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<td>1</td>
<td>Nitadori et al.</td>
<td>Immunohistochemical differential diagnosis between large cell neuroendocrine carcinoma and small cell carcinoma by tissue microarray analysis with a large antibody panel.</td>
<td>Am J Clin Pathol.</td>
<td>2006;125</td>
<td>682-92</td>
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<td>5</td>
<td>Galloway et al.</td>
<td>The use of the monoclonal antibody mesothelin in the diagnosis of malignant mesothelioma in pleural biopsies.</td>
<td>Histopathology</td>
<td>2006; 48</td>
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<td>Palau et al.</td>
<td>Corticotropin-producing pulmonary gangliocytic paraganglioma associated with Cushing’s syndrome.</td>
<td>Hum Pathol</td>
<td>2006; 37</td>
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<td>9</td>
<td>Nakata et al.</td>
<td>The methylation status and protein expression of CDH1, p16, and fragile histidine triad in nonsmall cell lung carcinoma.</td>
<td>Cancer</td>
<td>2006;106</td>
<td>2190–9</td>
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<td>11</td>
<td>Berbescu et al.</td>
<td>Transbronchial biopsy in usual interstitial pneumonia.</td>
<td>Chest</td>
<td>2006; 129</td>
<td>1126-31</td>
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<td>12</td>
<td>Inoue et al.</td>
<td>Clinicopathologic study of resected, peripheral, small-sized, non-small cell lung cancer tumors of 2cm or less in diameter: pleural invasion and increase serum carcinoembryonic antigen level as predictors of nodal involvement.</td>
<td>J Thorac CV Surg</td>
<td>2006; 131</td>
<td>988-993</td>
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AM J CLIN PATHOL

Purpose:
- By 1999 WHO, LCNEC morphologically distinct from SCLC.
- Outcome of LCNEC controversial: better vs same vs worse than SCLC
- Optimal treatment debated, some suggesting same as for SCLC
- Differences in molecular expression not well characterized except for TTF-1, reported as more often positive in SCLC than LCNEC
- The purpose of this study was to evaluate phenotypic differences between LCNEC and SCLC using TMA

Methods:
- 1992-2003 lung cancer reviewed based on WHO classification:
  - 49 (2.6%) diagnosed as LCNEC and 39 with sufficient tissue for study
  - 14 (0.7%) pure SCLC
  - “control” 3 cases of combined SCLC-LCNEC.
- TMA 2 cores of 2mm with normal control TMA
- 48 antibodies: 13 keratins, 4 intermediate filaments, 6 drug resistant gene, 5 apoptosis associated proteins, 6 receptors growth and hormone, 5 adhesion molecules, 5 mucin related proteins, CD15, CD30, TTF-1 and SPPB
- Positive case with >10% of cells positive
- Staining score: %cells X intensity (1, 2, 3+)

Results:
- Positive cases:
  - CK 18 + 97% LCNEC vs 71% SCLC p=0.0143
  - E-cadherin + in 77% LCNEC vs 43% SCLC p=0.0419
  - TTF-1 + in 23% LCNEC vs 43% SCLC p NS
- Staining score:
  - CK 7: 113 LCNEC vs 49 SCLC
  - CK18 171 LCNEC vs 60 SCLC
  - B-catenin 191 LCNEC vs 120 SLCL
  - E-cadherin 77 LCNEC vs 9 SCLC

Take-home message:
- Not sure about the significance of these findings.
- Can’t use for diagnostic tool, didn’t evaluate in terms of prognosis or response to treatment

**Purpose:** Histologic review and staging of lung cancers diagnosed during baseline screening, Early Lung Cancer Action Project (ELCAP).

