PULMONARY PATHOLOGY JOURNAL CLUB
(July 2015 articles)

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I. ARTICLES FOR DISCUSSION

Review of the role of the immune system in cancer as a whole and more specifically on NSCLC.

IMMUNE SYSTEM AND CANCER

The immune system can recognize and destroy tumor cells

1. Innate immunity:
   a. antigen non-specific immunity: NK cells, mast cells, polymorphonuclear cells
   b. Antigen specific immunity: macrophages, DCs

2. Adaptive antigen specific
   a. Immature DCs capture Ag released by tumor cells
   b. Leads to maturation of DC as an antigen presenting cell and initiation of the cascade of Tcell (CD4+ CD8+) activation and proliferation and recruitment of other immune cells and secretion of various cytokines and other

The immune system can promote tumor growth

Immunomodulation:

1. Elimination: Initially tumor volume is low, immune system can destroy the cells. BUT selects for clones that are capable of surviving the immune system
2. Equilibrium: No tumor growth, continued shaping of the immune system by various pressures. The selected clones remain dormant. This shaping lay lead to immune conditions that facilitates tumor growth
3. Escape: The clones now can subvert the immune response in their favor and allow tumor growth

Key players

1. T reg cells (CD4, CD25, Foxp3 +) suppress the function of the tumor specific CD4, CD8 and NK cells
2. Myeloid derived suppressor cells (MDSC) induces the T reg cells
3. Tumor macrophages secrete cytokines (IL-10 and TGF-B) that inhibit the adaptive immune response

Checkpoints

Even if the T-cells could be activated, the check-points limit the extent of the immune response – physiologic response that tumor exploit to their advantage

1. Cytotoxic T-lymphocyte antigen 4 (CTLA-4). CTLA-4 is expressed on T cells mainly T reg cells and share the same ligands necessary to T-cell activation. In fact has a higher affinity for these ligands and will de facto inhibit T-cell activation. This favors tumor survival.
2. Programmed death-1 (PD-1). PD-1 is expressed on T-cells and binds to different ligands, PD-L1 or PD-L2. PD-1 is present on T reg, can be induced on activated NK cells. Overexpression of PD-1 inhibits the effector phase of T-cell response. PD-L1 is not only expressed on hematopoietic cells but also on tumor cells. This pathway activation leads to tumor survival. Chronic inflammation broadly promotes tumor growth.

IMMUNE SYSTEM AND NSCLC

*Tumor microenvironment*

NSCLC have T regs that express CTLA-4.
CD8+T cells have increased PD-1.
PD-L1 expression on NSCLC tumor cells which correlates with suppression of DCs and reduced T-cell infiltration.
Down regulation of MHC class I/tumor antigen expression so evasion of the immune system
Tumor cells release IL-10 and TGF-B

*Correlate with clinical outcome*

Preformed antitumor T cells and antibodies can be found in the blood of patients with NSCLC
Improved survival with increased TILS CD8+, CD8 and CD4 +, CD3+ T cells, DCs
Decreased survival with increased T reg and tumor macrophages, tumor expression of PD-L1

IMMUNOTHERAPY IN NSCLC

*Immune checkpoint inhibitors*

Most current drugs being tested in clinical trials target PD-1 or PD-L1, but also CTLA-4 (Tables 1 and 2).
Several drugs currently being investigated in phase II and III trials. Overall show promising results when compared to standard of care or in refractory patients, with manageable toxicity.
Some trials do not use a specific biomarker target, others are looking at PD-L1 as a target that may predict response to therapy. Many issues being assessed for PD-L1 as a biomarker (see second article for discussion).

