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ABSTRACTS

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1863 Large Vessel Venous Invasion is a Poor Prognostic Factor for Pancreatic Neuroendocrine Tumors

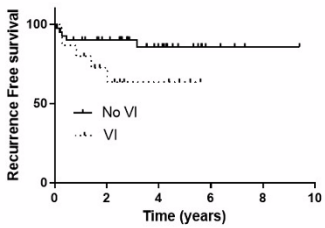
Amrou Abdelkader[1], *Christopher Hartley*[2], *Catherine Hagen*[3]. [1]Wauwatosa, WI, [2]Milwaukee, WI, [3]Medical College of Wisconsin, Milwaukee, WI

Background: Histologic features to stratify prognosis and risk of recurrence in pancreatic neuroendocrine tumors (PanNETs) are limited. Large vessel venous invasion (LgVI) is a known prognostic factor for some cancers such as colorectal carcinoma. The prognostic significance of LgVI in PanNETs is largely unknown. The aim of this study was to evaluate for the presence of VI in a series of PanNETs and correlate with other histologic features and patient survival.

Design: The pathology database at our institution was retrospectively searched from 2006-2015 for resection specimens of well-differentiated PanNETs. Cases of well-differentiated PanNETs with high proliferative index were included. Poorly-differentiated neuroendocrine carcinomas and cases from patients with multiple endocrine neoplasia (MEN) syndrome were excluded. Cases were retrospectively reviewed for presence of LgVI, small vessel lymphovascular invasion (SmVI), perineural invasion (PNI), grade (WHO 2010), T stage, N stage, and presence of peripancreatic tumor deposits (TD). Clinical data including survival and presence of liver metastases was collected from chart review.

Results: 65 pancreatic resection specimens from an equal number of patients (M:F 1:1, mean age 60) were included in the study. 16 patients (24.6%) had evidence of LgVI. Compared to patients without LgVI, patients with LgVI had significantly higher rates of SmVI and PNI, more frequent TD, higher tumor grade, higher T stage, and larger tumor size (Table 1). Patients with LgVI also had worse progression free survival, although not statistically significant (HR 3.0, 95% CI 0.92-16.0, p=0.07)(Figure 1).

	LgVI, n (%)	No LgVI, n (%)	P value
SmVI	15 (93.8%)	18 (36.7%)	<0.0001
PNI	13 (81.3%)	17 (34.7%)	0.0015
TD	8 (50%)	5 (10.2%)	0.0017
Grade 2 or 3	12 (75%)	14 (28.6%)	0.0025
T3/T4	12 (75%)	15 (30.6%)	0.0029
Liver mets	8 (50%)	11(29.7%)	0.0584
Lymph node mets	10 (62.5%)	18 (36.7%)	0.0871
Size in cm, mean (range)	5.2 (2.2-10.7)	3.2 (0.6-12.0)	0.0053
Male gender	8 (50%)	24 (49%)	1.0
Age, mean (range)	57.4 (23-90)	60.4 (26-85)	0.4658



Conclusions: LgVI invasion is associated with other high risk prognostic features and a higher risk of recurrence in patients with PanNETs. LgVI should be included as a distinct histologic feature for synoptic reporting of PanNETs.

1864 Significance of Method of Lymph Node Involvement in Pancreatic Ductal Adenocarcinoma

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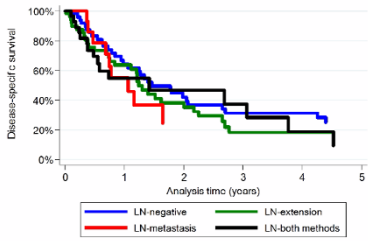
Background: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive neoplasm with notoriously poor disease-specific survival. Lymph node (LN) metastases are associated with adverse outcome. Unlike some other organs, peripancreatic LNs are anatomically situated very close to the head of the pancreas, allowing PDAC to sometimes involve nodes by direct extension rather than by lymphovascular invasion (LVI). To our knowledge, only one previous study has evaluated whether method of LN involvement impacted survival, finding no difference. This study aimed to examine the mechanism of LN involvement in PDACs further and to assess their clinicopathologic relevance.

Design: We identified 254 PDAC resections and evaluated patient age, sex, race, and disease-specific survival, and tumor site, size, grade, stage, margin status, LVI, perineural invasion, and LN involvement. LNs were further characterized as being involved either by direct extension (dir-LN) or lymphohematogenous spread (met-LN). Cases associated with intraductal papillary mucinous neoplasm or mucinous cystic neoplasm were excluded, as were unusual histologic variants (e.g., anaplastic carcinoma). Associations between method of LN involvement and clinicopathologic factors were assessed using standard bivariate statistical methods. Disease-specific survival was compared by log-rank test stratified on AJCC pM status.

Results: Only tumor size was correlated with number of lymph nodes involved by direct extension (linear regression coefficient 0.12, 95% confidence interval [CI] 0.19-0.22, *P*=0.020). Dir-LN had a slightly worse effect on survival than no LN disease (hazard ratio [HR] 1.20, 95% CI 0.80-1.83, *P*=0.38), while met-LN had an even worse effect on survival (HR 1.47, 95% CI 0.98-2.21, *P*=0.061). Comparing equality of disease-specific survivor functions, patients with no LN disease experienced fewer adverse events than expected, dir-LN patients experienced roughly as many adverse events as expected, and met-LN patients experienced more adverse events than expected, but these differences failed to reach statistical significance (Figure; *P*=0.27).



Conclusions: PDAC patients with dir-LN involvement fared slightly worse than those without LN involvement, but better than patients with met-LN involvement. These trends were not statistically significant in this single-institution cohort, suggesting that further investigation regarding potential prognostic differences between direct and metastatic LN involvement with larger sample sizes is warranted.

1865 Mural Nodules in Intraductal Papillary Mucinous Neoplasms: Gross and Histopathologic Correlates

Ramir S Arcega[1], *Deepti Dhall*[2], *Zhikai Chi*[3], *Srinivas Gaddam*[1], *Kevin M Waters*[2]. [1]Cedars-Sinai, [2]Cedars-Sinai Medical Center, Los Angeles, CA, [3]Cedars-Sinai Medical Center, Beverly Hills, CA

Background: A mural nodule in an intraductal papillary mucinous neoplasm (IPMN) is defined as a solid nodule within a main or branch pancreatic duct. The presence of a mural nodule is a radiologic determination. It is a risk factor for malignancy and an indication for resection. We aimed to describe the gross and histopathologic changes seen in IPMNs with mural nodules (MNs).

Design: Among 68 IPMN resections performed at a tertiary care hospital from 2008 through 2017, MNs were identified in 10 cases and possible MNs were identified in 8 cases (by endoscopic ultrasound, CT, or MRI). 8 cases without MNs were identified for comparison. Basic demographic variables were recorded. Gross photos and sections were examined to determine the pathologic correlate to a MN.

Results: There was no difference of age (means of 72 and 68) or sex predilection (40% and 66% male) between patients with MNs or possible MNs and without MNs, respectively. The IPMNs with MNs and possible MNs showed gastric epithelium in 66% of cases, intestinal epithelium in 17%, and mixed gastric/intestinal epithelium in 17%. All cases without MNs showed gastric epithelium. IPMNs with MNs and possible MNs showed high-grade dysplasia (HGD) in 65% and associated invasive adenocarcinoma in 23% of cases. No cases without MNs contained HGD or invasive adenocarcinoma. Gross findings from the cases with MNs and possible MNs demonstrated plaque-like growth (44%, 8/18), papillary excrescences (22%, 4/18), nodular growth within the cyst wall (22%, 4/18), and a tethered solid nodule (6%, 1/18) ranging in size from 0.2 to 3.2 cm in greatest dimension (average 1.0 cm). In 1 case there was no gross correlate to the MN. In patients with no MN, no papillary excrescence, plaque-like growth, or growth within the cyst wall was identified. Histologic sections from cases with MNs and possible MNs showed exuberant papillary architecture expanding the ducts in 72% (13/18) of cases. Wall thickening with prominent fibrosis and chronic inflammation was seen in the cases lacking exuberant papillary architecture. 3 cases without MNs (38%, 3/8) showed small papillary projections (measuring <0.2 mm) which did not expand the ducts.

Conclusions: Our study describes the gross and histologic correlates of a mural nodule which corresponds to a grossly visible prominent papillary excrescences or nodular growth and exuberant papillary

projections microscopically in the majority of cases. These cases also had an increased prevalence of HGD and invasive carcinoma.

1866 Expression of Calretinin, Marker of Mesothelial Differentiation, in Pancreatic Ductal Adenocarcinoma: A Potential Diagnostic Pitfall

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Background: Pancreatic ductal adenocarcinoma has an insidious growth pattern and is one of the most common causes of "peritoneal carcinomatosis". Thus, it falls into the differential diagnosis of other peritoneal malignancies including mesothelioma. Recently, we have encountered an undifferentiated carcinoma of the pancreas presenting with peritoneal disease and exhibiting immunoreactivity to calretinin, mimicking mesothelioma. In this study, we explored the incidence of calretinin expression in pancreatic ductal adenocarcinomas.

Design: Tissue microarrays (TMAs) of pancreatic ductal adenocarcinoma were created using three 0.6 mm diameter formalin-fixed paraffin-embedded punches per tumor (n=116). Calretinin (SP65, Ventana) immunohistochemical staining was performed on the TMAs. Distribution and intensity of expression were evaluated.

Results: The TMAs comprised 93 well/moderately differentiated and 23 poorly differentiated/undifferentiated carcinomas. Calretinin was positive in nine (7.8%) tumors; six with diffuse and strong staining (three well/moderately differentiated, three poorly differentiated/undifferentiated), three with focal and/or weak staining (two well/moderately differentiated, one poorly differentiated/undifferentiated). The incidence of calretinin expression was 17.4% in poorly differentiated/undifferentiated carcinomas (vs. 5.4% in well/moderately differentiated carcinomas).

Conclusions: Pancreatic ductal adenocarcinomas, especially when poorly differentiated/undifferentiated, may be diffusely and strongly positive for calretinin creating a potential diagnostic challenge with malignant mesothelioma. Therefore, caution should be exercised when using this marker to explore a diagnosis of mesothelioma. Tumors expressing calretinin without other mesothelial markers such as WT-1 and D2-40 should prompt a careful evaluation of the morphologic and immunohistochemical features to exclude other peritoneal malignancies. If the diagnosis of pancreatic ductal adenocarcinoma is considered, ductal differentiation can be demonstrated by using additional immunohistochemical markers such as mucin-related glycoproteins (MUC1 and MUC5AC) and/or oncoproteins (CEA, B72.3, and CA125).

1867 Clinicopathologic Spectrum of Undifferentiated Carcinoma of the Gallbladder: An Extremely Rare Subtype with Grave Prognosis

Munita Bal[1], *Prachi Patil*[1]. [1]Tata Memorial Hospital, Mumbai, India

Background: Undifferentiated carcinoma of gallbladder (UCGB) is an extremely rare malignant tumor that lacks a histologic direction of differentiation. Our aim was to study the clinicopathological spectrum of UCGB diagnosed at our centre.

Design: A retrospective review of clinical and pathologic findings of all UCGB cases diagnosed from 2005-2017 was undertaken.

Results: Thirty-two cases were studied. Mean age was 57 years. Male to female ratio was 1.3. Cholelithiasis was found in 83% (24/29) patients. Four patients received neoadjuvant-chemotherapy. Mean tumor size was 5.5 cm. Tumors were proliferative or showed diffuse wall thickening. Two histologic subtypes were identified: 'Spindle and Giant cell' type (n=29), and 'Undifferentiated carcinoma with osteoclastic giant cell' type (n=3). The former type displayed a wide phenotypic spectrum encompassing a dominant myofibroblastic (20), rhabdoid (3), anaplastic (5) and biphasic carcinosarcoma (1) morphology. The second group revealed undifferentiated ovoid malignant cells with uniformly distributed osteoclastic giant cells (OGC). Small cell subtype and nodular/lobular subtype were not identified in our cohort. Atypical mitosis and necrosis were common. On immunohistochemistry, tumor expressed vimentin and displayed focal reactivity for keratins (CK, CK7 and CK19) and occasional patchy SMA reactivity while were negative for S100, h-caldesmon, desmin, CD31, HMB45, synaptophysin, LCA, CD117 and INI-1; OGCs were reactive for CD68. Follow-up (FU) information was available in 28 patients; median FU was 9 months (range 1-36 months). Fifty percent (14/28) patients presented with distant metastasis. No evidence of disease, local recurrence and distant metastasis was observed in 14%, 14% and 79%, respectively. Liver (77%) and peritoneum (32%) were most common sites of metastasis.

Conclusions: UCGB is an under-recognised and very rare gallbladder malignancy with a wide pathologic spectrum and highly aggressive biology. Awareness of the morphologic appearances and immunohistochemical evaluation aids in distinction from soft tissue sarcomas and hence accurate diagnosis and optimal management.

1868 Sclerosing Epithelioid Mesenchymal Neoplasm of the Pancreas

Olca Basturk[1], *Britta Weigelt*[2], *Gokce Askan*[1], *Lu Wang*[3], *Maria Arcila*[4], *Giuseppe Zamboni*[5], *Noriyoshi Fukushima*[6], *Fresia Pareja*[7], *Pier Selenica*[8], *Rahul Kumar*[1], *Leona Doyle*[9], *Samuel J Reynolds*[10], *N. Volkan Adsay*[11], *Jorge Reis-Filho*[12], *David Klimstra*[13]. [1]MSKCC, New York, NY, [2]Memorial Sloan Kettering Cancer Center, New York, NY, [3]St Jude Children's Research Hospital, Memphis, TN, [4]New York, NY, [5]Univ of Verona, Verona, Italy, [6]Jichi Medical University, Shimotsuke, Tochigi, [7]MSKCC, New York, NY, [8]MSKCC, [9]Brigham and Women's Hospital, Boston, MA, [10]Univ of New Mexico HSC, Albuquerque, NM, [11]Medical College of Wisconsin, Milwaukee, WI, [12]Memorial Sloan-Kettering CC, New York, NY, [13]Memorial Sloan-Kettering, New York, NY

Background: We have encountered pancreatic tumors with unique features, which do not conform to any of the known types of pancreatic neoplasms or tumors from other anatomical sites. We aimed to define their clinicopathologic features and whether they are driven by recurrent somatic genetic alterations.

Design: Seven cases were identified; studied histologically and by immunohistochemistry. Four cases were also subjected to whole-exome and RNA-sequencing analyses and the Archer FusionPlex assay.

Results: 5 occurred in females, 2 in males. The mean age was 45 yrs (26-75). 5 lesions occurred in the tail/body, 2 in the head. All patients were treated surgically; none received neoadjuvant/adjuvant therapy. All patients are alive and free of disease after 53 mos of median follow-up. The tumors were well-circumscribed and the mean size was 2.2 cm (1.3-5). Microscopically, the unencapsulated tumors had a geographic pattern of epithelioid cell nests alternating with spindle cell fascicles. The predominant epithelioid cells had scant cytoplasm and round-oval nuclei with open chromatin. The spindle cells displayed irregular, hyperchromatic nuclei. Some areas showed dense fibrosis, in which enmeshed tumor cells imparted a "slit-like" pattern. At the periphery, the focal extension into the parenchyma and perineural invasion was noted in some cases. No extrapancreatic invasion or lymph node metastasis was identified. All tumors were positive for vimentin, CD99 and AE1:AE3/CK18 (weak), while negative for markers of solid pseudopapillary neoplasm, neuroendocrine, acinar, melanocytic, myoid, and vascular differentiation, as well as TTF-1, hepatocyte-1, CD21, CD35, and CD45. Whole-exome sequencing revealed no recurrent somatic mutations or amplifications/homozygous deletions in any known cancer genes. RNA-sequencing and Archer FusionPlex analysis did not detect any recurrent likely pathogenic fusion genes. Single sample gene set enrichment analysis revealed that these tumors display a mesenchymal transcriptomic program.

Conclusions: Here, we describe a series of pancreatic neoplasm with distinctive morphologic and immunophenotypic features, coupled with the lack of abnormalities in any of key genetic drivers of pancreatic or soft tissue neoplasms in the differential diagnosis, and argue that they represent a novel entity with an indolent, if not fully benign, clinical course. Given their mesenchymal transcriptomic features, we propose the designation of "sclerosing epithelioid mesenchymal neoplasm" of the pancreas".

1869 Use Of Quantitative Second Harmonic Generation(SHG) Microscopy To Characterize Stromal Collagen Organization In Pancreatic Ductal Adenocarcinomas(PDAC)

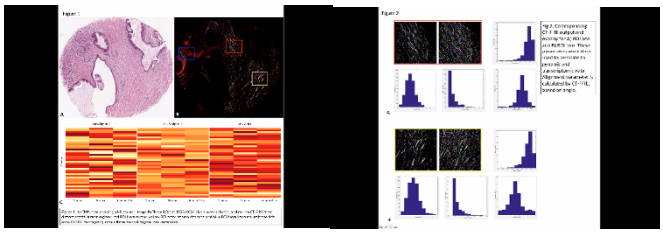
Prashant Bavi[1], *Joan Miguel Romero*[2], *Gun-Ho Jang*[3], *James Jonkman*[4], *Judith Cathcart*[4], *Sagedeh Shahabi*[5], *Sehrish Butt*[6], *Lucy Chu*[6], *Melanie Perlata*[7], *Amy Z Zhang*[3], *Stefano Serra*[8], *Julie M Wilson*[9], *Steven Gallinger*[10]. [1]University of Toronto, Toronto, ON, [2]University of Toronto, [3]Ontario Institute of Cancer Research, [4]University Health Network, [5]University Health Network, Toronto, ON, [6]University Health Network, [7]University Health Network, Toronto, ON, [8]University Health Network, Toronto, ON, [9]Ontario Institute for Cancer Research, Toronto, ON, [10]University Health Network and Mount Sinai Hospital University of Toronto

Background: PDAC tumors are characterized by an extensively desmoplastic stroma, accounting for up to 90% of tumor volume. This fibrotic response has been implicated in the resistance of PDAC to both conventional, immunotherapeutic and targeted therapies. Second Harmonic Generation (SHG) microscopy is a nonlinear microscopic technique reliant on the non-centrosymmetric property of biological molecules such as fibrillar collagen type 1.

Design: The collagen structure of 137 PDAC patients was analyzed using SHG microscopy performed on FFPE TMAs. Using curvelet transform plus fibre extraction (CT-FIRE) algorithm, an open-source program (http://loci.wisc.edu/software/ctfire), we quantified width, length, straightness, and alignment of collagen. Two regions of interest per core, measuring 1024 x 1024 pixels were analyzed and collagen topology correlated with clinic-pathological data, genomic

and transcriptomic signatures and immune infiltrates including tumor infiltratng lymphocytes(TILs). Grey-level co-occurrence matrix and relative correlation range (GLCM), another method of measuring collagen fibre linearity was used as an ancillary method to corroborate results.

Results: Median alignment, length, width, and straightness measurements were 0.5018 (1 being most aligned), 57.32, 4.667 (pixels) and 0.9117 respectively. Collagen linearity had a slight trend with $CD8^+$ TILs. Collagen fibre alignment and straightness showed an association with the PDAC immunogenic subtype (Bailey's classification) compared with ADEX, Pancreatic Progenitor, and Squamous subtypes. Increased angle alignment correlated with tumor recurrence (p = 0.0574). Heterogeneity of SHG signals within patient samples was likely not a confounding factor as we found that collagen straightness (18/40) and width (19/40) were most similar between the three tissue types namely tumor, stromal, and immune-rich cores.



Conclusions: PDAC stromal morphology and topology of fibrillar collagen are different in different molecular subtypes of PDAC and show distinct immune infiltrates. Findings of this study will potentially pave the way for elucidating clinical implications of reorganized collagen as a PDAC biomarker.

1870 Validation Of Transcriptomic Immunogenic Signature And Characterizing The Immune Contexture of Pancreatic Ductal Adenocarcinomas (PDACs)

Prashant Bavi[1], *Joan Miguel Romero*[2], *Gun-Ho Jang*[3], *Ashton A Connor*[2], *Robert Denroche*[4], *Dianne Chadwick*[5], *Sheng-Ben Liang*[6], *John M Bartlett*[7], *Ilinca Lungu*[8], *Sandra Fischer*[9], *Julie M Wilson*[10], *Stefano Serra*[5], *Steven Gallinger*[11]. [1]University of Toronto, Toronto, ON, [2]University of Toronto, [3]Ontario Institute of Cancer Research, [4]Ontario Institute for Cancer Research, [5]University Health Network, Toronto, ON, [6]Toronto, ON, [7]Ontario Institute for Cancer Research, Toronto, ON, [8]Ontario Institute of Cancer Research, Toronto, ON, [9]North York, ON, [10]Ontario Institute for Cancer Research, Toronto, ON, [11]University Health Network and Mount Sinai Hospital University of Toronto

Background: Conventional treatment modalities have failed to impact PDAC outcomes. PDAC is expected to be the second leading cause of cancer death by 2030. Lack of success with established therapies have led to trials of novel therapies especially immune checkpoint inhibitors, which are currently ineffective in PDAC.

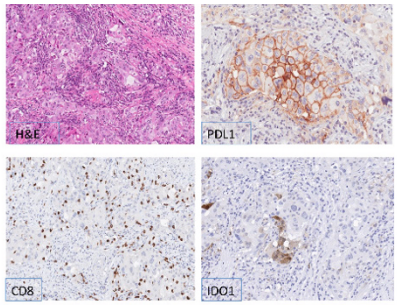
Design: TMAs with a 2-4-fold redundancy were constructed from a well-annotated set of 165 PDACs consisting of mostly treatment naïve, resected cases with clinical and transcriptomics data. RNA seq immunogenic signatures were validated by immunohistochemistry (IHC) analysis. IHC was performed using the following antibodies: PD-L1(clone28-8), IDO1(hIDO mAb cl4.16H1), CD8 and CD3. For PD-L1 and IDO1scoring, we counted the number of tumor cells showing membranous and cytoplasmic staining, respectively; PDAC cases were scored on a four point scale as 0: complete absence of expression; 1: 1-10 tumor cells with positive expression; 2: 11-50 tumor cells with positive expression; and 3: ≥ 50 tumor cells. For CD8 and CD3 scoring including Tumor infiltrating lymphocytes(TILs) we used computer aided image analysis (Definiens Tissue Studio) and QuPath software(https://qupath.github.io).

Results: PD-L1 expression at Scores 0, 1, 2 and 3 was observed in 128(82%), 13(8%), 10(7%) and 5(3%) PDACs respectively. Similarly, IDO1 expression at scores 0, 1, 2 and 3 was observed in 80(52%), 28(18%), 22(14%) and 25(16%) PDACs respectively. RNA seq fpkm values for PD-L1, IDO1, CD3 and CD8 genes were highly correlated with corresponding IHC protein expression (p from 0.0016 to 0.0001). Tumor PD-L1 expression was associated with high neoantigen counts and a trend was seen with Mofitt's basal signature. Both PD-L1 and IDO1 expression were associated with Baileys immunogenic signature, CD8, CD3 and CD8 TILs. No statistically significant association was identified between PD-L1 and IDO1 and outcome.

Distribution	n	%
IDO1 (155)		
Score 0	80	52%
Score 1	28	18%
Score 2	22	14%
Score 3	25	16%
PD-L1(156)		
Score 0	128	82%
Score 1	13	8%
Score 2	10	7%
Score 3	5	3%
CD8		
Median	706	
IQR	437-1205	
Median Count/Area(um^2)	0.000296	
CD8 TILs		
Median	13	
IQR	4-40	
Median Count/Area(um^2)	0.000005	
CD3		
Median	810	
IQR	216-1974	
Median Count/Area(um^2)	0.000411	
CD3 TILs		
Median	Ongoing	
IQR	Ongoing	
Median Count/Area(um^2)	Ongoing	

IQR Interquartile ranges(25% to 75%IQR)

Table summarizing the immune contexture that is quantified using image analysis.



A PDAC case showing high expression of PD-L1(Score 3) and IDO1(Score 2) with CD8 peritumoral infiltrate and CD8 TILs

Conclusions: Our study shows that high expression of PD-L1 and IDO1 is seen in 3% and 16% of PDACs thereby confirming that PDAC is indeed a desert for immunotherapy targets. However, IHC biomarkers are easy to use and if combined with genomic and transcriptomics correlates like mutation load, neo antigenicity and Mofitt's signatures, can lead to better clinical trial design. Precise quantification of novel immunogenic biomarkers, immune infiltrates including TILs and genomic correlates will identify subset of patients that can potentially benefit from combinatorial treatment regimes.

