD mutations (60%). Other actionable mutations (*EGFR*, *KRAS*, *SMARCA4*) were limited to those with HER2 amplification or non-TKD mutations (78%).
- Micropapillary histology frequently focal and more common in HER2 mutated tumors; micropapillary histology and lung-to-lung mets more common in HER2 TKD mutated tumors than in the control group ($P < .001$).
- Poorer overall survival in patients with HER2 alterations compared to controls; shortest survivals in those with non-TKD mutations.
- Neither scoring system performed better than the other with 2, 2, 5, and 21 amplified cases showing IHC scores of 0, 1, 2, and 3, respectively. Problem was 2+ scores in the gastric and breast systems for 14 and 9 HER2 mutated and 8 and 6 controls, respectively. Considering only 3+ as overexpression had highest accuracy (91%) and specificity (100%) but lower sensitivity than 2+ and 3+.
- Discordant IHC scores more common in HER2 amplified tumors with concomitant mutations.

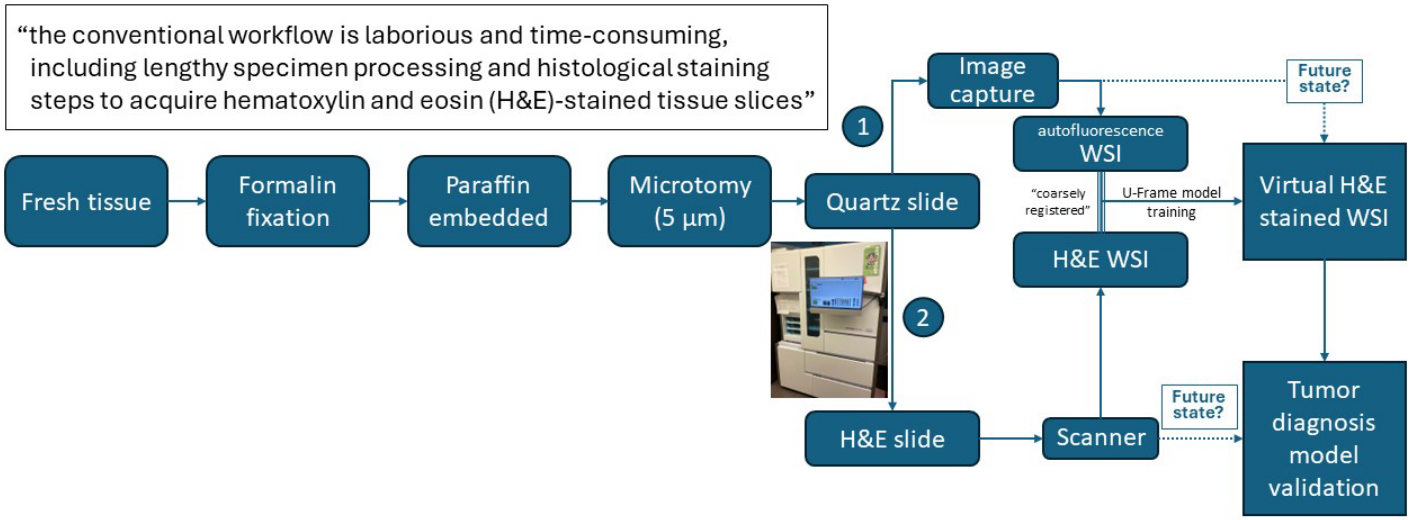
Take-home Message: HER2 alterations are present in small but significant subset of NSCLC and are associated with distinct clinicopathologic characteristics and poor prognosis. NGS is essential for identifying HER2 alterations due to the heterogeneous expression patterns seen with IHC. Understanding the molecular landscape of HER2-altered NSCLC may lead to better-targeted therapies and improved patient outcomes.

Chen Z et al. Lung cancer diagnosis on virtual histologically stained tissue using weakly supervised learning. Mod Pathol 2024; 37:100487.

