DECEMBER PULMONARY PATHOLOGY JOURNAL CLUB

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1. Analysis of recurrence in lung adenocarcinoma with spread through air spaces. Khalil et al. J Thorac Cardiovasc Surg 2023; 166: 1317- 1326

Background

- STAS is common in non-mucinous AD (38-51%) and is associated with higher locoregional recurrence and lower survival.
- What is less well studied are the features of STAS which could be prognostic and the post-op implications i.e. need to reoperate on patients with sublobar resection

Aim

Study their lung cancer experience and define potential features of STAS that could influence recurrence and survival

Material and Methods

Patient Selection

- Retrospective study from the Brigham of 968 patients with T1-3N0M0 lung AD, both mucinous and non-mucinous from 2010-2017 – 787 with feasible histologic examination

Pathology review

- Presence or absence of STAS
- STAS characteristics: micropapillary, solid nest, single cell
- Ave STAS density obtained by dividing the total # of clusters/ #slides
- MSD defined as farthest distance between tumor and STAS at low power

Statistics and Recurrence Metrics

- OS, RFS using KM curves and regression Cox proportional HR
- Locoregional recurrence defined as any growth within same lobe or LN ipsilateral lobar, hilar or mediastinal.
- Distant recurrence defined as contralateral LN, lung, pleural effusion and extrapulm sites
- If at multiple sites, recorded by the most distant site from the resection

Results

- STAS + in 49.4% - More in Male, COPD, smoker, higher T stage including both tumor size and pleural invasion, higher grade, mostly acinar but more solid/papillary, too few micropapillary, rare in LPA, more LVI
- More lobectomy and less segmentectomy and wedge in STAS+, higher stage disease
- STAS mostly in solid nest (58.6%), mean density 2.7 clusters/slide, mean MSD 2.2 mm
- Both OS, DFS local and distant statistically different between STAT+ and – cases, more so for distant
- DFS and OS no different for the various STAS characteristics
- Local DFS better in lobectomy vs sublobar resection but not different for Distant DFS and OS in STAS +. 5-yr DFS for lobectomy in STAS- vs STAS + 88.5 vs 80 %

Conclusion

- Confirm data from other studies
- Their study suggests negative impact on distant disease not just locoregional. Should this be considered simply an intrapulmonary metastasis?
- Data doesn't support going back to do a lobectomy (assuming one could) -Commentary from surgeon proposes that would be more useful to know status of STAT pre-operatively
- Good news none of the histologic STAS parameters were significant

2. BRAF testing modalities in histiocytic disorders. Comparative analysis and proposed testing algorithm. Acosta-Medina et al. AJCP 2023; 160:483-489

Background

- 50-60% of LCH and ECD show *BRAF-V600E* mutation with BRAF inhibitors approved in the treatment of these diseases.
- BRAF IHC eventually replaced DNA sequencing in the identification of mutation in cancers such as melanoma and thus extended to Histiocytic neoplasms without many validation studies in this tumor type.

Aim

1. Compare IHC and allele-specific PCR for *BRAF to NGS*
2. Study role of cell-free DNA based assay for the detection and prospective FU

Material and methods

- 2013-2020, 3 centers, LCH, ECD, RDD, HS, mixed.
- BRAF IHC (2+ in >10% cells), AS-PCR, NGS (mostly Tempus), cfDNA

Results

- 120 cases, 56 ECD, 55 LCH, 3 ECD/RDD overlap, 3 HS, 2 RDD, 1 atypical – 11 from lung
- Test performance
    - IHC in 69%, test failure in 2%, in 6.4% equivocal results(bone decal)
    - PCR failed in 5.7%
    - NGS insufficient DNA in 12.9%
    - See Table 1
- 2 IHC+ histiocytic infiltrates in the lung NEG by all 3 other means and considered false +
- Plasma cfDNA done in 47%, 5 of whom only had cfDNA. 4.5% inconclusive
  See Table 2

Conclusions

- IHC test good performance – issues mostly with decal bone but subject, although rare to false + and mostly some false – using NGS as gold standard.
- Another limitation of IHC or AS-PCR is the inability to detect other mutation in *BRAF* or in *MAP2K1*
- Proposed algorithm which seems reasonable in practice (Figure 4)

3. Deep Learning for Predicting Effect of Neoadjuvant Therapies in Non-small Cell Lung Carcinomas With Histologic Images. Terada et al. Mod Pathol 2023; 36 (11)

Background

- Increase in neo-adjuvant therapy for NSCLC with determinant of efficacy of treatment being MPR defined as ≤ 10% viable tumor cells in the tumor bed.
- Assessment of viable tumor can be challenging, burdensome with interobserver disagreement

Aim

To develop a Deep learning model to assess pathological response

Material and Methods

- 125 consecutive treated NSCLC 2005-2009 with pre-op dx of 72 AD, 46 SQCC, 7 other
- Average **2.1** slides/case, viable tumor estimated in 10% increments except <10 %- single digit 1-5%
- % of viable tumor from original record (primary data) compared to data generated from the 2 pathologists on the study (reviewed data) vs data provided by the model
- Divided cohort in 55 training/validation and 70 test data set and matched for all known prognostic variables
- Construction of the model
    - Validation cohort- Annotation consisted of 1 of nonneoplastic lung, 1 of tumor bed without tumor, 1 of viable tumor – with randomly flipped images, over and under sampling of images
    - Testing on other data set with input of the 3 patches – only at the patch level not the WSI for % of viable tumor
    - Many formulas to calculate Accuracy and Precision based on recall (sensitivity), specificity, precision, mean F1 score (calculated with recall and precision)
- 3-way comparison MPR vs non-MPR and correlation with DFS, OS

