immunohistochemical differential diagnosis includes metastatic signet-ring/histiocytoid carcinoma, especially histiocytoid lobular carcinoma from the breast, axillary skin, or other internal organs. Extensive systemic work-ups in both cases were negative for a primary site. Positron emission tomography and computerized tomography scans showed extensive orbital involvement. Orbital exenteration was performed in one case and showed diffuse involvement of upper and lower eyelids, conjunctiva, lacrimal gland, and orbit. Tumor cells focally involved the outer one-third of the sclera, but did not enter the eye.

Conclusions: We emphasize the patchy distribution, and in some small biopsies only a few tumor cells may be seen, giving the tissue the impression of being hypercellular. In these cases, immunostains for cytokeratin are useful.

1835 Accuracy of Frozen Section in the Intraoperative Diagnosis of Ophthalmic Diseases

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Background: Frozen section procedure is often employed during surgery to diagnose obscure lesions, to differentiate between malignant and benign lesions, to determine negative margins in oncological surgeries, and to confirm the presence of lesional tissue. In ophthalmic surgery this procedure is not widely used. This may be attributed to the small quantity of tissue obtained during surgery and lack of proper training in frozen section preparation and diagnosis among ophthalmic pathologists. In this study, we aim to determine the accuracy of intraoperative frozen section diagnosis in ophthalmic pathology at a major tertiary care ophthalmic institute.

Design: Data collection was done by searching the computer data bank for intra-operative and final diagnoses of ophthalmic specimens submitted to the Pathology Department between January 2005 and January 2010. Pathology reports were reviewed and classified as: accurate, inaccurate, and deferred.

Results: Between 2005 and 2010, 1501 ophthalmic specimens were submitted for frozen section diagnosis. Thirty cases (1.9%) were deferred for permanent section diagnosis. Out of the remaining 1471 cases, 1359 (92.4%) frozen section diagnoses were consistent with final diagnosis based on permanent sections, while 112 (7.6%) cases showed discrepancies between frozen section and final diagnosis. By location, highest diagnostic accuracy was achieved for anterior chamber (100%), optic nerve (100%), temporal artery (100%), and eyelid (96.5%) biopsies. Diagnostic accuracy was slightly lower for biopsies of conjunctiva (89.4%), orbit (88.1%), and eyebrow (87.5%). Clinically significant negative discrepancies were highest in the diagnosis of conjunctival/corneal lesions (5.02%). Clinically significant positive discrepancies were highest in orbital biopsies (6.5%). The specificity and sensitivity for frozen section diagnosis are 92.4%; with a positive predictive value of 93.1% and a negative predictive value of 91.6%.

Conclusions: Our data confirm that frozen section diagnosis is a reliable method for ophthalmic surgeries. Diagnostic errors may be reduced by adequate tissue sampling, complete clinical information, and good communication between surgeon and pathologist.

1836 Gender Differences and Estrogen and Progesterone Receptor Expression in Uveal Melanoma

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Background: Older reports have not demonstrated estrogen receptor (ER) expression in uveal melanoma (UVM). A recent study reporting differences in incidence and metastasis-related mortality by gender prompted a re-examination of ER and progesterone receptor (PR) expression by immunohistochemistry with comparison to clinical outcome and chromosome 3 status.

Design: 33 cases of UVM from 2004-09 treated by enucleation were examined for incidence and survival. 23 cases were evaluated for ER and PR by immunohistochemistry. Chromosome 3 status was determined by FISH and SNP array analysis.

Results: There were 19 men (58%) and 14 women (42%). 11 patients were DOD: 8 men (67%) and 3 women (25%); 1 woman was alive with metastasis. 10 men (56%) and 8 women (44%) were alive without metastasis. 3 patients died of other causes. ER was positive in 7 women (11 positive cases) and negative in UVM arising in men (8 of 12 negative cases). PR was negative in 20 of 23 cases and weakly positive or negative in 3. ER did not predict either clinical outcome or chromosome 3 status. Of the ER positive cases, 4 were DOD and 6 were alive without metastasis. Of the ER negative cases, 5 were DOD and 6 alive without metastasis. When compared to chromosome 3 abnormalities, ER was positive in 9/18 monosomy 3 cases and 2/5 disomy cases.

Conclusions: Gender may play a role in UVM. ER expression was present in 48% of cases of uveal melanoma and more likely in women in this small study, but it does not appear to be prognostic. We propose further study, including quantitative evaluation using image analysis.

1837 Association of Chlamydophila Psittaci in Cases of Ocular Adnexal MALT Lymphoma

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Background: Extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue type (MALT lymphoma) is the most common type of malignant lymphoma of the ocular adenexa. Recently several studies have indicated that *Chlamydophila psittaci (C.psittaci*) has been associated to ocular adenexal lymphomas with variable geographic distribution. This observation points toward the opportunity to investigate the prevalance of *C.Psittaci* infection in ocular adenexal MALT lymphoma.

Design: Nine patients with ten cases of biopsy proven ocular adenexal MALT lymphoma from over the past 10 years (from January 1st 2001 to August 31st 2011) were selected from the archived file. Paraffin embedded, formalin fixed specimens were studied for *C.Psittaci* by immunohistochemistry and molecular analyses.

Immunohistochemistry was performed using anti-genus-specific lipopolysaccharide polyclonal antibody (BDI168, Santa Cruz Biotechnology). The presence of *C.psittaci* was determined by amplification of two separate targets of the *C.psittaci* genome. Nested PCR for the *16S-23S* spacer region was performed using touchdown PCR followed by realtime amplification with visualization of melt curves. The second target used for identification was the *omp 1* gene of *C. psittaci*. A real time PCR with primers and FRET probes were used for amplification.

Results: In our study four of ten biopsy cases show immunoreactivity to anti-genus-specific lipopolysaccharide polyclonal antibody indicating that Chlamydial species are present in the lesional tissue. Furthermore, none of the specimens tested showed amplification for *C.psittaci* by molecular studies. The positive control used was successfully amplified and confirmed by sequencing for both targets.

Conclusions: In ten-year retrospective study of ocular MALT lymphomas in our institution, we could not identify *C.psittaci* by molecular studies. Our results correlate well with the current literature that *C.psittaci* vary widely between geographic regions and even within the same country. The prevalence range varies from 11-50%. Further collaborative large international study is still necessary to clarify the role of *C.Psittaci* in the pathogenesis of the disease.

Pancreas

1838 Gallbladder Pathology in IgG4-Related Sclerosing Disease

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Background: Originally recognized as autoimmune pancreatitis (AIP), IgG4-related sclerosing disease (ISD) is now well established as a systemic autoimmune process that can involve various organs and is characterized by increased number of tissue IgG4 plasma cells (PCs). Gallbladder (GB) manifestations of this disease have not yet been fully elucidated.

Design: Patterns of inflammation in 29 GBs from patients with proven ISD were contrasted with those in 2394 cholecystectomies with various etiologies. IgG4 immunostaining was performed in 156 (Table). The number of IgG4+ PCs was graded as negative (<10/HPF), low (10-29), moderate (30-49), or high (≥50).

Results: 7/29 GBs from ISD patients revealed a distinctive pattern of inflammation associated with delicate fibrosis akin to that seen in AIP (Fig.1). IgG4+ PC grade in these patients was low in 1, moderate 1, high 5. Of the remaining 22, 10 revealed mucosal-predominant lymphoplasmacytic cholecystitis, 2 had eosinophilic chronic cholecystitis, and 10 had non-specific chronic inflammation. Overall, high numbers (≥50/HPF) of IgG4+ PCs were seen in 24% of ISD GBs. However, they were also seen in GBs with non-ISD etiologies, including 10% of GBs with obstructive tumor in the CBD (Table). Among the 10 non-ISD patients with moderate/high numbers of IgG4+ PCs, 5 had diabetes mellitus and 1 had hypothyroidism.

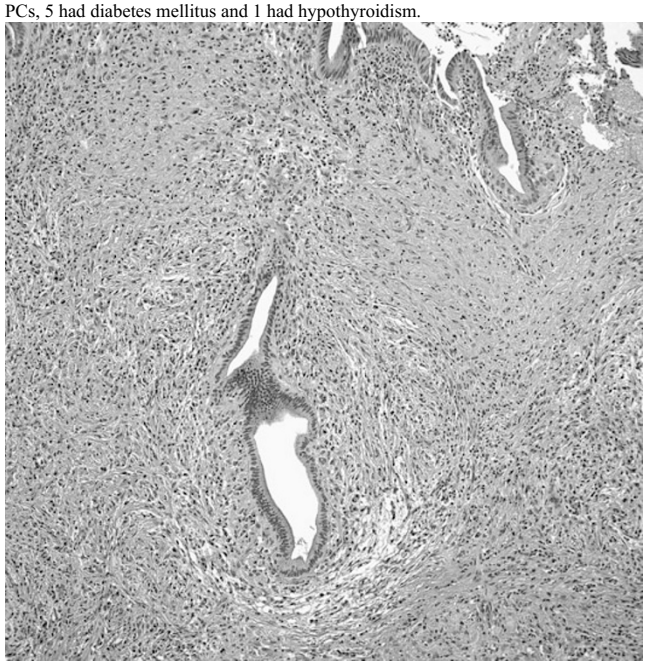

Table: IgG4 positive plasma cell scores (/HPF) compared to the etiology

ETIOLOGY (n,%)	NEGATIVE (<10)	LOW (10-29)	MODERATE (30-49)	HIGH (≥50)
Autoimmune Pancreatitis/ISD (29, 18%)	16 (55%)	4 (14%)	2 (7%)	7 (24%)
Primary sclerosing cholangitis (20, 13%)	14 (70%)	6 (30%)	0	0
Obstructive tumor in the CBD (31, 20%)	23 (74%)	4 (13%)	1 (3%)	3 (10%)
Ordinary cholecystitis with plasma cells (76, 49%)	66 (87%)	4 (5%)	5 (7%)	1 (1%)

Conclusions: About a quarter of the patients with ISD show a distinctive inflammation in the GB that is similar to the one seen in AIP pancreata. While moderate/high numbers of IgG4 + PCs are relatively specific for AIP/ISD (92%), they are not sensitive (31%); and are also seen in 10% of the patients with obstructive etiologies.

1839 Comparative Analysis of Different Counting Methodologies for Ki-67 in Pancreatic Neuroendocrine Tumors

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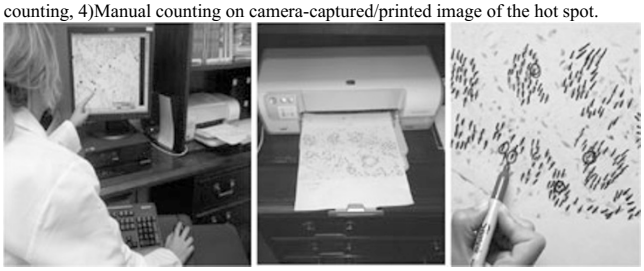
Background: Ki-67 labeling index is now one of the 2 parameters in the classification of pancreatic NETs in the WHO-2010 classification. However, in adapting this into daily practice, it becomes clear that there are serious challenges in the counting methodologies.

Design: Ki-67 immunohistochemical staining was performed on full sections from 21 NETs, and percentage of the tumor cells stained was counted by 4 different methods by 3 observers: 1) "Eye-balling", 2) "Eye-counting" through the microscope, 3) Automated counting, 4)Manual counting on camera-captured/printed image of the hot spot.



Results: Considering the balance of accuracy, practicality, and reproducibility, the method that was found to be by far the most preferable (Table) was the manual counting on camera-captured/printed image.

	Impact on turnaround time	Average time it takes (minutes)	Practicality	Accuracy	Miscounting of non-target cells	Interobserver agreement (Pearson's correlation)	Additional Cost
Eye-balling	None	1	Highest	Very low	Unlikely	R=23%	None
Eye-counting through microscope	None	6	Low	High	Unlikely	R=32%	None
Manual counting on camera captured/ printed image of the hot spot	Minimal (depending on accessibility of a camera/ printer setup)	13	Very high	Highest	Unlikely	R=43%	Printer + camera $5,400
Automated	Highest (depends on the technician availability)	5	Low (accessibility issues)	Moderate	Very likely	N/A	Image analyzer $150,000

Conclusions: Among the 4 methods of counting Ki-67 in pancreatic NETs, the method that was found to be the most accurate, practical and reproducible is the one in which counting is performed on camera-captured/printed image of the hot spot.

1840 The Significance of Poorly Differentiated (Undifferentiated) Component in Gallbladder Carcinomas (GBC): Clinicopathologic Analysis of 54 Cases Identified in 628 GBC

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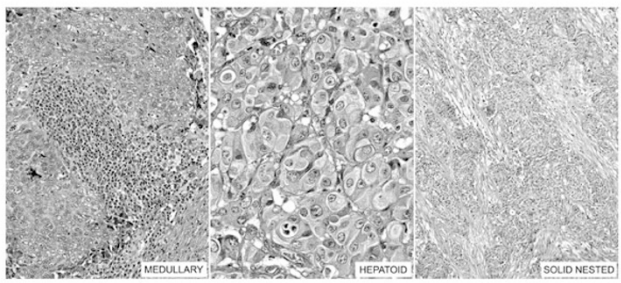
Background: Recent studies have revealed that even a small poorly-differentiated epithelioid component (PDE) in endometrial and GI-tract carcinomas is of biologic and prognostic significance, and a percentage is associated with MSI and even HNPCC. PDE has not been investigated in gallbladder carcinomas (GBC) although GB is cited among the HNPCC-related organs.

Design: The presence and potential associations of PDE component was investigated in 628 GBCs.