*Vaccines*

*Nonspecific immune stimulation*
2. Programmed Death-Ligand 1 Immunohistochemistry in Lung Cancer In what state is this art? Kerr et al. JTO 2015; 10:985 Concise Review

Review article on all the issues relating of detecting PD-L1 by IHC in NSCLC

EXISTING DATA AND ASSOCIATED ISSUES
Positivity rates for PD-L1 ranges from 13-70%
Treatment response: correlation between response and positive PD-L1 13-83%
1- Biomarker positivity and response
   Although for the most part there is a correlation between + PD-L1 and tumor response to treatment, up to 20% of tumors that are negative for PD-L1 show response when treated. So is this a valid predictive biomarker?
2- Biomarker thresholds
   Variable definition for a positive PD-L1, variable intensity, number of cells required to test. Some studies call positive as low as 1%.
3- Heterogeneity and prior therapy
   Tumor heterogeneity: biopsy versus resection, primary versus metastasis, multifocal lung tumors
   Dynamic nature of PD-L1. Effect of prior therapy on PD-L1 expression so original chemo-naïve biopsy with different expression than the recurrent treated tumor. May explain tumor response in PD-L1 negative tumors
4- PD-L1 in tumor infiltrating immune cells
   Some studies suggest considering tumors as positive for PD-L1 if tumor cells and/or immune cells are positive. What about in a small sample size? What about in metastatic lymph node? Limit the type of specimen usable for this biomarker if assessing immune cells.

TEST REPRODUCIBILITY AND EPITOPE STABILITY
Reproducibility of the test, of the pathologist’s interpretation, archived tumors, preanalytical issues of fixation and processing.

MULTIPLE DRUGS AND MULTIPLE ASSAYS
Currently, each drug is or has been developed in association with a different PD-L1 assay i.e. each drug has its own predictive biomarker. So laboratories expected to have multiple PD-L1 assays validated, each unique to a drug?
   This means different kits, different platforms, large costs
   This means confusion over which PD-L1 to order depending on which drug is being given
   All this on top of different cut-offs of positivity or inclusion of immune cells in the interpretation depending on the test and drug used.

Is harmonization of all these potential tests possible? This would require collaboration and transparency between pharma, diagnostic companies and academic centers, internationally. Many unanswered questions that could also be addressed by a large international multicenter industry study.

**Background**

- CTLA-4, PD-1 and PD-L1 expression in NSCLC has been correlated with survival
  - Small numbers, IHC with various cutoffs and antibodies
- Clinical trials showing early promise with CTLA-4 and PD-1/PD-L1 inhibitors.
  - Squamous more than nonsquamous carcinoma are responsive to ipilimumab (anti-CTLA-4)
  - Tumors positive for PD-L1 higher response to nivolumab
  - Nivolumab and MPD:3280A (anti PD-L1) more active in current/former smokers vs never smokers.

**Aim**

Explore the clinicopathologic factors of tumors with gene expression of *CTLA-4* and *PDCD1* (PD-1) by microarray database

**Material and methods**

- Creating one large database from 3 different data bases caArray, GEO and TCGA
  - Clinical data: age, sex, smoking, histology, grade, stage, survival but not treatment
- Gene expression cut-off as a median over the entire dataset.
- Statistical analysis

**Results**

- 1715 patients
  - 1432 with OS
  - Clinicopath data not available on all (n?)
    - 556 AD and 500 SQCC
    - I:441, II:186, III:67, IV:4
    - 634W:908M
    - 187 never smokers vs 689 current/former smokers
- Gene expression
  - *PDC1* med 65 (2-760) and *CTLA-4* med 95 (2-689)
    - *PDC1* and *CTLA-4* higher in SQCC p<0.01
    - *PDC1* and *CTLA-4* higher in smokers p<0.01
    - *PDC1* and *CTLA-4* higher in higher stage (IV excluded from analysis) p<0.01
  - *PDC1* high expression correlates with OS (but no very impressive when looking at the survival curves with HR=1.29). No correlation with *CTLA-4*. In multivariate we see the opposite with *PDC1* HR 1.22 versus *CTLA-4* 1.96
  - Survival of SQCC not affected by either gene high expression. For AD, high expression of both genes associated with poorer OS HR 1.8 and 1.57
  - In never-smokers, higher expression of both associated with poorer OS HR4.78 and 2.87. In smoking only *PDC1* was still significant
  - In Stage I, higher expression of both were associated with worse OS HR2.14 and 2.12

**Conclusion**
Study on a large number of patients with similar findings of smaller studies looking at IHC. Interesting spin using gene expression. Would have been nice to see how gene expression correlates with IHC. Also would be interesting to see how gene expression correlates with tumor response. Should we be using gene expression instead of IHC?

