PBPath Journal Watch

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Contents

PANCREATOBILIARY PATHOLOGY SOCIETY

Surgical Pathology

- **PD-1, PD-L1 and CD163 in pancreatic undifferentiated carcinoma with osteoclast-like giant cells: expression patterns and clinical implications**

Human pathology 2018 Jul;():

Undifferentiated carcinoma with osteoclast-like giant cells (UCOGC), a variant of pancreatic ductal adenocarcinoma (PDAC), has striking genetic similarity to PDAC but a significantly improved overall survival. We hypothesize that this difference could be due to the immune response to the tumor, and as such, we investigated the expression of PD-1, PD-L1 and CD163 in a series of UCOGC. To this aim, 27 pancreatic UCOGCs (11 pure and 16 PDAC-associated), 5 extra-pancreatic tumors with osteoclast-like giant cells and 10 pancreatic anaplastic carcinomas (ACs) were immunostained using antibodies against PD-1, PD-L1 and CD163. In pancreatic UCOGCs, PD-L1 was expressed in neoplastic cells of 17/27 (63%) cases, more often in cases with an associated PDAC (P=.04). Expression of PD-L1 was associated with poor prognosis, confirmed by multivariate analysis: patients with PD-L1-positive UCOGCs had a risk of all-cause mortality that was 3 times higher than patients with PD-L1-negative UCOGCs (HR: 3.397, 95%CI: 1.023-18.375, P=.034). PD-L1 expression on tumor cells was also associated with aberrant P53 expression (P=.035). PD-1 was expressed on rare lymphocytes in 12 UCOGCs (44.4%), mainly located at the tumor periphery. CD163 was expressed on histiocytes, with a diffuse and strong staining pattern in all UCOGCs. Extra-pancreatic

tumors with osteoclast-like giant cells showed very similar staining patterns for the same proteins. ACs have some similarities to UCOGCs, but PD-L1 has no prognostic roles. Our results may have important implications for immunotherapeutic strategies in UCOGCs; these tumors may also represent a model for future therapeutic approaches against PDAC.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30031096

doi: https://doi.org/10.1016/j.humpath.2018.07.006

- **TFE3 is a diagnostic marker for solid pseudopapillary neoplasms of the pancreas**

Human pathology 2018 Jul;():

Aberrant Wnt signaling is a hallmark of solid pseudopapillary neoplasms of the pancreas (SPN). Transcription factor E3 (TFE3) plays a critical role in activation and regulation of the Wnt pathway, and is predicted to be a candidate gene implicated in SPN by gene regulatory network analysis. The aim of this study was to evaluate TFE3 as a marker for SPN. Paraffin embedded tissues of SPN (n = 75) and other primary pancreatic tumors were analyzed, including pancreatic neuroendocrine tumors (PanNET) (n = 17), pancreatic ductal adenocarcinomas (PDAC) (n = 14), pancreatic neuroendocrine carcinomas (PanNEC) (n = 4) and acinar cell carcinomas (ACC) (n = 3). The clinicopathological features were summarized as well. Differentiation of specific pancreatic duct or acinus was not found in any SPN tissue. Morphological and immunohistochemical results indicated that SPN displays certain characteristics of neuroendocrine cells. Overall, 71 (94.67%) cases of SPN showed nuclear accumulation for TFE3, most of which displayed moderate to intense expression. The TFE3 positive rate in PanNET, PDAC and PanNEC was 23.53%, 14.29%, and 25%, respectively. All three cases of ACC were negative for TFE3. We conclude that SPN may originate from primordial pancreatic cells and is accompanied by some characteristics of neuroendocrine tumors. TFE3, besides -catenin, can be an additional diagnostic marker of SPN in differential diagnosis.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30030118

doi: https://doi.org/10.1016/j.humpath.2018.07.005

- **Acute Pancreatitis Caused by Isolated Pancreatic Metastasis From Uterine Choriocarcinoma**

International journal of gynecological pathology : official journal of the International Society of Gynecological Pathologists 2018 Jul;():

Choriocarcinoma is an aggressive gestational trophoblastic neoplasia known for its widely metastatic potential. However, isolated pancreatic metastasis is an extremely rare occurrence and has not been documented in the English literature to the best of our knowledge. The metastatic deposits in the index case led to widespread hemorrhage and necrosis of the pancreatic parenchyma, causing severe acute pancreatitis. The patient succumbed to her illness before chemotherapy was administered. Thus, we present an autopsy case of a uterine choriocarcinoma with isolated pancreatic metastasis presenting as severe acute pancreatitis in a 27-yr-old woman following a molar pregnancy.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30028356

doi: https://doi.org/10.1097/PGP.0000000000000532

- **S100A10, a Novel Biomarker in Pancreatic Ductal Adenocarcinoma**

Molecular oncology 2018 Jul;():

