**Journal Club**
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## Articles for Discussion

1. Pathologic processing of lung cancer resection specimens after neoadjuvant therapy. Weissfert A, Leung CH, Lin H, Sepesi B, William WN, Swisher SG, Cascone T, Lee JJ, Pataer A. Mod Pathol. 2024;37:100353.

   **Background**:
   Neoadjuvant treatment of non-small cell lung cancer challenges the traditional processing of pathology specimens. Induction therapy before resection allows evaluation of the efficacy of neoadjuvant agents at the time of surgery. Many clinical trials use pathologic tumor response, measured as major pathologic response (MPR, <=10% residual viable tumor [RVT]) or complete pathologic response (CPR, 0% RVT) as a surrogate of clinical efficacy. Consequently, accurate pathologic evaluation of RVT is crucial. However, pathologic assessment has not been uniform, which is particularly true for sampling of the primary tumor, which instead of the traditional processing, requires different tissue submission because the focus has shifted from tumor typing alone to RVT scoring.

   **Methods**:
   These authors analyzed the accuracy rates of %RVT, MPR, and CPR of 31 pretreated primary lung tumors using traditional grossing (1 section per cm of greatest tumor dimension) compared with the gold standard of submitting the entire residual primary tumor. With a simulation study, they sampled the traditional number of slides from the total number available and repeated the process 1,000 times for each patient. Accuracy rates were calculated and the minimum number of tumor sections to be submitted to ensure the most accurate scoring of %RVT, MPR, and CPR were identified.

   **Results**:
   Accurate %RVT, MPR, and CPR calls were achieved in 52%, 87%, and 81% of cases, respectively, using the traditional grossing method. Accuracy rates of at least 90% for these parameters require either submission of all residual primary tumor or at least 20 tumor sections.

   **Discussion**:
   Accurate %RVT, MPR, and CPR scores cannot be achieved with traditional tumor grossing. Submission of the entire primary tumor, up to a maximum of 20 sections, is required for the most accurate reads.

   Comment:
   There are many guidelines available for determination of %RVT and no universal consensus. Unlike these authors, some guidelines recommend use of weighted calculations of %RVT. Some recommend submitting the entire tumor bed when CPR is determined based on a lesser sampling, or when high viable tumor is seen grossly on cross-section. I wonder whether any of these ideas factors into your decision-making, and what you think of the more “numerical” approach presented here.

2. Micropapillary and solid components as high-grade patterns in IASLC grading system of lung adenocarcinoma: clinical implications and management. Mikubo M, Tamagawa S, Kondo Y, Hayashi S, Sonoda D, Naito M, Shiomi K, Ichinoe M, Satoh Y. Lung Cancer. 2024;187:107445.

**Background**: The IASLC uses a combination of predominant histologic subtypes and proportion of high-grade components with a cutoff of 20% in the proposed grading system. The authors wanted to determine the clinical implications of this grading system beyond patient prognosis and to assess biologic differences among high-grade subtypes.

**Methods**: 648 consecutive patients who underwent complete resection were examined for clinicopathologic, genotypic, immunophenotypic features and treatment outcomes.

Additionally, the clinical impact of different high-grade components specifically micropapillary (MIP) and solid (SOL) patterns was individually evaluated.

Patients with CIS, mucinous carcinoma, non-curative resection, and those with clinically or pathologically confirmed metastasis, pleural involvement or prior induction therapy were excluded.

**Results**:

- Survival outcomes were well stratified according to the proposed grading system
- Grade 3 tumors exhibited aggressive clinicopathologic feature including visceral pleural invasion, LVI and lymph node mets
- Five year overall survival rates were significantly worse for those patients with high-grade tumors compared to low and intermediate grade tumors ($p<0.0001$)
- Authors then analyzed grade 3-MIP and grade 3-SOL as tumors containing ≥ 20% MIP and SOL patterns without other high-grade components
    - OS and RFS patients with grade 3-MIP and grade 3-SOL tumors significantly worse than those with grade 1 and 2 tumors
    - Although RFS with grade 3-MIP tumors was significantly worse than grade 3-SOL tumors, the OS did not significantly differ between these tumors
- Authors then examined prognostic impact of small proportions of high grade component
    - Prognosis of patients with grade 2 tumors <20% MIP was significantly worse than grade 2 tumors lacking MIP component.
    - Same was true for patients with small proportions of SOL
- There was a survival advantage for adjuvant chemotherapy in patients with high-grade adenocarcinoma
- EGFR mutations more frequently identified in low- and moderate-grade tumors as well as grade 3-MIP tumors compared to grade 3-SOL tumors
- SOL tumors more commonly had ALK BRAF V600E than KRAS mutations as well as higher PD-L1 expression

**Discussion**: The authors appear to validate the usefulness of the IASLC grading system. The authors also show that MIP and SOL patterns independently have a negative impact in multivariant analysis consistent with prior studies.

The negative impact remains even in small proportions of MIP and SOL components included in grade 2 tumors.

Differences in survival between patients with MIP and SOL patterns suggest that further stratification may be necessary.

Authors highlight a few limitations including challenges in diagnosing small amounts of MIP and SOL.

**Comment**: Reasonable study. Appreciate their comment about challenges in diagnosis of small amounts of high grade patterns.

3. A new global definition of acute respiratory distress syndrome. Matthay MA, Arabi Y, Arroliga AC, Bernar G, Bersten AD, Brochard LJ, Calfee CS, Combes A, Daniel BM, Ferguson ND, Gong MN, Gotts JE, Herridge MS, Laffey JG, Liu KD, Machado FR, Martin TR, McAuley DF, Mercat A, Moss M, Mularski RA, Pesenti A, Qiu H, Ramakrishnan N, Ranieri VM, Riviello ED, Rubin E, Slutsky AS, Thompson BT, Twagirumugabe T, Ware LB, Wick KD. Am J Respir Crit Care Med. 2024 Jan;209(1):37-47.

   **Background**: The last major update to the definition of ARDS was in 2012, the Berlin Criteria. Since that time several developments in the management and study of ARDS have prompted consideration of an expansion of the Berlin definition. Some of the changes include the validation of pulse oximetry for evaluating oxygenation, the use of high flow nasal oxygen to manage severe hypoxemic respiratory failure, the Berlin definition did not allow for these in low resource settings and finally, ultrasound imaging has been increasingly used in critically ill patients supplanting traditional chest radiography.

   **Methods**: Committee of experts (approximately 30) convened to develop criteria for an updated definition through the use of working groups. Each working group proposed revisions to the definition and through a consensus process (greater than 70% agreement) new criteria were established. Input was also obtained from numerous international societies.

