Pancreatobiliary Pathology Society Journal Watch

August September 2018

Last Update on 2018-08-24

Contents

The Current PBPath Journal Watch Articles

Wellcome to our journal watch for pancreatobiliary pathology articles, which is released every other month.

We have created several categories for convenience; however, articles in each category are in no particular order.

Please feel free to fill out our feedback form. You may also recommend articles to be included.

Surgical Pathology

Pancreas

- Is an atypical flat lesion (AFL) a precursor lesion of the pancreatic ductal adenocarcinoma in human?

Pathology international 2018 Apr;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29664180

- Tumor grade as significant prognostic factor in pancreatic cancer: validation of a novel TNMG staging system

Neoplasma 2018 ;65(4):637-643

Aim of the study was to asses the tumor grade prognostic value in the Czech pancreatic cancer patients and to evaluate the accuracy of TNMG prognostic model. Retrospective analysis of 431 pancreatic cancer patients undergoing pancreatic resection in seven Czech oncological centers between 2003 and 2013 was performed. The impact of tumor grade and the accuracy of TNMG prognostic model were evaluated. Lymph node status, tumor size, tumor stage and grade were proved as statistically significant survival predictors. The lower tumor differentiation (grade 3 and 4) was associated with poorer prognosis in all stages (stage I: HR 2.23 [1.14; 4.36, CI 95%] p=0.019, stage II: HR 3.09 [2.01; 4.77, CI 95%] p=0.001, stage III and IV: HR 3.52 [1.73; 7.18, CI 95%] p=0.001). Kaplan-Meier analysis verified statistically significant impact of new TNMG stages on survival after resection for pancreatic cancer (p=0.001). In conclusion, we can state that the tumor grade was confirmed as statistically significant prognostic factor in pancreatic cancer. Its incorporation into the current TNM classification enables more accurate prognosis prediction within particular clinical stages. That is why an inclusion of the grade to the standard TNM classification should be discussed.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30064236

- Pathologic Evaluation of Surgical Margins in Pancreatic Cancer Specimens Using Color Coding With Tissue Marking Dyes

Pancreas 2018 Aug;47(7):830-836

OBJECTIVES: Processing of pancreatoduodenectomy specimens is not standardized; the clinical impact of pathologic surgical margins remains controversial. We used the color-coding method using tissue-marking dyes to evaluate margin status of resected specimens to assess its association with postoperative recurrence. METHODS: We developed a unified processing approach to assess pancreatoduodenectomy specimens. Five surgical margins of resected pancreatic specimens were marked with 5 colors. Microscopic resection margin distance (RMD) from margin closest to the tumor was evaluated for each surgical margin. Forty patients assessed using nonunified protocols, and 98 patients assessed using unified protocols were included. RESULTS: The frequency of tumors with RMD of 1 mm or less in posterior margin was significantly lower and that in portal vein/superior mesenteric vein margin was significantly higher in unified protocol group

than in nonunified protocol group (P < 0.001). In unified protocol group, tumors with RMD of 1 mm or less correlated with locoregional recurrence (P = 0.025) and recurrence-free survival (P = 0.030). Multivariate analysis revealed that tumor size and lymph node metastasis were independent indicators for disease recurrence. CONCLUSIONS: Resection margin distance of 1 mm or less was a predictor for disease recurrence, particularly for locoregional recurrence. Early detection of small-sized tumors without lymph node metastasis is necessary for improved clinical outcomes in pancreas cancers.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29975353

- High-grade PanIN presenting with localised stricture of the main pancreatic duct: A clinicopathological and molecular study of 10 cases suggests a clue for the early detection of pancreatic cancer

Histopathology 2018 Aug;73(2):247-258

AIMS: This study aimed to identify the pathological features of high-grade PanIN that presents with imaging-detectable abnormalities. METHODS AND RESULTS: Ten cases of isolated, main-duct, high-grade PanIN as the primary clinical presentation were identified. All patients presented with stenosis of the main pancreatic duct, with two being associated with extensive upstream duct dilatation (>5 mm in diameter). Pancreatic juice cytology suggested adenocarcinoma in all seven cases examined. In resected specimens, high-grade PanIN was present chiefly in the main pancreatic duct, with longitudinal extension ranging between 3 and 40 mm in length (median = 18 mm). In four cases, in which hypoechoic or hypovascular masses were observed on imaging, radiopathology correlations suggested that they represented parenchymal atrophy and subsequent fibrosis around affected ducts, but not invasive malignancy. On immunohistochemistry, the loss of p16 expression was found in five (50%), p53 overexpression in two (20%) and loss of SMAD4 expression in none (0%). KRAS mutations were detected in nine cases, with two dominant clones being found in three by ultrasensitive droplet digital polymerase chain reaction, suggesting the genetic heterogeneity of dysplastic cells composing individual lesions. Mutant GNAS was also observed in one case. CONCLUSIONS: Isolated high-grade PanIN may present with pancreatic duct stenosis. Therefore, intensive investigations including pancreatic juice cytology will be required for patients with unexplained pancreatic duct stenosis. The abnormal expression of p53 and SMAD4 is infrequent, while GNAS may be mutated in premalignant lesions mainly affecting the main pancreatic duct, similar to KRAS.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29660164

- The "T" now Matters: The Eighth Edition of the Union for International Cancer Control Classification of Pancreatic Adenocarcinoma

Annals of surgery 2018 Aug;268(2):e36-e37

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=28938271

- Significance of microcystic, elongated, and fragmented glandular-like features in intraductal papillary mucinous neoplasm of the pancreas

Human pathology 2018 Aug;78():18-27

Microcystic, elongated, and fragmented (MELF) glandular features are associated with epithelial-mesenchymal transition, invasion, and progression in endometrioid adenocarcinoma of the uterus. Similar histological features are also observed at the periphery of pancreatic intraductal papillary mucinous neoplasms (IPMNs). However, the clinicopathological significance of MELF-like features-particularly whether

they represent regenerative or truly neoplastic conditions-in IPMNs remains unclear. We assessed a total of 152 surgically resected IPMNs. Fifty cases exhibited MELF-like features, including 26 cases of IPMNs with accompanying adenocarcinomas and 24 cases of IPMNs without accompanying adenocarcinomas. MELF-like features were more frequently observed in IPMN cases with accompanying adenocarcinomas, larger tumors, main-duct type, and non-gastric histologic subtype. A positive correlation between the presence of MELF-like features and high-grade dysplasia was observed in IPMNs without accompanying adenocarcinomas. Moreover, DPC4 loss and p53 overexpression in MELF-like glands were more commonly observed in IPMNs with high-grade dysplasia. IPMN patients with MELF-like features had worse overall and disease-specific survival by univariate analyses. Our observations suggest that MELF-like features in some IPMNs with high-grade dysplasia could be related to stromal invasion. Hence, when MELF-like features are observed in IPMNs, pathologists should carefully evaluate the results of microscopic examinations to identify the invasive components; and, immunohistochemical staining for DPC4 and p53 could help clarify its clinicopathological significance.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29410139

- Immune Cell and Stromal Signature Associated with Progression-free Survival of Patients with Resected Pancreatic Ductal Adenocarcinoma

Gastroenterology 2018 Aug;():

BACKGROUND & AIMS: Changes to the microenvironment of pancreatic ductal adenocarcinomas (PDACs) have been associated with poor outcomes of patients. We studied the associations between composition of the pancreatic stroma (fibrogenic, inert, dormant, or fibrolytic stroma) and infiltration by inflammatory cells and times of progression-free survival (PFS) of patients with PDACs after resection. METHODS: We obtained 1824 tissue microarray specimens from 385 patients included in the European Study Group for Pancreatic Cancer trial 1 and 3 and performed immunohistochemistry to detect alpha smooth muscle actin, type 1 collagen, CD3, CD4, CD8, CD68, CD206, and neutrophils. Tumors that expressed high and low levels of these markers were compared with patient outcomes using Kaplan-Meier curves and multivariable recursive partitioning for discrete-time survival tree analysis. Prognostic index was delineated by a multivariable Cox-proportional-hazards-model of immune cell and stromal markers and PFS. Findings were validated using 279 tissue microarray specimens from 93 patients in a separate cohort. RESULTS: Levels of CD3, CD4, CD8, CD68, and CD206 were independently associated with tumor recurrence. Recursive partitioning for discrete-time survival tree analysis identified a high level of CD3 as the strongest independent predictor for longer PFS. Tumors with levels of CD3 and high levels of CD206 associated with a median PFS time of 16.6 months and a median prognostic index of -0.32 (95% CI, -0.35 to -0.31), whereas tumors with low level of CD3 cell and low level of CD8 and high level of CD68 associated with a median PFS time of 7.9 month and a prognostic index of 0.32 (95% CI, 0.050-0.32)-we called these patterns histologic signatures. Stroma composition, when unassociated with inflammatory cell markers, did not associate significantly with PFS. In the validation cohort, the histologic signature resulted in an error matrix accuracy of predicted response of 0.75 (95% CI, 0.64-0.83; accuracy P<.001). CONCLUSIONS: In an analysis of PDAC tissue microarray specimens, we identified and validated a histologic signature, based on leukocyte and stromal factors, that associates with PFS times of patients with resected PDACs. Immune cells might affect the composition of the pancreatic stroma to affect progression of PDAC. These findings provide new insights into the immune response to PDAC.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30092175

- Tumour origin and R1 rates in pancreatic resections: towards consilience in pathology reporting

Virchows Archiv : an international journal of pathology 2018 Aug;():

To evaluate differences in the R1 rates of ampullary (AC), pancreatic (PC), and distal bile duct (DBD) cancers in pancreatoduodenectomies (PD) using standardised pathology assessment. Data of PD (2010-2011) analysed in accordance with the Royal College of Pathologists (UK) protocol, were retrieved. Clinicopathologic features, including frequency, topography, and mode of margin involvement in AC (n = 87), PC (n = 18), and DBD (n = 5) cancers were evaluated. The R1 rate was 7%, 67%, and 20% in the AC, PC, and DBD cancers ($p < 0.001$). Within the PC cohort, R1 rate was heterogeneous (chemo-naïve, 77%; post-neoadjuvant, 40%). Commonest involved margins were as follows: posterior in overall PD (35%), AC (43%), overall PC (33%), and post-neoadjuvant PC (100%); superior mesenteric artery margin in chemo-naïve PC (38%) and common bile duct margin in DBD (100%) cancers. In AC, majority (66%) of R1 were signet ring cell type. Indirect margin involvement due to tumour within lymph node, perineural sheath or lymphovascular space was observed in 26% cases, and altered R1 rate in AC, PC, and DBD cohorts by 1%, 12%, and 0%, respectively. Although not statistically significant, patients with R1 had lower disease-free survival than those with R0 (mean, 25.4 months versus 44.4 months). Tumour origin impacts R1 data in PD necessitating its accurate classification by pathologists. Indirect involvement, histology, and neoadjuvant therapy influence the R1 rate, albeit in a minority of cases. Generating cogent R1 data based on standardised pathology reporting is the foremost need of the hour.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30091124

https://link.springer.com/article/10.1007/s00428-018-2429-7

- From somatic mutation to early detection: Insights from molecular characterization of pancreatic cancer precursor lesions

The Journal of pathology 2018 Aug;():

Pancreatic cancer arises from non-invasive precursor lesions, including pan creatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN), which are curable if detected early enough. Recently, these types of precursor lesions have been extensively characterized at the molecular level, defining the timing of critical genetic alterations in tumorigenesis pathways. The results of these studies deepen our understanding of tumorigenesis in the pancreas, providing novel insights into tumor initiation and progression. Perhaps more importantly, they also provide a rational foundation for early detection approaches that could allow clinical intervention prior to malignant transformation. In this review, we summarize the results of comprehensive molecular characterization of PanINs, IPMNs, and MCNs, and discuss the implications for cancer biology as well as early detection.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30105857

- Multinational validation of the AJCC 8th edition pancreatic cancer staging system in a pancreas head cancer cohort

Journal of hepato-biliary-pancreatic sciences 2018 Aug;():

BACKGROUND: The aim was to compare the 7th and 8th editions of the AJCC staging system for pancreas head cancer and to validate the 8th edition using three multinational tertiary center data. METHODS: Data of 2,864 patients with pancreas head cancer were collected from Korea (571), Japan (824), and the USA (1,469). Survival analysis was performed to compare the 7th and 8th editions. Validation was performed by log-rank tests and test for trend repeated 1,000 times with random sets. RESULTS: In the 7th edition, 4.1%, 3.1%, 18.6%, 67.5%, 3.6%, and 3.1% were stage IA, IB, IIA, IIB, III, and IV. In the 8th edition, 8.8%, 13.9%, 3.1%, 38.2%, 32.9%, and 3.1% were stage IA, IB, IIA, IIB, III, and IV, respectively. The change in T category down-staged 459 patients from IIA to the new IA and IB. The new N2 category upstaged 856 patients from the former IIB to III. The 7th edition reversely stratified IA and IB. The 8th edition

corrected this mis-stratification of the 7th edition, but lacked discriminatory power between IB and IIA (p=0.271). Validation using the log-rank showed that the 8th edition provided better discrimination in 6.387 test sets among 10 tests. The test for trend validated the 8th edition to stratify stages in correct order more often (7.815/10). CONCLUSION: The 8th edition provides more even distribution with more powerful discrimination compared to the 7th edition. IRB REGISTRATION NUMBER BY SEOUL NATIONAL UNIVERSITY: H-1504-062-664:

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30118171

- Solid-pseudopapillary neoplasms of the pancreas do not express major pancreatic markers in pediatric patients

Human pathology 2018 Aug;():

Solid pseudopapillary neoplasms of the pancreas (SPN) are classified as "exocrine" pancreatic tumors by the World Health Organization. However, despite numerous studies using immunohistochemistry, electron microscopy, animal models and molecular biology, the histogenesis of SPN remains unclear. At the same time, our knowledge of human pancreas development has significantly increased. It is now well known that the undifferentiated PDX1+ pancreatic progenitors proliferate and differentiate into endocrine, ductal, and acinar cells, thanks to the expression of numerous transcription factors, which can be used to better characterize pancreatic tumors. In a series of 14 pediatric SPN, we investigated the expression of four transcription factors associated with pancreatic development (PDX1, SOX9, PTF1A and NKX2.2) to obtain new insights into the pathogenesis of SPN. In addition, we tested the expression of different markers of epithelial, endocrine, exocrine, and neural differentiation, using both immunohistochemical and immunofluorescence analyses. All tumors displayed the typical histological features of SPN, with both pseudopapillary and solid patterns. The immunoprofile was characterized by immunoreactivity for ß-catenin (100%), progesterone receptor (100%), cyclin D1 (100%), synaptophysin (65%) and S100 (15%). In all cases, tumor cells were negative for the following markers: PDX1, SOX9, PTF1A, NKX2.2, chromogranin A, glucagon, insulin, somatostatin, ghrelin, pancreatic polypeptide, amylase, GFAP, calretinin, EPCAM and estrogen receptor . To conclude, SPN do not express major transcription factors involved in pancreatic development and differentiation, which does not allow to precise pancreatic lineage of tumor cells. Thus additional studies are still required to determine origin of SPN.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30130629

- CD200 expression is a feature of solid pseudopapillary neoplasms of the pancreas

Virchows Archiv : an international journal of pathology 2018 Aug;():