Pancreatic cancer is arguably the deadliest cancer type. The efficacy of current therapies is often hindered by the inability to predict patient outcome. As such, the development of tools for early detection and risk prediction is key for improving outcome and quality of life. Here, we introduce the plasminogen receptor S100A10 as a novel predictive biomarker and a driver of pancreatic tumor growth and invasion. We demonstrated that S100A10 mRNA and protein are overexpressed in human pancreatic tumors compared to normal ducts and non-ductal stroma. S100A10 mRNA and methylation status were predictive of overall survival and recurrence-free survival across multiple patient cohorts. S100A10 expression was driven by promoter methylation and the oncogene KRAS. S100A10 knockdown reduced surface plasminogen activation, invasiveness and in vivo growth of pancreatic cancer cell lines. These findings delineate the clinical and functional contribution of S100A10 as a biomarker in pancreatic cancer.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30009399

doi: https://doi.org/10.1002/1878-0261.12356

- **Comparison of 3 Ways of Dissecting the Pancreatoduodenectomy Specimen and Their Impact in the Lymph Node Count and the Lymph Node Metastatic Ratio**

International journal of surgical pathology 2018 Jun;():1066896918780343

BACKGROUND: Lymph node metastasis (LNM) is a strong prognostic factor in the cancer of the pancreatobiliary tree, but it is influenced by the number of lymph nodes (LNs). The lymph node ratio (LNR) is considered a more reliable factor than the number of LNM. The aim was to examine the LN retrieval and the LNR of 3 pathologic work-up strategies. METHODS: Pancreaticoduodenectomies (n = 165) were analyzed comparing 3 pathological dissection techniques, classified as "control," "Verbeke method," and "Adsay method" groups. RESULTS: The mean of the dissected LNs and the number of cases with >20 LNs were superior in the Adsay method group, compared with the other groups ($P < .001$). The LNR was different between the Adsay and Verbeke groups (0.144 vs 0.069, $P = .032$). The median of the 3 positive LNs was associated with decreased survival compared with an absence of LNM (3-year specific survival of 48% vs 22%, $P = .011$). In the multivariate analysis, LNM (hazard ratio = 6.148, 95% confidence interval = 2.02-8.1, $P = .042$) and the evaluation of >15 LNs (hazard ratio = 12.52, 95% confidence interval = 5.51-21.01, $P = .001$) were independent predictors of survival. CONCLUSION: The Adsay technique for LN retrieval was associated with a better LN count, more cases with LNM, and an LNR >0.1.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29873282

doi: https://doi.org/10.1177/1066896918780343

- **Pancreatic Lipomatous Hamartoma: A Hitherto Unrecognized Variant**

The American journal of surgical pathology 2018 Jul;42(7):891-897

Pancreatic masses consisting of lipomatous components clinically include lipoma, liposarcoma, lipomatous pseudohypertrophy of the pancreas, fat-containing neoplasms such as perivascular epithelioid cell tumor, and malignant neoplasm with lipoid degeneration. We present pancreatic lipomatous hamartoma, which has not been reported hitherto. A solid pancreatic mass was detected from a computed tomographic scan check-up in each of 3 cases of Japanese men. Macroscopically, well-demarcated solid lipomatous masses were detected at the uncus, body, and tail of the pancreas, respectively. Microscopically, the masses predominantly consisted

of mature adipocytes with no atypia, but contained characteristics components of pancreatic hamartoma, such as small ducts, a well-preserved acinar structure, and/or fibrous stroma. On the basis of the unique features, lack of islets and absence of periductal elastic fibers, these tumors are a distinct variant of pancreatic hamartoma. Furthermore, high-mobility group AT-hook 2 expression in the fibro-adipocytes of this tumor indicated that these cells are an integral component of the pancreatic lipomatous hamartoma. Consequently, the unique tumors described herein are pancreatic lipomatous hamartoma, which must be discriminated from other lipomatous lesions of the pancreas.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29738363

doi: https://doi.org/10.1097/PAS.0000000000001075

- **Primary Hepatoid Carcinoma of the Pancreas: A Clinicopathological Study of 3 Cases With Review of Additional 31 Cases in the Literature**

International journal of surgical pathology 2018 Jun;():1066896918783468

Primary pancreatic hepatoid carcinoma (PHC) is very rare. Here, we reported 3 such cases with review of additional 31 cases in the literature. Our 3 patients were male (83, 72, and 54 years old, respectively). Serum -fetoprotein (AFP) was elevated in 1 patient (case 3, 8338 ng/mL) and not measured in the other two. The PHC in patient 1 (pathological stage pT2N0M0) and patient 2 (pT3N0M0) showed pure hepatocellular carcinoma (HCC)-like morphology, whereas in case 3 it was a PHC with true glandular differentiation (pT4N0M0). The diagnosis of PHC was confirmed with positive immunohistochemical staining in the tumor cells for AFP (2/3), Hep Par 1 (3/3), glypican-3 (2/3), arginase-1 (2/3), and Sal-like protein 4 (1/3). CD10 and polyclonal carcinoembryonic antigen stains show focal canalicular pattern in 2/3 tumors. Patient 1 did not receive further treatment after resection and was alive with no evidence of disease at 107 months. Patient 2 died of postoperative complications, whereas patient 3 received postsurgical chemoradiation and died of disease at 29 months. Our findings and literature review indicate that PHCs can be divided into 4 histological subtypes: with pure HCC-like morphology (n = 22), with neuroendocrine differentiation (n = 8), with true glandular differentiation (n = 3), and with acinar cell differentiation (n = 1). On univariate analysis, pure HCC-like morphology was associated with better disease-specific survival (DSS; P = .04), whereas lymph node and distant metastases were associated with worse DSS (P = .002 for both). Age, gender, presenting symptoms, serum AFP level, and T stage were not associated with DSS. On multivariate analysis, none of these parameters was significantly associated with DSS.