Results: 54 (8.6%) GBC had a PDE component manifested in 3 patterns (Figure): medullary (syncitial growth of large zones of epithelioid cells forming nodules with pushing-border infiltration, associated with inflammatory cells; n=41); hepatoid (sheet-like zones of hepatoid cells in trabecular arrangement; n=4) and in widely separated small, solid, rounded nests (n=9). Cases with PDE as compared to those without were: F/M=3.3 (vs 4); mean age=67 (vs 64); advanced stage (T3)=57% (vs 49%; p=0.13). Six had an intramucosal PDE component. PDE was associated with more aggressive behavior [67% increase in mortality with HR=1.67 (95% CI=1.2-2.33); p=0.003]. However, this appeared to be partially stage dependent. MSI was shown by immunohistochemistry in 14% (3/22 tested), 2 of which were hepatoid. PDE component was positive for AE1/AE3 in all, CK18 in 91%, CK20 in 14%, MUC1 in 68%, CEA in 53%, EMA in 86%, CA 19-9 in 28%, p63 in 41%, p53 in 73%. KI-67 index was ≥ 15% in 83%. Hepatoid cases were positive for Heppar1 in 3/4 tested and closely mimicked hepatocellular carcinoma.



Conclusions: Poorly differentiated epithelioid (PDE) component occurs in 8.6% of GBC, and shows an aggressive behavior as expected from undifferentiated/high-grade carcinomas including endometrial ones, although the adverse prognosis may be related to its propensity for advanced stage. MSI by IHC is seen in 14%. The presence of PDE component in GBC should be duly reported and considered for MSI testing, especially those with hepatoid pattern.

1841 Multipotent Progenitor Cells in Mouse Fetal Pancreas Are Defined by High Sox9 and Low Ngn3

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Background: There has been considerable controversy regarding the location of multipotent progenitor cells (MPCs) within the developing pancreas and the elucidation of when MPCs become restricted to specific lineages. Neurogenin 3 (Ngn3) has been regarded as an on/off switch for endocrine differentiation; however, lineage-tracing studies in mice show that some Ngn3-expressing cells give rise to ductal and acinar tissue. The transcription factor Sox9 is expressed in fetal pancreatic ducts and is a positive regulator of *NGN3.* We have studied the location and behavior of cells expressing these factors in order to gain a better understanding of the phenotype of pancreatic MPCs.

Design: Genetic lineage-tracing was performed in transgenic mice expressing Cre recombinase under control of regulatory elements from the *NGN3* and *SOX9* gene loci. The mice carried a reporter gene allele that produces yellow fluorescent protein (YFP) after Cre-mediated recombination. The lineage-tracing studies were repeated in combination with conditional knock-out of the *PDX1* gene, an essential regulator of pancreas development, to assess the function of the putative MPC populations in the developing pancreas.

Results: Ngn3 is expressed in progenitors of pancreatic duct and endocrine tissue. The bipotential duct/endocrine progenitor cells have a characteristic molecular signature of $Ngn3^{low}Sox9^{+}Muc1^{+}$. The ability of the progenitor cells to give rise to endocrine tissue requires Pdx1, and strong expression of Pdx1 is required for production of beta cells. In the absence of Pdx1, cells specified to endocrine fate undergo apoptosis.

Conclusions: We have identified a proliferative population of bipotential duct/endocrine progenitors that resides in the epithelial layer lining the lumen of the embryonic pancreatic ducts. This progenitor population gives rise to new duct and endocrine cells continuously during embryogenesis, and the ability of these cells to generate endocrine tissue is dependent on Pdx1.

1842 Histologic Grading the Extent of Residual Carcinoma Following Neoadjuvant Chemoradiation in Pancreatic Ductal Adenocarcinoma: A Predictor for Patient Outcome

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Background: Several grading schemes for the extent of residual tumor in post-treatment pancreaticoduodenectomy (PD) specimens have been proposed. However, the prognostic significance of these grading schemes is unknown.

Design: Histopathologic slides of 223 cases who received neoadjuvant chemoradiation and PD were reviewed. The extent of residual tumor was graded using both the College of American Pathologists (CAP) and the Evans grading systems. The grading results were correlated with clinicopathological parameters and survival.

Results: Among the 223 patients, 6 patients (2.7%) showed pathologic complete response (pCR, CAP Grade 0 or Evans grade IV), 36 cases (16.1%) with minimal residual tumor (CAP Grade 1 or Evans grade III), 124 cases (55.6%) with moderate response (CAP Grade 2 or Evans grade IIb) and 57 cases (25.6%) with poor response (CAP grade 3, 18 with Evans Grade I and 39 with Evans Grade IIa response). Patients with pCR or minimal residual tumor (response group 1) had better survivals than those with moderate and poor response (response group 2). Response group 1 patients had lower post-therapy tumor and AJCC stages and lower rates of lymph node metastasis and positive resection margin. Grading the extent of residual tumor is an independent prognostic factor for OS in multivariate analysis.

Conclusions: pCR or minimal residual tumor in post-treatment PD specimens correlate with better survival in patients with PDAC who received neoadjuvant therapy and PD. Histologic grading of the extent of residual tumor in PD specimen is an important prognostic factor in patients with PDAC who received neoadjuvant therapies.

1843 Altered ATRX/DAXX Expression and Telomere Length of Pancreatic Neuroendocrine Tumors in MEN-1 Syndrome

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Background: Approximately 45% of well-differentiated large sporadic pancreatic neuroendocrine tumors (PanNETs) harbor mutations in either the *ATRX* (α-thalassemia/mental retardation syndrome X-linked) or *DAXX* (death-domain associated protein) gene. These mutations are associated with loss of protein expression as determined by immunolabeling and correlate with the alternative lengthening of telomeres (ALT) phenotype. Patients with multiple endocrine neoplasia type 1 (MEN-1) syndrome, genetically defined by a germ line mutation in the *MEN1* gene, are predisposed to developing PanNETs and thus represent a unique model for studying the timing of *ATRX* and *DAXX* inactivation in the development of PanNETs.

Design: We characterized ATRX and DAXX protein expression and the ALT status of 109 well-differentiated pancreatic neuroendocrine lesions in 28 MEN-1 patients. The study set consisted of 47 neuroendocrine microadenomas (< 0.5 cm), 50 PanNETs (≥ 0.5 cm), and 12 PanNET lymph node metastases. ATRX and DAXX were evaluated by immunohistochemistry, and ALT was assessed by telomere-specific fluorescence *in situ* hybridization (FISH).

Results: ATRX and DAXX expression was intact in all 47 microadenomas, and none showed the ALT phenotype. ATRX and/or DAXX expression was lost or aberrant in 3 of 50 (6%) PanNETs. In all 3 of these cases, the tumor was ≥ 3 cm, and loss of ATRX and/or DAXX expression correlated with the presence of the ALT phenotype. In 2 of the 3 cases, defective ATRX/DAXX expression and ALT were also present in the corresponding lymph node metastases.

Conclusions: These findings establish the existence of ATRX/DAXX defects and the ALT phenotype in the context of MEN-1 syndrome. Overall, these alterations were relatively uncommon. The finding that ATRX/DAXX defects and the ALT phenotype occurred only in tumors ≥ 3 cm and their lymph node metastases suggests that these changes are a late event in the development of PanNETs.

1844 Combined Progesterone Receptor and PTEN Expression Predicts Metastasis and Survival in Patients with Pancreatic Neuroendocrine Tumors

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Background: Lack of progesterone receptor (PR) expression has been shown to be associated with worse prognosis in pancreatic neuroendocrine tumors (PNETs). For endometrial and breast carcinoma, lack of PR expression is associated with loss of PTEN expression. This association and its utility to predict metastatic potential and survival have not been studied in low and intermediate grade PNETs.

Design: 104 resected PNETs (52 low and 52 intermediate grade) were analyzed for PR and PTEN immunohistochemical expression. PR stain was scored as positive or negative using <5% as cut-off. Tumors with reduced PTEN expression exhibited diffuse faint staining compared with strong staining of stromal cells (internal positive control). None of the tumors demonstrated complete loss of PTEN expression. Combined PR and PTEN expression was correlated with distant metastasis and overall survival using chi-squared and Kaplan-Meier analyses.

Results: 36 of 104 (35%) patients had distant metastasis at diagnosis. Among the remaining 68 patients with stage 1 and 2 disease, 8 (12%) developed distant metastasis at last follow-up. 12 (12%) patients had combined PR negative-PTEN reduced, 26 (25%) had either PR negative-PTEN strong or PR positive-PTEN reduced, and 66 (64%) had PR positive-PTEN strong PNETs. 8 of 11 patients (73%) with PR negative-PTEN reduced PNETs presented with distant metastasis compared to 15 of 64 patients (23%) with PR positive-PTEN strong PNETs (p=0.002). The combination of positive PR and strong PTEN expression was significantly associated with prolonged time to distant metastasis (p=0.034, Figure 1) and improved overall survival (p<0.001, Figure 2).

Figure 1: Combined PR and PTEN expression and Time to Distant Metastasis

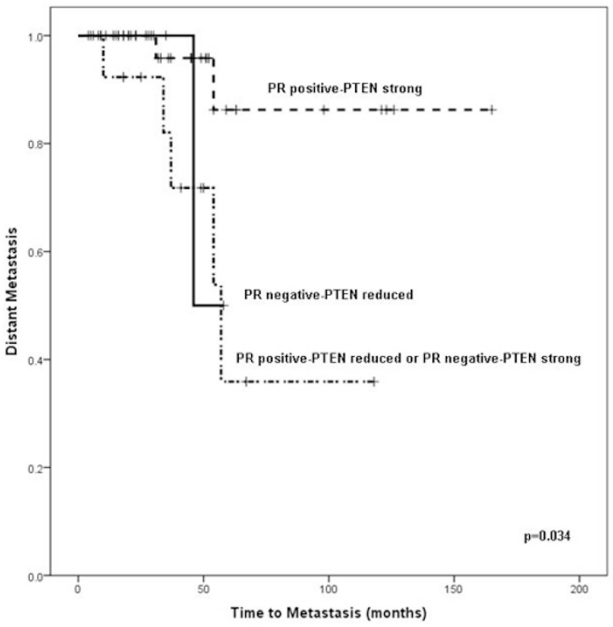
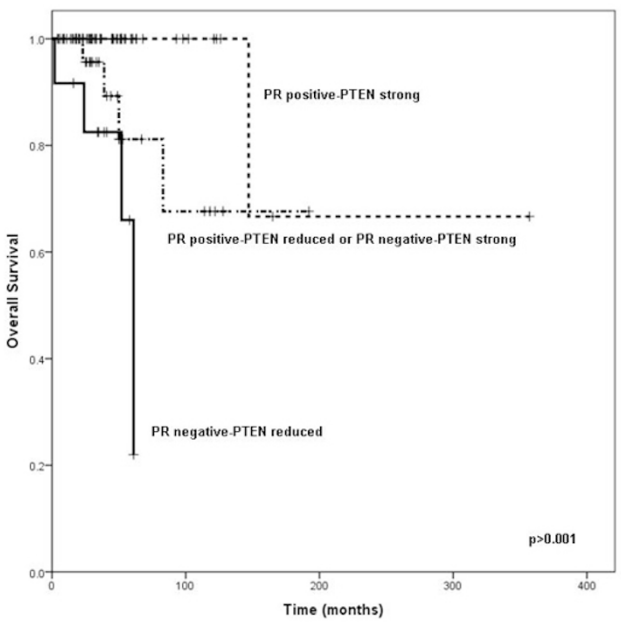


Figure 2: Combined PR and PTEN expression and Overall Survival



Conclusions: Immunohistochemical assessment of PR and PTEN can help identify a subset of PNETs with clinically aggressive behavior. These patients may be candidates for therapeutic approaches.

1845 Loss of PTEN Expression in Pancreatic Ductal Adenocarcinoma Is Associated with Poor Survival

W Foo, A Rashid, H Wang, S Hamilton, MH Katz, JE Lee, HF Gomez, JL Abbruzzese, JB Fleming, H Wang. University of Texas, M.D. Anderson Cancer Center, Houston, TX.

Background: PTEN is a tumor suppressor in the AKT/mTOR pathway. Animal model studies have shown that loss of PTEN function is involved in the progression of pancreatic cancer. However, the prognostic significance of loss of PTEN expression in pancreatic cancer is unclear.

Design: A tissue microarray was constructed from 133 surgically resected stage II pancreatic ductal adenocarcinomas (PDA). The microarray included 78 males and 57 females with a median age of 64 (range, 25 - 85). PTEN expression was evaluated by immunohistochemistry (IHC). The IHC slides were evaluated independently by two pathologists. The IHC results were categorized into PTEN-negative (no staining or staining in <5% of the tumor) and PTEN-positive (positive staining in ≥5% of the tumor cells). The staining results were correlated with clinicopathologic features and survival.

Results: Thirty-four of 133 (25.6%) cases were PTEN-negative. Recurrence/metastasis was observed in 88% (30/34) of patients whose tumors were PTEN-negative compared to 69% (68/99) in patients whose tumor were PTEN-positive (p=0.03). Patients whose tumors were PTEN-negative had shorter overall survival (median: 19.9±3.6 months) than

those whose tumors were PTEN-positive (32.7±5.0 months, p = 0.03). In multivariate analysis, loss of PTEN expression was an independent prognostic factor for poor overall survival in patients with stage II PDA. No significant correlations between PTEN expression and other clinicopathologic parameters were observed.
Conclusions: Loss of PTEN expression is associated with poor survival in patients with stage II PDA. Assessment of PTEN expression may be used as a prognostic marker for patients with resected PDA.