   **Results:** New definition in Table 1 is "ARDS is an acute diffuse inflammatory lung injury precipitated by a predisposing risk factor such as pneumonia, non-pulmonary infection, trauma, transfusion, burn, aspiration, or shock. The resulting injury leads to increased pulmonary vascular and epithelial permeability, lung edema and gravity-dependent atelectasis, all of which contribute to loss of aerated lung tissue. The clinical hallmarks are arterial hypoxemia and diffuse radiographic opacities, associated with increased shunting, increased alveolar dead space, and decreased lung compliance. The clinical presentation is influenced by medical management (position, sedation, paralysis, positive end-respiratory airway pressure, and fluid balance). Histologic findings may vary and may include intraalveolar edema, inflammation, hyaline membrane formation, and alveolar hemorrhage."

   Table 1 expands on this global definition with specific criteria. Table 2 summarizes key differences between the new global definition of ARDS and the Berlin definition.

   ARDS can also be diagnosed in the presence of chronic lung disease including COPD, ILD and pulmonary hypertension provided that the acute hypoxemic respiratory failure is not primarily attributable to these underlying conditions (see supplement D-2 and Table E1 and E2).

   **Discussion**: These new global criteria are expected to be the basis of future studies. Limitations include the lack of a stringent methodology for reviewing the literature, recommendations were based on consensus opinion with dialogue with major societies, no formal prospective testing of the predicted validity of various clinical parameters were performed and although some pulmonologists from low resource settings were involved, future refinements will need the input of a broader group of pulmonologists from low resource settings.

   **Comment**: Where do patients with acute interstitial pneumonia fit or those with acute exacerbation. We may end up with severe acute hypoxemic respiratory failure does that not also represent the acute respiratory distress syndrome? It appears from this paper that maybe not.

   There is a website being developed which may be worth peeking at (https://globalARDSdefinition.org).

4. POU2F3-expressing small cell lung carcinoma and large cell neuroendocrine carcinoma show morphologic and phenotypic overlap. Jimbo N, Ohbayashi C, Takeda M, Fujii T, Mitsui S, Tsukamoto R, Tanaka Y, Itoh T, Maniwa Y. Am J Surg Pathol. 2004;48:4-15.

**Background**: Small cell carcinoma has begun to be classified into four subtypes based on key transcriptional factors (ASCL1, NEUROD1, POU2F3, and YAP1).

- POU2F3 is a lineage defined transcription factor involved in generation of tuft cells, chemosensory cells distributed in the respiratory tract (and elsewhere). Small cell carcinomas expressing POU2F3 (SCLC-P) generally don't express neuroendocrine markers and have low or no expression of TTF-1.
- POU2F3 expression has also been identified in LCNEC (12-20%) in addition to SCLC (7-12%), as well as pulmonary squamous and adenocarcinomas (<5%). No large cohort studies have examined the relationship between the molecular/biologic classification of lung cancer and morphology. This study examined LCNEC and SCLC to determine whether there were differences between the molecular classification and morphology or protein expression.

**Methods**: 95 cases of SCLC and 51 of LCNEC. There was some discordance among the 146 cases – 18 were agreed upon by consensus and included in the final analysis.

Authors developed cytomorphologic score 0-12 (defined as the sum of 6 parameters: nuclear size, nuclear molding, chromatin pattern, length-to-width ratio, cytoplasm and nucleoli (0, 1 and 2). Cases with SCLC like features tended to have lower values.

Degree of tumor stroma and nest formation was also evaluated on a 3-point scale (0-2). Comedo necrosis, bronchial intraepithelial involvement, and background lung fibrosis were also evaluated (yes/no). Detailed methods are present in the Supplemental Digital Content. 18 types of antibodies were used including ASCL1, NEUROD1, POU2F3, YAP1, synaptophysin (SYN), Chromogranin A (CGA), CD56, INSM1, TTF-1, CEA, bcl-1, c-Myc, c-kit, CD5, p40, CK 5/6, Rb1, and PD-L1.

2626 sections were evaluated; 57% of cases were reviewed by whole slides and the remaining (43%) on spiral arrays. Rb1 expression scored as retained or lost, PD-L1 evaluated by TPS score (≥ 1% positive), while the other 16 markers were evaluated using an H-score (0-300). Additional details on scoring system (quite complicated) can be found in the paper and in prior studies.

Survival among the various neuroendocrine carcinomas was also evaluated.

**Results**: Major results include

- POU2F3 dominant SCLC and LCNEC showed overlapping cytomorphology, while non-POU2F3 dominant SCLC (71) and LCNEC (37) showed distinct differences in cytomorphology
- POU2F3 dominant NEC exhibited significantly more abundant tumor stroma, more prominent nest formation, more frequent bronchial epithelial involvement, and less frequent background fibrosis than non-POU2F3 dominant NECs
- POU2F3 dominant SCLC and LCNEC were characterized by lower expression of TTF-1, CEA, NE markers and higher expression of BCL-2, c-Myc and c-kit
- POU2F3 dominant NEC had significantly better prognosis than non-POU2F3 dominant NEC, and had a higher smoking index than non-POU2F3 dominant NEC
- POU2F3 dominant NEC may form a unique population exhibiting intermediate cytomorphologic features between SCLC and LCNEC

**Discussion/Comment**: Are we back to defining an intermediate category of small cell carcinoma?

**Non-Neoplastic Notations**

1. Effects of cooking with liquefied petroleum gas or biomass on stunting in infants. Checkley W, Thompson LM, Sinharoy SS, Hossen S, Moulton LH, Chang HH, Waller L, Steenland K, Rosa G, Mukeshimana A, Ndagijimana F, McCracken JP, Diaz-Artiga A, Balakrishnan K, Garg SS, Thangavel G, Aravindalochanan V, Hartinger SM, Chiang M, Kirby MA, Papegeorghiou AT, Ramakrishnan U, Williams KN, Nicolaou L, Johnson M, Pillarisetti A, Rosethal J, Underhill LJ, Wang J, Jabbarzadeh S, Chen Y, Davila-Roman VG, Naeher LP, McCollum ED, Peel JL, Clasen TF, for the HAPIN Investigators. N Engl J Med 2024;390:44-54.

   **Background**: Household air pollution is associated with stunted growth in infants. This study examined whether the replacement of biomass fuel with liquefied petroleum gas (LPG) for cooking reduced the risk of infant stunting.

   **Methods**: Randomized trial with 3200 pregnant women 18 to 34 years of age in four low- and middle-income countries. Women were randomly assigned to use free LPG cookstoves for 18 months or continue using biomass cookstoves. Infant length was measured and exposure to fine particulate matter was monitored during the start of pregnancy and continuing until the infants were 1 year of age.

   Primary outcome was defined as length for age score at 12 months of age.

   **Results**: Adherence to intervention was high and intervention resulted in lower prenatal and postnatal 24 hour personal exposure to fine particulate matter. However, stunting was not significantly different between the two groups.