**Methods:**
- 2968 M and W screened 1993-2004; 77 (2.6%) with lung cancer dx
- 65 underwent resection (wedge, segmentectomy, lobectomy and bi-lobectomy)
  - 42 W 22M median 47 pack-yr
  - Median 14 slides/case with median 4 slides per tumor

**Results:**
- 49 cases of solitary carcinoma and 16 cases of multiple carcinomas
  - **Solitary**
    - 44 peripheral vs 5 central
    - Median 1.5cm
    - 42 adenocarcinoma, 3 SCC, 1 large cell, 2 typical carcinoid, 1 combined SCLC/NSCLC
    - Adenocarcinoma: 5 nonmucinous BAC, 3 acinar, 34 mixed (76% with BAC component: 7 75-99%, 5 50-74%, 4 25-49%, 12 1-24%)
    - AAH found in 6 cases of adeno and 3 of BAC
    - 30 Stage IA, 13 IB, 3 IIA, 2 IIB, 1 IIIA
  - **Multiple**
    - 10 dx before resection and 6 found at surgery
    - 9 with main tumor adenocarcinoma, median 1.4 cm, other tumors in same lobe (7 with 1 more and 2 with 2 more) median 0.4 cm: 3 with second adenocarcinoma, 5 BAC, 1 adenosquamous and 1 SCC
    - 7 with main tumor adenocarcinoma or large cell carcinoma, median 1.7 cm, had one or more tumors in different lobe, median 0.8 cm: 5 with second tumor same histology, 1 with 2 BAC, 1 with adeno (main large cell) and BAC.
    - 6 with different histology 5 I A for both, 1 IA and IIB
    - 10 with same histology 3 II B and 7 IV
- **Discrepancies:**
  - 1 case submitted as scar unanimously classified as BAC
  - 3 patients with 6 lesions dx as AAH, 4 re-classified as BAC and 2 as adeno, mixed
  - 1 SCC to adeno and 1 adeno solid type to Large cell
  - 16 adeno NOS reclassified as 13 mixed and 3 acinar
  - 18 BAC reclassified as invasive adeno 11 having more than 50% BAC component
  - 5 (of 65) cases not unanimous, 4 adeno with BAC and 1 BAC

**Take-home message:**
- Descriptive study, similar to what has been reported in previous screening studies except significant number of multiple carcinomas
- Highlights common problems of histologic classification and staging

**Background:**
- CCAM classified mainly into 3 groups based on size of cyst
- Hypothesis of airway obstruction, such as bronchial atresia, in the pathogenesis of CCAM particular type 2 and 3.
- Description and classification of CCAM mainly based on postnatal lung resection or stillborn autopsy, likely not applicable to fetal lung as per Cha et al.

**Aim:**
- To better characterize fetal pulmonary malformations

**Materials and Methods:**
- 1996-2004 from resections in utero (16/23) or ex utero intrapartum therapy (EXIT) (6/23) and 1-2 hours after delivery.
- Resections: lobectomies, pneumonectomies; if more than 1 lobe involved, multiple resections.

**Results**
- 23 cases which grossly showed wide range of cyst size, judged not useful for classification
- Parenchyma between cysts useful for classification:
  - **Group 1 (9/21)**
    - Age 21 5/7 to 29 2/7
    - 5 deaths
    - Cysts up to 3 cm
    - Parenchyma comprised of tubules, pseudostratified, subnuclear clear vacuoles
    - Interspersed bronchial structures and moderate interstitium with loose stroma
    - Clusters of mucus cells
  - **Group 2 (6/21)**
    - Age 21 5/7 to 23 ½
    - 2 death
    - Cysts were microscopic to 1 cm
    - Round airspaces lined by cuboidal epithelium, central nuclei, pink cytoplasm
    - Abundant mesenchyma with prominent smooth muscle
    - No mucus cells
  - **Group 3 (6/21)**
    - Age: 26 4/7 to 38 2/7 (older)
    - 4/6 EXIT
    - All alive but one
    - Cysts microscopic to 3.5 cm
    - Mature-appearing parenchyma but with dilated alveolar-type airspaces
    - Cuboidal to flat epithelium
    - Less abundant stroma, no prominent smooth muscle cells
- Mucus cells
  - 2 non-classifiable
    - One case diffusely cystic, pseudostratified ciliated columnar epithelium with smooth muscle, normal parenchyma except looking overinflated
    - One case with 2 extralobar sequestrations, 1 was non cystic with unremarkable lung, the second diffusely cystic, abundant fibrous stroma and skeletal muscle
- Abnormal vascular supply in 7, 3 considered extralobar sequestrations
- No evidence of bronchial obstruction except in one case