1871 Mutational Landscape of Metastatic Pancreatic Adenocarcinoma

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Background: Pancreatic cancer is one of the most lethal malignancies. Genomic characterization has led to better understanding of primary pancreatic tumors but there is paucity of data on the metastatic counterpart. We report the molecular aberrations of metastatic pancreatic cancer (mPC) from our precision medicine clinical trial.

Design: 28 patients with history of pancreatic ductal adenocarcinoma were prospectively enrolled between February 2013 and May 2017. Metastatic biopsy was performed with full clinico-pathological characterization. Whole exome sequencing (WES) of paired tumor & normal control samples was performed on 30 metastases (lung, liver, stomach, soft tissue, vagina and peritoneum) from these patients.

Results: Median age at diagnosis was 67 years. Male to female ratio was 0.75:1. 75% of patients had distant metastasis at time of diagnosis. Until last follow-up 39% of patients were alive. Average mutation count was 40 per sample (range 7-98). One case showed a higher mutation rate of 2684.

Overall 97% of mPC showed mutation in one or more clinically

significant genes. The most commonly mutated genes included *KRAS* (87%), *TP53* (53%), *FAM47C* (20%), *CDKN2A, KIF1A* (17% each), *SMAD4, ZNF208, COL18A1* (13%) and *ERBB2, RB1, PIK3CA, BRAF, PTCH1* and *SMO* (7% each). *For KRAS* wild-type cases, mutations in at least one of the other driver genes *such as TP53, SMAD4, EGFR, IDH1* and *KIF1A* were detected.

Genetic alterations seen in major signaling pathways include Ras-Raf-MEK-Erk/JNK signaling in 97% (29 cases), p53 signaling genes in 60% (18 cases), cell cycle control genes in 40% (12 cases), PI3K-AKT-mTOR signaling in 17% (5 cases), survival cell death regulation signaling in 13% (4 cases) and DNA damage response in 10% (3 cases) (**Table 1**).

Most common somatic copy number variants (SCNV) were *CDKN2A* del (23.3%), *CDKN2B* del (20%), *SMAD4* del (16.7%), *MTAP* del (13.3%), *TGFBR2* del, *MYC* amp, *MAP2K4* del, and *FANCG* amp (6.7% each). 1 case showed *ERBB2* amplification. *TP53* and *KRAS* mutation showed tendency towards co-occurrence.

Pathogenic germline variants were detected in 5 patients (16.7%) in *BRCA1, BRCA2, APOB, APC* and *NBN* genes.

Table1: Mutated genes of major signaling pathways	
Ras-Raf-MEK-Erk/JNK signaling	KRAS,BRAF,MAP3K4,MAP3K1
p53 signaling genes	TP53,CDKN2A,TP53BP1
cell cycle control genes	CDKN2A,RB1,RBL1,MYC,CDKN1A,CDKN-1B,E2F2,E2F4,E2F7
PI3K-AKT-mTOR signaling genes	PIK3CA,PIK3R1,PTEN,AKT1
Survival cell death regulation signaling	TGFBR2,BCL2,WWOX,CASP8,PEG3
DNA damage response	BRCA1,BRCA2,ATM,ATR,MDC1,PARP1,FANCF

Conclusions: Spectrum of gene alterations in mPC is similar to that of primary tumor with KRAS being most common driver mutation. mPC lacking KRAS mutation showed alterations in other known driver genes in all cases. Incidence of pathogenic germline variants in mPC was higher compared to the reported incidence in primary tumors.

1872 Diagnostic and Prognostic Value of Atypical Protein Kinase C iota (PRKCI) in Pancreatic Ductal Adenocarcinoma

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Background: Loss of cell polarity is a hallmark of invasive carcinoma cells. However, it is difficulty to recognize it, especially in the early changes of malignant transformation. Atypical protein kinase C iota (PRKCI) is an important molecule in regulating apical-basal cell polarity in normal epithelial cells and has been shown to be overexpressed in many carcinomas including pancreatic ductal adenocarcinoma (PDA). In this study, we aimed to evaluate the expression of PRKCI and its clinicopathological correlation in pancreatic intraepithelial neoplasia (PanIN) and PDA.

Design: Immunohistochemical stains of PRKCI were performed on two sets of tissue microarrays (TMA). The first TMA contained 45 low grade PanINs and 10 high grade PanINs. The second TMA had 214 PDAs and each case was represented by 3 tissue dots. The PRKCI expression can be identified at the apical membrane with no or very faint cytoplasmic staining in normal ductal epithelium which was considered as negative, while the stain was scored as positive if there was diffuse cytoplasmic staining. Staining intensity of each dot was scored as 0, 1, 2, and 3, and the PRKCI staining score of each case was the average of three dots. A cutoff of 1.67 was used to divide PDAs into low and high expression group.

Results: No positive PRKCI was observed in benign acinar and ductal cells and 45 low grade PanINs, while 70% (7/10) high grade PanINs showed positive staining. Positive PRKCI staining was seen in all PDAs. Low expression of PRKCI was observed in 54% (115/214), and 46% cases (99/214) had high expression level. High PRKCI expression group had a significantly increased median survival (848 days vs. 581 days, p= 0.03). Patients with high PRKCI expression also had significantly lower incidence of self-reported diabetes (24% vs. 40%, p=0.01), while no association of PRKCI expression level was identified with other clinicopathological factors including age, gender, obesity, tumor grade, and lymph node and distant metastases.

Conclusions: We demonstrated that PRKCI was expressed in most high grade PanINs and all PDAs, and it may be a useful marker in diagnosing pancreatic epithelial malignancy in daily practice when difficult cases are encountered such as in small biopsies. Furthermore, PDA patients with high expression PRKCI tend to have better survivals, and future studies for the significance of this finding are warranted.

1873 Evaluation of GATA-3 and Estrogen Receptor Expression in Pancreatic Neuroendocrine Tumors by Immunohistochemistry

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Background: While pancreatic neuroendocrine tumors (NET) are morphologically similar to many other NETs, discrimination of site of origin remains of clinical importance. Breast carcinoma is a known mimicker of neuroendocrine tumors and can often have focal neuroendocrine differentiation. GATA-3 and estrogen receptor-alpha (ER-α) expression are traditionally associated with breast origin. However, GATA-3 is also expressed in a portion of pancreatic adenocarcinomas. While pancreatic NETs have been previously reported as consistently GATA-3 negative, these studies are performed on tissue microarray samples, are limited in number, and use mixed grades. Similarly, expression of ER-α is seen in a low proportion of pancreatic NETs, although studies either do not clarify grade or specifically exclude grade 3 (G3) cases. We seek to investigate the immunohistochemical expression of both GATA-3 and ER-α across all grades of pancreatic NETs to further elucidate the roles of these stains in evaluating pancreatic origin.

Design: Forty-four cases were retrospectively selected from 1996 to 2016. Ten cases diagnosed as "neuroendocrine carcinoma" prior to 2010 (before standardized use of Ki-67) were reclassified as grade 2 following subsequent Ki-67 staining. Two cases were excluded after follow-up information revealed a non-pancreatic primary. Following exclusion and reclassification based on World Health Organization 2010 guidelines, forty-two cases of primary pancreatic NETs were used for whole slide immunohistochemical staining with GATA-3 and ER-α, including grade 1 (G1; n=12), grade 2 (G2; n=22), and grade 3 (G3; n=8). The stained slides were then evaluated for percentage and intensity of nuclear staining.

Results: Significant GATA-3 expression (5% or greater) was present in 8% of G1 NETs (n=1; moderate intensity; 60% of tumor cells) and 25% of G3 NETs (n=2; moderate to strong intensity; 5-100% of tumor cells). Significant ER-α expression (5% or greater) was seen in 8% of G1 NETs (n=1; weak to moderate intensity; 20% of tumor cells), 18% of G2 NETs (n=3; weak to moderate intensity; 5-70% of tumor cells), and 36% of G3 NETs (n=3; weak to strong intensity; 5-100% of cells). Only one case showed both GATA-3 and ER-α expression.

NET Grade	GATA-3 Expression	ER-α Expression
G1	8%	8%
G2	0%	18%
G3	25%	36%

Conclusions: GATA-3 and ER-α expression can sometimes be seen in primary pancreatic neuroendocrine tumors of all grades. This study suggests that positivity of GATA-3 and/or ER-α does not exclude pancreatic origin and may be misleading, especially in limited biopsies.

1874 The Combination of Bile Duct Biopsy and Bile Duct Brushing Significantly Increases the Sensitivity of Pancreatobiliary Adenocarcinoma Detection

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Background: We frequently receive concurrent bile duct biopsies and bile duct brushings from patients with suspected pancreatic or biliary adenocarcinoma at our institution. The aim of this study is to determine the utility of the combination of bile duct biopsies and brushings in comparison to bile duct biopsy or bile duct brushing alone in the diagnosis of pancreatobiliary adenocarcinoma.

Design: We conducted a retrospective study including patients who underwent bile duct biopsy, bile duct brushing, or both, at a single academic center from January 2006 to December 2016. We compared the sensitivity of bile duct biopsy to bile duct brushing alone, and the sensitivity of a combination of bile duct brushing and bile duct biopsy to biopsy alone and brushing alone.

Results: We identified a total of 115 patients (median age 61 years; 55% male), of whom 52 were diagnosed with adenocarcinoma. Nearly half (48%) of cases were located in common bile duct (CBD), and 27% were pancreatic in origin. Twenty-five cases were diagnosed by biopsy alone, 10 brush alone, 12 both brush and biopsy, and 5 by FNA after negative biopsy and brush. The sensitivity of biopsy alone was higher than brush alone but this did not reach statistical significance

(71% vs. 54%, p=0.08). The sensitivity of combination biopsy/brushing was significantly higher than biopsy alone (88% vs. 71%; p=0.05) or brushing alone (88% vs. 54%; p=0.001). In exploratory subgroup analyses, combination biopsy/brushing continued to have higher sensitivity than biopsy alone (100% vs. 76%; p=0.02) or brushing alone (100% vs. 67%; p=0.004) in those with CBD tumors; however, this was not true in the subgroup of pancreatic tumors (67% vs. 57%; p=0.62 for combo vs. biopsy and 67% vs. 33%; p=0.10 for combo vs. brushing).

Conclusions: Performing combination biopsy and brushing significantly increases sensitivity for detecting pancreaticobiliary adenocarcinoma compared to doing either in isolation; however, this combination still misses over 10% of tumors, suggesting better diagnostic techniques are needed.

1875 Molecular Profiling of Gallbladder Adenocarcinoma vs. Extrahepatic Cholangiocarcinoma Reveals Similar Genetic Alternations

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Background: Gallbladder adenocarcinoma and extrahepatic cholangiocarcinoma are aggressive adenocarcinomas arising from the biliary epithelium. These carcinomas are frequently inoperable and often recur after surgery. Patients are in need of more effective treatment. We aim to identify molecular signatures in gallbladder vs. extrahepatic cholangiocarcinoma for prognostic and therapeutic implications by using next generation sequencing (NGS) technology.

Design: 100 resections, including 62 gallbladder, 21 distal, and 17 perihilar cholangiocarcinomas were identified at our institution from 2000 to 2014. Cholangiocarcinoma-focused mutation AmpiSeq panel (IAD 106149) was developed using Lift Technology (Ampliseq design site https://ampliseq.com). Panel includes 30 genes, total 27.87 kb, covering pathways that are commonly involved in biliary tract oncogenesis, such as chromatin remodeling, MAPK, AKT/PI3K/mTOR, Wnt, and inflammation. 412 amplicons were divided into two pools with an overall 99.82% base coverage. 3 genes (TP53, BRAF, and PTEN) had the entire coding regions sequenced; while the other 27 genes had hotspots only (APC, ARID1A, ATM, BAP1, BRCA1, BRCA2, CDKN2a, EGFR, ERBB2, ERCC1, FBXW7, FGFR2, IDH1, IDH2, IL6, JAK2, KRAS, NF1, NRAS, PBRM1, PIK3CA, PTCH1, SMAD4, SRC, STAT3, VEGFA, XRCC1).

Results: All 100 samples were successfully analyzed using the cholangiocarcinoma Ampliseq panel. We confirmed hot spots in 7 genes that were previously reported in cholangiocarcinomas (ARID1a, ERCC1, IL-6, JAK2, SRC, STAT3, and XRCC1), but did not find previously reported hotspots in the other 23 genes. For the alterations in the 7 genes (Table 1), there is no significant difference between gallbladder vs. distal and perihilar cholangiocarcinomas by Fisher's exact test. These alterations also show no significant association with overall survival by Cox regression modeling. Few hot spots in SRC gene show a trend towards association (p<0.1) with overall survival. Furthermore, we detected novel single nucleotide pleomorphisms (SNPs) and/or mutations in all 30 genes.

Table 1. Mutation hotspots of 7 genes associated with gallbladder adenocarcinoma and extrahepatic cholangiocarcinoma.

Genes	Hotspots	# of Samples	p-Value for Group Difference (Fisher's Exact Test)	p-Value for Overall Survival (Cox Regression Modeling)
ARID1a	rs 201172639 @ 27100889	6	0.1640	0.3110
ERCC1	rs 11615 @45923653	68	1	0.2146
IL-6	rs1800795 @ 22766645	88	0.7783	0.6890
	rs 1800796 @22766246	16	0.5439	0.4655
JAK2	rs10758669 @ 4981602	84	1	0.4993
SRC	rs12106024 @35979348	37	0.9129	0.5512
	rs 6017916 @35971278	45	1	0.7152
	rs 6017944 @35977571	41	0.8782	0.6162
	rs 6017996 @3598665	24	0.3551	0.6134
	rs 6018027 @35990792	42	0.2996	0.4347
	rs 6018148 @36005780	38	0.6703	0.0769
	rs 6018199 @36009657	32	0.7182	0.4117
	rs 6018256 @36022154	22	0.4815	0.9761
	rs6018257@36022539	25	0.3657	0.7360
	rs6063022 @35993327	30	0.7826	0.5970
	rs6090575 @36005315	21	0.7256	0.0817
	rs6090585 @36009145	15	0.6677	0.4847
	rs747182 @35982889	24	0.3551	0.6416
	rs 754626 2@36017340	44	0.2218	0.7331
STAT3	rs3816769 @40498273	65	0.2456	0.9609
	rs744166 @40514201	76	0.8491	0.9466
XRCC1	rs11615 @45923653	4	0.7975	0.9886
	Rs25487 @44055726	95	0.2127	0.7389

Conclusions: Gallbladder and extrahepatic cholangiocarcinomas demonstrate similar genetic alterations in the 7 genes commonly involved in biliary tract cancer, and we confirmed mutation hotspots in these genes. Importantly, we identified novel SNPs that have not been previously reported in billiary tract cancer; additional studies are in progress to elucidate the significance of these.

1876 Do Frozen Sections Make a Difference in the Surgical Management of Intraductal Papillary Mucinous Neoplasms of the Pancreas?

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Background: Intraoperative frozen section (FS) evaluation of the pancreatic parenchymal resection margin (RM) in cases of intraductal papillary mucinous neoplasm (IPMN) is challenging. It is generally agreed that the RM should be assessed intraoperatively for high-grade dysplasia (HGD) and invasive carcinoma (CA), but it is unclear whether involvement of the RM by IPMN with low-grade dysplasia (LGD) affects surgical management and clinical outcomes. This study examines the impact of FS evaluation of RMs on the surgical management of IPMN in a tertiary surgical center.

Design: All resections (excluding 5 enucleations) for IPMN performed at Cedars-Sinai Medical Center from 2005 to the present (n= 63) were reviewed. The FS diagnosis of the RM(s) (if performed) and the status of the final RM were recorded. Patients were monitored for recurrence with follow-up imaging.

Results: 63 FSs of the pancreatic RM(s) were performed in 44 patients, 28 (64%) of whom had non-negative FS diagnoses, including IPMN with CA (n=1), IPMN with HGD (n=4), IPMN with LGD (n=18), atypical epithelium (n=3), and denuded epithelium (n=2). An additional RM was resected in only 15 (54%) of these 28 patients, including 3 of the 5 IPMNs with HGD/CA, 9 of the 18 IPMN with LGD, and all 3 with atypical epithelium. A negative final RM was achieved in 10 (67%) of these 15 patients; the other 5 cases remained positive for IPMN (2 with HGD and 3 with LGD). Of the 19 patients who did not have FS evaluation of the RM, 7 had positive RMs, including 6 positive for IPMN with LGD and 1 positive for IPMN with CA; the RM was negative in the remaining 12 patients. In 25 patients with a minimum of 24 months of follow-up (median 47 months, range 24-124 months), only one recurrence (4%) was noted, occurring after 12 months in a patient whose final margin was positive for IPMN with LGD. Interestingly, 5 other patients in whom the final margin was positive for IPMN with LGD and 1 patient whose final margin was positive for IPMN with HGD did not develop recurrence after a median follow-up of 45 months (range 24-124 months).

Conclusions: 1) A positive FS of the RM does not always prompt further resection, but negative final margins are often achieved with resection of additional tissue. 2) FS may be underutilized in the surgical management of IPMN. 3) Longer follow-up of a larger cohort of patients is needed to draw conclusions regarding the impact of FS on recurrence rates of IPMN.

1877 Increased Expression of the Hypoxic Marker Carbonic Anhydrase IX is Associated with Improved Prognosis in Resected Pancreatic Ductal Adenocarcinoma

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Background: Carbonic anhydrase IX (CAIX), a transmembranous enzyme that is part of the hypoxia-inducible factor pathway, has been implicated as an adverse prognostic marker in various malignancies. The aim of this study was to assess CAIX as a prognostic marker in a cohort of pancreatic ductal adenocarcinomas (PDACs).

Design: A duplicate 0.6mm core tissue microarray containing tumor samples of PDACs from 258 patients was stained for CAIX with the M75 antibody. CAIX membranous expression was assessed by two independent pathologists blinded to treatment and outcome. Each core was scored as the product of a semi-quantitative estimate of percentage of positive cells and staining intensity (0 = negative, 1 = weak, 2 = moderate, and 3 = strong). The maximum score was used for each case. Comparisons with clinicopathologic variables were performed as well as univariate and multivariate analysis of disease-specific survival (DSS).

Results: Tumors with a higher expression of CAIX were less likely to show lymphovascular invasion (p = 0.001) or perineural invasion (p = 0.003), and were more likely to be associated with an R0 resection (p = 0.02). On univariate survival analysis between cases with high (N = 81) and low (N = 177) expression of CAIX, high expression showed a median DSS advantage of 0.54 year (95% confidence interval 0.42 - 0.79). On multivariate analysis, CAIX expression was not an independent prognostic marker.

Conclusions: High expression of CAIX in resectable PDACs may be associated with improved prognosis. PDACs with high expression of CAIX may be exhibiting a less perfused phenotype leading to a more resectable and less aggressive tumor phenotype.

1878 Effects of FOLFIRINOX Neoadjuvant Therapy for Pancreatic Cancer on Frozen Section Error Rates

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Background: The use of neoadjuvant therapy with FOLFIRINOX for pancreatic ductal adenocarcinomas (PDAC) has resulted in improved survival, and increased total or near-total histologic responses. However, this therapy can present challenges to the pathologist, as marked reactive epithelial atypia and alterations in tumor morphology may occur in response. Distinguishing reactive glands from viable cancer at frozen section may be very challenging. We hypothesized that neoadjuvant therapy would be associated with an increased rate of errors at frozen section during pancreatic tumor resections.

Design: We identified 116 cases of pancreatic cancer resected following FOLFIRINOX therapy: 101 Whipples, 15 distal pancreatectomies (DPs). Each margin frozen section was classified as one of three categories: benign, malignant, or atypical/other. We then compared each frozen section diagnosis with the diagnosis on its corresponding permanent section, stratified into the same three groups. Discordance occurred where the frozen and permanent section were in different groups. A control cohort of 115 pancreatic resection cases which had not received neoadjuvant therapy (103 Whipples, 12 DPs) was also examined. Rates of discordance were analyzed with chi-squared testing, and log-rank testing was used to compare survival between R0 and R1 resections.

Results: There were 267 frozen-permanent pairs evaluated in the FOLFIRINOX cohort and 206 pairs in the control group. There was no statistically significant increase in the frozen section error rate: 17 (6.4%) discordant in the FOLFIRINOX cohort, and 14 (6.8%) in the control cohort (p=0.60). 15 of these discordances resulted in an under-called margin, and 16 resulted in over-calling of benign changes as cancer. In both cohorts, the pancreatic transection margin had the greatest rates of discordance (9.1% and 6.5%, respectively). The bile duct margin had the lowest rate of discordance (1.2% and 0%). In the treatment-naïve control cohort, R1 resections had inferior survival (p=0.007). Based on available follow-up on 35 patients, R1 resection in the neoadjuvant-treated cohort did not correlate with survival (p=0.52).

Conclusions: Although distinguishing between PDAC and reactive glands in the setting of neoadjuvant FOLFIRINOX therapy is challenging, our data suggests that this does not lead to a significantly increased rate of errors at frozen section. We advocate for continued judicious use of frozen sections in the FOLFIRINOX era.

1879 Loss of ARID1A Expression Predicts Worse Overall Survival in Patients with Resected Pancreatic Adenocarcinoma and Is Associated with Inactivating Mutations of the ARID1A Gene

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Background: *ARID1A* is a component of the SWI/SNF chromatin remodeling complex that has recently been identified as one of the recurrently mutated genes in pancreatic adenocarcinoma (PDAC). However, the clinical and prognostic significance of ARID1A alterations in PDAC are uncertain, as is the degree of correlation between ARID1A protein expression and *ARID1A* mutation status. We therefore investigated the prevalence of ARID1A alterations in resected PDAC specimens in relation to clinicopathologic features, outcome and other key molecular features.

Design: Paired tumor and normal sequencing was performed using a custom hybrid-capture-based massively parallel sequencing panel designed to interrogate 429 genes specifically implicated in PDAC pathogenesis. Expression of ARID1A was evaluated using immunohistochemistry (IHC) on tissue microarrays and scored based upon presence or complete absence of expression in tumor cells. Fisher's exact test was used to evaluate correlation between ARID1A status and clinicopathologic and molecular features. A multivariate Cox proportional hazards model was used to test associations with disease-free survival and overall survival.

Results: In our multi-institutional cohort of 343 cases, ARID1A expression was lost in 15 cases (4%). ARID1A expression status was not associated with T or N stage, tumor differentiation, lymphovascular invasion, or resection margin status (p > 0.05 for all). However, loss of protein expression was significantly correlated with overall survival (OS), with a median OS of 10.7 months for ARID1A-null tumors and 21.1 months for ARID1A-intact tumors (HR = 2.20, 95% CI 1.15-4.16). Loss of ARID1A showed a trend towards decreased disease-free survival, although the association did not reach statistical significance. Overall, 5% of cases harbored *ARID1A* mutations that were predicted to disrupt protein function. Inactivating *ARID1A* mutations were identified in 53% of ARID1A-null tumors, and in only 2.8% of ARID1A-intact tumors. ARID1A status, as assessed by IHC, was not significantly associated with alterations in other key PDAC driver genes, including *KRAS*, *TP53*, *CDKN2A* (p16), and *SMAD4*.

Conclusions: Our findings demonstrate that ARID1A expression is lost in a subset of PDACs, and that loss is driven largely by inactivating mutations in the *ARID1A* gene. Loss of ARID1A is predictive of substantially worse overall survival, and ARID1A may function in a molecular role that is independent from other key PDAC driver genes.

1880 Comparison of AJCC7 and 8 Pathologic T Categorization in Pancreatic Ductal Adenocarcinoma

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Background: Beginning with the 5th edition (1997) of the *AJCC Cancer Staging Manual* extrapancreatic extension has defined pT3 category disease in pancreas cancer. In *AJCC8* the pT1-3 categories have been reconfigured based on size alone. Both schema have their weaknesses. The margin of the pancreas is ill-defined such that assessment of extrapancreatic spread is fraught with difficulty; it is unlikely that patients with «minimal» extrapancreatic extension fare as poorly as those with gross extrapancreatic spread, though a majority of patients are assigned to the pT3 category based on «histologic» extrapancreatic spread. Basing the T category on size is seemingly arbitrary as the gross dimensions of a ductal adenocarcinoma are inherently ill-defined, with much of the gross mass typically representing peritumoral chronic pancreatitis on the H&E. The purpose of this study is to compare the frequency of T categories in ductal adenocarcinoma based on *AJCC7* and *8* criteria.

Design: A clinical database of 188 pancreas cancers resected from 1997-2014 had been updated to include *AJCC7* T category. Based on tumor size derived from pathology reports, an *AJCC8* T category could be inferred for 181 of these (i.e., 7 reports did not mention tumor size). For 148 of these patients, updated date of last follow up and vital status were available. Based on this, Kaplan-Meier curves were produced relating T category to survival; log-rank tests were used to compare survival distributions with p<0.05 considered significant.