Purpose: The title suggests that this article is about lung cancer but only tangentially; it's really about virtual "H&E" staining. The authors claim traditional H&E staining is labor-intensive and time-consuming with similarly hyperbolic claims re pathologist effort (". . . *exhaustive inspection of the histopathology slides by pathologists under a brightfield microscope or a while-slide tissue scanner*"). In two parts they set out to, 1) show proof of concept for creating virtually H&E stained WSIs from unstained ("label-free") sections. and 2) classify lung adenocarcinoma (LUAD) using virtually stained WSIs and a "weakly supervised" deep learning model. Primary focus a rapid, cost-effective, interpretable alternative for traditional H&E based diagnosis.

Methods: The study uses a two-step process: 1) virtual histological staining using a weakly supervised deep generative model, and 2) tumor diagnosis on virtually stained digital WSI using weakly supervised learning.

- Autofluorescence images of label-free tissue were converted to virtual H&E-stained images using the U-Frame model, a deep learning framework. No time studies or anything else relevant to interests in showing that this is rapid or cost-effective compared to traditional workflows.



- For the classification task, the attention-based multiple-instance learning (MIL) model was trained on H&E-stained whole-slide images (WSIs) from the Cancer Genome Atlas (TCGA) and validated using WSIs & H&E stained sections ("ground truth") from two hospitals. The dataset consisted of 785 WSIs from TCGA and 1059 WSIs from the Clinical Proteomic Tumor Analysis Consortium (CPTAC), with further validation on 117 virtually vs H&E paired WSIs separated into training (59) and test (58) sets. Diagnostic performance of the models using accuracy and area under the curve (AUC).

Results

The weakly supervised model achieved high diagnostic performance. The model demonstrated an average AUC of 0.973 on virtual H&E-stained WSIs, comparable to an AUC of 0.977 on standard H&E-stained WSIs. The attention heatmaps generated from both virtual and standard H&E-stained WSIs accurately indicated tumor regions.

Take-home message: Virtually H&E stained WSIs are feasible with diagnostic performance equivalent to WSI's from traditionally stained sections. In either case, AI-assisted diagnosis continues to make headway. Claims of reduced TAT and more efficient workflows are neither well documented nor believable. Oh yeh . . . and just because a paper sounds interesting doesn't mean you should want to review it for journal club.

Ito H et al. A deep learning-based assay for programmed death ligand 1 immunohistochemistry scoring in non-small cell lung carcinoma: Does it help pathologists score? Mod Pathol 2024; 37:100485.

Purpose: The current manual scoring method for PD-L1 expression in NSCLC (using the tumor proportion score, TPS) is subjective and can vary among pathologists. In addition, doing it isn't very fun. An objective, repeatable method that ensures consistent and accurate PD-L1 assessment is needed. Papers reviewed in previous journal clubs (eg, April 2022) show promise for AI-driven decision support tools. In 4 iterative experiments this study demonstrates the effectiveness of a deep learning (DL)-based AI model to assist pathologists in scoring PD-L1 in NSCLC.

Methods

- 2 mm cores of representative tumor regions from 665 NSCLC and 27 normal lung tissue samples from surgical specimens resected at Kyoto University Hospital (2001-2015) in patients with no prior chemoradiotherapy. Dako pharmDx kits for PD-L1 (clone 22C3) staining; scanned at 40x → WSI.
- Experiment #1 (54 NSCLC + 1 normal) – develop/validate DL model for PD-L1 IHC
  - ✓ Divided into 3 sets and annotated as ground truth (GT) regions: nontumor, positive tumor, negative tumor (target class).
- Experiment #2 (584 NSCLC) – Interobserver Variability Study
  - ✓ 3 pathologists independently scored PD-L1 expression x 3 (>2 weeks washout)
  - ✓ GT = consensus using 3 category scoring (584 cases): <1%, ≥1%; <50%; ≥50%).
- Experiment #3 (584 NSCLC) – Utility of DL model in predicting TPS
  - ✓ DL determined TPS as continuous variable (%) and generated visual overlays mapping PD-L1 positive (1) and negative (2) tumors cells and non-tumor cells (3)
  - ✓ Compared 3 models for TPS: 1. pathologist w/out AI (**Path-TPS**); 2. AI stand-alone (**AI-TPS**); 3. AI-assisted scoring (**AI assisted-TPS**) using 4 methods: *second* (path then AI) and *concurrent* (path + AI) *reader* modes, each with 1) [AI=TPS/% only], and 2) AI [AI=TPS/% + visual overlay]
- Experiment #4 (47 whole slides – not TMAs – from surgically resected NSCLC), repeating methods for Experiment #2 and AI assisted-TPS (concurrent reading mode, AI=TPS/% only)