   **Discussion**: The interventional strategy did not reduce the risk of stunting infants.

2. Liquefied petroleum gas or biomass cooking and severe infant pneumonia. McCollum ED, McCracken JP, Kirby MA, Grajeda LM, Hossen S, Moulton LH, Simkovich SM, Goodman-Palmer D, Rosa G, Mukeshimana A, Balakrishnan K, Thangavel G, Garg SS, Catanaza A, Thompson LM, Diaz-Artiga A, Papageorghiou AT, Davila-Roman VG, Underhill LJ, Hartinger SM, Williams KN, Nicolaou L, Chang HH, Lovvorn AE, Rosenthal JP, Pillarisetti A, Ye W, Naeher LP, Johnson MA, Waller LA, Jabbarzadeh S, Wang J, Chen Y, Steenland K, Clasen TF Peel JL, Checkley W, for the HAPIN Investigators. N Engl J Med. 2024;390:32-43.

   **Background**: Exposure to household air pollution is a risk factor for severe pneumonia. This study was designed to determine whether replacing biomass cookstoves with liquified petroleum gas cookstoves affected severe pneumonia in infants.

   **Methods**: A randomized, controlled trial in India, Guatemala, Peru, and Rwanda.

   Women were assigned to cook with unvented LPG stoves and fuel or continue using biomass fuel. Primary outcomes were the occurrence of severe pneumonia in the first year of life.

   **Results**: 3200 pregnant women underwent randomization among whom 3195 remained eligible and gave birth to 3061 infants. No significant difference in the rate of severe pneumonia was associated with the use of LPG.

**Discussion**: The incidence of severe pneumonia among infants did not differ significantly between the mothers assigned to cook with LPG or biomass stoves.

**Comment**: The authors of both articles (similar authors) speculate on potential reasons for the lack of significance of these two studies.

3. Treatment of systemic sclerosis-associated interstitial lung disease: evidence-based recommendations. An official American Thoracic Society Clinical Practice Guideline. Raghu G, Montesi SB, Silver RM, Hossain T, Macrea M, Herman D, Barnes H, Adegunsoye A, Azuma A, Chung L, Gardner GC, Highland KB, Hudson M, Kaner RJ, Kolb M, Scholand MB, Steen V, Thomson CC, Volkmann ER, Wigley FM, Burille D, Kemper KA, Knight SL, Ghazipura M; on behalf of the American Thoracic Society Assembly on Clinical Problems. Am J Respir Crit Care Med. 2024 Jan;209(2):137-152.

   **Background**: ILD in patients with systemic sclerosis is a significant cause of morbidity and mortality. The assembled authors propose evidence-based recommendations for treatment of the ILD.

   **Methods**: Systematic review with evidence-based guidelines which include (Grade – Grading of the Recommendations, Assessment, Development and Evaluation) approach.

   **Results**: Figure 1 summarizes the recommendations
   For treatment of patient with SSc-ILD, the committee recommends

   - Recommends mycophenolate (strongly favor)
   - Recommends further research into the safety and efficacy of (a) pirfenidone and (b) the combination of pirfenidone plus mycophenolate
   - Conditional recommendation for use of cyclophosphamide, rituximab, tocilizumab, nintedanib, and the combination of nintedanib plus mycophenolate

   **Discussion**: Recommendations provide evidence-based clinical practice guidelines intended to serve as a basis for informed and shared decision making by clinicians and patients.

**Neoplasia**

1. Clinical impact of mixed pulmonary carcinoma and carcinoid: the driver from their mono-clonal origin. Graziano P, Parente P, Centra F, Millione M, Centonze G, Volante M, Cavazza A, Urbano D, Di Maggio G Balsamo T, Di Micco C, Rossi G, Rossi A, Muscarella LA. Virchows Archiv. 2024;484:37-46.

   **Background**: The combination of neuroendocrine/non-neuroendocrine lung tumors is mentioned in the recent WHO, but a combination of typical or atypical carcinoids with non-small cell carcinoma is not included in the category but case reports of this do exist. The authors present four new cases of mixed non-small cell carcinoma – carcinoid and performed targeted-DNA and RNA-based NGS on both primary and lymph node metastases methods. In two cases, synchronous lymph node metastases were also available.

   **Results**: Tumors consisted of combination of adenocarcinoma and atypical carcinoids. Subtypes could be relatively distinct and juxtaposed to one another or “intermingled”. In all cases, both components showed at least one common mutation including KRAS driver mutations, AKAP13-RET fusion, and missence KRAS driver mutation reinforcing the hypothesis that these represent clonal rather than collision tumors.

**Discussion**: Mixed lung adenocarcinoma and typical or atypical carcinoids should be included among the histotypes for which molecular characterization of both components is needed to identify the presence of potential druggable genetic alterations.

2. Multivariate evaluation of prognostic markers in synovial sarcoma. Larque AB, Lozano-Calderon S, Cote GM, Chen YL, Hung YP, Deshpande V, Nielsen GP, Chebib I. J Clin Pathol. 2024;77:16-21.

   **Background**: Synovial sarcoma (SS) is an aggressive neoplasm with varied clinical outcomes despite standard treatment protocols. The aim of this study was to evaluate SS from a single institution for prognostically relevant clinicopathologic and immunohistochemical factors.

   **Methods**: A single institution (Mass General) cohort with follow-up.

   **Results**: 133 patients and sites of involvement included 37% in the lung or pleura with 100 having complete dataset for all study covariates.

   On Cox regression multivariate analysis location, p16 and p16 expression were significantly associated worse overall survival whereas PTEN (phosphatase and tensin homolog) immunohistochemical intensity score and p53 expression were correlated with improved overall survival. Location (axial), tumor size and high MYC expression were associated with inferior disease-free survival. Only PTEN intensity score was correlated with improved disease-free survival.

   **Discussion**: This study shows that location, AJCC stage, p16, p53 and PTEN expression were prognostically significant. For overall survival, while location, tumor size, MYC, and p10 expression were significantly associated with disease-free survival.

3. Tumor heterogeneity confounds lymphocyte metrics in diagnostic lung cancer biopsies. Elfving H, Thurfjell V, Mattsson JSM, Backman M, Strell C, Micke P. Arch Pathol Lab Med. 2024;148:e18-e24.

   **Background**: The immune microenvironment and immune scores are being developed for clinical diagnostics. This study was designed to evaluate how well small diagnostic biopsies and tissue microarrays reflect immune cell infiltration compared to whole tumor slides.

   **Methods**: TMAs were constructed from surgical specimens with NSCLC. Whole sections, biopsies, and TMAs were stained for CD3 and immune cell infiltration assessed semiquantitatively.