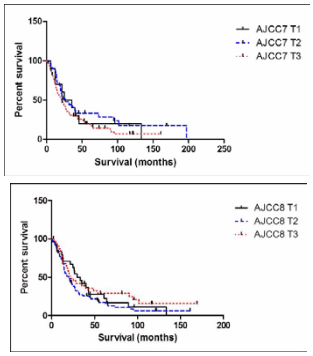
Results: Using *AJCC7,* pT3 category disease predominates (73%), while with *AJCC8* pT2 category disease is most frequent

(64%). Complete frequency data are presented in the Table.

Table: *AJCC7* vs *8* T Categorization

AJCC7 (n=188)		AJCC8 (n=181)	
pT1	6%	pT1a	0%
		pT1b	2%
		pT1c	12%
pT2	20%	pT2	64%
pT3	73%	pT3	22%
pT4	0.5%	pT4	0.5%

For *AJCC7* the survival curve of pT3 category disease is beneath that of pT2 disease, while for *AJCC8* the pT3 and pT2 curves appear inverted (see Figures), though neither set of survival curves were significantly different (p=0.23 for both).



Conclusions: We anticipate that application of *AJCC8* to pancreas cancer will result in a 3-fold increase in assignment of the pT2 category with a reciprocal 3-fold reduction in pT3 disease. Increased attention to the maximum gross dimension of a pancreas cancer will be required for optimal staging.

1881 Expression and Prognostic Value of NSD1 and SETD2 in Pancreatic Ductal Adenocarcinoma (PDA) and its Precursor Lesions

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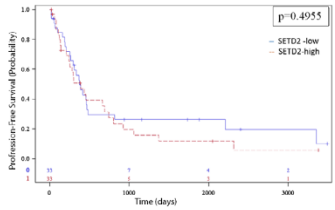
Background: Epigenetic regulation has been emerging as a critical mechanism for PDA development. Many epigenetic regulator genes are altered and considered as drivers in PDA. Histone methylation is one of the most important mechanisms of epigenetic regulations. These modifications can alter chromatin structure and promoter accessibility, and thus lead to aberrant gene expression. Recent genomic sequencing studies showed that NSD1 and SETD2, genes encoding two histone H3K36 methyltransferases, are mutated or altered in about 10% of PDA cases. However, whether there is altered protein expression of NSD1 or SETD2 in PDA and its precursors, and whether they have diagnostic or prognostic utility is not known.

Design: Tissue microarrays (TMAs) composed of a total of 190-195 duplicated cases of PDA (n=74-75), metastatic PDA (n= 17-18), pancreatic intraepithelial neoplasia (PanIN; n=19-25), intraductal papillary mucinous neoplasm (IPMN; n=36), mucinous cystic neoplasm (MCN; n=12) and benign pancreatic tissues (n=29-32) were analyzed for expression of NSD1 and SETD2 by immunohistochemistry. We assessed intensity (0, 1, 2, 3), and percentage of positive cells (score=intensity x % positive cells). Overall and progression-free survival was compared between NSD1/SETD2-low and high expression patients using Kaplan-Meier analysis.

Results: Both NSD1 and SETD2 showed a trend toward either increased (NSD1) or decreased (SETD2) protein staining in PDA/metastatic PDA and its precursor lesions compared to benign ducts. In addition, decreased expression of SETD2 appears to be a slightly favorable independent prognostic factor for progression-free survival of PDA. However, these findings did not reach statistical significance (p=0.1 and p=0.4955), probably due to the variability of the protein levels in dysplastic/neoplastic lesions.

Table 1

Diagnosis	NSD1 score (Mean ± SD)	SETD2 score (Mean ± SD)
Normal	78.3 ± 47.5	176.6 ± 58.8
PanIN	83.2 ± 65.2	134.2 ± 47.4
IPMN	99.4 ± 57.8	167.5 ± 61.1
MCN	83.3 ± 73.9	125.8 ± 65.3
PDA (primary tumor)	87.2 ± 48.3	157.8 ± 53.8
PDA (metastasis)	118.3 ± 61.8	144.7 ± 44.3



Conclusions: Expression of NSD1 and SETD2 are altered in some cases of PDA and its precursor lesions, supporting their important role in PDA development. Decreased expression of SETD2 is associated with a slightly favorable outcome in PDA. However, these findings did not reach statistical significance.

1882 Expression of PD-L1 in Type-2 Autoimmune Pancreatitis May Aid in Distinguishing it from Morphologic Mimics

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Background: Autoimmune pancreatitis (AIP) encompasses a heterogeneous disease group that includes the IgG4-related type 1 AIP and non-IgG4 related type 2 AIP. Importantly, type 2 AIP may mimic pancreatic ductal adenocarcinoma (PDAC) clinically and on imaging and discriminatory markers may significantly aid proper diagnosis. In this study, expression of the immunomodulatory proteins PD-L1 and indoleamine 2,3-dioxygenase (IDO) were investigated in type 2 AIP and correlated to histologic findings. Furthermore, PD-L1 expression in type 2 AIP was also compared to expression seen in type 1 AIP and pancreatic ductal adenocarcinoma.

Design: For type 2 AIP, inclusionary criteria included periductal lymphoplasmacytic infiltrate and intra-ductal neutrophilic infiltrates. The inflammatory infiltrates were scored, as was interlobular fibrosis and pancreatic atrophy. 27 type 2 AIP, 14 type 1 AIP and 237 cases of PDAC were identified and were subject to immunohistochemical staining for PD-L1 or IDO. PD-L1 and IDO staining was graded as present or absent (>1% membranous staining for PD-L1 and any cytoplasmic staining of IDO). Statistical analysis was performed using chi-square, Fisher's exact, and Student's t-test, where appropriate; p values less than 0.05 were considered significant.

Results: The cases of type 2 AIP were from patients with an average age of 49 years without gender predilection. The ductal cells of 55% (15/27) of type 2 autoimmune pancreatitis cases were positive for PD-L1 and an equal number of cases were positive for IDO; 76% showed ductal reactivity for either PD-L1 or IDO. There was no correlation between PD-L1 and IDO reactivity (Pearson's correlation p=0.6). By comparison, pancreatic ducts in type 1 AIP showed no staining for either PD-L1 or IDO. Furthermore, 6 of 237 (2.5%) pancreatic ductal adenocarcinoma cases were positive for PD-L1, and notably, the adjacent inflamed pancreatic ducts and acini, present in 210 cases, were negative for PD-L1 reactivity. In type 2 AIP, PD-L1 and/or IDO correlated with higher grade intraductal neutrophilic infiltrates (p=0.0003), as well as the extent of pancreatic atrophy (p=0.016) and fibrosis (p=0.0003).

Conclusions: PD-L1 expression has the potential to assist in the distinction between type 2 AIP and mimics, including PDAC and type 1 AIP. The upregulated checkpoint proteins may represent a mechanism to suppress the deleterious effects of the immune response.

1883 Diagnostic Value of "Floating Cancer-cell Cluster" (Cancer Cells Detached from the Stroma) in Bile Duct Mapping Biopsy Specimens

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Background: Endoscopic transpapillary bile duct mapping biopsy is performed to evaluate extension of bile duct carcinoma. In some cases, biopsy contains only isolated or clusters of cancer cells detached from the stroma ("floating cancer-cell cluster", FCC). It is uncertain if FCCs represent cancer cells derived from the biopsy site or contamination.

Design: We assessed 470 preoperative biopsy specimens from 68 patients who underwent resection of bile duct carcinoma (43 hepatectomy, 20 pancreaticoduodenectomy, 5 hepatopancreaticoduodenectomy) between January 2011 and December 2016. Diagnostic categories of biopsy were as follows: C1) Inadequate, no epithelium is observed; C2) Negative (benign epithelium or atypical epithelium of undetermined significance); C3) FCC only; C4) Positive (cancer cells in contact with the stroma).

Results: The median number of biopsy per patient is 5 (range: 1 to 31). The number of biopsies categorized as C1, C2, C3, and C4 were 72 (15%), 273 (58%), 34 (7%), and 91 (19%), respectively. False negative rate of C1 and C2 was 18% (13/72), 37% (102/273) by comparison with resected specimens. False positive rate of C3 was significantly higher than that of C4 (35%, 12/34 vs. 11%, 10/91, p<0.01).

Conclusions: FCC can be associated with considerable percentage of false positivity in mapping biopsy of bile duct carcinoma. If FCC pattern is observed in biopsy sites affecting operability, re-biopsy should be suggested.

1884 Residual Tumor Index: A Prognostically Significant Pathologic Parameter in Resections for Neoadjuvant Treated Pancreatic Ductal Adenocarcinomas

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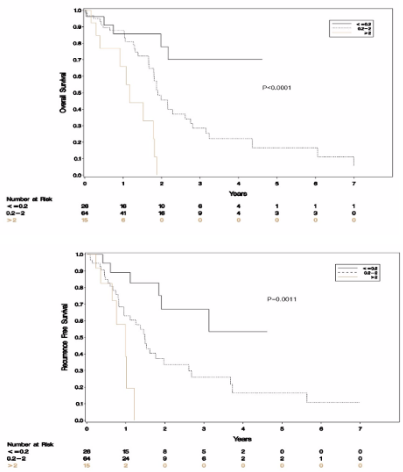
Background: Pancreatic ductal adenocarcinoma (PDAC) is an infiltrative tumor with a prominent desmoplastic stroma. Often the adjacent stroma is fibrotic, exaggerated by neoadjuvant therapy (NAT). In this setting, accurate measurement of tumor size, and consequently, staging based on AJCC 8th edition, is frequently very difficult. The aim of this study is to identify a prognostically meaningful pathologic parameter which can be an adjunct to tumor staging in the neoadjuvant setting.

Design: A cohort of patients with PDAC located in the head of pancreas, who underwent NAT followed by pancreaticoduodenectomy (PD), was identified from a prospectively maintained database. Archival H&E slides were reviewed to assess the percentage of residual tumor, along with other usual pathologic parameters, and a record of tumor size and tumor bed size was noted from the pathology reports, and in ambiguous cases, by a microscopic review. Residual tumor index (RTI) was arbitrarily defined as the product of residual tumor percentage and tumor bed. Univariate and multivariate analyses were performed to determine the association of RTI with overall survival (OS) and recurrence free survival (RFS). Cox proportional-hazards models were used to evaluate the relationship of the clinical and pathologic variables.

Results: A total of 105 cases of PD after NAT were analyzed using clinical (age, gender, race, pre-operative treatments) and pathologic (tumor grade, margin status, perineural invasion and lymphatic invasion) characteristics. On univariate analysis, total number of lymph nodes involved and RTI were significantly associated with RFS (p-value=0.0132 & 0.0027, respectively). On multivariate analysis, only RTI was identified as an independent predictor of RFS (HR=1.650 (1.189, 2.289), p=0.003). Lymphatic invasion, number of lymph nodes involved and RTI were also associated with OS on univariate analysis (p-value=0.0458, 0.0015 and 0.0004, respectively), however, number of lymph nodes involved and RTI were the independent predictors of OS on multivariate model (HR=1.073 (0.999-1.152), p=0.053; HR=1.539 (1.115-2.126), p=0.009). The cutoffs for RTI classified the patients into low (RTI<0.2), mid (RTI=0.2-2.0) and high (RTI>2.0) risk groups. Low RTI was associated with significantly longer OS (p=0.0001) and RFS (p=0.0011) (see figure).



Conclusions: RTI is a useful parameter for pathologic classification of PDAC post resection in patients undergoing NAT and can be used as adjunct to current pathological staging for patients underg

1885 Global Methylation Status and CfDNA Integrity Using ALU115 and ALU 247 Repeats in Gallbladder Carcinoma

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Background: Gallbladder cancer (GBC) is frequent in India, Chile, Pakistan, Equador & Japan. Current preoperative diagnostic modalities are radiological studies. Inflammatory conditions form a close differential diagnosis and incidental GBC may be discovered post simple cholecystectomy. Hence the need for a sensitive and specific marker for preoperative diagnosis exists. We have analyzed circulating free DNA (cfDNA) for long DNA fragments (ALU247) derived from tumor necrosis & short apoptotic fragments (ALU115) and calculated cfDNA integrity ratio in GBC. cfDNA global methylation status was estimated.

Design: Study group included 60 cases of GBC and 36 controls including 12 cases of cholecystitis and 9 cases of Xanthogranulomatous cholecystitis & 15 healthy individuals. cfDNA was extracted using ChargeSwitch® gDNA 1mL Serum Kit (Invitrogen, USA). cfDNA integrity was calculated as ratio of ALU247/ALU115 detected in qPCR. Global methylation status in cfDNA was quantified using Methyl Flash Methylated DNA Quantification Kit (Epigentek Group Inc.,USA).

Results: The sensitivity and specificity of ALU115, ALU 247, cfDNA integrity index and global methylation was highest for cfDNA integrity index (Table 1). Mean levels of ALU115, ALU247 and cfDNA integrity were significantly different in GBC at 2246.81,1186.97,0.5091 vs. 947.48,195.92,0.2194 ng/ml in controls respectively. Global DNA methylation was not significantly different between GBC at 0.679% and controls at 0.695%. Analysis of Clinico-pathological parameters and cfDNA integrity, ALU115, ALU247 levels showed significantly higher values with poorly differentiated histology, lympho-vascular invasion and lymph node metastasis, T stage and overall AJCC stage (p= 0.002, 0.033, 0.015, 0.011, 0.006 respectively). Further ROC curve analysis, showed significant diagnostic discrimination for cfDNA integrity between increasing tumor size, lympho-vascular invasion, AJCC stage and histological grade.

Diagnostic test	Cut off value (ng/ml)	AUC	p Value	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	Diagnostic Accuracy (%)
ALU 115	>1128.429	0.748	0.000	71.70 (58.56-82.55)	66.7 (49.03-81.44)	78.20 (68.73-85.38)	58.54 (47.02-69.19)	69.7
ALU247	>406.5825	0.901	0.000	80.00 (67.67-89.22)	86.11 (70.50-95.33)	90.60 (80.82-95.63)	72.10 (60.50-81.33)	82.2
cfDNA Integrity	>0.35628	0.895	0.000	78.33 (65.80-87.93)	80.56 (63.98-91.81)	87.04 (77.31-92.97)	69.05 (57.33-78.74)	80.2
Global Mrthylation	<0.7135	0.509	0.906	55.0 (38.49-70.74)	50.0 (27.20-72.80)	68.75 (56.67-78.73)	35.71 (24.16-49.21)	51.6
ALU115+ALU247	96.67 (88.47-99.59)			83.33 (71.48-91.71)	66.67 (49.03-81.44)	80.65 (72.14-87.02)	70.59 (56.57-81.56)	77.08
ALU115+ Integrity index	52.78 (35.49-69.59)			77.33 (70.66-82.86)	90.48 (70.14-97.46)	80.20		
ALU247+ Integrity index	93.33 (83.80-98.15) 72.22 (54.81-85.80)			84.85 (76.70-90.50)	86.67 (71.17-94.48)	85.41		

Conclusions: The study in novel in terms of evaluation of ALU115, ALU247 and cfDNA integrity in GBC. The use of a combination of ALU247 and cfDNA integrity provides highest diagnostic value in discriminating GBC from inflammatory disease. Levels are associated with disease progression and tumor burden.

1886 Histopathology of Pancreatic Cancer in Patients with Germline Mutations in Ataxia Telangiectasia Mutated (ATM) Gene

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Background: The ataxia telangiectasia mutated (ATM) protein is a serine/threonine kinase involved in DNA damage repair. Germline mutations in the *ATM* gene are found in a subset of patients with pancreatic cancer and are important to identify since these tumors may be more susceptible to certain chemotherapeutics and may provide cancer risk information for family members. Since specific germline mutations are associated with histologic subtypes of pancreatic cancer (e.g. DNA mismatch repair proteins and medullary carcinoma), we sought to study the histopathology of pancreatic cancer in patients with germline *ATM* mutations.

Design: Fifteen patients harboring germline *ATM* mutations with pancreatic cancer were identified and the available histopathology was reviewed for each.

Results: The patients mean age was 60 years (range 35-74 yrs), 67% were male and 33% were female. 14 tumors were from pancreatic resections and 1 was from biopsy. The histologic subtype was ductal adenocarcinoma, not otherwise specified (NOS) in 12 cases (80%), colloid carcinoma in 2 cases (13%) and adenosquamous carcinoma in 1 case (7%). One patient with ductal adenocarcinoma, NOS was treated with neoadjuvant chemoradiation prior to resection. In resection specimens, carcinomas were located in the pancreatic head in 83% of cases, the neck in 8% and the body in 8%. The mean tumor size was 2.9 cm (range 1.6-4.0 cm). Lymph node metastasis was seen in 62% of cases. Perineural and lymphovascular invasion was seen in 79% and 42% of cases respectively. Intraductal papillary mucinous neoplasms (IPMN) were present in 2 cases (16%), including 1 case of colloid carcinoma arising in an IPMN with high-grade dysplasia and 1 case of ductal adenocarcinoma, NOS with background incipient IPMN showing intermediate-grade dysplasia. Pancreatic intraepithelial neoplasia (PanIn) was present in 85% of cases with 83% showing intermediate-grade dysplasia and 17% showing low-grade dysplasia.

Conclusions: This is the largest series examining the histopathology of pancreatic cancer in patients with germline *ATM* mutations. We found that pancreatic cancers in *ATM* mutation carriers are frequently associated with precursor lesions (85% of cases) and moreover, are morphologically diverse, supporting the utility of widespread molecular testing for germline mutations in pancreatic cancer.

1887 Cancerization of the Pancreatic Ducts: Demonstration of a Common and Under-Recognized Process Using Immunolabeling of Paired Duct Lesions and Invasive Pancreatic Ductal Adenocarcinoma for p53 and Smad4

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Background: The extension and growth of invasive carcinoma into pancreatic ducts or ductules (known as cancerization of ducts (COD)) has been reported in pancreatic ductal adenocarcinoma (PDAC). COD can histologically mimic high-grade pancreatic intraepithelial neoplasia (HG-PanIN). In this study, we defined the prevalence of COD in a series of surgically resected pancreata using immunolabeling for p53 and Smad4.

Design: Pancreatic resections from 100 patients with PDAC from 2009 to 2010 were identified using our electronic pathology database. Available hematoxylin and eosin (H&E) stained slides from each case were reviewed, and the presence or absence of ducts with histologic features of COD, defined as a markedly atypical intraductal lesion with an abrupt transition to normal duct epithelium, was documented. Since p53 and Smad4 are frequently targeted in invasive PDAC, but not isolated HG-PanIN lesions, paired PDAC and histologically suspected COD lesions were immunolabeled with antibodies to p53 and Smad4.

Results: COD was identified on H&E stained sections in 78 of 100 cases (78%, 95% confidence interval 69-86%). Immunolabeling for p53 and SMAD4 was performed in 48 cases with available tissue. The p53 was interpretable in both the invasive PDAC and COD components in 39 cases. All 39 cases showed a matching pattern of p53 immunolabeling between the invasive PDAC and the COD lesions, with 25 cases (64%) having aberrant p53 immunolabeling. The Smad4 was interpretable in both the invasive PDAC and COD in 45 cases. The pattern of Smad4 immunolabeling matched that seen in the paired COD lesions in 44 cases (98%). There was matched loss of Smad4 immunolabeling in both the invasive PDAC and COD components in 21 cases (47%). In one case, Smad4 labeling was lost in the invasive PDAC and retained in the COD.

Conclusions: Cancerization of the ducts was identified in 78% of the PDACs we studied. Among cases with interpretable immunolabeling, there was high concordance in the immunolabeling pattern of invasive PDAC and COD for p53 (39/39 cases) and Smad4 (44/45 cases) validating the high prevalence observed on H&E and highlighting the utility of p53 and Smad4 immunolabeling in the differentiation of COD and HG-PanIN.

1888 PAX8 Expression in Cholangiocarcinoma

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Background: Cholangiocarcinoma is the most common biliary malignancy & second most common hepatic malignancy after hepatocellular carcinoma. It may arise from a variety of cells: biliary epithelial cells, hepatic progenitor cells, or peribiliary glands. Cholangiocarcinoma has a high metastatic rate. A recent study reported 34% of cholangiocarcinoma cases present with metastatic disease. Therefore, cholangiocarcinoma must be considered in carcinomas of unknown primary. The diagnosis of cholangiocarcinoma is challenging and often requires a multidisciplinary approach that includes imaging as well as pathologic analysis.

PAX8 is a transcription factor that is involved in development of kidneys, thyroid, and organs of Müllerian derivation. The expression of PAX8 is believed to be evidence that a tumor has originated in one of these sites. The expression of PAX8 in cholangiocarcinoma remains undefined, with a few studies revealing mixed results. A study by Laury found PAX8 expression in 2/2 cholangiocarcinomas; however, a study by Tacha reported 0/5 cholangiocarcinomas expressed PAX8. The purpose of this study is to further examine the role of PAX8 immunohistochemistry in diagnosing cholangiocarcinoma.

Design: A retrospective review of 23 cholangiocarcinoma cases was performed. The cases were identified via a keyword search for "cholangiocarcinoma" in our pathology database. A representative section was taken from each case, and PAX8 immunohistochemical staining was performed. The pattern and intensity of PAX8 expression was evaluated by three reviewers: GI pathologist, surgical pathologist, and pathology resident.

Results: The 23 cases exhibited a broad spectrum of results in both PAX8 intensity and percent of tumor expressing PAX8. Most cases showed patchy expression and in a minority of tumor cells. 83% (19/23) of cases exhibited at least some expression of PAX8. Interestingly, of the four cases of intrahepatic cholangiocarcinoma included in the study, 75% (3/4) showed no PAX8 expression. These cases accounted for 75% (3/4) of all cases lacking PAX8 expression and suggest a difference in protein expression based on site of origin in the biliary tract tumors.

Conclusions: PAX8 is expressed, at least focally, in a majority of extrahepatic cholangiocarcinoma cases and a minority of intrahepatic cholangiocarcinoma cases. Our findings suggest that in small biopsy specimens, particularly from widely metastatic tumors of unknown origin, the finding of PAX8 expression does not exclude cholangiocarcinoma.

1889 Loss of Acetylated PBRM1 is Associated with Worse Survival in Pancreatic Ductal Adenocarcinoma - A Tumor Microarray Study

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Background: SWI/SNF is a chromatin remodeling complex whose components are mutated in >20% of pancreatic cancer. Somatic mutations of PBRM1, which encodes the targeting subunit of this complex, were also found in pancreatic cancer, and low expression of PBRM1 has been associated with worse survival. Yang lab has recently identified an acetylated form of PBRM1 - K1505Ac, which was found to be critical for PBRM1 to form a complex with other SWI/SNF components, thus serving as a marker for functional PBRM1 (unpublished data, H. Yang et al). We aim to investigate the incidence of loss of PBRM1 and AcPBRM1 in Pancreatic Ductal Adenocarcinoma (PDA), and whether their loss is associated with patient outcome.

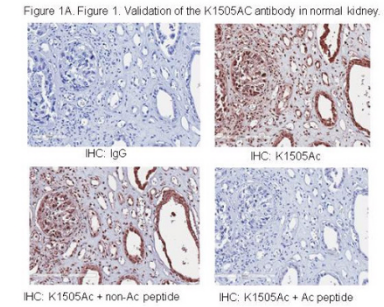
Design: Tissue Microarray (TMA) of PDA was created from 79 PDA surgical specimens in 2012-2013 from our institution. For each tumor, three dots (each 1 mm) are selected representing morphologic heterogeneity. Clinical and pathologic variables were analyzed (Table 1). Immunohistochemistry using PBRM1 antibody (Bethyl labs) and

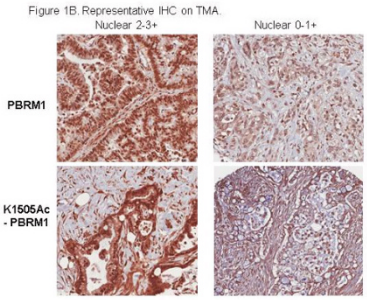
K1505Ac antibody (custom made against an acetylated peptide that corresponds to the c-terminal tail of PBRM1, Figure 1A). Two pathologists performed the scoring independently. Nuclear staining is scored as 0-3, and loss of staining for each tumor is defined as >5% tumor cells with 0-1+ in any one of the three tumor dots (Figure 1B). Standard statistical methods including Kaplan Meier were performed.