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doi: https://doi.org/10.1177/1066896918783468

- **Hereditary Pancreatitis in the United States: Survival and Rates of Pancreatic Cancer**

The American journal of gastroenterology 2018 Jul;():

OBJECTIVES: Hereditary pancreatitis (HP), an autosomal dominant disease typically caused by mutations in PRSS1, has a broad range of clinical characteristics and high cumulative risk of pancreatic cancer. We describe survival and pancreatic cancer risk in the largest HP cohort in the US. METHODS: HP probands and family members prospectively recruited from 1995 to 2013 completed medical and family history questionnaires, and provided blood for DNA testing. Overall survival (until 12/31/2015) was determined from the Social Security Death Index (SSDI), National Death Index (NDI), and family members. Cause of death was obtained from the NDI. RESULTS: 217 PRSS1 carriers (181 symptomatic) formed the study cohort. The most frequently detected mutations were p.R122H (83.9%) and p.N29I (11.5%). Thirty-seven PRSS1

carriers (30 symptomatic, 7 asymptomatic) were deceased at conclusion of the study (5 from pancreatic cancer). Median overall survival was 79.3 years (IQR 72.2-85.2). Risk of pancreatic cancer was significantly greater than age- and sex- matched SEER data (SIR 59, 95% CI 19-138), and cumulative risk was 7.2% (95% CI 0-15.4) at 70 years. DISCUSSION: We confirm prior observations on survival and pancreatic cancer SIR in PRSS1 subjects. Although risk of pancreatic cancer was significantly high in these patients, its cumulative risk was much lower than previous reports.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30018304

doi: https://doi.org/10.1038/s41395-018-0194-5

- **Distribution of dysplasia and cancer in the gallbladder: an analysis from a high cancer-risk population**

https://www.sciencedirect.com/science/article/pii/S004681771830282X

Human pathology 2018 Jul;():

Gallbladder dysplasia can progress to cancer and may be associated with increased cancer risk at other biliary tract sites. Thus, its accurate identification is relevant both for etiologic understanding and for clinical purposes. Data on the frequency and distribution of gallbladder dysplasia are lacking due to limited gallbladder sampling and inability to visualize dysplasia grossly. An expert pathology group used consensus criteria to review 140 totally sampled consecutive cholecystectomy specimens from Chilean women. Three cases (2%) revealed incidental invasive carcinoma, all T2, along with high-grade dysplasia (HGD). The surface area covered by dysplasia or cancer in these cases was 9%, 37%, and 87%. Although the first longitudinal ("diagnostic") section of the whole gallbladder captured HGD or cancer in all three cases, the deepest focus of invasive carcinoma was not present in this section. Fourteen additional cases (10%) had low-grade dysplasia (LGD), which was typically very focal (covering <5% of the surface) and most often occurred in the fundus. LGD was not present in the diagnostic section of five cases (38%) and would have been missed without additional sampling. None of the cancers or dysplasias were grossly visible. Although HGD and carcinoma are likely to be identified in "diagnostic" sections, accurate staging requires total sampling. LGD is typically very focal and would often be missed in routine practice. To identify cancer precursors, additional sampling, particularly of the fundus, may be warranted. The predominance of LGD in the fundus also provides etiologic insight, supporting the contribution of gallstones and chronic inflammation.

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doi: https://doi.org/10.1016/j.humpath.2018.07.015

- **Epithelial Inclusions in Gallbladder Specimens Mimic Parasite Infection: Histologic and Molecular Examination of Reported Cystoisopora belli Infection in Gallbladders of Immunocompetent Patients**

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

Recent publications have described epithelial cytoplasmic vacuoles and inclusions incidentally noted within gallbladder epithelium and concluded that they represent coccidian parasite infection, in particular, Cystoisospora belli. We identified 8 gallbladder specimens from our institution in the past 3 years in which this diagnosis was suggested or in which similar epithelial alterations were prominent. Molecular analysis was performed on the 8 gallbladder specimens and on 3 positive control specimens: small bowel biopsies from acquired immunodeficiency syndrome patients with diarrhea. Polymerase chain reaction using primers designed to amplify an internal transcribed spacer (ITS2) in the C. belli ribosomal gene cluster was performed

on the DNA samples. All 8 gallbladder specimens were negative for amplification, while a product consistent with C. belli was amplified from all 3 positive controls. Histologically, the gallbladder cytoplasmic inclusions stained diffusely positive for Grocott-Gomori's methenamine silver and Periodic acid-Schiff with diastase. In contrast, sections from a positive control small bowel biopsy demonstrated organisms that were negative for Grocott-Gomori's methenamine silver and showed a distinct capsular and punctate internal staining on Periodic acid-Schiff with diastase in various parasite forms. Together, the lack of molecular evidence of C. belli and the distinct morphologic and special staining patterns in these gallbladders compared with positive control small bowel suggest that these epithelial changes do not represent true C. belli infection. Our results suggest that gallbladders of immunocompetent patients may occasionally show epithelial changes that can morphologically mimic C. belli infection. Pathologists should be aware of this histologic variant to minimize unnecessary treatment, testing, and patient anxiety.