**Background**
- No significant therapeutic progress for the treatment of SQCC since 1999 with introduction of docetaxel.
- Nivolumab is a fully human IgG4 PD-1 immune-checkpoint-inhibitor antibody that disrupts PD-1-mediated signaling and thus restores anti-tumor immunity.
- Prior Phase 1 and 2 trials showed response rates of 15-17% with OS 8.2 and 9.2 mos and 1yr survival of 41% and 3yrs of 19yrs in previously treated advanced SQCC.

**Goal**
Report results of phase 3 randomized trial that compare nivolumab to docetaxel in platinum based chemo refractory advanced SQCC.

**Materials and methods**
- **Eligibility:**
  - IIIB or IV SQCC recurrence post 1 platinum based treatment
  - Pre-treatment tumor tissue submitted
- **Excluded:**
  - Prior tx with docetaxal or check-point inhibitors
  - Systemic immunosuppression
  - More than one prior systemic therapy
- 352 enrolled patients with 272 randomized
  - 135 to nivolumab – BMS – FDA approved
  - 137 to docetaxel
  - Treatment until progression or discontinuation due to toxic effects
- **Endpoints and assessments**
  - Primary endpoint OS; confirmed objective response removed based on Phase 1 trial results.
  - Other endpoints: PFS, patient reported outcomes, correlation with PD-L1 expression and safety
  - Tumor response using RECIST, QOL questionnaire, adverse events monitoring
- PD-L1 retrospectively analyzed by IHC with Epitomics clone 28-8. Tumor membranous cell staining and categorized as + for 1%, 5%, 10% or more in specimens with at least 100 cells.

**Results**
- 260 received treatment with 1 of the 2 drugs. FU min 11 mos
- Baseline characteristics in Table 1. No surprise predominance of white males current or former smokers with stage IV disease.
- Median OS was 9.2 mos for Nivolumab versus 6.0 mos for docetaxel p<0.001
  - HR0.59 versus 0.76
- Rate of confirmed objective response significantly higher with Nivolumab with mean duration not reached at analysis p=0.008
- Median PFS was 3.5 mos versus 2.8 mos, at 1yr was 21% versus 6%
- Adverse events less with Nivolumab with 7% having grade 3 and 4 events and 0 grade 5 versus docetaxel 55% with grade 3 or 4 events and 2% with grade 5.
  - Lead to discontinuation in 3% vs 10%
• PD-L1 expression in 225 patients, positive cases balanced between both groups
  o In both groups up to 40% <1% staining and 24/27% with >10% cells staining
  o PD-L1 expression was neither prognostic nor predictive

Conclusions
• Superior survival with better safety profile versus standard of care
• Also superior for objective response, longer PFS
• PD-L1 assay likely does not reflect the complex interactions between tumor and immune system and thus not predictive
II. ARTICLES FOR DISCUSSION/NOTATION

1. BAP1 IHC and p16 FISH to separate benign from malignant mesothelial proliferation. Sheffield et al. AJSP 2015; 39:977

   **Background**
   - Distinguishing benign mesothelial proliferation from MM can be challenging and remains mainly based on identifying invasion on H&E.
   - Several markers have been studied, EMA, p53, GLUT1, IMP3 and desmin, with lack of appropriate specificity for a useful clinical test.
   - FISH for p16 deletion highly specific for malignancy but low rate in MM
   - BAP-1 germline mutation associated with increased cancers including MM

   **Aim**
   To study p16 and BAP1 as a diagnostic panel to separate benign from MM

   **M&M**
   - TMA with multiple cores of 83 cases: 52 benign and 31 MM (27 pleural)
   - FISH for p16
   - IHC for BAP1, p53, EMA
   - Used their prior published data on GLUT1 and IMP3 for comparisons