**Take-home message:**
- The largest series and thorough description of cystic abnormalities as seen in fetus
- Different than those seen in post natal period
- Presence of systemic vascular supply suggest congenital rather than acquired theory
- Absence of bronchial obstruction identified in most does not support obstruction theory for CCAM
HISTOPATHOLOGY

Background:
- TSC pulmonary manifestations include LAM, MNPH, clear cell tumor, angiomyolipoma, interstitial clear cell LAM-like proliferations

Case report:
- 49 yo W, asymptomatic, normal labs and PFT
- Incidental 25mm nodule on chest x-ray in RLL
- CT scan non calcified soft tissue density well demarcated DDx hamartoma
- Microscopy of main nodule shows features of MNPH with CK and TTF-1 +
- Adjacent lung parenchyma shows multiple smaller foci 1-4mm of MNPH and LAM
- Findings led to further investigation and patient had facial angiofibroma and HRCT showing multiple pulmonary cysts

Take home message:
- First manifestation of TSC can be that of a solitary pulmonary nodule
- Case of MNPH can present as a large nodule

**Background:**
- Mesothelin initially considered sensitive and specific for the dx of mesothelioma
- Several studies showed mesothelin immunoreactivity in pulmonary adenocarcinomas (38 to 53%) and other primary adenocarcinomas (ovary and pancreas)
- However, studies actually used tissue from lung primaries and not from metastatic tumors i.e. pleural tissue with adenocarcinoma.

**Material and methods:**
- Pleural biopsies 1995-2003
- 31 metastatic adenocarcinoma (15 lung, 3 breast, 2 colon and 11 unknown) and 62 mesotheliomas (39 epithelial, 15 desmoplastic/sarcomatous, 8 biphasic)

**Results:**
- 82% mesothelioma + : 100% epithelial and biphasic (usually epithelial component) vs 40% desmoplastic/sarcomatous
- 52% adeno – and 48% + (23% strongly)

**Take home message:**
- Mesothelin not useful in the ddx of adenocarcinoma vs mesothelioma
HUMAN PATHOLOGY

Background:
- SEL1L ubiquitous in developing fetal tissue and down-regulated in adult tissue except pancreas
- SEL1L documented in breast, pancreatic and esophageal cancers
- Potential role in cell growth regulation, may prevent invasion
- No demonstrated mutations
- No extensive studies on lung

Methods:
- 76 NSCLC from surgical specimens:
  - Stage IA to IV (17 IIIA, IIIB and IV)
  - 18 SCC, 54 AC (3 BAC), 1 ASC, 3 LCC
  - 6 G1, 34 G2, 36 G3
  - Med FU 23 months
- IHC:
  - Cytoplasmic staining: scored % cells and intensity, for final score 1 to 6
  - Nuclear staining + or –
- Cell cultures for IHC and RT-PCR
- Screening of mutations with direct sequencing
- Computer analysis to look at potential function of gene

Results:
- Normal: Only weak sporadic reactivity in ciliated and basal cells
- Squamous metaplasia and dysplasia: weak cytoplasmic and nuclear
- IHC:
  - SCC 89% +: mainly cytoplasmic (p=0.0005) with rarely nuclear, mostly in G2
  - AC 59% +: cytoplasmic and/or nuclear, mostly G2 (p=0.006)
- No correlation with patient outcome
- mRNA present in cell lines
- No mutations
- Identification of different protein isoforms both as nuclear import and export signals

Take-home message:
- Another expressed gene in lung cancer
- Could not determine prognostic significance
- Possible role in carcinogenesis since expressed in metaplasia and dysplasia
- No mutation identified but limited part of gene sequenced, methylation?
- Mechanism and function for nuclear transport and explanation for both nuclear and cytoplasmic staining remains unclear

Background:
- Histologic classification does not classify up to 40% of tumors
- SCLC important to separate from NSCLC but also value in separating AC from SCC for treatment and prognosis
- P63, CK5/6, CK7 and SP-A promising markers.

