Articles for Discussion


Background: The real impact of patient outcome of IHC-based subtyping of morphologically undifferentiated NSCLCs, NOS compared with the behavior of cases having morphology-driven diagnoses has not been established. This was the purpose of the current study: comparing outcome of pts with IHC subtyped tumors to two separate groups of morphology only tumors: ADC and NSCLC NOS phenotype.

Methods: 224 consecutive patients with advanced NSCLC, 2005 to 2010. Patients received a variety of platinum-based and other therapies. Patients were not routinely checked for EGFR mutations or ALK translocations during this time frame.

Two groups were identified: ADC based on morphology and NSCLC-NOS (cases which might have had NE morphology excluded). NSCLC-NOS group further analyzed using a minimalist ICH approach (TTF, p40, Napsin-A, DSC3).

Statistical analysis

Fisher’s t test, and Kaplan-Meier and log-rank tests for survival.

Results: 67% of cases: ADC based on morphology, 33% as NSCLC.

Then, IHC profiling identified 43.2% as NSCLC, favor ADC, 10.8% NSCLC favor squamous and 46% NSCLC-NOS.

Survival curves showed no difference for outcome between morphologic ADC and NSCLC, favor ADC.

Significantly poorer outcome for NSCLC NOS group including best response, progression free survival and overall survival.

Conclusion: Tumors with ADC-like IHC profile had overall survival comparable to that of morphologically defined ADC supporting the use of IHC to optimize lung cancer typing and therapy.

Comment: Authors ought to be congratulated for at least attempting to make sense of the current WHO recommendations. Their panel of only four markers, however, is double what the new WHO is going to recommend. They do not comment on any apparent discordance with IHC immunophenotype stating 43% showed TTF and/or Napsin reactivity (NP40/DSC3 negative) and 11% showed p40 and/or DSC3 reactivity with TTF-1/Napsin-A negative. I find this rather hard to believe.

**Background:** There have been few studies evaluating interobserver variability of WHO criteria for classification of pulmonary carcinoids (PC) into typical (TC) and atypical (AC). The authors hypothesize that apoptotic cells may be misinterpreted as mitotic figures leading to frequent misclassification.

**Methods:** 123 tumors diagnosed from a variety of European centers were classified by five observers into unanimous agreement, consensus agreement, 4/5; and disagreement, 3/5. In a consensus meeting involving 4 of 5 pathologists, all disagreement cases were reevaluated and reallocated to TC and AC categories along with possible reasons for disagreement.

Stains also performed with antibodies to Ki-67 and orthopedia homeobox protein (OTP).

Statistical analysis included calculation of kappa values compared to proliferative index, OTP immunostaining and follow-up Kaplan-Meier data.

**Results:** Overall agreement was 79% with considerable variation with an individual assessor’s classification.

Among 114 cases of accepted PC’s a unanimous diagnosis was only reached in 55.3% with consensus diagnosis reached in 25.4%. In 19%, there was disagreement. Kappa = 0.316 (fair).

ACs were underrepresented in the unanimous and consensus categories and overrepresented in disagreement cases.

Most differential diagnoses were based on mitotic count. Necrosis was detected in only eight cases but there was only one tumor where all pathologists agreed that necrosis was indeed present.