Results

- DL Model Validation: Achieved a mean precision of 0.686, mean recall of 0.857, and F1 score of 0.762.
- Interobserver Variability: Fleiss' kappa coefficients showed moderate to substantial agreement, with higher variability in a three-tiered assessment.
- AI-TPS vs. Path-TPS: For all 584 cases, AI-TPS showed comparable accuracy to Path-TPS. In discordant cases, AI-assisted TPS methods significantly improved accuracy (OR: 1.28-1.29). No significant differences were found between the concurrent and second-reading modes.
- Surgical Specimens Assessment: AI-assisted TPS also improved agreement rates in actual clinical specimens compared to Path-TPS.

Take-home message: There is hope for those who read PD-L1 slides (although TPS cases not usually the problem; CPS is where most struggle)! DL-based AI model did not significantly differ from pathologist scoring (GT) in the overall cohort but showed significant improvement in discordant cases. Both concurrent and second-reading AI-assisted methods effectively enhanced diagnostic accuracy and reduced pathologist burden in challenging cases.

Articles for notation

Neoplastic

Chen Q et al. EGFR-mutant NSCLC may remodel TME from non-inflamed to inflamed through acquiring resistance to EGFR-TKI treatment. Lung Cancer 2024; 192:107815.

Summary: This study investigates the immune microenvironment remodeling in EGFR-mutant non-small cell lung cancer (NSCLC) as patients acquire resistance to EGFR tyrosine kinase inhibitor (TKI) treatments. The research was conducted on a cohort of 37 advanced-stage NSCLC patients who developed resistance to at least one type of TKI. By analyzing pre-treatment and post-resistance tumor samples using transcriptional profiling and bioinformatics, the study found that TKI treatment can lead to a significant increase in proinflammatory signaling, including interferon-γ and PD-L1 expression. Approximately one-third of the resistant tumors were classified as "hot," indicating an inflamed state, especially in patients with the EGFR L858R mutation. This change was linked to increased effector cell infiltration, suggesting that the immune activation induced by TKI resistance could enhance the efficacy of subsequent immunotherapy.

Take-home message: EGFR-TKI treatment in EGFR-mutant NSCLC patients may trigger immune activation and increase immune cell infiltration upon resistance, converting tumors to an inflamed state ("hot" tumors). This transformation potentially improves the efficacy of immunotherapy in these patients, particularly in those with the EGFR L858R mutation.

Li M et al. Mutational analysis of pulmonary large cell neuroendocrine carcinoma: *APC* gene *mutations* identify a good prognostic factor. Lung Cancer 2024; 192:107825.

Summary: The study investigates the clinicopathologic, immunohistochemical, and genomic characteristics of pulmonary large cell neuroendocrine carcinoma (LCNEC) and its association with APC gene mutations. The analysis included 19 patients with LCNEC and 9 patients with atypical carcinoid (AC). The researchers identified high mutation frequencies of TP53 (89.5%), RB1 (42.1%), APC (31.6%), and MCL1 (31.6%) in LCNEC, with APC mutations being notably absent in AC. The study revealed that APC mutations primarily occurred in LCNEC with wild-type RB1 and were associated with lower tumor mutational burden (TMB) and better overall survival (OS) compared to LCNEC with wild-type APC.

Key Findings:

- LCNEC-APCMT tumors had lower TMB and relatively mild cytologic atypia.
- APC mutations led to downregulated expression of neuroendocrine markers (CD56 and synaptophysin) and altered expression of APC downstream genes (β-catenin, c-Myc).
- The overall survival of patients with LCNEC-APCMT was intermediate between AC and LCNEC-APCWT, suggesting a better prognosis for LCNEC-APCMT.