Aim: To evaluate combination of p63 and CK5/6 vs CK7 and SP-A in separating NSCLC

Methods:
- FFPE tissue from 42 cases: 18 SCC, 17 ACC, 5 LCC, 2 combined (although the n changes depending on immuno)
- IHC for p63, CK5/6, CK7 and SP-A

Results:

<table>
<thead>
<tr>
<th></th>
<th>SCC</th>
<th>AC</th>
<th>LCC</th>
<th>Combined</th>
</tr>
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<tbody>
<tr>
<td>P63</td>
<td>14/18 (78%)</td>
<td>0/17 (0)</td>
<td>1/5 (20%)</td>
<td>1/2 (50%) in SCC</td>
</tr>
<tr>
<td>CK5/6</td>
<td>8/17 (47%)</td>
<td>9/16 (56%)</td>
<td>1/5 (20%)</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td>CK7</td>
<td>1/18 (5.5%)</td>
<td>16/17 (94%)</td>
<td>3/5 (60%)</td>
<td>2/2 (100%)</td>
</tr>
<tr>
<td>SP-A</td>
<td>1/13 (7.7%)</td>
<td>4/15 (27%)</td>
<td>1/5 (20%)</td>
<td>0/1 (0)</td>
</tr>
</tbody>
</table>

Take-home message:
- Premise not always accurate
- Confirms some previously published reports, however concerns about accuracy (CK5/6) and usefulness to be determined; other antibodies to consider would have included TTF-1, other high molecular weight keratin (K903)

Background:
- GP are rare tumors, mostly of the duodenum although other sites reported
- No cases of GP resulting in an endocrine syndrome reported thus far

Case report:
- 55 yo man consulted for weight gain, muscle weakness, easy bruisability over 10 years
- High urine free cortisol, bilateral adrenal enlargement and normal pituitary gland
- Multiple negative exhaustive investigations to look for source
- At a FU visit, CT scan showed lesion in mediastinum
- Surgery revealed 0.8cm nodule in “left inferior pulmonary ligament”
- Post-op drop of cortisol
- Histology typical of GP with 1- zellballen of NE cells 2- ganglion like cells 3- spindle cells
- Multiple smaller nodules including one in lung parenchyma
- NE cells positive for synaptophysin, chromogranin, corticotrophin
- Ganglion like cells positive for NF
- Spindle cells positive for NF and S100 prot

Take-home message:
- Case report of an extremely rare case
CANCER

Purpose:
- Evaluate the relationship between mutations in EGFR, Her-2 and KRAS and clinical features
- Evaluate for the presence of simultaneous multiple-gene hypermethylation of TSG (CIMP) and relationship between clinical features
- Evaluate relationship between mutation and methylation

Methods:
- 150 cases from 1995-1998, surgical resection, no neoadjuvant therapy
- 79 adeno, 58 SCC, 11LCC, 2 AS
- Mutation assay:
  - Sequencing for EGFR in 4 exons (18-21)
  - Sequencing of 2 exons for Her-2
  - Sequencing of 1 exon for KRAS
- Methylation assay
  - 9 genes: HPP1, SPARC, Reprimo, CRBP1, RAR-B, RASSFIA, APC, CDH13, p16
  - Negative controls
- Statistical analysis including MI (methylation index) = Tot genes methylated/ Tot genes analyzed

Results
- Mutations:

<table>
<thead>
<tr>
<th></th>
<th>EGFR</th>
<th>Her-2</th>
<th>KRAS</th>
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<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>36 (46%)</td>
<td>4 (5%)</td>
<td>5 (6%)</td>
</tr>
<tr>
<td>Others</td>
<td>2 (3%)</td>
<td>0 (0)</td>
<td>1 (1%)</td>
</tr>
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- EGFR statistically more common in adenocarcinoma, women, and non-smokers
- Her-2 more common in women and T1
- Mutations occurred exclusively

- Methylation:

