Pancreatobiliary Pathology Society Journal Watch

June July 2019

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Contents

PBPath Journal Watch Articles

Wellcome to the PBPath Journal Watch!

This bi-monthly journal watch features exciting recently published pancreas and biliary pathology articles that will provide up to date medical knowledge in our field. These articles will be showcased in several convenient categories, including surgical pathology, cytopathology, and molecular pathology among others. The articles in each category are in no particular order. See the list of journals we search regularly here. Previous months' issues may be found in our *archive* and you may see the drafts of upcoming issue here.

We encourage members to actively participate by recommending new articles and providing feedback using the forms provided below.

We hope that you will enjoy the new PBPath Journal Watch!

Feedback

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Back to top

Surgical Pathology

Pancreas

Morphology, Diagnostics, IHC

Morphology, Diagnostics, IHC

- Pancreatic schwannoma, an extremely rare and challenging entity: Report of two cases and review of literature

Pancreatology : official journal of the International Association of Pancreatology (IAP) ... [et al.] 2019 Jul;19(5):729-737

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31153779

Pancreatic schwannoma is a rare benign tumor, for which the preoperative and intraoperative definitive diagnosis is quite challenging. We present the clinical, radiological and pathologic features of two primary pancreatic schwannomas identified in our pathology database over a period of 30 years at our tertiary care hospital. To better understand the clinico-pathological and radiological features of this entity, we provide a comprehensive review of 73 cases described in the English literature, along with our two cases. This review will especially focus on preoperative and intraoperative diagnosis to assess their accuracy for pancreatic schwannoma. The three most common preoperative diagnoses based on imaging for pancreatic schwannomas were cystic neoplasm (56%), pancreatic neuroendocrine tumor (29%) and mucinous cystic neoplasm (26%). Imaging could not definitely diagnose pancreatic schwannoma in any of the reported cases. To obtain a definite diagnosis before surgery, 25 cases underwent imaging-guided fine-needle aspiration (FNA)/biopsy, of which 60% were correctly reported as benign with definite diagnosis of pancreatic schwannoma in 48%. A higher diagnostic accuracy was observed in biopsies (71%) than FNA (37%). In addition, an intraoperative frozen section was carried out in 15 cases, and 47% were correctly diagnosed. Despite relatively low accuracy, preoperative histological assessment can be helpful in surgical managment. A core tissue specimen is recommended to improve the diagnostic accuracy in this setting.

- Lipase hypersecretion syndrome: A distinct form of paraneoplastic syndrome specific to pancreatic acinar carcinomas

Seminars in diagnostic pathology 2019 Jul;36(4):240-245

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31300257

Lipase hypersecretion syndrome (LHS) is a paraneoplastic syndrome seen exclusively as a result of pancreatic acinar cell carcinoma (ACC). In LHS, acinar enzymes (lipase, trypsin and chymotrypsin) which are normally secreted to the duodenum for digestive purposes, are instead released to the blood by the carcinoma cells. In a way, it is "endocrine-ization" of an "exocrine" function. These circulating enzymes, especially lipase, exerts its digestive action on other tissues, especially on the subcutaneous tissues in the pressure poins of legs, creating a picture often mistaken as erythema nodosum or rheumatic nodules. The bone and joints may also be effected, which mostly appears to be secondary to the complications and super-infection of the skin lesions. Eosinophilia also often accompanies this syndrome. The accurate diagnosis of LHS requires the identification of the pancreatic primary as well as its correct classification as acinar because a variety of pancreatic tumors can be associated with skin lesions, ranging from rare metastasis of adenocarcinoma to the necrolytic migratory erythema caused by glucagon-producing neuroendocrine tumors. Towards this differential, the diagnostic characteristics of acinar cell carcinomas that have been better elucidated in the past decade often need to be employed in increasingly smaller specimens and the liver, especially since most LHS cases also have

liver metastasis (presumably due to the by-pass of the "first-pass" liver metabolism phenomenon). ACC (and LHS) occur in patients in their 60's. The pancreatic mass is often large, round, demarcated and closely resemble neuroendocrine and solid-pseudopapillary neoplasms but are more atypical/proliferative, and commonly show single prominent nucleoli and a distinctive chromophilia. Immunostaining with trypsin/chymotrypsin, negativity of beta-catenin help in the differential; as a caveat, neuroendocrine differentiation is common in ACCs. In conclusion, LHS is a rare type of paraneoplastic syndrome specific to ACC. The accurate diagnosis requires attention to their subtle diagnostic characteristics.

Back to top

Staging

Pancreas TNM staging, Margins, Survival

- Pancreatic ductal adenocarcinoma and paraaortic lymph nodes metastases: The accuracy of intraoperative frozen section

Pancreatology : official journal of the International Association of Pancreatology (IAP) … [et al.] 2019 Jul;19(5):710-715

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31174978

BACKGROUND: Pancreatoduodenectomy for pancreatic ductal adenocarcinoma (PDAC) with paraaortic lymph nodes metastases (PALN +) is associated with poor survival. Still, there are no current guidelines advocating systematic detection of PALN+. METHODS: All consecutive patients who underwent surgical exploration/resection with concurrent paraaortic (group 16) lymphadenectomy for PDAC between 2009 and 2016 were considered for inclusion. Resection was systematically aborted in case of intraoperative PALN + detection. Diagnostic performance of preoperative imaging upon blind review and intraoperative PALN dissection with frozen section (FS) for PALN detection were evaluated. Additionally, the prognostic significance of PALN + on overall survival (OS) was analyzed. RESULTS: Over the study period, among 129 patients undergoing surgery for PDAC, 113 had intraoperative PALN dissection with FS analysis. Median number of resected PALN was 3 (range, 1-15). Overall, PALN+ was found in 19 patients (16.8%). Upon blind review, preoperative imaging performed poorly for PALN + detection with a low agreement between imaging and final pathology (Kappa-Cohen index<0.2). In contrast, PALN FS showed high detection performances and strong agreement with final pathology (Kappa-Cohen index = 0.783, 95%CI 0.779-0.867, $p < 0.001$). Regarding survival outcomes, there was no difference between patients with PALN+ and patients not resected in the setting of liver metastases or locally unresectable disease found at exploration ($p = 0.708$). CONCLUSIONS: Before PD for PDAC, intraoperative PALN dissection and FS analysis yields accurate PALN assessment and allows appropriate patient selection. This should be routinely performed and aborting resection should be strongly considered in case of PALN+.

Back to top

Preneoplastic and Preinvasive Lesions

Preneoplastic and Preinvasive Lesions, PanIN, IPMN, MCN, ICPN

- Pancreatic Cysts and Intraductal Papillary Mucinous Neoplasm in Autosomal Dominant Polycystic Kidney Disease

Pancreas 2020 05;48(5):698-705

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31091218

OBJECTIVES: Pancreatic lesions in autosomal dominant polycystic kidney disease (ADPKD) are primarily cysts. They are increasingly recognized, with isolated reports of intraductal papillary mucinous neoplasia (IPMN). METHODS: Retrospective study to determine prevalence, number, size, and location of pancreatic abnormalities using abdominal magnetic resonance imaging (MRI) of genotyped ADPKD patients (seen February 1998 to October 2013) and compared with age- and sex-matched non-ADPKD controls. We evaluated presentation, investigation, and management of all IPMNs among individuals with ADPKD (January 1997 to December 2016). RESULTS: Abdominal MRIs were examined for 271 genotyped ADPKD patients. A pancreatic cyst lesion (PCL) was detected in 52 patients (19%; 95% confidence interval, 15%-23%). Thirty-seven (71%) had a solitary PCL; 15 (28%) had multiple. Pancreatic cyst lesion prevalence did not differ by genotype. Intraductal papillary mucinous neoplasia was detected in 1% of ADPKD cases. Among 12 IPMN patients (7 branch duct; 5 main duct or mixed type) monitored for about 140 months, 2 with main duct IPMNs required Whipple resection, and 1 patient died of complications from small-bowel obstruction after declining surgical intervention. CONCLUSIONS: With MRI, PCLs were detected in 19% and IPMNs in 1% of 271 ADPKD patients with proven mutations, without difference across genotypes. Pancreatic cyst lesions were asymptomatic and remained stable in size.

Back to top

Microenvironment

Tumor Stroma Interactions, Microenvironment, Inflammatory Response

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- Stromal hyaluronan accumulation is associated with low tumor grade and nodal metastases in pancreatic ductal adenocarcinoma

Human pathology 2019 Aug;90():37-44

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31121193

Pancreatic ductal adenocarcinoma is an aggressive malignancy characterized by abundant desmoplastic stroma. Hyaluronan is a prominent stromal component of pancreatic ductal adenocarcinoma and is associated with unique clinical-pathological profiles in other tumor types. The current study aimed to delineate clinical and pathological features associated with hyaluronan accumulation in pancreatic ductal adenocarcinoma using a novel hyaluronan-binding assay currently being used in a clinical trial targeting hyaluronan. Sixty-four formalin-fixed, paraffin-embedded samples of pancreatic ductal adenocarcinomas from 49 patients treated at a single tertiary care hospital were stained. Fifty-two percent of tumors had high levels of hyaluronan. High levels were associated with low tumor grade and lymph node metastases, novel associations not previously seen in pancreatic ductal adenocarcinoma. This study has elucidated a novel clinical-pathological profile in pancreatic ductal adenocarcinomas using a new assay, suggesting hyaluronan may act as a biomarker for a subset of pancreatic tumors that could be targeted by hyaluronan-degrading agents.

- Quasimesenchymal phenotype predicts systemic metastasis in pancreatic ductal adenocarcinoma

Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc 2019 Jun;32(6):844-854

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30683911

Metastasis following surgical resection is a leading cause of mortality in pancreatic ductal adenocarcinoma. Epithelial-mesenchymal transition is thought to play an important role in metastasis, although its clinical relevance in metastasis remains uncertain. We evaluated a panel of RNA in-situ hybridization probes for epithelial-mesenchymal transition-related genes expressed in circulating tumor cells. We assessed the predictive value of this panel for metastasis in pancreatic ductal adenocarcinoma and, to determine if the phenotype is generalizable between cancers, in colonic adenocarcinoma. One hundred fifty-eight pancreatic ductal adenocarcinomas and 205 colonic adenocarcinomas were classified as epithelial or quasimesenchymal phenotype using dual colorimetric RNA-in-situ hybridization. SMAD4 expression on pancreatic ductal adenocarcinomas was assessed by immunohistochemistry. Pancreatic ductal adenocarcinomas with quasimesenchymal phenotype had a significantly shorter disease-specific survival ($P = 0.031$) and metastasis-free survival ($P = 0.0001$) than those with an epithelial phenotype. Pancreatic ductal adenocarcinomas with SMAD4 loss also had lower disease-specific survival ($P = 0.041$) and metastasis-free survival ($P = 0.001$) than those with intact SMAD4. However, the quasimesenchymal phenotype proved a more robust predictor of metastases-area under the curve for quasimesenchymal $= 0.8$; SMAD4 $= 0.6$. The quasimesenchymal phenotype also predicted metastasis-free survival ($P = 0.004$) in colonic adenocarcinoma. Epithelial-mesenchymal transition defined two phenotypes with distinct metastatic capabilities-epithelial phenotype tumors with predominantly organ-confined disease and quasimesenchymal phenotype with high risk of metastatic disease in two epithelial malignancies. Collectively, this work validates the relevance of epithelial-mesenchymal transition in human gastrointestinal tumors.