Take-home message: APC gene mutations in pulmonary large cell neuroendocrine carcinoma (LCNEC) are associated with a lower tumor mutational burden and better overall survival, identifying APC mutations as a potential prognostic factor. This highlights the significance of genetic profiling in guiding prognosis and potentially tailoring therapeutic strategies for LCNEC patients.

Florez N et al. When the unimaginable happens: Lung cancer diagnosis during pregnancy. Cancer 2024; 130(11):1905-1909.

Summary: This commentary begins with a case of a 32-year-old woman diagnosed with metastatic lung cancer at 28 weeks pregnant, outlining the complex medical and ethical decisions involved in her treatment. Lung cancer during pregnancy is rare, with only 66 cases reported in the literature. Diagnostic delays are common due to overlapping symptoms with pregnancy-related conditions and a general lack of awareness among clinicians. Treatment options, such as chemotherapy, tyrosine kinase inhibitors (TKIs), and surgery, are discussed with an emphasis on their safety and efficacy during different trimesters of pregnancy. The article also underscores the need for more research and a multidisciplinary approach to care.

Take-home message:

- The incidence of lung cancer is increasing faster in young women than men, often involving targetable mutations.
- Overlapping symptoms with pregnancy and a lack of awareness can delay diagnosis.
- Chemotherapy can be administered during the second and third trimesters, while the safety of TKIs remains uncertain. Surgery may be an option in early-stage lung cancer.
- Managing lung cancer in pregnant patients requires a team approach involving oncologists, obstetricians, and other specialists.
- More studies are needed to understand the effects of lung cancer treatments on both maternal and fetal health.

Szentkereszty M et al. Density of tumor-infiltrating NK and Treg cells is associated with 5 years progression-free and overall survival in resected lung adenocarcinoma. Lung Cancer 2024; 192:107824.

Summary: This study investigates the prognostic significance of tumor-infiltrating natural killer (NK) and regulatory T (Treg) cells in resected pulmonary adenocarcinoma. The research involved 115 patients with early-stage lung adenocarcinoma, who were observed over a 60-month period post-surgery. Immunohistochemical analysis was used to detect NKp46 and FoxP3 markers for NK and Treg cells, respectively.

The study found that higher densities of both NK and Treg cells were predominantly located in the tumor stroma. The presence of these cells was associated with longer progression-free survival (PFS) and overall survival (OS). Specifically, high densities of NK cells were linked with female gender, non-smoking status, and KRAS wild-type status. The combination of high NK and Treg cell densities ($NK^{high}/Treg^{high}$) was identified as an independent prognostic factor for both PFS and OS, indicating a potentially synergistic role in anti-tumor immunity.

Take Home Message:

- The combination of high NK and Treg cell densities can serve as an independent prognostic factor, suggesting their combined role in enhancing anti-tumor immune responses.

Goto E et al. Clinicopathological differences between *EGFR* mutated and *EGFR* wild-type lung adenocarcinoma with papillary predominant pattern. Lung Cancer 2024; 192:107830.

Summary: This study investigates the clinicopathological differences between EGFR-mutated and wild-type (WT) lung adenocarcinoma (LUAD) with a focus on the papillary predominant pattern (PPA). It includes 352 patients with EGFR mutations and 370 with WT stage I LUAD from The Cancer Genome Atlas (TCGA) cohort. Immunohistochemical stains for galectin-3, a protein associated with tumor metastasis and resistance to anoikis, were also performed.

Take-home message: EGFR-mutated PPA exhibits a poorer prognosis compared to wild-type PPA and is associated with higher galectin-3 expression.

Petrarulo S et al. Endobronchial ultrasound-guided cryobiopsy of pulmonary artery intimal sarcoma. Am J Respir Crit Care Med 2024; 209(12):1497-1500.

Summary: A pulmonary artery intimal sarcoma (PAIS) characterized by multiple hypodense filling defects in the right pulmonary artery and segmental branches was biopsied using endobronchial ultrasound (EBUS)-guided cryobiopsy after a transbronchial needle aspirate failed to yield diagnostic material. This was done at one of the world's most experienced centers "in the bronchoscopic suite, situated in close proximity to the ICU and cardiothoracic operating rooms". The patient survived the procedure and was alive at 6 months.