1846 Downregulation of SMAD4 Is Significantly Associated with Poor Prognosis of Pancreatic Cancer: A Clinicopathologic Study of 643 Cases in a Single Cancer Center

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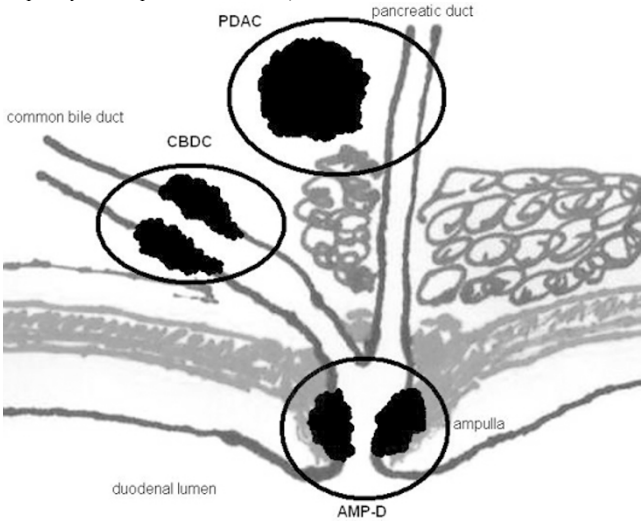
Background: SMAD4 and transforming growth factor (TGF) ß are important biomarkers in pancreatic cancer. TGF-ß exerts its effects through the TGF-ßR1/ R2 receptors and the SMAD transcriptional regulators. We investigated the prognostic value of these related biomarkers in pancreatic cancer.
Design: 643 total patients were studied retrospectively. TGFßR2 and SMAD4 protein expression were measured in available pancreatic cancer biopsies using immunohistochemisty (IHC). IHC was evaluated for intensity (0: none, 1: weak, 2: moderate, 3: strong) and percentage of positive tumor cells (0: 0%+, 1: 1-10%+, 2: 10-25%+, 3: >25%+). The final IHC score was then calculated (intensity x percentage). Plasma TGFß1 level was also measured using the Meso Scale Discovery Multi-array® Human TGFß1 Assay. The relationship between IHC score and overall survival (OS) was assessed using multivariate Cox proportional hazards models with relevant clinical covariates. Kaplan-Meier and log-rank tests were also used to analyze OS by plasma TGFß1 levels.
Results: In the multivariate Cox model, after adjusting for baseline stage, CA 19-9, PS, age, and TGFßR2 expression, complete loss of SMAD4 expression (IHC score 0) was significantly associated with lower OS (HR: 1.85, 95% CI: 1.06-3.23; p = 0.03). Progressive disease on a first-line gemcitabine-base regimen was more likely in loss of SMAD4 group as compared with retained SMAD4 group (score higher than 0) (46.5% vs. 38.1% progressed; chi square p = 0.069). In patients with locally advanced and metastatic disease, a significant difference in OS (27.7 weeks compared to 40 weeks) between the top quartile of plasma TGFß1 levels (>19.05 ng/mL) and lower levels, respectively (log-rank p = 0.0125, adjusted).
Conclusions: This large retrospective study suggests that downregulation of SMAD4 plays a role in prognosis of pancreatic cancer. Assessment of SMAD4 by readily available immunohistochemistry may have potential utility to evaluate the clinical outcome of this malignancy.

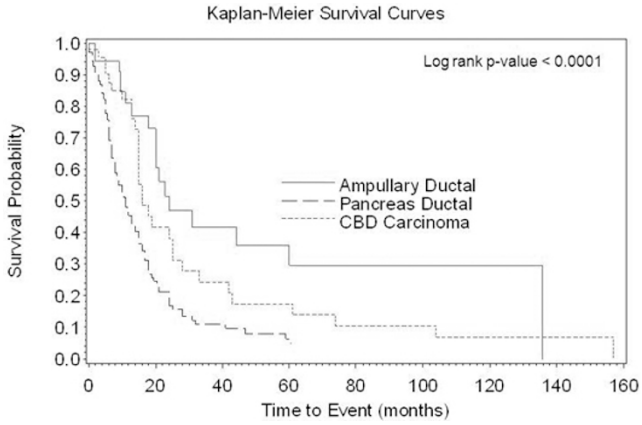
1847 Distal Common Bile Duct Adenocarcinoma: Analysis of 47 Cases and Comparison with Pancreatic and Ampullary Ductal Carcinomas

RS Gonzalez, P Bagci, SY Kong, K-T Jang, N Ohike, T Tajiri, O Basturk, S Bandyopadhyay, L Ducato, A Krasinskas, G Kim, J Cheng, V Adsay. Emory U, Atlanta; Showa U, Tokyo, Japan; MSKCC, New York; WSU, Detroit; UPMC, Pittsburgh; UCSF, San Francisco; Piedmont Hospital, Atlanta.
Background: Distal common bile duct carcinoma (CBDC; aka "intrapancreatic cholangiocarcinoma") is a well-known but poorly characterized entity.
Design: Of 1017 whipples with primary adenocarcinoma, 52 qualified as non-ampullary CBDC based on gross (Fig1) and microscopic findings. 5 associated with an intraductal papillary neoplasm (9%) were excluded; the remaining 47 were compared to 112 pancreatic ductal adenocarcinomas (PDAC) and 40 pancreatobiliary-type adenocarcinomas of ampullary ductal origin (AMP-D; >75% of tumor in the intra-ampullary/distal tip of the CBD or PD).



Results: Clinicopathologic characteristics of CBDC (Table, p-values <0.001) included younger age and prognosis significantly better than PDAC but worse than AMP-D (Fig2). Parallel with the average size, LN mets and margin positivity rates. Grossly, CBDCs were subtle, scirrhous, constrictive lesions forming circumferential plaque-like thickening of the CBD wall. 4 showed cystic duct–CBD union within the pancreas (what we propose to call low union), with the tumor immediately distal to this abnormal junction. Microscopically, many cases formed an even band around the CBD, with careful analysis revealing more infiltrative foci. Compared to PDACs, CBDCs more commonly showed intraglandular neutrophil-rich debris and a smaller tubular pattern.

	AMP-D	CBDC	PDAC
Age (years)	69	60	64
Average Tumor Size (cm)	1.9	2.9	3.6
Lymph Node Metastases	42%	60%	73%
Positive Margins	3%	23%	33%
Median Survival (months)	24	16	11



Conclusions: Primary CBDC is uncommon in the west. It is seen in younger patients than PDAC or AMP-D and has a significantly better prognosis than the former and worse than the latter, presumably in part due to an average size and nodal metastasis and margin positivity rates between the two.

1848 Is Islet 1 (Isl1) a Sensitive and Specific Marker for Pancreatic Neuroendocrine Tumors and Their Metastases

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Background: Islet 1 (Isl1) is a transcription factor involved in the development of pancreatic islet cells. An Isl1 antibody has been shown to be a sensitive lineage marker of pancreatic neuroendocrine tumors (NETs) and their metastases. However, the specificity of this marker has not been studied in a large series of NETs and their metastases from specific anatomic sites.
Design: A total of 244 primary NETs and 40 NETs metastatic to the liver from known primaries were studied. The primary sites were confirmed by pathology and radiology reports and clinical history. The primary tumors included: pancreas (N=102), stomach (N=10), duodenum (N=9), ileum (N=16), appendix (N=22), lung (N=17), colorectal (N=15), breast (N=12) and ovary (N=1). The hepatic metastases were from the pancreas (N=21), jejunum (N=2), ileum (N=12), cecum (N=1), rectum (N=2), and lung (N=2). Immunostaining was performed using antibodies to Isl1 (clone 1H9, 1:800, Abcam, MA) and CDX2 (AMT28; 1:50, Novocastra, UK), and nuclear staining in at least 5% of the tumor cells was considered positive. The correlation of Isl1 and CDX2 expression was studied using a tissue microarray (TMA) containing 46 pancreatic NETs. Combined staining of Isl1 and CDX2 was performed in a subset of NETs from other sites.
Results: Isl1 was positive in 90% of pancreatic, 89% of duodenal, 67% of colorectal, 14% of appendiceal, and 6% of ileal primaries. Isl1 was negative in all lung, gastric, breast and ovarian NETs. In addition, 76% of pancreatic (16 of 21) and 2 of 2 colorectal NETs metastatic to the liver were positive for Isl1 while all metastases from jejunal, ileal, cecal and lung primaries were negative. Thus, the overall sensitivity of Isl1 in identifying primary pancreatic NETs was 88% with a specificity of 80%. 78% pancreatic NETs in the TMA were positive for Isl1; 9% of these, all of which were negative for Isl1, were positive for CDX2. CDX2 was positive in only a few duodenal (2/9) or colorectal NETs (2/15).
Conclusions: This study confirms that Isl1 is a sensitive marker to support pancreatic origin in the case of metastatic NET. However, this study highlights that Isl1 does not allow for clear distinction from duodenal and colorectal NETs, even in combination with CDX2. Clinical/radiological correlation is required to exclude these primaries. Pathologists should be cautious in the use of Isl1 immunohistochemistry without a panel of other markers for determining the primary site of metastatic NETs.

1849 ALK Rearrangements in Pancreatic Ductal Adenocarcinoma and Neuroendocrine Tumors

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Background: *ALK* rearrangements were first identified in anaplastic large cell lymphomas. Subsequently, they have been observed in other malignancies, including, most recently, in pulmonary adenocarcinoma. Targeted therapy by ALK inhibitors has demonstrated efficacy in *ALK*-translocation positive tumors and is now a standard therapy. *ALK* rearrangements in pancreatic tumors including ductal adenocarcinoma and neuroendocrine tumors (NETs) have not been systematically studied before and we sought to evaluate *ALK* rearrangements in a large series of pancreatic tumors.
Design: Immunohistochemical expression of ALK has been shown to correlate with *ALK* rearrangements in tumors in other sites. Immunohistochemical stains with ALK antibody (Clone ALK1; 1:25-1:50; Dako) were performed using two tissue microarrays (TMA)

to select ALK positive cases. The TMAs included 140 cases of ductal adenocarcinoma, and 46 cases of NET. The immunoreactivity was scored for each case in the microarray as 0, 1+, 2+ or 3+ using established criteria. The diagnosis of the positive TMA cases was confirmed by review of H&E-stained full sections. Thereafter, the ALK immunoreactivity was confirmed by performing the ALK immunohistochemical stain on full sections. Fluorescent in situ hybridization assay (FISH) using a break-apart assay with probes for *ALK* (ALK probe; Abbott, IL) was performed to detect *ALK* rearrangements in ALK immunohistochemistry positive cases.
Results: Of 140 ductal adenocarcinoma cases on the TMA, 5 showed immunoreactivity for ALK1 with the following degree of expression: N=1 (3+), N=2 (2+), N=2 (1+). All 46 NETs were negative. Review of H&E sections confirmed 5 adenocarcinomas including one associated with an intraductal papillary mucinous neoplasm. However, FISH for *ALK* locus rearrangements was negative in all five cases.
Conclusions: After screening with TMA, 5 ductal adenocarcinoma cases (3.5%) showed ALK expression, and one case showed strong immunoreactivity. However, FISH for *ALK* translocations was negative in all cases. Therefore, ALK expression is uncommon in pancreatic carcinomas and NETs. The rare immunohistochemical expression of the protein is not induced by *ALK* translocation but rather, alternative mechanisms may be responsible. These results indicate that *ALK* rearrangements are not a fundamental event in pancreatic tumorigenesis, and ALK is unlikely to be a major therapeutic target in pancreatic tumors.

1850 Tumoral Epithelial and Stromal Expression of SMAD Proteins in Pancreatic Ductal Adenocarcinomas

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Background: SMAD proteins, intracellular mediators of the TGFbeta pathway, function within two axis, the SMAD1/5/8 and SMAD2/3, connected to TGFbeta and BMP ligands. They dimerise with SMAD4 and translocate to the nucleus. SMAD signaling is characterized by a dichotomic functioning with tumor suppressive functions and with loss of normal growth inhibitory responses, depending on carcinogenesis stage. SMAD proteins also have pro-tumor effects including abnormal extracellular matrix production. Among tumors, pancreatic cancers harbor SMAD4 inactivation the most frequently and the SMAD proteins are considered key factors in pancreatic carcinogenesis.
Design: We aimed to study the expression patterns of the different types of SMAD proteins in a large series of pancreatic ductal adenocarcinomas (PDAC) treated by surgical resection and their correlations to morphological and clinical characteristics. We examined the immunohistochemical expression of SMAD4, SMAD1/5/8 and SMAD2/3 in 99 PDAC. Antibodies directed against the activated, phosphorylated forms of proteins have been used when appropriate (SMAD1/5/8, SMAD2/3). Protein expression in the epithelial tumor cells and in stromal fibroblasts was analyzed with regard to morphological and clinical data.
Results: The SMAD1/5/8, SMAD2/3 and, SMAD4 proteins were expressed in tumor epithelial cells in 13.5%, 96% and 49% of the tumors and in 5%, 11% and 23% PDAC in stromal fibroblasts. Epithelial SMAD4 was associated to a low, T1 or T2 TNM stage and to the presence of an abundant stroma ($p=0.05$ and <0.01, respectively). Activated stromal fibroblast SMAD2/3 expression was correlated to presence of a fibrotic focus ($p=0.01$), whereas fibroblast SMAD4 related to a tendency for shorter postsurgical overall survival ($p=0.07$). The relationship of stromal, fibroblast SMAD4 to a worse outcome attained statistical significance in the groups of patients with T1 and with N1 stage tumors ($p<0.01$ and $p=0.04$, respectively).
Conclusions: In PDAC, SMAD protein expression in epithelial tumor cells or in stromal fibroblasts was related to stroma features and to worse outcome. Our results point out that the SMAD proteins play a role in the microenvironment of this highly fibrotic tumor type.