   **Results**

   **TABLE 2.** Test Characteristics of p16 FISH, BAP1, EMA, p53, IMP3, and GLUT1 IHC

<table>
<thead>
<tr>
<th>Marker</th>
<th>BAP1 IHC</th>
<th>p16 FISH</th>
<th>EMA</th>
<th>p53</th>
<th>IMP3*</th>
<th>GLUT1*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>75</td>
<td>67</td>
<td>81</td>
<td>77</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>Benign</td>
<td>0/49</td>
<td>0/40</td>
<td>8/50</td>
<td>23/49</td>
<td>13/48</td>
<td>6/48</td>
</tr>
<tr>
<td>Malignant</td>
<td>7/26</td>
<td>14/27</td>
<td>10/31</td>
<td>16/28</td>
<td>16/30</td>
<td>18/30</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>27 (17-37)</td>
<td>52 (40-64)</td>
<td>32 (22-42)</td>
<td>57 (46-68)</td>
<td>53 (42-64)</td>
<td>60 (49-71)</td>
</tr>
<tr>
<td>Specificity</td>
<td>100 (100-100)</td>
<td>100 (100-100)</td>
<td>84 (76-92)</td>
<td>53 (42-64)</td>
<td>73 (63-83)</td>
<td>88 (80-95)</td>
</tr>
</tbody>
</table>

   **TABLE 3.** Test Characteristics of BAP1 IHC or p16 FISH Compared With Other Proposed Panels*

<table>
<thead>
<tr>
<th>Panel</th>
<th>BAP1 IHC</th>
<th>EMA p53</th>
<th>EMA and p53</th>
<th>IMP3 and GLUT</th>
<th>p53 and IMP3 and GLUT</th>
<th>EMA and IMP3 and GLUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>61</td>
<td>76</td>
<td>76</td>
<td>78</td>
<td>73</td>
<td>76</td>
</tr>
<tr>
<td>Benign</td>
<td>0/37</td>
<td>24/48</td>
<td>6/48</td>
<td>2/48</td>
<td>2/45</td>
<td>1/46</td>
</tr>
<tr>
<td>Malignant</td>
<td>14/24</td>
<td>18/28</td>
<td>7/28</td>
<td>13/30</td>
<td>10/28</td>
<td>6/30</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>58 (46-71)</td>
<td>64 (54-75)</td>
<td>25 (15-35)</td>
<td>43 (32-54)</td>
<td>36 (25-47)</td>
<td>20 (11-29)</td>
</tr>
<tr>
<td>Specificity</td>
<td>100 (100-100)</td>
<td>50 (39-61)</td>
<td>88 (80-95)</td>
<td>96 (91-100)</td>
<td>96 (91-100)</td>
<td>98 (95-100)</td>
</tr>
</tbody>
</table>

   **Conclusions**
   - BAP1 and p16 appears to be a good panel although sensitivity still on the lower side.
     - I would have been curious about adding IMP3 and/or GLUT1 to that panel and see the effect on sensitivity
   - BAP1 loss by IHC could be used as an indication to look for germline mutation
   - And not mentioned in this article, **BAP1 is a potential therapeutic target** being looked at in uveal melanoma

Background

7th Ed published in 2009 based mostly on retrospective data so not everything could be validated. So IASLC launched a new database to collect new prospective data.