https://journals.lww.com/ajsp/Pages/articleviewer.aspx?year=9000&issue=00000&article=97799&type=Abstract

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30020094

doi: https://doi.org/10.1097/PAS.0000000000001094

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

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

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

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

doi: https://doi.org/10.1097/PAS.0000000000001117

- **Clinical relevance of PD-L1 expression in gallbladder cancer: a potential target for therapy**

Histopathology 2018 Jun;():

AIMS: Programmed death-ligand 1 (PD-L1), a potential target for immune checkpoint inhibitors in various solid neoplasms, has been studied in very few cases of Gall Bladder Carcinoma (GBC). The current study aimed to evaluate PD-L1 expression at primary and metastatic sites of GBC, and its associations with standard prognostic clinicopathological parameters, as well as with overall survival. METHODS AND RESULTS: One hundred and seventy-four cases of GBC were evaluated for PD-L1 expression by the use of the SP263 clone in tissue microarrays. Clinicopathological characteristics and survival data were correlated with PD-L1 expression analysed at different cut-offs of 1%, 10% and 50% in tumour cells and tumour-infiltrating lymphocytes (TILs). The mean age of patients was 49.9 years, and the male/female ratio was 1:2.9. Of the cases, 73.6% presented with stage 3/4 disease. Tumour cells expressed PD-L1 in 23.0% of cases, and TILs expressed PD-L1 in 24.1% of cases. At a cut-off of 10%, 14.9% of cases expressed PD-L1, and at a cut-off of 50%, 7.5% of cases expressed PD-L1. Significant associations were seen between tumour proportion score and histological type (P = 0.004), histological grade (P = 0.004), nuclear grade (P = 0.008), nodal metastasis (P = 0.051), higher stage (P = 0.058), and TILs (P < 0.001). Tumour size, growth pattern, the presence of necrosis and lymphovascular emboli showed no significant associations with PD-L1 in tumour cells or TILs. In synchronous paired samples from primary and metastatic lymph nodes, discordantly higher PD-L1 expression was evident in lymph nodes. Overall survival was not associated with PD-L1 expression (P = 0.546). CONCLUSION: PD-L1 does not appear to be a prognostic marker or influence survival in GBC patients. However, PD-L1 expression occurs in one of four GBCs, supporting the future possibility of immune-modulation therapy to improve the dismal overall survival.

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doi: https://doi.org/10.1111/his.13669

- **DJ-1 is a useful biomarker for invasive extrahepatic cholangiocarcinoma**

Human pathology 2018 Jun;76():28-36

We have previously reported that DJ-1 protein is up-regulated in cholangiocarcinoma compared with non-neoplastic epithelium of the bile duct in a study using liquid-chromatography mass spectrometry-based proteomics. The aim of this study was to clarify whether DJ-1 expression offers a biomarker for patients with invasive extrahepatic cholangiocarcinoma (EHCC) who undergo surgical resection with curative intent. Positive immunohistochemical (IHC) staining of DJ-1 was significantly more frequent in the cytoplasm of 96 invasive EHCCs (n = 28, 29.2%) than in that of 66 non-neoplastic epithelial lesions adjacent to invasive EHCC (n = 7, 10.6%; P = .006). No significant difference in clinicopathological features was evident between invasive EHCC patients with negative (n = 68) and positive (n = 28) IHC staining. However, negative IHC staining for DJ-1 in cytoplasm was selected as an independent risk factor for adverse prognosis on multivariate analysis (P = .004, hazard ratio 2.13, 95% confidence interval 1.28-3.57). Serum levels of DJ-1 in 16 invasive EHCC patients with metastasis were compared with 12 invasive EHCC patients without metastasis. Serum levels of DJ-1 tended to be higher in 16 patients with metastasis (median, 40.9 ng/ml) than in 12 patients without (27.6 ng/ml, P = .137). In addition, patients with high serum levels (40 ng/ml) of DJ-1 tended to have metastasis more frequently than those without (P = .054, Fisher's exact test). We concluded that IHC staining pattern and serum level of DJ-1 in patients with invasive EHCC might be predictive of prognosis and metastasis, respectively.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29447925

doi: https://doi.org/10.1016/j.humpath.2018.02.010

- **Intrahepatic Cholangiocarcinomas Have Histologically and Immunophenotypically Distinct Small and Large Duct Patterns**