**Reclassification related to clinical follow-up and possible additional value of molecular markers**

When the “majority classification” into TC and AC were combined, differences in prognosis were not significant! \( P = 0.11 \) (A). There were differences between consensus and unanimous TCs and ACs in Kaplan-Meier curves \( (P = 0.0036, B) \) but the survival graphs of the disagreement cases crossed with the TCs exhibiting a slightly worse prognosis as compared to ACs (C).
FIGURE 2. Survival analysis based on reclassified pulmonary carcinoids and the efficacy of the utilization of consensus reclassification or molecular markers in disagreement cases. Twenty-year overall survival rates of pulmonary carcinoid tumors using either reclassifications only (A–C) or a combination of reclassification and the results of a consensus meeting (D) or molecular markers (E and F). A, Comparison between the complete group of TCs (solid line) and ACs (dotted line) as reclassified by the majority of pathologists. B, Survival analysis of consensus and unanimous TCs (solid line) and ACs (dotted line) only. C, Survival analyses of disagreement TCs (solid line) and ACs (dotted line) only. D–F, Survival analyses of disagreement cases redistributed after a consensus meeting (D), or by use of Ki-67 proliferative index <5% (solid line) or ≥5% (dotted line) (E), or positive (solid line) or negative (dotted line) OTP immunostaining (F).

Disagreement cases in relation to consensus reclassification and molecular data

Most difficulties were related to distinguishing mitotic figures from apoptotic cells. Using Ki-67 (<5% versus ≥5%), the prediction of prognosis improved significantly ($P = 0.0085$, D). OTP immunostain
was also strongly correlated with decreased 20 year survival within combined AC/TC group as well as within TC group.

**Discussion:** There remains considerable interobserver variability in classification of AC/TC possibly related to low numbers of mitotic figures that need to be counted in a large microscopic area.

- WHO does not specify how mitotic figures should be counted.
- Results are similar to other studies reported on this topic.
- Consensus classification did not improve prediction of prognosis (ask who is not surprised by this result who used to have a mullet).
- Authors suggest that the use of molecular markers may improve classification.

**Comments:** It is surprising that this group did not go even further and suggest that lung carcinoids be classified similar to pancreatic neuroendocrine tumors where thousands of fields are supposed to be counted. Study anyone?


**Background:** The paired box transcription factor PAX8 is a nephric kidney-lineage transcription factor expressed in various normal tissues. It has been identified in thyroid, kidney and müllerian tumors but has also been reported in thymic NEC, B lymphocytes and B cell lymphomas. Recent studies employing PAX8 polyclonal antibodies have shown cross-reactivity with the B cell-specific transcription factor PAX5 and so previously reported PAX8 immunopositive normal tissues and tumors represented by B lymphocytes that did not express PAX8 mRNA could be considered to be due to cross-reactivity. The present study was performed to compare IHC profiles of PAX8 polyclonal, monoclonal and PAX5 monoclonal and PAX6 monoclonal antibodies in several histologic types of primary thoracic and thyroid tumors. PAX8 mRNA expression using ISH was also performed.

**Methods:** Nine hundred sixty-two (962) cases were analyzed from a broad spectrum of thoracic and thyroid neoplasms in TMAs.

IHC: PAX8 polyclonal (Proteintech, Chicago, IL), PAX8 monoclonal (Abcam, Cambridge MA), PAX5 monoclonal (clone 24, BD Biosciences, Franklin Lakes, NJ), and PAX6 monoclonal (P3U1, Developmental Studies Hybridoma Bank, Iowa City, IA).

Tumors considered positive if >5% of nuclei stained.

**Results:**
When using thyroid tumors as the gold standard of PAX8 antibodies the sensitivity was 98% for both monoclonal and polyclonal PAX8. Monoclonal, however, showed lower intensity and percent of positive cells.

PAX5 reactivity observed in 3.5% of lung carcinoma, mostly neuroendocrine tumors, and 20% of thymic carcinomas. Thyroid tumors, other lung tumors and mesotheliomas and thymomas were negative for PAX5.

PAX6 positive in rare thyroid tumors but 15% of lung carcinomas, 12% mesotheliomas and 14% of thymic tumors.

No PAX8 mRNA was detected in non-thyroid tumors.

Discussion: Their figure 3 shows some attractive Venn diagrams showing overlapping positive cases.

Conclusion: Monoclonal PAX8 showed high specificity for thyroid tumors and was superior to the polyclonal antibody. The authors suggest switching to the monoclonal PAX8 antibody for routine practice. PAX5 and PAX6 antibodies are not very useful in the context of solid organ tumors. PAX5 may be useful in distinguishing pulmonary NETs from non-NETs.