M&M

- 77,156 patients, 70,967 with NSCLC and 6,189 with SCLC
- Only M0 with complete set of either cTNM or pTNM with known tumor size and enough T descriptors, and no induction treatment. Resection completeness as R0 or R1
- Asia contributed the most and AD represented 64% of all NSCLC
- T descriptors evaluated individually, including when associated with other T descriptors. If potential for reclassification, then assessed in multivariate. Specific comparisons made between new and prior 7th Ed descriptors looking at survival

Results/Recommendations

- T1 classified as T1a ≤ 1cm, T1b >1 ≤ 2cm, T1c >2 ≤ 3cm
- T2 classified as T2a >3 ≤ 4cm, T2b > 4≤ 5cm
- T that are > 5≤7cm to be classified as T3
- T >7cm to be classified as T4
- Tumor more than 2 cm away from carina AND < 2cm without invading carina now all T2
- Tumor with partial atelectasis/obstructing pneumonia AND complete atelectasis/obstructing pneumonia now all T2
- Invasion of diaphragm to be classified as T4
- To remove invasion of mediastinal pleura as a T descriptor

Conclusions

- These recommended changes result in clear distinct survival curves with more define differences between T3 and T4 compared to prior 7th Ed
- They make no recommendation for the AIS/MIA/LPA tumor in terms of using invasion to measure the T. A separate subcommittee was created to write a white paper on the topic. Currently, Union for International Cancer Control recommended the use of invasion for T. This is what we received in the e-mail from the Pulm Path Society.
- Limitation of the database for many T3 and T4 descriptors so many could not be validated
- Although PL1 and PL2 show differences in survival still remain lumped as VPI and a T2 descriptor
3. Molecular Characterization of Inflammatory Myofibroblastic Tumors With Frequent ALK and ROS1 Gene Fusions and Rare Novel RET Rearrangement
Antonescu et al. AJSP 2015; 39:957

**Background**
- About 50% of IMT have ALK translocation involving >10 different partners.
- The morphology is so varied that ALK- IMT may not be IMT
- One NGS study of 9 ALK-IMT showed other fusion for ALK, ROS1 and PDGFB

**Aim**
Study IMT for wide variety of actionable kinases

**M&M**
- Identified IMT using the WHO definition
- FISH for ALK, ROS1, PDGFB, NTRK1, RET
  - If ALK rearranged, PCR for EML4 and if ROS1 for TFG
- RNA seq

**Results**
- 62 IMT 18 of which were from the lung
  - 15/18 with rearrangements
  - 12 ALK including 5 with ELM4
  - 2 ROS1
  - 1 novel RET
- ALK IHC was neg in 24% of cases with ALK rearrangement. At least one was a lung and a lung with ALK-ELM4 done with 2 different Ab.
  - Can’t tell how many others were neg for ALK IHC but since lung was the one organ with the most ALK rearrangement, likely more than 1

**Conclusions**
- If you are using ALK IHC to confirm your dx of IMT, this study indicates you can’t, not only because IMT may be neg for ALK IHC but that ALK IHC had high rate of false negative so FISH would be better
- If dealing with a higher stage IMT consider doing ALK, ROS1 and RET like for our lung AD since they may be rearranged and thus a therapeutic target
III. Articles for notation


   **Background**
   Bronchoscopy has limitations in assessing patients with lung nodules suspicious for cancer. This often leads to additional invasive procedures with increased rate of complications and mortality and with possible end result of a diagnosis of a benign lesion.

   **Aim**
   To assess the value of adding a panel of cancer associated gene expression pattern in cytologically normal bronchial cells

   **M&M**
   - Smokers, current or former, enrolled prospectively in 2 clinical trials AEGIS-1 and 2
   - FU to diagnosis or 12 mos after bronchoscopy. Free of cancer defined as having a diagnosed benign lesion or resolution/stable nodule on imaging after 12 mos.
   - Pre-test probability calculated and divided as low <10%, intermediate as 10-60% and high >60%
   - 23 gene panel previously published.
   - Assessed AUC of ROC and sensitivity, specificity, PPV and NPV

   **Results**
   - 289 patients in AEGIS-1 and 341 in AEGIS-2
   - Non dx bronch in 43% with bronch sensitivity of 74-76%
   - Most patients with neg bronch had second invasive procedures
   - AUC for the panel was 0.78 and 0.74 with sensitivity of 88-89% AND specificity of 47%
   - Adding panel to bronch increased the sensitivity of 96%
   - Non dx bronch in 83% of patients with intermediate pre-test probability and gene panel in that group with NPV of 91% and PPV of 40%

   **Conclusion**
   Interesting data. The gene panel mostly valuable in determining close follow-up versus second invasive procedure. And really close follow-up since there were false negatives.