- The Importance of a Conjoint Analysis of Tumor-Associated Macrophages and Immune Checkpoints in Pancreatic Cancer

Pancreas 2019 Aug;48(7):904-912

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31268976

OBJECTIVES: Tumor-associated macrophages are dominant players in establishing the inmmunosuppressive microenvironment in pancreatic ductal adenocarcinoma (PDAC). Immune checkpoint inhibitor monotherapy has achieved limited clinical effectiveness. To date, the interaction of macrophages and checkpoint regulators and their correlation with clinicopathologic characteristics in PDAC have been largely unavailable. METHODS: Macrophages and immune checkpoint expression were assessed by immunohistochemistry from 80 PDAC samples. Clinicopathologic features and the prognostic value of each marker were evaluated. In vitro changes in the expression of immune markers in cocultured macrophages and PDAC cells were detected by Western blot and immunosorbance assays. RESULTS: The macrophages marker CD163 and the checkpoint marker programmed death-ligand 1 (PD-L1) remained as the independent prognostic factors for overall survival (hazard ratio, 2.543; $P = 0.017$ and hazard ratio, 2.389; $P = 0.021$). Furthermore, integrated analysis of CD163 and PD-L1 served as more optimal indicators of survival ($P = 0.000$). In vitro coculture of macrophages and PDAC cells significantly increased the expression of CD163 and PD-L1, compared with monocultured counterpart ($P < 0.05$). CONCLUSIONS: Combined analysis of CD163 and PD-L1 was enhanced indicators of survival in PDAC patients. The interaction of macrophages and immune checkpoints implied the value of the combination therapy.

Back to top

SPN

Solid Pseudopapillary Neoplasm

- Solid-pseudopapillary Neoplasms of the Pancreas is still an Enigma: a Clinicopathological Review

Pathology oncology research : POR 2019 Jun;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31209654

The solid-pseudopapillary neoplasm of the pancreas is a rare but enigmatic entity occurring mainly in young women. Since the first description by V. Frantz in 1959 the terminology of this tumor has continuously changed but it has remained simply descriptive, because the exact histogenesis is still obscure. Although in majority of cases the survival is excellent, nevertheless, the expected prognosis is not exactly predictable. In this review the authors aim to summarize its clinico-pathological features, the expected biological behavior, the molecular alterations, the immune phenotype and discuss the putative histogenesis. From diagnostic point of view, the salient histological characteristic findings are analyzed that would help to differentiate it from other, look-alike pancreatic tumors, and suggestions are made about the desirable content of the histological report.

Back to top

Pancreatitis & Other Diseases

- Autoimmune Pancreatitis Type 2: Diagnostic Utility of PD-L1 Immunohistochemistry

The American journal of surgical pathology 2019 Jul;43(7):898-906

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31135488

BACKGROUND: Autoimmune pancreatitis (AIP) encompasses a heterogenous disease group that includes IgG4-related type 1 AIP and non-IgG4-related type 2 AIP. Clinically and on imaging, type 2 AIP mimics type 1 AIP, other forms of chronic pancreatitis and pancreatic ductal adenocarcinoma (PDAC); therefore, discriminatory markers may aid proper diagnosis. Herein, we examine the expression of PD-L1 and indoleamine 2,3-dioxygenase (IDO1) as a diagnostic tool to distinguish type 2 AIP from other forms of pancreatitis and PDAC. DESIGN: We evaluated 35 pancreatectomy specimens diagnosed with type 2 AIP and potential mimics of this disease including type 1 AIP (n=14), chronic pancreatitis-not otherwise specified (n=10), groove pancreatitis (n=14), and PDAC (n=278). We scored inflammatory infiltrates, fibrosis and atrophy and performed immunohistochemical staining for PD-L1 and IDO1. We validated our findings on a series of endoscopic ultrasound-guided biopsies from patients with suspected type 2 AIP and inflammatory and neoplastic mimics of this disease (n=37). RESULTS: The mean age of patients with type 2 AIP was 50 years with a F:M ratio of 1.2:1. Patients with type 2 AIP showed pancreatic ductal staining for PD-L1 and IDO1 in 69% (24/35) and 60% (15/25) of cases, respectively. PD-L1 reactivity was noted in 3% of patients with other forms of chronic pancreatitis and 3% of PDACs; notably, peritumoral ducts and acini were negative. Eight of 9 endoscopic ultrasound-guided biopsies with pancreatic ductal epithelium from patients with type 2 AIP were positive for PD-L1, while the inflammatory and neoplastic mimics were negative. Collectively, the sensitivity and specificity of PD-L1 as a marker of type 2 AIP was 70% and 99%, respectively. CONCLUSIONS: Ductal PD-L1 reactivity has the potential to distinguish type 2 AIP from other forms of pancreatitis and PDAC.

- Pancreatobiliary Versus Head and Neck Manifestations in Immunoglobulin G4-related Disease: Distinct Subsets of the Same Disease?

Pancreas 2019 Jul;48(6):799-804

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31210660

OBJECTIVES: We compared the clinical profiles and organ manifestations of the commonly encountered immunoglobulin G4-related diseases (IgG4-RDs) on either side of the diaphragm: head and neck (HN) versus pancreatobiliary (PB) in IgG4-RD. METHODS: From the Mayo Clinic, Rochester, database, we identified 53 HN and 88 PB IgG4-RD based on the first affected organ manifestation. RESULTS: Compared with HN IgG4-RD, subjects with PB IgG4-RD were likely to be older (median, 64.8 vs 50.2 years; $P < 0.0001$), male (83% vs 60.4%; $P = 0.003$), and with a shorter duration of follow-up (24.4 vs 48.7 months; $P < 0.0001$). In HN versus PB-IgG4-RD orbital, lacrimal gland, submandibular, parotid gland, asthma, and sinusitis manifestations were more common (77% vs 4.5%, 21% vs 0%, 32% vs 8%, 13% vs 0%, 36% vs 9%, and 51% vs 6.8%; $P < 0.0001$, respectively), whereas lung manifestations were similar (13.2% vs 5.6%; $P = 0.12$). In contrast, in PB versus HN IgG4-RD, pancreas and biliary were more frequent (98.8% vs 15%, 56.8% vs 3.7%; $P < 0.0001$), whereas renal lesions were similar (12.5% vs 7.5%; $P = 0.36$). CONCLUSION: Pancreatobiliary and HN IgG4-RD have distinct clinical profiles. Proximity matters in other organ involvement in IgG4-RD, and organs involved tend to cluster close to each.

Back to top

Bile Ducts

Morphology, Diagnostics, IHC

Morphology, Diagnostics, IHC

- The Pathologic and Genetic Characteristics of the Intestinal Subtype of Intraductal Papillary Neoplasms of the Bile Duct

The American journal of surgical pathology 2019 Sep;43(9):1212-1220

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31166202

The present study aimed to identify the pathologic and genetic characteristics of intestinal subtype of intraductal papillary neoplasm of the bile duct (iIPNB) showing columnar cells with pseudostratified, cigar-shaped nuclei, and basophilic or amphophilic cytoplasm with the diffuse immunohistochemical expression of CK20 and/or CDX2. A total of 34 cases of iIPNB were pathologically examined according to their anatomic location (the bile duct) and were then compared with the intestinal subtype of intraductal papillary mucinous neoplasm (iIPMN) of the pancreas (n=22). Mutations of 26 somatic genes were examined in formalin-fixed paraffin-embedded tissue specimens from 21 cases of iIPNB using the TruSight Tumor 26 gene panel and next-generation sequencing. iIPNB cases were divided into intrahepatic (n=6) and extrahepatic (n=28) categories. Intrahepatic IPNBs showed a less-complicated villous-papillary pattern, while extrahepatic IPNBs showed a papillary pattern with tubular and/or villous components and predominant high-grade dysplasia with complicated architectures. MUC5AC was frequently and extensively expressed in intrahepatic iIPNBs and iIPMNs but not in extrahepatic iIPNBs. CD10 was frequently expressed in extrahepatic IPNBs but not in intrahepatic iIPNBs or iIPMN. Genetic mutations of TP53 and PIK3CA, which were infrequent or absent in iIPMNs, were frequently detected in extrahepatic iIPNBs, while KRAS and GNAS, which were commonly observed in iIPMNs, were frequently detected in intrahepatic iIPNBs. Intrahepatic iIPNBs showed villous-papillary growth with features reminiscent of iIPMNs, while extrahepatic iIPNBs showed papillary growth with tubular and/or villous components, complicated histology and variable differences from iIPMNs, suggesting differences in the tumorigenesis of iIPNBs along the biliary tree.

- Programmed cell death ligand-1 (PD-L1) expression in extrahepatic biliary tract cancers: a comparative study using 22C3, SP263 and E1L3N anti-PD-L1 antibodies

Histopathology 2019 May;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31081949

AIMS: Pembrolizumab has shown promising results for patients with programmed cell death ligand-1 (PD-L1)-positive advanced biliary tract cancer in an ongoing clinical trial. However, data on PD-L1 expression in bile duct cancers is limited, and the frequency of PD-L1 positivity varies, which may be partly due to the assay used. The aim of this study was to evaluate PD-L1 expression status in bile duct cancers by using 22C3, SP263 and E1L3N antibodies. METHODS AND RESULTS: We evaluated PD-L1 expression in tissue microarrays of 183 extrahepatic bile duct cancers, including 89 perihilar and 94 distal bile duct cancers, by using 22C3, SP263 and E1L3N. When the 22C3 assay was used, tumoral PD-L1 was shown to be expressed in 16.9% of cases at a 1% threshold. When the SP263 and E1L3N assays were used, tumoral PD-L1 was shown to be expressed in 26% and 7.1% of cases, respectively. When whole tissue sections were examined, 59.6% of PD-L1-positive cases showed a low percentage (<10%) of positive tumour cells. Tumoral PD-L1 positivity was associated with poor histological differentiation (P = 0.017) and the biliary epithelial phenotype (P = 0.041). High tumoral PD-L1 expression (10%) was associated with worse overall survival (OS) and disease-free survival (DFS) (OS, P = 0.012; DFS, P = 0.042). CONCLUSIONS: PD-L1 was expressed in a small subset of patients with bile duct cancer, and the percentage of positive tumour cells was low in PD-L1-positive cases. The SP263 assay showed the highest PD-L1 positivity in both tumour cells

and immune cells, followed by the 22C3 and E1L3N assays. High PD-L1 expression was associated with a poor prognosis in extrahepatic bile duct cancer patients.