Take Home Message: While the authors conclude that EBUS-guided cryobiopsy can be an effective, minimally invasive diagnostic tool for an extraordinarily rare tumor at high-volume centers with experienced interventional pulmonologists. In other words, there is little rationale for trying this at home!

Shi M et al. Rare SMARCA4-deficient thoracic tumor: Insights into molecular characterization and optimal therapeutics methods. Lung Cancer 2024; 192:107818.

Summary: The study investigates the molecular characteristics and optimal therapeutic strategies for SMARCA4-deficient thoracic tumors (SDTTs). This rare tumor type includes SMARCA4-deficient non-small cell lung cancers (SMARCA4-dNSCLCs) and SMARCA4-deficient undifferentiated thoracic tumors (SMARCA4-dUTs). Unfortunately their methods do not explain how they sorted SDTTs into dNSCLCs (154 + 25) and dUTs (42 + 9) except to say that "Pathological diagnosis was made independently by two experienced pathologists." NGS was limited to 87 (of 196) SDTTs from cohort 1. Most comparisons were between SDTTs (dNSCLCs + dUTs) and SMARCA4 intact NSCLCs.

Key Findings:

- Compared to SMARCA4 intact NSCLCs, SDTTs were more frequently males and smokers, were larger, and more frequently had adrenal metastases with no significant differences between dNSCLCs & dUTs.
- The majority of SMARCA4-deficient tumors harbor truncating SMARCA4 mutations, with other mutations like TP53, KEAP1, and KRAS also common. EGFR mutations did not occur.
- SDTTs have significantly shorter overall survival (OS) compared to those with intact SMARCA4 expression; protein expression more predictive than molecular alterations. OS worse for SDTT-dUTs compared to SDTT-dNSCLCs ($p < 0.0001$).
- Treatment: SDTTs show resistance to chemotherapy but are sensitive to chemoimmunotherapy. Paclitaxel-based chemoimmunotherapy yields better progression-free survival (PFS) and overall response rate (ORR) compared to pemetrexed-based regimens.

Take-home message: SMARCA4 protein deficiency predicts aggressive behavior and poor prognosis (didn't we already know this?). Chemoimmunotherapy, particularly paclitaxel-based regimens, represents the most effective current treatment strategy for these patients.

Non-Neoplastic

Malet K et al. Intracellular *Pseudomonas aeruginosa* within the Airway Epithelium of Cystic Fibrosis Lung Tissues. Am J Respir Crit Care Med 2024; 209(12):1453-1462.

Summary: Pseudomonas aeruginosa is a common pathogen in CF airways, causing persistent infections despite antibiotic treatments. Intracellular bacteria can evade the immune system and antibiotics, potentially contributing to chronic infections. This study investigates the presence of intracellular P. aeruginosa in human CF lung tissues, a phenomenon previously demonstrated in vitro but not in vivo.

Lung tissues from CF patients undergoing lung transplantation and from a non-CF lung donor were analyzed using a variety of techniques including quantitative culture, microscopy, histopathology, airway morphometry, immunohistochemistry (IHC), and tissue clearing with immunofluorescence. *P. aeruginosa* was isolated from seven CF patients' lung tissues. Microscopy revealed intracellular *P. aeruginosa* in the airway epithelial cells of three patients at low frequencies. These intracellular bacteria were predominantly found in lung regions with a high bacterial burden. IHC and confocal microscopy provided detailed visualization of intracellular P. aeruginosa within the epithelial cells.

Take-home message: Intracellular *Pseudomonas aeruginosa*, although relatively rare, exists within the airway epithelial cells of CF patients' lungs. This finding implies that these bacteria may serve as a hidden reservoir, contributing to the persistence of chronic infections in CF, despite aggressive antibiotic treatments.

Editorial: Crabbe A. Intracellular Pseudomonas aeruginosa: An overlooked reservoir in the lungs of people with cystic fibrosis? Am J Respir Crit Care Med 2024; 209(12):1421-1423.