1851 Cellular Prion Protein Regulates Notch1 Expression in Pancreatic Ductal Carcinoma

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Background: The Cellular Prion protein (PrP) is a GPI-anchored glycoprotein that is widely expressed on many normal cell surfaces. Over-expressions of PrP have been identified in many cancers including pancreas, breast, and colorectum. Our previous studies have found that PrP over-expression in PDAC patients was associated with a worse prognosis, as PrP enhanced PDAC invasiveness through binding with filamin A. Notch1 pathway plays an important role in cell proliferation, differentiation, and apoptosis in pancreatic organ development. The role of Notch1 in PDAC is controversial. Although one study suggested Notch might function as a tumor suppressor gene, many other studies suggested it promoted the development of pancreatic cancer. Inhibition of Notch signaling pathway has recently been explored as a therapeutic target for PDAC. In this study, we tested whether PrP interacts with Notch1 by using knockout cell lines.
Design: We used human PDAC cell line BxPC-3 with high expression of PrP (BxPC3-PrP-WT) and BxPC-3 cells after PrP shRNA treatment (BxPC-3-PrP-KO). PrP protein expressions in knockout cell lines were examined by Western blot. Gene array (Affymetrix GeneChip U133 plus 2.0 array) and flow cytometry were used to examine RNA and protein levels of PrP and Notch1 in these two cell lines.
Results: Knock-down of PrP via shRNA decreased PrP protein level by >90%. Consistently, there was an approximately 50% reduction of PrP mean fluorescent intensity (MFI) in PrP knock out (KO) pancreatic cancer cells compared with that of wild type (WT) cancer cells by flow cytometry. PrP KO cells showed a three fold reduction of Notch1 RNA compared with PrP WT cells by cDNA microarray analysis. This is further confirmed by our flow cytometric analysis that there was an approximately 50% reduction of cell surface Notch1 MFI in PrP KO cells compared with that of PrP WT cells.
Conclusions: Our data indicates that PrP up-regulates Notch1 expression in PDAC cell lines, and inhibition of PrP down-regulates Notch1 expression. It suggests that PrP may play an important role in the tumorigenesis of PDAC through regulation of Notch1 signaling, which provides a rationale for future study of this pathway as a novel therapeutic target for treating PDAC.

1852 Diagnostic Accuracy of Endoscopic Ultrasound-Guided Fine-Needle Aspiration in Patients with Pancreatic Adenocarcinoma Using Histology as the Gold Standard

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Background: Endoscopic ultrasound (EUS)–guided fine-needle aspiration (FNA) of the pancreas has been well established, by numerous single center studies, as an effective minimally invasive modality in confirming pancreatic malignancy. We recently performed a meta-analysis of EUS-FNA of pancreatic adenocarcinoma (PA) in solid pancreatic lesions to determine the true diagnostic accuracy since variance amongst the published reports exists. We found that less than half (17/40) of the eligible studies consistently had rapid on-site examination (ROSE) provided by a cytopathologist, only 7/40 used histology alone, and none of the studies solely focused on PA. Due the lack of data on the diagnostic accuracy of PA by EUS-FNA, we decided to evaluate this modality using ROSE and histology alone as the reference standard since the results of our meta-analysis suggested that a composite reference standard tends to inflate the diagnostic accuracy.
Design: We reviewed our ten year experience with EUS-FNA in patients with solid pancreatic lesions; data were assessed from all patients who presented with CT imaging of a pancreatic mass and underwent EUS-FNA at our institution between January 1, 2000 and December 1, 2010.
Results: EUS-FNA was performed in 2397 patients; 500 patients had subsequent histological follow-up. A final diagnosis of PA was established in 274/500 patients (54.8%); 242 true-positives, 224 true-negatives, and 2 false-positives. The sensitivity, specificity, and accuracy of EUS-FNA for diagnosis of PA were 88.68%, 99.1%, and 93.4%, respectively. The positive predictive value (PPV) and negative predictive value (NPV) of EUS-FNA for PA were 99.18% [95% confidence interval (CI) 97.07 to 99.78%] and 87.84% (CI 83.26 to 91.30%), respectively.
Conclusions: We conclude that the diagnostic accuracy of EUS-FNA of PA is slightly lower when histology alone is used as the reference standard, suggesting clinical follow-up as a reference component portends bias.

1853 Error Assessment of Cytopathologic Diagnosis of EUS-FNA of Pancreatic Ductal Carcinoma

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Background: Endoscopic ultrasound(EUS)-guided fine-needle aspiration(FNA) of the pancreas is an effective modality in confirming pancreatic adenocarcinoma(PA). However, the extent of error occurring in cytopathologic diagnosis of EUS-FNA of PA is unknown. Moreover, the impact(harm) of these errors on clinical outcomes has not been evaluated.
Design: A database was constructed utilizing the clinical notes, endoscopic, pathologic, and radiographic reports, and tumor bank registry to correlate clinical management, progression, and outcome. Utilizing a modified standardized error classification proposed by Raab et al, we evaluated for type and cause of error, recurrent diagnoses, interobserver agreement of discrepancies, and the impact of diagnostic inaccuracy, particularly harm resulting in delayed diagnosis, management or inappropriate treatment.
Results: 2399 cases from 2000-2010 with corroborating histology existed for 506 cases allowing for evaluation of cytologic error. The database confirmed 274 PA and uncovered incongruity between 40(7.9%) of the cytopathologic and surgical diagnoses. 32 cases(80%) were available for cytohistologic disconcordance review. 81.3%(26/32) were due to cytology specimen sampling error(CSE), of which 96.2%(25/26) were of no/minimal harm, the remaining case had minor clinical significance(no morbidity). Cytology interpretation error(CIE) accounted for 12.5%(4/32), 3 cases were determined to have error which could impact patient outcome (minor/moderate morbidity), and 1 resulted in inappropriate management. CSE/CIE delayed diagnosis on average 26 days(4-186days) in FN cases. CIE of the one FP case resulted in major harm(inappropriate treatment). Specimens which were more prone to cytologic diagnostic error had more passes(avg.5.25) and were either associated with chronic pancreatitis or a mucinous cystic lesion. Individual CIE was not assessed in this study. Interobserver assessment of the discrepant cases showed 27/32 and 5/32 agreement and disagreement with the cytohistologic original interpretation. The kappa scores ranged from.87-.93 for pairwise agreement of discrepant cases.
Conclusions: We found that the clinical impact of CSE/CIE typically results in no/minimal error. However in patients with unusual presentation or suspicion for diagnostic/sampling error was low, the clinical impact was more often consequential(delayed diagnosis/management or inappropriate treatment). Recognizing the impact of error in cytopathologic diagnosis of EUS-FNA PA may create quality assurance practices to reduce error, minimize healthcare cost, and decrease morbidity.

1854 Vascular Invasion in Infiltrating Ductal Adenocarcinoma of the Pancreas Can Mimic Pancreatic Intraepithelial Neoplasia: A Histopathologic Study of 209 Cases

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Background: Although vascular invasion is a well-established indicator of poor prognosis for patients with infiltrating ductal adenocarcinoma of the pancreas (PDAC), the histopathologic characteristics of vascular invasion are not well described.

Design: Hematoxylin and eosin stained slides from 209 surgically resected infiltrating PDACs were systematically evaluated for the presence or absence of microscopic vascular invasion. For the cases with vascular invasion, we further categorized the histologic pattern of invasion into conventional and pancreatic intraepithelial neoplasia-like (PanIN-like). In addition, several histopathologic factors in the surrounding blood vessels, including lymphocytic infiltration and luminal fibrosis were carefully accessed. Data were compared to clinicopathologic variables, including patient survival.

Results: Microscopic vascular invasion was observed in 136 of the 209 PDACs (65.1%). Vascular invasion mimicking pancreatic intraepithelial neoplasia (PanIN-like invasion) was observed in 94 of the 136 cases (69.1%) with vascular invasion. Microscopic vascular invasion was associated with moderate or poor differentiation ($p=0.02$), higher pT classification ($p<0.0001$), lymph node metastasis ($p<0.0001$), and perineural invasion ($p=0.005$). Vascular invasion was inversely correlated with neo-adjuvant therapy ($p<0.0001$). Examination of adjacent blood vessel revealed that peritumoral blood vessels with intimal lymphocytes ($p=0.002$), intimal ($p=0.007$) and medial ($p=0.001$) fibrosis, and cancer cells in vascular wall ($p<0.0001$), were all highly associated with intraluminal vascular invasion. In univariate analysis, patients whose cancers had microscopic vascular invasion (median survival, 12.9 months) had a significantly worse survival than did patients with carcinomas without vascular invasion (17.6 months; $p=0.01$, log-rank test).

Conclusions: Microscopic vascular invasion is a poor prognostic indicator and can histologically mimic PanIN.

1855 Immunophenotypic and Molecular Alterations in the Carcinogenetic Progression of Mucinous Cystic Neoplasm of the Pancreas

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Background: Mucinous cystic neoplasm (MCN) is one of the precursors of invasive pancreatic carcinoma. The molecular alterations that take place during the progression of MCNs, however, have not been fully elucidated, with most of the literature focusing on the non-invasive examples.

Design: Immunolabeling of MUC1, MUC2, MUC5AC, MUC6, CDX2, and p53 were examined in 40 MCNs, consisting of 9 low-grade, 8 high-grade and 23 with an associated invasive carcinoma. Mutational analysis for *BRAF* and *KRAS* was performed in 15 (4; low-grade, 6; high-grade, 5; invasive).

Results: Among low-grade MCNs, 4 of 9 (44%) expressed MUC5AC and MUC6, but MUC1/MUC2/CDX2 were negative in all. MUC1 was expressed in 50% (4/8) of high-grade and 92% (20/23) of invasive carcinoma. However, MUC2/5AC/6 and CDX2 expression was rarely identified in either high-grade or invasive cases. p53 was expressed in 25% (2/8) high-grade and 39% (9/23) invasive carcinoma, but not in low-grade MCNs. Immunophenotypic changes are summarized in Table 1. No *BRAF* mutations were identified, but *KRAS* was mutated in 5 of 6 high-grade and 5 of 5 invasive carcinoma (Table 2).

Immunophenotypic changes of MCN

	MUC1	MUC2	CDX2	MUC5AC	MUC6	P53
Low-grade (n=9)	0	0	0	4/9 (44%)	4/9 (44%)	0
High-grade (n=8)	4/8 (50%)	1/8 (13%)	1/8 (13%)	0	2/8 (25%)	2/8 (25%)
Invasive carcinoma (n=23)	20/23 (92%)	0	0	2/23 (9%)	1/23 (4%)	9/23 (39%)

Mutational study of BRAF and KRAS in MCN

	Low-grade (n=4)	High-grade (n=6)	Invasive carcinoma (n=4)
BRAF	0	0	0
KRAS	0	5/6	5/5

Conclusions: At immunohistochemical and molecular levels, MCN pathway of carcinogenesis in the pancreas shows various parallels with that of PanIN pathway and is dissimilar to intraductal papillary mucinous neoplasms: While gastric-lineage markers (MUC5AC/6) are expressed in low-grade lesions, these are replaced by MUC1 as the disease progresses, and p53 and *KRAS* also play a role in the carcinomatous transformation. By contrast *BRAF* mutation is not involved in MCN carcinogenesis.

1856 Are Pancreatic Endocrine Neoplasms in Tuberous Sclerosis Complex a Syndrome Associated Lesion?

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Background: Pancreatic endocrine tumors (PanNET) occur either sporadically or associated with a genetic syndrome, principally MEN-1, VHL and NF-1. Tuberous sclerosis complex (TSC) is an autosomal dominant disorder due to germline mutations in *TSC1/TSC2*. Loss of *TSC1/2* in vitro and in vivo leads to mTOR cascade activation. Rare reports of PanNET in TSC exist, however, the association of PanNET in TSC has not been systematically studied and it is debated whether these are syndrome associated tumors. To better understand the nature of PanNET in TSC, we studied the clinicopathologic features of 5 PanNET in TSC with immunohistochemical (IHC) staining for S6K and 4E-BP1, surrogate markers for activation of the mTOR pathway, and array CGH analysis in 2 tumors.

Design: A retrospective search of records at this institution was performed for patients with pancreatic lesions detected on abdominal imaging. Of 219 patients with tuberous sclerosis who underwent abdominal imaging, 8 pancreatic lesions were initially identified. Of these, 3 patients underwent resections. A retrospective review of the pathology records identified 2 additional TSC patients with PanNET. Representative sections of tumor were stained for S6K and 4E-BP1. Demographic and clinical data were collected from patient files. Array CGH was performed in two cases in which snap frozen tissue was available.

Results: The 5 cases comprised 3 males and 2 females with a mean age of 37.4 yrs (range 20-54 yrs). Germline mutation was known in 3 of 5 patients, all with *TSC2* mutations. The lesions were asymptomatic and incidentally detected on abdominal MRI (n=3), during laparoscopic appendectomy (n=1) and at autopsy (n=1). Of 4 surgically resected tumors, 3 were cystic and 1 solid, with mean tumor size of 37.4mm (range 7-48mm) and locations in the tail (n=2) and body (n=2) of the pancreas. The 5th case was a microscopic finding at autopsy with no visible macroscopic tumor. IHC staining of all 5 tumors showed positive staining for S6K and 4E-BP1. Array CGH did not demonstrate copy number variation in *TSC1/2* gene loci in one case but demonstrated gains in *TSC2* in the other case.

Conclusions: The uniform finding of mTOR activation in TSC associated PanNET contrasts with sporadic PanNET, 14% of which have been reported with mutations in mTOR pathway genes. This feature, together with the relative young age of onset, suggests that PanNET in TSC may be syndrome related lesions. These findings may also have implications for both surveillance and therapy.

1857 Cystic Mucinous Duct Lesion of the Pancreas: A Clinicopathologic Analysis of 40 Examples of a Diagnostically Challenging and Terminologically Controversial Entity

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Background: Cystic pancreatic lesions that are ≥1cm and lined by non-papillary mucinous epithelium, variably termed "mucinous non-neoplastic cyst," "retention cyst," or "secondary ectasia" form a poorly characterized entity.