- Smoking, Alcohol, and Biliary Tract Cancer Risk: A Pooling Project of 26 Prospective Studies

Journal of the National Cancer Institute 2019 May;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31127946

BACKGROUND: Tobacco and alcohol are well-established risk factors for numerous cancers, yet their relationship to biliary tract cancers remains unclear. METHODS: We pooled data from 26 prospective studies to evaluate associations of cigarette smoking and alcohol consumption with biliary tract cancer risk. Study-specific hazard ratios (HRs) and 95% confidence intervals (CIs) for associations with smoking and alcohol consumption were calculated. Random effects meta-analysis produced summary estimates. All statistical tests were two-sided. RESULTS: Over a period of 38,369,156 person-years of follow-up, 1,391 gallbladder, 758 intrahepatic bile duct, 1,208 extrahepatic bile duct, and 623 ampulla of Vater cancer cases were identified. Ever, former, and current smoking were associated with increased extrahepatic bile duct and ampulla of Vater cancers risk (e.g., current versus never smokers hazard ratio [HR] = 1.69, 95% confidence interval [CI] = 1.34 to 2.13 and 2.22, 95%CI = 1.69 to 2.92, respectively), with dose-response effects for smoking pack-years, duration, and intensity (all P-trend<0.01). Current smoking and smoking intensity were also associated with intrahepatic bile duct cancer (e.g., >40 cigarettes/day versus never smokers HR = 2.15, 95%CI: 1.15 to 4.00; P-trend=0.001). No convincing association was observed between smoking and gallbladder cancer. Alcohol consumption was only associated with intrahepatic bile duct cancer, with increased risk for individuals consuming 5 versus 0 drinks/day (HR = 2.35, 95%CI = 1.46 to 3.78; P-trend=0.04). There was evidence of statistical heterogeneity between several cancer sites, particularly between gallbladder cancer and the other biliary tract cancers. CONCLUSIONS: Smoking appears to increase the risk of developing all biliary tract cancers except gallbladder cancer. Alcohol may increase the risk of intrahepatic bile duct cancer. Findings highlight etiologic heterogeneity across the biliary tract.

- Distinct histomorphological features are associated with IDH1 mutation in intrahepatic Cholangiocarcinoma

Human pathology 2019 May;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31121195

Intrahepatic cholangiocarcinoma has known histological heterogeneity. Mutations in IDH1 (mIDH1) define a molecular subclass of intrahepatic cholangiocarcinoma and IDH-targeted therapies are in development. Characterizing mIDH1 ICC histomorphology is of clinical interest for efficient identification. Resected ICCs with targeted next generation sequencing by MSK-IMPACT were selected. Clinical data were obtained. By slide review, blinded to IDH status, data were collected for histology type, mucin production, necrosis, fibrosis, cytoplasm cell shape (low cuboidal, plump cuboidal/polygonal, and columnar), and architectural pattern (anastomosing, tubular, compact tubular, and solid). A tumor was considered architecturally heterogeneous if no dominant pattern represented 75% of the tumor. Parameters were compared between mIDH1and IDH wild type controls. In the examined cohort (113 ICC: 29 mIDH1 and 84 IDH wild type), all IDH1 mutant tumors were of small duct type histology, thus analysis was limited to 101 small duct type tumors. mIDH1cases were more likely to have plump cuboidal/ polygonal shape (P=.014) and geographic-type fibrosis (P=.005) while IDH1 wild type were more likely to have low cuboidal shape (P=.005). Both groups were predominantly architecturally heterogeneous with no significant difference in the distribution of architectural patterns. Plump cuboidal/polygonal cell shape and a geographic-type pattern of intra-tumoral fibrosis are more often seen in mIDH1compared to IDH wild type tumors, however IDH1 mutation is not associated with a distinct histoarchitectural pattern.

Back to top

Gallbladder

Morphology, Diagnostics, IHC

Morphology, Diagnostics, IHC

- Intracholecystic papillary-tubular neoplasms of the gallbladder - A clinicopathological study of 36 cases

Annals of diagnostic pathology 2019 Jun;40():88-93

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31077876

Intracholecystic papillary-tubular neoplasms (ICPNs) account for <0.5% of all cholecystectomies. There is a lack of significant published data from the Indian subcontinent on ICPN to the best of our knowledge. The objective of the current study was to describe the clinicopathological features of ICPN of gallbladder from the departmental archives during a 5.5-year period. We also aimed to classify them into various histological subtypes and to correlate the clinicopathological parameters of ICPN with invasive adenocarcinoma. This study included 36 cases diagnosed over a period of 5.5 years (2013-2018). Clinical, radiological and histopathological data were analyzed in detail. The incidence of ICPN was 0.8%. The mean age of patients was 45.7 years with a female to male ratio of 1.3:1. Biliary phenotype was associated with invasion (p 0.001). Papillary pattern was present in 15 cases (41.6%) and was associated with invasion (p 0.001). High grade dysplasia was seen in 34 cases (94.4%), of which invasion was seen in 18 cases (50%). One case in our study also had synchronous common bile duct carcinoma. Majority (92%) of the patients were alive and well at the end of available follow-up (mean of 7 months and 25 days). ICPNs are mass forming neoplasms of the gallbladder with a slight female predominance. Biliary phenotype has an aggressive course, often associated with an invasive adenocarcinoma component. Papillary configuration of the lesion is significantly associated with an invasive component. Diligent follow-up of these lesions is warranted as they can be associated with other malignancies of the biliary system.

- Sarcomatoid carcinomas of the gallbladder: clinicopathologic characteristics

Virchows Archiv : an international journal of pathology 2019 Jul;475(1):59-66

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31177317

Sarcomatoid carcinomas recently came into the spotlight through genetic profiling studies and also as a distinct model of epithelial-mesenchymal transition. The literature on sarcomatoid carcinomas of gallbladder is limited. In this study, 656 gallbladder carcinomas (GBC) were reviewed. Eleven (1.7%) with a sarcomatoid component were identified and analyzed in comparison with ordinary GBC (O-GBC). Patients included 9 females and 2 males (F/M = 4.5 vs. 3.9) with a mean age-at-diagnosis of 71 (vs. 64). The median tumor size was 4.6 cm (vs. 2.5; P = 0.01). Nine patients (84%) presented with advanced stage (pT3/4) tumor (vs. 48%). An adenocarcinoma component constituting 1-75% of the tumor was present in nine, and eight had surface dysplasia/CIS; either in situ or invasive carcinoma was present in all cases. An intracholecystic papillary-tubular neoplasm was identified in one. Seven showed pleomorphic-sarcomatoid pattern, and four showed subtle/bland elongated spindle cells. Three had an angiosarcomatoid pattern. Two had heterologous elements. One showed few osteoclast-like giant cells, only adjacent to osteoid. Immunohistochemically, vimentin, was positive in six of six; P53 expression was > 60% in six of six, keratins in six of seven, and p63 in two of six. Actin, desmin, and S100 were negative. The median Ki67 index was 40%. In the follow-up, one died peri-operatively, eight died of disease within 3 to 8 months (vs. 26 months median survival for O-GBC), and two were alive at 9 and 15 months. The behavior overall was worse than ordinary adenocarcinomas in general but was not different when grade and stage were matched. In summary, sarcomatoid component is identified in < 2% of GBC. Unlike sarcomatoid carcinomas in the remainder of pancreatobiliary tract, these are seldom of the "osteoclastic" type and patients present with large/advanced stage tumors. Limited

data suggests that these tumors are aggressive with rapid mortality unlike pancreatic osteoclastic ones which often have indolent behavior.

- Epithelial Inclusions in Gallbladder May Mimic Parasite Infection

American journal of clinical pathology 2019 Aug;152(3):399-402

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31189015

Back to top

Neuroendocrine

PanNET

PanNET, Pancreatic Neuroendocrine Tumors and related neuroendocrine neoplasms

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- Insulinoma-associated protein 1 expression in primary and metastatic neuroendocrine neoplasms of the gastrointestinal and pancreaticobiliary tracts

Histopathology 2019 May;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31077609

AIMS: Insulinoma-associated protein 1 (INSM1) is a transcription factor that is expressed in developing and mature neuroendocrine tissue. Recent studies have shown that INSM1 is a sensitive marker for neuroendocrine tumours. The aims of this study were to evaluate INSM1 expression in primary gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) and in their known metastases, in order to assess its sensitivity as compared with chromogranin-A (CgA) and synaptophysin (SYN), and to evaluate any change in expression between primary and metastatic disease. METHODS AND RESULTS: We identified 30 patients with primary GEP-NEN. Liver metastatic tissue was available for 26 patients; two patients had two metachronous metastatic foci, yielding a total of 28 metastatic cases. An additional two and seven non-paired cases of primary and metastatic grade 3 GEP-NEN, respectively, were included. To assess specificity, we evaluated the expression of these markers in other primary tumours (colorectal adenocarcinoma, acinar cell carcinoma, solid pseudopapillary neoplasm, cholangiocarcinoma, and hepatocellular carcinoma) and metastatic tumours in the liver (adrenal cortical, breast and prostate carcinomas) that may present as differential diagnoses. In our cohort, all of the primary GEP-NENs and 94% of the metastatic GEP-NENs expressed INSM1. INSM1 showed similar sensitivity to SYN and higher sensitivity than CgA in both primary and metastatic neoplasms. INSM1 has comparable specificity to CgA, and higher specificity than SYN. CONCLUSIONS: The nuclear reactivity and the high sensitivity and specificity of INSM1 make it a preferred neuroendocrine marker. In conclusion, INSM1 can be used as a single first-line marker for primary and metastatic GEP-NEN.

- Is the Real Prevalence of Pancreatic Neuroendocrine Tumors Underestimated? A Retrospective Study on a Large Series of Pancreatic Specimens

Neuroendocrinology 2019 05;109(2):165-170

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31117106

BACKGROUND/AIMS: The annual incidence of pancreatic neuroendocrine tumors (PanNET) has been estimated to be around 0.8/100,000 inhabitants. The aim of this study was to determine the frequency of incidental histological diagnosis of PanNET in pancreatic specimen evaluation for a purpose other other than PanNET diagnosis. METHODS: One thousand seventy-four histopathological examinations of pancreatic specimens performed in 3 centers in Italy were retrospectively reviewed. All cases with a main pathological diagnosis of PanNET were excluded. RESULTS: An incidental associated diagnosis of PanNET was made in 41 specimens (4%). Among those 41 cases, 29 (71%) had a largest diameter <5 mm (microadenoma), whereas the other 12 (29%) had a maximum size 5 mm (median diameter of the whole series = 3 mm, range 1-15). The association with a main diagnosis of intraductal papillary mucinous neoplasms (IPMN) was significantly higher for patients who had an incidental PanNET (p = 0.048). There was no association between incidental diagnosis of PanNET and age, gender, BMI, smoking habit, diabetes, and type of operation. CONCLUSIONS: The frequency of incidental histological diagnosis of PanNET is considerably high, suggesting that their real prevalence is probably underestimated. The present study suggests a possible correlation between the incidental occurrence of PanNET and IPMN.