   **Results and Conclusions**: Although overall lymphocyte infiltration is relatively represented on TMAs, the representativity in diagnostic lung biopsies was poor, challenging the concept of being able to use biopsies to establish immune scores as prognostic or predictive biomarkers in diagnostic applications.

4. Detection of clinically actionable gene fusions by next-generation sequencing-based RNA sequencing of non-small cell lung cancer cytology specimens: a single-center experience with comparison to fluorescence in situ hybridization. Diks J, Tang Z, Altan M, Anderson S, Chen H, Rashid A, Yang RK, Routbort MJ Patel KP, Toruner GA, Medeiros LJ, Tang G, Luthra R, Roy-Chowdhuri S. Cancer Cytopathol. 2024;132:41-49.

   **Background**: The authors evaluate the utility of an RNA-based NGS assay to detect genomic alterations in NSCLC cytology specimens and compare the results to FISH.

**Methods**: Retrospective review of 264 NSCLC cytology specimens concurrently tested for gene fusions by RNA-based NGS and ALK, RET, and/or ROS1 by FISH.

**Results/Conclusions**: RNA-based NGS can be used to detect fusions in NSCLC cytology cases in high concordance with FISH.

RNA-based NGS may have high failure rates and therefore a low threshold for reflexing inadequate cases to orthogonal testing methods is essential for comprehensive genomic profiling.

5. Rapid on-site evaluation (ROSE) of image-guided FNA specimens improves subsequent core biopsy adequacy in clinical trial patients: the impact of preanalytical factors and its correlation with survival. Graham AJ, Robinson MT. Kahler J, Azadi JR, Maleki Z. Cancer Cytopathol. 2024;132:30-40.

   **Background**: The objectives of this study were to evaluate the role of ROSE in trial-associated FNA samples and to analyze predictors of adequacy and cumulative survival from in-house FNA cases used in clinical trials.

   **Methods**: Clinical trial FNA biopsies performed over 10 months.

   **Results/Conclusions**: 325 FNAs were collected for 57 clinical trials among 225 individual patients. There was a statistically significant association between adequate sampling and ultrasound-guided biopsies (83%) compared with computed tomographic-guided biopsies (59%). The effect of body mass index on mortality was also a significant finding. There was a survival benefit in patients with an elevated BMI compared to those who were underweight.

   The best predictor of adequacy and mortality were imaging modality and BMI, respectively.

6. Prognostic value of KRAS mutations, TP53 mutations and PD-L1 expression among lung adenocarcinomas treated with immunotherapy. Tonnesen EMT, Stougaard M, Meldgaard P, Lade-Keller J. J Clin Pathol. 2024;77:54-60.

   **Background**: The study was to investigate the association between oncogenic alterations and PD-L1 expression as well as prognostic value of KRAS and/or TP53 mutations in patients treated with immunotherapy.

   **Methods**: 519 patients

   **Results/Conclusions**: Mutations in TP53 together with KRAS may serve as a potential biomarker for survival benefit in patients being treated with immunotherapy.

7. Occupational benzene exposure and lung cancer risk: a pooled analysis of 14 case-control studies. Wan W, Peters S, Portengen L, Olsson A, Schuz J, Ahrens W, Schejbaloba M, Boffetta P, Behrens T, Bruning T, Kendzia B, Consonni D, Demers PA, Fabianova E, Fernandez-Tardon G, Field JK, Forastiere F, Foretova L, Guenel P, Gustavsson P, Jockel KH, Karrasch S, Landi MT, Lissowska J, Barul C, Mates D, McLaughlin JR, Merletti F, Migliore E, Richiardi L, Pandics T, Pohlabeln H, Siemiatycki J, Swaitkowska B, Wichmann HE, Zaridze D, Ge C, Straif K, Kromhout H, Vermeulen R. Am J Respir Crit Care Med. 2024 Jan;2009(2):185-196.

**Background**: Benzene has been classified as carcinogenic but there is limited evidence linking benzene exposure to lung cancer. Occupational exposure to benzene occurs in numerous industries including petroleum, chemical, painting, rubber, coke making and manufacturing.

**Methods**: 14 case-control studies across Europe and Canada were pooled.

**Results/Conclusions**: The authors found a consistent and robust association between different dimensions of occupational benzene exposure and lung cancer risk after adjusting for smoking and main occupational lung carcinogens.

These associations were observed across different subgroups, including nonsmokers.

Their findings support the hypothesis that occupational benzene exposure increases the risk of lung cancer.

8. Validation of the proposed International Association for the Study of Lung Cancer Residual Tumor Classification to upgrade extracapsular extension of tumor in nodes from R0 to incomplete resection. Xie H, Dai C, Gu C, Zhao S, Xu L, Wang F, Gao J, Su H, Wu J, She Y, Ren Y, Wu C, Chen C. J Thorac Oncol. 2024; 19(1):130-140.

   **Summary**: The author studied 4061surgical patients with NSCLC and reclassified them according to a proposed revised R classification to upstage due to the presence of extracapsular lymph node extension from R0 to R1.

   The prognosis of ECE patients is comparable to that of R1 patients suggesting that upgrading ECE into incomplete resection patients is reasonable.

9. Comprehensive genomic and transcriptomic analysis of sclerosing pneumocytoma. Yeh YC, Chu PY, Lin SY, Wang SY, Ho HL, Wang YC. Mod Pathol. 2024;37:100354.

   **Background**: Although the pathogenic role of AKT1 point mutation in sclerosing pneumocytoma has been recognized, the significance of AKT1 ITD (internal tandem duplications) in oncogenesis remains unexplored.

   **Methods**: Comprehensive genomic and transcriptomic analysis of sclerosing pneumocytoma (SP) to address the knowledge gap.

   RNA-sequencing from 23 tumors and whole-exome sequencing from 44 tumors is used to gain insight into the genetic and transcriptomic profile.

   **Results**: There was a high degree of genetic and transcriptomic similarity between tumors carrying AKT1 ITD and those with AKT1 point mutations.

   **Comment**: Interested readers may want to read the overall details of the article (which are beyond my ability to explain!)

**Thymus/Mediastinum**

1. The International Association for the Study of Lung Cancer Thymic Epithelial Tumors Staging Project: proposals for the N and the M Components for the forthcoming (ninth) edition of the TNM Classification of Malignant Tumors. Fang W, Girard N, Cilento V, Goren E, Dibaba D, Ruffini E, Ahmad U, Appel S, Bille A, Boubia S, Brambilla C, Cangir AK, Detterbeck F, Falkson C, Filosso PL, Giaccone G, Guerrera F, Huang J, Infante M, Kim DK, Lucchi M, Marino M, Marom EM, Nicholson AG, Okumura M, Rami-Porta R, Rimner A, Simone II CB, Asamura H, members of the Staging and Prognostic Factors Committee, Members of the Advisory Boards and Participating Institutions of the Thymic Domain. J Thorac Oncol. 2024;19(1):52-70.