Design: 40 patients who underwent resection for such lesions were analyzed. Cysts detected incidentally during operations for other tumors were excluded.

Results: F/M:4. Mean age: 65 (22-85). Mean cyst size: 2.6 cm (1-8). All had a well defined paucicellular fibrous band surrounding the epithelium (0.5-3.5 mm). None had ovarian type stroma (PR negative in all 40). Most had innocuous appearing lining; attenuated in some areas, and all had at least partial mucinous lining, but without the papilla, undulation, tributary duct pattern of branch-duct IPMNs. The cyst lining showed focal high grade dysplasia in 3, intermediate in 17, but 21 had no significant atypia. Degenerative changes were common (26): hemorrhage, myxoid/hyalinized stroma in 16, calcification 4, histiocytic aggregates 12. No visible obstructive process (tm, pancreatitis, stones) to attribute the lesion to "secondary ectasia" was identified. Immunohistochemically (28 tested) the epithelium showed gastric differentiation (MUC5AC 79%, MUC6 93%, CK7 100%), but no intestinal differentiation (MUC2 0, CDX2 14%, CK20 4%). DPC4 was retained in all 20 tested. Foci of high ki-67 index (≥ 10%) were seen in 23%. P53 was positive in 4%. *KRAS* mutation was identified in tissue sections in only 4/19 however, 15/16 had mutation identified in the cyst fluid. Original diagnosis was IPMN in 10, MCN 6,"mucinous non-neoplastic cyst" 18, SCA 1, retention cyst 2, congenital cyst 1.

Conclusions: The fundamental lesion in these cases are cystic (mass forming), non-papillary version of PanIN-1A/mucinous duct lesion or a non-papillary (1A?) version of IPMN, for which cystic mucinous duct lesion (CMDL) would be the most appropriate term until their nature is further characterized. While the presence of degenerative changes and attenuated epithelium suggest a secondary ectasia (although no other cause of obstruction is demonstrable), preponderance for postmenopausal women suggests that these may be atrophic (regressed) version of MCNs. KRAS mutation is identified in the lining in 20%, and is commonly present in the cyst fluid, and further, there are foci of overt dysplasia in 48%, which warrants CMDL to be regarded neoplastic, albeit a very early (1A-type) lesion.

1858 Undifferentiated Carcinomas of the Pancreas Are Characterized by *KRAS* Mutant Allele-Specific Imbalance

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Background: Activating point mutations in codon 12 of the *KRAS* oncogene are present in the majority of pancreatic ductal adenocarcinomas (PDAs) and in pancreatic undifferentiated carcinomas with pleomorphic or osteoclast-like giant cells. The role of *KRAS* mutant allele specific imbalance (MASI), which is associated with increased mutant allele transcription and kinase activity, has not been systematically studied in carcinomas of the pancreas.

Design: *KRAS* mutational analysis was performed using direct Sanger sequencing. Peak heights of *KRAS* mutant and wild-type alleles were compared on sequencing electropherograms. *KRAS* MASI was defined in mutated cases as mutant allele peak (M) higher than or equal to the wild type (W) allele peak (M≥W). *KRAS* amplification (KRAS/CEP12 >2) was evaluated in a subset of cases (18 PDA, 9 undifferentiated carcinomas) using fluorescence in situ hybridization.

Results: *KRAS* mutations, all at codon 12, were found in 83 of 101 (82%) cases of PDA and 10 of 11 (91%) cases of undifferentiated carcinoma. Data on the 93 *KRAS* mutated cases are shown below.

	Pancreatic Ductal Adenocarcinomas (n=83)	Undifferentiated Carcinomas (n=10)
Female/Male	39 / 44	5 / 5
Average age	67	61
Most common KRAS mutations	G12D (55%), G12V (28%)	G12D (40%), G12V (40%)
KRAS allele peak heights on sequencing electropherograms:		
M≥W (MASI)	6	7
M<W	77	3
KRAS/CEP12 by FISH:		
>2	0 /18	5 / 9
<2	18 /18	4 / 9

KRAS MASI (M≥W) is present in 7/10 (70%) undifferentiated carcinomas of the pancreas versus 6/83 (7.2%) of typical PDA (odds ratio 30, 95% confidence interval 6.1 - 146; p<.0001). MASI is associated with *KRAS* gene amplification by FISH (4/8 in M≥W versus 1/19 in M < W; odds ratio 18, 95% confidence interval 1.5 - 207; p = .017).
Conclusions: *KRAS* MASI as determined by allelic peak height on sequencing electropherograms is present in 70% undifferentiated carcinomas of the pancreas and is associated with *KRAS* gene amplification by FISH. Only 7.2% of typical PDAs have MASI. This study is the first to correlate *KRAS* MASI with a specific morphologic tumor subtype and suggests that MASI contributes to the clinicopathologic phenotype of undifferentiated carcinomas of the pancreas.

1859 Clinico-Pathologic and Prognostic Study of 59 Acinar Cell Carcinomas of the Pancreas

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Background: Due to its relative rarity, many clinicopathologic characteristics of acinar cell carcinoma (ACC) remain to be further elucidated and there are not established prognostic factors.
Design: 59 ACCs were investigated for the following parameters: site, size, local infiltration, node and distant metastases, architectural pattern (acinar, pseudoglandular, trabecular, solid structure), nuclear atypia, presence of necrosis, expanding versus infiltrating growth, lymphovascular and perineural invasion, mitotic and Ki67 indices, BCL10, trypsin, CEL, amylase, lipase, PDX1, chromogranin A, CK19, CK7, and β-catenin expression.
Results: The patients were predominantly males (M/F:2.3). Mean age was 59 years (28-88 years). Mean tumor size was 7.8 cm (2-29 cm). 32 tumors showed an acinar/pseudoglandular pattern, while 27 a solid architecture often associated with an acinar/trabecular structure. BCL10 and trypsin were the most reliable immunohistochemical markers, while amylase and lipase were not. 45 patients underwent surgery, while 14 showed unresectable cancers. Surgery was statistically correlated with a better prognosis (p:0.0007). 10 cases showing more than 25% chromogranin A positive cells were classified as mixed endocrine/ACCs, but there was not a different survival between pure ACCs and mixed cancers. 12 patients were alive free of disease after a mean follow-up time of 78 months, 4 were alive with disease after a mean follow-up time of 43 months, while 34 died of disease after a mean follow-up time of 24 months. In operated patients, the factors significantly correlated with poor prognosis were UICC-stage (p:0.003) and, in particular, size >6.5cm (p:0.04), lymph node (p:0.03) and distant (p:0.008) metastases. Vascular and perineural invasion and CK19 expression also showed a trend for poor prognosis, but did not reach statistical significance.
Conclusions: ACCs show heterogeneous morphological features. Factors associated with adverse prognosis are stage including resectability, size, lymph node and distant metastases.

1860 Overexpression of Transcriptional Intermediary Factor 1 Gamma (TIF1) and Loss of SMAD4 Are Common Events but Are Not Correlated with Each Other in Pancreatic Ductal Carcinoma

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Background: TIF1γ is a transcriptional cofactor which plays an important role in the regulation of TGFβ pathway through degradation of, or in competition with, Smad4. There is an inverse relationship between expression of TIF1γ and inactivation of Smad4 in *in vitro* studies. However, it is unclear whether the inverse relationship could also be present in pancreatic ductal carcinomas and how these two factors interact with each other.
Design: We performed Western blot and RT-PCR to confirm the inverse relationship between TIF1γ expression and Smad4 inactivation/loss on three pancreatic cancer cell lines (Panc-1, BxPC-3, and Capan-1) and two immortalized normal pancreatic cell lines (HPDE and HPNE). The relationship between TIF1γ expression and Smad4 inactivation in pancreatic cancer was investigated by immunohistochemistry using tissue microarray prepared from 125 pancreatic cancer resection specimens. Results were analyzed by the Fisher's exact test.
Results: Pancreatic cell lines BxPC-3 and Capan-1 demonstrated the highest TIF1γ expression and lowest Smad4 expression, whereas Panc-1, HPDE, and HPNE had the lowest TIF1γ expression and highest Smad4 expression at both the protein and mRNA levels. In 125 human pancreatic cancer tissue specimens, overexpression of TIF1γ (64%) and loss of Smad4 (53%) were commonevents, but the inverse relationship between them was not evident (P>0.05).
Conclusions: Overexpression of TIF1γ and loss of Smad4 appears to play independent roles in pancreatic carcinogenesis. TIF1γ overexpression, in combination with Smad4 loss, may provide a diagnostic tool for early detection of pancreatic cancer.

1861 Clinicopathologic Characteristics and Biologic Behavior of Concurrent Pancreatic Ductal Adenocarcinoma (PDAC)

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Background: Intraductal Papillary Mucinous Neoplasm (IPMN), especially of the branch-duct type, carries a risk of not only malignant transformation (invasive IPMN), but can also be associated with development of a separate invasive ductal adenocarcinoma (concurrent PDAC). Several studies have described the clinicopathologic features and biologic behavior of invasive IPMN. In contrast, our understanding of concurrent PDAC is limited, although a recent study has reported equally favorable outcomes of invasive IPMN and concurrent PDAC compared to PDAC not associated with IPMN (conventional PDAC).
Design: The study cohort consisted of 555 patients with conventional PDAC, 17 with concurrent PDAC, and 22 with invasive IPMN with tubular/ductal histology arising in a predominantly branch-duct type IPMN. Clinicopathologic features of the resection specimens and patient survival were compared among these groups. Protein expression of SMAD4 and p53 was analyzed in cases of concurrent PDAC and invasive IPMN with available blocks using tissue microarray.
Results: All concurrent PDACs and invasive IPMNs were associated with gastric-type IPMN. Compared to invasive IPMNs, concurrent PDACs were associated with more proximal location (76% vs. 32%, P = 0.0095), higher incidence of lymphatic (71% vs. 32%, p=0.025) and vascular (65% vs. 27%, P=0.026) invasion, lower 2-year survival (21% vs. 57%), and increased mortality by multivariate analysis (HR: 2.17; 95% CI: 0.92 to 5.15, P = 0.078). Compared to conventional PDACs, concurrent PDACs were associated with older age at presentation (73.4 ± 12.2 vs. 64.6 ± 10.4, P = 0.019) and higher incidence of lymphatic (71% vs. 36%, P = 0.0046) and vascular (65% vs. 34%, P = 0.017) invasion. The 2-year survival of concurrent PDAC was lower than that of conventional PDAC (21% vs. 39%), although the difference was not statistically significant. Loss of SMAD4 was seen in 62% of 13 examined concurrent PDACs, while only 33% of 12 invasive IPMNs lost SMAD4 expression. There was no difference in overexpression of p53 between the 2 groups (54% vs. 58%).
Conclusions: Concurrent PDACs exhibit higher degrees of aggressive pathologic features and increased mortality in comparison with invasive IPMNs and conventional PDACs. Whether the survival disadvantage of concurrent PDACs is conferred by genetic and/or epigenetic alterations, including loss of SMAD4 expression, needs to be elucidated by larger scale studies.

1862 Comparison of Histologic Grading Schemes for Response to Neoadjuvant Therapy in Pancreatic Adenocarcinoma (PDAC)

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Background: Pancreatic ductal adenocarcinoma (PDAC) is known for poor survival rates despite treatment with neoadjuvant therapy. Other gastrointestinal malignancies have shown complete histologic response to neoadjuvant therapy to be a positive prognostic factor. However, complete histologic responses in pancreatic adenocarcinoma to neoadjuvant therapy are rare. Furthermore, the assessment of histologic response to treatment in PDAC is limited by the existence of multiple classification systems. Moreover, no prior published studies have compared results of existing classifications systems with clinical outcome.
Design: The study cohort consisted of 33 pancreaticoduodenectomy resection specimens with PDAC from patients treated with a single neoadjuvant chemoradiation protocol. Each case was evaluated histologically and classified according to published classifications schemes for tumor response to treatment (Ishikawa, Evans, and White). Survival rates after resection were compared within classification schemes to evaluate each system's capability of predicting survival outcome.
Results: The median survival of the study cohort was 15 months. Of the 33 evaluated cases, none showed a complete response to treatment. According to the Ishikawa classification system, a majority of cases showed therapy effect in <33% of tumor cells (58% Grade 1, 24% Grade 2, and 18% Grade 3). When Grade 2 (therapy effect in 33-67% of tumor cells) and Grade 3 (therapy effect in >67% tumor cells) subgroups were combined and compared against Grade 1 (therapy effect in <33% of tumor cells), there was a difference in median survival, although this did not reach statistical significance (P=0.0990). The Evans and White classification systems did not predict outcome.
Conclusions: Of the existing classification systems, the Ishikawa grading scheme was the easiest to apply to surgical resection specimens. None of the classification systems could predict survival outcome to a statistically significant degree. However, a modified two-tiered version of Ishikawa's classification may be useful in predicting survival in patients with PDACs who have received neoadjuvant therapy.

1863 Ki-67 Proliferation Index and Mitotic Rate Discordance in Pancreatic Neuroendocrine Tumors Correlates with Aggressive Histologic Features and Decreased Overall Survival

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Background: By World Health Organization (WHO) guidelines, pancreatic neuroendocrine tumors (PanNETs) may be graded by either mitotic rate or Ki-67/

MIB-1 proliferation index, with grade 1 defined as a mitotic rate less than 2 per 10 high-power fields and/or a Ki-67 proliferation index of less than 3%. Grade 2 is defined as a 2-20 mitoses per 10 high-power fields and/or a Ki-67 index of 3-20%. In order determine whether these two grading parameters are comparable, we performed Ki-67 immunohistochemical labeling on all mitotic grade 1 PanNETs in our institutional database and examined histologic features and survival outcomes.