<table>
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<tr>
<th></th>
<th>HPP1</th>
<th>SPARC</th>
<th>Repri</th>
<th>CRBP1</th>
<th>RAR-B</th>
<th>RASSF</th>
<th>APC</th>
<th>CDH13</th>
<th>P16</th>
</tr>
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<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>30 (38)</td>
<td>38 (48)</td>
<td>27 (34)</td>
<td>7 (9)</td>
<td>31 (39)</td>
<td>23 (29)</td>
<td>32 (41)</td>
<td>23 (29)</td>
<td>16 (20)</td>
</tr>
<tr>
<td>Others</td>
<td>26 (37)</td>
<td>43 (61)</td>
<td>22 (31)</td>
<td>12 (17)</td>
<td>17 (24)</td>
<td>25 (35)</td>
<td>21 (30)</td>
<td>17 (24)</td>
<td>28 (39)*</td>
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- RAR-B statistically more in cases of LN mets and higher stage
- P16 statistically higher in smokers
- 16% of adenocarcinoma without methylation vs 2% of SCC
- Methylation were frequent and synchronous supporting CIMP
- CIMP correlates with survival in adenocarcinoma (in multivariate): 5-yr survival of CIMP- 61.3% vs CIMP+ 35.2
- SPARC and p16 methylation higher in cases without EGFR mutation

Take-home message:
- Some novel interesting findings i.e. CIMP which will need further studies

Background:
- Methylation is responsible for inactivation of several genes in lung cancer
- Novel therapy aimed at methylation (AZA) is currently studied

Aim:
- Look at methylation status of 3 genes (p16, FHIT and CDH1) and the expression of corresponding protein
- Correlate the above with clinicopathologic features

Material and methods:
- 224 of surgically resected cases 1993-1998
  o 160 M, 159 smokers
  o 126 adeno, 78SCC, 7 AS, 13 LCC
  o 49 Stgae IA, 74 IB, 31 II, 54 IIIA, 13 IIIB, 3 IV
  o Med FU 60.8 mos
- Methylation for p16, Fhit and CDH1
- IHC for p16, FHIT, E-cadherin:
  o E-cadherin + = 70% and more + cells
  o P16 + =10% or more + cells
  o Fhit + = 30% or more + cells

Results
- Methylation and clinicopathologic correlation
  o 92% of tumors were methylayed in 1 or more gene, 39% in 2 and 18% in 3 with CDH1 in 58%, FHIT in 52, and p16 in 22
  o P16 was more commonly methylated in SCC and more than 20 pack-yr smokers
  o FHIT more commonly methylated in node positive patients
- Protein expression and clinicopathologic correlation
  o Reduce Fhit expression in 56%, E-cadherin in 43 and p16 in 40
  o E-cadherin reduced more in men
  o P16 reduced more in SCC
- Survival analysis for methylation and protein expression
  o Patients with CDH1 methylation poorer prognosis (44% vs 58%, p=0.047)
  o In multivariate, CDH1 methylation (RR 1.58, p=0.026) and reduced E-cadherin (RR1.50) independent unfavorable prognostic factor
- Only p16 methylation and expression correlated (p=0.0002)

Take-home message:
- Confirms previously published data
- P16 methylation possibly induced by smoking
- FHIT inactivation possibly plays a role in tumor progression
- Prognostic value suggested for CDH1
- Other mechanisms besides methylation plays a role in gene inactivation
CHEST

Background:
- Association between HD and arterial thromboembolism well established but not with venous TE.
- Difficult to make diagnosis of PE in patients with HD because of overlapping findings.

Aim:
- Look at prevalence of PE in post-mortem population
- Establish importance of PA as cause of death in patients with HD

Methods:
- Review of autopsy reports and charts of autopsies performed from 1985-1994
- Massive PE as cause of death if obstruction of MPA or more than 2 lobar arteries without other causes of death
- Gross morphology of LV and RV noted
- Determined if PE suspected antemortem and treated
- Recorded clinical manifestations of PE
- Classified HD in 4 groups: ischemic, congenital, valvular and other