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

Intrahepatic cholangiocarcinomas are histologically heterogenous. Using a cohort of 184 clinically defined, resected intrahepatic cholangiocarcinomas, we retrospectively classified the histology into 4 subtypes: large duct (LD), small duct (SD) (predominantly tubular [SD1] or predominantly anastomosing/cholangiolar, [SD2]), or indeterminate. Then, we tested the 4 subtypes for associations with risk factors, patient outcomes, histology, and immunophenotypic characteristics. SD was the most common (84%; 24% SD1 and 60% SD2) with lower proportions of LD (8%), and indeterminate (8%). Primary sclerosing cholangitis was rare (2%), but correlated with LD (P=0.005). Chronic hepatitis, frequent alcohol use, smoking, and steatosis had no histologic association. LD was associated with mucin production (P<0.001), perineural invasion (P=0.002), CA19-9 staining (P<0.001), CK7, CK19, CD56 immunophenotype (P=0.005), and negative albumin RNA in situ hybridization (P<0.001). SD was histologically nodular (P=0.019), sclerotic (P<0.001), hepatoid (P=0.042), and infiltrative at the interface with hepatocytes (P<0.001). Albumin was positive in 71% of SD and 18% of LD (P=0.0021). Most albumin positive tumors (85%) lacked extracellular mucin (P<0.001). S100P expression did not associate with subtype (P>0.05). There was no difference in disease-specific or recurrence-free survival among the subtypes. Periductal infiltration and American Joint Committee on Cancer eighth edition pT stage predicted survival by multivariable analysis accounting for gross configuration, pT stage, and histologic type. pT2 had worse outcome relative to other pT stages. Significant differences in histology and albumin expression distinguish LD from SD, but there is insufficient evidence to support further subclassification of SD.

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doi: https://doi.org/10.1097/PAS.0000000000001118

- **Ampullary adenocarcinoma: Defining predictors of survival and the impact of adjuvant therapy following surgical resection for stage I disease**

Journal of surgical oncology 2018 Jun;117(7):1500-1508

BACKGROUND AND OBJECTIVES: Outcomes and recommendations regarding adjuvant therapy (AT) for stage I ampullary adenocarcinoma (AAC) are inadequately described. We sought to determine factors associated with survival and better define the impact of AT. METHODS: The NCDB was queried for stage I AAC patients undergoing resection. We evaluated variables influencing the administration of AT and affecting survival, including the receipt of AT. RESULTS: Five hundred thirty-seven patients were identified. 1, 3, and 5-year OS were 91.3%, 78.8%, and 67.4%, respectively. 103 received AT: 101 chemotherapy, 31 radiation, and 29 a combination of both. AT was more commonly utilized in patients with poorly differentiated and T2 tumors. Comorbid disease was inversely associated with use of AT. Age 65 was associated with decreased survival for stage IA and IB, while positive resection margins and sampling of <12 LNs were associated with decreased OS for stage IA and IB, respectively. After propensity matching key covariates, no significant difference in OS was observed between those receiving and not receiving AT ($P = 0.449$). CONCLUSION: This analysis revealed a modest 5-year OS for stage I AAC. Age, positive resection margins, and evaluation of <12 LNs negatively influenced OS and AT did not convey a survival benefit.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29518820

doi: https://doi.org/10.1002/jso.25021

- **Prognostic factors of non-ampullary duodenal adenocarcinoma**

Japanese journal of clinical oncology 2018 Aug;48(8):743-747

Background: Non-ampullary duodenal adenocarcinoma, excluding carcinoma in the ampulla of Vater, is a rare disease. Although several prognostic factors have been reported, they remain controversial due to the rarity of non-ampullary duodenal adenocarcinoma. The aims of this study were to investigate prognostic factors in patients with non-ampullary duodenal adenocarcinoma and to assess chemotherapy in patients with recurrence. Patients and methods: Records of 25 patients who underwent surgical treatment for non-ampullary duodenal adenocarcinoma from 2004 to 2016 were retrospectively reviewed. The relationship between the clinicopathological factors and outcomes was investigated. Results: Serum level of CA19-9, gross appearance, tumor size, tumor invasion, lymph node metastases, TNM stage and lymphatic and vascular invasion were significant risk factors of recurrence. Patients with recurrence who received chemotherapy according to regimens used to treat colorectal cancer had a better prognosis than those without chemotherapy (P = 0.016). Conclusion: Advanced non-ampullary duodenal adenocarcinoma has a poor prognosis, but chemotherapy possibly improves the prognosis in the patients with recurrent non-ampullary duodenal adenocarcinoma.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29931295

doi: https://doi.org/10.1093/jjco/hyy086

- **The Problem of High-Grade Gastroenteropancreatic Neuroendocrine Neoplasms: Well-Differentiated Neuroendocrine Tumors, Neuroendocrine Carcinomas, and Beyond**

https://www.sciencedirect.com/science/article/pii/S0889852918305279?via%3Dihub

https://www.endo.theclinics.com/article/S0889-8529(18)30527-9/fulltext

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- **Ampullary neuroendocrine neoplasms: surgical experience of a rare and challenging entity**

Langenbeck's archives of surgery 2018 Jul;():