   **Summary**: As a result of this large international collaborative data analysis of over 9000 cases of thymomas, thymic carcinomas, and neuro-endocrine thymic tumor the authors do not suggest changing the N and M components of the staging system for the new 9$^{th}$ edition of the staging manual.

2. On the histologic classification of thymoma. Suster D, Suster S. Adv Anat Pathol. 2024;31:22-33.

   **Summary**: The authors propose a new thymoma classification based on cell type and cytology. Interested readers are referred to the numerous illustrations and tables to get details of the proposal.

**Case Reports, Reviews, Letters**

1. Silicone depositions: an unusual finding in the explanted and newly transplanted lungs. Bos S, Majo J, Funston W, Fisher AJ, Meachery G. Thorax. 2024;79:98-99.

2. Chronic lung injury after COVID-19 pneumonia: clinical, radiologic, and histopathologic perspectives. Cha MJ, Solomon JJ, Lee JE, Choi H, Chae KJ, Lee KS, Lynch DA. Radiology 2024;310(2):e231643.

   **Background**: Long COVID, also termed "post-COVID-19 condition" (PCC) can result from a variety of the acute changes in the lung. This article reviews the CT, histology, and novel imaging techniques of patients with PCC.

   **Methods**: Review article of multiple prior publications.

   **Results**: Figure 1 is a nice diagram illustrating the concepts presented in the paper.

   Topics covered include:
   - PFT abnormalities
   - Lung parenchymal abnormalities (nicely summarized in Table 2)
   - Effects of variants and vaccines on chronic lung injury
   - Pathology
   - Treatment of PCC
   - Emerging imaging techniques (summarized in Table 3) and include such things as photon-counting detector CT, hyperpolarized $^{129}$Xe MRI, advances in artificial intelligence in the chronic COVID-19 era
   - Conclusion.

**Discussion**: Overall, a reasonable review.

**Comment**: Pathology articles quoted are limited and do include some by journal club numbers.

3. A 37-year-old man with dyspnea, bilateral lung consolidation, and a tracheal mass. Shirgaonkar R, Panigrahi MK, Girija A, Sharma P, Chappity P, Tripathy SR. Chest, 2024;165(1):e5-e10.

   **Comment**: Case presentation of a patient with giant cell granuloma involving the trachea associated with osseous metaplasia.

**NOTE**: The entire issue of histopathology is devoted to reviews of lung pathology, some by journal club members. Specific articles are not reviewed here since the titles seem to say it all.

4. Editorial. Thoracic tumour pathology. Mino-Kenudson M, von der Thusen J. Histopathol. 2024;84:3-5.

5. Review. Benign lesions of the mediastinum. Gerber TS, Porubsky S. Histopathol. 2024;84:183-195

6. Review. Primary germ cell tumours of the mediastinum: a review with emphasis on diagnostic challenges. Fichtner A, Marx A, Strobel P, Bremmer F. Histopathol. 2024;84:216-237.

7. Review. Updates on lung adenocarcinoma: invasive size, grading and STAS. Willner J, Narula N, Moreira AL. Histopathol. 2024;84:6-17.

8. Review. Updates on lung neuroendocrine neoplasm classification. Trucco GV, Righi L, Volante M, Papotti M. Histopathol. 2024;84:67-85.

9. Review. Mesenchymal tumours of the pleura: review and update. Rerkpichaisuth V, Hung YP. Histopathol. 2024;84:163-182.

10. Review. Molecular pathology of non-small cell carcinoma. Yatabe Y. Histopathol. 2024;84:50-66.

11. Review. Neurogenic tumours of the posterior mediastinum and differential diagnosis considerations. den Bakker MA, Weissferdt A. Histopathol. 2024;84:238-252.

12. Review. What's new in benign lung tumours? Boland JM. Histopathol. 2024;84:124-135.

13. Review. New developments in mesothelial pathology. Churg A. Histopathol. 2024;84:136-152.

14. Review. NUT carcinoma and thoracic SMARCA4-deficient undifferentiated tumour: facts and controversies. Yoshida A. Histopathol. 2024;84:86-101.

15. Review. Recent developments in the pathology of primary pulmonary salivary gland-type tumours. Naso JR, Roden AC. Histopathol. 2024;84:102-123.

16. Review. Pulmonary invasive mucinous adenocarcinoma. Chang WC, Zhang YZ, Nicholson AG. Histopathol. 2024;84:18-31.

17. Review. Pulmonary squamous cell carcinoma and lymphoepithelial carcinoma – morphology, molecular characteristics and differential diagnosis. Berezowska S, Maillard M, Keyter M. Blsig B. Histopathol. 2024;84:32-49.

18. Review. Thymic epithelial tumours: histopathological classification and differential diagnosis. Von der Thusen J. Histopathol. 2024;84:196-215.

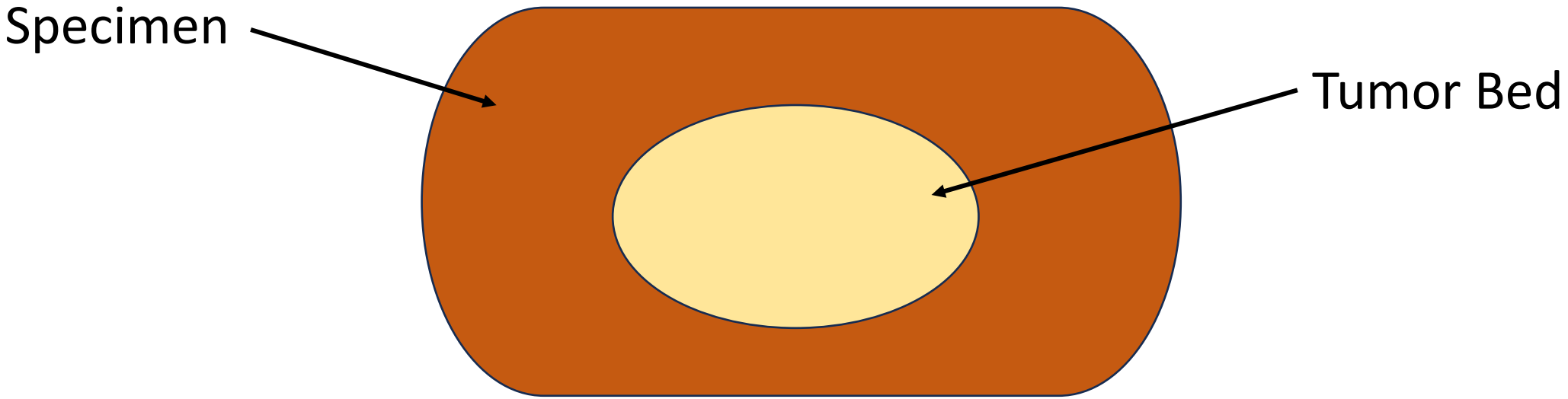
19. Review. Updates on grading mesothelioma. Schulte JJ, Husain AN. Histopathol. 2024;84:153-162.