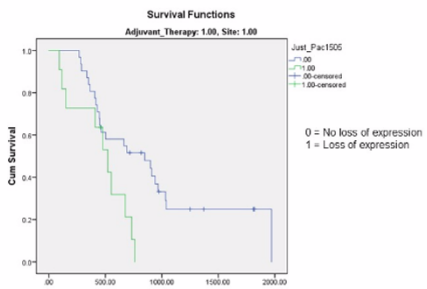
Results: Of 214 total 1 mm dots, loss of PBRM1nuclear staining in >5-50% cells was found in 49 (23%), in >50% cells in 19 (9%). Of 199 total 1 mm dots, K1505Ac loss in >5-50% cells was found in 53 (27%), in >50% cells in 51 (26%). Of 79 cases, 29% showed >5% loss of PBRM1 (n=23), all of which also showed loss of K1505Ac. 58% showed >5% loss of K1505Ac (n=46), indicating a more prevalent functional loss in PDA. The loss of expression of either showed no significant effect on survival, although in adjuvant therapy subgroup, loss of K1505Ac alone showed a trend with worse survival. In a subgroup of PDA within the head of pancreas who have received adjuvant therapy (n=42), loss of K1505Ac without protein loss showed association with worse survival (HR=2.624, p=0.016).

Table1. Clinicopathologic characteristics of the pancreatic ductal adenocarcinomas included in this study

Age (years)	Mean= 69 (range= 42 to 91)
Sex	M: F= 41:38
Race	White= 89%, African American= 8%, Asian= 2%, Hispanic= 1%
Smoker	58% (n=45/77)
Tumor size (cm)	Mean= 4 (range= 1.2 to 11.6)
Site	Head and/uncinated=72% (n=57/79), body= 5% (n=4/79), tail=7% (n=6/79), tumors involving > 1 site= 15% (n=12/79)
Tumor differentiation	Well= 4%(n=3/78), moderate= 73%(n=57/78), poor=23%(n=18/78)
Positive lymph node metastasis	76% (n=60/79)
Distant metastasis	2% (n=2/79)
Adjuvant therapy	77% (n=51/66)
Alive	30% (n=27)
Tumor stage (pT)	T1= 4% (n=3), T2=9% (n=8), T3= 86% (n=67), T4= <1% (n=1)
OS (days)	Mean=609 (range=12 to 1971)







Conclusions: An acetylated form of PBRM1 was lost in a subset of PDA, whose function seems to be associated with worse survival in resectable PDA with adjuvant therapy. Future studies are needed to explore K1505Ac PBRM1 as a potential biomarker for PDA therapy.

1890 Validation of the 8th American Joint Committee on Cancer Staging System for Distal Bile Duct Carcinoma

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Background: The T-category of the newly proposed 8th edition of the American Joint Committee on Cancer (AJCC) staging system for distal bile-duct carcinoma (DBDC) was changed to include tumor invasion depth measurement, while the N-category adopted a 3-tier classification system based on the number of metastatic nodes.

Design: To validate cancer staging, a total of 200 surgically resected DBDCs were staged and compared according to the 7th and 8th editions.

Results: T-categories included T1 (n = 37, 18.5%), T2 (n = 114, 57.0%), and T3 (n = 49, 24.5%). N-categories included N0 (n = 133, 66.5%), N1 (n = 50, 25.0%), and N2 (n = 17, 8.5%). Stage groupings included I (n = 33, 16.5%), II (n = 150, 75.0%), and III (n = 17, 8.5%). The overall 5-year survival rates (5-YSRs) of T1, T2, and T3 were 59.3%, 42.4%, and 12.2%, respectively. T-category could discriminate patient survival by both pairwise (T1 and T2, $P = 0.011$; T2 and T3, $P < 0.001$) and overall ($P < 0.001$) comparisons. The overall 5-YSRs of N0, N1, and N2 were 47.3%, 17.0%, and 14.7%, respectively. N-category could partly discriminate patient survival by both pairwise (N0 and N1, $P < 0.001$; N1 and N2, $P = 0.579$) and overall ($P < 0.001$) comparisons. The overall 5-YSRs of stages I, II, and III were 59.0%, 35.4%, and 14.7%, respectively. Stages could distinguish patient survival by both pairwise (I and II, $P = 0.002$; II and III, $P = 0.015$) and overall ($P < 0.001$) comparisons. On multivariate analyses, T- and N-categories ($P = 0.014$ and 0.029) and pancreatic invasion ($P = 0.006$) remained significant prognostic factors.

Conclusions: The T- and N-categories of the 8th edition AJCC staging system for DBDC accurately predict patient prognosis.

1891 Does Gene Expression in the Epithelial and Stromal Compartment of Resected Pancreatic Ductal Adenocarcinoma Allow for Prognostication?

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Background: It has been suggested that non-negative matrix factorization can be used to virtually micro-dissect stroma from the epithelial component in pancreatic ductal adenocarcinoma (PDAC). This method was used to discover a set of basal and classical genes (N~50), derived from the epithelial component where inferior prognosis was associated with increased expression of basal genes. We sought to confirm this prognostic finding using conventional laser capture micro-dissection (LCM) and explore whether the result was specific to the epithelium compared to the peritumoral stroma.

Design: A total of 96 patient samples, 47 with >=3 years (long term) and 49 with > 0.5 <= 1 year (short term) survival. These samples were interrogated by direct RNA expression quantification of 25 basal type genes and 23 classical type genes derived from the literature. LCM was used to segregate stromal from epithelial components and each was subjected to the assay. Data were normalized to a set of housekeeping genes and Log2 values for each component were subjected to unsupervised hierarchical clustering using Ward's algorithm. The resultant cluster classifications were subjected to univariable and multivariable disease specific survival (DSS) analysis.

Results: The clustering procedure yielded 3 distinct clusters within the epithelial and stromal components with n's ranging from 22 to 47 members. In the epithelial component (Fig 1), over-expression of the basal genes was observed in 2 clusters (n = 70) that were composed of 63% short term survivors compared to 19% in the cluster with lower expression of basal genes (p = 0.0005). In the stromal component (Fig 2), the basal genes showed a gradient of expression from high to intermediate to low. The corresponding prevalence of short term survivors also declined from 71% to 53% to 4% (p<0.0001). Univariable DSS for both the epithelial and stromal components demonstrated superior survival trends for those cases with low basal gene expression (p = 0.02 & p = 0.04 respectively). Multivariable DSS indicated that only the clustering derived from the stromal component was of independent prognostic significance.

Conclusions: These results suggest that basal gene expression in the epithelial component is a surrogate for clinico-pathologic factors with a negative prognostic effect. However, the negative prognostic effect of basal expression in stromal component is independent of clinico-

pathologic factors and is indicative of cases likely to have short term survival.

1892 The Importance of Complete Margin Submission in Assessment of True R1 Resection Status and Other Pathologic Data That Correlate with Patient Outcome in Whipple Specimens for Pancreatic Ductal Adenocarcinoma

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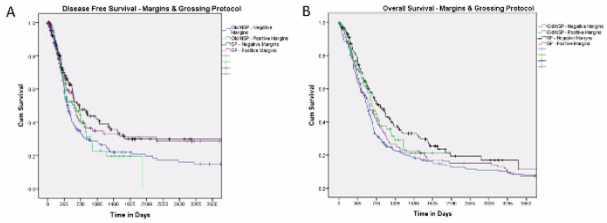
Background: Pancreatic ductal adenocarcinoma (PDAC) is notorious for its infiltrative pattern of invasion into desmoplastic stroma, complicated by the frequent presence of chronic pancreatitis in the surrounding parenchyma, which is exaggerated by neoadjuvant therapy. Moreover, the tumor spreads frequently by perineural invasion into the adjacent soft tissue, which is not grossly identified. These factors make evaluation of margin status very challenging. The purpose of our study is to compare complete submission of margins versus submission of representative margins as prognostic determinant in PDAC treated with Whipple procedure.

Design: At our institute, standard four-color inking for margin analysis (uncinate, neck, portal groove, posterior soft tissue) in Whipple specimens for PDAC is consistently used. A standardized grossing protocol (SP) using axial sectioning with complete surgical margin submission was instituted and systematically used between 6/1/2011-7/30/2016. At other times, other grossing techniques such as "bivalving" and "breadloafing" were used, with selective margin submission, taken grossly closest to the tumor. Two such cohorts selected for comparison with the "SP" group are designated as "Old NSP" (9/1/1997-12/31/2008), and "New NSP" (8/1/2016-9/1/2017). Clinical and pathologic data were retrieved from a prospectively maintained hospital database. Kruskal-Wallis test and Chi-square test were used to compare among the three groups, as appropriate, and Kaplan-Meier curve analysis with Mantel-Cox log rank test was used for survival studies, with significance set at $p < 0.05$.

Results: In all three study groups, the uncinate margin was the most frequently positive margin, followed by portal vein groove, posterior surface, pancreatic neck margin, and common bile duct margin, respectively. There was a significantly higher margin positivity (R1) rate, significant increase in mean total and positive lymph node counts, significantly higher rates of lymphatic, venous, and perineural invasion in the "SP" group as compared to both "Old NSP" and "New NSP" groups (see Table). Moreover, only in the "SP" group did the R1 and R0 status show a statistically meaningful correlation to survival (see Figure).

Variable	Old NSP (1997-2008)	SP (2011-2016)	New NSP (2016-2017)	P-Value
Median Lymph Nodes Examined	15	27	21.5	.000
Mean Lymph Nodes Examined	17.5 (9.8)	27.9 (11)	22.6 (9.5)	.000
Median Lymph Nodes Positive	2	3	1	.000
Mean Lymph Nodes Positive	2.5 (3.0)	4.8 (5.2)	3.3 (5.1)	.000
Positive Lymphatic Invasion	53.6%	69.7%	56.1%	.000
Positive Venous Invasion	41.3%	69.7%	56.1%	.000
Positive Perineural Invasion	77.2%	85.4%	78.9%	.025
Positive Surgical Margin Rate	26.4%	44.1%	28.1%	.000
Pancreatic Neck Margin Rate	5.1%	7.8%	1.89%	.146
Common Bile Duct Margin Rate	1.1%	1.2%	0.0%	.720
Uncinate Margin Rate	15.4%	30.9%	19.3%	.000
Portal Vein Groove Margin Rate	6.5%	29.3%	31.6%	.000
Posterior Margin Rate	4.6%	16.0%	8.8%	.000
Received Neoadjuvant Therapy	2.4%	27.3%	45.6%	.000



Conclusions: Submission of representative margins deemed closest to the tumor can lead to inaccurate pathologic reporting and under-staging of the disease. A standardized grossing protocol with comprehensive margin sampling directly influences patient care in Whipple specimens for PDAC.

1893 Prognostic Metabolic Signatures in Pancreatic Ductal Adenocarcinoma (PDAC).

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Background: Oncogenic mutant *KRAS* (*KRAS*^{mut}), present in over 90% of pancreatic ductal adenocarcinoma (PDAC), mediates tumour progression in part through metabolic reprogramming, including the induction of glycolysis. Metabolic subtypes including glycolytic and lipogenic, were identified in PDAC cell lines but their influence on clinical outcome is not known. We aimed to determine the clinical utility of metabolic gene signatures in PDAC, and their association with *KRAS*^{mut}.

Design: We accessed the TCGA and cBioPortal databases for expression data for glycolysis and cholesterol synthesis genes, *KRAS* mutation and copy number alteration, as well as survival data for 151 PDAC cases. The prognostic utility of metabolic subtypes was further investigated using an in-house tissue microarray (TMA) comprising 261 resected PDAC tumors with associated clinical outcome data.

Results: Hierarchical clustering of gene expression revealed the presence of distinct prognostic glycolytic (glyc) and cholesterogenic (chol) subtypes. Tumours with a 'low glyc/low chol' profile were associated with longest survival (median overall survival (MOS): 1.92 years, $p = 0.025$). Among 'high glyc' tumours, those with high expression of 'chol' genes did better than 'low chol' tumours (MOS: 1.30 vs. 0.76 years). 'High glyc/low chol' tumours had lowest levels of mitochondrial pyruvate carriers 1 and 2 (MPC1/MPC2), suggesting that reduced pyruvate uptake into the mitochondria may lead to increased lactate production and more aggressive phenotype observed in this subtype. Interestingly, 'high glyc/low chol' tumours had the highest prevalence of *KRAS*^{mut} copy gain (75% vs. 14% ('low glyc/low chol') and 17% ('high glyc/high chol')). TMA analysis showed that high co-expression of glycolytic proteins glucose transporter GLUT1 and lactate transporter MCT4 was a marker of poor prognosis.

Conclusions: Our findings indicate that PDAC outcome is dependent on the tumour metabolic subtype and that *KRAS*^{mut} copy gain may contribute to the subtype associated with worse prognosis. This underscores the significance of metabolic reprogramming in PDAC and suggests that therapeutic agents targeted at metabolic subtypes may improve outcome.

1894 Tumor Size Determination by Imaging Modalities Versus Gross Examination in Assessing the T-Stage of Pancreatic Ductal Adenocarcinoma

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Background: One of the major changes in the 8th edition of the AJCC Staging Manual for pancreatic carcinomas is to solely rely on tumor size to separate T1, T2 and T3 tumors. Specifically, a size cut-off of 2 cm is used to separate T1 from T2 and 4 cm is used to separate T2 from T3. Therefore, an accurate measurement of tumor size appears critical to T-staging. In this study, we assessed the difference between preoperative measurements of tumor size by imaging modalities (MRI, CT, EUS) versus gross examination on resected specimens and evaluated the impact of the difference on tumor staging.

Design: Pathology and Radiology database was retrospectively queried at our institution for patients who had undergone resection for pancreatic ductal adenocarcinoma between 2011-2017. Tumor sizes measured by most recent preoperative imaging studies and by gross examination were recorded. Cases without a recent imaging study or without a documented tumor size were excluded. Tumors were staged according to the new 8th edition AJCC manual.

Results: A total of 163 patients with resected pancreatic ductal adenocarcinomas were included in this study. Overall, the median tumor size measured by imaging studies was smaller than gross examination (2.4 cm vs 3 cm). This resulted in an altered T stage in 64 (39.3%) cases. In comparison with tumor size by imaging, 48 (29.5%) primary tumors were upstaged and 16 (9.8%) were downstaged by gross examination (Table 1). There was no T-stage change in the remaining 99 (60.7%) cases despite the presence of variable size discrepancies (ranging from 0.1 to 1.7 cm) noted in 87 (87.9%) cases. When nodal and distant metastases were also considered, only 8 (4.9%) cases were upstaged from IA to IB (4), IA to IIA (1) and IB to IIA (3), and only 2 (1.2%) were downstaged from IB to IA.

Table 1. Impact of size discrepancies on tumor staging (n=163)

Tumor stage	Imaging (%)	Gross examination (%)
T-stage		
T1	51 (31.3)	34 (20.9)
T2	101 (62)	97 (59.5)
T3	9 (5.5)	30 (18.4)
T4	2 (1.2)	2 (1.2)
Stage Group		
IA	16 (9.8)	13 (8)
IB	19 (11.7)	18 (11)
IIA	1 (0.6)	5 (3.1)
IIB	59 (36.2)	59 (36.2)
III	42 (25.8)	42 (25.8)
IV	26 (15.9)	26 (15.9)

Conclusions: Accurate measurement of tumor size for pancreatic ductal adenocarcinoma by gross examination can be difficult. Preoperative imaging studies provide an additive tool to help determine the tumor size and aid clinicians in formulating a treatment plan. Our data shows a general underestimation of tumor size by imaging modalities in comparison with gross examination on resected specimens. However, in only 6.1% of patients would the size discrepancy result in an altered tumor stage. For cases where the tumor size cannot be accurately assessed by gross examination, the imaging measurement may be safely referenced for tumor staging, particularly when nodal and/or distant metastasis is present.

1895 Impact of Changes in AJCC Staging Manual 8th Edition for Pancreatic Ductal Adenocarcinomas

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Background: Investigators have questioned the clinical relevance and reproducibility of previous AJCC T and N staging systems for pancreatic carcinomas. Concerns have centered on the definitions for T-stage, particularly the concept of ''extension beyond the pancreas''. The N classification has also been criticized because it has only included node-negative (N0) and node-positive (N1) categories. The changes to be implemented in the new AJCC 8th edition have focused on tumor size for T-stage and creation of an N2 category. The goal of the current study was to evaluate how these changes would affect T, N and overall tumor stages, if they would correlate with patient survival and if there would be any impact on decision-making for postoperative adjuvant therapy.

Design: Pathology and clinical follow-up database was retrospectively queried at our institution for patients who had undergone resection for pancreatic ductal adenocarcinoma between 2011-2017. Tumors were restaged according to the new definitions described in the 8th edition AJCC manual. Patient survival data were analyzed and hypothetical recommendations for adjuvant therapy were considered by gastrointestinal oncologists.

Results: A total of 200 patients with resected pancreatic ductal adenocarcinomas were included in this study. As shown in Table 1, when restaged using the AJCC 8th edition, 73% of cases were downstaged from T3 to T1 (a,b,c) and T2. Among the cases with positive lymph nodes, 41% were restaged as N2. The overall TNM stage was changed in 72 (36%) cases, upstaged in 44 (22%) and downstaged in 28 (14%). The vast majority of upstaged cases were from IIB to III (98%). All downstaged cases were from IIA to IA and IB. The average patient survival was 35.8, 19.8 and 16.2 months for T1, T2 and T3 diseases, respectively, according to the 8th edition There did not appear to be a significant survival difference between cases with N1 and N2 diseases. An assessment by a gastrointestinal oncologist hypothesized that a small number of patients (16.1%) who had received adjuvant therapy would not be recommended for the treatment based on new stages.

Table 1. Comparison of tumor stages between AJCC 7th and 8th editions (n=200)

Tumor stage	7th edition (%)	8th edition (%)
T-stage		
T1	12 (6)	44 (22)
T2	4 (2)	118 (59)
T3	182 (91)	36 (18)
T4	2 (1)	2 (1)
N-stage		
N0	54 (27)	54 (27)
N1	146 (73)	86 (43)
N2	Not applicable	60 (30)
Stage Group		
IA	8 (4)	17 (8.5)
IB	3 (1.5)	21 (10.5)
IIA	33 (16.5)	6 (3)
IIB	120 (60)	77 (38.5)
III	2 (1)	45 (22.5)
IV	34 (17)	34 (17)

Conclusions: The new staging system for pancreatic carcinomas allows for a fnier stratification of primary tumor staging, which appears to correlate with patient survival. However, only a small fraction of patients would be affected in terms of postoperative recommendation for adjuvant therapy.

1896 HHLA2 Expression Demonstrated by Immunohistochemistry in Non-Ductal Pancreatic Tumors

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Background: Immune checkpoint inhibition is a new therapeutic approach to cancer. Immune checkpoint inhibitors prevent tumor cells from inactivating T cells, which allows T cells to retain their effector function. HHLA2 is a recently discovered member of the B7 family of ligands in the immune checkpoint family which also includes PDL-1. It has been posited that HHLA2 may have both costimulatory and coinhibitory effects on T cells. HHLA2 is expressed in a high percentage of malignant epithelial tumors, including pancreatic adenocarcinomas, as described in the Human Protein Atlas. No study to date has analyzed HHLA2 expression in non-ductal pancreatic tumors. This study aims to investigate HHLA2 expression by immunohistochemistry in a range of non-ductal pancreatic tumors.

Design: Immunohistochemical staining for HHLA2 was performed using polyclonal rabbit antibody (clone HPA55478, Sigma Aldrich (St. Louis, MO), dilution 1:1000), on tissue microarrays of pancreas specimens from 81 patients, representing 59 pancreatic neuroendocrine tumors, 10 solid pseudopapillary tumors, 9 acinar carcinomas, and 3 pancreatoblastomas, as well as adjacent uninvolved tissue from each patient. Staining was scored as follows: <1% staining of tumor cells was considered negative, >1% was considered positive.

Results: Positive staining (range: 1-100%) was seen in 6/59 neuroendocrine tumors (10%), 4/9 acinar carcinomas (44%), 1/3 pancreatoblastomas (33%), and 1/10 solid pseudopapillary tumors (10%). Positive staining was also seen in rare, isolated, benign acinar cells, but represented <1% of the total cells. Weak positive staining was also noted in scattered benign pancreatic ducts, as has been previously reported.

Conclusions: HHLA2 expression may be seen immunohistochemistry in non-ductal pancreatic tumors, particularly those with acinar differentiation (acinar carcinomas and pancreatoblastomas). If the function of HHLA2 is confirmed as an immune checkpoint, HHLA2 expression may become useful in guiding therapy, if new therapeutic agents are developed along this pathway.

1897 Overexpression of Matriptase in Tumor Stroma is a Poor Prognostic Indicator of Extrahepatic Bile Duct Cancer

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Background: Extrahepatic bile duct cancer is a highly aggressive epithelial malignant neoplasm. Tumor associated stroma has been increasingly recognized to play an important role in many kinds of tumors including bile duct cancer. In the previous report, bile duct cancer cell recruit cancer-associated fibroblasts (CAFs), main component of tumor stroma, by secreting platelet-derived growth factor-D (PDGF-D) which needs serine proteases, such as matriptase, to behave as a ligand. However, the distribution, frequency, and prognostic value of PDGF-D and matriptase in extrahepatic bile duct cancer have not been clarified.

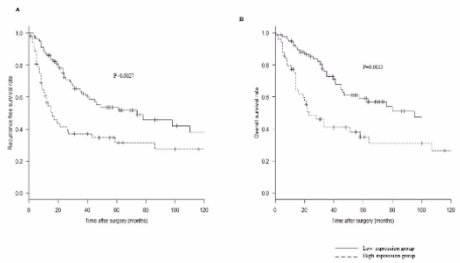
Design: We investigated the clinicopathological significance of expression of PDGF-D and matriptase in patients with extrahepatic bile duct cancer. The tumor samples were obtained from 257 patients who underwent the surgical resection between 1991 and 2015, and expression of PDGF-D and matriptase was evaluated immunohistochemically. Staining intensity and positive frequency were scored, and finally classified them into low and high expression group.

Results: Most cancer cells expressed PDGF-D and matriptase to a certain degree, whereas the expression of matriptase in cancer stroma was easier to divide into low and high expression group. High expression of matriptase in the cancer stroma was detected in 91 (40%) tumors. Stromal matriptase expression was significantly associated with lymph node metastasis (P=0.028), recurrence (P=0.013) and shorter survival time (P=0.00035). Stromal matriptase expression was also associated with significantly shorter recurrence-free survival time (RFS) and overall survival time (OS) (P=0.0027 and 0.0023, respectively). On multivariate analyses, stromal matriptase expression was determined to be an independent influential factor in RFS (P=0.0032) and OS (P=0.0021).

Prognostic factors according to a multivariate Cox proportional hazards regression model

	Variables	Hazard ratio (95% confidence interval)	Multivariate analysis P-value
RFS	Lymph node metastasis	1.8 (1.3-2.6)	0.00077
	Residual tumor	2.0 (1.4-2.9)	0.00013
	Matriptase expression in cancer stroma	1.7 (1.2-2.4)	0.0032
OS	Age	1.5 (1.0-2.2)	0.041
	Main location	1.5 (1.0-2.3)	0.045
	Lymph node metastasis	1.6 (1.1-2.4)	0.014
	Residual tumor	1.8 (1.2-2.8)	0.0065
	Matriptase expression in cancer stroma	1.8 (1.2-2.7)	0.0021

PDGF (platelet-derived growth factor), RFS (recurrence free survival), OS (overall suvival)



Conclusions: Stromal matriptase expression was strongly associated with tumor progression, recurrence and poor outcomes in patients with extrahepatic bile duct cancer, and may be an independent prognostic factor.

1898 Clinicopathologic Characteristics and KRAS Mutational Status of Forty-Eight Pancreatic Adenosquamous Carcinomas

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Background: Adenosquamous carcinoma of the pancreas (ASCP) is a rare histologic subtype of pancreatic exocrine neoplasm, accounting for 1-4% of all pancreatic exocrine tumors. This tumor has a highly aggressive behavior showing a worse prognosis than their adenocarcinoma counterpart. However, the histogenesis, clinicopathologic factors that might be associated with its aggressive behavior and molecular alterations remain unclear due to rarity of this tumor. In this study, we evaluate the clinicopathologic findings of 48 patients with ASCP who underwent a surgical resection and compared *KRAS* mutational status of 20 ASCPs with 100 pancreatic ductal adenocarcinomas (PDACs) to find any sharing *KRAS* mutation alterations between two tumors.

Design: All H&E stained slides from surgically resected 48 ASCPs and 100 PDACs with matched T category were reviewed. Immunohistochemistry for p53, cerbB2 and SMAD4 and a KRAS mutation testing covering codon 12, 13 and 61 by polymerase chain reaction were performed on selected whole tissue sections containing squamous cell carcinoma (SCC) component only and were analyzed.