**Background:** It is well known that NSIP may have overlap features with other interstitial pneumonias. The aim of this study was to determine whether subgroups defined by minor criteria could be identified prospectively and be shown to have prognostic significance.

**Methods:** One hundred thirty-six (136) consecutive patients with NSIP on SLBs seen at Avicenne University Hospital from 1983 to 2010. Pathologic diagnosis approved by two expert pathologists (A.G.N. and M.K.).

Seven pathologic subgroups were identified: NSIP/ UIP, NSIP/cHP (including rare granulomas), NSIP/organizing DAD, NSIP/DIP, NSIP/LIP, and “essential NSIP” where there is an absence of any of the features which might suggest an overlap pattern.

**Results:** Medical records not available for 9/136 patients so n=127 formed the study group and were correlated with clinical settings: CTDs 22.8%, cHP 11.8%, idiopathic NSIP 65.3%. No patient had prior ARDS. Classification after histologic review: essential NSIP 36%, NSIP/UIP 25.7%, NSIP/cHP 10.3%, NSIP/OP 5.9%, NSIP/organizing pneumonia 9.6%, NSIP/DIP 6.6%, NSIP/LIP 2.2%. Interobserver concordance kappa = 0.87. No consensus could be reached on five patients and these cases were therefore not classified.

Clinical correlation: subgroups did not differ for age, sex or smoking. Significant differences were observed for duration of symptoms before SLB for pts having NSIP/organizing DAD overlap with a more rapid course. Patients with NSIP/cHP were more likely to have a clinical diagnosis of cHP and those with NSIP/OP often had a diagnosis of CTD.

Most patients had some type of immunosuppressive therapy.

Survival: patients with NSIP/organizing DAD had the worst survival (32% at 5 years), next worst NSIP/UIP overlap (57% at 5 years).

Multivariate analysis: factors associated with higher mortality were the presence of NSIP/organizing DAD overlap, NSIP/UIP overlap, and clinical diagnosis of cHP.

**Discussion:** Most cases were classified as essential NSIP with a predominant fibrotic pattern.

Although none of the patients with NSIP/organizing DAD overlap had a history of acute lung injury or experienced rapid worsening of dyspnea, the results suggest there is a subgroup of patients who experience an accelerated fibrotic process which meets NSIP criteria.

They suggest that the presence of organizing pneumonia be clearly noted in the report to compel clinicians to search for an autoimmune disease.

No clear association to NSIP/DIP overlap group could be identified with a history of smoking.

**Comment:** Overall, I thought this was an interesting and worthwhile paper. It certainly fits with our experience and offers some additional insights which may be beneficial in diagnosing and caring for patients with NSIP. But, why not call NSIP with granulomas HP outright, or least NOT NSIP? Also, no CT results given. Perhaps with MDD, some patients would have been classified as poorly sampled UIP.
Neoplasms


Case Report
A 40-year-old woman who presented with multiple scattered mass-like nodular opacities found to be epithelioid hemangioendothelioma reactive with antibodies to ETS-related gene (ERG), CD31 and Fli-1. Metastases were present in regional lymph nodes.

Comment: A reasonable case report and interesting genetics, but rather surprising it got published in Chest.


Objective: To show a comprehensive description of recent histologic cancer incidence rates and trends using the CDC National Program of Cancer Registries (NPCR) and National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) Program.

Results: Overall rates for lung carcinoma have decreased but the incidence remains stable for women greater than 50 years. Adenocarcinoma rates continue to increase in men and squamous cell has increased in women only. All histologic subtypes for white women exceed rates for black women. Histologic rates for black men exceed those for white men except for small cell carcinoma. The incidence rate for Hispanics is half that for blacks and whites.

Similar results to other studies that have been recently published and discussed at journal club.

Comment: It’s here if you need it!