Design: 361 PanNETs surgically resected at our institution from 1980-2009 were reviewed for mitotic rate, clinical data, and histologic features. 264 mitotic grade 1 cases were immunolabeled with an antibody to Ki-67. The percentage of Ki-67 positive cells was quantified using image analysis. Survival outcome was determined using the Social Security Death Index.

Results: Of 264 mitotic grade 1 PanNETs, 33% were grade 2 by Ki-67 proliferation index. Grade-discordant tumors were more likely to have lymph node (56% vs. 34%) (P = 0.0014) and known distant (46% vs 12%) (P < 0.0001) metastases than grade 1 concordant tumors. Grade-discordant PanNETs also showed statistically significantly more infiltrative growth pattern, perineural invasion and small vascular invasion. Median size was also greater (3.5 cm vs. 2.4 cm (P = 0.0009)). Overall survival was statistically significantly different (P = 0.0017), with grade-discordant tumors showing a median survival of 12 years, and grade 1 concordant tumors having greater than 50% of patients still alive, up to 25 years after resection. Grade-discordant tumors and grade 1 concordant tumors had no significant difference in median age at resection, gender, presence of necrosis, or large vascular invasion.

Conclusions: Our data demonstrate that mitotic rate and Ki-67-based grading of PanNETs are often discordant, and where the Ki-67 grade is greater than the mitotic grade, clinical outcomes and histopathologic features are significantly worse. Patients with discordant tumors have shortened overall survival and larger tumors with more metastases and more aggressive histologic features. These data strongly suggest that Ki-67 labeling be performed on all PanNETs to more accurately determine tumor grade and prognosis.

1864 Expression of Amphiregulin, Epidermal Growth Factor Receptor (EGFR) and Phosphorylated EGFR in Ampullary Carcinoma

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Background: Most ampullary carcinomas have either pancreaticobiliary or intestinal type morphology. Activation of the EGFR signaling pathway has been implicated in both pancreatic and intestinal carcinogenesis. In addition, amphiregulin (AR) is thought to be an important ligand for EGFR activation in colorectal cancer. The contribution of the EGFR signaling pathway in the development of ampullary carcinoma has not been established.

Design: Fifty two surgically resected ampullary carcinomas were immunohistochemically labeled for AR, EGFR, and phosphorylated EGFR (pEGFR). The results were correlated with pathologic type and tumor stage. Fisher's exact test was used to determine significant association.

Results: The pathologic types included pancreaticobiliary type (14/52, 27%), intestinal type (33/52. 63%), and rare variants (5/52, 10%). The rare variants were 1 signet ring cell carcinoma, 3 mucinous carcinomas and 1 adenosquamous carcinoma. Five of 14 pancreaticobiliary type tumors showed a very prominent papillary architecture. Overall, moderate to strong AR expression was observed in 33 of 52 (64%) cases. This expression was more common in the intestinal type (75%) than in the pancreaticobiliary type without prominent papillae (33%, $p<0.05$). However, 4 of 5 pancreatobiliary type carcinomas with prominent papillae showed strong AR expression. EGFR and pEGFR were labeled in 14 (26.9%) and 11 (21.2%) of 52 ampullary carcinomas, respectively. While no difference in EGFR expression was observed between two major pathologic types (43% versus 19%, p>0.05), more pancreaticobiliary type (43%) had activated EGFR than the intestinal type (9%, p<0.05). Interestingly, three mucinous adenocarcinomas showed no expression of AR, EGFR or pEGFR. The expression of AR was not correlated to that of pEGFR, whereas EGFR labeling was significantly associated with activation of EGFR (p<0.05). Neither AR labeling nor EGFR activation was correlated with tumor stage (p>0.05).

Conclusions: Activation of EGFR may play a role in carcinogenesis in a subset of ampullary carcinomas. While AR is commonly expressed in the intestinal type carcinomas, it does not appear to be a key ligand for activation of EGFR in ampullary carcinomas.

1865 Comparison of the Immunohistochemical Staining Methods for the Diagnosis of Lymphoplasmacytic Sclerosing Pancreatitis

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Background: Presence of abundant IgG4-positive plasma cells is a significant pathologic finding for the diagnosis of lymphoplasmacytic sclerosing pancreatitis (LPSP), or type 1 autoimmune pancreatitis. Various methods to evaluate the immunohistochemical stains have been proposed. However, these methods have not been compared so far.

Design: Resected or open biopsy specimens of LPSP (18 patients), chronic pancreatitis (CP; 24), and pancreatic ductal adenocarcinoma (PDA; 45) were evaluated. In each case, serial sections were made from a representative block for H&E stain and immunostaining for IgG, IgG1, IgG4, and CD138. The number of immunostaing-positive cells was counted in 10 high power fields (HPFs) by selecting fields with the most numerous positive cells (Method A), or by selecting fields randomly in the affected areas (Method B). We evaluated 1) mean number of IgG4-positive plasma cells/HPF, 2) number of fields with ≥11 IgG4-positive plasma cells, and 3) IgG4/ IgG1 ratio (total number of IgG4-positive plasma cells/ total number of IgG1-positive plasma cells), 4) IgG4/ IgG ratio, and 5) IgG4/ CD138 ratio. The best cutoff values and area under curve (AUC) to differentiate LPSP from CP and PDA were evaluated by receiver operator characteristic (ROC) curve and AUCs of these five groups were compared within each Method and between Method A and B.

Results:

Outcome analyzed ROC curves

	Method A			Method B		
	Cutoff value	**Sensivity/ Specifity**	**AUC**	**Cutoff value**	**Sensivity/ Specificity**	**AUC**
1) mean IgG4-positive plasma cells	54.6	94.4%/ 92.8%	0.9782	34.9	83.3%/ 100%	0.9744
2) number of fields with ≥11 IgG4-positive plasma cells	10	100%/ 79.7%	0.8929	6	94.4%/ 97.1%	0.9828
3) IgG4/ IgG1	1.082	88.9%/ 87.0%	0.9235	0.903	94.4%/ 90.3%	0.9370
4) IgG4/ IgG	0.197	88.9%/ 49.3%	0.6857	0.332	100%/ 81.2%	0.9143
5) IgG4/ CD138	0.487	100%/ 21.7%	0.4303	0.424	88.9%/ 76.8%	0.8534

In 2), 4) and 5), Method B had significantly higher AUCs than Method A. Compared within each Method, 1) and 3) had higher AUCs in Method A whereas 1), 2), and 3) had higher AUCs in Method B.

Conclusions: For the diagnosis of LPSP, immunostaing-positive cells should be counted by selecting fields randomly in the affected areas. More than 5 of 10 HPFs with ≥11 IgG4-positive plasma cells by choosing fields randomly in the affected areas is a useful and simple diagnostic method for LPSP, although counting number of IgG4 or IgG4/ IgG1 ratio are highly diagnostic.

1866 Lymphoplasmacytic Sclerosing Pancreatitis with Neutrophilic Infiltration: Comparison with Cases without Neutrophilic Infiltration

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Background: Lymphoplasmacytic sclerosing pancreatitis (LPSP) and idiopathic duct-centric pancreatitis (IDCP) are recognized as different clinicopathologic entities; however sporadic examples with mixed features have been reported. The significance of such cases has not yet been elucidated.

Design: 31 Resected specimens of LPSP were selected for the study. The diagnosis of LPSP was based on at least 3 out of the following features: dense lymphoplasmacytic infiltration with fibrosis, numerous (>10/high power field) IgG4-positive plasma cells, storiform fibrosis and obliterative phlebitis. All the available H&E stained slides were reviewed. Due to neutrophilic infiltration being mainly identified in the lobules as detailed below, the number of foci (x10 objective) that contained 10 or more neutrophils in the lobules was counted in one slide. In 12 cases with multiple H&E slides, a slide with the most numerous neutrophilic infiltration was evaluated. Presence or absence of granulocytic epithelial lesion (GEL), which was defined as neutrophilic infiltration within the epithelia and/or lumens, in interlobular or intralobular ducts was also recorded.

Results: Lobular neutrophilic infiltration (LNI) was identified in 11 patients, among whom more than 5 such foci were identified in 6. Compared to cases with only one slide available, LNI was more common in cases with multiple slides (4/19 *vs.* 7/12; p<0.05), with the latter cases comprising of 5 out of 6 cases with more than 5 foci of LNI. LNI was more common at the periphery of the typical LPSP lesion. GEL in the intralobular ducts was identified in every case with LNI; although that in the interlobular ducts was observed only focally in one case. There was no difference of age and gender of patients between the two groups and the histological features as well as the number of IgG4-positive plasma cells were otherwise not different.

Conclusions: LNI was commonly observed in cases with otherwise typical LPSP, especially when multiple tissue blocks were examined. In addition, LNI ocurred preferentially at the periphery of the LPSP, indicating that LNI itself may be a different process from LPSP itself. GEL in the intralobular ducts was always observed in the foci with LNI, and this finding should not be used as a diagnostic hallmark of IDCP. On the other hand, GEL in the interlobular ducts was extremely rare in LPSP and is a highly specific feature of IDCP.

1867 Comparison of Three Ki-67 Index Quantification Methods and Clinical Significance in Pancreatic Neuroendocrine Tumors

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Background: Ki-67 index is essential in the pathological reports for pancreatic neuroendocrine tumors (PNETs). Pathologists usually use three methods to determine Ki-67 index including eyeball estimation (EE), manual counting (MC) or automated quantitation using the Automated Cellular Imaging System III (ACIS) (Dako, Carpinteria, CA). However, there is no sufficient data regarding the concordance among these three methods and their correlations with clinical outcome. The goal of this study was to compare three quantification methods with clinical outcome to determine the best method for clinical practice.

Design: Ki-67 immunostaining was performed on 97 resected PNETs with clinical follow-up information. Three methods of quantification were employed: 1) An average of EE by three pathologists. 2) MC of at least 500 tumor cells within the hot spots. 3) ACIS quantitation by selecting 8-10 hot spot regions (40x tool). Lin's concordance correlation coefficients were used to evaluate agreement among the methods. C indexes from Cox proportional hazards regression models were used to evaluate the ability of each method to predict clinical outcome.

Results: The concordance between the MC and ACIS and between the MC and average EEs were 0.97 and 0.88, respectively. The difference between the MC and ACIS assessments was -0.23, which was not significantly different from zero. But the difference between the MC and EEs was -2.56, which was significantly different from zero (p <0.001). The concordance among the three pathologists' EE was 0.86.

More cases were classified as 2010 WHO grade 1 in the EE group due to lower Ki-67 values obtained by this method (65 grade 1 cases by eyeball *vs.* 31 and 35 by MC and ACIS assessments). There were five grade 3 PNETs and three of them were common by all methods. All three methods were significantly associated with patient survival. The EE had a higher predictive ability for survival compared with the manual and ACIS assessments.

Conclusions: The three quantification methods for Ki-67 index had almost perfect agreement and all of them were significantly associated with clinical outcome. The MC and ACIS assessments were almost equivalent. The EE scores were significantly less than the other two methods and tended to down-grade more tumors to grade 1, but had higher predictive ability for survival. The results suggest the necessity of consensus among pathologists for the method to determine Ki-67 index and proper cutpoint of Ki-67 index for better clinical correlation.

1868 Correlation of Pancreatic Fibrosis and Post Islet Cell Autotransplantation (IAT) Liver Biopsy with Islet Cell Yield and Insulin Requirement in Patients Undergoing Total Pancreatectomy (TP) with IAT

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Background: In patients with chronic pancreatitis (CP), TP with IAT can preserve endocrine function and help manage the complications of diabetes. The factors that determine the success of TP-IAT have not been clearly defined. The aim of our study is 2 fold: 1) to correlate the histopathological finding of pancreatic fibrosis with islet yield and function, and 2) to determine the usefulness of post IAT liver biopsy in assessment of islet engraftment.

Design: From 2009-2011, a total of 25 patients underwent TP with IAT. Islet yield is calculated in islet equivalents per kg (IEQ/kg) for each patient. 21(84%) patients underwent pancreatic biopsy. The histologic degree and extent of fibrosis is scored by a pathologist from a score of 1 to 6 (*Detlefsen et al, Virchows Arch 2005*). The correlation between fibrosis and islet yield is evaluated (Kendall Tau b correlation). 22(88%) patients underwent transplant liver biopsy. The pre and post IAT liver biopsies are evaluated with H & E sections as well as with immunohistochemical (IHC) stains (Synaptophysin, CD56, Insulin and Glucagon) to determine islet engraftment. Insulin requirement at the time of discharge for patients with TP-IAT (n=21) is compared to that of patients with TP without IAT (n=12).

Results: Islet recovery correlates negatively with pancreatic fibrosis (r = -0.506). Mean islet recovery is 4426 IEQ/kg (range 76-19744) with a mean fibrosis score of 4.22. Out of 21 patients, only 2 patients show positive IHC staining for Insulin and Glucagon in post-transplant liver biopsies irrespective of IEQ/kg yield. The patients with TP-IAT had a significant lower insulin requirement at the time of discharge than patients who underwent TP alone ($P < 0.001$). The median insulin requirement for the group with TP-IAT is 11 units (range 4-32), while median for the group with TP only is 26.5 units (range 5-120).

Conclusions: The histologic change of fibrosis in the pancreas at the time of TP clearly correlates with islet yield. Our data suggest that TP- IAT should be considered in the early phase of CP to better preserve beta cell mass. Our study clearly demonstrates that post operative liver biopsy is not a useful tool for the evaluation of successful engraftment. TP-IAT is an effective and safe procedure to prevent or minimize postsurgical diabetes for patients with CP requiring TP.

1869 Loss of PTEN Expression Is Associated with Poor Prognosis in Patients with Ampullary Adenocarcinoma

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Background: PTEN is one of the most frequently inactivated tumor suppressor genes in the development of many cancers such as glioblastomas, endometrial, prostate, lung and breast cancer. However, the expression of PTEN and its significance in ampullary adenocarcinoma (AA) has not been studied.