CD200 has been recently indicated as a robust marker of well-differentiated neuroendocrine neoplasms. Here, we evaluate its role in differential diagnosis of solid pancreatic neoplasms. We immunostained for CD200 22 solid pseudopapillary neoplasms (SPNs), 8 acinar carcinomas (ACs), 2 pancreatoblastomas (PBs), 138 neuroendocrine tumors (PanNETs), and 48 ductal adenocarcinomas. All SPNs showed strong cytoplasmic and membranous staining for CD200, while only one case of AC had focal positivity. The two PBs showed focal CD200 positivity, mainly located in squamoid nests. The vast majority of PanNETs (96%) showed strong cytoplasmic and membranous staining for CD200, whereas all PDACs were negative. As both PanNETs and SPNs express CD200, it has no role in the differential diagnosis between these two entities.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30132130

- "Pancreatic Mucoepidermoid Carcinoma" is not a Pancreatic Counterpart of CRTC1/3-MAML2 Fusion Gene-related Mucoepidermoid Carcinoma of the Salivary Gland, and May More Appropriately be Termed Pancreatic Adenosquamous Carcinoma With Mucoepidermoid Carcinoma-like Features

The American journal of surgical pathology 2018 Aug;():

"Mucoepidermoid carcinoma (MEC)" has been accepted as a synonym for pancreatic adenosquamous carcinoma (ASC). Pancreatic ASC can show salivary gland-type MEC-like morphology. CRTC1/3-MAML2 fusion gene is a characteristic molecular feature of MEC of the salivary gland. We conducted this study to clarify whether the pancreatic ASC with salivary gland-type MEC-like morphology (Pan-MEC) is a pancreatic counterpart of salivary gland-type MEC (Sal-MEC). We retrospectively analyzed 37 pancreatic ASCs including 16 Pan-MECs and 21 tumors without MEC-like features (ASC-NOS [not otherwise specified]), and we investigated (1) clinicopathologic features, (2) the presence of CRTC1/3-MAML2 fusion gene by reverse transcription polymerase chain reaction, (3) the presence of rearrangement of MAML2 gene by fluorescence in situ hybridization, and (4) mucin core proteins by immunohistochemistry. We also compared 16 Pan-MECs with 20 Sal-MECs by immunohistochemistry for mucin core protein. There were no significant differences of any clinicopathologic characteristics and survival analysis between the Pan-MECs and ASCs-NOS. Of note, the pancreatic ASCs (including Pan-MEC and ASC-NOS) were significantly more aggressive than conventional pancreatic ductal adenocarcinoma. In addition, all Pan-MECs were histologically high-grade. CRTC1/3-MAML2 fusion gene and MAML2 gene rearrangement were not detected in any ASCs including Pan-MECs. There were significant differences of MUC5AC and MUC6 between the Pan-MECs and Sal-MECs, but no significant differences of mucin core protein between the Pan-MECs and pancreatic ASCs-NOS. Pan-MEC is histologically and biologically high-grade and unrelated to CRTC1/3-MAML2 fusion gene, unlike Sal-MEC which is related to CRTC1/3-MAML2 fusion gene. Pan-MEC is not a pancreatic counterpart of CRTC1/3-MAML2 fusion gene-related Sal-MEC.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30138216

IPMN

- Does Surgical Margin Impact Recurrence in Noninvasive Intraductal Papillary Mucinous Neoplasms?: A Multi-institutional Study

Annals of surgery 2018 Sep;268(3):469-478

OBJECTIVE: The relevance of margin positivity on recurrence after resection of intraductal papillary mucinous neoplasms (IPMNs) is poorly defined and represents one reason controversy remains regarding optimal surveillance recommendations. METHODS: Patients undergoing surgery for noninvasive IPMN at 8 academic medical centers from the Central Pancreas Consortium were analyzed. A positive margin was defined as presence of IPMN or pancreatic intraepithelial neoplasia. RESULTS: Five hundred two patients underwent surgery for IPMN; 330 (66%) did not have invasive cancer on final pathology and form the study cohort. Of these, 20% harbored high grade dysplasia. A positive margin was found in 20% of cases and was associated with multifocal disease ($P = 0.02$). The majority of positive margins were associated with low grade dysplasia. At a median follow-up of 36 months, 34 (10.3%) patients recurred, with 6.7% developing recurrent cystic disease and 3.6% developing invasive cancer. On multivariate analysis, margin positivity was not associated with recurrence of either IPMN or invasive cancer ($P > 0.05$). No association between margin status and development of recurrence at the margin was found. Only 6% of recurrences developed at the resection margin and median time to recurrence was 22 months. Of note, 18% of recurrences occurred > 5 years following surgery. CONCLUSION: Margin positivity after resection for noninvasive IPMNs is primarily due to low grade dysplasia and is not associated with developing recurrence in the remnant pancreas

or at the resection margin. Long-term surveillance is required for all patients, as a significant number of recurrences developed over 5 years after the index operation.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30063495

https://journals.lww.com/annalsofsurgery/Abstract/2018/09000/Does_Surgical_Margin_Impact_Recurrence_in.10.aspx

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- **Transmembrane mucin MUC13 distinguishes intraductal papillary mucinous neoplasms from non-mucinous cysts and is associated with high-risk lesions**

https://www.sciencedirect.com/science/article/pii/S1365182X18326947

- **Importance of main pancreatic duct dilatation in IPMN undergoing surveillance**

https://onlinelibrary.wiley.com/doi/abs/10.1002/bjs.10948

- Comparison of the Survival Outcomes of Pancreatic Cancer and Intraductal Papillary Mucinous Neoplasms

Pancreas 2018 Sep;47(8):974-979

OBJECTIVES: The aims of the study were to compare survival outcomes between patients with pancreatic ductal adenocarcinoma (PDAC) and invasive intraductal papillary mucinous neoplasms (IPMN) and to determine candidates for adjuvant chemotherapy. METHODS: A total of 579 consecutive patients, including 375 PDAC and 204 IPMN patients, were reviewed. Stage-matched comparisons of survival data were conducted using the Cox proportional hazards model and propensity analysis. To evaluate prognostic factors, univariate and multivariate Cox regression analyses were performed. RESULTS: The overall survival for invasive IPMN was significantly longer than that for PDAC (hazard ratio, 2.34; P = 0.0001). When the analysis was limited to stage I patients, the 5-year overall survival rate of invasive IPMN patients was significantly better than that of PDAC patients (100% vs 74.1%, P = 0.0092); however, no difference was observed between stage II patients with invasive IPMN and PDAC (hazard ratio, 1.49; P = 0.09). The Cox proportional hazards model and propensity analysis demonstrated no difference in stage-matched survival. Multivariate analysis revealed that only T (3) was an independent prognostic factor for invasive IPMN. CONCLUSIONS: Stage-matched analysis did not show a significant survival difference between invasive IPMN and PDAC patients, and T3 or higher was an independent prognostic factor for invasive IPMN.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30028445

Biliary Tract

- **Data set for the reporting of intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma and hepatocellular carcinoma: recommendations from the International Collaboration on Cancer Reporting (ICCR)**

https://onlinelibrary.wiley.com/doi/abs/10.1111/his.13520?campaign=woletoc

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- Interleukin-33 overexpression reflects less aggressive tumour features in large-duct type cholangiocarcinomas

Histopathology 2018 Aug;73(2):259-272

AIMS: The aim of the present study was to elucidate the clinicopathological significance of interleukin (IL)-6 and IL-33 expression in intrahepatic cholangiocarcinomas (iCCAs) and perihilar cholangiocarcinomas (pCCAs). METHODS AND RESULTS: IL-6 and IL-33 mRNA expression levels were examined in iCCAs (n = 55) and pCCAs (n = 32) by the use of quantitative real-time polymerase chain reaction and a highly sensitive in-situ hybridisation protocol (RNAscope), and expression levels were correlated with clinicopathological features. According to a recently proposed classification scheme, iCCAs were separated into small-duct (n = 33) and large-duct (n = 22) types. IL-6 and IL-33 expression levels were higher in large-duct iCCAs and pCCAs than in small-duct iCCAs, and there was a positive correlation between the expression levels of these cytokines. Double in-situ hybridisation/immunostaining showed that IL-6 mRNA was expressed in actin-positive (myo)fibroblasts, whereas IL-33 mRNA was mainly produced by CD31-positive endothelial cells. With the average expression level as a cut-off point, cases were classified as IL-6high and IL-6low or IL-33high and IL-33low . In the combined cohort of large-duct iCCAs and pCCAs, IL-6high and IL-6low cholangiocarcinomas shared many features, whereas IL-33high cases had less aggressive characteristics than IL-33low cases, as shown by lower tumour marker concentrations, smaller tumour sizes, less common vascular invasion, lower pT stages, and higher lymphocyte/monocyte ratios in blood. KRAS mutations were slightly less common in IL-33high cases than in IL-33low cases (9% versus 29%; P = 0.061). The strong expression of IL-33 in tissue appeared to be an independent favourable prognostic factor. CONCLUSIONS: IL-33high cholangiocarcinomas may represent a unique, less aggressive carcinogenetic process of the large bile ducts.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29675965

doi: https://doi.org/10.1111/his.13633

- Postradiation Synovial Sarcoma of the Common Bile Duct: A Previously Unreported Anatomic Site *International journal of surgical pathology 2018 Aug;26(5):469-474*

Synovial sarcoma is a ubiquitous neoplasm predominantly affecting soft tissues of young adults of any gender; few cases have been described in the digestive system, mostly in the stomach. The (X;18)(p11.2; q11.2) translocation yields unique SS18-SSX fusion genes. Synovial sarcoma has been related to radiotherapy, but no synovial sarcoma has been associated with the digestive system. This article describes the case of a synovial sarcoma arising along the extrahepatic biliary tree, 10 years after the application of an abdominal radiotherapy schedule due to a retroperitoneal metastatic seminoma in a male who developed progressive obstructive jaundice. Ninety percent of the analyzed cells carried the SS18 gene with separation of sequences, thus denoting a translocation. There are only 8 post-radiotherapy synovial sarcomas that have been reported previously, and this is the first report of a radiotherapy-related synovial sarcoma arising from the extrahepatic biliary tree, and the second case described in this anatomic region.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29336183

doi: https://doi.org/10.1177/1066896917752863

- Mucinous intrahepatic cholangiocarcinoma: a distinct variant

Human pathology 2018 Aug;78():131-137

Mucinous variant of intrahepatic cholangiocarcinoma (iCC) is rare, and its clinicopathological features and prognosis are far less clear. Six patients who had iCCs with more than 50% of mucinous component and 79 conventional iCCs were included in the study. The mean size of mucinous and conventional iCCs was 6.2 and 6.0 cm, respectively. Most patients (83%) with mucinous iCC presented at T3 stage or above compared with 28% of the conventional group ($P < .01$). Three patients with mucinous iCC (50%) died within 1 year. The average survival time of patients with mucinous iCCs was significantly reduced compared with that of the conventional group (9 months versus 2 years; $P < .001$). Immunohistochemistry was performed on 6 mucinous and 12 conventional iCCs with matched age, sex, and stage, which revealed positive immunoreactivity in MUC1 (83% versus 58%), MUC2 (33% versus 17%), MUC5AC (100% versus 42%), MUC6 (50% versus 0), CK7 (83% versus 83%), CK20 (0 versus 17%), CDX2 (17% versus 0), p53 (67% versus 67%), Smad4 (67% versus 58%), and EGFR (83% versus 42%) in mucinous and conventional iCCs, respectively. Molecular studies showed one mucinous iCC with KRAS G12C mutation and no BRAF or IDH1/2 mutations. Mucinous iCC is a unique variant that constitutes 7% of iCCs. It is more immunoreactive for MUC1, MUC2, MUC5AC, and MUC6. Unlike adenocarcinomas of colorectal primary, mucinous iCCs are often CK7+/CK20-/CDX2- and microsatellite stable. Patients with mucinous iCC likely present at advanced stage upon diagnosis with shorter survival time compared with the conventional counterparts.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29698701

Gallbladder

- Validation of American Joint Committee on Cancer eighth staging system for gallbladder cancer and its lymphadenectomy guidelines

The Journal of surgical research 2018 Oct;230():148-154

BACKGROUND: For gallbladder cancer (GBC), the American Joint Committee on Cancer eighth edition (AJCC 8) staging system classifies lymph node (LN) stage by the number of positive LN and recommends sampling of 6 LNs. We evaluated the prognostic capability of the AJCC 8 for patients undergoing resection and the current national trends in LN staging in the context of these new recommendations for nodal (N) sampling. METHODS: Utilizing the National Cancer Data Base, we identified all gallbladder adenocarcinoma patients treated with surgical resection in 2004-2014. Cox regression modeling was used to calculate the concordance index of AJCC 8 in predicting overall survival. N sampling and positivity rates were analyzed over the study period. RESULTS: In our cohort, predicted 5-year overall survival by AJCC 8 was: stage I, 62.5%; II, 50.2%; IIIA, 25.7%; IIIB, 22.1%; IVA, 15.7%; IVB, 6.7% ($P < 0.01$). The concordance index for the staging system was 0.832. Only 50.7% of the patients had any LN sampling to determine the N stage. LN sampling rates improved from 45.6% in 2004 to 55.1% in 2013 ($P < 0.001$). However, only 24.5% of patients with any LN sampling had 6 LNs resected (12.4% of eligible cohort), with a median LN sample of two. CONCLUSIONS: AJCC 8 offers adequate discrimination for GBC staging, especially for node-positive patients. With actual GBC LN sampling rates at 50.7%, and far short of the 6 LN threshold, quality improvement measures may need to focus on requiring any LN sampling before raising the minimum to six LNs.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30100032

- **Clinicopathological features and survival of gallbladder squamous cell carcinoma: analysis of 121 cases**

http://www.ijcep.com/files/ijcep0076184.pdf

- **Pyloric Gland Adenoma (PGA) of the Gallbladder: A Unique and Distinct Tumor from PGAs of the Stomach, Duodenum, and Pancreas**

The American journal of surgical pathology 2018 Sep;42(9):1237-1245

Twenty-four surgically resected, gallbladder pyloric gland adenomas (GB-PGAs) were examined and their features were compared with the reported features of stomach, duodenum, and pancreatic PGAs to better understand GB-PGAs. Clinical information on background gallbladder lesions and histologic data, including tumor grade, existence of squamoid morules, intratumoral cholesterosis, and intracytoplasmic mucins were collected. Immunohistochemical staining for MUC2, MUC5AC, MUC6, CDX2, pepsinogen I, p53, and MIB-1/nuclear -catenin were evaluated. Targeted mutational analyses of KRAS exon2, GNAS exon 7, and CTNNB1 exon 3 were conducted. We found that 29.2% of the GB-PGAs were histologically high-grade dysplasias/carcinomas; 70.8% were low grade; and 20.8% and 33.3% contained squamoid morules and intratumoral cholesterosis, respectively. In addition, 45.8% and 54.2% of GB-PGAs were mucin-rich and mucin-poor types, respectively. Immunohistochemically, MUC6 was diffusely positive in all GB-PGAs; MUC2, MUC5AC, and CDX2 were only focally positive, and no pepsinogen-I positive cells were observed. Nuclear -catenin accumulation was observed in all cases; however, the ratio varied among cases. Mucin-poor types were significantly associated with high histologic grade dysplasias/carcinomas and high nuclear -catenin labeling indices. Mutational analyses identified CTNNB1 mutations in 100% of GB-PGAs (21/21), KRAS in 4.2% (1/23), and GNAS in 0% (0/22). The present study clarified the unique histologic features, phenotypic differentiation, and molecular statuses frequently associated with GB-PGAs. Altogether, our data suggest that tumorigenesis of GB-PGA is distinct from that of stomach, duodenum, and pancreatic PGAs.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29975247

https://journals.lww.com/ajsp/Abstract/2018/09000/Pyloric_Gland_Adenoma___PGA___of_the_Gallbladder___A.12.aspx