This is a short paper outlining how the ITMIG has developed a large centralized database to advance knowledge about these rare tumors. Over a six month period 47 institutions in 15 countries contributed a total of 6,097 cases.

WHO type B2 was the most frequent histologic type of thymoma.
Squamous carcinoma the most common thymic carcinoma.

Thirty-eight percent (38%) of patients with thymoma had myasthenia gravis compared to less than 5% for thymic carcinoma and thymic carcinoid.

**Conclusion:** This database provides a rich resource for research into these tumors.


**Background:** Authors report four new cases of PPMS.

**Methods:** Four cases identified at Seoul National University Hospital (2000 – 2012).

Initial diagnoses included low grade pulmonary myxoid sarcoma of uncertain histogenesis (3 cases) and IMT (1 case). No patient had previous tumor at an extra-pulmonary site.

IHC and RT-PCR as well as FISH and EM performed.

**Results:** Patients ranged from 26 to 65 years of age and tumors ranged from 4 to 13 cm in greatest dimension.

Histology: all tumors were adjacent to a bronchus with or without endobronchial component; were well circumscribed, multi-nodular, and distinctly gelatinous. Tumors had other characteristic features including variable cellularity, and extensive myxoid change with rare mitoses and no necrosis. Tumor cells generally reactive with antibodies to vimentin; EMA and smooth muscle actin only focally positive. Tumors negative for desmin, caldesmon, SM-MHC and calponin, epithelial and myoepithelial, endothelial, neuroendocrine, chondroid, and melanocytic markers all negative. Ultrastructural features suggestive of primitive mesenchymal cells with myofibroblastic or fibroblastic differentiation were identified.

EWSR1 translocation was detected in the majority of tumor cells by FISH in all cases. RT-PCR revealed EWSR1-CREB1 exon 7 fusion transcripts in all cases.

Follow-up: three patients have had no recurrence up to eight years and one patient had a metastasis but is currently free of disease 72 months later.

**Discussion:** Nicely illustrated and worked up cases and the photos serve as a good reminder of what this tumor looks like.

Review of factors which should be considered in obtaining and processing biopsy specimens to enable routine molecular analysis in NSCLC patients.

Manuscript outline:

Introduction
The selection of biopsy site
Type of sample for molecular testing
Preanalytic processing of the specimens
The role of the pathologists
Conclusions

Comment: A good overview and a nice comprehensive reference if you need one for this topic.


Background: The authors evaluate whether serum CEA and the presence of lymphvascular invasion affect progression free survival in patients with surgically resected stage I NSCLC.

Methods: Seven hundred fifty-eight (758) surgically resected stage I NSCLC patients were selected.

Results: Five year progression free survival was 82.3% for stage IA and 64% for stage IB.

Multivariate analysis revealed poor or moderate histologic differentiation and elevated preoperative serum CEA statistically significant for recurrence in stage IA.

Poor or moderate histologic differentiation, elevated preop serum CEA, lymphvascular invasion and tumor size greater than 2 cm statistically significant risk factors for recurrence.

Conclusion: The authors suggest that serum CEA and histologic differentiation as well as lymphvascular invasion were independent risk factors for recurrence among patients with stage IA. The authors comment that this is one of the largest studies to analyze these parameters.

Comments: Despite their conclusion, they give no guidance on how to classify tumors as well moderate or poorly differentiated. How do these papers get published?


This article represents an external quality assessment scheme for ALK rearrangement by FISH in 34 Italian laboratories.
Seventy percent (70%) of the laboratories passed the first round of tests and six the second round. Overall, 86% of laboratories passed the ALK EQA scheme.

The rate of false negative results was higher compared to false positives.

**Conclusion:** This is the first Italian EQA scheme for ALK testing and most centers passed. Similar studies should probably be performed under the CAP aegis.


Short image based case of a 20-year-old woman with Carney triad including a GIST and pulmonary chondroma.