- Diagnostic and Management Challenges in Vasoactive Intestinal Peptide Secreting Tumors: A Series of 15 Patients

Pancreas 2019 Aug;48(7):934-942

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31268974

OBJECTIVES: Vasoactive intestinal peptide-secreting tumors (VIPomas) are rare functioning neuroendocrine tumors often characterized by a difficult-to-control secretory syndrome and high potential to develop metastases. We hereby present the characteristics of 15 cases of VIPomas and provide a recent literature review. METHODS: This was a retrospective data analysis of 15 patients with VIPoma from 3 different centers and literature research through PubMed database during the last 10 years. RESULTS: Fifteen patients with VIPomas (9 with hepatic metastases at diagnosis) with watery diarrhea and raised VIP levels were studied. Ten patients (67%) had grade 2 tumors, 6 of 15 had localized disease and underwent potentially curative surgery, whereas the remaining 9 received multiple systemic therapies; 3 patients died during follow-up. The median overall survival was 71 months (range, 41-154 months). Patients who were treated with curative surgery (n = 7) had longer median overall survival compared with patients who were treated with other therapeutic modalities (44 vs 33 months). CONCLUSIONS: The management of VIPomas is challenging requiring the application of multiple treatment modalities. Patients who underwent surgical treatment with curative intent appear to have higher survival rate. Central registration and larger prospective studies are required to evaluate the effect of currently employed therapies in these patients.

- Ki-67 Index of 5% is Better Than 2% in Stratifying G1 and G2 of the World Health Organization Grading System in Pancreatic Neuroendocrine Tumors

Pancreas 2019 Jul;48(6):795-798

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31210659

OBJECTIVE: The World Health Organization (WHO) grading system for the stratification of G1 and G2 pancreatic neuroendocrine tumors (pNETs) using an optimal Ki-67 index cutoff is still controversial. The present study aimed at finding one optimal Ki-67 cutoff value that distinguishes G1 and G2 tumors by analyzing the prognosis of patients with pNET in our center. METHODS: Data from 84 patients with pNET undergoing surgical resection in The First Affiliated Hospital of Sun Yat-sen University between March 2003 and October 2015 were retrospectively analyzed. RESULTS: The 5-year overall survival rate was 74.2%. Univariate analysis revealed that functional secretion, WHO grade, and TNM stage were significantly associated with long-term survival (all $P < 0.05$). Multivariate analysis demonstrated that WHO grade ($P = 0.023$) and TNM stage ($P = 0.040$) were independent prognostic factors. The receiver operating characteristic curve showed that the Ki-67 index of 5% had the best predictive ability (76.7%) for 5-year survival with a hazard ratio of 44.7. The hazard ratio was only 8.14 when the Ki-67 index cutoff was 2%. CONCLUSIONS: TNM stage and WHO grade were independent prognostic factors of pNETs. A Ki-67 index of 5% is better than 2% in stratifying G1 and G2 pNET tumors.

Back to top

Staging

PanNET TNM staging, Margins, Survival

- Prognostic Validity of the American Joint Committee on Cancer Eighth Edition TNM Staging System for Surgically Treated and Well-Differentiated Pancreatic Neuroendocrine Tumors: A Comprehensive Analysis of 254 Consecutive Patients From a Large Chinese Institution

Pancreas 2019 5;48(5):613-621

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31091206

OBJECTIVES: We aimed to validate the novel American Joint Committee on Cancer (AJCC) eighth edition staging manual for well-differentiated (G1/G2) pancreatic neuroendocrine tumors (pNETs). METHODS: Data of eligible patients were retrospectively collected, grouped, and analyzed by applying the new AJCC system. RESULTS: According to the AJCC eighth staging manual for pNETs, 93, 66, 53, and 42 patients had stage I, II, III, and IV disease, respectively, with estimated 5-year overall survival (OS) rates of 96.9%, 92.8%, 48.4%, and 16.8% ($P < 0.005$), respectively. A total of 57, 28, 20, and 17 patients with G1 pNETs and 36, 38, 33, and 25 ones with G2 tumors were defined by the new AJCC system as having stage I, II, III, and IV disease, respectively. The estimated 5-year OS for stage I, II, III and IV disease was 100.0%, 97.1%, 52.5%, and 18.2%, respectively, for G1 pNETs ($P < 0.005$) and 94.2%, 90.3%, 38.7%, and 12.7%, respectively, for G2 tumors ($P < 0.005$). The novel AJCC classification, tumor grading, and radical resection were all prognostic predictors for OS in patients with pNETs. CONCLUSIONS: The new AJCC eighth staging system for well-differentiated pNETs was prognostic and might be adopted in clinical practice.

- Significance of Lymph Node Metastasis in Resectable Well-differentiated Pancreatic Neuroendocrine Tumor

Pancreas 2019 Aug;48(7):943-947

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31268980

OBJECTIVES: Understanding the effect of lymph node metastasis (LNM) on prognosis in pancreatic neuroendocrine neoplasm is helpful for surgery and follow-up. In this study, we investigated the significance of LNM in well-differentiated pancreatic neuroendocrine tumors (PanNETs) according to the World Health Organization 2017 classification. METHODS: We retrospectively collected data for 95 consecutive patients with PanNET who underwent pancreatic resection with curative intent between January 2008 and December 2017 at 6 institutions. The clinicopathological factors were compared in patients with and without LNM, and prognostic factors were analyzed. RESULTS: Lymph node metastasis was significantly associated with malignant potential of PanNET, such as larger tumor size, higher Ki-67 index, higher tumor grade, and higher incidence of lymphatic, vessel, and neural invasion. Lymph node metastasis was also associated with disease-free but not overall survival. Multivariate analysis identified NET grade 2 (G2) and G3 as independent risk factors for recurrence after curative resection. CONCLUSIONS: World Health Organization 2017 classification was the most independent prognostic factor in patients with resectable well-differentiated PanNETs. Patients with G2 and higher-grade tumors require lymph node dissection to improve prognosis.

Back to top

Cytopathology

Pancreas

- Diagnostic Efficacy of Liquid-Based Cytology in Endoscopic Ultrasound-Guided Fine Needle Aspiration for Pancreatic Mass Lesions During the Learning Curve: A Retrospective Study

Pancreas 2019 5;48(5):686-689

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31091216

OBJECTIVES: The diagnostic yield of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) cytology widely varies depending on the treatment method used. Liquid-based cytology (LBC) has gained popularity in the gynecological field because of its efficacy in collection of target cells and simplicity in the manipulation of specimens. Since the introduction of EUS-FNA at our institution, we have used LBC for the diagnosis of pancreatic mass lesions. This study aims to investigate the diagnostic efficacy of EUS-FNA with LBC in patients with pancreatic mass lesions during the learning curve for EUS-FNA. METHODS: In this study, we retrospectively enrolled 222 patients with pancreatic mass lesions who were diagnosed using EUS-FNA with LBC between 2011 and 2016. The diagnostic yields for EUS-FNA with LBC for pancreatic mass lesions were evaluated. RESULTS: The diagnostic sensitivity, specificity, and accuracy for malignancy were found to be 93.9%, 95.1%, and 94.1%, respectively. CONCLUSIONS: This study suggests that EUS-FNA with LBC for specimens provides good diagnostic efficacy in patients with pancreatic mass lesions even during the learning curve for EUS-FNA.

- Ultrasound-guided fine needle aspiration cytology in the diagnosis of hepatic and pancreatic perivascular epithelioid cell tumors: A case series

Diagnostic cytopathology 2019 Apr;47(4):315-319

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30417984

Perivascular epithelioid cell tumors (PEComas) are rare mesenchymal tumors that can affect any part of the body. They can be sporadic or arise in the setting of tuberous sclerosis (TSC). In this article, we report a series of three hepatic and two pancreatic PEComas diagnosed preoperatively with ultrasound-guided fine needle aspiration (FNA). All patients were female (age range 28-70), had no personal history of TSC and presented with a single, localized painless mass. Rapid on-site evaluation (ROSE) of cytologic samples was performed for all cases to evaluate for cellular content and adequacy of specimens. Direct smears and cell block preparations revealed a proliferation of medium to large polygonal epithelioid cells, with abundant eosinophilic and vacuolated cytoplasm, arranged in sheets and nests. On immunohistochemistry (IHC), neoplastic cells showed co-expression of melanocytic and smooth muscle markers and a diagnosis of PEComa was rendered. PEComas of the pancreas and liver are rare neoplasms, but should always be considered when examining “clear cell” neoplasms, especially in young female patients. If good quality cytologic samples are obtained by FNA, a correct diagnosis can be achieved with the help of IHC. This is of particular importance in order to plan adequate surgical strategy and to avoid overtreatment.

- Cytohistological diagnosis of pancreatic serous cystadenoma: a multimodal approach

Journal of clinical pathology 2019 Sep;72(9):615-621

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31235542

AIMS: Serous cystadenomata (SCAs) are benign pancreatic cystic neoplasms that present a diagnostic challenge despite many investigational approaches. Notwithstanding the promise of molecular diagnostics, these tests have limited accessibility in day-to-day surgical pathology practices. We aim to corroborate and

build on recent evidence which suggests that positive -inhibin immunohistochemistry (IHC) is a helpful adjunct in the biopsy confirmation of pancreatic SCA. METHODS: We retrospectively reviewed 22 fine-needle aspirates/biopsies from 14 patients (mean age 65 years, 47-83 years) with pancreatic multicystic lesions radiologically suspicious for SCA (location: 6 body, 2 head, 4 tail, 1 neck, 1 uncinate; cyst size: mean 3.7 cm, 2.0-7.6 cm), as well as an additional 10 pancreatic resection specimens with confirmed SCA; -inhibin IHC was performed on all cell blocks, biopsy slides and representative resection specimen sections. Where available, associated cyst fluid was analysed for correlative vascular endothelial growth factor A (VEGF-A) and carcinoembryonic antigen levels. RESULTS: An -inhibin IHC sensitivity of 80% was observed in the cases with resection confirmed SCA. Of the fine-needle aspirate/biopsy specimens, 59% (13/22) contained epithelial cells strongly positive for -inhibin. When selecting for specimens that exhibited distinct strips of epithelium, the -inhibin strong positivity rate increased to 73% (8/11). VEGF-A values were supportive of false-negative -inhibin IHC in three cases and true-negative -inhibin IHC in one case. CONCLUSION: This study postulates a diagnostic algorithm to confirm pancreatic SCA which may help to decrease unnecessary follow-up endoscopy/surgical resection and would decrease the associated morbidity, mortality and financial costs in patients with this otherwise benign condition.