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Ampulla of Vater

- **Intraobserver and Interobserver Variability in the Assessment of Dysplasia in Ampullary Mucosal Biopsies** *The American journal of surgical pathology 2018 Aug;42(8):1095-1100*

Endoscopic mucosal biopsies of the ampulla of Vater (AmpBx) are obtained to histologically assess for dysplasia or carcinoma. However, biopsy material is often scant and a host of factors can induce histologic changes that pose diagnostic challenges. We sought to investigate observer variability in interpretation of AmpBx and the impact clinical data may have on diagnostic interpretation. Thirty-one cases from institutional archives were selected, including 12 cases of reactive atypia (RA), 8 indefinite for dysplasia (ID), and 11 showing low-grade dysplasia (LGD). Slides were independently reviewed at 3 time points with and without clinical information by 6 pathologists who categorized the biopsies RA, ID, or LGD. Following the reviews, intraobserver and interobserver agreement was assessed. Review of AmpBx without clinical data showed fair (, 0.27), poor (, 0.07), and good (, 0.42) interobserver agreement for diagnoses of RA, ID, and LGD, respectively. Interobserver agreement improved for LGD (, 0.66 and 0.73) when clinical information was provided; however, agreement remained fair for RA (, 0.4 and 0.42) and poor-to-fair for ID (, 0.17 and 0.25). When follow-up data were reviewed, all cases that reached unanimous agreement had that diagnosis substantiated by subsequent endoscopic or histologic findings. The same was true of 13 of 19 cases that reached majority consensus. Given the potential clinical consequences of these diagnoses combined with the significant intraobserver and interobserver variability found in this study, we conclude that better-defined

diagnostic criteria and consensus reads on difficult cases would assist in the histologic assessment of these challenging cases.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29738360

doi: https://doi.org/10.1097/PAS.0000000000001079

PanNET Neuroendocrine

- **ATRX loss is an independent predictor of poor survival in pancreatic neuroendocrine tumours**

https://www.sciencedirect.com/science/article/pii/S0046817718303009

- ATRX loss is an independent predictor of poor survival in pancreatic neuroendocrine tumours

Human pathology 2018 Aug;():

Pancreatic neuroendocrine tumours (PanNETs) are rare neoplasms accounting for 1-2% of all pancreatic tumours. The biological behaviour of PanNETs is heterogeneous and unpredictable, adding to the difficulties of clinical management. The DAXX (death domain associated protein) and ATRX (alpha-thalassemia/mental retardation syndrome X-linked) genes encode proteins involved in SWI/SNF-like chromatin remodelling. Somatic inactivating mutations in DAXX and ATRX are frequent in PanNETs, mutually exclusive, and associated with telomere dysfunction resulting in genomic instability and alternate lengthening of telomeres. We sought to assess the clinical significance of the loss of the ATRX and DAXX proteins as determined by immunohistochemistry (IHC) in patients with PanNET. From an unselected cohort of 105 patients, we found ATRX loss in 10 tumours (9.5%) and DAXX loss in 16 (15.2%). DAXX and ATRX loss were confirmed mutually exclusive and associated with other adverse clinicopathological variables and poor survival in univariate analysis. In addition ATRX loss was also associated with higher AJCC stage and infiltrative tumour borders. However only ATRX loss, lymphovascular invasion and perineural spread were independent predictors of poor overall survival in multivariate analysis. In conclusion, loss of expression of ATRX as determined by IHC is a useful independent predictor of poor overall survival in PanNETs. Given its relative availability, ATRX loss as determined by IHC may have a role in routine clinical practice to refine prognostication in patients with PanNET.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30081149

- Recurrence of Pancreatic Neuroendocrine Tumors and Survival Predicted by Ki67

Annals of surgical oncology 2018 Aug;25(8):2467-2474

BACKGROUND: Despite evidence of different malignant potentials, postoperative follow-up assessment is similar for G1 and G2 pancreatic neuroendocrine tumors (panNETs) and adjuvant treatment currently is not indicated. This study investigated the role of Ki67 with regard to recurrence and survival after curative resection of panNET. METHODS: Patients with resected non-functioning panNET diagnosed between 1992 and 2016 from three institutions were retrospectively analyzed. Patients who had G1 or G2 tumor without distant metastases or hereditary syndromes were included in the study. The patients were re-categorized

into Ki67 0-5 and Ki67 6-20%. Cox regression analysis with log-rank testing for recurrence and survival was performed. RESULTS: The study enrolled 241 patients (86%) with Ki67 0-5% and 39 patients (14%) with Ki67 6-20%. Recurrence was seen in 34 patients (14%) with Ki67 0-5% after a median period of 34 months and in 16 patients (41%) with Ki67 6-20% after a median period of 16 months ($p < 0.001$). The 5-year recurrence-free and 10-year disease-specific survival periods were respectively 90 and 91% for Ki67 0-5% and respectively 55 and 26% for Ki67 6-20% ($p < 0.001$). The overall survival period after recurrence was 44.9 months, which was comparable between the two groups ($p = 0.283$). In addition to a Ki67 rate higher than 5%, tumor larger than 4 cm and lymph node metastases were independently associated with recurrence. CONCLUSIONS: Patients at high risk for recurrence after curative resection of G1 or G2 panNET can be identified by a Ki67 rate higher than 5%. These patients should be more closely monitored postoperatively to detect recurrence early and might benefit from adjuvant treatment. A clear postoperative follow-up regimen is proposed.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29789972

- Neuroendocrine tumor of the pancreas with rhabdoid feature

Virchows Archiv : an international journal of pathology 2018 Jun;():

Imaging of a 53-year-old Japanese man revealed two tumors in the liver and a tumor in the head of the pancreas with a swelling lymph node. A needle biopsy for the liver tumors was performed, revealing a neuroendocrine tumor. Enucleation, lymphadenectomy, and partial hepatectomy were performed. The microscopic examination identified many tumor cells with intracytoplasmic inclusions arranged in a nested, cord, or tubular fashion. The intracytoplasmic inclusions displayed densely eosinophilic globules and displaced the nuclei toward the periphery, which constitutes “rhabdoid” features. The tumor cells were positive for synaptophysin and weakly positive for NCAM, but negative for chromogranin A. Epithelial markers (AE1/AE3 and CAM5.2) accentuated intracytoplasmic globules. Pancreatic neuroendocrine tumors with rhabdoid features are very rare. Generally, rhabdoid features are aggressive and dedifferentiated characteristics of various types of tumor. Pancreatic neuroendocrine tumors containing rhabdoid cells tend to display extrapancreatic spread at the time of presentation, although some of these tumors with rhabdoid features are not always associated with aggressive behavior.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29938394

- Prognostic Significance of Preoperative Neutrophil-to-Lymphocyte Ratio in Surgically Resectable Pancreatic Neuroendocrine Tumors

Medical science monitor : international medical journal of experimental and clinical research 2017 Nov;23():5574-5588

BACKGROUND The aim of this study was to evaluate the predictive and prognostic value of the preoperative neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in pancreatic neuroendocrine tumor (PNET) patients undergoing potentially curative resection. MATERIAL AND METHODS A retrospective review of 172 patients with PNETs was conducted. Kaplan-Meier curves and multivariate Cox proportional models were used to calculate overall survival (OS) and disease-free survival (DFS). The predictive performance of the NLR was compared with other inflammation-based scores and conventional stratification systems using receiver operating characteristic (ROC) curve analysis. RESULTS Elevated NLR and PLR were both associated with advanced AJCC stage and high grade. In the univariate analysis, elevated NLR and PLR were both significantly associated with decreased OS and DFS. In the multivariate analysis, the preoperative NLR, but not the PLR, was an independent risk factor for OS (HR=4.471, 95% CI 1.531-13.054, p=0.006) and DFS (HR=2.531, 95% CI 1.202-5.329, p=0.015). The discriminatory capability of the NLR was superior to that of other inflammation-based scores in OS prediction. Furthermore,

the predictive range was expanded by incorporating the NLR into the conventional stratification systems, including the AJCC stage and WHO classification systems. CONCLUSIONS As an independent prognostic factor, an elevated preoperative NLR is superior to the PLR with respect to predicting clinical outcomes in PNET patients undergoing potentially curative resection. The incorporation of the NLR into the existing conventional stratification systems improved the predictive accuracy.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29168979

- **Variability of the Ki-67 proliferation index in gastroenteropancreatic neuroendocrine neoplasms - a single-center retrospective study** https://link.springer.com/article/10.1186/s12902-018-0274-y

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- **APOBEC3B High Expression in Gastroenteropancreatic Neuroendocrine Neoplasms and Association With Lymph Metastasis**

Applied immunohistochemistry & molecular morphology : AIMM 2018 Aug;():

PURPOSE: Apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3B (APOBEC3B) is known as a source of mutations in multiple cancers. Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are a group of heterogeneous tumors. However, the expression and significance of APOBEC3B in GEP-NENs remains unclear. MATERIALS AND METHODS: A total of 158 cases of GEP-NENs, including 78 cases of biopsy or endoscopic submucosal dissection resection specimens and 83 cases of surgical resection specimens were collected in this study. The cases were grouped according to tumor classification grade, including 42 cases of neuroendocrine tumors G1 (NET G1), 36 cases of NET G2, 36 cases of NET G3, 44 cases of neuroendocrine carcinoma (NEC). All of the 158 tumors were immunohistochemically studied using a polyclonal antibody against APOBEC3B. We evaluated APOBEC3B expression in GEP-NENs and investigated the relationships among the immunoreactivity of APOBEC3B, clinical and pathologic features, such as age, sex, tumor site, Ki67 cell proliferation index, and lymph metastasis. RESULTS: A total of 33 cases (78.6%) of NET G1 showed high expression of APOBEC3B. A total of 28 cases (77.8%) of NET G2 demonstrated high expression of APOBEC3B. In NET G3 and NEC cases, the positive rates were 52.8% and 2.3%, respectively. The expression of APOBEC3B in NETs was significantly higher than that in NECs, NET G1 and NET G2 were higher than NET G3, and the difference was statistically significant. APOBEC3B high expression cases have lower lymph node metastasis rate, lower Ki67 cell proliferation index. CONCLUSIONS: In this study, APOBEC3B is highly expressed in GEP-NETs and is a predictor of lymph node metastasis in NET G3 and NEC cases. These findings might provide new insights into the biological mechanisms of GEP-NENs tumorigenesis and progression.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30095460

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Cytopathology

Pancreas

- Acute Pancreatitis History Carries Higher Risk in Endoscopic Ultrasound-Guided Fine-Needle Aspiration of Pancreatic Lesions

Pancreas 2018 Aug;47(7):e38-e40

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29985847

Biliary Tract

Gallbladder

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PanNET Neuroendocrine

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Molecular Pathology

Pancreas

- WIPF1 antagonizes the tumor suppressive effect of miR-141/200c and is associated with poor survival in patients with PDAC *Journal of experimental & clinical cancer research : CR 2018 Jul;37(1):167*

BACKGROUND: Aberrant expression of Wiskott-Aldrich syndrome protein interacting protein family member 1 (WIPF1) contributes to the invasion and metastasis of several malignancies. However, the role of WIPF1 in human pancreatic ductal adenocarcinoma (PDAC) remains poorly understood. METHODS: Human pancreatic cancer samples from PDAC patients were collected for methylation analysis. Bioinformatic prediction program and luciferase reporter assay were used to identify microRNAs regulating WIPF1 expression. The association between WIPF1 expression and the overall survival (OS) of patients with PDAC was evaluated by using The Cancer Genome Atlas (TCGA) database. The roles of miR-141/200c and WIPF1 on the invasion and metastasis of PDAC cells were investigated both in vitro and in vivo. RESULTS: We found that compared to the surrounding non-cancerous tissues, there was significantly increased methylation of miR-200c and miR-141 in human PDAC tissues that resulted in their silencing, whereas the members of the other cluster of miR-200 family including miR-200a, miR-200b and miR-429 were hypomethylated. Our data show that forced expression of miR-141 or miR-200c suppressed invasion and metastasis of PDAC cells both in vitro and in xenograft and identified WIPF1 as a direct target of miR-141 and miR-200c. Both miR-141 and miR-200c inhibit WIPF1 by directly interacting with its 3'-untranslated region. Remarkably, silencing of WIPF1 blocked PDAC growth and metastasis both in vitro and in vivo, whereas forced WIPF1 overexpression antagonized the tumor suppressive effect of miR-141/200c. Additionally, by using TCGA database we showed that high expression of WIPF1 correlated with poor survival in patients with PDAC. Moreover, we show that miR-141 and miR-200c blocked YAP/TAZ expression by suppressing WIPF1. CONCLUSIONS: We have identified WIPF1 as an oncoprotein in PDAC and a direct target of miR-141/miR-200c. We have also defined the miR-141/200c-WIPF1-YAP/TAZ as a novel signaling pathway that is involved in the regulation of the invasion and metastasis of human PDAC cells.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30041660

- Liquid Biopsies for Management of Pancreatic Cancer

https://www.sciencedirect.com/science/article/pii/S1931524418301099

- Smad4/DPC4

Journal of clinical pathology 2018 Aug;71(8):661-664

Smad4 or DPC4 belongs to a family of signal transduction proteins that are phosphorylated and activated by transmembrane serine-threonine receptor kinases in response to transforming growth factor beta (TGF-) signaling via several pathways. The gene acts as a tumour suppressor gene and inactivation of smad4/DPC4 is best recognised in pancreatic cancer. However, smad4/DPC4 is also mutated in other conditions and cancers such as juvenile polyposis syndrome with and without hereditary haemorrhagic telangiectasia, colorectal and prostate cancers.Immunohistochemistry for smad4/DPC4 protein is most useful in separating benign/reactive conditions from pancreatic cancer in needle/core biopsies. In normal and reactive states, the protein is

localised to the cytoplasm and nucleus, while the protein is lost in high-grade pancreatic intraepithelial neoplasia/carcinoma in situ and pancreatic cancer.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29720405

- Prospective Study of Germline Genetic Testing in Incident Cases of Pancreatic Adenocarcinoma

Cancer 2018 Aug;():

BACKGROUND: The objective of this study was to investigate the prevalence of pathogenic germline variants (PGVs) in 32 cancer susceptibility genes in individuals with newly diagnosed pancreatic ductal adenocarcinoma (PDAC). A key secondary objective was to evaluate how often PGVs would have been undetected with existing genetic testing criteria. METHODS: From May 2016 through May 2017, this multicenter cohort study enrolled consecutive patients aged 18 to 89 years with histologically confirmed PDAC diagnosed within the previous 12 weeks. Demographics, medical histories, and 3-generation pedigrees were collected from participants who provided samples for germline DNA analysis. RESULTS: Four hundred nineteen patients were deemed eligible, 302 were enrolled, and 298 were included in the final cohort. Clinically actionable variants were reported in 29 PDAC patients (9.7%), with 23 (7.7%) having a PGV associated with an increased risk for PDAC. Six of 23 individuals (26%) with PDAC-associated gene mutations did not meet currently established genetic testing criteria. According to guideline-based genetic testing, only 11 of the 23 PGVs (48%) in known PDAC genes would have been detected. Six additional patients (2%) had PGVs associated with an increased risk for other cancers. CONCLUSIONS: These findings support the significant prevalence of PGVs associated with PDAC and the limitations of current paradigms for selecting patients for genetic testing, and they thereby lend support for universal germline multigene genetic testing in this population. Cancer 2018;000:000-000. © 2018 American Cancer Society.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30067863