**Background:** The rabbit polyclonal p40 (RPp40) antibody demonstrates better specificity for diagnosing squamous cancer than p60. The authors wanted to develop an anti-p40 mouse monoclonal antibody (MMp40) for IHC.

**Results:** The MMp40 provided equivalent staining to RPp40 and p63 in lung squamous carcinoma but stained a lesser percentage of lung adenocarcinomas than p63. The MMp40 was observed in urothelial, squamous and basal cell skin cancers, and head and neck cancers of squamous origin. No breast or prostatic adenocarcinoma stained. MMp40 expression in basal cells of prostate glands and PIN were virtually identical to those of p63.

**Conclusion:** The MMp40 (BC28) monoclonal antibody appears to be a high-quality antibody for determining squamous cell carcinomas of lung, skin cancers of squamous or basal cell origin, squamous cell head and neck cancers, and urothelial carcinomas.


**Background:** To investigate the relationship between EGFR mutational status and histologic subtype, 200 consecutive adenocarcinoma resection specimens from 2000 – 2011 were analyzed.
**Results:**

Table 2. Clinical and Pathologic Characteristics of *EGFR* Mutant and *EGFR* Wild-Type Pulmonary Adenocarcinomas

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>EGFR Mutant, No. (%)</th>
<th>EGFR Wild Type, No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor size, cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>23 (56)</td>
<td>99 (62)</td>
<td>.25</td>
</tr>
<tr>
<td>2–3</td>
<td>11 (27)</td>
<td>24 (15)</td>
<td></td>
</tr>
<tr>
<td>3–5</td>
<td>6 (15)</td>
<td>24 (15)</td>
<td></td>
</tr>
<tr>
<td>&gt;5</td>
<td>1 (2)</td>
<td>12 (8)</td>
<td></td>
</tr>
<tr>
<td>Predominant pattern</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lepidic</td>
<td>18 (44)</td>
<td>23 (15)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Acinar</td>
<td>17 (42)</td>
<td>109 (69)</td>
<td></td>
</tr>
<tr>
<td>Papillary</td>
<td>2 (5)</td>
<td>5 (3)</td>
<td></td>
</tr>
<tr>
<td>Solid</td>
<td>3 (7)</td>
<td>20 (13)</td>
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</tr>
<tr>
<td>Micropapillary</td>
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<td>0</td>
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<tr>
<td>Variants of adenocarcinoma</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mucinous</td>
<td>1 (2)</td>
<td>2 (1)</td>
<td>.50</td>
</tr>
<tr>
<td>MIA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (20)</td>
<td>14 (9)</td>
<td>.05</td>
</tr>
<tr>
<td>No</td>
<td>33 (80)</td>
<td>145 (91)</td>
<td></td>
</tr>
<tr>
<td>TTF-1 positivity</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Positive</td>
<td>32 (100)</td>
<td>101 (89)</td>
<td>.05</td>
</tr>
<tr>
<td>Negative</td>
<td>0 (0)</td>
<td>12 (11)</td>
<td></td>
</tr>
<tr>
<td>Pleural status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI present</td>
<td>5 (12)</td>
<td>29 (18)</td>
<td>.35</td>
</tr>
<tr>
<td>PI absent</td>
<td>36 (88)</td>
<td>130 (82)</td>
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</tr>
<tr>
<td>Nodal status</td>
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<tr>
<td>N0</td>
<td>32 (84)</td>
<td>109 (78)</td>
<td>.52</td>
</tr>
<tr>
<td>N1</td>
<td>2 (5)</td>
<td>16 (11)</td>
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<tr>
<td>N2</td>
<td>3 (8)</td>
<td>14 (10)</td>
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<tr>
<td>N3</td>
<td>1 (3)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Patients developing brain metastasis</td>
<td>2 (5)</td>
<td>13 (8)</td>
<td>.47</td>
</tr>
</tbody>
</table>

Abbreviations: *EGFR*, epidermal growth factor receptor gene; MIA, minimally invasive adenocarcinoma; PI, pleural invasion (visceral); TTF-1, thyroid transcription factor –1.
Comment: Although the predominant subtype of EGFR positive tumors has a lepidic predominant growth pattern all types of adenocarcinomas may show EGFR mutations. Not a whole lot new here, unless I am missing something.