Back to top

Ampulla Duodenum

- Cytologic features of pancreatobiliary neoplasm of duodenum

Diagnostic cytopathology 2019 Jul;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31276311

Small intestinal adenomas are uncommon. Majority of these occur in the region of the ampulla of Vater. Adenomas of the ampulla can be further subdivided into two types-intestinal and pancreatobiliary. While intestinal adenomas are more frequent, pancreatobiliary adenomas are rare. There is limited literature regarding the role of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) in the diagnosis of ampullary/peri-ampullary neoplasms. Here, we describe the cytologic features of a pancreatobiliary neoplasm of the duodenum that was sampled by EUS-FNA. The aspirate was cellular and revealed cells with moderately abundant oncocytic cytoplasm. The nuclei were round with fine chromatin and focally prominent nucleoli. Although the concurrent biopsy showed no high-grade dysplasia or invasive carcinoma, the EUS and imaging findings were highly suspicious for invasion. A broad differential diagnosis is under consideration for a duodenal mass that encompasses neoplasms of the biliary tract, pancreas, duodenum, and ampulla of Vater. To our knowledge, cytologic features of a pancreatobiliary neoplasm of the duodenum have not been previously reported. Our case highlights the features seen on cytology with histologic correlation in the hopes of elucidating features to better characterize these lesions.

Back to top

Molecular Pathology

Pancreas

Pancreas

- Morphological classification of pancreatic ductal adenocarcinoma that predicts molecular subtypes and correlates with clinical outcome

Gut 2019 Jun;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31201285

INTRODUCTION: Transcriptional analyses have identified several distinct molecular subtypes in pancreatic ductal adenocarcinoma (PDAC) that have prognostic and potential therapeutic significance. However, to date, an indepth, clinicomorphological correlation of these molecular subtypes has not been performed. We sought to identify specific morphological patterns to compare with known molecular subtypes, interrogate their biological significance, and furthermore reappraise the current grading system in PDAC. DESIGN: We first assessed 86 primary, chemotherapy-naive PDAC resection specimens with matched RNA-Seq data for specific, reproducible morphological patterns. Differential expression was applied to the gene expression data using the morphological features. We next compared the differentially expressed gene signatures with previously published molecular subtypes. Overall survival (OS) was correlated with the morphological and molecular subtypes. RESULTS: We identified four morphological patterns that segregated into two components ('gland forming' and 'non-gland forming') based on the presence/absence of well-formed glands. A morphological cut-off (40% 'non-gland forming') was established using RNA-Seq data, which identified two groups (A and B) with gene signatures that correlated with known molecular subtypes. There was a significant difference in OS between the groups. The morphological groups remained significantly prognostic within cancers that were moderately differentiated and classified as 'classical' using RNA-Seq. CONCLUSION: Our study has demonstrated that PDACs can be morphologically classified into distinct and biologically relevant categories which predict known molecular subtypes. These results provide the basis for an improved taxonomy of PDAC, which may lend itself to future treatment strategies and the development of deep learning models.

- NRG1 Gene Fusions Are Recurrent, Clinically Actionable Gene Rearrangements in KRAS Wild-Type Pancreatic Ductal Adenocarcinoma

Clinical cancer research : an official journal of the American Association for Cancer Research 2019 Aug;25(15):4674-4681

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31068372

PURPOSE: Gene fusions involving neuregulin 1 (NRG1) have been noted in multiple cancer types and have potential therapeutic implications. Although varying results have been reported in other cancer types, the efficacy of the HER-family kinase inhibitor afatinib in the treatment of NRG1 fusion-positive pancreatic ductal adenocarcinoma is not fully understood. EXPERIMENTAL DESIGN: Forty-seven patients with pancreatic ductal adenocarcinoma received comprehensive whole-genome and transcriptome sequencing and analysis. Two patients with gene fusions involving NRG1 received afatinib treatment, with response measured by pretreatment and posttreatment PET/CT imaging. RESULTS: Three of 47 (6%) patients with advanced pancreatic ductal adenocarcinoma were identified as KRAS wild type by whole-genome sequencing. All KRAS wild-type tumors were positive for gene fusions involving the ERBB3 ligand NRG1. Two of 3 patients with NRG1 fusion-positive tumors were treated with afatinib and demonstrated a significant and rapid response while on therapy. CONCLUSIONS: This work adds to a growing body of evidence that NRG1 gene

fusions are recurrent, therapeutically actionable genomic events in pancreatic cancers. Based on the clinical outcomes described here, patients with KRAS wild-type tumors harboring NRG1 gene fusions may benefit from treatment with afatinib.See related commentary by Aguirre, p. 4589.

- Oncogenic NRG1 Fusions: A New Hope for Targeted Therapy in Pancreatic Cancer

Clinical cancer research : an official journal of the American Association for Cancer Research 2019 Aug;25(15):4589-4591

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31164372

Approximately 8%-10% of pancreatic ductal adenocarcinoma cases are KRAS wild type. In a subset of these tumors, NRG1 gene fusions have been identified as targetable oncogenic drivers, a discovery that highlights the importance of deep molecular characterization for KRAS wild-type pancreatic cancers and provides a novel treatment strategy in this disease.See related article by Jones et al., p. 4674.

- Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer

The New England journal of medicine 2019 07;381(4):317-327

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31157963

BACKGROUND: Patients with a germline BRCA1 or BRCA2 mutation make up a small subgroup of those with metastatic pancreatic cancer. The poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor olaparib has had antitumor activity in this population. METHODS: We conducted a randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy of olaparib as maintenance therapy in patients who had a germline BRCA1 or BRCA2 mutation and metastatic pancreatic cancer and disease that had not progressed during first-line platinum-based chemotherapy. Patients were randomly assigned, in a 3:2 ratio, to receive maintenance olaparib tablets (300 mg twice daily) or placebo. The primary end point was progression-free survival, which was assessed by blinded independent central review. RESULTS: Of the 3315 patients who underwent screening, 154 underwent randomization and were assigned to a trial intervention (92 to receive olaparib and 62 to receive placebo). The median progression-free survival was significantly longer in the olaparib group than in the placebo group (7.4 months vs. 3.8 months; hazard ratio for disease progression or death, 0.53; 95% confidence interval [CI], 0.35 to 0.82; $P = 0.004$). An interim analysis of overall survival, at a data maturity of 46%, showed no difference between the olaparib and placebo groups (median, 18.9 months vs. 18.1 months; hazard ratio for death, 0.91; 95% CI, 0.56 to 1.46; $P = 0.68$). There was no significant between-group difference in health-related quality of life, as indicated by the overall change from baseline in the global quality-of-life score (on a 100-point scale, with higher scores indicating better quality of life) based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (between-group difference, -2.47 points; 95% CI, -7.27 to 2.33). The incidence of grade 3 or higher adverse events was 40% in the olaparib group and 23% in the placebo group (between-group difference, 16 percentage points; 95% CI, -0.02 to 31); 5% and 2% of the patients, respectively, discontinued the trial intervention because of an adverse event. CONCLUSIONS: Among patients with a germline BRCA mutation and metastatic pancreatic cancer, progression-free survival was longer with maintenance olaparib than with placebo. (Funded by AstraZeneca and others; POLO ClinicalTrials.gov number, NCT02184195.).

- Circulating Tumor DNA as a Clinical Test in Resected Pancreatic Cancer

Clinical cancer research : an official journal of the American Association for Cancer Research 2019 Aug;25(16):4973-4984

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31142500

PURPOSE: In research settings, circulating tumor DNA (ctDNA) shows promise as a tumor-specific biomarker for pancreatic ductal adenocarcinoma (PDAC). This study aims to perform analytical and

clinical validation of a KRAS ctDNA assay in a Clinical Laboratory Improvement Amendments (CLIA) and College of American Pathology-certified clinical laboratory. EXPERIMENTAL DESIGN: Digital-droplet PCR was used to detect the major PDAC-associated somatic KRAS mutations (G12D, G12V, G12R, and Q61H) in liquid biopsies. For clinical validation, 290 preoperative and longitudinal postoperative plasma samples were collected from 59 patients with PDAC. The utility of ctDNA status to predict PDAC recurrence during follow-up was assessed. RESULTS: ctDNA was detected preoperatively in 29 (49%) patients and was an independent predictor of decreased recurrence-free survival (RFS) and overall survival (OS). Patients who had neoadjuvant chemotherapy were less likely to have preoperative ctDNA than were chemo-naïve patients (21% vs. 69%; $P < 0.001$). ctDNA levels dropped significantly after tumor resection. Persistence of ctDNA in the immediate postoperative period was associated with a high rate of recurrence and poor median RFS (5 months). ctDNA detected during follow-up predicted clinical recurrence [sensitivity 90% (95% confidence interval (CI), 74%-98%), specificity 88% (95% CI, 62%-98%)] with a median lead time of 84 days (interquartile range, 25-146). Detection of ctDNA during postpancreatectomy follow-up was associated with a median OS of 17 months, while median OS was not yet reached at 30 months for patients without ctDNA ($P = 0.011$). CONCLUSIONS: Measurement of KRAS ctDNA in a CLIA laboratory setting can be used to predict recurrence and survival in patients with PDAC.

- Next-Generation Sequencing in Pancreatic Cancer

Pancreas 2019 Jul;48(6):739-748

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31206465

Pancreatic ductal adenocarcinoma (PDAC) is lethal, and the majority of patients present with locally advanced or metastatic disease that is not amenable to cure. Thus, with surgical resection being the only curative modality, it is critical that disease is identified at an earlier stage to allow the appropriate therapy to be applied. Unfortunately, a specific biomarker for early diagnosis has not yet been identified; hence, no screening process exists. Recently, high-throughput screening and next-generation sequencing (NGS) have led to the identification of novel biomarkers for many disease processes, and work has commenced in PDAC. Genomic data generated by NGS not only have the potential to assist clinicians in early diagnosis and screening, especially in high-risk populations, but also may eventually allow the development of personalized treatment programs with targeted therapies, given the large number of gene mutations seen in PDAC. This review introduces the basic concepts of NGS and provides a comprehensive review of the current understanding of genetics in PDAC as related to discoveries made using NGS.

- p110 deficiency protects against pancreatic carcinogenesis yet predisposes to diet-induced hepatotoxicity

Proceedings of the National Academy of Sciences of the United States of America 2019 Jul;116(29):14724-14733

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31266893

Pancreatic ductal adenocarcinoma (PDAC) is notorious for its poor survival and resistance to conventional therapies. PI3K signaling is implicated in both disease initiation and progression, and specific inhibitors of selected PI3K p110 isoforms for managing solid tumors are emerging. We demonstrate that increased activation of PI3K signals cooperates with oncogenic Kras to promote aggressive PDAC in vivo. The p110 isoform is overexpressed in tumor tissue and promotes carcinogenesis via canonical AKT signaling. Its selective blockade sensitizes tumor cells to gemcitabine in vitro, and genetic ablation of p110 protects against Kras-induced tumorigenesis. Diet/obesity was identified as a crucial means of p110 subunit up-regulation, and in the setting of a high-fat diet, p110 ablation failed to protect against tumor development, showing increased activation of pAKT and hepatic damage. These observations suggest that a careful and judicious approach should be considered when targeting p110 for therapy, particularly in obese patients.