Results: Patients with ASCP were diagnosed at the age of 63 years old with a male predominance (M: F=2:1). The proportion of the SCC component in ASCPs ranged from 40% to 95%. ASCPs demonstrated multiple worse pathologic factors such as high frequencies of lymphovascular invasion, direct splenic vessel invasion, positive microscopic radial margin, lymph node metastasis, distant metastasis at the time of diagnosis and early recurrence or distant metastasis within one year (p<0.05). 80% of patients with ASCP died of disease (survival time, 3 to 22 months). All ASCPs showed aberrant expression or loss of p53. Only one tumor showed strong and diffuse labelling of cerbB-2 (3+). Fourteen ASCPs had loss of SMAD4 expression. *KRAS* mutations were identified in 16 (80%) of 20 ASCPs. The most frequently mutated site was codon 12 (G12D/V) and followed by codon 61(Q61H).

Conclusions: In our study, ASCPs demonstrate multiple worse clinicopathologic factors which influence an aggressive behavior of this tumor compared to PDACs. In *KRAS* mutational analysis, 80% of ASCPs reveal frequent mutations of *KRAS* in codon 12, also frequently identified mutations in PDACs. Based on *KRAS* mutation profile, ASCPs harbor similar molecular alteration of *KRAS* with PDACs and suggest that the histogenesis of ASCPs may be similar or same with PDACs.

1899 Gene Expression Analysis of Pancreatic Solid Pseudopapillary Tumor Using RNA Sequencing

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Background: Pancreatic solid pseudopapillary tumor (PSPT) is an unusual pancreatic neoplasm of low malignant potential that most frequently affects young women. Genetic events contributing to the development of PSPTs are largely unknown except alterations of the APC/β-catenin pathway. In this study, we used RNA sequencing to perform more complete analyses to determine genetic alterations in PSPT.

Design: Transcriptome sequencing on formalin-fixed paraffin-embedded tissue of six resected PSPTs and paired normal tissue was performed. Sequencing reads were aligned using STAR against the HG38 reference genome, using the ENSEMBL reference release 78. Paired differential expression analysis was performed using edgeR and genes with a False Discovery Rate (FDR) less than 5% and fold change expression over 2 fold were selected. Ingenuity Pathway Analysis (IPA) was performed separately on the up and down regulated genes.

Results: Six patients with PSPT were composed of 5 women and 1 man with a median age of 38 years (range, 22-64). A median tumor size was 7.2 cm (range, 2.1-12.2). RNA sequencing revealed no significant gene fusion identified in PSPT. Principle component analysis and hierarchical clustering for each of the samples revealed they follow 2 distinct groups (tumor vs normal) according to the phenotype. The differential expression analysis (tumor vs normal) showed tumors harbor 2,177 genes up-regulated genes and 2,598 downregulated genes as compared to normal tissue when using an FDR<0.05 and fold change over 2 fold. Among them, the top 5 up-regulated genes were *DKK4, SPOCK, APCDD1, MME,* and *C10orf90* and down-regulated genes were *PDE8B, MLK4, KIAA1244, MST1L,* and *ATHL1*. IPA revealed that pathways related to primary immunodeficiency (13 out of 48 genes, p<0.001) and WNT/beta-catenin signaling pathway (23 out of 172 genes, p=0.027) were upregulated while the STAT3 pathway (22 out of 74 genes, p<0.001) and the ERK/MAPK signaling pathways (40 out of 199 genes, p<0.001) were downregulated in PSPTs.

Conclusions: We demonstrated that PSPTs did not harbor gene translocation and showed upregulation of the WNT signaling pathway which parallels a previously described finding that somatic mutations of *CTNNB1* are found in almost all PSPTs. Further analyses to identify expressed single nucleotide variants and tissue specific gene expression profile from transcriptome sequencing data are on the way.

1900 Full Cross Sections Can Facilitate Tumor Size Assessment in Pancreatic Ductal Adenocarcinoma for the 8th Edition of the AJCC Staging Manual

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Background: Compared to the 7th Edition tumor stage, which was based on both size and extent of invasion, the updated versions of AJCC tumor staging protocols (8th edition) are based on the tumor size. However, therapy-induced fibrosis commonly occurs in pancreatic ductal adenocarcinoma (PDAC) after neoadjuvant treatment and makes it difficult to assess the tumor size by gross measurement alone. We therefore compared the tumor size by gross assessment and microscopic measurement on full cross sections of the tumor.

Design: Prospective, continuous collection of thirteen patients with PDAC (5 women and 8 men with a median age of 68 years) was included in the study. These included 5 patients who had neoadjuvant therapy (3 women and 2 men with a median age of 68 years), and 8 patients had pancreatoduodenectomy (PD) without neoadjuvant therapy (2 women and 6 men with a median age of 68 years). The size of tumor was determined first by gross measurement, and then by microscopic measurement of the largest dimension of tumor on a full cross-section slide. The tumor stage was graded according to the

7th and 8th editions of the AJCC tumor staging manuals, respectively.

Results: Compare to 7th edition stage which all were T3 cancer, the new edition stage protocol showed 23% T1, 69% T2, and 8% T3. In PDAC without neoadjuvant therapy, there is a good consistency by the new tumor staging using tumor size determined either by gross or microscopically by full cross section assessment. However, for PDAC with neoadjuvant therapy, the tumor size measured microscopically on a full cross-section slide and by gross assessment showed discrepancy in tumor staging in two of five (40%) patients.

Conclusions: The 8th AJCC tumor staging for pancreatic ductal adenocarcinoma offers better stratification for tumor staging which correlated with patient survival (Crippa et al., 2016). In patients received neoadjuvant therapy, full tumor cross sections are critical for accurate tumor size assessment because of various amount of treatment-related fibrosis.

1901 Immunohistochemical Evaluation of PAX-6 in Neuroendocrine and Non-neuroendocrine Tumors from Various Organs

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Disclosures:
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Background: Metastatic neuroendocrine carcinomas can be diagnosed by morphology, and confirmed by neuroendocrine markers if necessary; however, the identification of tumor origin can be challenging. PAX6, a transcription factor known to be crucial for differentiation and function of islet cells and endocrine cells in gastrointestinal tract, was reported to be expressed in pancreatic neuroendocrine tumors (PNETs). However, data are limited for its expression in neuroendocrine tumors (NETs)/non-neuroendocrine tumors (non-NETs) arising from various organs. In this study, we immunohistochemically evaluated PAX6 expression in 996 cases of NETs and non-NETs using the Leica Bond III staining platform.

Design: Immunohistochemical evaluation of PAX6 (AC-0310RUO, 1:150, Epitomics, Inc.) was performed on 996 cases of NETs and non-NETs from various organs including NETs of lung (LNET), PNET, stomach/duodenum (Stom/Duo), ileum, appendix and rectum on tissue microarray (TMA) sections. The staining intensity was recorded as strong (S) or weak (W); the distribution were recorded as negative (<5% cell staining), 1+ (5-25%), 2+ (25-50%), 3+ (50-75%) and 4+ (>75%).

Results: The staining results are summarized in Table 1. PAX6 expression was identified in PEN (94%), rectal NET (87%), small cell carcinoma (SmCC) of the urinary bladder (34%), squamous cell CA (SqCC) of lung (43%) and papillary serous CA (PSC) of ovary (27%); rare W, focal in NET of appendix, low grade (LG) LNET, SqCC of ENT, endometrial CA, urothelial CA and mesothelioma.

Table 1. Summary of PAX-6 Immunostaining Results on 996 Cases

Tumors (N)	1+ W/S	2+ W/S	3+ W/S	4+ W/S	Pos % (N)
PEN (16)/LMet (2)	0/0	0/0	0/1	0/16	94% (17/18)
NET, Rectum (15)	0/0	1/0	1/4	0/7	87% (13/15)
NET, Appendix (9)	0/0	0/1	0/0	0/0	11% (1/9)
NET, Ileum/Duo/Stom (29)/ LMet (10)	0/0	0/0	0/0	0/0	0% (0/39)
LNET/LG (24)	1/0	0/0	0/0	0/0	4% (1/24)
LNET/HG (27 SmCC&LCC)/ Met (11)	0/0	0/0	0/0	0/0	0% (0/38)
NET, Bladder, SmCC (32)	0/0	2/3	0/4	0/2	34% (11/32)
PSC, Ovary (41)	1/0	1/4	0/5	0/0	27% (11/41)
ADC, endometrium (60)	1/0	0/2	0/0	0/0	5% (3/60)
SqCC, ENT (49)	3/0	1/1	0/0	0/0	10% (5/49)
SqCC, Lung (21)	0/0	4/0	0/5	0/0	43% (9/21)
Mesothelioma (17)	1/0	0/0	0/0	0/0	6% (1/17)
Urothelial CA (88)	2/0	0/0	0/0	0/0	2% (2/88)
ADC of lung, breast, colon, esophagus and prostate (248); Hepatocellular CA (39); CCRCC and PRCC (111); Thyroid CA (88); Bone Marrow (12), Melanoma (47)	0/0	0/0	0/0	0/0	0% (0/545)

N: number of cases; LMet: liver metastasis; HG: high grade; LCC: large cell CA; ADC: adenocarcinoma; CCRCC: clear cell RCC; PRCC: papillary RCC.

Conclusions: Our data demonstrate that PAX6 is a sensitive and relatively specific biomarker for PNETs and rectal NETs when encountering a NET with LG morphology. PAX6 may help to distinguish SmCC of the bladder from the lung. Caution should be exercised when interpreting PAX6 expression in a tumor presenting with focal weak staining.

1902 Concordance of Tumor Regression Grade After Neoadjuvant Therapy for Locally Advanced/ Borderline Resectable Pancreatic Cancer (LA-PDAC)

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Background: An increasing number of patients with LA-PDAC have been treated with neoadjuvant therapy. Pathology assessments on the treatment effect may be important to predict patient outcomes after pancreatectomy. There are two grading systems often used to assess tumor regression, and a new system has been put forth by the Japanese pancreas society (JPS); however, interobserver concordance along with the prognostic value of those have not been well studied.

Design: The study cohort consisted of 85 LA-PDAC patients treated with post-neoadjuvant pancreatectomy. Gemcitabine and S-1 (GS)-based chemotherapies +/- radiation were used for the vast majority. Two observers reviewed post-neoadjuvant resections to assess residual tumor using the following grading systems: 1) College of American Pathologists (CAP) that evaluates the amount of residual cancer cells in correlation with fibrosis, 2) Evans that evaluates the fraction of necrotic cells among residual cancer cells and 3) JPS that combines the CAP and Evans systems. Interobserver concordance was compared between the 3 systems, and recurrence free survival (RFS) and disease specific survival (DFS) were correlated to the grades with each system.

Results: The interobserver agreement of CAP (68.0%) was significantly higher than those of Evans (50.4%) and JPS (47.8%). When the scores were dichotomized (no or minimal residual tumor vs. moderate or minimal/no response), the interobserver agreement (99.1%) and kappa value (0.88) of Evans were higher than those of CAP (96.5% and 0.65) and JPS (97.1% and 0.71). As for the prognosis, pathologic response was not correlated to RFS or DSS with any of the 3 systems.

Conclusions: Although the 3 grading systems have substantial to almost perfect interobserver concordance when the scores are dichotomized, neither system appears to be predictive of patient outcomes after resection post GS-based neoadjuvant therapy for LA-PDAC. Larger-cohort studies to further evaluate the prognostic value of the grading systems as well as to establish more accurate assessments on residual tumor, possibly with biomarkers, are warranted.

1903 Pancreatobiliary Maljunction-Associated Gallbladder Cancer is as Common in the West as in the East, Shows Distinct Clinicopathologic Characteristics and Offers an Invaluable Model for Reflux-Associated Physio-Chemical Carcinogenesis

Takashi Muraki[1], *Burcin Pehlivanoglu*[2], *Bahar Memis*[3], *Michelle Reid*[4], *Takeshi Uehara*[5], *Olca Basturk*[6], *David Klimstra*[7], *William R Jarnagin*[8], *Jennifer S Golia Pernicka*[9], *Tetsuya Ito*[10], *Osamu Hasebe*[11], *Shinji Okaniwa*[12], *Naoto Horigome*[13], *Takeshi Hisa*[14], *Pardeep Mittal*[8], *Shishir Maithel*[8], *Juan M Sarmiento*[3], *Alyssa Krasinskas*[2], *Jill Koshiol*[15], *Gwen Lomberk*, *Raul Urrutia*, *Susan Tsai*, *Kathleen K Christians*, *Douglas Evans*, *N. Volkan Adsay*[16]. [1]Alpharetta, GA, [2]Emory University, Atlanta, GA, [3]Emory University, [4]Emory University Hospital, Atlanta, GA, [5]Shinshu University School of Medicine, Matsumoto, [6]MSKCC, New York, NY, [7]Memorial Sloan-Kettering, New York, NY, [8]MSKCC, [9]Memorial Sloan Kettering Cancer Center, New York, NY, [10]Shinshu University, [11]Nagano Municipal Hospital, Nagano, [12]Iida Municipal Hospital, Iida, Nagano, [13]Iida Municipal Hospital, [14]Saku Center Hospital, [15]NIH/NCI, [16]Medical College of Wisconsin, Milwaukee, WI

Background: In Asia, pancreatobiliary maljunction (PBM; supra-Oddi union of CBD and MPD; "long common channel") has been shown to be associated with a "200-fold" increased risk of gallbladder cancer (GBC) such that they are integrated into population screening protocols, and prophylactic cholecystectomies are often performed. This risk is attributed to reflux of pancreatic enzymes. PBM is largely un-recognized in the West.

Design: Radiologic images of 840 patients in the U.S., who

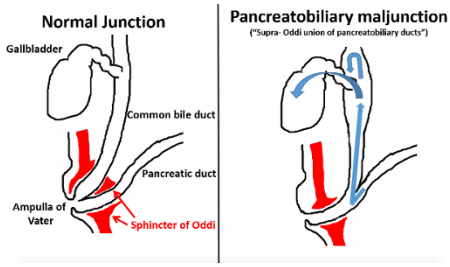
underwent pancreatobiliary resections for various disorders, were carefully reviewed in order to identify the GBCs associated with PBM. Detailed clinicopathologic analyses of these cases were performed in comparison with non-PBM cases.

Results: PBM was found in 8% of GBCs (24/300) in the U.S., a frequency similar to that in Japan (15/171, 8.8% p=0.770). Additionally, 1/42 distal bile duct carcinoma and 5/33 choledochal cysts disclosed PBM. Interestingly, none of the PBM cases had been diagnosed as PBM in the original radiologic work up in US. PBM was not found in 465 other pancreatobiliary disorders. Detailed clinicopathologic analysis of the 39 PBM-associated GBCs revealed that they occurred predominantly in females (F/M=3); manifested at a younger age (21% of the cases younger than 50, vs 6.5% in non-PBM GBCs; p=0.012); had less association with gallstones (14%, vs 58%); arose in intracholecystic papillary tubular neoplasm (ICPN)(31% had ICPNs, vs 12%; p=0.017); and possessed a higher rate of non-conventional carcinomas such as neuroendocrine, squamous, mucinous and others (21%, vs 7%; p=0.032). Peri-tumoral inflammation, especially lymphocytic, was more common (69, vs 44%; p=0.038). T-stage at presentation and survival rates were similar. PBM-associated GBCs from Japan and the U.S. showed similar characteristics.

Table. The clinicopathological characteristics of pancreatobiliary maljunction –associated gallbladder carcinomas.

	GBC cases with PBM (n=39)	GBC cases without PBM (n=73)	P value
Age, mean (range)	63 (34-81)	67 (34-95)	0.069
Gender, female, n (%)	30 (77%)	49 (67%)	0.279
Gallstones, n (%)	5/35 (14%)	38/66 (58%)	<0.001
ICPN, n (%)	12 (31%)	9 (12%)	0.017
Non-conventional carcinomas (n%)	8 (21%)	5 (7%)	0.032

PBM: pancreatobiliary maljunction, GBC: gallbladder carcinoma.
ICPN: Intracholecystic papillary-tubular neoplasms.



Conclusions: PBM has a strong association with gallbladder/biliary cancers. It accounts for 8% of GBCs, and is equally common in US and Japan. PBM is present in a substantial percentage of young patients with GBC. PBM-GBCs often develop through adenoma-carcinoma sequence and culminate in unusual carcinoma types. If PBM is encountered, prophylactic cholecystectomy and evaluation of bile ducts is warranted. PBM-associated GBCs offer a novel model for chemical (refluxed pancreatic enzyme)-related carcinogenesis, which may have far-reaching implications in understanding cancer formation in the PB tract.

1904 Fine Needle Aspiration (FNA) Biopsy Is Safe To Perform On Pancreatic Body/Tail Adenocarcinomas: An Analysis Of 132 Resected Cases Reveals That Prior FNA Does Not Alter Clinical Outcome In Body/Tail Carcinomas

Takashi Muraki[1], *Michelle Reid*[2], *Burcin Pehlivanoglu*[3], *Bahar Memis*[4], *Yue Xue*[2], *Alyssa Krasinskas*[3], *Daniel Abbott*[5], *Serdar Balci*[6], *Bryan Hunt*[7], *Tamar Giorgadze*[8], *Juan M Sarmiento*[4], *Susan Tsai*[8], *Kathleen K Christians*[7], *Douglas Evans*[7], *N. Volkan Adsay*[7]. [1]Alpharetta, GA, [2]Emory University Hospital, Atlanta, GA, [3]Emory University, Atlanta, GA, [4]Emory University, [5]Medical College of Wisconsin Affiliated Hospitals, Milwaukee, WI, [6]Ankara, Ankara, Turkey, [7]Medical College of Wisconsin, Milwaukee, WI, [8]Medical College of Wisconsin, Milwaukee, WI, [9]Medical College of Wisconsin

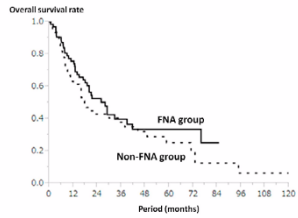
Background: In Japan and some other parts of the world performing fine needle aspiration (FNA) biopsy on pancreatic ductal adenocarcinoma (PDAC) in the pancreatic body/tail is contraindicated due to fear of iatrogenic tumor spread along the needle tract which is not routinely included in the subsequent resection (unlike PDACs of the head where the duodenum/needle-tract is part of the pancreatoduodenectomy).

Design: Records of patients diagnosed with pancreatic tail PDAC who underwent distal pancreatectomy with curative intent were reviewed. Only cases with ordinary PDAC were included. Other tumor types (including IPMN/MCN-associated PDACs) were excluded.

Results: Of the 132 patients who qualified and had adequate information regarding previous work-up, 68 had undergone FNA and 64 had not. Both groups had similar baseline clinicopathological characteristics (i.e, there did not seem to be any specific selection bias). [table1] The survival of the group that had received FNA (1/3 yr surv, 76/40%) was not significantly different than the non-FNA group (1/3 yr surv, 63/38%; p=0.289). [figure1] There was also no survival difference between 59 patients with "positive" (for PDAC) or "suggestive" diagnosis on FNA versus 9 patients with a "negative" FNA diagnosis (1y/3y surv, 76/41% vs 71/29%, p=0.375).

Table. Characteristics

	FNA group (n=68)	Non-FNA group (n=64)	p-value
Age, years±SED	66.6±1.4	67.8±1.3	0.736
Gender, male n (%)	35 (51%)	31 (48%)	0.728
Size, cm±SED	3.6±0.3	4.0±0.3	0.170
T-stage			0.433
T1	12	5	
T2	12	12	
T3	40	42	
T4	4	4	
unknown	0	1	
Nodal metastasis, n (%)	28/67 (42%)	31/63 (49%)	0.396
Margin positive, n (%)	8 (12%)	12 (19%)	0.263



Conclusions: We failed to identify any difference in survival between patients with resected pancreatic body/tail PDAC who had previously undergone FNA versus those who had not (despite positive/suspicious versus negative FNA diagnoses). Considering the innumerable benefits of preoperative FNA diagnosis, and the limited and mostly anecdotal evidence for tumor track seeding by FNA in the literature, our study supports the applicability of FNA in patients with pancreatic body/tail PDACs.

1905 Low Union (Lower Insertion of Cystic Duct into Common Hepatic Duct) as a Major Etiologic Factor in the Development of Pancreatic, Distal Bile Duct and Ampullary Cancers: An analysis of 860 pancreatobiliary resections

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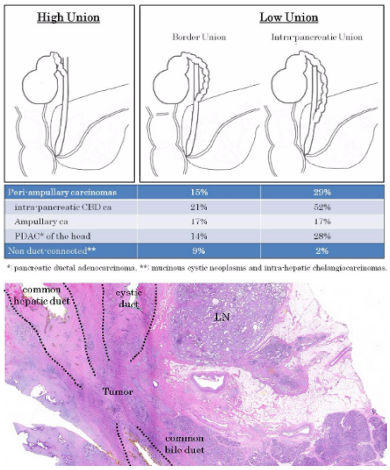
Background: Pancreatic/biliary cancers are the 3rd leading cause of cancer deaths in the US. Except for rare genetic disorders which account for a minor percentage, their etiopathogenesis is unknown. Uncommon anatomic/congenital variations such as pancreatobiliary maljunction and choledochal cysts are now established risk factors, emphasizing the role of altered chemical milieu in carcinogenesis.

Design: The role of another anatomic variation, low union of the cystic duct with hepatic duct (intra-pancreatic or within 5 mm of pancreatic edge) was investigated by retrospective review of 860 patients who underwent pancreatobiliary resections for various disorders.

Results: Low union was significantly higher (44%) in patients with peri-ampullary cancers (73 % of distal-CBD, 42% of pancreatic head and 34% of ampullary cancers). In contrast, low union was less frequent (~ 10 %) in conditions with no connection to the ductal system and thus no exposure to the same milieu (mucinous cystic neoplasms and intra-hepatic cholangiocarcinomas (CC); p<0.001). More specifically, intra-pancreatic low union was seen in 16% of peri-ampullary cancers (distal-CBD 30%, ampullary 17%, and pancreatic 13%) versus 2% in the non-duct connected group (p<0.001). Intra-pancreatic union was only rarely associated with hilar CC (2%; vs 30% in distal-CBD ca, p=0.0001) (figure 1). In pancreatoduodenectomies with intra-pancreatic union, tumor often extended from the junction and grew distally (figure 2). While the size of invasive carcinoma was slightly larger in low union-associated PDACs (32.3mm vs 27.8, p=0.005), no survival difference

was identified.



Peri-ampullary carcinomas	15%	25%
intra-pancreatic CBD ca	21%	52%
Ampullary ca	17%	17%
PDAC* of the head	14%	28%
Non duct-connected**	9%	2%

* pancreatic ductal adenocarcinoma, ** mucinous cystic neoplasms and intra-hepatic cholangiocarcinomas.

Conclusions: This study highlights the previously unrecognized relationship between an anatomic variation of the biliary tract, i.e. low union (of cystic duct and common hepatic duct), and pancreatobiliary cancers, and points to bilious carcinogenesis as an important culprit. This parallels recent literature on carcinogenetic effect of altered bile acids and may explain the much higher frequency of PDAC in the head. Moreover, seemingly unexplainable recently discovered risk factors for pancreas cancer (such as edentulism/periodontitis, cholecystectomy and peptic ulcer disease) may exert their effect through alteration of bile activity as in low union, bring new perspectives to pancreatobiliary carcinogenesis and offer potential mechanisms for prevention.

1906 Keratins and p63 Immunohistochemical Markers Predict the Basal Molecular Subtype in Pancreatic Ductal Adenocarcinoma

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Background: Pancreatic ductal adenocarcinoma (PDAC) is a deadly tumour with a 5-year survival rate of <5%. Transcriptional analyses have identified multiple molecular subtypes of PDAC. One subtype in particular is associated with more aggressive behaviour and linked to acquiring a basal molecular programme. Herein, we performed a morphological analysis and specific immunohistochemical panel to identify the basal molecular subtype of PDAC.

Design: Using RNAseq data from 168 primary PDACs, two molecular subtypes (basal and classical) were identified by non-negative matrix factorization. Eight representative basal (BTs) and classical tumours (CTs) were selected. Immunohistochemistry IHC was performed for basal markers (CK5, CK14, P63, delta P63) and MUC5AC. The proportion of positive staining cells within the tumour was quantified as <25%, 25-50%, 51-75% and >75%.

Results: Of 8 BTs, 3 (38%) showed an adenosquamous (ADSQ) morphology, 4 (50%) were poorly differentiated (PoorD) and 1(12%) was moderately differentiated (ModD). All ADSQ cases were positive for 4/4 basal markers with >75% staining in all cases. PoorD tumour showed positivity for 2/4 basal markers in 3 cases and 3/4 basal markers in 1 case with a variable proportion of staining between the markers. The ModD tumour showed positivity for only 1/4 basal markers with <25% of staining. (see Table 1). All CTs were uniformly negative for basal markers and showed only patchy staining for MUC5AC (<25 in 87% of cases). The positive markers together with the proportion of staining seen in BTs were directly proportional to the TPM (*transcripts per million)* levels of the corresponding genes by gene expression.