PURPOSE: Ampullary neuroendocrine neoplasms (NENs) account for $< 0.3\%$ of gastrointestinal NENs. Surgical options include transduodenal ampullectomy/tumour excision or pancreaticoduodenectomy (PD). We report the experience of two high-volume pancreatic surgical centres of ampullary NENs. METHODS: Clinical records of patients who underwent surgery for ampullary NENs (January 2007-November 2017) in the study centres were retrieved retrospectively. We evaluated clinical-pathological features, post-operative outcome and follow-up (FU). RESULTS: Eighteen patients (9 M/9 F, averaging 62 years) were enrolled. All but one were non-functioning NENs; four (22%) patients presented with jaundice. Seven (39%) of the patients underwent ampullectomy/excision (median tumour size 1.5 cm), and 11 (61%) patients underwent PD (median tumour size 2.4 cm). The median operation time of ampullectomy/excision was 221 min with operative blood loss of 75 ml (vs. 506 min and 425 ml in PD). The median hospital stay was 10 days in both groups. Overall surgical morbidity was 33%, due to four biochemical leaks, one pancreatic fistula and one abdominal haemorrhage. No reoperations were needed. The median tumour size was 1.8 (range 0.5-6.7) cm. All G2-G3 NENs were N1 (vs. 1/7 in G1 NENs). Three (17%) cases were mixed exocrine/G3 NECs. After a median FU of 45 (up to 124) months, recurrence occurred in four G3 NEC (31%) patients (median disease-free survival 14 months) after an R0 PD. Disease-related survival was 93, 77 and 66% at 1, 3 and 5 years, respectively. CONCLUSION: Ampullary NENs are mostly G1-G2 neoplasms. Lymph node metastases rarely occur in G1 NENs < 2 cm in size, which may be treated with ampullectomy/excision. Survival is 66% 5 years after surgery.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30043166

doi: https://doi.org/10.1007/s00423-018-1695-9

- **Neoplasms of the Neuroendocrine Pancreas: An Update in the Classification, Definition, and Molecular Genetic Advances**

Advances in anatomic pathology 2018 Jun;():

This review focuses on discussing the main modifications of the recently published 2017 WHO Classification of Neoplasms of the Neuroendocrine Pancreas (panNEN). Recent updates separate pancreatic neuroendocrine tumors into 2 broad categories: well-differentiated pancreatic neuroendocrine tumors (panNET) and poorly differentiated pancreatic neuroendocrine carcinoma (panNEC), and incorporates a new subcategory of "well-differentiated high-grade NET (G3)" to the well-differentiated NET category. This new classification algorithm aims to improve the prediction of clinical outcomes and survival and help clinicians select better therapeutic strategies for patient care and management. In addition, these neuroendocrine neoplasms are capable of producing large quantity of hormones leading to clinical hormone hypersecretion syndromes. These functioning tumors include, insulinomas, glucagonomas, somatostatinomas, gastrinomas, VIPomas, serotonin-producing tumors, and ACTH-producing tumors. Although most panNENs arise as sporadic diseases, a subset of these heterogeneous tumors present as parts on inherited genetic syndromes, such as multiple endocrine neoplasia type 1, von Hippel-Lindau, neurofibromatosis type 1, tuberous sclerosis, and glucagon cell hyperplasia and neoplasia syndromes. Characteristic clinical and morphologic findings for certain functioning and syndromic panNENs should alert both pathologists and clinicians as appropriate patient management and possible genetic counseling may be necessary.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29912000

doi: https://doi.org/10.1097/PAP.0000000000000201

Cytopathology

- **Factors Impacting the Performance Characteristics of Bile Duct Brushings: A Clinico-Cytopathologic Analysis of 253 Patients**

Archives of pathology & laboratory medicine 2018 Jul;142(7):863-870

CONTEXT: - Literature on factors impacting bile duct brushings (BDBs) performance characteristics remain limited. OBJECTIVE: - To capture the current state of daily practice with BDB sign-out. DESIGN: - Two hundred fifty-three of 444 BDBs signed out by more than 7 cytopathologists, with histopathologic and/or clinical follow-up of at least 18 months, were examined. RESULTS: - One hundred thirty-five of 253 BDBs (53%) had histologically confirmed malignancies, 22 (9%) had cancer-related deaths, and 96 (38%) were benign. Cytologic diagnoses in the 444 BDBs were nondiagnostic (11 [2.5%]), negative (284 [64%]), atypical (62 [13.9%]), suspicious (34 [7.7%]), and malignant (53 [11.9%]). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of malignancy detection were 35%, 100%, 100%, 58%, and 66%, respectively. When atypical, suspicious, and malignant (ASM) categories were combined, sensitivity increased (58%), specificity and PPV dropped (97%), and accuracy increased (73%). Carcinoma type (bile-duct versus pancreatic-ductal) had no effect on accuracy (P = .60) or diagnostic class (P = .84), nor did time of performance (first 7.5 versus latter 7.5 years, P = .13). Interestingly, ThinPrep + cell block (n = 41) had higher sensitivity (61%) and lower specificity (80%) than ThinPrep only (versus 51% and 100%, respectively). Sensitivity and specificity were higher (47% and 100%) in nonstented than stented specimens (59% and 97%). Relative risk of malignancy for "suspicious" (2.30) and "atypical" (2.28) categories was lower but not very different from that of "malignant" category (2.41). CONCLUSIONS: - Bile duct brushings had fairly low sensitivity but high specificity and PPV with no false positives. Sensitivity almost doubled and specificity dipped minimally when ASM categories were combined, highlighting the need

for better classification criteria for atypical/suspicious cases. Higher specificity, PPV, NPV, and accuracy but lower sensitivity in stented BDBs suggest that they be called malignant only when evidence is overwhelmingly convincing.