- Endogenous Gastrin Collaborates With Mutant KRAS in Pancreatic Carcinogenesis

Pancreas 2019 Aug;48(7):894-903

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31268978

OBJECTIVE: The KRAS gene is the most frequently mutated gene in pancreatic cancer, and no successful anti-Ras therapy has been developed. Gastrin has been shown to stimulate pancreatic cancer in an autocrine fashion. We hypothesized that reactivation of the peptide gastrin collaborates with KRAS during pancreatic carcinogenesis. METHODS: LSL-Kras; P48-Cre (KC) mutant KRAS transgenic mice were crossed with gastrin-KO (GKO) mice to develop GKO/KC mice. Pancreata were examined for 8 months for stage of pancreatic intraepithelial neoplasia lesions, inflammation, fibrosis, gastrin peptide, and microRNA expression. Pancreatic intraepithelial neoplasias from mice were collected by laser capture microdissection and subjected to reverse-phase protein microarray, for gastrin and protein kinases associated with signal transduction. Gastrin mRNA was measured by RNAseq in human pancreatic cancer tissues and compared to that in normal pancreas. RESULTS: In the absence of gastrin, PanIN progression, inflammation, and fibrosis were significantly decreased and signal transduction was reversed to the canonical pathway with decreased KRAS. Gastrin re-expression in the PanINs was mediated by miR-27a. Gastrin mRNA expression was significantly increased in human pancreatic cancer samples compared to normal human pancreas controls. CONCLUSIONS: This study supports the mitogenic role of gastrin in activation of KRAS during pancreatic carcinogenesis.

- Switchable CAR-T cells mediate remission in metastatic pancreatic ductal adenocarcinoma

Gut 2019 06;68(6):1052-1064

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30121627

OBJECTIVE: Pancreatic ductal adenocarcinoma (PDAC) is a disease of unmet medical need. While immunotherapy with chimeric antigen receptor T (CAR-T) cells has shown much promise in haematological malignancies, their efficacy for solid tumours is challenged by the lack of tumour-specific antigens required to avoid on-target, off-tumour effects. Switchable CAR-T cells whereby activity of the CAR-T cell is controlled by dosage of a tumour antigen-specific recombinant Fab-based 'switch' to afford a fully tunable response may overcome this translational barrier. DESIGN: In this present study, we have used conventional and switchable CAR-T cells to target the antigen HER2, which is upregulated on tumour cells, but also present at low levels on normal human tissue. We used patient-derived xenograft models derived from patients with stage IV PDAC that mimic the most aggressive features of PDAC, including severe liver and lung metastases. RESULTS: Switchable CAR-T cells followed by administration of the switch directed against human epidermal growth factor receptor 2 (HER2)-induced complete remission in difficult-to-treat, patient-derived advanced pancreatic tumour models. Switchable HER2 CAR-T cells were as effective as conventional HER2 CAR-T cells in vivo testing a range of different CAR-T cell doses. CONCLUSION: These results suggest that a switchable CAR-T system is efficacious against aggressive and disseminated tumours derived from patients with advanced PDAC while affording the potential safety of a control switch.

- Experimental microdissection enables functional harmonisation of pancreatic cancer subtypes

Gut 2019 06;68(6):1034-1043

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30658994

OBJECTIVE: Pancreatic ductal adenocarcinoma (PDA) has among the highest stromal fractions of any cancer and this has complicated attempts at expression-based molecular classification. The goal of this work is to profile purified samples of human PDA epithelium and stroma and examine their respective contributions to gene expression in bulk PDA samples. DESIGN: We used laser capture microdissection (LCM) and RNA sequencing to profile the expression of 60 matched pairs of human PDA malignant epithelium and stroma samples. We then used these data to train a computational model that allowed us to infer tissue

composition and generate virtual compartment-specific expression profiles from bulk gene expression cohorts. RESULTS: Our analysis found significant variation in the tissue composition of pancreatic tumours from different public cohorts. Computational removal of stromal gene expression resulted in the reclassification of some tumours, reconciling functional differences between different cohorts. Furthermore, we established a novel classification signature from a total of 110 purified human PDA stroma samples, finding two groups that differ in the extracellular matrix-associated and immune-associated processes. Lastly, a systematic evaluation of cross-compartment subtypes spanning four patient cohorts indicated partial dependence between epithelial and stromal molecular subtypes. CONCLUSION: Our findings add clarity to the nature and number of molecular subtypes in PDA, expand our understanding of global transcriptional programmes in the stroma and harmonise the results of molecular subtyping efforts across independent cohorts.

- Establishment and Analysis of a 3D Co-Culture Spheroid Model of Pancreatic Adenocarcinoma for Application in Drug Discovery

Methods in molecular biology (Clifton, N.J.) 2019 3;1953():163-179

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30912022

The high attrition rate of oncology drug candidates can be in part explained by the disconnect between the standard preclinical models (e.g., 2D culture, xenograft tumors) commonly employed for drug discovery and the complex multicellular microenvironment of human cancers. As such, significant focus has recently shifted to the establishment of preclinical models that more closely recapitulate human tumors, such as patient-derived xenografts, 3D spheroids, humanized mice, and mixed-culture models. For these models to be suited to drug discovery, they should optimally exhibit reproducibility, high-throughput, and robust and simple assay readouts. In this article, we describe a protocol for the generation of an in vitro 3D co-culture spheroid model that recapitulates the interaction of tumor cells with stromal fibroblasts in pancreatic adenocarcinoma. We additionally describe protocols relevant to the analysis of these spheroids in high-throughput drug discovery campaigns such as the assessment of spheroid proliferation, immunofluorescence and immunohistochemistry staining of spheroids, live-cell and confocal imaging and analysis of cell surface markers.

Back to top

SPN

Solid Pseudopapillary Neoplasm

- Targeted next generation sequencing of pancreatic solid pseudopapillary neoplasms show mutations in Wnt signaling pathway genes

Pathology international 2019 Apr;69(4):193-201

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30811747

Solid pseudopapillary neoplasms of the pancreas are rare neoplasms that have been shown to harbor recurrent somatic pathogenic variants in the beta-catenin gene, CTNNB1. Here, we used targeted next generation sequencing to analyze these tumors for other associated mutations. Six cases of solid pseudopapillary neoplasms were studied. DNA extracted from formalin-fixed paraffin embedded tissue blocks was analyzed using the Ion Torrent platform, with the 50-gene Ampliseq Cancer Hotspot Panel v2 (CHPv2), with further variant validation performed by Sanger sequencing. Four tumors (67%) were confirmed to harbor mutations within CTNNB1, two with c.109T > G p.(Ser37Ala) and two with c.94G > A p.(Asp32Asn). One case showed a frameshift deletion in the Adenomatous Polyposis Coli gene, APC c.3964delG p.(Glu1322Lysfs*93) with a variant allele frequency of 42.6%. Sanger sequencing on non-tumoral tissue confirmed the variant was somatic. The patient with the APC mutation developed metastasis and died. In addition to the four cases harboring CTNNB1 variants, we found a case characterized by poor outcome, showing a rare frameshift deletion in the APC gene. Since the APC product interacts with beta-catenin, APC variants may, in addition to CTNNB1, contribute to the pathogenesis of solid pseudopapillary neoplasms via the Wnt signaling pathway.

Back to top

Pancreatitis & Other Diseases

Molecular Studies on Pancreatitis & Other Diseases

- Heme Oxygenase-1 Polymorphism Is Associated With the Development of Necrotic Acute Pancreatitis Via Vascular Cell Adhesion Molecule-1 and the E-Selectin Expression Regulation Pathway

Pancreas 2019 Jul;48(6):787-791

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31210657

OBJECTIVES: Severe acute pancreatitis can lead to systemic complications. Here, we explore the mechanisms based on our previous study associated with the deregulation of heme oxygenase-1 (HO-1) and development of severe acute pancreatitis. METHODS: Acute pancreatitis patients (n = 135) and age- and sex-matched healthy controls (n = 108) were studied. The polymerase chain reaction products were analyzed with an ABI 3130 genetic analyzer and GeneMapper software. A short allele was defined 27 dinucleotide (GT) repeats, whereas a long allele was defined >27 GT. Levels of 12 different cytokines in blood serum were measured by enzyme-linked immunosorbent assay. All samples in this study were consistently stored in -80°C. RESULTS: Patients with the long long genotype expressed E-selectin and vascular cell adhesion molecule-1 at statistically significantly higher levels in serum compared with short short genotype or short long genotypes. Vascular cell adhesion molecule-1 and E-selectin serum levels significantly correlate with the total allele length of the HO-1 promoter region. CONCLUSION: Polymorphism of the GT repeats in the HO-1 promoter region may be a risk factor for developing acute necrotizing pancreatitis due to deregulation of the immune response.

Back to top

Molecular Research on Microenvironment

Tumor Stroma Interactions, Microenvironment, Inflammatory Response, Microbiome

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- Rethinking T Cells in Pancreas Cancer

Clinical cancer research : an official journal of the American Association for Cancer Research 2019 Jul;25(13):3747-3749

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31072844

Patients with pancreatic ductal adenocarcinoma do not benefit from checkpoint blockade. However, human tumors harbor evidence of adaptive immunity in clonally expanded T-cell populations. Immune intact modeling of human tumors identifies stromal sequestration as a mechanism of immune escape. Targeting the stroma combined with checkpoint blockade unleashes antitumor immunity.See related article by Seo et al., p. 3934.

- Vasohibin-2 plays an essential role in metastasis of pancreatic ductal adenocarcinoma

Cancer science 2019 Jul;110(7):2296-2308

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31074083

Vasohibin-2 (VASH2) is expressed in various cancers and promotes their progression. We recently reported that pancreatic cancer patients with higher VASH2 expression show poorer prognosis. Herein, we sought to characterize the role of VASH2 in pancreatic cancer. We used LSL-KrasG12D ; LSL-Trp53R172H ; Pdx-1-Cre (KPC) mice, a mouse model of pancreatic ductal adenocarcinoma (PDAC), and cells isolated from them (KPC cells). Knockdown of Vash2 from PDAC cells did not affect their proliferation, but decreased their migration. When Vash2-knockdown PDAC cells were orthotopically inoculated, liver metastasis and peritoneal dissemination were reduced, and the survival period was significantly prolonged. When KPC mice were crossed with Vash2-deficient mice, metastasis was significantly decreased in Vash2-deficient KPC mice. VASH2 was recently identified to have tubulin carboxypeptidase activity. VASH2 knockdown decreased, whereas VASH2 overexpression increased tubulin detyrosination of PDAC cells, and tubulin carboxypeptidase (TCP) inhibitor parthenolide inhibited VASH2-induced cell migration. We next clarified its role in the tumor microenvironment. Tumor angiogenesis was significantly abrogated in vivo when VASH2 was knocked down or deleted. We further examined genes downregulated by Vash2 knockdown in KPC cells, and found chemokines and cytokines that were responsible for the recruitment of myeloid derived suppressor cells (MDSC). Indeed, MDSC were accumulated in PDAC of KPC mice, and they were significantly decreased in Vash2-deficient KPC mice. These findings suggest that VASH2 plays an essential role in the metastasis of PDAC with multiple effects on both cancer cells and the tumor microenvironment, including tubulin detyrosination, tumor angiogenesis and evasion of tumor immunity.