Morphological phenotype and basal immunohistochemical marker staining in PDAC identified by gene expression profiling.

Cases	Morphological subtype	CK5	CK14	p63	Delta p63
1	Adenosquamous	>75%	>75%	>75%	>75%
2	Adenosquamous	>75%	>75%	>75%	>75%
3	Adenosquamous	>75%	>75%	>75%	>75%
4	Poorly diff PDAC	>75%	25-50%	<25%	Negative
5	Poorly diff PDAC	51-75%	Negative	<25%	Negative
6	Poorly diff PDAC	<25%	Negative	51-75%	Negative
7	Poorly diff PDAC	51-75%	Negative	25-50%	Negative
8	Mod diff PDAC	51-75%	Negative	Negative	Negative

Conclusions: Our study highlights that using a specific panel of basal IHC markers will accurately predict the basal molecular subtype of PDAC. The greater proportion of staining and number of IHC markers involved may reflect a more aggressive tumour behaviour. To the best of our knowledge this is the first study of its kind to morphologically and immunohistochemically distinguish a molecular subtype in PDAC.

1907 Analysis of Voluntary Extramural Second Opinions in Pancreatobiliary Pathology: A Multicenter Study

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Background: Pancreatobiliary (PB) pathology presents numerous diagnostic challenges. The diagnostic issues leading to extramural consultation in this area have not been specifically examined. Characterization of the diagnostic issues facing pathologists in PB pathology is of value for developing educational material or new diagnostic adjuncts for practicing pathologists.

Design: We collected data from consecutive gastrointestinal (GI), liver and PB extramural consults received by GI/Liver pathologists from 6 academic medical centers over the time period 2016 to 2017.

Results: The total GI consult volume included 1203 cases. There were 82 PB cases (5% of total) including 33 pancreatic, 23 gallbladder, 20 ampulla and 6 bile duct specimens. The majority of cases (65%) were needle core biopsy specimens. Patient ages ranged from 18 to 87. For the pancreas, 23 of 33 cases (70%) were submitted with questions on tumor classification and the final diagnoses included the less common types of pancreatic tumors such as undifferentiated carcinoma with osteoclast-like giant cells (n=1), solid pseudopapillary neoplasm (n=2), carcinomas with squamous differentiation (n=2), and acinar carcinoma (n=1) or pancreatic involvement by other tumors such as melanoma, GIST or Hodgkin's lymphoma (n=1 each). The most common query for the remaining cases (5 of 10) was in regard to autoimmune pancreatitis. For the gallbladder, 17 (74%) cases were submitted with regard to presence or degree of dysplasia or presence of adenocarcinoma. For the ampulla, the concern in 80% of cases (16 of 20) was with regard to the presence or degree of dysplasia and the final diagnoses for 13 of 16 cases were reactive atypia. Five of 6 bile duct specimens were sent with queries concerning the presence of dysplasia. Three of these were reactive and 2 were indefinite for dysplasia. Additional immunohistochemical stains were performed in 21 of total 82 cases (26%) and were mostly done for classification of pancreatic tumors.

Conclusions: Extramural consultation in PB pathology is most often related to tumor classification and evaluation for dysplasia. Our data indicate that pancreatic tumor classification on biopsies is a particular challenge, and the most common dilemma in the biliary tree and ampulla is distinguishing reactive atypia from dysplasia and the most common error is to overinterpret reactive changes as dysplasia. Educational programs and the development of ancillary tools can improve this by targeting these areas of focus.

1908 Immune Microenvironment in Gallbladder Adenocarcinomas

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Background: Immune microenvironment is gaining increasing importance in malignancy, particularly with therapeutic uses of PD1/PD-L1 checkpoint blockade. Our search of literature did not reveal studies on programmed death-ligand 1 (PD-L1) and programmed cell death 1 (PD1) expression in gallbladder adenocarcinomas. In this study we examined PD-L1 expression in tumor, and tumor infiltrating lymphocytes (TIL) positive for PD1, CD3 and CD8 in gallbladder adenocarcinomas.

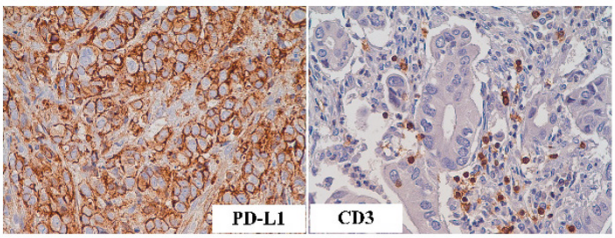
Design: We queried our records for gallbladder adenocarcinomas diagnosed from 2001 to 2017. Forty-four cases were included, and cases with other malignancies or pre-operative chemotherapy were excluded. Slides were reviewed to select 3 cores of tumor per case for tissue microarray. Clinicopathological parameters were recorded. Immunohistochemical staining for PD1, PD-L1, CD3 and CD8 was performed. PD-L1 membranous expression in >1% tumor cells was considered positive and scored as follows: 1+, >1 to 25%; 2+, 25 to 50%; and 3+, >50%. TILs were counted per 100 epithelial cells and in the stroma per high power field. Statistical analysis was performed with SAS software.

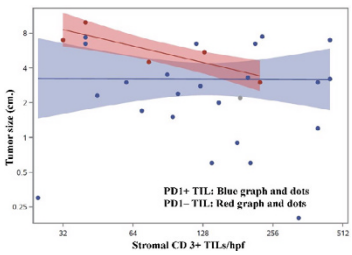
Results: 98% (43/44) cases were PD-L1+ with 84% cases being PD-L1

3+ (see table 1) [Table 1]. Figure 1 is representative image of PD-L1 and CD3+ TILs [Figure 1]. In PD-L1+ tumors, time to metastases or death of disease did not differ between PD1+ and PD1- TILs. CD3+ cells (100±6.5) in stroma of PD-L1+ tumors with PD1+ TILs were significantly higher than in PD-L1+ tumors with PD1- TILs (77±21.8). However, there was no significant difference in epithelial CD3+ and CD8+ TILs, stromal CD8+ TILs, lymphovascular invasion, or pathological stage between PD1+ and PD1- TIL cases. In PD1- TIL cases (figure 2 red graph), increasing CD3+ TIL counts and increasing CD3+/CD8- TIL counts in stroma correlated with reduced tumor size (p=0.002 and p=0.029, respectively) [Figure 2]. In PD1+ TIL cases (figure 2 blue graph), however, CD3+ and CD8+ TILs had no correlation with tumor size.

Table 1: Clinicopathological features of gall bladder adenocarcinomas and expression of immune microenvironment biomarkers.

Parameter	Gallbladder adenocarcinomas, all cases (n=44)
Age median (range)	70 years (37-92)
Sex Male, Female n (%)	11 (25), 33 (75)
Tumor Size median (range)	3 (0.2-10.0)
Grade n (%)	
1	10 (23)
2	12 (27)
3	22 (50)
Lymphovascular invasion n (%)	18 (41)
Perineural invasion n (%)	13 (29)
Stage n (%)	
T1	4 (9)
T2	28 (64)
T3	11 (25)
T4	1 (2)
Lymph node	
Positive	6 (14)
Negative	11 (25)
No lymph nodes submitted	27 (61)
Metastases n (%)	16 (36)
Death of disease n (%)	7 (16)
Cholelithiasis n (%)	41 (93)
Cholecystitis n (%)	41 (93)
Post-operative Chemotherapy n (%)	21 (48)
Post-operative Radiation n (%)	5 (11)
PD-L1 n (%)	43 (98)
Score1+	1 (2)
Score 2+	5 (11)
Score 3+	37 (84)
PD1+ n (%)	37 (84)
CD3+ TILs median (range)	
Per 100 epithelial cells	4 (1-100)
Stroma per high power field	117 (25-450)
CD8+ TILs median (range)	
Per 100 epithelial cells	2 (0-80)
Stroma per high power field	50 (6-450)





Conclusions: PD-L1 is expressed in 98% of gallbladder adenocarcinomas. Stromal CD3+ cells in PD-L1+ tumors with PD1+ TILs are significantly higher than in PD-L1+ tumors with PD1- TILs. Stromal CD3 TILs and CD3+/CD8- TILs correlated with reduced tumor size in PD-L1+ tumors with PD1- TILs. This finding supports the important role of immune system against these tumors. Our study indicates an immense potential for immune based therapies targeted at the PD1/PD-L1 checkpoint blockade in gallbladder adenocarcinomas.

1909 BAP1 Loss in Cholangiocarcinoma is Strongly Associated with Tumor Site

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Background: BRCA1-associated protein 1 (BAP1) is a nuclear deubiquitinating enzyme involved in chromatin remodeling and functions as a tumor suppressor gene. Cholangiocarcinomas (chca) are malignant neoplasms arising from biliary epithelium and generally carry a poor prognosis. Chca can be divided based on their site of origin into intrahepatic, perihilar, and distal bile duct carcinomas—each of which is staged by a distinct cancer protocol. Recently, intrahepatic chca have been shown to harbor a loss of function mutation in BAP1, and exhibit loss of BAP1 immunohistochemical (IHC) expression in up to 26% of cases. Loss of BAP1 is associated with a better prognosis (both recurrence-free and overall survival). Importantly, loss of BAP1 by IHC can help identify patients who may benefit from treatment with histone deacteylase inhibitors. To date, there has been no study of BAP1 IHC expression in distal chca and only minimal data in perihilar chca. We therefore sought to establish the frequency of loss of BAP1 IHC expression in distal chca, compare this frequency of BAP1 IHC loss to that in intrahepatic and perihilar chca, and further characterize the grade and morphology of chca exhibiting loss of BAP1 IHC.

Design: Staining for BAP1 was performed on tissue microarrays of 102 carcinomas arising from the intrahepatic (38 cases), perihilar (35 cases), or distal (29 cases) bile duct. Positive staining was defined as a minimum of 5% of tumor cells with nuclear staining. Negative staining was defined as complete loss of nuclear staining. Non-neoplastic bile ducts and tumor infiltrating lymphocytes served as internal positive controls.

Results: Loss of BAP1 IHC expression was observed in 7 of 38 (18%) intrahepatic, 2 of 35 (6%) perihilar, and 0 of 29 (0%) distal chca. There was a significant difference in frequency of BAP1 loss by IHC expression between intrahepatic (18%) and extrahepatic chca (3%) (p=.0125). Of note, loss of BAP1 staining was observed in tumors that were well, moderately, and poorly differentiated.

Conclusions: Intrahepatic chca frequently exhibit loss of BAP1 IHC expression in contrast to extrahepatic chca where BAP1 IHC expression is lost in only a small minority of cases, and in this cohort, is only seen in perihilar extrahepatic chca. No distal bile duct chca showed loss of expression.

1910 Risk Stratification of Intraductal Papillary Mucinous Neoplasm (IPMN) With 8th Edition AJCC Tumor Staging: A Single Institution Experience

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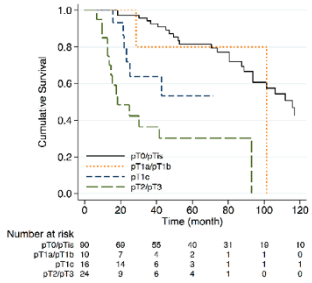
Background: The 8th edition AJCC tumor (T) stage has been introduced as an improvement over the 7th edition AJCC to better categorize primary pancreatic cancer. In our study, we sought to evaluate the prognostic significance of invasive carcinoma associated with intraductal papillary mucinous neoplasm (IPMN), classified by the new AJCC T-stage system.

Design: The retrospective study group comprised a cohort of 144 consecutive IPMN cases who underwent de novo pancreaticoduodenectomy from January 1998 to December 2016 in our tertiary care hospital. Clinicopathologic and outcome information were obtained from the medical record system and a prospectively maintained hospital database. All cases were reviewed by a GI pathologist to confirm the diagnosis, grade of dysplasia, and presence, type and size of invasive carcinoma, and whether the tumor was entirely submitted for pathologic evaluation. Non-invasive IPMNs that were not submitted entirely for histologic evaluation were excluded from statistical analysis. Kaplan-Meier survival estimate analyses was used to evaluate the post-resection overall survival.

Results: IPMN with low-grade dysplasia was diagnosed in 81 (56.2%, pT0), IPMN with high-grade dysplasia in 9 (6.3%, pTis), and IPMN-associated invasive carcinoma in 54 (37.5%) resections. IPMNs were further stratified as non-invasive (pT0/pTis) in 90 (62.5%), pT1a tumors in 8 (8/144, 5.5%), pT1b tumors in 2 (2/144, 1.4%), pT1c tumors in 18 (18/144, 12.5%), pT2 tumors in 17 (17/144, 11.8%) and pT3 tumors in 9 (9/144, 6.3%) patients. The estimated 5-year overall survival after resection of non-invasive IPMN (pT0/pTis, 81%) was similar to patients with pT1a/pT1b invasive carcinoma (80%, p-value=0.499, 95%CI: 0.61-2.66). The estimated 5-year overall survival was 53% in patients with pT1c tumors, which was superior to those patients who had a pT2/pT3

tumor resection (30%, p-value=0.043, 95%CI: 1.1-6.7), (figure).



Conclusions: IPMN-associated invasive carcinoma can be prognostically stratified by the AJCC 8th edition staging system. The survival for patients with small invasive component (<1cm; pT1a/pT1b) is comparable to those with non-invasive IPMN. Survival of patients after resection of pT1c tumors is lower in comparison to patients with pT1a/pT1b tumors, but is markedly superior compared to patients with a pT2/pT3 tumor resection.

1911 Galectin-3 is Expressed in Cholangiocarcinomas and Associated with the Large-Duct Phenotype

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Background: Galectin-3 (Gal-3) is a secreted lectin which augments tumor growth through regulation of cell signaling cascades (including MAP-kinase/KRAS signaling), cell-cell adhesion, and immune surveillance. Inhibitors of Gal-3 have emerged and are currently the subject of many clinical trials, yet the expression of Gal-3 across tumors sets remains unclear. While some studies have shown elevated Gal-3 expression in cholangiocarcinomas (CC) and an association with poor prognosis, others have shown reduced expression in poorly differentiated CC. We sought to examine the expression of Gal-3 in a series of CC, and correlate its expression with current prognostically significant classification schemes.

Design: 93 cases of cholangiocarcinoma (54 ICC and 39 ECC) from 2000-2015 were reviewed. CC we classified as follows: extrahepatic (ECC) and intrahepatic (ICC) of small duct type (SDT; or peripheral type; typically CD56/NCAM+ and mucin-) or large duct type (LDT; resembling ECCs; typically S100P+ and mucin+). Large duct phenotype was defined as ECC or ICC-LDT. Tissue microarrays and whole sections were stained with Galectin-3, CD56, and S100P. Staining was interpreted as positive (>10% staining) or negative.

Results: We find that Gal-3 was expressed in 38 of 92 (41%) of CC analyzed. Gal-3 was present in 48% (16/33) of ECC and 36% of ICC (19/53). There was a trend towards expression in CC with the large-duct phenotype (49% vs 33%, p = .09). Moreover, when compared compared with S100P and CD56, two surrogate markers of the large-duct phenotype and SDT, respectively, Gal-3 was significantly reduced in CD56-positive tumors (8% Gal-3+/CD56+ vs 47% Gal-3+/CD56-, p = 0.01) and showed a trend towards increased expression in S100P-positive tumors (51% Gal-3+/S100P+ vs 25% Gal3+/S100P-, p=.06), suggesting that indeed Gal-3 may be associated with the large-duct phenotype.

Conclusions: These studies show that Gal-3 is expressed in a significant number of CC, and suggest that it may be involved in the pathogenesis of large-duct type disease (e.g., KRAS mutant, fluke associated, etc). Moreover, given the recent data highlighting the sensitivity of KRAS-mutant tumors to Gal-3 inhibition (PMID:28893801), offer insight into an intriguing therapeutic avenue.

1912 CTNNB1-Mutations Define a Subset of Preinvasive Mass-Forming Lesions in the Gallbladder with Reduced Malignant Potential

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Background: Intracholecystic papillary tubular neoplasms (ICPNs) represent preinvasive mass-forming (adenomatous/papillary) lesions (aka, tumoral intraepithelial neoplasms) of the gallbladder that are greater than 1cm. A subset of these, termed "complex-pyloric ICPN's" (or CP-ICPN's), are lesions composed of small, non-mucinous tubules with complex architecture which appear to be virtually never associated with invasive adenocarcinoma or malignant behavior (compared to other subsets where invasion is seen in > 2/3 of the cases), are poorly understood.

Design: We performed whole-exome sequencing on a series of four CP-ICPNs and three non-CP-ICPNs (eg., biliary or gastric-type). In addition, whole sections from sequenced cases as well as additional cases were stained with β-catenin, LEF1, and TP53.

Results: All of the cases of CP-ICPN cases sequenced showed "hot-spot" mutations in exon 3 of CTNNB1 (4/4), while non-CP-ICPN did not (0/3). Using immunohistochemistry, we analzyed β-catenin pathway activity on a series of cases (including sequenced samples), as well as TP53, which has previously been shown to be a driver of gallbladder neoplasia. We find that all CP-ICPN cases analyzed showed strong nuclear β-catenin and LEF-1 staining (7/7 and 5/5 cases, respectively) with virtually no positivity for TP53 (only 1/10). Conversely, all non-CP-ICPN cases showed no nuclear β-catenin or LEF-1 labeling (0/6 and 0/4 cases, respectively) and an abundance of TP53 positivity (4/5 cases).

Conclusions: In summary, this study elucidate that ICPNs indeed show activation of cancer associated pathways that occur in a subtype-specific manner, and provide a molecular basis (e.g., CTNNB1 mutations and subsequent WNT/β-catenin-pathway activation) as a key regulator of the histogenesis and behavior of a distinctive and invasion resistant variant of ICPN (CP-ICPNs).

1913 Cystoisospora is a Frequent Finding in Pediatric Cholecystectomy Specimens

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Background: *Cystoisospora belli* is an intracellular parasite associated with gastrointestinal disease in immunocompromised hosts. While infection has been classically associated with intestinal disease, recent studies have identified *Cystoisospora* in the gallbladder in immunocompetent patients.

Design: We retrospectively reviewed 180 pediatric cholecystectomy specimens over a 24-month period for *Cystoisospora.* Positive cases were confirmed by at least two pathologists. A detailed histologic comparison of gallbladders with *Cystoisospora* and an equal number of randomly selected negative control cases was performed.

Results: As previously reported, *Cystoisospora* is an oval- to banana-shaped, intracellular parasite found in supra- or sub-nuclear vacuoles. We identified *Cystoisospora* in 11 out of 180 gallbladder specimens (6.1%). Of these, 9 cases had areas with more than 5 organisms per high power field, and 2 cases had 2 to 5 organisms per high power field. Patients with positive cases were similar in age to the controls (positive cases: mean patient age 13.4 years (range: 2-23 years); negative cases: mean patient age 14.7 years (range 12 weeks-31 years, p=0.35). Positive cases had a male-skewed M:F ratio of 1:1.2, compared to the M:F ratio of 1:3.1 in the negative cases, though not statistically significant (p=0.15). Gallbladders with *Cystoisospora* showed no significant association with cholelithiasis (54.5% vs. 65.1%, p=0.52), cholesterolosis (0% vs. 22.5%, p=0.12), acute cholecystitis (9.1% vs. 10.1%, p=1.00), or chronic cholecystitis (45.5% vs. 66.3%, p=0.20). There were no significant differences in epithelial vacuolation (81.8% vs. 72.7%, p=1.00), intraepithelial lymphocytosis (45.5% vs. 36.4%, p=1.00), lymphoid aggregates (54.5% vs. 63.6%, p=1.00), mucosal eosinophils (27.3% vs. 9.1%, p=0.59), mucosal plasma cells (27.3% vs. 18.2%, p=1.00), or epithelial atrophy (18.2% vs. 27.3%, p=1.00).

Conclusions: To our knowledge, this is the first series of *Cystoisospora* in pediatric cholecystectomies. We retrospectively identified these organisms in 6% of pediatric cholecystectomies. In comparison with a previously published review of adult cholecystectomies that found 1 case of *Cystoisospora* in 200 consecutive specimens, it appears that children could have a 10 times greater incidence of *Cystoisospora.* Since the background histology in positive cases shows no significant differences when compared to negative cases, it is critical to be aware of *Cystoisospora's* typical morphology for accurate diagnosis.

1914 Gross tumor size using the AJCC 8th ed. t staging criteria does not provide prognostic stratification for neoadjuvant treated pancreatic ductal adenocarcinoma

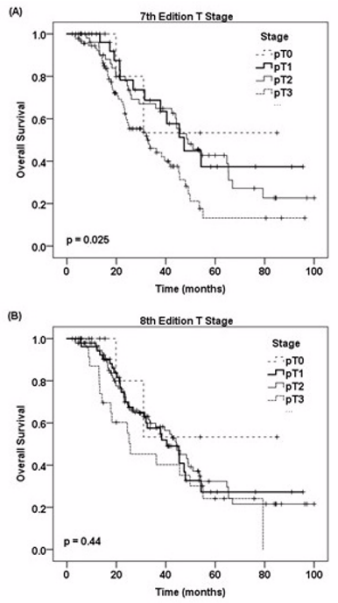
Daniel Rowan[1], *Mohammed Aldakkak*[2], *Kathleen K Christians*[1], *Susan Tsai*[2], *Catherine Hagen*[1]. [1]Medical College of Wisconsin, Milwaukee, WI, [2]Medical College of Wisconsin

Background: The new AJCC staging criteria (8th ed.) for pancreatic ductal adenocarcinoma (PDAC) has several changes in T and N stage. T stage is now solely size based to make staging more objective. The revised system provides better prognostic stratification in patients who were not treated with neoadjuvant therapy. Only one study has assessed the prognostic significance in a cohort of patients who received neoadjuvant therapy, using a more labor-intensive mapped approach to determine tumor size. The optimal method for determining tumor size in the post-treatment setting is therefore

uncertain. The aim of this study was to determine if gross tumor size provides prognostic stratification using the new AJCC staging criteria for PDAC.

Design: All patients who underwent pancreatic resection for PDAC following neoadjuvant therapy at our institution from 2009-2017 were included in the study. Gross tumor size was collected from corresponding pathology reports and used to determine T stage for AJCC 8th ed. Microscopic tumor size was used only if tumor was present on one slide. Patient survival was collected from banked data. Kaplan-Meyer survival curves were compared using log-rank test. Chi square test was used to compare categorical variables.

Results: 294 patients (M:F 1:1.1, mean age 66) were included in the study. By AJCC 7th ed., there were 12 (4.1%) pT0, 34 (11.6%) pT1, 65 (22.1%) pT2, and 183 (62.2%) pT3 patients. By AJCC 8th ed., there were 12 (4.1%) pT0, 85 (28.9%) pT1 (9 pT1a, 4 pT1b, 72 pT1c), 155 (52.7%) pT2, and 42 (14.3%) pT3 patients. 186 patients had negative lymph nodes (N0) and 108 had positive lymph nodes. 78 patients were N1 and 30 were N2 by 8th ed. 7th ed. T stage correlated significantly with overall survival (OS) in N0 patients (p=0.025); 8th ed. T stage did not (p=0.44, figure 1). When all patients were included, the 7th ed. T stages better stratified OS than the 8th ed. (p=0.12 vs. p=0.34), although neither was significant. Higher 7th ed. T stage correlated with higher N stage (p=<0.001) more strongly than 8th ed. T stage (p=0.052). 7th ed. and 8th ed. N stage correlated significantly with OS (p=0.028 and p=0.004, respectively).



Conclusions: Using the new 8th ed. AJCC staging criteria, gross tumor size alone does not provide good prognostic stratification in neoadjuvant treated PDAC. More complex mapping approaches combing gross and microscopic examination to determine tumor size may provide more accurate staging of neoadjuvant treated tumors.

1915 Adenomyomas of the gallbladder with papillary proliferations and cystic change ("Mural IPMN" pattern). An analysis of 17 cases

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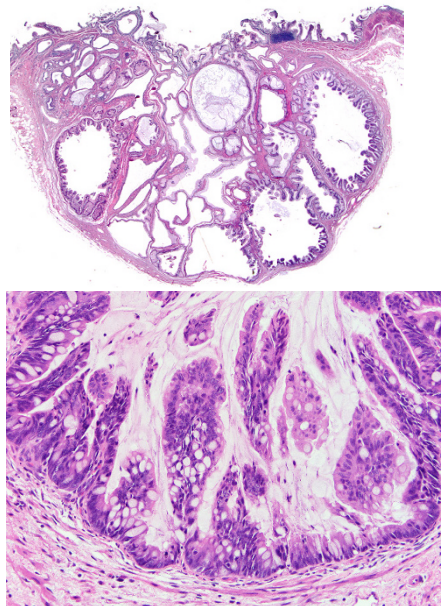
Background: Until recently, the so-called adenomyomas (AM) of the gallbladder (GB) have been regarded as entirely innocuous lesions, seldom showing neoplastic change. However, a recent study (PMID:22038508) claimed AM as the source of 26% of GB carcinomas. Separately, few examples of cystic AM with papillary proliferations were recently reported as "mural IPMN pattern".