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- **UroVysion Multi-Target Fluorescence in situ Hybridization Assay for the Detection of Malignant Bile Duct Brushing Specimens: A Comparison with Routine Cytology**

Acta cytologica 2018 ;62(4):295-301

OBJECTIVE: Routine bile duct brushing cytology is an important diagnostic tool in the evaluation of bile duct stricture. The purpose of this study was to evaluate the performance of the UroVysion fluorescence in situ hybridization (FISH) assay for the detection of malignant bile duct brushing specimens. STUDY DESIGN: Thirty-five bile duct brushing specimens were included in the study. The FISH assay utilized the commercially available UroVysion probes. The indeterminate cytology results were considered as negative for statistical analysis. RESULTS: Twenty-two of 35 patients were diagnosed as having malignancy based on tissue diagnosis or clinical progression of disease by image assessment. The sensitivity of routine cytology and FISH for the detection of malignancy was 14% (3/22) and 55% (12/22), respectively ($p = 0.003$). The specificity of routine cytology and FISH was 100% (13/13) and 62% (8/13), respectively ($p = 0.025$). The false-positive rate for routine cytology and FISH was 0% (0/13) and 38% (5/13), respectively. CONCLUSIONS: Our study shows that FISH is significantly more sensitive than routine cytology for the detection of malignancy in bile duct brushing specimens. However, in our study, the specificity of FISH was poor compared to the excellent specificity of routine cytology. The compromised specificity of FISH may limit its utility in the detection of malignant bile duct brushing specimens.

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doi: https://doi.org/10.1159/000488636

- **The Diagnostic Accuracy of Cytology for the Diagnosis of Hepatobiliary and Pancreatic Cancers**

Acta cytologica 2018 ;62(4):311-316

OBJECTIVE: Although cytology testing is considered a valuable method to diagnose tumors that are difficult to access such as hepato-biliary-pancreatic (HBP) malignancies, its diagnostic accuracy remains unclear. We therefore aimed to investigate the diagnostic accuracy of cytology testing for HBP tumors. STUDY DESIGN: We performed a retrospective study of all cytology samples that were used to confirm radiologically detected HBP tumors between 2002 and 2016. The cytology techniques used in our center included fine needle aspiration (FNA), brush cytology, and aspiration of bile. Sensitivity, specificity, positive and negative predictive values, and likelihood ratios were calculated in comparison to histological confirmation. RESULTS: From a total of 133 medical records, we calculated an overall sensitivity of 76%, specificity of 74%, a negative likelihood ratio of 0.30, and a positive likelihood ratio of 2.9. Cytology was more accurate in diagnosing lesions of the liver (sensitivity 79%, specificity 57%) and biliary tree (sensitivity 100%, specificity 50%) compared to pancreatic (sensitivity 60%, specificity 83%) and gallbladder lesions (sensitivity 50%, specificity 85%). Cytology was more accurate in detecting primary cancers (sensitivity 77%, specificity 73%) when compared to metastatic cancers (sensitivity 73%, specificity 100%). FNA was the most frequently used cytological technique to diagnose HBP lesions (sensitivity 78.8%). CONCLUSION: Cytological testing is

efficient in diagnosing HBP cancers, especially for hepatobiliary tumors. Given its relative simplicity, cost-effectiveness, and paucity of alternative diagnostic methods, cytology should still be considered as a first-line tool for diagnosing HBP malignancies.

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- **Fine-needle aspiration of a pancreatic neuroendocrine tumor with prominent rhabdoid features**

Diagnostic cytopathology 2018 Jul;46(7):600-603

Pancreatic neuroendocrine tumors (PanNETs) are uncommon neoplasms that conventionally possess architectural and cytomorphological features seen in neuroendocrine neoplasms found at other sites. When present, these features often allow rapid identification of neuroendocrine differentiation and an accurate diagnosis. Here, we report the cytologic findings seen on fine-needle aspiration (FNA) of a PanNET with distinct rhabdoid features. This morphology is rare in PanNETs and has been reported in only two case series examining surgical resection specimens and has not been described on FNA. It is important to recognize this morphology as this variant appears to portend an aggressive clinical course. Furthermore, unfamiliarity with this morphologic variant may lead to a larger initial differential and thus delay final diagnosis.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29359517

doi: https://doi.org/10.1002/dc.23892

- **Endoscopic ultrasound guided brush/fine-needle aspiration cytology: A 15-month study**