Another article on multicenter review analyzing IHC for ALK translocation detection.

Methods: TMAs were used and 53 centers in Germany, Austria and Switzerland responded to the survey.

Results: 60.3% received at least 19 points required for certification, lower than the group in Italy.

Conclusions: The ALK ISH round robin demonstrates the need for continued improvement in ALK testing.


Summary: two cases of combined thymoma and thymic seminoma reported in two men, aged 32 and age 34. Both patients alive and well 12 and 18 months after surgery.

The cases highlight the importance of sampling in mediastinal tumors.


The authors compare two different ALK clones (5A4 and D5F3) on two different detection platforms (Dako and Ventana).

Data from 30 ALK FISH-positive cases show the sensitivity of IHC varies from 93% to 96%. Head-to-head comparison of the two clones demonstrated similar staining potency.
Non-neoplastic Disease


   Primarily a microbiologic paper but turns out there is a host of different nocardia species which were subtyped according to their 16S ribosomal RNA gene sequences. Infections occurred in the lung, deep skin and soft tissue and were associated with bacteremia and brain abscesses.


   **Background:** There have only been a few reports on pulmonary pathology in patient with anti-synthetase syndrome. This is a case report of AS syndrome associated with AFOP.

   AS syndrome: Idiopathic inflammatory disorder characterized by autoantibodies to aminoacyl-tRNA synthetases and one or more of the following: myositis, ILD and joint involvement. It is generally considered a subset of DM/PM but rare patients may have another form CVD. The most prevalent antibody is against histidyl tRNA synthetase (Jo-1). Others include anti-threonyl (PL-7), anti-alanyl (PL-12), anti-isoleucyl (OJ), anti-glycyl (EJ), anti-asparaginyl (KS), anti-phenylalanyl (Zo) and anti-tyrosyl (YRS) antibodies.

   **Report:** A 66-year-old woman with a 20 pack-a-year smoking history and no occupational exposures who presented with pruritic rash. She was found to have an ANCA at 1:64 and anti-EJ autoantibodies.

   VATS showed AFOP pattern without hyaline membrane or eosinophils. Cultures were negative.

   **Follow-up:** After two years on steroids her symptoms improved allowing a steroid taper to be initiated.

   **Discussion:** Anti-EJ antibodies have been detailed in three patients with NSIP and one with UIP containing prominent lymphoid follicles. AFOP has not previously been reported in AS syndrome.


   A Chinese-based study which investigated whether Chinese water-pipe use and exposure were associated with the risk of COPD.

   **Conclusion:** Chinese water-pipe smoking significantly increases the risk of COPD, including risks to women. Chinese water-pipe use actually produces more exposure to more particulates than cigarette smoke!
Article contains some good photos but doesn’t comment on which flavors are the best.


An editorial highlighting the risks in water-pipe smoking and their increasing use in the West.


This year’s summary of lung and heart-lung transplant patients from the ISHLT focuses on retransplantation. As usual the report contains a plethora of information and graphs some of which may be useful for talks on lung transplantation.

In summary, the annual number of lung transplants has continued to increase while the number of heart-lung transplants has plateaued. Survival continues to improve over time mainly due to improved postoperative care. Morbidity rates continue to be high with the main contributors being BOS and infections. Lung retransplant procedures increased markedly from 2005 to 2010 but remain proportionate to the total number of lung transplants overall. Retransplantation still associated with consistently worse morbidity and mortality than initial transplant.


A case of nodular lymphoid hyperplasia with good discussion of inflammatory pseudotumor and silicone pseudotumor.