Pathologic processing of lung cancer resection specimens after neoadjuvant therapy.

Weissfert A, Leung CH, Lin H, Sepesi B, William WN, Swisher SG, Cascone T, Lee JJ, Pataer A.

Mod Pathol. 2024;37:100353.

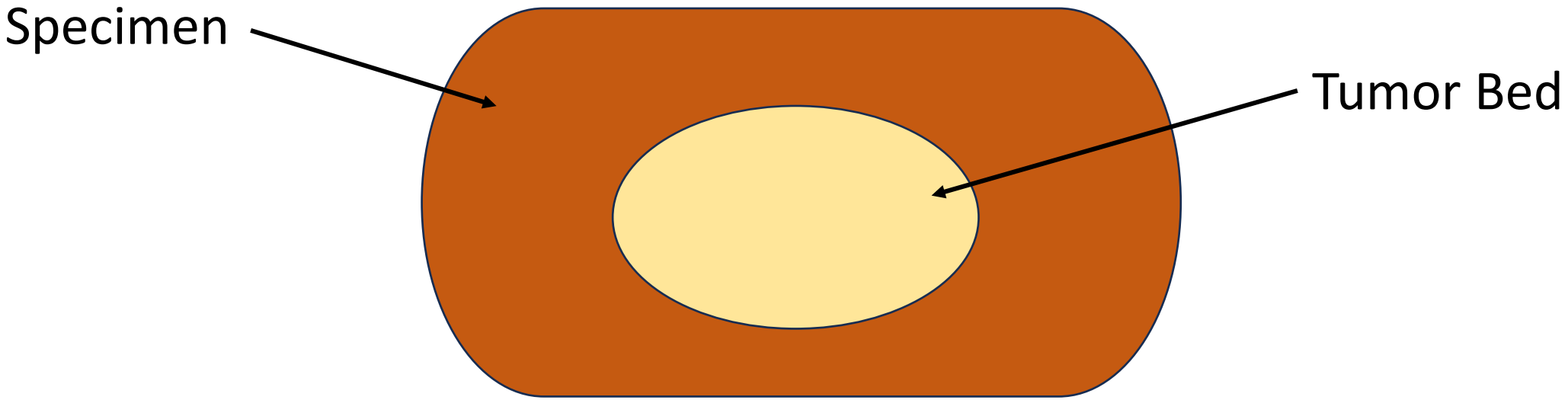
# Small Tumor Bed: Not Many Sections




Representative Sections of Tumor Bed (1 per cm):