Design: We constructed tissue microarrays using archival tissue from 113 patients with AA who underwent pancreaticoduodenectomy at our institution. There were 69 males and 44 females with age ranging from 28 to 87 years (median: 64 years). Each tumor was sampled in duplicate with a 1.0 mm punch from representative areas of the tumor. PTEN expression was evaluated by immunohistochemistry and scored semiquantitatively based on the staining intensity and the percentage of positive tumor cells. PTEN expression was categorized as PTEN-negative (negative or staining in <5% of tumor cells) or PTEN-positive (positive staining in ≥5% tumor cells). Staining results were correlated with clinicopathologic features and survival.

Results: Thirty of 113 (26.5%) cases were PTEN-negative. Loss of PTEN expression in AA correlated with CDX2 expression (p=0.03), higher tumor (pT) stage (p=0.005), lymph node metastasis (p=0.010), and advanced AJCC stage (p=0.017). Patients whose tumors were PTEN-negative had shorter overall survival (mean: 113.9±16.3 months) than those whose tumors were PTEN-positive (167.6 ± 10.5 months, p = 0.04). No correlation between PTEN expression with other clinicopathologic factors were observed (p>0.05). In multivariate analysis, PTEN expression was a prognostic factor for overall survival independent of pT stage, lymph node status, differentiation and resection margin status.

Conclusions: Loss of PTEN expression is associated with poor overall survival in patients with AA. PTEN expression may be used as a prognostic marker for patients with resected AA.

1870 Expression of O6-Methylguanine DNA Methyltransferase (MGMT) in Midgut and Pancreatic Neuroendocrine Tumors, Solid Pseudopapillary Tumors and Acinar Cell Carcinomas

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Background: MGMT is a DNA repair enzyme that demethylates DNA to prevent physiologically induced intrinsic apoptotic cell death initiated by the DNA-damage response pathway. Accordingly, silenced expression of MGMT has been shown to be detrimental to the response rate of many tumor entities to the oral alkylating agent, temozolomide (TMZ), including neuroendocrine tumors. To predict response rate of pancreatic and midgut neuroendocrine tumors (NET-P and NET-M), solid pseudopapillary tumors of the pancreas (SP) and acinar cell carcinoma of the pancreas (AC) to alkylating reagents, we analysed the expression of MGMT in these entities.

Design: NET-P, NET-M, SP and AC were located through review of the pathology records at Columbia University Medical Center. Tissue microarrays (TMAs) comprising 96 tumor samples, consisting of NET-P (n=54), NET-M (n=29), SP (n=10) and AC (n=2), were created. Each tumor was represented by three cores on the array to ensure representative expression analysis. TMAs were subjected to immunohistochemistry (IHC) by the application of a monoclonal antibody against MGMT (clone: MT3.1, dilution: 1:2000). Nuclear expression of MGMT was independently determined by two pathologists by virtue of a prospective evaluation. Nuclear MGMT expression was either scored as positive or negative.

Results: TMAs were analyzed for nuclear MGMT expression by IHC. IHC for MGMT in our subset of tumors produced a reliable, robust expression pattern. Out of 54 NET-P 26 tumors did not express MGMT (48.1%) in the presence of nuclear MGMT positivity in pancreatic ducts and acini (internal positive control). Similarly, among 29 NET-M 17 tumors were deficient for MGMT (58.6%). All SP and AC revealed nuclear expression of MGMT, none of these tumors were MGMT-deficient. Significant heterogenous expression of MGMT, particularly in NET-M, was detected and these tumors were classified as positive for MGMT expression.

Conclusions: In our study, both NET-P and NET-M reveal in almost 50% of our cases loss of MGMT expression. These results suggest that NET-P and NET-M, but not SP and AC might be equally responsive to treatment with alkylating reagents. Therefore, pathological analysis of MGMT expression in NET-P and NET-M is warranted in order to determine patients with better prognosis and to identify the subpopulation of patients that most likely will benefit from TMZ treatment.

1871 Acinar Cell Cystadenoma of the Pancreas: A Benign Neoplasm or Non-Neoplastic Ballooning of Ducts?

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Background: Acinar cell cystadenoma of the pancreas is a rare cystic lesion. Although it was initially described as the benign counterpart of acinar cystadenocarcinoma, and given the neoplastic designation "-oma," the nature of this process is unclear. We have collected a series of 6 cases and examine the possible pathogenesis of this entity using immunohistochemistry.

Design: Six resection specimens were collected from our institution between 2004 to 2011. In each case, clinical records, gross reports and H&E-stained slides were reviewed. Immunohistochemical stains for trypsin, chymotrypsin, CK7, CK19, synaptophysin and chromogranin were performed for each case.

Results: The majority of patients were female (5 of 6, 83%) and ranged in age from 18 to 57 years (mean, 41 years). One patient was noted to have a first-degree relative with a similar cystic lesion by imaging. Grossly, the lesions were either multilocular (n=3) or unilocular (n=3), and ranged in size from 2.5 to 15 cm. The cysts involved the head (n=3), body (n=1) or the entire pancreas (n=2). Histologically, the multilocular lesions were characterized by dilated ducts lined by patches of ductal and acinar epithelium. Immunolabeling highlighted the patchy nature of the ductal and acinar cells lining the dilated spaces and suggested that ducts had expanded into and appeared to incorporate the surrounding acinar parenchyma into their walls. In 2 of 3 multilocular lesions, the ducts also involved islets of Langerhans. In some areas, the ducts formed larger locules with incomplete septa as they appeared to fuse with other ducts. In contrast, the unilocular cases were lined by one-to-two cell layers of acinar cells with little intervening ductal epithelium and displayed a thick hyalinized cyst wall. Nuclear atypia and infiltrative growth were absent in all cases.

Conclusions: Acinar cell cystadenoma appears to evolve over multiple stages. We hypothesize that early lesions are marked by ductal dilatation that expands into and eventually incorporates the surrounding acinar and endocrine components of the pancreas. As the ducts increase in size, they begin to fuse forming larger cysts. Later lesions demonstrate a unilocular cyst lined by predominantly acinar epithelium with a thick hyalinized cyst wall. Regardless of the pathogenesis, acinar cell cystadenoma is not a neoplastic lesion as the name implies. We suggest the name should be changed to Cystic Acinar Adenomatoid Transformation (CAAT).

1872 Activation of cdk4/Cyclind D1 and the Associated Attenuation of Rb Function in Pancreatic Neuroendocrine Tumors (Pan-NETs)

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Background: Pan-NETs pose significant challenges in clinical management largely due to the lack of identifications of key oncogenic pathways in this neoplasm. Currently, there are no reliable biomarkers to predict the recurrence and progression and treatment option is limited for this disease. Although changes in genes of the retinoblastoma (Rb) pathway can lead to formation of Pan-NET in mice, genomic investigations in humans have not revealed Rb pathway mutations.

Design: We investigated abnormalities in the Rb pathway, including cdk4, cyclind D1 and Rb protein status, in Pan-NETs and identified significant genetic aberrations and associated functional consequence which culminated in attenuated Rb function via phosphorylation, which could be restored by a small molecule, PD 0332991 in Pan-NET cell lines.

Results: 1) Immunohistochemistry was carried out on tissue microarray constructed with 92 cases of well-differentiated Pan-NET. Cdk4 was overexpressed in 58% and Cydlin D1 in 68% of Pan-NETs; phospho-Rb was observed in 68% of tumors. There was a statistically significant correlation between phospho-Rb and cdk4/cyclin D1 protein expression (p=0.02).

2) Quantitative RT-PCR was performed using mRNA from fresh frozen samples of Pan-NETs. When compared with normal pancreas tissue, the cdk4 transcript was markedly increased ranging from 1.2 to 97 fold (mean 12.5±2.5). Increased cdk4 transcription correlated with cdk4 protein overexpression. Furthermore, cdk4 transcript was significantly higher ($p<0.001$) in non-functional Pan-NETs (mean 14.6±3.0) when compared with functional Pan-NETs (mean 3.8±0.5).

3) Real time PCR analysis revealed cdk4 to be amplified in a subset of tumors. FISH analysis revealed extra copies of cdk4 located in chromosome 12q.

4) Compound PD 0332991, a specific cdk4/6 inhibitor, effectively induced growth arrest at G1 phase cell cycle up to ten fold at low concentration (100 nM) and significantly decreased phosphorylated-Rb levels in two Pan-NET cell lines QGP1 and BON1 with IC50s of 60 nM and 130 nM, respectively.

Conclusions: We have characterized an attenuated Rb tumor suppressor pathway in pancreatic neuroendocrine tumors. The collective genomic, biologic and clinical substantiation suggest that combined cdk4 and cyclin D1 inhibition may prove to be an alternative beneficial therapeutic strategy for patients with this disease.

1873 Alternatively Spliced Tissue Factor Is Expressed in Pancreatic Ductal Adenocarcinoma Lesions and Promotes Tumor Spread in an Orthotopic Setting

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Background: Alternatively spliced tissue factor (asTF) is a minimally coagulant TF form that promotes neovascularization and monocyte recruitment via integrin ligation. While it has been shown that asTF is found in pancreatic ductal adenocarcinoma (PDAC) cell lines and that high asTF expression potentiates PDAC growth in a subcutaneous model, asTF presence in human PDAC tissue and its ability to promote metastatic spread have not previously been assessed.

Design: Tumor microarrays (PDAC, breast, urothelial, ovarian, and prostatic carcinomas) were evaluated for asTF expression and monocyte infiltration. Primary PDAC tumors and regional lymph node metastases were then analyzed. PDAC cell lines expressing various levels of asTF were implanted in the pancreases of nude mice and subsequent in-vivo imaging studies were performed. Grade I cell line Capan-1 was treated with recombinant asTF, and the resultant changes in gene expression were assessed using microarrays.

Results: While asTF protein was detected in lesional and stromal tissues in all five carcinoma types, PDAC tissue contained significantly higher levels of CD68+ monocytes ($p<0.05$). Analysis of 23 human cases of PDAC revealed detectable asTF in >90% of lesions with a range of staining intensities (low - 15%, medium - 70%, high - 15%). Lesional and stromal tissues showed varying intensities of cytoplasmic, perinuclear, and extracellular staining. Intense staining in cancer glands, perineurally invasive cancer glands, and pancreatic intraductal neoplasia lesions was identified. In nude mice, asTF-overexpressing cell line Pt45P1/asTF+ exhibited the most aggressive growth with metastases to distal lymph nodes, which stained intensely for asTF. Grade I PDAC line Capan-1 stimulated with asTF exhibited upregulation of genes involved in EGFR binding, epithelial branch elongation/development, and epithelial-mesenchymal signaling; EFEMP1, a gene recently shown to promote PDAC growth, was most upregulated in response to asTF.

Conclusions: We report for the first time that asTF 1) is expressed in PDAC lesions and lymph node metastases, 2) appears to fuel metastatic spread in an orthotopic model, and 3) elicits a tumor-promoting shift in gene expression in PDAC cells. asTF may thus be a promising new therapeutic target to treat PDAC.

1874 Expression of Other M2-Macrophage Markers in CD163$^+$ Dendritic Macrophages in Lymphoplasmacytic Sclerosing Pancreatitis

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Background: CD163$^+$ dendritic macrophages are one major component of lymphoplasmacytic sclerosing pancreatitis (LPSP). Although CD163 is considered to be a marker of M2-macrophages, further studies with other immunohistochemical markers are necessary to confirm the nature of these cells. In addition, these markers are potentially useful for the histological diagnosis of LPSP.

Design: Resected specimens of LPSP (13 patients), idiopathic duct-centric pancreatitis (IDCP, 2), acute pancreatitis (AP, 6), chronic pancreatitis (CP, 4) and pancreatic ductal adenocarcinoma (PDA, 17) were gathered. Serial sections from a representative block of each case were immunostained for M2-macrophage (CD163, CD204, CD205) and other monocyte/macrophage (CD11c, CD14, CD16) markers.

Results: In LPSP, dendritic macrophages seen in the lobules, pancreatic ducts and peripancreatic adipose tissue were consistently positive for CD163, CD204 and CD205. CD204 immunoreactivity of these cells was almost identical to CD163; and numerous cells were positive with both stains. CD205 immunoreactivity was weaker; and the number of positive cells was smaller. CD11c$^+$ macrophages were fewer, but tended to be present more in the lobules rather than in the peripancreatic adipose tissue, notably when there was abundant lymphoplasmacytic infiltrate. Although the intensity was weaker, CD16 showed a similar staining pattern to CD163 and CD204. CD14$^+$ cells were very few. In IDCP, AP, CP and PDA, small aggregates of CD163$^+$, CD204$^+$ and CD16$^+$ macrophages were observed; but the immunoreactive cells were fewer than in LPSP, and were plump in shape rather than dendritic. Notably, proliferation of dendritic macrophages in the lobules was limited; although it was one of the striking features in LPSP. Few were positive for CD11c and CD14. A LPSP-like reaction seen in one case with PDA showed numerous CD163$^+$ and CD204$^+$ dendritic macrophages, even in the lobules.

Conclusions: CD163$^+$ dendritic macrophages were also positive for CD204 and CD205, suggesting that they represent M2-macrophages. In addition to CD163, CD204 is also a useful marker to identify these dendritic macrophages. Although none of these markers are specific to LPSP, a larger number, diffuse distribution and dendritic shape of positive cells in LPSP are in contrast to other conditions except for rare PDAs with LPSP-like reaction. Identification of more CD11c$^+$ macrophages in the lobules than in the peripancreatic adipose tissue may indicate that these macrophages are, in fact, heterogeneous in LPSP.

1875 Comparison of Semi-Quantitative Versus Quantitative Grading System in Endocrine Tumors of the Pancreas: Which One Should Be Applied?