- Development of resistance to FAK inhibition in pancreatic cancer is linked to stromal depletion

Gut 2019 May;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31076405

OBJECTIVE: We investigated how pancreatic cancer developed resistance to focal adhesion kinase (FAK) inhibition over time. DESIGN: Pancreatic ductal adenocarcinoma (PDAC) tumours from KPC mice (p48-CRE; LSL-KRasG12D/wt; p53flox/wt) treated with FAK inhibitor were analysed for the activation of a compensatory survival pathway in resistant tumours. We identified pathways involved in the regulation of signal transducer and activator of transcription 3 (STAT3) signalling on FAK inhibition by gene set enrichment analysis and verified these outcomes by RNA interference studies. We also tested combinatorial approaches targeting FAK and STAT3 in syngeneic transplantable mouse models of PDAC and KPC

mice. RESULTS: In KPC mice, the expression levels of phosphorylated STAT3 (pSTAT3) were increased in PDAC cells as they progressed on FAK inhibitor therapy. This progression corresponded to decreased collagen density, lowered numbers of SMA+ fibroblasts and downregulation of the transforming growth factor beta (TGF-)/SMAD signalling pathway in FAK inhibitor-treated PDAC tumours. Furthermore, TGF- production by fibroblasts in vitro drives repression of STAT3 signalling and enhanced responsiveness to FAK inhibitor therapy. Knockdown of SMAD3 in pancreatic cancer cells abolished the inhibitory effects of TGF- on pSTAT3. We further found that tumour-intrinsic STAT3 regulates the durability of the antiproliferative activity of FAK inhibitor, and combinatorial targeting of FAK and Janus kinase/STAT3 act synergistically to suppress pancreatic cancer progression in mouse models. CONCLUSION: Stromal depletion by FAK inhibitor therapy leads to eventual treatment resistance through the activation of STAT3 signalling. These data suggest that, similar to tumour-targeted therapies, resistance mechanisms to therapies targeting stromal desmoplasia may be critical to treatment durability.

- MicroRNA modulated networks of adaptive and innate immune response in pancreatic ductal adenocarcinoma

PloS one 2019 05;14(5):e0217421

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31150430

Despite progress in treatment strategies, only ~24% of pancreatic ductal adenocarcinoma (PDAC) patients survive >1 year. Our goal was to elucidate deregulated pathways modulated by microRNAs (miRNAs) in PDAC and Vater ampulla (AMP) cancers. Global miRNA expression was identified in 19 PDAC, 6 AMP and 25 paired, histologically normal pancreatic tissues using the GeneChip 4.0 miRNA arrays. Computational approaches were used for miRNA target prediction/identification of miRNA-regulated pathways. Target gene expression was validated in 178 pancreatic cancer and 4 pancreatic normal tissues from The Cancer Genome Atlas (TCGA). 20 miRNAs were significantly deregulated (FC 2 and $p<0.05$) (15 down- and 5 up-regulated) in PDAC. miR-216 family (miR-216a-3p, miR-216a-5p, miR-216b-3p and miR-216b-5p) was consistently down-regulated in PDAC. miRNA-modulated pathways are associated with innate and adaptive immune system responses in PDAC. AMP cancers showed 8 down- and 1 up-regulated miRNAs (FDR $p<0.05$). Most enriched pathways ($p<0.01$) were RAS and Nerve Growth Factor signaling. PDAC and AMP display different global miRNA expression profiles and miRNA regulated networks/tumorigenesis pathways. The immune response was enriched in PDAC, suggesting the existence of immune checkpoint pathways more relevant to PDAC than AMP.

- Stromal Microenvironment Shapes the Intratumoral Architecture of Pancreatic Cancer

Cell 2019 Jun;178(1):160-175.e27

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31155233

Single-cell technologies have described heterogeneity across tissues, but the spatial distribution and forces that drive single-cell phenotypes have not been well defined. Combining single-cell RNA and protein analytics in studying the role of stromal cancer-associated fibroblasts (CAFs) in modulating heterogeneity in pancreatic cancer (pancreatic ductal adenocarcinoma [PDAC]) model systems, we have identified significant single-cell population shifts toward invasive epithelial-to-mesenchymal transition (EMT) and proliferative (PRO) phenotypes linked with mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription 3 (STAT3) signaling. Using high-content digital imaging of RNA in situ hybridization in 195 PDAC tumors, we quantified these EMT and PRO subpopulations in 319,626 individual cancer cells that can be classified within the context of distinct tumor gland "units." Tumor gland typing provided an additional layer of intratumoral heterogeneity that was associated with differences in stromal abundance and clinical outcomes. This demonstrates the impact of the stroma in shaping tumor architecture by altering inherent patterns of tumor glands in human PDAC.

- Metastasis of pancreatic cancer: An uninflamed liver micromilieu controls cell growth and cancer stem cell properties by oxidative phosphorylation in pancreatic ductal epithelial cells

Cancer letters 2019 Jul;453():95-106

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30930235

Pancreatic ductal adenocarcinoma (PDAC) is commonly diagnosed when liver metastases already emerged. We recently demonstrated that hepatic stromal cells determine the dormancy status along with cancer stem cell (CSC) properties of pancreatic ductal epithelial cells (PDECs) during metastasis. This study investigated the influence of the hepatic microenvironment - and its inflammatory status - on metabolic alterations and how these impact cell growth and CSC-characteristics of PDECs. Coculture with hepatic stellate cells (HSCs), simulating a physiological liver stroma, but not with hepatic myofibroblasts (HMFs) representing liver inflammation promoted expression of Succinate Dehydrogenase subunit B (SDHB) and an oxidative metabolism along with a quiescent phenotype in PDECs. SiRNA-mediated SDHB knockdown increased cell growth and CSC-properties. Moreover, liver micrometastases of tumor bearing KPC mice strongly expressed SDHB while expression of the CSC-marker Nestin was exclusively found in macrometastases. Consistently, RNA-sequencing and in silico modeling revealed significantly altered metabolic fluxes and enhanced SDH activity predominantly in premalignant PDECs in the presence of HSC compared to HMF. Overall, these data emphasize that the hepatic microenvironment determines the metabolism of disseminated PDECs thereby controlling cell growth and CSC-properties during liver metastasis.

Back to top

Preneoplastic and Preinvasive Lesions

Molecular Pathology Preneoplastic and Preinvasive Lesions, PanIN, IPMN, MCN, ICPN, IOPN

- Single-Cell Transcriptomics of Pancreatic Cancer Precursors Demonstrates Epithelial and Microenvironmental Heterogeneity as an Early Event in Neoplastic Progression

Clinical cancer research : an official journal of the American Association for Cancer Research 2019 Apr;25(7):2194-2205

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30385653

PURPOSE: Early detection of pancreatic ductal adenocarcinoma (PDAC) remains elusive. Precursor lesions of PDAC, specifically intraductal papillary mucinous neoplasms (IPMNs), represent a bona fide pathway to invasive neoplasia, although the molecular correlates of progression remain to be fully elucidated. Single-cell transcriptomics provides a unique avenue for dissecting both the epithelial and microenvironmental heterogeneities that accompany multistep progression from noninvasive IPMNs to PDAC. EXPERIMENTAL DESIGN: Single-cell RNA sequencing was performed through droplet-based sequencing on 5,403 cells from 2 low-grade IPMNs (LGD-IPMNs), 2 high-grade IPMNs (HGD-IPMN), and 2 PDACs (all surgically resected). RESULTS: Analysis of single-cell transcriptomes revealed heterogeneous alterations within the epithelium and the tumor microenvironment during the progression of noninvasive dysplasia to invasive cancer. Although HGD-IPMNs expressed many core signaling pathways described in PDAC, LGD-IPMNs harbored subsets of single cells with a transcriptomic profile that overlapped with invasive cancer. Notably, a proinflammatory immune component was readily seen in low-grade IPMNs, composed of cytotoxic T cells, activated T-helper cells, and dendritic cells, which was progressively depleted during neoplastic progression, accompanied by infiltration of myeloid-derived suppressor cells. Finally, stromal myofibroblast populations were heterogeneous and acquired a previously described tumor-promoting and immune-evading phenotype during invasive carcinogenesis. CONCLUSIONS: This study demonstrates the ability to perform high-resolution profiling of the transcriptomic changes that occur during multistep progression of cystic PDAC precursors to cancer. Notably, single-cell analysis provides an unparalleled insight into both the epithelial and microenvironmental heterogeneities that accompany early cancer pathogenesis and might be a useful substrate to identify targets for cancer interception.See related commentary by Hernandez-Barco et al., p. 2027.

- Multiple KRAS mutations in the non-mucinous epithelial lining in the majority of mucinous cystic neoplasms of the pancreas

Histopathology 2019 May;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31077597

AIMS: Mucinous cystic neoplasms (MCNs) of the pancreas are cystic neoplasms lined by mucinous lining epithelium (MLE) with associated ovarian-type stroma. Although a non-MLE (NMLE) can be observed in some MCNs, whether cystic neoplasms with ovarian-type stroma and NMLE should be classified as MCNs or separately designated is debated. METHODS AND RESULTS: To test this, NMLEs were defined as flat or cuboidal epithelial cells without intracytoplasmic mucin. A total of 112 MCNs were reviewed, and the epithelium was classified as NMLE or MLE. A total of 110 females and two males with a mean age of 46.5 $\pm$ 12.3 years were included in this study. At least focal NMLE was noted in 76.8% (86/112) of MCNs. The mean percentage of the neoplastic epithelium that was NMLE in these 86 cases was 46%. NMLE was predominant (>50%) in 38.4% (43/112) of cases. MCNs with NMLE were smaller (42 $\pm$ 21 mm) than those with MLE (60 $\pm$ 36 mm, $P < 0.001$), and all NMLEs had low-grade dysplasia. Twelve MCNs with NMLE or MLE were selected for KRAS mutation analysis with droplet digital polymerase chain reaction after laser capture microdissection. All 12 MCNs showed multiple types of KRAS mutation, which were detected in 92% (11/12) of NMLE foci and 89% (8/9) of MLE foci. Predominant NMLE was common in small MCNs

with low-grade dysplasia. CONCLUSIONS: Clonal KRAS mutations were observed in both NMLE and MLE, supporting the hypothesis that MCNs with NMLE should be classified as MCNs.