Results

- Average tumor bed size 30.8 mm +/- 14.5 mm
- MPR in primary data set 55.2%, reviewed 67.2%
- Recall and precision Model good to excellent – Best for non-neo and worst for viable
- Correlation between Reviewed and Model correlation=0.958 and Primary vs Model 0.878 both $p<0.001$
- Model vs reviewed and primary to predicted MPR both with excellent AUC
- Primary, reviewed and Model MPR all predicted for better DFS, none for OS

Conclusions

- Tumor bed sampling not as recommended by IASLC but not sure this really affects the basics of this study except for predicting OS
- Model appears to work and certainly would make our work easier, especially if we actually sample the tumor bed as recommended by IASLC

4. Loss of YAP1 C-terminus expression as an ancillary marker for metaplastic thymoma: a potential pitfall in detecting YAP1::MAML2 gene rearrangement. Wang et al. Histopathology 2023; 83:798

Background

- Metaplastic thymoma rare with usually indolent course with a ddx of type A thymoma and sarcomatoid carcinoma
- *YAP1:MAML2* gene fusion in almost all thymoma and potentially useful for the differential diagnosis
- FISH is the usual method of detection but risk of false negative with intrachromosal inversion since both genes are located close to each other.
- Good correlation between loss of expression for IHC for YAP1 C-terminus in rearranged tumors

Aim

Study the utility of IHC in the diagnosis of metaplastic thymoma

Material and Methods

- 10 cases of metaplastic thymomas – controls of 5 type A, 3 AB and thymic carcinomas for FISH and 50 conventional thymomas (10A, 10AB, 10 B1, 10 B2 and 10 B3) and 7 thymic carcinomas for IHC
- YAP1 IHC, FISH break apart and fusion, targeted NGS, RNA sequencing followed by validation with RT-PCR and Sanger sequencing

Results

- FISH-BA 100% equivocal, FISH-F, 100% positive, DNA sequencing 20% detection, RNA sequencing 100% (8/8) detection but confirmed by RT-PCR in only 4 (50%). All type A, AB, carcinomas were FISH neg.
- IHC in metaplastic thymoma – all cases had complete loss of expression in lymphocytes. In epithelial cells more variable, the epithelioid cells showed loss but in the spindled cells retained weak expression nuclear and cytoplasmic. In all the 50 thymomas and 7 carcinomas, no loss of YAP was observed and expression was both nuclear and cytoplasmic.

Conclusions

- IHC for YAP appears to be a good surrogate to FISH and in this small study has a 100% sensitivity and specificity for the diagnosis of metaplastic thymoma
- If FISH is used, should be the fusion type and not break apart probes

II. ARTICLES FOR NOTATION

Neoplastic

1. Frequent nuclear β-catenin expression in pulmonary enteric-type adenocarcinoma according to the current World Health Organization criteria. Kishikawa et al. Virchows Archiv 2023; 483:699

The authors identified 5 enteric-type AD (of 3895) consecutive surgically resected carcinomas. All had at least 3 markers of GI differentiation (CK20, CDX2, MUC2, SATB2 and HNF4A). None were positive for TTF – 1 and NKX 3.1. Three with nuclear accumulation of beta catenin, one of which had *APC* mutation. TP53 mutation detected in 3 and EGFR mutation or ALK not detected in all 5. The authors state these findings further support that these tumors share alterations with colorectal AD.

2. Molecular subtype expression and genomic profiling differ between surgically resected pure and combined small cell lung carcinoma. Zhu et al. Hum Pathol 2023; 141:118

The authors looked at the molecular subtypes (ASCL1, NEUROD1, POU2F3 and YAP1) in pure SCLC vs combined SCLC. The data is questionable. First YAP1 is not considered really relevant anymore. And the % of POU2F3 was in the 40%, while NEUROD1 in the 90% and ASCL1 in the 70%. And although there may be co-expression with NEUROD1 and ASCL1, the overall % is nowhere like published thus far especially where POU2F3 is mutually exclusive and should be lower than 10%.

Non-neoplastic

1. Nonspecific interstitial pneumonia pattern is a frequent finding in patients with post-acute COVID-19 syndrome treated with bilateral orthotopic lung transplantation: current best evidence. Mortazavi et al. Hum Pathol 2023; 141:90

The authors set out to report the histologic findings of late COVID in explants only of 20 patients and do a review of the literature. One issue is that all but 4 were on ECMO for 25-157 days which may affect the histomorphology. And they misquoted Anja's publication where it was stated that a diagnosis of late phase of DAD was made (over that of NSIP). And one could argue based on the images that some cases are later phase DAD. But nor here or there. Nothing else really new.

2. Pirfenidone in fibrotic hypersensitivity pneumonitis: a double-blind, randomised clinical trial of efficacy and safety. Perez et al. Thorax 2023; 78:1097

This clinical trial should that pirfenidone was sage and did slow progression of disease. Fits the current narrative of simply lumping all as "fibrosing" interstitial lung disease and treat in a similar way irrelevant of etiology.

Case Report/Correspondence

1. Coinciding kappa AL amyloidosis and kappa light chain deposition disease in the lung. Charles et al. Virchows Archiv 2023; 483:705

Authors describe a patient with Sjogren, LIP and co-existence, proven by mass spectrometry, of amyloid that was Congo Red positive and AL (kappa) type, and Light Chain Kappa where the amorphous material was Congo Red neg and without the amyloid proteins on mass spec.

Review articles

1. Advancing immunotherapy in small cell lung cancer. Carlisle and Leal. Cancer 2023;129:3525–3534

Nice review on the treatment of SCLC with immune therapy with description of results from clinical trial. They also refer to the biology of SCLC and the 4 transcription pathways.