Leonard KM et al. Diagnostic yield vs diagnostic accuracy for peripheral lung biopsy evaluation: Evidence supporting a future pragmatic end point. Chest 2024; 165(6):1555-1562.

Summary: This study addresses the inconsistency in using diagnostic yield and accuracy endpoints in evaluating advanced diagnostic bronchoscopy devices and techniques, which hinders between-study comparisons. The researchers explored whether a conservative diagnostic yield definition could approximate diagnostic accuracy by resulting in few false-negative results, making it a practical endpoint for future diagnostic studies. They analyzed 450 peripheral pulmonary lesions (PPLs) biopsied using navigational bronchoscopy from 2017 to 2019, comparing different definitions of diagnostic yield (conservative, intermediate, and liberal) with diagnostic accuracy, which was confirmed through a 2-year follow-up. The conservative diagnostic yield definition (including only malignant and specific benign findings) closely approximated diagnostic accuracy, with less than 1% discrepancy. This approach may facilitate the dissemination of reliable diagnostic utility data without the need for prolonged follow-up.

Take Home Message: Using a conservative diagnostic yield definition, which *excludes nonspecific benign diagnoses*, can provide reliable diagnostic utility data that closely matches diagnostic accuracy, thus reducing the delay in reporting data from new advanced diagnostic bronchoscopy devices and techniques.

Reviews & Case Reports

Leal TA et al. Commemorating the 20th anniversary of the discovery of epidermal growth factor receptor mutation in lung cancer: Translational research at its best. Cancer 2024 130(11):1910-1912.

Summary: This editorial commemorates the 20th anniversary of the discovery of epidermal growth factor receptor (EGFR) mutations in lung cancer, a milestone that significantly advanced translational research. The EGFR family includes four receptors (EGFR/ERBB1, ERBB2/HER2, ERBB3/HER3, and ERBB4/HER4), with dysregulation often leading to tumorigenesis in non-small cell lung cancer (NSCLC). EGFR mutations, particularly in exon 19 or 21, were identified as predictors of favorable responses to EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib and erlotinib. This discovery ushered in an era of precision medicine in lung cancer, emphasizing targeted therapies based on molecular diagnostics.

Key advances

- Identification of EGFR mutations as predictive biomarkers.
- Development and use of first, second, and third-generation TKIs.
- Discovery of resistance mechanisms like the T790M mutation and subsequent treatments, including osimertinib.
- Advances in molecular diagnostics, including circulating tumor DNA for detecting resistance mechanisms.
- Challenges and limited success with combining TKIs and immune checkpoint inhibitors due to toxicity and lack of efficacy in EGFR-mutated cancers.

Take Home Message: The discovery of EGFR mutations has profoundly transformed lung cancer treatment, shifting from cytotoxic chemotherapy to targeted therapies based on molecular profiles. This milestone has led to improved patient outcomes, long-term disease control, and has spurred significant advancements in translational research and drug development.

Russell AM et al. A local perspective on internal, external, and reflexive biomarker testing processes for lung cancer in an academic medical center. Cancer 2024 130(12):2085-2090.

Summary: Precision medicine, particularly targeted therapy, has improved patient outcomes in NSCLC. The rapid development of biomarker identification and treatments is contrasted with system-level barriers, primarily the turnaround time for test results. Internal testing capacity is being increased in many academic medical centers to mitigate delays associated with external testing. The authors (Northwestern University) interviewed 15 clinicians, including nurses, oncologists, and pathologists, from urban, suburban, and rural clinics between January and May 2022.

Findings

- Internal testing process: placing orders within health system EHR and receiving automatic notifications of results.
- External testing process: manually filling forms, sending samples to third-party laboratories, and manually uploading results into the EHR.
- Reflexive testing (ordered by pathology at diagnosis) aims to reduce turnaround time but faces resistance due to clinical and financial concerns.
- Both internal and external testing reported to have similar turnaround times (1-2 weeks).

Take-home message: Improving the efficiency and speed of biomarker testing processes through enhanced internal testing and standardized workflows optimizes NSCLC treatment outcomes. Addressing interoperability issues, standardizing preauthorization, and advocating for better insurance coverage are essential steps towards better integration of biomarker testing in clinical practice.