- Multi-institutional Validation Study of Pancreatic Cyst Fluid Protein Analysis for Prediction of High-risk Intraductal Papillary Mucinous Neoplasms of the Pancreas

Annals of surgery 2018 Aug;268(2):340-347

OBJECTIVE: Preliminary work by our group suggested that proteins within the pancreatic cyst fluid (CF) may discriminate degree of IPMN dysplasia. We sought to externally validate these markers and determine whether their inclusion in a preoperative clinical nomogram could increase diagnostic accuracy. SUMMARY BACKGROUND DATA: IPMN is the most common radiographically identifiable precursor to pancreatic cancer; however, the timing and frequency of its malignant progression are unknown, and there are currently no reliable preoperative tests that can determine the grade of dysplasia in IPMN. METHODS: Clinical and radiographic data, as well as CF samples, were obtained from 149 patients who underwent resection for IPMN at 1 of 3 institutions. High-risk disease was defined as the presence of high-grade dysplasia or invasive carcinoma. Multianalyte bead array analysis (Luminex) of CF was performed for 4 protein markers that were previously associated with high-risk disease. Logistic regression models were fit on training data, with and without adjustment for a previously developed clinical nomogram and validated with an external testing set. The models incorporating clinical risk score were presented graphically as nomograms. RESULTS: Within the group of 149 resected patients, 89 (60%) had low-risk disease, and 60 (40%) had high-risk disease. All 4 CF markers (MMP9, CA72-4, sFASL, and IL-4) were overexpressed in patients with high-risk IPMN ($P < 0.05$). Two predictive models based on preselected combinations of CF markers had concordance indices of 0.76 (Model-1) and 0.80 (Model-2). Integration of each CF marker model into a previously described clinical nomogram leads to increased discrimination compared with either the CF models or nomogram alone (c-indices of 0.84 and 0.83, respectively). CONCLUSIONS: This multi-institutional study validated 2

CF protein marker models for preoperative identification of high-risk IPMN. When combined with a clinical nomogram, the ability to predict high-grade dysplasia was even stronger.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=28700444

- Regulation of Epithelial Plasticity Determines Metastatic Organotropism in Pancreatic Cancer

Developmental cell 2018 06;45(6):696-711.e8

The regulation of metastatic organotropism in pancreatic ductal a denocarcinoma (PDAC) remains poorly understood. We demonstrate, using multiple mouse models, that liver and lung metastatic organotropism is dependent upon p120catenin (p120ctn)-mediated epithelial identity. Mono-allelic p120ctn loss accelerates KrasG12D-driven pancreatic cancer formation and liver metastasis. Importantly, one p120ctn allele is sufficient for E-CADHERIN-mediated cell adhesion. By contrast, cells with bi-allelic p120ctn loss demonstrate marked lung organotropism; however, rescue with p120ctn isoform 1A restores liver metastasis. In a p120ctn-independent PDAC model, mosaic loss of E-CADHERIN expression reveals selective pressure for E-CADHERIN-positive liver metastasis and E-CADHERIN-negative lung metastasis. Furthermore, human PDAC and liver metastases support the premise that liver metastases exhibit predominantly epithelial characteristics. RNA-seq demonstrates differential induction of pathways associated with metastasis and epithelial-to-mesenchymal transition in p120ctn-deficient versus p120ctn-wild-type cells. Taken together, P120CTN and E-CADHERIN mediated epithelial plasticity is an addition to the conceptual framework underlying metastatic organotropism in pancreatic cancer.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29920275

- A Highly Verified Assay for KRAS Mutation Detection in Tissue and Plasma of Lung, Colorectal, and Pancreatic Cancer

Archives of pathology & laboratory medicine 2018 Aug;():

CONTEXT: - KRAS Mutation Test v2 is used for the qualitative detection and identification of 28 mutations in exons 2, 3, and 4 of the human KRAS gene. OBJECTIVE: - To verify the performance of KRAS Mutation Test v2 and to evaluate its accuracy by correlation with a next-generation sequencing method on Illumina MiSeq. DESIGN: - In the study, we used formalin-fixed, paraffin-embedded tissue and plasma specimens from non-small cell lung cancer, colorectal cancer, and pancreatic cancer patients. Results of specificity, precision, analytical sensitivity, and accuracy as compared with a MiSeq method are reported. RESULTS: - The KRAS Mutation Test v2 demonstrated exquisite sensitivity and specificity and broad coverage of KRAS mutations. Precision was 100% (108 of 108) across all samples, operators, and instruments for formalin-fixed, paraffin-embedded tissue and 99.8% (615 of 616) for plasma. Analytical sensitivity was high with detection of 1% mutant sequence in formalin-fixed, paraffin-embedded tissue samples and as low as 25 mutant sequence copies/mL for plasma samples. The test also showed high overall concordance for formalin-fixed, paraffin-embedded tumor tissue as well as for plasma specimens when compared with MiSeq sequencing results. CONCLUSIONS: - The KRAS Mutation Test v2 is a highly robust, reproducible, and sensitive test for the qualitative detection of 28 mutations in exons 2, 3, and 4 of the KRAS gene in both solid (tissue) and liquid (plasma) biopsies from colorectal cancer, non-small cell lung cancer, and pancreatic cancer, and is a convenient option for KRAS mutation testing.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30088781

- **A systematic review on metabolomics-based diagnostic biomarker discovery and validation in pancreatic cancer**

https://link.springer.com/article/10.1007/s11306-018-1404-2

- **Circulating Tumor Cells Dynamics in Pancreatic Adenocarcinoma Correlate With Disease Status: Results of the Prospective CLUSTER Study**

https://journals.lww.com/annalsofsurgery/Fulltext/2018/09000/Circulating_Tumor_Cells_Dynamics_in_Pancreatic.4.aspx

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- **From somatic mutation to early detection: Insights from molecular characterization of pancreatic cancer precursor lesions**

https://onlinelibrary.wiley.com/doi/abs/10.1002/path.5154

- Germline Variants and Risk for Pancreatic Cancer: A Systematic Review and Emerging Concepts

Pancreas 2018 Sep;47(8):924-936

Pancreatic cancer requires many genetic mutations. Combinations of underlying germline variants and environmental factors may increase the risk of cancer and accelerate the oncogenic process. We systematically reviewed, annotated, and classified previously reported pancreatic cancer-associated germline variants in established risk genes. Variants were scored using multiple criteria and binned by evidence for pathogenicity, then annotated with published functional studies and associated biological systems/pathways. Twenty-two previously identified pancreatic cancer risk genes and 337 germline variants were identified from 97 informative studies that met our inclusion criteria. Fifteen of these genes contained 66 variants predicted to be pathogenic (APC, ATM, BRCA1, BRCA2, CDKN2A, CFTR, CHEK2, MLH1, MSH2, NBN, PALB2, PALLD, PRSS1, SPINK1, TP53). Pancreatic cancer risk genes were organized into key biological mechanisms that promote pancreatic oncogenesis within an oncogenic model. Development of precision medicine approaches requires updated variant information within the framework of an oncogenic progression model. Complex risk modeling may improve interpretation of early biomarkers and guide pathway-specific treatment for pancreatic cancer in the future. Precision medicine is within reach.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30113427

- **A Highly Verified Assay for KRAS Mutation Detection in Tissue and Plasma of Lung, Colorectal, and Pancreatic Cancer**

http://www.archivesofpathology.org/doi/pdf/10.5858/arpa.2017-0471-OA?code=coap-site

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- **PAR1 signaling on tumor cells limits tumor growth by maintaining a mesenchymal phenotype in pancreatic cancer**

https://www.researchgate.net/profile/Cansu_Tekin2/publication/326967265_PAR1_signaling_on_tumor_cells_limits_tumor_growth_by_maintaining_a_mesenchymal_phenotype_in_pancreatic_cancer/links/5b73188245851546c90320f1/PAR1-signaling-on-tumor-cells-limits-tumor-growth-by-maintaining-a-mesenchym pdf

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- Pancreatitis-Associated Genes and Pancreatic Cancer Risk: A Systematic Review and Meta-analysis

Pancreas 2018 Aug;():

OBJECTIVE: The aim of this study was to evaluate the connection between pancreatic cancer (PC) and genetic variants associated with chronic pancreatitis via systematic review and meta-analysis. METHODS: The data search was performed in 3 major databases (PubMed, EMBASE, and Cochrane Library). The selected studies have looked into the presence of the pancreatitis-associated genes in patients with PC and in control subjects, the outcome being the frequency of the mutations in the 2 groups. For the binary outcomes, pooled odds ratio (OR) and 95% confidence interval (CI) were calculated. RESULTS: Ten articles proved to be eligible for the qualitative synthesis, and 8 articles were suitable for statistical analysis. Six case-control studies, comprising 929 PC cases and 1890 control subjects for serine protease inhibitor Kazal type 1 (SPINK1) mutations, and 5 case-control studies, comprising 1674 PC cases and 19,036 control subjects for CFTR mutations, were enrolled in our analysis. SPINK1 mutations showed no association with PC (OR, 1.52; 95% CI, 0.67-3.45; P = 0.315), whereas mutations in CFTR modestly increased the risk of PC (OR, 1.41; 95% CI, 1.07-1.84; P = 0.013). CONCLUSION: Our meta-analysis showed that mutations in CFTR modestly increase the risk of PC, whereas no association was found between SPINK1 and PC.This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30134356

- Germline and Somatic DNA Damage Repair Gene Mutations and Overall Survival in Metastatic Pancreatic Adenocarcinoma Patients Treated with FOLFIRINOX

Clinical cancer research : an official journal of the American Association for Cancer Research 2018 Aug;():

PURPOSE: Pancreatic ductal adenocarcinoma (PDAC) is a lethal cancer with lack of predictive biomarkers. We conducted a study to assess DNA damage repair (DDR) gene mutations as a predictive biomarker in PDAC patients treated with FOLFIRINOX. EXPERIMENTAL DESIGN: Indiana University Simon Cancer Center pancreatic cancer database was used to identify patients with metastatic PDAC, treated with FOLFIRINOX and had tissue available for DNA sequencing. Baseline demographic, clinical and pathologic information was gathered. DNA isolation and targeted sequencing was performed using the Ion AmpliSeq protocol. Overall survival (OS) analyses was conducted using Kaplan-Meier, logistic regression and Cox proportional hazard methods. Multivariate models were adjusted for age, gender, margin status, CA 19-9, adjuvant chemotherapy, tumor and nodal stage. RESULTS: Overall, 36 patients were sequenced. DDR gene mutations were found in 12 patients. Mutations were seen in BRCA1 (N=7), BRCA2 (N=5), PALB2 (N=3), MSH2 (N=1) and FANCF (N=1) of all the DDR genes sequenced. Median age was 65.5 years, 58% were male, 97.2% were Caucasian and 51.4% had any family history of cancer. The median OS was near significantly superior in those with DDR gene mutations present vs. absent (14 vs. 5 months; HR 0.58

[0.29-1.14], log-rank p=0.08). Multivariate logistic (OR 1.47 [1.04-2.06], p = 0.04) and Cox regression (HR 0.37 [0.15-0.94], p = 0.04) showed presence of DDR gene mutations was associated with improved OS. CONCLUSION: In a single institution, retrospective study, we found that the presence of DDR gene mutations are associated with improved OS in PDAC patients treated with FOLFIRINOX.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30131383

Biliary Tract

- Hypoxia-Induced PLOD2 is a Key Regulator in Epithelial-Mesenchymal Transition and Chemoresistance in Biliary Tract Cancer

Annals of surgical oncology 2018 Aug;():

BACKGROUND: The prognosis of biliary tract cancer (BTC) is unfavorable due to its chemoresistance. Hypoxia triggers epithelial-to-mesenchymal transition (EMT), which is closely related to drug resistance. In this study, we focused on the functional roles of procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2 (PLOD2), a hypoxia-induced gene, in BTC, and assessed the clinical significance of PLOD2. METHODS: The expression of PLOD2 under hypoxia was assessed in BTC cell lines. Gemcitabine-resistant (GR) BTC cell lines were transfected with small interfering RNA (siRNA) against PLOD2, and EMT markers and chemoresistance were evaluated. PLOD2 expression was also characterized using immunohistochemistry in BTC clinical specimens following resection. Patient survival was analyzed and the role of PLOD2 expression was examined. RESULTS: The expression of PLOD2 was induced by hypoxia in vitro and was upregulated in BTC-GR cell lines, which had low expression of epithelial markers and high expression of mesenchymal markers. Downregulation of PLOD2 by siRNA resulted in improved chemoresistance, recovery of epithelial markers, and reduction of mesenchymal markers. In the resected BTC samples, PLOD2 expression was significantly correlated with lymph node metastasis ($p = 0.037$) and stage ($p = 0.001$). Recurrence-free survival ($p = 0.011$) and overall survival ($p < 0.001$) rates were significantly lower in patients with high expression of PLOD2. PLOD2 expression was an independent prognostic factor for overall survival ($p = 0.019$). CONCLUSIONS: The expression of PLOD2 influenced chemoresistance through EMT, and high expression of PLOD2 was a significant unfavorable prognostic factor in BTC patients. PLOD2 might be a potential therapeutic target for overcoming chemoresistance.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30105440

Gallbladder

Ampulla of Vater

PanNET Neuroendocrine

- **Molecular Genetic Studies of Pancreatic Neuroendocrine Tumors**

https://www.endo.theclinics.com/article/S0889-8529(18)30519-X/abstract

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Others

Pancreas

- Adjuvant Treatment in Potentially Curable Pancreatic Cancer: Need to Include Tumor Location in the Equation?