Results:
- Rate of autopsies was 27.5% (1,032/3,751)
- 231 cases (22.4%) with PE and 100 (9.7%) defined as massive PE (mean age 35 yrs)
- Table of distribution of HD indicate that all 1,032 patients had HD (?), IHD in 26%, Rheumatic valvular in 27%, CHD in 32%, other in 14%
- Massive PE third cause of death in patients with HD after cardiogenic shock and hypovolemic shock
- Affected mostly patients with “other” HD and patients that were treated medically (vs surgically) and over 22% were less than 10 years old
- 18% were suspected of having PE at time of death, and 32% were under some form of anticoagulation
- 64% dyspnea (14 on ventilator), 89% tachycardia (31 with VFib) and 79% hypotension
- Majority of morphologic abnormality involved the RV: dilation in 24/29, dilatation in hypertrophy in 10/13

Take-home message:
- Good effort in looking at PE in patients with HD with some interesting findings but study hampered by some flaws.

Background:
- UIP important to distinguish from other types of ILD because of poor prognosis and lack of treatment
- SLB considered biopsy of choice but potentially associated with significant morbidity and mortality in that patient population

Aim: Evaluate role of TBBX in the diagnosis of UIP

Material and Methods:
- 22 patients with TBBx and diagnosis of UIP confirmed on SLB/explanted lung in 21 and clinico-radiologic correlation in 1
- Mean 2.5 H&E slides/patient; number of fragments of alveolated parenchyma
- Histologic features: interstitial fibrosis, patchwork pattern, fibroblast foci (ff), HCC
- Final assessment:
  - Dx of UIP on TBBX if patchwork pattern + fibroblast focus and/or HCC
  - c/w UIP if interstitial fibrosis (but not patchwork) with fibroblast focus or HCC
  - Nonspecific if only in interstitial fibrosis
  - Insufficient if only bronchial wall

Results:
- Clinical features:
  - 9M:13W, mean age 51 yrs
  - 22 with dyspnea, 2 with family history of pulm fibrosis
  - 22 with bilateral infiltrates and 4/5 with HRCT typical UIP
  - SLB in 19, mean 4 months after TBBx, 2 lung transplant 3 years after TBBx
- Pathologic features:
  - Mean 2.5 alveolated fragments except 4 insufficient
  - 7 dx of UIP:
    - 1 patient with patchwork + ff + HCC
    - 5 patchwork + ff
    - 1 patchwork + HCC
  - 2 c/w UIP
    - Fibrosis + ff
    - Fibrosis + HCC
  - 9 nonspecific
    - 6 interstitial fibrosis
    - 3 patchwork
  - In dx and c/w cases, mean fragments of alveolated parenchyma 3.2 vs 2.1 for non specific but stat NS; dx made with as few as 2 fragments

Take home message:
- Study breaks the dogma of “UIP can not be diagnosed on TBBx”, helpful for patient care
- Because of size, always correlate with clinical and radiologic findings
- Beware of artifact such as atelectasis and ddx of ff such as BOOP
JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY
Inoue et al. Clinicopathologic study of resected, peripheral, small-sized, non-small cell lung cancer tumors of 2cm or less in diameter: pleural invasion and increase serum carcinoembryonic antigen level as predictors of nodal involvement. JTCVS 2006; 131: 988-993

Background:
- Increase in the % of lung cancers ≤ 2cm (17% to 34 to 43 % over 10 years at their institution)
- With hypothesis of limited surgery for stage I early lung cancer, identification of characteristics of small lung cancer, including the ones causing GGO’s, may be important

Material and Methods:
- 143 (of 565) lung cancers were ≤ 2cm and completely resected, with mean FU of 52.1 mos
- Limited resection was done when surgically indicated (15 cases) and for GGO (12 cases) or lesions < 1.5 cm (8 cases)
- GGO defined as mainly ground glass at least 2/3 of the area on thin section CT, otherwise considered as solid tumors
- Variables analyzed included age, gender, tumor size, histology, tumor density, operation type, LN mets, pleural invasion, pre-op serum CEA