Design: 17 AMs with mucinous/papillary/cystic changes (Am-PMN), were analyzed. Cellular atypia was graded per the 3-tiered grading used for BilIN/previously for PanIN (and also recently adopted in Santiago consensus conference): 1A (mucinous epithelium with minimal/no atypia), 1B (mild atypia), 2 moderate atypia (convincing dysplasia); 3 high-grade dysplasia (HGD).

Results: Clinical characteristics are summarized in table 1. By definition, all cases had at least some degree of papilla and cyst formation. Three were graded as 1A, 5 as 1B, 2 as 2, and 4 as HGD, with 3 also showing invasive carcinoma. All had gastric/endocervical-like mucinous epithelium, but 1 also had focal intestinal pattern (MUC2+, but CDX2-). Adjacent surface mucosa was free of dysplastic/mucinous changes in 16; one showed HGD in uninvolved mucosa. In 2, there were papillary/polypoid growth protruding from the AM into the surface mucosa (GB lumen). Follicular cholecystitis was present in 4 (24%; vs 2% in general population). Although there was stromal cellularity in some, this did not show the characteristics of ovarian-type stroma of mucinous cystic neoplasm.

	AM-PMN	AM without PMN	Ordinary GBC (without AM)	Non-neoplastic cholecystectomies
n	17	195	459	1190
Mean age	66 (47-81)	57 (21-95)	64 (22-94)	50 (14-94)
Female/male	0.8	1.9	3	2.6
Follicular cholecystitis	24%	17%	2%	2.75%



Conclusions: Adenomyomas of GB can develop mucinous dysplastic changes accompanied by cystic change, creating a pattern highly reminiscent of IPMNs. Similar to IPMNs, this occurs in elder patients (a decade older than other cholecystectomy groups), indicating a senescence/progression phenomenon. These AM-PMNs typically are *not* accompanied with dysplasia in the remainder of GB, indicating that it is a local phenomenon not a product of field effect/defect. Most AM-PMNs are gastric type, although MUC2+/CDX2- negative intestinal phenotype is also seen. Invasive adenocarcinoma seems to be uncommon (18%) although this may be an underestimate due to the replacement phenomenon (when invasive carcinoma develops it replaces and renders AM unrecognizable).

1916 The Metastatic Progression of Pancreatic Neuroendocrine Tumors is Characterized by Recurrent Genetic Alterations in Chromatin Remodeling Genes and CDKN2A

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Background: Despite the development of tumor prognostic grading and staging systems, the clinical behavior of pancreatic neuroendocrine tumors (PanNETs) can be unpredictable. Sequencing studies of primary PanNETs have identified recurrent alterations in *DAXX* and *ATRX*. Mutations in these genes correlate with shorter patient disease-free survival (DFS) and disease-specific survival (DSS). However, only 50% of distant metastases demonstrate loss of DAXX/

ATRX. Considering the genetic landscape of metastatic PanNETs remains relatively unknown, we hypothesized additional alterations are responsible for distant metastases and could serve as prognostic markers.

Design: Whole-exome sequencing was performed for 20 distant metastases and the most frequent genetic alterations were confirmed through orthogonal testing: immunohistochemistry and fluorescence *in situ* hybridization. Utilizing these orthogonal methods, a multi-institutional cohort of 347 primary PanNETs and 189 distant metastases from 52 patients were evaluated to assess the prognostic impact of these markers.

Results: In addition to *MEN1, DAXX* and *ATRX,* genetic alterations in metastatic PanNETs were identified in *SETD2, ARID1A* and *CDKN2A*. H3K36me3 (as a surrogate marker for SETD2), ARID1A and *CDKN2A* loss/deletion was identified in 28 (8%), 10 (3%) and 25 (7%) primary PanNETs, respectively, and correlated with larger tumor size, higher WHO grade and distant metastases ($p < 0.05$). Further, using a panel composed of DAXX, ATRX, H3K36me3, ARID1A and *CDKN2A*, loss/deletion of at least 1 of the 5 markers was detected in 81% of primary PanNETs that presented with synchronous and/or metachronous distant metastases, and 77% of distant metastatic PanNETs. Loss/deletion of at least 1 marker was associated with a 5-year DFS and 10-year DSS of 39% and 44%, as compared to 98% and 95%, respectively, for wild-type PanNETs ($p < 0.001$); and, a negative, independent prognostic factor for both DFS and DSS ($p < 0.001$).

Conclusions: The loss and/or deletion of DAXX, ATRX, SETD2/H3K36me3, ARID1A and *CDKN2A* represent prognostic markers of poor clinical outcome for patients with PanNETs. While further studies are required, these observations highlight the potential role of chromatin remodeling genes and *CDKN2A* in driving the metastatic progression of PanNETs.

1917 Can the 8th Edition AJCC Tumor (T) Staging for Pancreatic Ductal Adenocarcinoma Adequately Predict Patient Outcomes?

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Background: The new exocrine pancreas staging system by American Joint Committee for Cancer (AJCC, 8th edition) for pancreatic ductal adenocarcinoma (PDAC) is entirely size-based. Tumors are classified as pT1, ≤2 cm (pT1a, ≤0.5 cm; pT1b, >0.5 cm and <1 cm; pT1c, 1-2 cm), pT2, >2 cm and ≤4 cm, and pT3, >4 cm. The previous stage T3, tumor extension beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery, does not exist in the AJCC 8th edition. A validation study is required for evaluation of prognostic stratification using the new staging system.

Design: We retrospectively analyzed 247 consecutive cases of PDAC (with or without neoadjuvant therapy) between 2003 and 2017 and restaged them based on the new AJCC, 8th edition system. Cases that lacked follow up data, had metastatic disease at presentation or led to death due to causes unrelated to cancer were excluded. Follow up data was available for 153 cases. The statistical analysis for overall and disease free survival was performed using Kaplan-Meyer plots and log-rank tests.

Results: A total of 153 cases (77 females and 76 males; mean age of 64 years) of PDAC with follow up data were restaged based on the AJCC, 8th edition system. Reclassifying the cases by AJCC 8th edition resulted in restaging of 107 cases (70%): 78 cases (51%) were downstaged; 63 cases (41%) were downstaged from T3 to T2, while 15 cases (10%) were downstaged from T3 to T1. Overall 9 cases (6%) were upstaged from T2 to T3 and 20 cases (13%) were laterally staged from T1 to T1a, T1b or T1c. There was no change in the staging of 46 cases (30%). AJCC 7th edition adequately stratified patients into 3 stages with different outcomes. AJCC 8th edition did not show a statistically significant difference in overall or disease free survival between stage T1, T2 and T3 in our patient population (Figure 1a/1b).

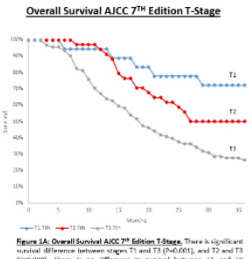

Figure 1A: Overall Survival AJCC 7th Edition T-Stage. There is significant survival difference between stages T1 and T3 (P<0.001), and T2 and T3 (P=0.008). There is no difference in survival between T1 and T2 (P=0.329).

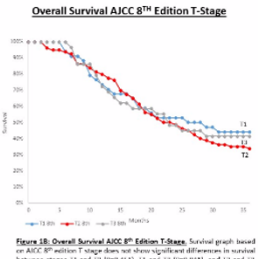

Figure 1B: Overall Survival AJCC 8th Edition T-Stage. Survival graph based on AJCC 8th edition T stage does not show significant differences in survival between stages T1 and T2 (P=0.453), T1 and T3 (P=0.843), and T2 and T3 (P=0.677).

Conclusions: T classification of PDAC using the 8th AJCC cancer staging system did not stratify prognosis in our patient population based on the T stage. The 8th edition N-stage shows a statistically significant difference in overall and disease free survival between N1 and N2. A size based staging system is complicated by lack of well-established criteria for measurement of residual post-treatment tumor foci often in background of chronic pancreatitis, desmoplasia and treatment related fibrosis. Thus additional studies are require to validate the new system and determine if the staging can be generalized to the larger patient population.

1918 Mismatch Repair Protein and PD-L1 Expression in Distal, Peri-Hilar and Intrahepatic Cholangiocarcinoma

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Background: Microsatellite instability (MSI) and expression of Programmed Death Ligand 1 (PD-L1) expression by immunohistochemistry (IHC) are predictive of response to immunomodulating therapies. MSI has been sporadically studied in cholangiocarcinomas of various sites, however rates of instability in cholangiocarcinomas by site have not been systematically investigated. Similarly, PD-L1 IHC has not been compared in cholangiocarcinomas by site. The goal of this study is to compare microsatellite instability and PD-L1 expression between intrahepatic, peri-hilar, and distal cholangiocarcinoma.

Design: Tissue microarrays (TMA) were created which included approximately 100 cholangiocarcinomas, roughly evenly distributed between distal, peri-hilar, and intrahepatic duct primary sites (29, 36 and 39 cases respectively). IHC studies characterizing MSH6 and PMS2 were done on the TMAs, as these are the obligate heterodimers in the MLH1 and MSH2 pathways respectively. Additionally, PD-L1 expression in the TMAs was also characterized with IHC analysis. Mismatch repair (MMR) protein expression was characterized as either loss or retained, while PD-L1 expression was quantified as a percentage within the tumor cells.

Results: 2 distal cholangiocarcinoma cases were MMR deficient out of 29 total cases, 6 peri-hilar cases were MMR deficient out of 33 total cases, and 6 intrahepatic cases were MMR deficient out of 27 total cases. 1 distal cholangiocarcinoma case showed PD-L1 expression (10%), 1 peri-hilar case showed PD-L1 expression (60%), and 2 intrahepatic cholangiocarcinoma cases showed PD-L1 expression (both 5%). See Table 1.

Table 1. MMR Protein and PD-L1 expression in Cholangiocarcinoma by site

Site	MLH1/PMS2 Pathway Deficient	MSH2/MSH6 Pathway Deficient	PD-L1 Positive (Quantification)
Distal	0	2	1 (10%)
Peri-Hilar	1	5	1 (60%)
Intrahepatic	3	3	2 (Both 5%)

Conclusions: By IHC analysis, 10% of distal, 21% of peri-hilar and 30% of intrahepatic cholangiocarcinoma would be expected to be potential responders to immune checkpoint inhibitor drugs, allowing these patients access to additional therapeutic options. Additional studies are needed to clarify whether the IHC patterns found in this study are predictive in cholangiocarcinoma.

1919 Follicular Cholecystitis: Clinicopathologic Associations

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Background: Follicular cholecystitis (FC) is a relatively rare entity, and causal associations reported infrequently in literature have mainly included gram-negative bacterial infection. In this study, we aimed to explore different clinicopathologic associations of FC, and to better characterize the entity.

Design: A retrospective review of all archival H&E slides and pertinent clinical information from the medical records was undertaken for all cholecystectomy cases with a rendered diagnosis of "follicular cholecystitis", between January 1991 and August 2017, at our tertiary medical center. Diagnostic criteria for FC was maintained as more than occasional reactive lymphoid follicles, distributed anywhere in the gallbladder wall. Concurrent conventional chronic cholecystitis (CC) component was noted when there was fibromuscular hyperplasia of the gallbladder wall along with the presence of Rokitansky-Aschoff sinuses. Concurrent lymphocytic cholecystitis (LC) was noted based

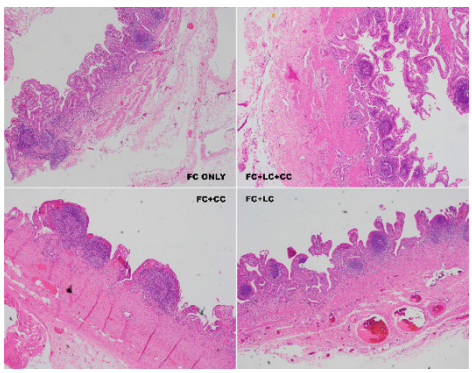
on the presence of diffuse mucosal infiltrate of lymphocytes (Figure 1).

Results: Forty-three consecutive patients were confirmed to have FC, whose demographic profile and significant clinicopathologic findings are summarized in Table 1. The majority of the patients (88.4%) had at least one other histologic association in the gallbladder (either LC, CC, or both). Remarkably, functional distal biliary obstruction (from choledocholithiasis, sclerosing cholangitis, distal biliary strictures, or malignancies of the pancreatic head or ampulla) was found in 76.7% of the patients, irrespective of the presence of other concurrent histologic findings. FC associated with CC was relatively more common in females (61%) and strongly associated with cholelithiasis (70%). However, those without CC were predominantly males (70%) and had a significant association with LC (75%). All four cases of FC without any other histologic associations who had clinical information available showed some form of distal biliary obstruction. FC cases without concurrent LC were often associated with CC (74%).

Table 1: Demographics and clinicopathologic association of follicular cholecystitis

Histological findings	Age (median, years)	Gender (% males)	Race (% African-American)	Functional distal biliary obstruction (%)	Association with gallstones (%)	Other histologic association
All FC (n=43, 100%)	67	53.5	23	76.7	53.5	
FC+CC (n= 23, 53.5%)	67	39	17	83	70	39% with LC
FC-CC (n=20, 46.5%)	68	70	32	70	35	75% with LC
FC+LC (n=24, 55.8%)	70	63	21	75	46	38% with CC
FC-LC (n=19, 44.2%)	66	42	26	79	63	74% with CC
FC+LC+CC (n=9, 20.9%)	74	56	0	89	67	1 case with Actinomycetes infection of gallbladder
FC+CC-LC (n=14, 32.6%)	63.5	29	29	79	71	
FC+LC-CC (n=15, 34.9%)	62	67	33	67	33	
FC alone (n=5, 11.6%)	71	80	20	100[ψ]	40	

FC: Follicular cholecystitis; CC: Conventional chronic cholecystitis; LC: Lymphocytic cholecystitis.
[ψ] missing clinical record in 1 patient.



Conclusions: FC is commonly associated with other concomitant histologic abnormalities in the gallbladder such as CC and/or LC. Additionally, it is strongly associated with extrahepatic biliary obstruction distal to the gallbladder. Therefore, this finding at routine cholecystectomy may warrant further evaluation to rule out a cause for distal biliary tract obstruction.

1920 Utility of the Ki67 marker in the differentiation between reactive ductal proliferation and adenocarcinoma in surgical margins in pancreatic cancer specimens

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Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive and lethal malignancies. Only 20% of patients with pancreatic cancer are surgical candidates. Among those, recurrence rates are high and cure is rare. Margin status, a prognostic factor of PDAC after resection, has gained increased attention in recent years, because of conflicting data in basic concepts of margin involvement and pathologic assessment. In the literature there is a dramatic variability in the reported margin positivity rate, ranging from 10% to 84%. These rates of margin involvement are often incongruent with local tumor recurrence or overall survival. Such margins may be difficult to assess, either in surgical specimens or in small biopsies, because of the cauterization effect or because the neoplasia develops in the context of an advanced chronic pancreatitis (CP), facts that make it difficult to discern benign lesions from neoplastic glands in surgical margins. The aim of this study is to explore the utility of the Ki67 marker in the differentiation between reactive ductal proliferation and PDAC in surgical margins.

Design: We studied a total of the 64 cases of PDCA and 15 cases of CP, resected during the period of 2003-2009 in Vall d'Hebron Hospital. We evaluated, with Ki67, proliferative activity in reactive ductular proliferative lesions in CP and in PDAC. In the statistical study we employed the Mann-Whitney test and the ROC analysis.

Results: We observed a higher Ki67 expression in PDAC compared to expression in reactive ductal proliferations, with a statistically significant difference between them (Median (sd) PDAC:66.54 (19.17), Median (sd) CP:1.23 (1.59), p=0.000). The ROC analysis allowed us to establish a cutoff point, based on the area under the curve, of 20%, which would serve to discriminate between reactive ductal proliferations and PDCA, with a PPV of 100%. We obtained an area under the curve of 1, which classifies our test as excellent.

Conclusions: 1) a Ki67 value ≥ 20% permits distinction to discern between reactive ductal proliferations and PDAC, with a PPV of 100%. 2) The determination of Ki67 may be useful in confirming the involvement of the surgical margins of the resection specimens in which PDAC developes in the context of chronic pancreatitis, and 3) Ki67 may be useful in assessing the presence of PDCAC in small biopsies of pancreas in which architecture are lost.

1921 RNF43, Beta-Catenin And E-Cadherin Expression in Biliary Tract Carcinomas: A Tissue Microarray-Based Study

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Background: RING finger protein 43 (RNF43) is proposed to inhibit Wnt signaling by interacting with the Wnt receptors of the Frizzled family. We aim to determine the expression by immunohistochemistry of RNF43, β-catenin and E- cadherin in biliary tract carcinomas and correlate it with clinicopathological features.

Design: A search for adenocarcinomas of the biliary tract was run in the database of the Department of Pathology, University Health Network. Tissue microarrays were stained with RNF43, β-catenin and E- cadherin antibodies. The immunostains were scored according to the percentage of positive cells stained as negative (0%-30%) and positive (>30% -100%). In addition, cell localization of the stain (nuclear, cytoplasmic and membrane) was recorded. Data analysis was performed using IBM SPSS Statistics (Version 21).

Results: A total of 163 cases of biliary tract carcinomas (52 gallbladder, 48 extrahepatic bile duct, 25 hilar and 38 intrahepatic, respectively) were included in the study. There was a slight increased prevalence of females (54.3%) and mean patients' age was 65 years. RNF43 was nuclear in 60/163 (36.8%) cases, cytoplasmic in 23/163 (14.1%), nuclear and cytoplasmic in 25 (15.3%) and negative in both in 55 (33.7%) cases. Absent nuclear RNF43 staining was significantly associated with carcinomas of gallbladder and extrahepatic bile ducts, while a positive nuclear stain with intrahepatic and hilar cholangiocarcinomas. Absent cytoplasmic stain was more frequently seen in carcinomas of the gallbladder and intrahepatic cholangiocarcinomas, while positive cytoplasmic staining was more frequent in extrahepatic bile duct carcinoma (p=0.0001). Nuclear and/or cytoplasmic absence of RNF43 expression was mainly associated with loss of membranous β-catenin stain, while absent nuclear RNF43 stain was associated with abnormalities of E-cadherin expression. Positive metastatic lymph nodes were more frequently associated with loss of nuclear stain and cytoplasmic expression of RNF43.

Cytoplasmic expression of RNF43 was significantly associated with perineural invasion (p=0.05) and with stage I/II (p= 0.007).

Conclusions: These preliminary data suggest that expression of RNF43 is variable and may be associated with abnormal localization of β-catenin and E-cadherin, presence of metastatic lymph nodes, perineural invasion and lower disease stages.

1922 Atypical Cells on Pancreatic Endoscopic Ultrasound Guided FNA: A Retrospective Analysis of the Utility of Repeat FNA

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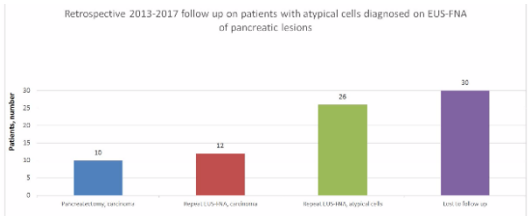
Background: In the United States over 50,000 people are diagnosed with pancreatic cancer annually. It is the fifth highest cause of cancer-related death, and has a high mortality. Unfortunately, due to the indolent course of the disease, patients usually present late. Definitive histopathological diagnosis of pancreatic lesions is ultimately required before definitive management can be be undertaken. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is a highly sensitive and specific diagnostic procedure to evaluate pancreatic lesions, however occasional cases are non-diagnostic, yielding only the result of atypical cells.

Design: Our institution has a high volume of pancreatic EUS-FNA, with approximately 600 gastrointestinal EUS procedures annually. A significant majority of those cases are pancreatic FNAs, and most can be classified as either benign or malignant on initial pancreatic EUS-FNA. A small number of cases, either due to lack of quantity or quality of material for diagnosis, are classified as atypical. We performed a 4 year retrospective analysis of cases diagnosed as atypical on initial pancreatic EUS-FNA to investigate the utility of repeat EUS-FNA after a diagnosis of atypical cells.

Results: There were 76 patients with an initial diagnosis of atypical cells. Almost forty percent of patients (30/76 patients) were lost to follow up. Forty-six (46/76) patients underwent repeat diagnostic procedures. Twelve patients (12/46, 26%) had a confirmatory diagnosis of adenocarcinoma. Twenty 26 patients (26/46, 57%) had a second diagnosis consistent with atypical cells. In addition, 10 patients (10/46, 17%) had a pancreatectomy that confirmed pancreatic carcinoma. We showed that repeat EUS-FNA has a 25% rate of definitively diagnosing pancreatic adenocarcinoma on repeat EUS-FNA. Taking into account the low cost and side-effect profile it is reasonable to counsel clinicians and patients to attempt additional EUS-FNA to achieve definitive histopathologic diagnosis.



Conclusions: We showed that repeat EUS-FNA had a 25% rate of definitively diagnosing pancreatic adenocarcinoma on repeat EUS-FNA in the setting a first diagnosis of atypical cells. Taking into account low cost of procedure and low side-effect profile it is reasonable to counsel clinicians and patients to attempt additional EUS-FNA to achieve definitive histopathologic diagnosis.

1923 PREVIOUSLY PUBLISHED

1924 The Immune Microenvironment of Adenosquamous Carcinoma of the Pancreas: A Pilot Study

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Background: Adenosquamous carcinoma of the pancreas is an aggressive malignancy in need of new therapeutic options in addition to chemotherapy and radiation. While immunomodulatory therapy has shown promise in other tumors, little is known regarding the tumor immune microenvironment of adenosquamous carcinomas. Here, we investigate the tumor immune microenvironment (TME) of 34 cases of primary adenosquamous carcinoma of the pancreas (ASQ).

Design: Tissue microarrays (TMAs) with 34 ASQ (2 cores per tumor) were labeled by immunohistochemistry for PD-L1, PD-1, CD4, CD8, CD68 and FoxP3. Percentage ASQ cells with clear membranous PD-L1 expression was scored (>1% labeling positive). Percentage PD-L1 expression by tumor immune stromal cells (TILs) was scored as none (0), focal (1, <5%), moderate (2, 5-50%) or diffuse (3, >50%). TIL infiltrate density was scored as none (0), rare (1, TIL <5% of tumor area), mild (2, TIL 5-10% of tumor area), moderate (3, TIL 11-50% of tumor area) or brisk (4, TIL >50% of tumor area). Density of CD68+ cells was scored as percentage of tumor area. Other immune cell markers were counted in a representative high power field and averaged across tumor cores.

Results: All ASQ contained TIL (47% rare, 24% mild, 26% moderate and 3% brisk). 92% ASQ showed PD-L1 labeling in TIL (21% focal, 68% moderate, and 3% diffuse) and 65% showed PD-L1 labeling by tumor cells. PD-L1+ tumors were more likely to have moderate/brisk TIL infitrate (41%) than PD-L1- tumors (8%) (p=0.06) and PD-L1+ tumors were more likely to have moderate/diffuse PD-L1+ TIL (95%) than PD-L1- tumors (25%) (p<0.001). CD8+ T cell counts were higher in PD-L1+ tumors than PD-L1- tumors (p=0.13) and highest CD8+ infiltrates were present in PD-L1+ tumors with moderate/diffuse PD-L1+ TIL (p=0.03). Average FoxP3+ counts were also higher in PD-L1+ tumors relative to PD-L1- tumors (p=0.06) and highest FoxP3 infiltrates were present in PD-L1+ tumors with moderate/diffuse PD-L1+ TIL (p=0.002). CD8:FoxP3 ratios were similar in PD-L1+ and PD-L1- tumors. PD-L1+ tumors were more likely to have high CD68+ infiltrates (>5% of tumor area) (77%) than PD-L1- tumors (42%) (p=0.06).

Conclusions: ASQ display an active TME with PD-L1+ TIL and robust tumor cell expression of PD-L1 with correlation between overall TIL infiltrate and PD-L1 expression. While pancreatic adenocarcinomas lack high intrinsic immunogenicity, these results suggest that ASQ may be amenable to immunotherapy and support additional exploration of the immune response to ASQ.

1925 The Inflammatory Microenvironment of Pancreatic Intraepithelial Neoplasia

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Background: Increasing efforts focus on harnessing the tumor immune microevironment (TME) of pancreatic adenocarcinoma as a therapeutic target. However, little is known regarding the development of the TME across different time points of neoplastic evolution. Here, we investigate the inflammatory milieu of pancreatic intraepithelial neoplasia (PanIN), a precursor lesion to pancreatic adenocarcinoma.