Pancreas 2018 Sep;47(8):e50-e52

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30113430

- Loss of PDPK1 abrogates resistance to gemcitabine in label-retaining pancreatic cancer cells

BMC cancer 2018 Jul;18(1):772

BACKGROUND: Label-retaining cancer cells (LRCC) have been proposed as a model of slowly cycling cancer stem cells (CSC) which mediate resistance to chemotherapy, tumor recurrence, and metastasis. The molecular mechanisms of chemoresistance in LRCC remain to-date incompletely understood. This study aims to identify molecular targets in LRCC that can be exploited to overcome resistance to gemcitabine, a standard chemotherapy agent for the treatment of pancreas cancer. METHODS: LRCC were isolated following Cy5-dUTP staining by flow cytometry from pancreatic cancer cell lines. Gene expression profiles obtained from LRCC, non-LRCC (NLRCC), and bulk tumor cells were used to generate differentially regulated pathway networks. Loss of upregulated targets in LRCC on gemcitabine sensitivity was assessed via RNAi experiments and pharmacological inhibition. Expression patterns of PDPK1, one of the upregulated targets in LRCC, was studied in patients' tumor samples and correlated with pathological variables and clinical outcome. RESULTS: LRCC are significantly more resistant to gemcitabine than the bulk tumor cell population. Non-canonical EGF (epidermal growth factor)-mediated signal transduction emerged as the top upregulated network in LRCC compared to non-LRCC, and knock down of EGF signaling effectors PDPK1 (3-phosphoinositide dependent protein kinase-1), BMX (BMX non-receptor tyrosine kinase), and NTRK2 (neurotrophic receptor tyrosine kinase 2) or treatment with PDPK1 inhibitors increased growth inhibition and induction of apoptosis in response to gemcitabine. Knockdown of PDPK1 preferentially increased growth inhibition and reduced resistance to induction of apoptosis upon gemcitabine treatment in the LRCC vs non-LRCC population. These findings are accompanied by lower expression levels of PDPK1 in tumors compared to matched uninvolved pancreas in surgical resection specimens and a negative association of membranous localization on IHC with high nuclear grade ($p < 0.01$). CONCLUSION: Pancreatic cancer cell-derived LRCC are relatively resistant to gemcitabine and harbor a unique transcriptomic profile compared to bulk tumor cells. PDPK1, one of the members of an upregulated EGF-signaling network in LRCC, mediates resistance to gemcitabine, is found to be dysregulated in pancreas cancer specimens, and might be an attractive molecular target for combination therapy studies.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30064387

- Intraductal papillary mucinous neoplasms of the pancreas - a cost-effectiveness analysis of management strategies for the branch-duct subtype

HPB : the official journal of the International Hepato Pancreato Biliary Association 2018 Jul;():

BACKGROUND: Branch-duct intraductal papillary mucinous neoplasm (BD-IPMN) presents a clinical conundrum. Rigorous long-term surveillance or surgical resection is recommended. The economic consequences of the management have not been fully investigated. METHODS: A Markov decision model compared 4 strategies for low-risk BD-IPMN: I = upfront total pancreatectomy, II = upfront partial pancreatectomy, III = initial surveillance, IV = watchful waiting. Surveillance was based on the Swedish Guidelines for Pancreatic Cancer. Probabilities and costs were obtained from the participating unit and from the scientific literature. The incremental cost-effectiveness ratios (ICERs) were calculated and sensitivity analyses were performed by varying relevant parameters. Survival was reported in quality-adjusted life-years (QALYs). RESULTS: Strategy III was the most cost-effective strategy with an ICER of €31 682 compared to strategy IV. Strategy I was the most expensive but yielded the best QALY (9.32). Total number of years, annual risk of pancreatic cancer and annual risk of a low-risk BD-IPMN turning into a high-risk lesion had the greatest impact in the model. CONCLUSIONS: Initial surveillance seems to be the most cost-effective strategy in the management of low-risk asymptomatic BD-IPMN. However, the possibility of personalized approaches remains to be investigated.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30064727

- The Lymph Node Ratio Is an Independent Prognostic Factor in Pancreatic Cancer Patients Who Receive Curative Resection Followed by Adjuvant Chemotherapy

Anticancer research 2018 Aug;38(8):4877-4882

BACKGROUND/AIM: The present study investigated the impact of the lymph node ratio (LNR) on survival and recurrence in patients with pancreatic cancer after curative surgery followed by adjuvant chemotherapy. PATIENTS AND METHODS: This study included 189 patients who underwent curative surgery followed by adjuvant chemotherapy for pancreatic cancer between 2005 and 2014. The risk factors for overall survival (OS) and recurrence-free survival (RFS) were identified. RESULTS: A lymph node ratio of 0.1 was considered to be the optimal cut-off point for classification based on the 3-year and 5-year survival rates. The OS rates at three and five years after surgery were 34.4% and 28.2% in the LNR <0.1 group, respectively, and 23.1% and 5.8% in the LNR 0.1 group, which amounted to a statistically significant difference (p=0.003). The RFS rates at one and three years after surgery were 26.6% and 20.5% in the LNR <0.1 group, respectively, and 8.0% and 0% in the LNR 0.1 group, which was a significant difference (p=0.001). A multivariate analysis demonstrated that the LNR was a significant independent risk factor for both the OS and RFS. CONCLUSION: The LNR was a risk factor for overall survival in patients who underwent curative surgery followed by adjuvant chemotherapy for pancreatic cancer. It is necessary to develop strategies to effectively utilize the lymph node metastasis status.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30061263

- Well differentiated liposarcoma, sclerosing type, of the pancreas a case report

Experimental and molecular pathology 2016 12;101(3):320-322

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=27840110

- Growth rate of serous pancreatic neoplasms in vivo: a retrospective, observational study

Acta radiologica (Stockholm, Sweden : 1987) 2018 Jul;():284185118787350

Background Determining the growth rate of pancreatic cystic lesions on follow-up imaging is important in managing patients with these lesions. However, the growth rates of serous pancreatic neoplasms (SPNs) have

been reported to vary among studies. Purpose To determine the in vivo growth rate of SPNs. Material and Methods This retrospective, single-institutional study included patients diagnosed with SPNs during 2006-2015. The diagnosis of SPNs was based on the results of surgery, endoscopic ultrasonography (EUS)-guided fine needle aspiration (FNA) or core needle biopsy (CNB), or typical radiologic features of SPN. A linear mixed-effects model was utilized to determine whether the diagnostic intervention was associated with tumor growth rate in all patients. The in vivo growth rate of SPNs was estimated from patients without or before diagnostic intervention. SPN growth rates were compared before and after diagnostic intervention. Results SPN growth rates in the overall patient cohort (n = 304) differed significantly between patients who did and did not undergo diagnostic interventions. The in vivo SPN growth rate in 204 patients without or before diagnostic intervention was 1.9 mm/year (95% confidence interval [CI] = 1.6-2.2). In the 130 patients who underwent diagnostic intervention, the SPN growth rate was significantly greater before than after diagnostic intervention (1.8 vs. 0.2 mm/year). Conclusions In the absence of diagnostic intervention, the in vivo growth rate of SPNs was 1.9 mm/year (95% CI = 1.6-2.2). EUS-guided FNA or CNB may affect the growth rate of SPNs.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30056739

- Progression to pancreatic ductal adenocarcinoma from pancreatic intraepithelial neoplasia: Results of a simulation model

https://www.pancreatology.net/article/S1424-3903(18)30636-7/abstract

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- Serotonin uptake is required for Rac1 activation in Kras-induced acinar-to-ductal metaplasia in the pancreas

The Journal of pathology 2018 Jul;():

Pancreatic ductal adenocarcinoma (PDAC), the primary cause of pancreatic cancer mortality, is poorly responsive to currently available interventions. Identifying new targets that drive PDAC formation and progression is critical to develop alternative therapeutic strategies to treat this lethal malignancy. Using genetic and pharmacologic approaches, we investigated in vivo and in vitro whether uptake of the monoamine serotonin is required for PDAC development. We demonstrated that pancreatic acinar cells have the ability to readily take up serotonin in a transport-mediated manner. Serotonin uptake promoted the activation of the small GTPase Ras-Related C3 Botulinum Toxin Substrate 1 (Rac1), which is required for trans-differentiation of acinar cells into acinar-to-ductal metaplasia (ADM), a key determinant in PDAC development. Consistent with the central role played by Rac1 in ADM formation, inhibition of the serotonin transporter Sert (Slc6a4) with fluoxetine reduced ADM formation both in vitro and in vivo in a cell autonomous manner. In addition, fluoxetine treatment profoundly compromised the stromal reaction and affected proliferation and lipid metabolism of malignant PDAC cells. We propose that Sert is a promising therapeutic target to counteract the early event of acinar-to-ductal metaplasia with the potential to stall initiation and progression of pancreatic carcinogenesis.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30058725

- Clinical Features and Prognosis of Patients With the Bone Metastasis of Pancreatic Cancer: A Single-Institutional Cohort Study

Pancreas 2018 Aug;47(7):e43-e46

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29985850

- Spatial Distribution of Pancreatic Stones in Chronic Pancreatitis

Pancreas 2018 Aug;47(7):864-870

OBJECTIVES: The aim of this study was to establish a standard to describe the spatial distribution of pancreatic stones in chronic pancreatitis (CP). METHODS: Two hundred forty-seven CP patients with pancreatic stones from June to December 2012 were enrolled. Two-dimensional images from coronal projection of 3-dimensional computed tomography images of pancreatic stones were gained. The number (n) of all stones and the geometric standard deviation ( ) of distances between the centroid of all stones and the centroids of every stone that represented the spatial distribution nonuniformity were calculated by Stone Reconstruction and Identification Programming System. RESULTS: The mean value of n and were 13.6 and 22.5; n > 13.6 and > 22.5 were determined as "multistones" and "nonuniform," respectively. Compared with alcoholic CP, idiopathic CP was less prone to multistones (odds ratio [OR], 0.310) and more prone to nonuniform (OR, 3.247). Pancreatic pseudocyst (OR, 2.211) in CP course was a risk factor of multistones, whereas diabetes mellitus in first-/second-/third-degree relatives (OR, 0.382) was a protective factor. Age at diagnosis of pancreatic stones (OR, 1.022) was a risk factor of nonuniformity. CONCLUSIONS: Compared with idiopathic CP, alcoholic CP patients were prone to more pancreatic stones that distribute more uniformly.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29975348

- Sweet Predictions Speak Volumes for Early Detection of Pancreatic Cancer

Gastroenterology 2018 08;155(2):265-268

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29966611

- Implications of the Pattern of Disease Recurrence on Survival Following Pancreatectomy for Pancreatic Ductal Adenocarcinoma

Annals of surgical oncology 2018 Aug;25(8):2475-2483

BACKGROUND: After radical resection of pancreatic ductal adenocarcinoma (PDAC), approximately 80% of patients will develop disease recurrence. It remains unclear to what extent the location of recurrence carries prognostic significance. Additionally, stratifying the pattern of recurrence may lead to a deeper understanding of the heterogeneous biological behavior of PDAC. OBJECTIVE: The aim of this study was to characterize the relationship of recurrence patterns with survival in patients with resected PDAC. METHODS: This single-center cohort study included patients undergoing pancreatectomy at the Johns Hopkins Hospital between 2000 and 2013. Exclusion criteria were neoadjuvant therapy and incomplete follow-up. Sites of first recurrence were stratified into five groups and survival outcomes were estimated using Kaplan-Meier curves. The association of specific recurrence locations with overall survival (OS) was analyzed using Cox proportional-hazards models with and without landmark analysis. RESULTS: Accurate follow-up data were available for 877 patients, 662 (75.5%) of whom had documented recurrence at last follow-up. Patients with multiple-site (n = 227, 4.7 months) or liver-only recurrence (n = 166, 7.2 months) had significantly worse median survival after recurrence when compared with lung- (n = 93) or local-only (n = 158) recurrence (15.4 and 9.7 months, respectively). On multivariable analysis, the unique recurrence patterns had variable predictive values for OS. Landmark analyses, with landmarks set at 12, 18, and 24 months, confirmed these findings. CONCLUSIONS: This study demonstrates that specific patterns of PDAC recurrence result in different survival outcomes. Furthermore, distinct first recurrence locations have unique independent predictive values for OS, which could help with prognostic stratification and decisions regarding treatment after the diagnosis of recurrence.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29948425

- Vanishing Pancreas

Gastroenterology 2018 08;155(2):280-281

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29409874

- Don't Mess With the Pancreas (Wherever It May Be): Acute Pancreatic Rest"itis" Presenting as a Submucosal Mass With Gastric Outlet Obstruction

Gastroenterology 2018 08;155(2):e1-e2

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29409828

- **The Use of Biomarkers in the Risk Stratification of Cystic Neoplasms**

https://www.giendo.theclinics.com/article/S1052-5157(18)30725-6/abstract

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- **Current Guideline Controversies in the Management of Pancreatic Cystic Neoplasms**

https://www.giendo.theclinics.com/article/S1052-5157(18)30724-4/abstract

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- **To resect or not to resect: a review of pancreatic cyst disease management**

https://journals.lww.com/co-gastroenterology/Abstract/2018/09000/To_resect_or_not_to_resect____a_review_of.13.aspx

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- Epithelial-Mesenchymal Transition in Pancreatic Cancer: A Review

BioMed research international 2017 ;2017():2646148

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive solid malignancies and is characterized by its insensitivity to current therapy. The invasion and metastasis of solid tumors such as PDAC are complex processes involving many factors. Recent insights into the role of cancer stem cells (CSCs) and the epithelial-mesenchymal transition (EMT) in tumorigenesis have increased the knowledge base and highlighted new therapeutic targets of this disease. The process of EMT is regulated by a complex network of cytokines, transcription factors, growth factors, signaling pathways, and the tumor microenvironment, exhibiting CSC-like properties. The transition of solid cancer cells from an epithelial to a mesenchymal phenotype increases their migratory and invasive properties, thus promoting metastasis. In PDAC, the exact influence of EMT on the biological behaviors of cancer cells and its impact on clinical therapy remain controversial, but the therapeutic strategy of combining EMT inhibition with chemotherapy deserves attention. Alternatively, anti-inflammatory therapy that targets the interaction between inflammation and EMT is a valid strategy for treating the premalignant stage of tumor progression. In this review, we summarize the latest research on EMT and the potential relationship between EMT and PDAC.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29379795

- A Phase II Clinical Trial of Molecular Profiled Neoadjuvant Therapy for Localized Pancreatic Ductal Adenocarcinoma

Annals of surgery 2018 Aug;():

OBJECTIVES: One facet of precision medicine is the use of tumor molecular profiling to guide chemotherapeutic selection. We conducted the first prospective clinical trial of molecular profiling to guide neoadjuvant therapy in patients with operable pancreatic ductal adenocarcinoma (PDAC). We hypothesized that more effective systemic therapy would prevent disease progression during neoadjuvant therapy and, therefore, allow more patients to undergo surgery. METHODS: In patients with resectable and borderline resectable (BLR) PDAC, molecular profiling consisted of immunocytochemical staining of pretreatment endoscopic ultrasound-guided fine needle aspiration tumor biopsies using 6 biomarkers. Neoadjuvant systemic therapy was selected based on the molecular profiling results. The primary endpoint was the completion of all intended neoadjuvant therapy and surgery. RESULTS: The trial enrolled 130 patients; 61 (47%) resectable and 69 (53%) BLR. Molecular profiling was reported within a median of 5 business days (IQR: 3). Of the 130 patient samples, 95 (73%) had adequate cellularity for molecular profiling and 92 (71%) patients received molecular profile-directed therapy. Of the 92 patients who had predictive profiling, 74 (80%) received fluoropyrimidine-based therapy and 18 (20%) received gemcitabine-based therapies. Of the 130 patients, 107 (82%) completed all intended neoadjuvant therapy and surgery; 56 (92%) of the 61 with resectable PDAC and 51 (74%) of 69 with BLR PDAC. CONCLUSIONS: We report the first prospective clinical trial that utilized molecular profiling to select neoadjuvant therapy in patients with operable PDAC. Such high resectability rates have not been observed in prior neoadjuvant trials, suggesting that molecular profiling may improve the efficacy of chemotherapy in these patients.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30080723

- Functions of the CXC ligand family in the pancreatic tumor microenvironment

Pancreatology : official journal of the International Association of Pancreatology (IAP) … [et al.] 2018 Aug;():

Therapeutic resistance is the major contributor to the poor prognosis of and low survival from pancreatic cancer (PC). Cancer progression is a complex process reliant on interactions between the tumor and the tumor microenvironment (TME). Members of the CXCL family of chemokines are present in the pancreatic TME and seem to play a vital role in regulating PC progression. As pancreatic tumors interact with the TME and with PC stem cells (CSCs), determining the roles of specific members of the CXCL family is vital to the development of improved therapies. This review highlights the roles of selected CXCLs in the interactions between pancreatic tumor and its stroma, and in CSC phenotypes, which can be used to identify potential treatment targets.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30078614

- Possible Autocrine Function of Galectin-3 in Pancreatic Stellate Cells

Gastroenterology 2018 Aug;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30092185

- Retrospective evaluation of patients diagnosed solid pseudopapillary neoplasms of the pancreas

Current problems in cancer 2018 Jul;():