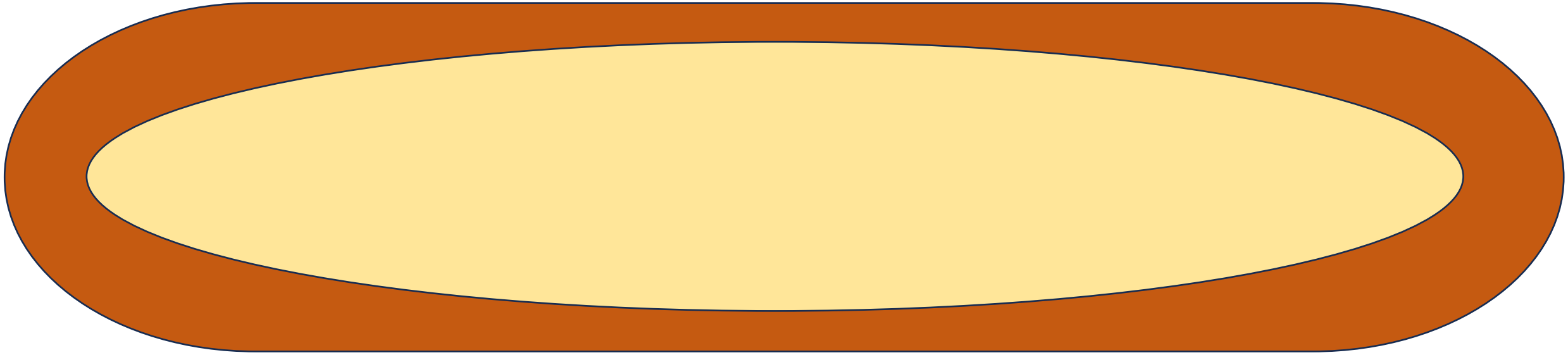
*Image courtesy of www.biorender.com*

# Small Tumor Bed: Not Many Sections

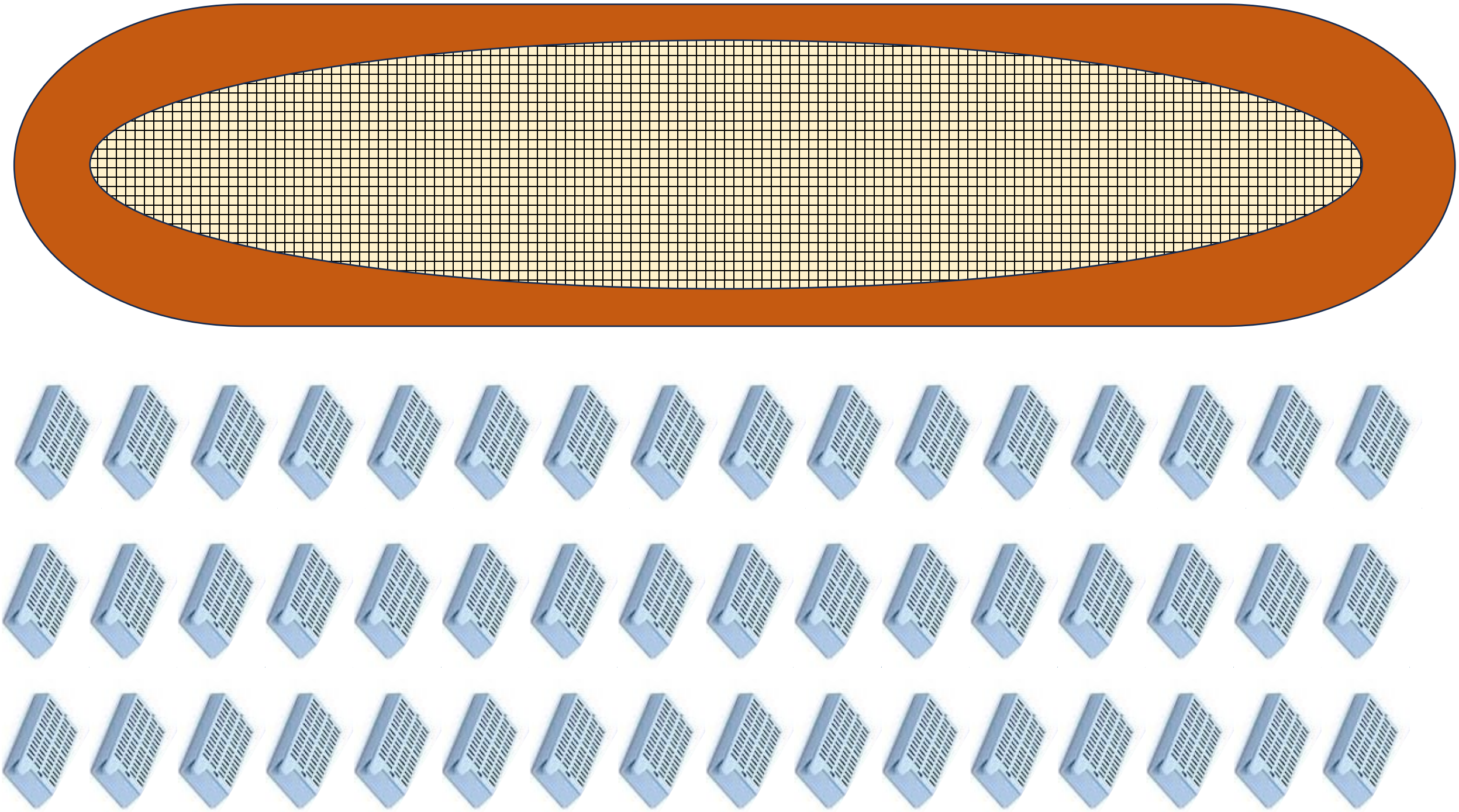



Tumor Bed Entirely Submitted (Gold Standard):

# Large Tumor Bed: Too Many Sections



Representative Sections of Tumor Bed (1 per cm):



How many sections do we actually *need?*

Take 31 tumors

Submit them entirely

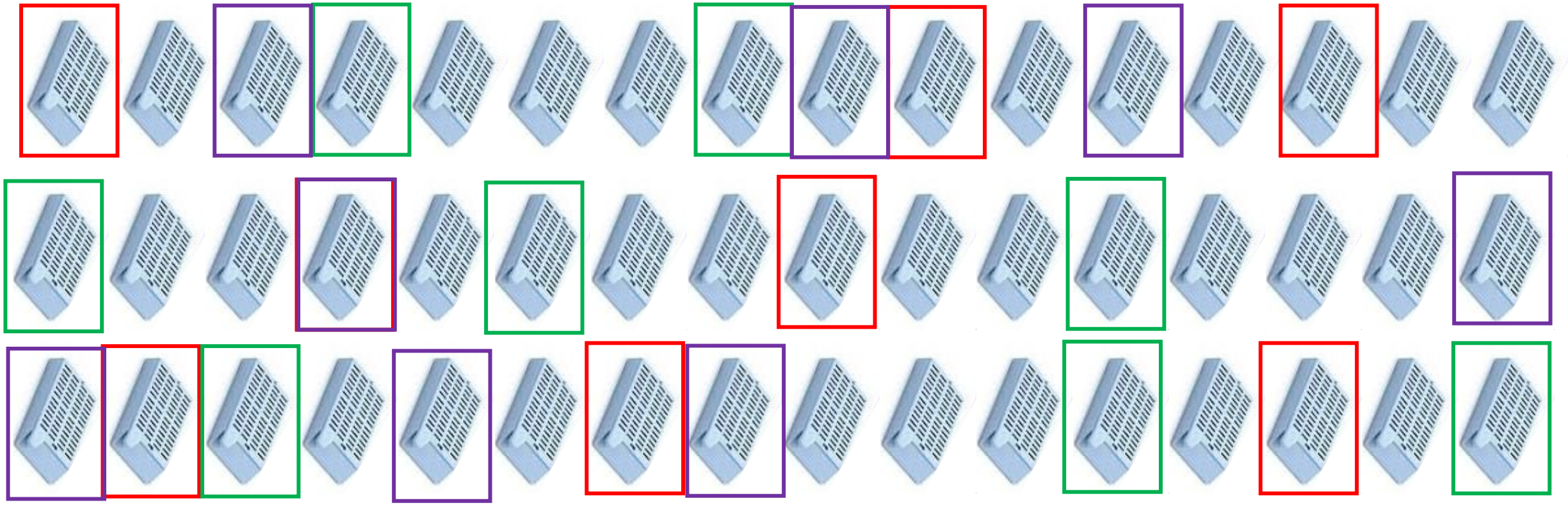
Determine %RVT (Residual Viable Tumor)

Determine MPR (Major Pathologic Response)
or
CPR (Complete Pathologic Response)

From the tumor bed submitted entirely:

Pick a subset, calculate %RVT.
Compare to the Gold Standard %RVT result.
Pick another subset, calculate %RVT.

Do this 1,000 times.

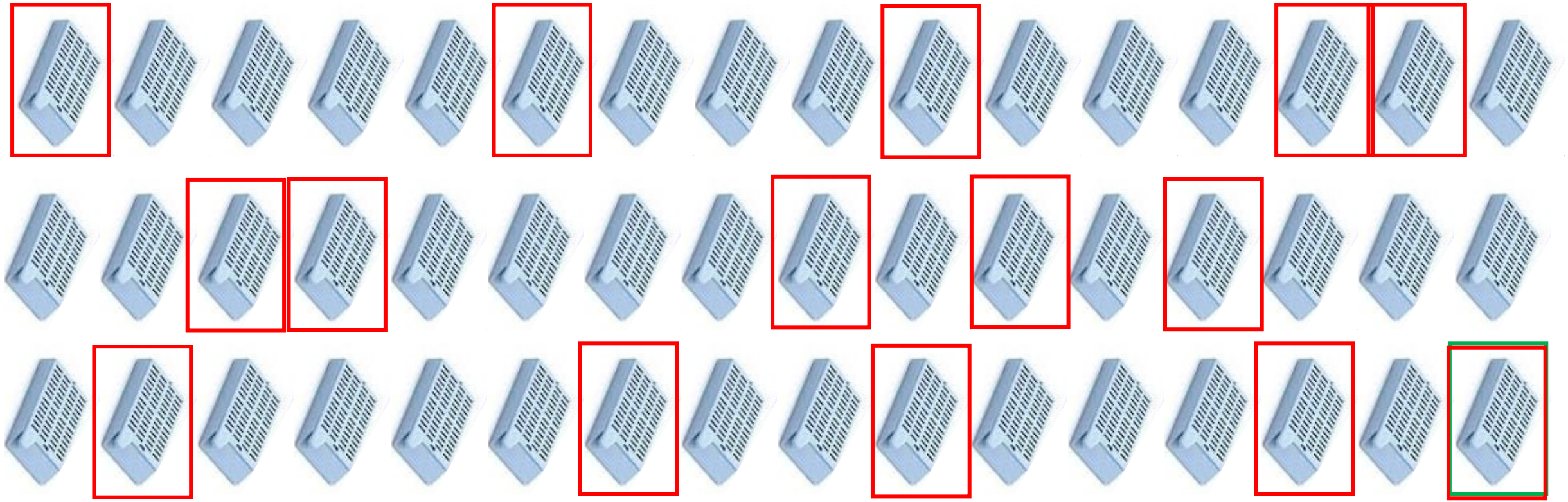


Now pick a bigger subset.  (Or a smaller one.)