Design: Whole slides from resection specimens containing 24 PanIN (12 low grade (LG) PanIN and 12 high grade (HG) PanIN) were labeled by immunohistochemistry for CD4, CD8, CD20 and FoxP3. Slides were scanned and normal ducts, LG PanIN and HG PanIN were separately annotated and the density of immune cells quantified using image analysis software (HALO, Indica Labs).

Results: While normal ducts had only rare lymphocytes, both LG and HG PanIN contained lymphocytes infiltrating around involved ducts and within neoplastic epithelium (p>0.001). While, on average, LG and HG PanIN had similar densities of CD8+ cytotoxic T cells (per mm^2), HG lesions could be split into CD8^{hi} and CD8^{lo} groups. HG CD8^{hi} PanIN contained more CD8+ T cells than LG lesions (p=0.17), while HG CD8^{lo} PanIN contained far fewer CD8+ cytotoxic T cells than LG lesions (p=0.0005). In contrast, LG PanIN contained fewer FoxP3+ regulatory T cells than HG lesions, while CD8^{lo} HG PanIN contained more FoxP3+ regulatory T cells than either LG or CD8^{hi} HG PanIN. While the CD8:FoxP3 ratio was highest in LG PanIN than in either HG lesion, the CD8:FoxP3 ratio was higher in the CD8^{hi} HG PanIN group than in the CD8^{lo} HG PanIN group. This suggests that a more suppressed immune microenvironment may be present in the CD8^{lo} HG PanIN group based on disproportionate infiltration of FoxP3+ regulatory T cells and/or lack of efficient recruitment of CD8+ cytotoxic T cells.

Conclusions: These results show evidence of an immune response to pancreatic neoplasia at a very early stage, LG PanIN, that continues to develop as lesions progress to HG. While CD8+ T cells dominated in LG PanIN, FoxP3+ cells increased in HG lesions and a subset of HG PanIN showed decreased CD8+ T cell infiltration relative to both other HG lesions and LG PanIN. This suggests dynamic evolution of the TME of pancreatic precursor lesions and indicates that immune suppression may begin in a subset of PanIN prior to the development of invasive adenocarcinoma. Further investigation may elucidate the mechanisms allowing for the maintenance of CD8+ T cell infiltration in some, but not all, HG PaIN.

1926 Proposal of the Regression and Risk Grouping of Perihilar Cholamgiocarcinoma Following Neoadjuvant Systemic Chemotherapy and Radiation Therapy

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Background: Although the standard treatment for perihilar cholangiocarcinoma (pCAA) is surgical resection, the efficacy of surgery-first approach is limited because of the difficulty in obtaining negative surgical margins. Recently, neoadjuvant chemotherapy and/or radiation therapy to improve curative resection rate has been proposed. Our study aims to assess histological response to neoadjuvant therapy and establish regression and risk grouping for pCCA.

Design: Among 73 patients with cytologically/histologically proven pCCA, 35 patients with curative-intent resection after chemotherapy and/or radiation therapy at Mie University Hospital were enrolled. The regression rate was based on an estimation of the percentage of microscopically identifiable cancer cells to the macroscopically identifiable tumor bed. The regression grouping was classified into following two groups: high responder (the estimated residual tumor rate was less than 30%) and low responder (the estimated residual tumor rate was 30 or more). The risk grouping was based on a combination of the regression group and status of surgical margin (low risk: high responder + R0, intermediate risk: high responder + R1 or low responder + R0, high risk: low responder + R1). Log-rank and Wilcoxon were used to test the equality of the survival distribution.

Results: Median survival time (MST) in high and low responders was 52.4 months and 21.3months, respectively. The 1-, 2-, and 3-year disease specific survival (DSS) in high responders were significantly higher than in low responders (97.7%, 80.2%, and 51,4% vs 21.3, 68.6%, and 34.2%). As for the risk grouping, MST in intermediate and high risk groups were 30.4 and 15.8 months, respectively, whereas DSS in low risk group was not reached. Prognosis of low risk group was significantly better than high risk group.

Conclusions: We established histological regression and risk grouping for pCCA. Our study indicates the utility of both grouping protocols to assess the survival of pCCA.

1927 Mass-Forming Intraductal Neoplasms of the Biliary Tract Comprise Morphologically and Genetically Distinct Entities

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Background: Mass-forming intraductal neoplasms of the biliary tract are not well characterized at the genetic level, and correlations between morphologic subtypes, immunohistochemical (IHC) features, and molecular alterations have not been made.

Design: Forty-one cases were identified and classified as gastric-, intestinal-, pancreatobiliary (PB)-, oncocytic-type intraductal papillary neoplasm (IPN) or intraductal tubular neoplasm (ITN) based on histologic features and IHC staining patterns (MUC1, MUC2, MUC5AC, MUC6, CK7, CK20, CDX2). All neoplasms were subjected to targeted next generation sequencing with a panel that interrogates >400 genes for somatic aberrations and copy number variants (CNVs). Clinicopathologic, genetic features and outcome of these subtypes were assessed.

Results: The mean age at diagnosis was 69 years (42-81), male/female ratio was 1.3. Most (59%) neoplasms were extrahepatic and tended to be large (mean overall size, 5.0 cm). The majority (83%) contained high grade dysplasia, 72% were associated with invasive carcinoma. Gastric-type IPNs (n=9) showed consistent co-labeling for MUC6 and CK7, which was less common among other subtypes (100% vs 44%; p=0.005). Intestinal-type IPNs (n=5) showed higher rates of CK20 expression than other subtypes (80% vs 10%; p=0.003). Overall, the most commonly mutated genes included *TP53* (22%) and *APC* (20%), while CNVs affected *ELF3* (17%) and *CDKN2A/B* (15%). All gastric-type IPNs contained an alteration affecting Wnt signaling and 78% showed aberrations in the MAPK pathway. Mutations in *APC* (55%) and *KRAS* (44%) were common in gastric-type IPNs compared with other subtypes (p<0.02 for both). Intestinal-type IPNs more frequently (60%) showed *SMAD4* mutations, which affect TGFβ signaling (p=0.02). PB-type IPNs (n=14) exhibited frequent alterations in tumor suppressor genes including *p53* (43%), *CDKN2A/B* (36%), and *ARID2* (36%) (p<0.04 for all). Oncocytic-type IPNs (n=7) and ITNs (n=6) showed relatively few distinct or recurrent genetic aberrations. Follow-up information was available for 32 (78%) patients (mean, 42 months). The 3-year overall survival rates of patients with and without an invasive component were 85% and 100%; there were no survival differences between the subtypes.

Conclusions: This comprehensive analysis helps elucidate the genetic landscape of intraductal neoplasms of the bile ducts. Similar to intraductal neoplasms of the pancreas, those of the bile ducts are heterogeneous in nature, not only morphologically but also genetically.

1928 A KRAS Wild Type Mutational Status Confers a Survival Advantage in Pancreatic Ductal Adenocarcinoma

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Background: The *KRAS* oncogene is a driver mutation and is present in greater than 90% of pancreatic ductal adenocarcinomas (PDAC). A subset of these tumors, however, do not harbor mutations in *KRAS* (wild type *KRAS*). Studies have shown that patients with mutated *KRAS* have a poorer survival on first-line gemcitabine based chemotherapy compared to wild type *KRAS*. In this study, we examined a cohort of patients with PDAC at our institution who were either wild type or mutant for the *KRAS* gene and assessed for differences in survival and response to different chemotherapeutic regimens.

Design: We examined clinical records of patients treated at our cancer center from 2013-2017. Patients with a pancreatic mass and a histologic diagnosis of pancreatic or pancreaticobiliary adenocarcinoma were identified. Thirty-nine patients with PDAC who underwent tumor sequencing at our Center for Personalized Diagnostics (CPD) were selected for further study. Twelve patients were identified whose tumors were *KRAS* wild type. Twenty-seven patients with PDAC whose tumors harbored *KRAS* mutations were selected as controls (*KRAS* mutant).

Results: We noted a longer overall survival among *KRAS* wild type patients compared to *KRAS* mutant patients (p=0.026). This was independent of the age at diagnosis, patient gender, stage of diagnosis, tumor morphology, mismatch repair status, and chemotherapeutic regimen.

Conclusions: Similar to previously reported studies, pancreatic ductal adenocarcinomas with a *KRAS* wild type mutational profile have a better prognosis with a longer overall survival. This improved prognosis is independent of the protocol utilized in therapy for these patients. Our findings suggest that future clinical trials in pancreatic cancer should take into consideration the presence of *KRAS* mutations in their pre-planned analysis when assessing the efficacy of a novel therapeutic approach. This may be a crucial factor in trial concepts and outcomes.

1929 MFAP5 Distinguishes Between Benign Desmoplasia-Like Reaction and True Desmoplasia in Invasive Adenocarcinoma of the Gallbladder.

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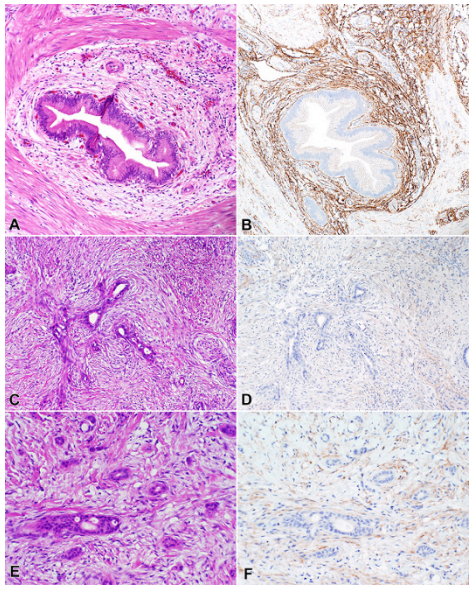
Background: The diagnosis of invasive adenocarcinoma of the gallbladder can sometimes be challenging, and often one relies on the presence of desmoplasia. However, desmoplasia-like changes can be observed in benign gallbladder conditions. MFAP5 (microfibrillar-associated protein 5) is a fibrillin-interacting component of the extracellular matrix. Loss of MFAP5 expression had been observed in the desmoplastic stroma of colon cancer. Our aim was to determine if MFAP5 can distinguish between benign desmoplasia-like reaction and true desmoplasia in invasive adenocarcinoma of the gallbladder.

Design: We collected 18 benign gallbladders with desmoplasia-like reaction and 19 cases of invasive adenocarcinoma of the gallbladder. Immunohistochemistry for MFAP5 was performed and evaluated.

Results: In all 18 benign gallbladders with desmoplasia-like reaction, MFAP5 revealed fine fibrillary circumferential staining around the individual glands (Fig 1A, B). In contrast, invasive adenocarcinomas showed variable degree and extent of MFAP5 loss. The *degree* of MFAP5 loss was graded as complete loss (totally negative, Fig 1C, D), partial loss (non-circumferential, weak non-fibrillary staining, Fig 1E, F) or no loss. The *extent* of MFAP5 loss was graded as diffuse (≥50% of glands with MFAP loss) or patchy (<50% of glands with MFAP loss). Cases with any extent (diffuse or patchy) of complete loss were classified as complete loss. In the 19 adenocarcinoma cases, 15 cases (79%) showed diffuse complete MFAP5 loss, 3 cases (16%) showed patchy complete MFAP5 loss, and only one case (5%) showed no significant loss. For those with patchy complete MFAP5 loss, the remaining areas showed diffuse partial loss.



MFAP5 loss characterizes desmoplastic stroma of invasive adenocarcinoma of the gallbladder. When a definitive diagnosis is difficult to make based on routine H&E, MFAP5 may be of clinical value to help distinguishing invasive adenocarcinoma from its mimickers.

1930 Fluorescence in Situ Hybridization (FISH) Adds Value to Cytology in the Diagnosis of Bile Duct Brushing in Patients with Primary Sclerosing Cholangitis

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Background: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease that leads to inflammation and fibrosis of intrahepatic and extrahepatic bile ducts. Cholangiocarcinoma is a leading cause of morbidity and mortality in patients with PSC. Bile duct brushing (BDB) cytology is challenging with poor sensitivity for the detection of malignancy in PSC patients. The search for improvement in diagnostic accuracy has led some to suggest triple testing (brush cytology, molecular testing and biopsy). The aim of this study is to assess the added value of FISH testing of BDB in PSC patients.

Design: Our study included 18 patients with PSC who had BDB cytology and FISH testing. FISH testing was performed with centromere probes for chromosomes 3 (D3Z1), 7 (D7Z1), 17 (D17Z1), and a locus specific probe for 9p21. Cytologic and FISH results were correlated with patients' outcome including surgical and/or imaging follow-up.

Results: Cholangiocarcinoma was confirmed in 6 of 18 patients (5 based on surgical resection, 1 based on radiological evidence). The BDB cytology of these 6 patients were suspicious for malignancy (2 cases) and negative (4 cases). FISH was reported as abnormal (5 cases) and negative (1 case). The remaining 12/18 patients were presumed to have benign strictures based on imaging, additional BDB, biliary biopsies, imaging studies and clinical follow-up. Cytology was negative in all 12 cases, while FISH was abnormal in 2/12. One patient with abnormal FISH had a subsequent liver transplant and showed no evidence of malignancy after 4 years of follow-up. The second patient had no evidence of malignancy by biopsy or imaging but was lost to follow-up after one year. Based on our results, the sensitivity of cytology and FISH were 33%, and 83%, respectively. The specificity of cytology and FISH were 100% and 83%, respectively.

Conclusions: In PSC patients, the specificity of BDB cytology for the detection of malignant biliary strictures is high, but its sensitivity is poor. The addition of FISH to detect chromosomal aneuploidy improved the sensitivity in the detection of malignancy. However, two patients with abnormal FISH results showed no evidence of malignancy on follow-up. A multimodal approach that integrates clinical, imaging, cytologic, and molecular findings is needed to increase both sensitivity and specificity and stratify PSC patients for individualized dysplasia surveillance.

1931 Morphologic Repertoire of Well-Differentiated Pancreatic Neuroendocrine Tumors (Pannets): A Clinicopathologic Analysis of 139 Cases

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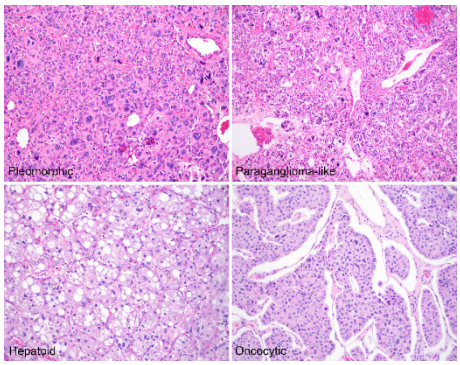
Background: The morphologic spectrum of well-differentiated pancreatic neuroendocrine tumors (PanNETs) have recently been shown to be wider than previously appreciated, with limited data on their frequency and associations, some creating substantial diagnostic difficulties in daily practice (especially at metastatic sites).

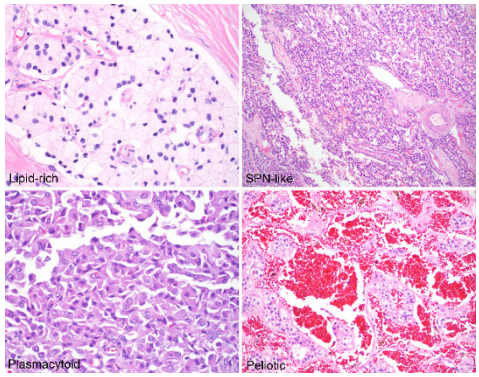
Design: To investigate frequency and characteristics of morphologic findings, 139 consecutive immunohistochemically (IHC) - confirmed PanNETs were reviewed. Morphologic patterns were recorded as focal (<25%), substantial (25-75%), or diffuse (>75).

Results: The variants, their frequency, main pathologic characteristics and diagnostic pitfalls are described in Table 1 and select examples are illustrated in Figures.

Table 1: Frequency and characteristic histopathologic features of different morphologic patterns of well-differentiated pancreatic neuroendocrine tumors.

Patterns	Characteristic histopathologic features	Diagnostic Challenges
Common morphologic patterns		
Pleomorphic (10 cases, diffuse in 7)	Marked "symplastic" (degenerative) nuclear atypia, often with bizarre cells, without increased proliferative activity (mean Ki67 index, 2.7%).	Misdiagnosed as adenocarcinoma in cytology
Paraganglioma-like (9 cases, diffuse in 6, substantial in 3)	"Zellballen-like" small rounded cell clusters virtually indistinguishable from paragangliomas (CK+ in 7/7 tested); 8 also showing pleomorphism due to symplastic/degenerative atypia (7 diffuse, 1 focal)	Misdiagnosed as paraganglioma
Hepatoid (5 cases, diffuse in 4)	3/5 with steatohepatitic pattern, arginase and HepPar1 positivity (1 diffuse, 2 patchy) and PAS-D+ globules in 2/2; 1/5 had fibrolamellar features	Misdiagnosed as hepatocellular carcinoma
Oncocytic (4 cases, diffuse in all)	N/C ratio < ¼, prominent eccentric nucleoli, cytoplasmic granules and Hurthleoid appearance	Misdiagnosed as adenocarcinoma and hepatocellular carcinoma
Lipid-rich (5 cases, diffuse in all)	Abundant foamy/microvesicular cytoplasm reminiscent of adrenal cortex	Misdiagnosed as adrenal cortical and renal cell carcinoma
Solid pseudopapillary neoplasm-like (4 cases, diffuse in 3)	Pseudopapillae with hyalinized fibrovascular cores surrounded by bland discohesive cells with clear-eosinophilic cytoplasm, round/oval nuclei with finely stippled chromatin and occasional grooves, mimicking SPN (negative for nuclear beta-catenin and chromogranin + [2 patchy, 1 diffuse])	Misdiagnosed as solid pseudopapillary neoplasm
Plasmacytoid (3 cases, substantial in all)	Moderate to abundant cytoplasm, eccentric nuclei, some with cytoplasmic condensations and frequent anisonucleosis	Misdiagnosed as mammary carcinoma
Peliotic (2 cases, diffuse in both)	prominent cavernous blood-filled cavities lined by tumor cells	Misdiagnosed as hemangioma
Ductuloinsular (3 cases, diffuse in 1)	Prominent ductular proliferation within tumor nodules, abruptly ending where NET cells stopped.	Misdiagnosed as mixed adenocarcinoma-neuroendocrine tumor
Pseudoglandular (3 cases, diffuse in 2)	Gland-like formation, 1 showing prominent intraluminal mucin (mucicarmine +)	Misdiagnosed as adenocarcinoma
Rare morphologic patterns		
Mammary tubulolobular carcinoma-like (1)	Intimate mixture of small tubular elements and cord-like tumor cells in the hyalinized and fibrotic stroma	N/A
Adenoid cystic-like (1)	Cribriform, solid or tubular pattern of round/oval cells surrounded by desmoplastic stroma with extensive perineural invasion	Misdiagnosed as high-grade adenocarcinoma
Pinkus-like (1)	interconnecting trabecula separated by myxoid matrix resembling "fibroepithelioma of Pinkus"	N/A
Other features		
Mega-vacuoles (11)	Large clear intracytoplasmic vacuoles, similar to those described in SPN (PMID: 18484644).	Misdiagnosed as SPN
Osteoid-like matrix (1)	Deposition of osteoid-like matrix	Osteoblastic tumor was considered





Conclusions: PanNETs show a spectrum of morphologic patterns that may create substantial diagnostic challenges. Recognition of these patterns may help prevent diagnostic errors including misdiagnosis as metastasis. The biologic significance of some "variants" such as hepatoid, oncocytic, ductuloinsular, pleomorphic and paraganglioma-like needs further analysis.

1932 Analysis of Immunosuppressive Checkpoint Molecules in Pancreatic Adenocarcinomas Reveal that IDO Expression is Associated with a Poor Outcome, and PD-L1 is Uncommonly Expressed by Tumor Cells

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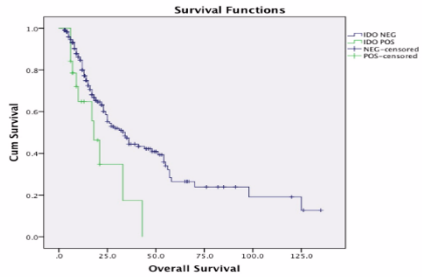
Background: Pancreatic cancer is an aggressive malignancy with a 5-year survival rate of less than 5%. The limited therapeutic armamentarium has encouraged investigations into the role of immunotherapy. Recent studies have examined pancreatic adenocarcinomas (PDACs) related immune tolerance pathways that permit tumors to evade the host immune system. Here we interrogate two such established checkpoint therapy targets, Indoleamine 2,3-dioxygenase (IDO) and program death ligand-1 (PD-L1) in a large cohort of PDACs.

Design: Immunohistochemistry for PD-L1, CD8 and IDO was performed on 297 consecutive treatment naïve pancreatic ductal adenocarcinomas. Whole slide scan images were evaluated for the percentage of tumor cells positive for IDO and PD-L1; tumor with > 20% IDO and >1% of PD-L1 positive tumor cells were termed positive. CD8 positive lymphocytes associated with the tumor were counted manually and expressed per mm2. Data for PDACs was downloaded from the Tumor Cancer Genome Atlas (TCGA) and assessed for IDO and PD-L1 expression.

Results: The mean age was 67 years with a M:F ratio of 1.1: 1. 10% of tumors were positive for IDO. 2% of tumors were positive for PD-L1. IDO (p=0.008) but not PD-L1 (p=0.99) correlated with survival in a univariate setting. IDO positivity also correlated with lymph node metastasis (p=0.04) and R1 resections (p=0.0006). Notably, CD8 did not correlate with survival (p=0.43), and CD8 counts did not correlate with either PD-L1 or IDO reactivity (p=0.82 and 0.81, respectively). On a multivariate analysis, only tumor size and IDO positivity correlated with survival. IDO expression in the TCGA cohort also correlated with inferior survival (p= 0.0282).



Conclusions: IDO predicts an inferior outcome in PDACs and our results support current trials using IDO inhibitor. PD-L1 reactivity is uncommon in PDAC and the results do not support the use of dual IDO and PD-L1 inhibitor use. Lastly, the mechanism of IDO does not appear to be depletion of lymphocytes.

1933 Microscopic Size Measurements Predict Outcomes in Post-Neoadjuvant Resections of Pancreatic Ductal Adenocarcinoma (PDAC)

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Background: Increasing numbers of PDACs, particularly borderline resectable (BR)/locally advanced (LA) tumors, are treated with neoadjuvant therapy. However, the AJCC 8th Edition does not reflect treatment effect on tumor size in T staging. The assessment of tumor size is hampered by heterogeneous response to therapy within the tumor, often resulting in multiple, small foci of residual tumor cells in a background of mass-forming fibrosis. Thus, we evaluated the performance of AJCC 8th Edition T staging in predicting patient outcomes based on several tumor size measurement methods.

Design: 97 post-neoadjuvant therapy pancreatectomy specimens (pT1-3) were reviewed, and all tumor foci were measured. T stages based on gross size with microscopic adjustment (GS), largest dimension of microscopic foci (LD), and average size of all microscopic foci (AS), were examined in association with clinicopathologic variables and patient outcomes.

Results: The mean age was 64.3 years; 49 (50.5%) were female. The majority (73.2%) of tumors were located in the pancreatic head, with an average pre-treatment tumor size (PS) of 3.2cm. Of 97 cases, 12.4% were clinically resectable, while 12.4% and 75.2% were BR and LA, respectively. After treatment, average GS, LD and AS were 2.5cm, 1.3cm, and 0.8cm, respectively; 41, 76, and 96 cases were classified as T1, 38, 21, and 1 cases as T2, and 18, 0, and 0 cases as T3, based on the GS, LD, and AS, respectively. A higher GS- and LD-based T stage was significantly associated with higher CAP tumor regression grade (TRG), lymphovascular and perineural invasion, uncinate margin involvement, and higher N stage. As for patient outcomes, higher TRG was associated with shorter overall survival (OS), but not disease-free survival (DFS). Higher LD-based T stage was significantly associated with shorter DFS (p=0.003 and p=0.068 by uni- and multivariate analyses, respectively) and shorter OS (p=0.094 and p=0.008, respectively). GS was marginally associated with OS by multivariate analysis (p=0.059), but PS and AS were not associated with any clinicopathologic factors or survival.

Conclusions: In post-neoadjuvant PDAC resections, determination of T stage based on GS and LD provides the best association with important histopathologic factors. However, LD-based T staging is superior to GS-based T staging for predicting DFS and OS, suggesting that microscopic measurements may have clinical utility beyond the conventional use of GS measurements alone. Evaluation of a larger cohort is underway.