Results:
- 86 M: 57 W with 108 lobectomy and 35 partial, for 127 adeno, 14 SCC, 2 other
- Solid 102 and GGO 41
- Stage IA 123, IB 4, IIA 5, IIB 2, IIIA 9
- All tumors < 1cm showed no recurrence over 43.7 months
- 5-yr survivals
  o Overall 88.1%
  o ≤ 1.5 cm 100%
  o 1.6-2cm 84%
  o Adenocarcinoma 89.8% (p=0.03) even after removing GGO (p=0.05)
  o GGO 96.3% vs solid 85.1 but NS
  o No diff between lobectomy 88% and limited 87% (all limited either were N0 or had no LN staging)
  o N0 91.6% vs N1-N2 62.5% p<0.01
  o Pleural invasion did not affect survival (89.6 vs 75.8)
  o Increase CEA 77.6% vs normal 92.1 p<0.01
  o After multivariate of all these variable, only CEA level was independent prognostic factor
- LN mets seen in 9% of <1cm nodule, 6.7% of 1.1-1.5cm nodule, 17% of >1.5cm nodule NS. No LN mets in GGO
- Correlation between LN mets and increased CEA

Take home message:
- Even very small tumors can have LN mets, thus evaluation of limited surgery should be done in the context of a clinical trial before being considered as routine
- No comment on how many GGO were BAC and interesting that not prognostic
Sun et al. Histologic grade is an independent prognostic factor for survival in non-small cell lung cancer: an analysis of 5,018 hospital and 712 population based cases. JTCVS 2006; 131: 1014-1020

Background:
- Controversy whether or not histologic grade is an independent prognostic feature of NSCLC

Aim: Determine in a large population of patients role of histologic grading in prognosis

Material and methods:
- 1997-2003 5018 patients prospectively enrolled
- Classification according to WHO, grade as well, mod, poorly and undifferentiated
- Full epidemiologic data and FU
- Second study population from Olmsted county (less referral bias), since 1984, 712 patients
- Complex statistical analysis univariate, multivariate with logistic regression models, relative risk of death. Since no diff between poorly diff and undiff, lumped together for stratified and subset analysis for survival. Also looked at role in recurrence

Results:
- **Univariate analysis**
  - Poorly or undiff more in younger, men and smokers
  - Poorly and undiff found at later stages (III and IV)
  - Well-diff tumors mostly adeno
  - Histologic grade (along with stage, histologic subtype, treatment, age and gender) associated with survival (p<0.001)
    - Well diff: 1-yr 80.5%, 5-yr 43.5 med 3.7 yrs
    - Mod diff: 1-yr 65.5%, 5-yr 23.4%, med 1.7 yrs
    - Poorly diff: 1-yr 47.7%, 5-yr 13.4%, med 0.9 yrs
    - Undiff: 1-yr 40.0%, 5-yr 8.3%, med 0.8 yrs
    - RR undiff vs well-diff 3.5, poorly vs well-diff 2.7, mod diff vs well-diff 1.8

- **Multivariate analysis**
  - Histologic grade remained an independent prognostic factor (using age, stage, gender, histologic type, smoking, and treatment) with RR 1.8, 1.7 and 1.4 (but no diff between undiff and poorly diff)
  - Histologic grade the 3rd most significant factor after stage and treatment

- **Stratified analysis**
  - Tumor stage: unfavorable impact of poorly/undiff and mod diff on all stages except stage II. For stage I: 51 and 34% increased risk vs well-diff, for Stage IV 90 and 48%
  - Histologic type: 70 and 41% increased risk for poorly/undiff and mod diff in adeno, 53 and 34% for SCC
  - Regardless of treatment modalities, 35-85% increased risk

- **Subgroup analysis for Olmsted**
  - Unadjusted RR for poorly/undiff and mod diff 3.0 and 1.9
  - Adjusted RR 1.6 and 1.4
o Still independent
- **Recurrence group**
  o 1302 patients with complete surgical resection, recurrence rate of 47.3% for poorly diff/undiff, 32.7% for mod diff and 20.8% for well-diff
  o After adjustment, 2.1 increased risk for recurrence in undiff/poorly diff vs well-diff, 1.4 for mod diff

**Take home message:**
- Likely that histologic grade has a role in prognosis (similar to other cancers)
- Perhaps role for refinement and more uniform definition of grade