Then a different combination of that same number again.

And again.

Do that 1,000 times.

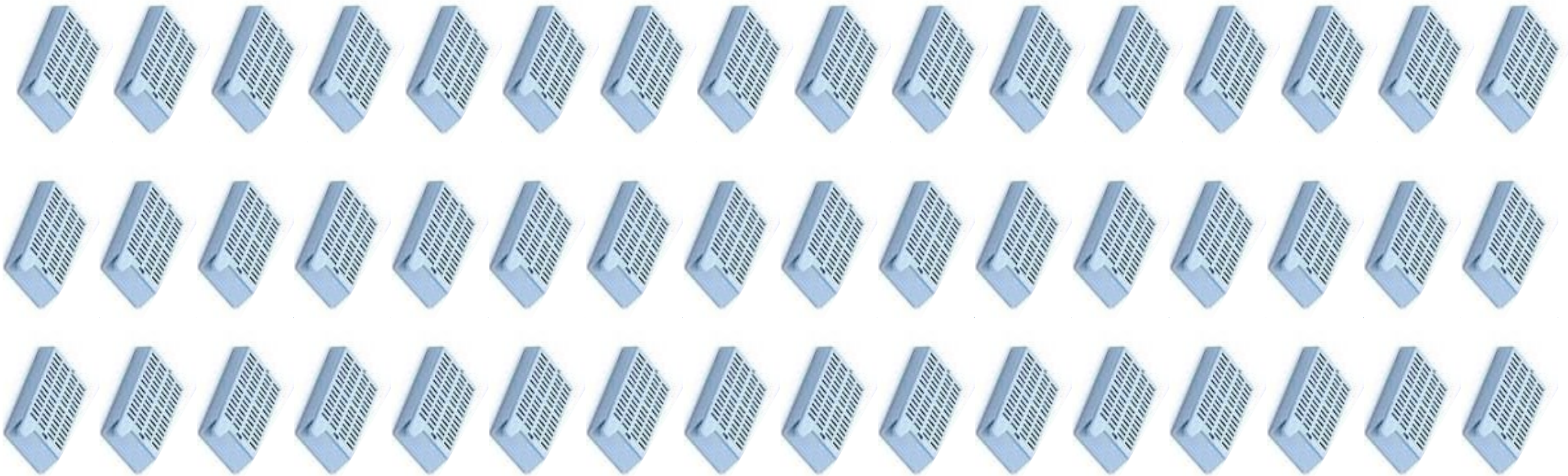


For the results of each (differently-sized) subset:

Compare %RVT to the Gold Standard.

How many sections do we need for 90% accuracy?

*(90% chance of scoring the %RVT within ± 5% of the AuStd)*



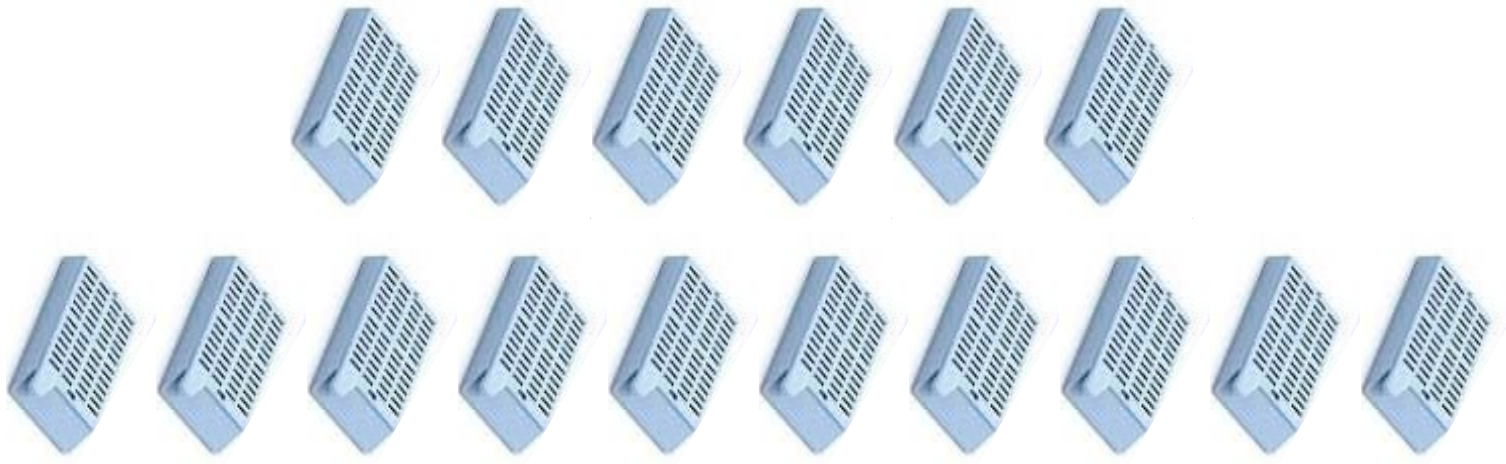
For the results of each (differently-sized) subset:

Compare %RVT to the Gold Standard.

How many sections do we need for 90% accuracy?

*(90% chance of scoring the %RVT within ± 5% of the AuStd)*

Result: 21 slides.



# Summary of Various Recommendations

Cottrell *et al.* 2018:

- 1 section per cm +
- Cross-section of greatest area submitted entirely

Travis *et al.* 2020 (IASLC):

- 1 section per cm +
- Cross-section of most representative of viable tumor (as seen grossly) submitted entirely

Saqi *et al.* 2022 (Colby, Leslie):

- Tumor < 3 cm = submit entirely
- For possible CPR, submit entirely
- All else: submit 50%

Weissferdt *et al.* 2024 (This Article):

- For tumor beds ≤ 20 sections, submit entirely
- For tumor beds ≥ 20 sections, submit 20 sections