PURPOSE: Solid pseudopapillary neoplasm (SPN) is a rare, low-grade neoplasm with excellent prognosis. In this study, we evaluated clinicopathological characteristics of patients diagnosed with SPN retrospectively. METHODS: This is a retrospective study intended to characterize patients with the diagnosis of SPN between 2005 and 2015. Clinicopathological features, recurrence rate, and overall survival of 28 patients were recorded. Malignant SPN criteria were defined as the presence of distant metastasis (developed at diagnosis or during follow up) or lymph node involvement. RESULTS: The mean age at diagnosis was 42 (range: 17-41). Among patients, 82% (n = 23) were female and 17.9% (n = 5) were male. The mean size of tumor was 5.81 cm (range: 2-15). The mean follow up period was 55.6 months, 1-year survival was 96.5% and 5-year survival rate was 88%. A total of 25 patients were alive at the end of follow-up period and 3 of the patients became exitus due to disease. Two patients had a metastatic presentation in livers at the diagnosis and metastasis developed in 3 patients during follow-up (liver of 1 patient, peritoneum in 1 patient and liver and peritoneum in 1 patient). The reason of admission was headache in 68% patients. The type of operation was frequently subtotal pancreatectomy (n = 11, 39.3%) and distal pancreatectomy (n = 10, 35.7%). Tumors were located frequently in body and tail regions (n = 18, 64.3%) and the number of patients with malignant criteria was 6 (21.4%). Although the mean age of malignant patients was significantly higher than benign patients (P = 0.046), there was no significant difference between 2 groups in terms of gender, tumor size, capsule invasion, perineural invasion, vascular invasion, and margin status. CONCLUSION: SPN is a rarely seen tumor with low malignity potential. Surgical resection provides long-term survival rate even in local invasion or metastasis conditions.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30104029

- **Immune Checkpoint Inhibition for Pancreatic Ductal Adenocarcinoma: Current Limitations and Future Options**

https://www.frontiersin.org/articles/10.3389/fimmu.2018.01878/full

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- Gut Microbiota Promotes Tumor Growth in Mice by Modulating Immune Response

Gastroenterology 2018 07;155(1):33-37.e6

We studied the effects of gut microbiome depletion by oral antibiotics on tumor growth in subcutaneous and liver metastases models of pancreatic cancer, colon cancer, and melanoma. Gut microbiome depletion significantly reduced tumor burden in all the models tested. However, depletion of gut microbiome did not reduce tumor growth in Rag1-knockout mice, which lack mature T and B cells. Flow cytometry analyses demonstrated that gut microbiome depletion led to significant increase in interferon gamma-producing T cells with corresponding decrease in interleukin 17A and interleukin 10-producing T cells. Our results suggest that gut microbiome modulation could emerge as a novel immunotherapeutic strategy.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29630898

- Gut microbiome-immune crosstalk affects progression of cancer

Translational gastroenterology and hepatology 2018 ;3():34

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30050994

- **Intrapancreatic recurrence of intraductal tubulopapillary neoplasm (ITPN) 16 years after the initial surgery for noninvasive ITPN: a case report**

https://surgicalcasereports.springeropen.com/articles/10.1186/s40792-018-0497-1

Pancreas Techniques & Research Methods

- Organoidomics - falling star or new galaxy in pancreatic cancer?

Nature reviews. Gastroenterology & hepatology 2018 Jul;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30046146

- The Research of Acellular Pancreatic Bioscaffold as a Natural 3-Dimensional Platform In Vitro

Pancreas 2018 Sep;47(8):1040-1049

OBJECTIVE: The aim of the study was to investigate the biochemical and functional properties of a rat acellular pancreatic bioscaffolds (APBs). METHODS: Fresh pancreata from 10 rats were soaked and perfused through portal veins using Easy-Load Digital Drive peristaltic pumps. The histological structure, extracellular matrix composition, and the DNA content of the APBs were evaluated. Biocompatibility studies had also been performed. The proliferation and differentiation of AR42J pancreatic acinar cells were assessed. RESULTS: The pancreatic tissue became translucent after decellularization. There were no visible vascular endothelial cells, cellular components, or cracked cellular debris. The extracellular matrix components were not decreased after decellularization ($P > 0.05$); however, the DNA content was decreased significantly ($P < 0.05$). The subcutaneous implantation sites showed low immunological response and low cytotoxicity around the APB. The proliferation rate was higher and the apoptosis rate was lower when AR42J cells were cultured on APB ($P < 0.05$). The gene expression and the protein expression were higher for the APB group ($P < 0.001$). CONCLUSIONS: Our findings support the biological utility of whole pancreas APBs as biomaterial scaffolds, which provides an improved approach for regenerative medicine.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30086100

- Transforming growth factor- modulates pancreatic cancer associated fibroblasts cell shape, stiffness and invasion

Biochimica et biophysica acta 2018 07;1862(7):1537-1546

BACKGROUND: Tumor microenvironment consists of the extracellular matrix (ECM), stromal cells, such as fibroblasts (FBs) and cancer associated fibroblasts (CAFs), and a myriad of soluble factors. In many tumor types, including pancreatic tumors, the interplay between stromal cells and the other tumor microenvironment components leads to desmoplasia, a cancer-specific type of fibrosis that hinders treatment. Transforming growth factor beta (TGF-) and CAFs are thought to play a crucial role in this tumor desmoplastic reaction, although the involved mechanisms are unknown. METHODS: Optical/fluorescence microscopy,

atomic force microscopy, image processing techniques, invasion assay in 3D collagen I gels and real-time PCR were employed to investigate the effect of TGF- on normal pancreatic FBs and CAFs with regard to crucial cellular morphodynamic characteristics and relevant gene expression involved in tumor progression and metastasis. RESULTS: CAFs present specific myofibroblast-like characteristics, such as -smooth muscle actin expression and cell elongation, they also form more lamellipodia and are softer than FBs. TGF- treatment increases cell stiffness (Young's modulus) of both FBs and CAFs and increases CAF's (but not FB's) elongation, cell spreading, lamellipodia formation and spheroid invasion. Gene expression analysis shows that these morphodynamic characteristics are mediated by Rac, RhoA and ROCK expression in CAFs treated with TGF- . CONCLUSIONS: TGF- modulates CAFs', but not FBs', cell shape, stiffness and invasion. GENERAL SIGNIFICANCE: Our findings elucidate on the effects of TGF- on CAFs' behavior and stiffness providing new insights into the mechanisms involved.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29477748

Pancreas Analogue Tumors

- Intraductal Papillary Mucinous Neoplasms of Minor Salivary Glands With AKT1 p.Glu17Lys Mutation

The American journal of surgical pathology 2018 Aug;42(8):1076-1082

The spectrum of low-grade intraductal papillary proliferations of the salivary glands is heterogenous, and reproducible morphologic diagnostic criteria have not yet been established. Recognized types are sialadenoma papilliferum, inverted ductal papilloma, and intraductal papilloma, but some lesions have been possibly included in the morphologic spectrum of cystadenoma or low-grade intraductal carcinomas. We herein present detailed morphologic, immunophenotypic, and genotypic features of 3 minor salivary gland neoplasms affecting 2 men (aged 65 and 71 y) and 1 woman (aged 78 y). They ranged in size from 1 to 2.5 cm. All tumors showed atypical papillary intraductal growth that presented either as uninodular/unicystic lesions (intraductal papilloma-like; n=2) or as a discontinuous growth along the ductal system in a manner similar to pancreatic intraductal papillary mucinous neoplasm (n=1). Variable cytologic and architectural atypia was observed, ranging from bland intraductal papilloma-like features, to areas mimicking atypical ductal hyperplasia and low-grade ductal carcinoma in situ of the breast. Amplicon-based massive parallel sequencing revealed an identical AKT1 p.Glu17Lys mutation in all 3 cases, but absence of concurring mutations in other genes of the RAS or PI3K pathway. This small series represents the first genetic study on salivary intraductal papillary neoplasms. Our cases showed significant variation in the degree of cytologic and architectural atypia, which overlaps with intraductal papillomas at the one end and with low-grade intraductal carcinoma at the other end of the spectrum, suggesting a disease continuum. As the full biological and morphologic characteristics of these ductal papillary lesions remain to be defined, the noncommitted term "intraductal papillary neoplasms" might be more appropriate. Our novel genetic findings mirror similar activating mutations of AKT1 and other PI3K pathway members in intraductal papillary lesions of the breast and anogenital glands.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29738361

- Low-grade intraductal carcinoma of the salivary gland with prominent oncocytic change: a newly described variant

Histopathology 2018 Aug;73(2):314-320

AIMS: Low-grade intraductal carcinoma (LG-IDC) is a clinically indolent malignant tumour of the salivary glands. Because of its rarity, the histological variants of LG-IDC have not been well characterised. Herein, we describe five LG-IDC cases with prominent oncocytic change in the major salivary glands. METHODS AND RESULTS: We examined five cases, three males and two females (mean age = 63 years), of LG-IDC with oncocytic change. The sites affected by LG-IDC were the parotid and submandibular glands. The lesions were macroscopically unilocular or multilocular cysts with a solid tumour arising from the cyst wall. Smaller tumour cell nests were also observed. As with classic LG-IDC, the cyst wall was surrounded by myoepithelial cells with no invasive component. The tumour cells had abundant oncocytic cytoplasm and proliferated in a low-papillary, tubular or cribriform pattern. Immunohistochemically, the tumour cells were diffusely positive for pan-cytokeratin, S100, mammaglobin and antimitochondria antibody, and were negative for androgen receptor and gross cystic disease fluid protein-15. Unlike classic LG-IDC, some of these cases demonstrated focal invagination of myoepithelial cells in the intraductal tumour. CONCLUSION: Oncocytic LG-IDC should be recognised as a histologically unique variant of LG-IDC. Awareness of this entity is important to avoid erroneous diagnosis and inappropriate treatment for histological mimics.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29574881

- Solid pseudopapillary neoplasm (SPN) of the testis: Comprehensive mutational analysis of 6 testicular and 8 pancreatic SPNs

Annals of diagnostic pathology 2018 Aug;35():42-47

BACKGROUND: Recently, we came with the theory of a possible relationship between a group of testicular and pancreatic tumors. We used one case of a pancreatic analogue solid pseudopapillary neoplasm of the testis composed partially of areas reminiscent of solid pseudopapillary neoplasm (SPN) of the pancreas and partially of structures identical to primary signet ring stromal tumor of the testis (PSRSTT) as a connecting link between these two entities. After demonstrating that PSRSTT and pancreatic analogue SPN of the testis share the same immunoprofile and genetic features characteristic for pancreatic SPN, we came to the conclusion that pancreatic analogue SPN of the testis and PSRSTT represent a morphological spectrum of a single entity and that both are related to the pancreatic SPN. DESIGN: The aim of this study is to present a series of 6 cases of testicular tumors, which lacked the signet ring cell component and were thus morphologically very similar to the SPN of the pancreas. The goal of this study is to compare the genetic background of these testicular tumors that are obviously related to the PSRSTT/pancreatic analogue SPN of the testis with the series of 8 pancreatic SPN. RESULTS: The mutational analysis revealed an oncogenic somatic mutation in the exon 3 of the CTNNB1 (-catenin) gene in all analyzable (5/6) testicular and all pancreatic (8/8) tumors. The immunoprofile (positivity with -catenin, CD10, vimentin, NSE, CD56, and negativity with inhibin, calretinin, chromogranin) was identical in all testicular and pancreatic tumors. CONCLUSION: This study expanded the morphological spectrum of the PSRSTT/pancreatic analogue SPN of the testis by adding 6 cases without the signet ring cell component. Considering the obvious analogy of PSRSTT/pancreatic analogue SPN of the testis/SPN of the testis and their relationship to the pancreatic SPN we propose the collective term “solid pseudopapillary neoplasm of the testis” for these tumors. The mutational profile of the SPN of the testis and pancreas was the same in both groups of tumors which we consider as a final proof that SPN of the testis is identical to the SPN of the pancreas.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29705715

- Pseudo-“solid pseudopapillary neoplasms” of the testis: in reality Sertoli cell tumors

Human pathology 2018 Aug;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30110596

- Pseudo-"solid pseudopapillary neoplasms" of the testis: in reality Sertoli cell tumors-reply

Human pathology 2018 Aug;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30120970

Animal Studies

- Characterization of Peribiliary Gland-Constituting Cells Based on Differential Expression of Trophoblast Cell Surface Protein 2 in Biliary Tract

The American journal of pathology 2018 Sep;188(9):2059-2073

Peribiliary glands (PBGs) are accessory glands with mucinous and serous acini in the biliary tree. The PBG is composed of a heterogeneous cell population, such as mucus- and pancreatic enzyme-producing epithelial cells, whereas it constitutes niches for multipotential stem/progenitor cells in the human extrahepatic bile duct (EHBD). By contrast, the nature of PBGs in the mouse EHBD remains unclear. Our aim was to establish a method for isolating and characterizing PBG-constituting cells in the mouse EHBD. We found that trophoblast cell surface protein 2 (Trop2) was expressed in the luminal epithelium of mouse EHBD exclusively, but not in the PBG. On the basis of the differential expression profile of Trop2, lumen-forming biliary epithelial cells (LBECs) and PBG-constituting epithelial cells (PBECs) were separately isolated for further characterization. Gene expression analysis revealed that the isolated mouse PBECs expressed several marker genes related to human PBGs. In the colony formation assay, PBECs showed significantly higher colony formation capacity than LBECs. In the organoid formation assay, PBECs formed cystic organoid with LBEC-like phenotype. Interestingly, PBECs proliferated, accompanied by reexpression of Trop2 in vivo after bile duct ligation. Furthermore, the unique expression profile of Trop2 was conserved in human EHBD. Our findings indicate that Trop2 is a useful marker in investigating the pathophysiological roles and characteristics of mouse and human PBGs in biliary diseases.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30126547

- Disruption of C1galt1 Gene Promotes Development and Metastasis of Pancreatic Adenocarcinomas in Mice

Gastroenterology 2018 Aug;():

BACKGROUND & AIMS: Pancreatic ductal adenocarcinomas (PDACs) produce higher levels of truncated O-glycan structures (such as Tn and sTn) than normal pancreata. Dysregulated activity of core 1 synthase, glycoprotein-N-acetylgalactosamine 3-beta-galactosyltransferase 1 (C1GALT1) leads to increased expression of these truncated O-glycans. We investigated whether and how truncated O-glycans contributes to development and progression of PDAC using mice with disruption of C1galt1. METHODS: We crossed C1galt1 floxed mice (C1galt1loxP/loxP) with KrasG12D/+; Trp53R172H/+; Pdx1-Cre mice (KPC mice) to create KPCC mice. Growth and progression of pancreatic tumors were compared between KPC and KPCC mice; pancreatic tissues were collected and analyzed by immunohistochemistry; immunofluorescence; and Sirius red, alcian blue, and lectin staining. We used the CRISPR/Cas9 system to disrupt C1GALT1 in human PDAC cells (T3M4 and CD18/HPAF) and levels of O-glycans were analyzed by lectin blotting, mass spectrometry and lectin-pull down assay. Orthotopic studies and RNA sequencing analyses are performed with control and C1GALT1 knockout PDAC cells. C1GALT1 expression was analyzed in well differentiated (n=36) and

poorly differentiated (n=23) PDAC samples by immunohistochemistry. RESULTS: KPCC mice had significantly shorter survival times (median, 102 days) than KPC mice (median, 200 days), and developed early pancreatic intraepithelial neoplasias at 3 weeks, PDAC at 5 weeks, and metastases at 10 weeks compared to KPC. Pancreatic tumors that developed in KPCC mice were more aggressive than those of KPC mice (more invasive and metastases), had a decreased amount of stroma, and had increased production of Tn. Poorly differentiated PDAC specimens had significantly lower levels of C1GALT1 than well-differentiated PDACs. Human PDAC cells with knockout of C1GALT1 had aberrant glycosylation of MUC16 compared with control cells, and increased expression of genes that regulate tumorigenesis and metastasis. CONCLUSIONS: In studies of KPC mice with disruption of C1galt1, we found that loss of C1galt1 promotes development of aggressive PDACs and increased metastasis. Knockout of C1GALT1 leads to increased tumorigenicity and truncation of O-glycosylation on MUC16, which could contribute to increased aggressiveness.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30086262