- Cross Validation of the Monoclonal Antibody Das-1 in Identification of High-Risk Mucinous Pancreatic Cystic Lesions

Gastroenterology 2019 Sep;157(3):720-730.e2

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31175863

BACKGROUND & AIMS: Although pancreatic cystic lesions (PCLs) are frequently and incidentally detected, it is a challenge to determine their risk of malignancy. In immunohistochemical and enzyme-linked immunosorbent assay (ELISA) analyses of tissue and cyst fluid from pancreatic intraductal papillary mucinous neoplasms, the monoclonal antibody Das-1 identifies those at risk for malignancy with high levels of specificity and sensitivity. We aimed to validate the ability of Das-1 to identify high-risk PCLs in comparison to clinical guidelines and clinical features, using samples from a multicenter cohort. METHODS: We obtained cyst fluid samples of 169 PCLs (90 intraductal papillary mucinous neoplasms, 43 mucinous cystic neoplasms, and 36 non-mucinous cysts) from patients undergoing surgery at 4 tertiary referral centers (January 2010 through June 2017). Histology findings from surgical samples, analyzed independently and centrally re-reviewed in a blinded manner, were used as the reference standard. High-risk PCLs were those with invasive carcinomas, high-grade dysplasia, or intestinal-type intraductal papillary mucinous neoplasms with intermediate-grade dysplasia. An ELISA with Das-1 was performed in parallel using banked cyst fluid samples. We evaluated the biomarker's performance, generated area under the curve values, and conducted multivariate logistic regression using clinical and pathology features. RESULTS: The ELISA for Das-1 identified high-risk PCLs with 88% sensitivity, 99% specificity, and 95% accuracy, at a cutoff optical density value of 0.104. In 10-fold cross-validation analysis with 100 replications, Das-1 identified high-risk PCLs with 88% sensitivity and 98% specificity. The Sendai, Fukuoka, and American Gastroenterological Association guideline criteria identified high-risk PCLs with 46%, 52%, and 74% accuracy (P for comparison to Das-1 ELISA <.001). When we controlled for Das-1 in multivariate regression, main pancreatic duct dilation >5 mm (odds ratio, 14.98; 95% confidence interval, 2.63-108; P < .0012), main pancreatic duct dilation 1 cm (odds ratio, 47.9; 95% confidence interval, 6.39-490; P < .0001), and jaundice (odds ratio, 6.16; 95% confidence interval, 1.08-36.7; P = .0397) were significantly associated with high-risk PCLs. CONCLUSIONS: We validated the ability of an ELISA with the monoclonal antibody Das-1 to detect PCLs at risk for malignancy with high levels of sensitivity and specificity. This biomarker might be used in conjunction with clinical guidelines to identify patients at risk for malignancy.

- Intraductal Papillary Mucinous Neoplasms Arise from Multiple Independent Clones, Each With Distinct Mutations

Gastroenterology 2019 Jun;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31175866

BACKGROUND & AIMS: Intraductal papillary mucinous neoplasms (IPMNs) are lesions that can progress to invasive pancreatic cancer and an important system for studies of pancreatic tumorigenesis. We performed comprehensive genomic analyses of entire IPMNs to determine the diversity of somatic mutations in genes that promote tumorigenesis. METHODS: We microdissected neoplastic tissues from 6-24 regions each of 20 resected IPMNs, resulting in 227 neoplastic samples that were analyzed by capture-based targeted sequencing. Somatic mutations in genes associated with pancreatic tumorigenesis were assessed across entire IPMN lesions, and the resulting data were supported by evolutionary modeling, whole-exome sequencing, and in situ detection of mutations. RESULTS: We found a high prevalence of heterogeneity among mutations in IPMNs. Heterogeneity in mutations in KRAS and GNAS was significantly more prevalent in IPMNs with low-grade dysplasia than in IPMNs with high-grade dysplasia (P<.02). Whole-exome sequencing confirmed that IPMNs contained multiple independent clones, each with distinct mutations, as originally indicated by

targeted sequencing and evolutionary modeling. We also found evidence for convergent evolution of mutations in RNF43 and TP53, which are acquired during later stages of tumorigenesis. CONCLUSIONS: In an analysis of the heterogeneity of mutations throughout IPMNs, we found that early-stage IPMNs contain multiple independent clones, each with distinct mutations, indicating their polyclonal origin. These findings challenge the model in which pancreatic neoplasms arise from a single clone. Increasing our understanding of the mechanisms of IPMN polyclonality could lead to strategies to identify patients at increased risk for pancreatic cancer.

- Pancreatobiliary-type intraductal papillary mucinous neoplasm of the pancreas may have two subtypes with distinct clinicopathological and genetic features

Human pathology 2019 Jun;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31175918

We recently experienced cases of pancreatobiliary-type intraductal papillary mucinous neoplasms (PB-IPMNs) with imaging features resembling pancreatic ductal adenocarcinomas (PDACs), and histological appearance of purely pancreatobiliary morphology and highly distorted papillary growth, which led to the present study aiming to systematically investigate PB-IPMNs in comparison with PDACs. Surgical cases of PB-IPMNs (n=31) and PDACs (n=24) were examined. PB-IPMNs were classified into monotypic tumors (n=12; 39%) consisting of entirely high-grade pancreatobiliary-type neoplastic cells and polytypic cases (n=19; 61%) associated with components of low-grade dysplasia and/or other histological types (e.g., gastric, intestinal, or oncocytic types). Clinically, monotypic PB-IPMNs less commonly had dilatation of the ampullary orifice (0% vs. 74%) and mucin hypersecretion (17% vs. 89%) than polytypic cases. In most cases of monotypic PB-IPMNs, cystic dilatation of the lesional ducts were less obvious on imaging; therefore, 33% were radiologically diagnosed as PDACs. Histologically, intraductal tumors in monotypic cases showed a highly complex papillary architecture with tubular/cribriform glands and irregular branching, and all these cases were associated with invasive malignancy. GNAS mutations were detected in polytypic PB-IPMNs (6/19; 32%), but there were no GNAS mutations in monotypic cases. The recurrence-free survival of patients with monotypic PB-IPMN or PDAC was similar and significantly worse than that of patients with polytypic PB-IPMN. In conclusion, some cases of monotypic PB-IPMNs lacked the classic characteristics of IPMNs and shared features with PDACs, raising the possibility that these cases may be better classified as a papillary variant of PDACs rather than IPMNs.

- KRAS in Cyst Fluid Obtained by Endoscopic Ultrasound-Fine-Needle Aspiration in Pancreatic Cystic Lesions: A Systematic Review and Meta-analysis

Pancreas 2019 Jul;48(6):749-758

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31206466

To evaluate the diagnostic accuracy of KRAS mutation in pancreatic cystic fluid and compare it with carcinoembryonic antigen and cytology, we identified studies with cyst fluid obtained by endoscopic ultrasound prior to surgery. We classified cysts as malignant, premalignant, and benign. A random-effects model was used for quantitative meta-analysis. Pooled sensitivities, specificities, and summary receiver operating characteristic curve analysis were conducted. We analyzed 16 studies, with 3429 patients, including 731 referred for surgery. Carcinoembryonic antigen was better for clinically significant cysts (premalignant and malignant) with sensitivity = 0.58 (95% confidence interval [CI], 0.53-0.65), specificity = 0.9 (95% CI, 0.76-0.97), and area under the curve (AUC) = 0.69. Cytology performed better in malignant cysts, with sensitivity = 0.37 (95% CI, 0.27-0.48), specificity = 0.96 (95% CI, 0.93-0.98), and AUC = 0.78. Isolated, KRAS mutation failed the diagnosis of malignant and significant cysts, with sensitivities = 0.43 (95% CI, 0.34-0.43) and 0.46 (95% CI, 0.42-0.51), specificities = 0.62 (95% CI, 0.56-0.68) and 0.97 (95% CI, 0.92-0.99), and AUCs = 0.56 and 0.53, respectively. Carcinoembryonic antigen and cytology are more accurate than KRAS. Additional studies are lacking to recommend KRAS as a single diagnostic test.

Back to top

Neuroendocrine

- Microenvironment and tumor inflammatory features improve prognostic prediction in gastro-entero-pancreatic neuroendocrine neoplasms

The journal of pathology. Clinical research 2019 May;():

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Microenvironment-related immune and inflammatory markers, when combined with established Ki-67 and morphology parameters, can improve prognostic prediction in gastro-entero-pancreatic neuroendocrine neoplasms (GEP-NENs). Therefore, we evaluate the prognostic value of microenvironment and tumor inflammatory features (MoTIFs) in GEP-NENs. For this purpose, formalin-fixed paraffin-embedded tissue sections from 350 patients were profiled by immunohistochemistry for immune, inflammatory, angiogenesis, proliferation, NEN-, and fibroblast-related markers. A total of 314 patients were used to generate overall survival (OS) and disease-free survival (DFS) MoTIFs prognostic indices (PIs). PIs and additional variables were assessed using Cox models to generate nomograms for predicting 5-year OS and DFS. A total of 36 patients were used for external validation of PIs and nomograms' prognostic segregations. From our analysis, G1/G2 versus G3 GEP-NENs showed phenotypic divergence with immune-inflammatory markers. HLA, CD3, CD8, and PD-1/PD-L1 IHC expression separated G3 into two sub-categories with high versus low adaptive immunity-related features. MoTIFs PI for OS based on COX-2Tumor(T) $>$ 4, PD-1Stromal(S) $>$ 0, CD8S $<$ 1, and HLA-IS $<$ 1 was associated with worst survival (hazard ratio [HR] 2.50; 95% confidence interval [CI], 2.12-2.96; $p < 0.0001$). MoTIFs PI for DFS was based on COX-2T $>$ 4, PD-1S $>$ 4, HLA-IS $<$ 1, HLA-IT $<$ 2, HLA-DRS $<$ 6 (HR 1.77; 95% CI, 1.58-1.99; $p < 0.0001$). Two nomograms were developed including morphology (HR 4.83; 95% CI, 2.30-10.15; $p < 0.001$) and Ki-67 (HR 11.32; 95% CI, 5.28-24.24; $p < 0.001$) for OS, and morphology (PI = 0: HR 10.23; 95% CI, 5.67-18.47; PI = 5: HR 2.87; 95% CI, 1.21-6.81; $p < 0.001$) and MoTIFs PI for DFS in well-differentiated GEP-NENs (HR 6.21; 95% CI, 2.52-13.31; $p < 0.001$). We conclude that G1/G2 to G3 transition is associated with immune-inflammatory profile changes; in fact, MoTIFs combined with morphology and Ki-67 improve 5-year DFS prediction in GEP-NENs. The immune context of a subset of G3 poorly differentiated tumors is consistent with activation of adaptive immunity, suggesting a potential for responsiveness to immunotherapy targeting immune checkpoints.

Back to top

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Back to top