   **Background**
   - AD in smokers have a different profile than AD in never smokers (more male, higher grade, solid, KRAS mutation, EGFR wild, low TTF1 and high mucin)
   - These differences noted in invasive adenocarcinoma, not studied in AIS
   - pAKT and pStat 3 associated with never smokers and pERK with smokers in invasive AD. Pathways important in tumor development

   **Aim**
   - Compare AIS in smokers vs never smokers

   **M&M**
• 2087 resected NSCLC, 1549 with AD of which 110 (7.1%) with AIS
• Mutational status of EGFR and KRAS
• IHC for pERK, pSTAT3 and pAKT using TMA (1 2mm punch per tumor).

**Results**

- AIS vs AD, younger, more female, more never smokers
- AIS with 74 never and 36 smoker
  - AIS never with more female otherwise no differences
  - No difference for EGFR and KRAS
    - Therefore looked at EGFR and KRAS in random 216 AD
    - EGFR more in never, no difference with KRAS
    - EGFR was more prevalent in never smokers, more male with invasive AD
  - No difference for pAKT, pERK and pStat3
- Mucinous AIS (n=8) to non mucinous AIS
  - Younger, TTF1 neg, and wild type EGFR
  - Less pStat 3
  - BUT only 1 with KRAS mutation

**Conclusions**

Interesting observations. AIS being so low grade with TTF1 + would have predicted more never smokers and more EGFR mutated….And same mucinous AIS would have predicted a more similar profile with mucinous AD…


Potentially is the operative word here. Well done study, very nice photomicrographs. But same limitations as all these prognostic studies targeting a few markers in a relatively small cohort of NSCLC with various other confounding prognostic factors. Study looked at various vascular markers along with VEGF and VE-cadherin and showed lower MVD in SQCC particularly in the center of the tumors and higher CD105 in AD.

4- **Implementation of Amplicon Parallel Sequencing Leads to Improvement of Diagnosis and Therapy of Lung Cancer patients. Konig et al. JTO 2015; 10:1049**

Methodology paper describing the generation of NGS lung cancer panel and its validation against standard of methods for testing of common mutated genes in lung cancer. The panel is comprised of over 100 amplicons covering 14 genes for both AD and SQCC. Tested more than 2,500 lung cancers. Their test method was comparable to current PCR testing with TAT of about 15 days (up to 21 days if FISH ALK done). There are many advantages to such panels including reduced requirement of tissue (in contrast to the 1 x 1 current test strategy). Furthermore, once testing for SQCC also becomes routine, with such panels, discerning AD from SQCC is no longer critical and leads to tissue preservation (ie avoiding the need to IHC for dx). This particular panel has limitation because only looks at mutations not rearrangements.

Similar study as above but much smaller in scope, using 35 amplicons for 10 genes and validated in 23 lung cancers. Similar advantages as stated above. Although also recognized high technology not available to all.

6- **An Integrated Prognostic Classifier for Stage I Lung Adenocarcinoma Based on mRNA, microRNA and DNA methylation Biomarkers. Robles et al. JTO 2015; 10:1037**

Study looking to prognosticate patients with Stage I lung cancer and identify patients at high risk of recurrence and death of their disease who may benefit from adjuvant therapy. “may” is the operative word as it seems oncologists are reticent to look at the role of adjuvant therapy in patients with Stage I disease. They identified a methylation marker HOXA9 (which was also identified as a good marker in another study) which by itself separates in multiple cohorts patients with higher risk of recurrence and death. This marker combined to miR-21 and a previously studied 4 panel gene (XPO1, BRCA1, HIFalpha, DLC1), separates with very high p-value high risk Stage I patients. This panel is nicely validated across multiple different cohorts. Added value. But could be a complicated clinical test to put together.