- Local phototherapy synergizes with immunoadjuvant for treatment of pancreatic cancer through induced immunogenic tumor vaccine

Clinical cancer research : an official journal of the American Association for Cancer Research 2018 Aug;():

PURPOSE: To develop a synergistic combination therapy for advanced pancreatic cancer, using local phototherapy and immunotherapy, and to determine the efficacy and mechanism of the novel combination therapy using a highly metastatic pancreatic tumor model in mice. EXPERIMENTAL DESIGN: Mice bearing Panc02-H7 pancreatic tumors (both subcutaneous and orthotopic) were treated with non-invasive or interventional photothermal therapy, followed by local application of an immunoadjuvant. Tumor growth and animal survival were assessed. Immune cell populations within spleen and tumors were evaluated by FACS and IHC, and cytokine levels were determined by ELISA. RESULTS: Up to 75% of mice bearing subcutaneous tumors treated with combination therapy had complete tumor regression. Local photothermal therapy exposed/released damage-associated molecular patterns, which initiated an immunogenic tumor cell death, resulting in infiltration of antigen presenting cells and a T helper 1 (Th1) immunity. Concomitant application of immunoadjuvant amplified Th1 immunity, especially the tumor-specific cytotoxic T lymphocytes response, with increased quantity and quality of T cells. Combination therapy also induced tumor-specific immune memory, as demonstrated by resistance to tumor rechallenge and production of memory T cells. For the treatment of orthotopic tumor, the combination therapy significantly reduced the primary tumors and metastases, and prolonged the animal survival time. CONCLUSIONS: This study indicated that combination of local phototherapy and immunotherapy induced a systemic immunity against established tumors and metastases in an aggressive, preclinical pancreatic tumor model, leading to a potential clinical method for patients with advanced pancreatic cancer.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30068705

- Systemic Depletion of Nerve Growth Factor Inhibits Disease Progression in a Genetically Engineered Model of Pancreatic Ductal Adenocarcinoma

Pancreas 2018 Aug;47(7):856-863

OBJECTIVES: In patients with pancreatic ductal adenocarcinoma (PDAC), increased expression of proinflammatory neurotrophic growth factors (eg, nerve growth factor [NGF]) correlates with a poorer prognosis, perineural invasion, and, with regard to NGF, pain severity. We hypothesized that NGF sequestration would reduce inflammation and disease in the KPC mouse model of PDAC. METHODS: Following biweekly injections of NGF antibody or control immunoglobulin G, beginning at 4 or 8 weeks of age, inflammation and disease stage were assessed using histological, protein expression, and quantitative polymerase chain reaction analyses. RESULTS: In the 8-week anti-NGF group, indicators of neurogenic inflammation in the dorsal

root ganglia (substance P and calcitonin gene-related peptide) and spinal cord (glial fibrillary acidic protein) were significantly reduced. In the 4-week anti-NGF group, TRPA1 mRNA in dorsal root ganglia and spinal phosphorylated ERK protein were elevated, but glial fibrillary acidic protein expression was unaffected. In the 8-week anti-NGF group, there was a 40% reduction in the proportion of mice with microscopic perineural invasion, and no macrometastases were observed. CONCLUSIONS: Anti-NGF treatment beginning at 4 weeks may increase inflammation and negatively impact disease. Treatment starting at 8 weeks (after disease onset), however, reduces neural inflammation, neural invasion, and metastasis. These data indicate that NGF impacts PDAC progression and metastasis in a temporally dependent manner.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29975347

Biliary Tract

- Combined CDK4/6 and pan-mTOR inhibition is synergistic against intrahepatic cholangiocarcinoma

Clinical cancer research : an official journal of the American Association for Cancer Research 2018 Jul;():

PURPOSE: Intrahepatic cholangiocarcinoma (ICC) is an aggressive cancer type, lacking effective therapies and associated with a dismal prognosis. Palbociclib is a selective CDK4/6 inhibitor, which has been shown to suppress cell proliferation in many experimental cancer models. Recently, we demonstrated that pan-mTOR inhibitors, such as MLN0128, effectively induce apoptosis, while having limited efficacy in restraining proliferation of ICC cells. Here, we tested the hypothesis that Palbociclib, due to its ant-proliferative properties in many cancer types, might synergize with MLN0128 to impair ICC growth. EXPERIMENTAL DESIGN: Human ICC cell lines and the AKT/YapS127A ICC mouse model were used to test the therapeutic efficacy of Palbociclib and MLN0128, either alone or in combination. RESULTS: Administration of Palbociclib suppressed in vitro ICC cell growth by inhibiting cell cycle progression. Concomitant administration of Palbociclib and MLN0128 led to a pronounced, synergistic growth constraint of ICC cell lines. Furthermore, while treatment with Palbociclib or MLN0128 alone resulted in tumor growth reduction in AKT/YapS127A mice, a remarkable tumor regression was achieved when the two drugs were administered simultaneously. Mechanistically, Palbociclib was found to potentiate MLN0128 mTOR inhibition activity, whereas MLN0128 prevented the upregulation of cyclin D1 induced by Pa1bociclib treatment. CONCLUSIONS: Our study indicates the synergistic activity of Palbociclib and MLN0128 in inhibiting ICC cell proliferation. Thus, combination of CDK4/6 and mTOR inhibitors might represent a novel, promising, and effective therapeutic approach against human ICC.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30084835

- Preoperative CEA levels are supplementary to CA19-9 levels in predicting prognosis in patients with resectable intrahepatic cholangiocarcinoma.

https://www.researchgate.net/publication/326829300_Preoperative_CEA_levels_are_supplementary_to_CA19-9_levels_in_predicting_prognosis_in_patients_with_resectable_intrahepatic_cholangiocarcinoma

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- Improved Survival in Surgically Resected Distal Cholangiocarcinoma Treated with Adjuvant Therapy: a Propensity Score Matched Analysis *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract 2018 Jul;():*

BACKGROUND: Data on the efficacy of adjuvant therapy (AT) in distal cholangiocarcinoma (dCCA) is limited. This study aimed to determine the role of AT in resected dCCA and identify subgroups that benefit from AT. METHODS: We conducted a retrospective review of surgically resected dCCA in the NCDB from 2004 to 2013. Patients who received AT or observation (OB) were matched by propensity score. Log-rank test was used to compare OS. RESULTS: Of 1782 patients with resected dCCA, 840 (47%) were in the OB group and 942 (53%) in the AT group. AT was younger (64.0 vs. 68.7 years, $p < 0.001$), had less comorbidities (Charlson Deyo score 0) (74.6 vs. 68.0%, $p < 0.001$), and more likely to have private insurance ($p < 0.001$). AT was more likely to present with T3/T4 stage (72 vs. 57%, $p < 0.001$), N1/N2 disease (58 vs. 37%, $p < 0.001$), and positive surgical margins (26 vs. 16%, $p < 0.001$). After 1:1 propensity score matching, 500 OB and 500 AT patients were compared. AT was associated with better OS (HR 0.79; 95% CI 0.67-0.93). Median OS was 31 and 25 months for the AT and OB ($p = 0.006$). The 1-, 3-, and 5-year survival rates were 87, 46, and 31% for AT; 79, 39, and 24% for OB. Subgroup analysis revealed an associated survival advantage for AT in T3/T4 tumors (HR = 0.72; 95% CI 0.59-0.89), node positive disease (HR 0.70; 95% CI 0.56-0.87), and positive margins (HR 0.58; 95% CI 0.42-0.81). CONCLUSION: AT is associated with improved OS in resected dCCA, especially in T3/T4 tumors, node positive disease, and positive margins.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30030718

- Prognosis and Adherence with the National Comprehensive Cancer Network Guidelines of Patients with Biliary Tract Cancers: an Analysis of the National Cancer Database

Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract 2018 Aug;():

BACKGROUND: The National Comprehensive Cancer Network (NCCN) guidelines recommend chemotherapy for patients with inoperable biliary tract cancers (BTC), as well as patients following resection of BTC with lymph node metastasis (N1)/positive margins (R1). We sought to define overall adherence, as well as long-term outcomes, with the NCCN guidelines for BTC using the National Cancer Database (NCDB). METHODS: A total of 176,536 patients diagnosed with BTC at a hospital participating in the NCDB between 2004 and 2015 were identified. RESULTS: Among all patients, 63% of patients received medical therapy (chemotherapy or best supportive care), 11% underwent surgical palliation, and 26% underwent curative-intent surgery. According to the NCCN guidelines, 86% (n = 152,245) of patients were eligible for chemotherapy, yet, only 42.2% (n = 64,615) received chemotherapy. Factors associated with a lower adherence with NCCN guidelines included patient age (> 65 years: OR = 1.02), ethnicity (Black: OR = 1.14, Hispanic: OR = 1.21, Asian: OR = 1.24), and insurance status (non-private: OR = 1.45, all $p < 0.001$). A smaller subset of patients was either recommended chemotherapy but refused (n = 9269, 10.6%) or had medical factors that contraindicated chemotherapy (n = 8275, 9.4%). On multivariable analysis, adjusting for clinical and tumor-specific factors, adherence with NCCN guidelines was associated with a survival benefit for patients receiving medical therapies (HR = 0.74) or undergoing curative-intent surgery (HR = 0.73, both $p < 0.001$). CONCLUSION: Less than half of patients with BTC received systemic chemotherapy in adherence with NCCN guidelines. While a subset of patients had contraindications or refused chemotherapy, other factors such as insurance status and ethnicity were associated with adherence. Adherence with chemotherapy guidelines may influence long-term outcomes.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30112703

Gallbladder

- **Incidental Gallbladder Cancer: How Residual Disease Affects Outcome in Two Referral HPB Centers from South America**

https://link.springer.com/article/10.1007/s00268-018-4762-z

- Gallbladder adenocarcinoma diagnosed from cutaneous metastases occurring along the tract of a ventriculoperitoneal shunt

Journal of cutaneous pathology 2018 Jul;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30054926

Ampulla of Vater

- Using an endoscopic distal cap to collect pancreatic fluid from the ampulla (with video)

Gastrointestinal endoscopy 2017 Dec;86(6):1152-1156.e2

BACKGROUND AND AIMS: Duodenal collections of pancreatic fluid can be used as a source of mutations and other markers of pancreatic ductal neoplasia, but admixing pancreatic juice with duodenal contents lowers the concentrations of mutations. Collecting pancreatic fluid directly from the ampulla could yield a purer sample of pancreatic fluid. METHODS: We used an endoscopic distal cap attachment to "cap" the ampulla and collect secretin-stimulated pancreatic fluid samples for 5 minutes from 81 patients undergoing pancreatic evaluation as part of the Cancer of the Pancreas Screening studies. We compared mutation concentrations (K-ras and GNAS) measured by droplet-digital PCR (ddPCR) in "cap-collected juice" samples to those found in juice samples obtained from 77 patients collected by aspiration from the duodenal lumen without capping the ampulla. RESULTS: Among all subjects, mutation concentrations were higher in pancreatic juice samples collected using the endoscopic cap method (median, .028%; IQR, 0-.077) compared with the noncap-collected (median, .019%; IQR, 0-.044; P = .055). Among pancreatic juice samples with detectable mutations, mutation concentrations were higher in the cap-collected juice samples than in those collected without the cap (.055%; IQR, .026-.092 vs .032%; IQR, .020-.066; P = .031). CONCLUSIONS: Collecting pancreatic juice directly from the ampulla using an endoscopic distal cap yields higher concentrations of pancreatic fluid mutations.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=28259593

- Outcomes and Treatment Options for Duodenal Adenocarcinoma: A Systematic Review and Meta-Analysis

Annals of surgical oncology 2018 Sep;25(9):2681-2692

BACKGROUND: Duodenal adenocarcinoma (DA) is a rare tumor for which survival data per treatment modality and disease stage are unclear. This systematic review and meta-analysis aims to summarize the current literature on patient outcome after surgical, (neo)adjuvant, and palliative treatment in patients with DA. METHODS: A systematic search was performed according to the preferred reporting items for systematic reviews and meta-analyses guidelines, to 25 April 2017. Primary outcome was overall survival (OS), specified for treatment strategy or disease stage. Random-effects models were used for the calculation of pooled odds

ratios per treatment modality. Included papers were also screened for prognostic factors. RESULTS: A total of 26 observational studies, comprising 6438 patients with DA, were included. Of these, resection with curative intent was performed in 71% (range 53-100%) of patients, and 29% received palliative treatment (range 0-61%). The pooled 5-year OS rate was 46% after curative resection, compared with 1% in palliative-treated patients (OR 0.04, 95% confidence interval [CI] 0.02-0.09, $p < 0.0001$). Both segmental resection and pancreaticoduodenectomy allowed adequate assessment of lymph node involvement and resulted in similar OS. Lymph node involvement correlated with worse OS (pooled 5-year survival rate 21% for nodal metastases vs. 65% for node-negative disease; OR 0.17, 95% CI 0.11-0.27, $p < 0.0001$). In the current literature, no survival benefit for adjuvant therapy after curative resection was found. CONCLUSION: Resection with curative intent, either pancreaticoduodenectomy or segmental resection, and lack of nodal metastases, favors survival for DA. Further studies exploring multimodality (neo)adjuvant therapy are warranted to investigate their benefit.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29946997

- Mixed mucinous adenocarcinoma and somatostatinoma of the ampulla of Vater associated with neurofibromatosis type 1

Pathology 2017 Aug;49(5):553-555

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=28693748

PanNET Neuroendocrine

- **Periampullary neuroendocrine tumor with large intracellular mucin globules, an amphicrine tumor?**

https://www.sciencedirect.com/science/article/pii/S2214330018300063#

- **The Evolving Treatment Algorithm for Advanced Neuroendocrine Neoplasms: Diversity and Commonalities Across Tumor Types**

http://theoncologist.alphamedpress.org/content/early/2018/08/13/theoncologist.2018-0187.abstract

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- Pancreatic islets communicate with lymphoid tissues via exocytosis of insulin peptides

Nature 2018 Aug;560(7716):107-111

Tissue-specific autoimmunity occurs when selected antigens presented by susceptible alleles of the major histocompatibility complex are recognized by T cells. However, the reason why certain specific self-antigens dominate the response and are indispensable for triggering autoreactivity is unclear. Spontaneous presentation of insulin is essential for initiating autoimmune type 1 diabetes in non-obese diabetic mice1,2. A major set of pathogenic CD4 T cells specifically recognizes the 12-20 segment of the insulin B-chain (B:12-20), an

epitope that is generated from direct presentation of insulin peptides by antigen-presenting cells3,4. These T cells do not respond to antigen-presenting cells that have taken up insulin that, after processing, leads to presentation of a different segment representing a one-residue shift, B:13-214. CD4 T cells that recognize B:12-20 escape negative selection in the thymus and cause diabetes, whereas those that recognize B:13-21 have only a minor role in autoimmunity3-5. Although presentation of B:12-20 is evident in the islets3,6, insulin-specific germinal centres can be formed in various lymphoid tissues, suggesting that insulin presentation is widespread7,8. Here we use live imaging to document the distribution of insulin recognition by CD4 T cells throughout various lymph nodes. Furthermore, we identify catabolized insulin peptide fragments containing defined pathogenic epitopes in -cell granules from mice and humans. Upon glucose challenge, these fragments are released into the circulation and are recognized by CD4 T cells, leading to an activation state that results in transcriptional reprogramming and enhanced diabetogenicity. Therefore, a tissue such as pancreatic islets, by releasing catabolized products, imposes a constant threat to self-tolerance. These findings reveal a self-recognition pathway underlying a primary autoantigen and provide a foundation for assessing antigenic targets that precipitate pathogenic outcomes by systemically sensitizing lymphoid tissues.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30022165