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Background: Pancreatic endocrine tumors (PETs) are rare, representing 1-2% of all pancreatic tumors. ENETS and WHO have defined criteria for a grading system for PETs to assess their prognosis based on mitotic count or Ki67 labeling index (Ki67-LI). Mitotic count should be done on at least 40 fields at 40x magnification (10 HPF=2 mm^2) in areas of highest mitotic density. Ki67-LI should be assessed in 500-2,000 tumor cells in areas of highest nuclear labeling. This recommendation is difficult to implement in routine practice, because of the time-consuming aspect. Therefore many pathologists use a semi-quantitative approach for grading.

Aim: To compare semi-quantitative to quantitative assessment of PETs 'grading system.

Design: 36 surgically resected PETs from 35 patients were assessed after Ki67 immunohistochemistry. All were counted by 2 independent pathologists (BW=observer 1 and AJM=observer 2) (mean number of counted cells: 2001±49; minimum: 1480, maximum: 2130). The semi-quantitative assessment was done by scanning the tumor at low and high power. The same pathologists did this second evaluation after a 6 months interval.

Results: Semi-quantitative assessment was not concordant for 9 of 36 tumors (25%). Eight cases were discordant between G1 and G2 and one between G2 and G3. In 7 cases, observer 2 was higher than observer 1 and in 2 cases it was the opposite. When assessing Ki67-LI, discordance was observed in 1 case out of 36 PETs (2.8%), in which observer 1 classified the tumor as G1, whereas for observer 2, it was a G2. Interestingly, this case was discordant in both grading systems. Inter-observer correlation was very good and statistically highly significant for Ki67-LI (Pearson $r^2= 0.95$, $p<0.001$). Whereas, it was lower in the semi-quantitative assessment (Pearson $r^2= 0.57$, $p<0.001$)

Conclusions: Grading system for PETs is difficult to apply in routine practice because it is time-consuming. Therefore, many pathologists tend to use a semi-quantitative approach of mitotic count or Ki67 positivity in PETs. In this study on 36 PETs, it is shown that inter-observer correlation is much better when counting Ki67-LI. We therefore advocate all pathologists to count effectively Ki67 positive cells to assess prognosis of PETs.

1876 Downregulation of PTEN Expression in Intraductal Papillary Mucinous Neoplasm of the Pancreas Is Associated with an Invasive Phenotype

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Background: Tumor suppressor gene *PTEN* mutation is rare in pancreatic ductal adenocarcinomas (PDACs), but PTEN protein downregulation is seen in 70% of PDACs. It is hypothesized that PTEN downregulation facilitates activation of AKT, a downstream effector of *KRAS*. This hypothesis is especially relevant as 90% of PDACs harbor *KRAS* mutations. Intraductal papillary mucinous neoplasm (IPMN) is a precursor lesion to PDAC. Here we investigate PTEN expression as well as AKT activation and *KRAS* mutations in IPMN.

Design: Expression levels of PTEN (Cell Signaling) and phosphorated AKT (S473, Cell Signaling) are analyzed by immunohistochemistry on tissue microarrays consisting of multiple lesions from 43 IPMNs (mean age 67.2 yrs, M:F = 28:15) with matching non-neoplastic tissue. The 43 IPMNs consisted of 18 non-invasive IPMNs and 25 with an invasive component. In the invasive group, 15 cases harbored macroinvasion, and the remaining 10 cases contain only superficial invasion. The intraductal component was gastric-type in 12 cases, intestinal-type in 19, oncocytic-type in 6, pancreaticobiliary-type in 2 and mixed in 4. Immunostains were scored as 0 (negative), 1 (weak) and 2 (strong), as compared to the surrounding stroma. *KRAS* mutations were analyzed in 18 invasive cases by direct Sanger sequencing or by a PCR-based SNaPshot assay.

Results: Loss of PTEN expression (grade 0) was seen in only 5 of 43 (12%) IPMN cases, with strong or weak expression in the corresponding non-neoplastic glands. The frequency of PTEN loss was less than those reported in PDAC. All five cases contained an invasive component with four showing macroinvasion, suggesting an association of PTEN loss with an invasive phenotype ($p<0.05$). Three cases were of intestinal-type, and the remaining two cases were of oncocytic- or pancreaticobiliary-type. None of the 12 gastric-type IPMN showed PTEN loss. *KRAS* mutations were detected in 10 of 18 (56%) invasive IPMNs, similar to the reported frequencies in IPMN. Three of the

5 cases with PTEN loss harbored KRAS mutations. Strong pAKT expression (grade 2) was seen in 13 cases, 6 (46%) of which were invasive. Interestingly, none of the 5 cases with PTEN loss showed concomitant strong pAKT expression.
Conclusions: PTEN downregulation is less frequent in IPMN than reported in PDAC. PTEN loss appears to be associated with an invasive phenotype, suggesting that it may play a role in neoplastic progression of IPMN. However, PTEN loss is not associated with AKT activation nor KRAS mutations, suggesting an alternative PTEN signaling pathway involved.

1877 Ribonucleotide Reductase M2 Is Not Predictive of Adjuvant Gemcitabine Treatment Benefit in Patients with Resected Pancreatic Adenocarcinoma

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Background: Gemcitabine is used widely as an adjuvant treatment for pancreatic adenocarcinoma. Ribonucleotide reductase small subunit M2 (RRM2), the catalytic subunit of ribonucleotide reductase, is associated with tumor progression and resistance to gemcitabine. Recent studies showed that low mRNA expression of *RRM2*, was predictive of treatment benefit of gemcitabine in patients with resected pancreatic adenocarcinoma (Fujita H et al., Neoplasia 12: 807-17, 2010). This study aims to determine if RRM2 protein expression level assessed by immunohistochemistry is 1) prognostic in patients with resectable pancreatic adenocarcinoma and 2) a predictive marker for treatment benefit of gemcitabine.
Design: 117 patients underwent pancreatic resection for pancreatic adenocarcinoma were included. 44 of them received adjuvant gemcitabine treatment prior to disease recurrence/metastases. Tissue micro-arrays were constructed from paraffin-embedded tumors. RRM2 expression in tumors was determined by immunohistochemistry and grouped as negative or positive. The correlation of RRM2 expression and overall survival (OS) or progression-free survival (PFS) was determined using the Kaplan-Meier method. Cox's proportion hazards multivariate model was also employed to identify prognostic factors.
Results: RRM2 expression showed no prognostic value in the entire group regarding OS (median OS 30.9 vs 13.7 months, p=0.26) and PFS (median OS 20.6 vs 11.8 months, p=0.46). *RRM2* expression was not predictive of OS and PFS in the subgroup of 44 patients who received gemcitabine treatment as an adjuvant therapy either (median OS 31.2 vs 15.2 months, p=0.62; median PFS 11.3 vs 14 months, p=0.35, respectively). Cox's proportion hazards multivariate model showed no prognostic effect of RRM2 expression on OS (HR 0.89, p=0.76) and PFS (HR 1.45, p=0.44) in the subgroup of 44 patients who received gemcitabine therapy. However, the number of positive lymph nodes and perineural invasion are prognostic factor for OS (HR 1.21, p=0.01) and for PFS (HR 5.44, p=0.001), respectively.
Conclusions: RRM2 protein expression level determined by immunohistochemistry on paraffin-embedded pancreatic carcinoma tissue is neither prognostic nor predictive of adjuvant gemcitabine treatment benefit in patients with resectable pancreatic adenocarcinoma.

1878 Low Expression of Ribonucleotide Reductase M1 Predicts Adjuvant Gemcitabine Treatment Benefit in Patients with Resectable Pancreatic Adenocarcinoma

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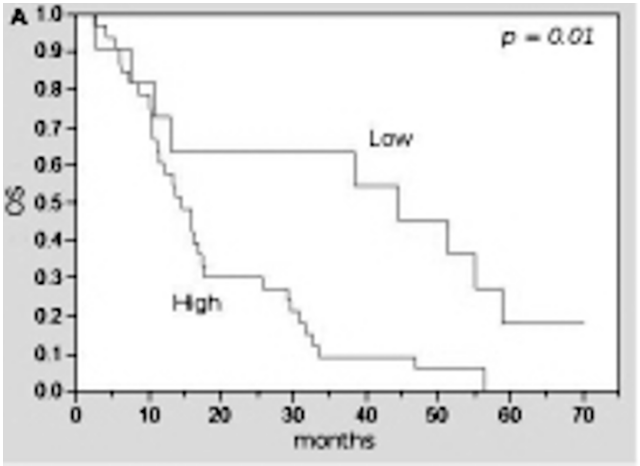
Background: Gemcitabine has been a cornerstone of current chemotherapy for pancreatic cancer. Our previous pilot study in 18 patients suggested low expression of *RRM1* was predictive of adjuvant gemcitabine treatment benefit in patients with resectable pancreatic adenocarcinoma (W Jiang et al., Mod Path 23:357A, 2010). This study aims to confirm our previous finding in a larger cohort of patients.
Design: 122 patients underwent pancreatic resection at our institution for resectable pancreatic adenocarcinoma from 10/1999 to 12/2007; 44 of them received adjuvant gemcitabine treatment prior to disease recurrence/metastases. Total RNA was isolated from micro-dissected paraffin-embedded tumors. The expression of *RRM1* in tumors was determined by QRT-PCR and the expression levels were normalized to two endogenous reference genes and stratified into high expression group and low expression group using recursive partitioning analysis. Overall survival (OS) and progression-free survival (PFS) of these two groups were estimated with the Kaplan-Meier method. The prognostic value of *RRM1* expression on OS and PFS was examined with Cox proportion hazards analysis.
Results: *RRM1* expression did not have prognostic value in the entire cohort of patients regarding OS (p=0.14) and PFS (p=0.68). However, in the subgroup of 44 patients who received gemcitabine treatment as an adjuvant therapy, patients with low *RRM1* expression had significantly longer OS (median OS 44.4 vs. 14.5 months; p=0.01, figure A). While Cox proportion hazards multivariate analysis identified number of positive lymph nodes and perineural invasion as predictors of shorter OS (HR 1.18, p=0.02) and shorter PFS (HR 3.5, p=0.004), respectively, it confirmed that low expression of *RRM1* was associated with longer OS (HR 0.35, p=0.009) and PFS (HR 0.37, p=0.004).



Conclusions: Low *RRM1* expression determined by QRT-PCR on paraffin-embedded pancreatic carcinoma tissue in patients who received gemcitabine as an adjuvant treatment predicts a progression-free and overall survival benefit.

1879 *MDM2* SNP-309 Promoter Polymorphism, MDM2 and p53 Expression in Pancreatic Ductal Adenocarcinoma

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Background: The mouse double minute 2 homolog (MDM2) is the primary regulator of p53. A functional single nucleotide polymorphism (SNP) of the *MDM2* promoter (309 T>G) enhances the Sp1 binding to *MDM2* promoter and MDM2 expression resulting in attenuation of p53. Small molecules antagonizing the MDM2-p53 interaction have been shown to promote p53-dependent tumor regression in vitro. The *MDM2* SNP-309 has been recently associated with the development and prognosis of a variety of tumors. We hypothesized that the *MDM2* SNP-309 is associated with increased risk of pancreatic ductal adenocarcinoma (PDAC) and worse outcome.
Design: Genotyping of *MDM2* SNP-309 was performed on genomic DNA extracted from benign lymph node tissue of 189 PDAC by PCR amplification flanking the corresponding promoter region followed by temperature gradient capillary electrophoresis and direct sequencing. Tissue microarrays of PDAC were constructed and immunohistochemically stained for MDM2 and p53. Expression intensity was scored as 0 (absent), 1+ (modest) or 2+ (high). In addition, FISH analysis for *MDM2* amplification was done in 20 PDAC (15 with modest or high expression). We evaluated the association between *MDM2* SNP-309 and the risk of PDAC using Cramer's V Test (with 100 controls). We also investigated the relationships between *MDM2* SNP-309 genotype, MDM2 and p53 expression and tumor stage and survival time.
Results: The *MDM2* SNP-309 genotypes of PDAC were statistically different from those of controls ($P = 0.041$). The frequency of the G allele in PDAC was significantly higher than that in controls ($P = 0.002$).

MDM2 SNP-309 Genotypes in PDAC and Controls

	PDAC (n = 189)	Controls (n = 100)
G/G	31 (16.3%)	12 (12%)
T/G	97 (51.3%)	40 (40%)
T/T	61 (32.1%)	48 (48%)

PDAC, pancreatic ductal adenocarcinoma; P = 0.041

Modest to high levels of MDM2 expression were detected in 56 tumors (29.6%; 1+ in 25, 2+ in 31), and modest to high levels of p53 were detected in 102 (54%; 1+ in 31, 2+ in 71). *MDM2* amplification was not detected in the 20 PDAC analyzed using FISH. No association was observed between *MDM2* SNP-309 genotype, MDM2 and p53 expression level and tumor stage or survival time.
Conclusions: The G allele of *MDM2* SNP-309 is associated with increased risk of PDAC. Modest to high expression levels of MDM2 and p53 are frequently present in PDAC. It is unlikely that *MDM2* SNP-309 or amplification contributes to the high expression level of MDM2. Further investigations with rigorous design are warranted to assess the magnitude of risk of PDAC with *MDM2* SNP-309 and the prognostic value of MDM2 and p53 expression.

Pan-genomic/Pan-proteomic Approaches to Diseases

1880 Identifying Cancer Mutations in Neuroendocrine Prostate Cancer through Massively Parallel DNA-Sequencing of Formalin-Fixed Paraffin Embedded Tissue

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Background: Neuroendocrine prostate cancer (NEPC) is an aggressive lethal variant of prostate cancer that most commonly arises from existing prostate adenocarcinoma (PCa). Despite chemotherapy, most patients survive less than one year. Little is known about the underlying biology of NEPC, as metastases are rarely biopsied. The purpose of this study was to determine the spectrum of somatic mutations in NEPC by using a