7- **Histologic variability in SFT reflects angiogenic and growth factor signaling pathway alterations. Demicco et al. Hum Pathol 2015; 46:1015**

Authors looked at various growth factors, RTKs and markers of AKT activation in SFT to see if differences between hypocellular and cellular HPC like, and between non-metastatic and metastatic SFT. Also looked for mutations. 114 SFTs (122 for sequenom study) including 22 pleural SFT. VEGF and PDGFR beta higher expressed in cellular SFT (no details on the pleural SFT). No prognostic impact for any of the studied markers. And potential MET involvement (thus potential therapeutic target) that requires confirmation.

8- **French multicentric validation of ALK rearrangement diagnostic in 547 lung adenocarcinomas. Lantuejoul et al. ERJ 2015; 46:207**

Authors report the French experience from 13 centers looking at ALK by FISH, IHC with 54A and D5F3 and by qRT-PCR. Of 547 AD, 140 ALK+ by FISH, 13 of which neg by IHC, higher number in 1 center and higher in FISH positive in only 10-20% of cells. Sensitivity better for D5F3 only by 2% (87 vs 89%) but specificity better for 5A4. Several variants found in ALK FISH+ cases. Their experience similar to reported in literature and the authors suggest a testing algorithm adopted by others i.e. screening with IHC and confirmation of + IHC by FISH. However, the FDA just approved using IHC results to determine patients eligible for treatment. So FISH really not necessary anymore.

9- **Immunohistochemical characterization of the mTOR pathway in stage I NSCLC. Shin et al. Lung Cancer 2015; 89:13**

Prognostic study looking at IHC of different markers of the mTOR pathway, PTEN, pm-TOR, pS6, eIF4E using TMA of 408 NSCLC Stage I 250 AD and 158 SQCC. AD was associated with retained PTEN and higher expression of pm-TOR, pS6, seen more with lower T. In univariate, gender, pT, vascular invasion, PTEN alone, PTEN-/pAKT+/pmTOR+ associated with worse OS. In multivariate, pT, vascular and PTEN-/pAKT+/pmTOR+ remained significant. Although looking at survival curves
not great OS for Stage I and not dramatic difference with this combination of markers.

10- Napsin A is frequently expressed in clear cell carcinoma of the ovary and endometrium. Iwamoto et al. Human Pathol 2015; 46:957

Another tumor type that can express Napsin A. Rare Napsin A+ case was TTF-1 + usually a few cells except for one case. There was no Napsin A AND TTF-1 + cases. And all were PAX-8 +. The authors did not have any lung cancer cases as controls.

**Review articles or consensus statements**


Panel review of the literature with recommendations. Most recommendations are not to use a variety of drugs. But there some advances since 2011 and few drugs or drug combination are now recommended with “low or moderate confidence in estimates of effect”.


This review article discusses the following cystic disease (as viewed by radiology as cystic): Birt-Hogg-Dube Syndrome, CPAM and other aberrant lung development with cystic changes, LIP, amyloid, light-chain disease, and a few miscellaneous. Very good review of all aspects: clinical, radiology, pathology and management. Followed by discussion on mechanism, radiologic evaluation, pathologic evaluation and diagnostic approach.


Routine lung cancer screening has not yet begun in Europe. This white paper reviews the current literature on lung cancer screening. FACTS: NLST study (53,000 participants) found mostly Stage I lung cancers yet 43% of participants in the screening arm died of lung cancer. Netherland’s NELSON trial (15,000 participants) will be completed end of 2105. Italian MILD and Denmark DLST showed no advantage to screening. CURRENT Recommendations on who should be screened has been modified numerous times trying to capture the high risk population yet trying to decrease the other challenges related with screening i.e. pre-test probability, overdiagnosis, radiation exposure, cost-effectiveness, and management of patient expectations. Also other considerations is to broaden the scope of screening to included Emphysema, ILD and calcific coronary and aortic disease as risk markers for cardiac diseases. The article concluded with long list of recommendations for a screening program in Europe.

**Case reports**


The title says it all….