- **Comparison Between Modified Extracellular-Type Trehalose-Containing Kyoto Solution and University of Wisconsin Solution in 18-Hour Pancreas Preservation for Islet Transplantation**

Pancreas 2018 Aug;47(7):e46-e47

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29985851

- **-Catenin Expression in Glucagon-Producing Cells of Human Fetal Pancreatic Islets Suggests Wnt Signaling-Dependent Development**

Pancreas 2018 Sep;47(8):e54-e55

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30113433

- **ASO Author Reflections: Serum Elastase 1 Level as a Risk Factor for Postoperative Recurrence in Patients with Well-Differentiated Pancreatic Neuroendocrine Neoplasms**

Annals of surgical oncology 2018 Aug;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30136123

Database SEER, NCDB, TCGA, Oncomine Studies

- **Pancreatic cancer survival analysis defines a signature that predicts outcome**

http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0201751

- Pancreatic cancer survival analysis defines a signature that predicts outcome

PloS one 2018 ;13(8):e0201751

Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer death in the US. Despite multiple large-scale genetic sequencing studies, identification of predictors of patient survival remains challenging. We performed a comprehensive assessment and integrative analysis of large-scale gene expression datasets, across multiple platforms, to enable discovery of a prognostic gene signature for patient survival in pancreatic cancer. PDAC RNA-Sequencing data from The Cancer Genome Atlas was stratified into Survival+ (>2-year survival) and Survival-(<1-year survival) cohorts (n = 47). Comparisons of RNA expression profiles between survival groups and normal pancreatic tissue expression data from the Gene Expression Omnibus generated an initial PDAC specific prognostic differential expression gene list. The candidate prognostic gene list was then trained on the Australian pancreatic cancer dataset from the ICGC database (n = 103), using iterative sampling based algorithms, to derive a gene signature predictive of patient survival. The gene signature was validated in 2 independent patient cohorts and against existing PDAC subtype classifications. We identified 707 candidate prognostic genes exhibiting differential expression in tumor versus normal tissue. A substantial fraction of these genes was also found to be differentially methylated between survival groups. From the candidate gene list, a 5-gene signature (ADM, ASPM, DCBLD2, E2F7, and KRT6A) was identified. Our signature demonstrated significant power to predict patient survival in two distinct patient cohorts and was independent of AJCC TNM staging. Cross-validation of our gene signature reported a better ROC AUC (0.8) when compared to existing PDAC survival signatures. Furthermore, validation of our signature through immunohistochemical analysis of patient tumor tissue and existing gene expression subtyping data in PDAC, demonstrated a correlation to the presence of vascular invasion and the aggressive squamous tumor subtype. Assessment of these genes in patient biopsies could help further inform risk-stratification and treatment decisions in pancreatic cancer.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30092011

- A simple matrix to predict treatment success and long-term survival among patients undergoing pancreatectomy

HPB : the official journal of the International Hepato Pancreato Biliary Association 2018 Aug;():

BACKGROUND: A more accurate measure of long-term survival among patients who have undergone a successful resection for pancreatic adenocarcinoma may be computed by accounting for time already survived during the initial treatment window. METHODS: Patients diagnosed with pancreatic adenocarcinoma, from 2004 through 2013, were identified from the American College of Surgeons National Cancer Database (NCDB). A risk-stratification matrix was constructed including age, histopathologic factors and the use of adjuvant therapy, given successful treatment and survival at 3-month following diagnosis. RESULTS: A total of 25,897 patients (50% male, 53% >65 years of age) presented with stage I-III pancreatic cancer. The majority of patients had tumors >2 cm size (82%), grade I/II (65%), lymphatic invasion (LI) (66%), and negative margins (76%). A survival advantage for adjuvant therapy was observed among all patients, independent of their risk-profile. For example, a patient 65 years of age, with early stage cancer (size 2 cm, grade I/II, -ve LI, -ve margins) who received adjuvant therapy had a 62% probability of being alive beyond three years (95%CI = 59%-66%). In contrast, the survival probability decreased to 53% (95%CI = 59%-66%) without adjuvant therapy. CONCLUSIONS: These results provide surgeons and patients with more accurate information regarding long-term survival, as well as the benefit of opting for adjuvant therapy after successful pancreatic surgery.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30087052

- Underutilization of Surgery in Periampullary Cancer Treatment

Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract 2018 Aug;():

BACKGROUND: Site-specific outcomes of resection for periampullary cancer have not been analyzed on a large, registry-based scale. METHODS: We assessed data on periampullary cancers from the SEER database. Site- and stage-specific outcomes were analyzed. Resection was compared to no resection. RESULTS: Resection was the main therapy in stages 1 and 2 (resection vs. no resection, 8644 vs. 7208 patients), was less frequent in stage 3 (1248 vs. 2783 patients) and was rarely-but still-used in stage 4 disease (541 vs. 11,212 patients). Pancreatic head (75.7%), 11.4% distal bile duct, 7.7% ampullary, and 5.3% duodenal cancers. Cancer subtype-independent median survival was 22.0 (resection) vs. 7.0 months (no resection) in stages 1 and 2, 21.0 vs. 8.0 months in stage 3, and 10.0 vs. 3.0 months in stage 4. Subtype-dependent median survival (resection vs. no resection) was 18.0 vs. 5.0 months in pancreatic head, 19.0 vs 4.0 months in distal bile duct, 41.0 vs 7.0 months in ampullary, and 38.0 vs 4.0 months in duodenal adenocarcinoma. On multivariable analysis, patient comorbidities, marital and insurance status, and income all influenced the decision to undergo resection. CONCLUSIONS: Surgery is still underutilized in the treatment of periampullary cancers. Patients with cancers originating from the duodenum or the ampulla of Vater benefit most from resectional surgery.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30088190

- Long-Term Survivors of Pancreatic Cancer: A California Population-Based Study

Pancreas 2018 Sep;47(8):958-966

OBJECTIVES: Pancreatic cancer continues to carry a poor prognosis with survival rates that have had minimal improvement over the past 4 decades. We report a population-based, comprehensive analysis of long-term survivors of pancreatic adenocarcinoma diagnosed in the diverse population of California. METHODS: Data from the California Cancer Registry were used to evaluate long-term survival. A total of 70,442 patients diagnosed with pancreatic adenocarcinoma between 1988 and 2009 were identified. Logistic regression was used to identify factors associated with achieving 5-year survival. RESULTS: The overall 5-year survival was 2.5%, with minimal incremental improvements throughout the 3 decades. Age, stage, degree of differentiation, and surgical resection were associated with 5-year survival. Furthermore, younger age and receiving care at a National Cancer Institute-designated cancer center were similarly correlated with 5-year survival regardless of surgical intervention. In addition, we identified stage, differentiation, and adjuvant chemotherapy as significant factors for long-term survival in surgically resected patients. In the unresectable patients, Asian/Pacific islanders and Hispanics were significantly more likely to reach the 5-year milestone than non-Hispanic whites. CONCLUSIONS: Although pancreatic cancer mortality remains high, our study highlights baseline characteristics, treatment, biological factors, and ethnicity that are associated with long-term survival. These findings may serve as a springboard for further investigation.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30074526

- Overall survival and cancer-specific survival in patients with surgically resected pancreatic head adenocarcinoma: A competing risk nomogram analysis

https://www.researchgate.net/publication/326829548_Overall_survival_and_cancer-specific_survival_in_patients_with_surgically_resected_pancreatic_head_adenocarcinoma_A_competing_risk_nomogram_analysis

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- Race and Health Disparities in Patient Refusal of Surgery for Early-Stage Pancreatic Cancer: An NCDB Cohort Study

Annals of surgical oncology 2018 Jul;():

AIM: To identify factors associated with refusal of surgery in patients with early-stage pancreatic cancer and estimate the impact of this decision on survival. METHODS: Using the National Cancer Data Base, 26,358 patients were identified with potentially resectable tumors (pretreatment clinical stage I: T1 or T2 N0M0). Multivariate models were employed to identify factors predicting failure to undergo surgery and assess the impact on survival. RESULTS: Of early-stage patients who were recommended surgery, 7.8% (N = 992) refused surgery for resectable early-stage pancreatic cancer. On multivariable analysis, patients were more likely to refuse surgery if they were older [odds ratio (OR) = 1.18; 95% confidence interval (CI) 1.16-1.19], female (OR = 1.52; 95% CI 1.33-1.73), African American (vs White, OR = 1.79; 95% CI 1.37-2.34), on Medicare/Medicaid (vs private, OR = 2.75; 95% CI 1.54-4.92) or had higher Charlson-Deyo score (2 vs 0, OR = 1.33; 95% CI 1.03-1.72). Patients were also significantly more likely to refuse surgery if they were seen at a center that is not an academic/research program (OR 1.9; 95% CI 1.6-2.27). Patients who were recommended surgery but refused had significantly worse survival than those with stage I who received surgery [median survival 6.8 vs 24 months, Cox hazard ratio (HR) 3.41; 95% CI 3.12-3.60]. CONCLUSIONS: The percentage of patients refusing surgery for operable early-stage pancreatic cancer has been decreasing in the last decade but remains a significant issue that affects survival. Disparities in refusal of surgery are independently associated with several variables including gender, race, and insurance. To mitigate national disparities in surgical care, future studies should focus on exploring potential reasons for refusal and developing communication interventions.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30043318

- Association Between Hepatitis B Infection and Pancreatic Cancer: A Population-Based Analysis in the United States

Pancreas 2018 Aug;47(7):849-855

OBJECTIVES: The aim of this study was to assess the role of hepatitis B (HepB) infection in the causation of pancreatic cancer and the predictors of pancreatic cancer and mortality. METHODS: We identified pancreatic cancer patients 11 to 70 years of age from the 2013-2014 National Inpatient Sample. Pearson test and Student's t-test were used for categorical and continuous variables, respectively. We assessed the association of HepB and pancreatic cancer and the independent mortality predictors by multivariate analyses. RESULTS: Of 69,210 pancreatic cancer patients, 175 patients with a history of HepB and 69,035 patients without a history of HepB were identified. Compared with the pancreatic cancer-non-HepB group, the pancreatic cancer-HepB group consisted more of younger (mean, 60.4 [standard deviation, 7.4] years vs 68.2 [standard deviation, 12.1] years), male, black, and Asian patients with low household income and nonelective admissions. The odds of developing pancreatic cancer among the HepB patients were significantly higher (adjusted odds ratio, 1.24; 95% confidence interval, 1.056-1.449; P = 0.008). Black race, age 65 years, and male sex demonstrated greater odds of mortality. CONCLUSIONS: This study concluded up to a 24% increased likelihood of pancreatic cancer among the HepB patients. Blacks showed greater odds of pancreatic cancer and related mortality.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29939908

- Impact of Prior Malignancy on Survival Outcomes of Stage IV Pancreatic Adenocarcinoma: SEER-Based Cohort

Journal of gastrointestinal cancer 2018 Aug;():

PURPOSE: Pancreatic cancer is one of the most fatal malignancies and the fourth leading cause of cancer-related mortality in the USA. Most clinical trials involving pancreatic adenocarcinoma (PAC) patients exclude subjects with a prior malignancy because of the possible effect of prior malignancies on survival. However, no data in the medical literature support this assumption. In this paper, we aim to study the impact of having a prior malignancy on the survival outcomes of stage IV PAC. METHODS: We used the surveillance, epidemiology, and end results database to review patients with stage IV PAC diagnosed between 1973 and 2014. We calculated overall and pancreatic cancer-specific survival of these patients using unadjusted Kaplan-Meier test and multivariable covariate-adjusted Cox models. RESULTS: We reviewed 66,874 stage IV PAC patients, of which 4942 had a prior malignancy. Kaplan-Meier and Cox models showed that a history of prior malignancy did not cause significant difference in overall survival (HR = 0.938, 95%CI = 0.880-1.000, p = .052). However, a prior malignancy was associated with a better pancreatic cancer-specific survival (HR = 0.855, 95% CI = 0.796-0.918, p < .001). CONCLUSION: A prior malignancy before stage IV PAC was not associated with worse survival outcomes. Researchers should take these results into consideration when including/excluding patients to improve the generalizability and accuracy of their results.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30105523

- **Treatment Outcomes in Patients with Metastatic Neuroendocrine Tumors: a Retrospective Analysis of a Community Oncology Database**

https://link.springer.com/article/10.1007/s12029-018-0160-x

- Genome-scale analysis to identify prognostic microRNA biomarkers in patients with early stage pancreatic ductal adenocarcinoma after pancreaticoduodenectomy

Cancer management and research 2018 ;10():2537-2551

Background: The aim of the study was to investigate potential prognostic microRNA (miRNA) biomarkers for patients with early stage pancreatic ductal adenocarcinoma (PDAC) after pancreaticoduodenectomy using a miRNA-sequencing (miRNA-seq) data set from The Cancer Genome Atlas (TCGA). A miRNA expression-based prognostic signature was generated, and the potential role of target genes in overall survival (OS) in patients with PDAC was examined. Methods: A miRNA-seq data set of 112 PDAC patients who underwent pancreaticoduodenectomy was obtained from TCGA. Survival analysis was performed to identify potential prognostic biomarkers. Results: Eleven miRNAs (hsa-mir-501, hsa-mir-4521, hsa-mir-5091, hsa-mir-24-1, hsa-mir-126, hsa-mir-30e, hsa-mir-3157, hsa-let-7a-3, hsa-mir-133a-1, hsa-mir-4709, and hsa-mir-421) were used to construct a prognostic signature using the step function. The 11-miRNA prognostic signature showed good performance for prognosis prediction (adjusted P<0.0001, adjusted hazard ratio =4.285, 95% confidence interval =2.146-8.554), and the time-dependent receiver operating characteristic analysis showed an area under the curve of 0.864, 0.877, and 0.787 for 1-, 2-, and 3-year PDAC OS predictions, respectively. Comprehensive survival analysis suggested that the prognostic signature could serve as an independent prognostic factor for PDAC OS and performs better in prognosis prediction than other traditional clinical indicators. Functional assessment of the target genes of the miRNAs indicated that they were significantly enriched in multiple biological processes and pathways, including cell proliferation, cell cycle biological processes, the forkhead box O, mitogen-activated protein kinase, Janus kinase/signal transducers and activators of transcription signaling pathways, pathways in cancer, and the ErbB signaling pathway. Several target genes of these miRNAs were also associated with PDAC OS. Conclusion: The present study identified a novel miRNA expression signature that showed potential as a prognostic biomarker for PDAC after pancreaticoduodenectomy.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30127641

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Journals Reviewed

Advances in Anatomic Pathology

American Journal of Clinical Pathology

The American Journal of Gastroenterology

The American Journal of Pathology

American Journal of Surgical Pathology

Annals of Diagnostic Pathology

Annals of Surgery

Annals of Surgical Oncology

Annual Review of Pathology-Mechanisms of Disease

APMIS

Applied Immunohistochemistry & Molecular Morphology

Archives of Pathology & Laboratory Medicine

Cancer

Cancer Cell

Cancer Cytopathology

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Cellular Oncology

Clinical Cancer Research

Cochrane Database Systematic Reviews

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