Diagnostic cytopathology 2018 Jun;46(6):461-472

BACKGROUND: Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) has become increasingly popular for the diagnosis and staging of gastrointestinal diseases and peri-gastrointestinal lesions. The application of FNA/Brush has dramatically expanded the clinical utility of EUS. AIMS AND OBJECTIVE: To evaluate the diagnostic accuracy, study the spectrum of lesions encountered in EUS-FNAC/brush cytology of gastrointestinal and peri-gastrointestinal lesions. MATERIALS AND METHODS: Total of 124 patients during the period from August 2015 to November 2016 was included in the study. Routine staining was done. RESULTS: A total of 124 cases were studied with 86% (107 cases) being satisfactory for evaluation. M:F ratio was 1:1.03, mean age of 50.5 years. The most common site was common bile duct (CBD) (37%) followed by lymph node (21%), pancreas (17.7%), esophagus (17%), stomach (3.5%), liver (1.8%), gallbladder (1%), and spleen (1%). In total, 53.4% lesions were benign, in 6.5% atypical cells were seen, 12.1% were suspicious for malignancy, and 28% cases were positive for malignancy. Follow-up was available in 102 cases with cyto-histopathological concordance rate of 90%. CONCLUSION: EUS-FNA/Brush is a reliable, sensitive, specific and minimally invasive way to establish a diagnosis. It can be utilized as a pre-operative procedure for the management of many intra-abdominal lesions and prevent unnecessary invasive procedures.

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- **Immunohistochemical Staining for S100P, SMAD4, and IMP3 on Cell Block Preparations is Sensitive and Highly Specific for Pancreatic Ductal Adenocarcinoma**

https://www.sciencedirect.com/science/article/pii/S2213294518301042

Molecular Pathology

- **Reduced RNA-binding protein HuD in pancreatic neuroendocrine tumors lowers p27Kip1 levels linked to poor prognosis**

The Journal of pathology 2018 Jul;():

For the majority of patients diagnosed with pancreatic neuroendocrine tumors (pancreatic NETs) there is a significant malignant potential with a poor prognosis, however the molecular abnormalities and pathogenesis of pancreatic NETs have not been firmly established. Here, we report that loss of RNA-binding protein HuD expression correlates with low p27Kip1 (p27) levels and poor prognosis in pancreatic NETs. HuD expression was frequently lost in many human pancreatic NETs and these pancreatic NETs showed aggressive clinico-pathological phenotypes with low p27 levels, increased tumor size, higher WHO grade and pathological T stage of the tumor, and presence of angioinvasion. Furthermore, loss of HuD was an independent, progress-free prognostic factor in multivariate survival analysis. However, level of HuR, the same Hu protein family member with HuD, was not significantly correlated with pancreatic NET size and progression. Mechanistically, HuD enhanced p27 mRNA translation by interacting with both 5'- and 3'-untranslated regions (UTRs) of p27 mRNA and consequently suppressed cell cycle progression and tumor growth. In addition, HuD competed with miR-30a-3p for binding to 3'UTR of p27 mRNA, suggesting interplay between HuD and miR-30a-3p in controlling p27 translation. Our results identify HuD as a pivotal suppressor of pancreatic NET growth, and propose that HuD has potential value as a prognostic factor of pancreatic NETs. This article is protected by copyright. All rights reserved.

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- **Pancreatic neuroendocrine carcinomas reveal a closer relationship to ductal adenocarcinomas than to neuroendocrine tumors G3**

Human pathology 2018 Jul;77():70-79

Pancreatic neuroendocrine carcinoma is a rare aggressive tumor commonly harboring TP53 and RB1 alterations and lacking neuroendocrine-related genetic changes such as mutations in MEN1 and ATRX/DAXX. Little is known about its genetic profile with regard to that of pancreatic ductal adenocarcinoma. We therefore conducted a detailed genetic study in 12 pancreatic neuroendocrine carcinomas of large cell (n = 9) and small cell type (n = 3) using massive parallel sequencing applying a 409-gene panel on an Ion Torrent system. The genetic data were compared with known data of pancreatic ductal adenocarcinoma and correlated with exocrine lineage marker expression. A similar analysis was performed in 11 pancreatic neuroendocrine tumors G3. Neuroendocrine carcinomas harbored 63 somatic mutations in 45 different genes, affecting most commonly TP53 (8/12 cases), KRAS (5/12 cases), and RB1 (loss of expression with or without deletion in 4/12 cases). Five carcinomas had both TP53 and KRAS mutations. Neuroendocrine tumors G3 only shared singular mutations in 5 different genes with neuroendocrine carcinomas, including TP53, CDKN2A, ARID1A, LRP1B, and APC, affecting 5 different cases. Most KRAS-positive neuroendocrine carcinomas also expressed MUC1 (4/5) and carcinoembryonic antigen (3/5) as markers of ductal differentiation. Our

data indicate that almost half of the pancreatic neuroendocrine carcinomas are genetically and phenotypically related to pancreatic ductal adenocarcinoma, and might therefore respond to chemotherapies targeting the latter carcinomas.

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doi: https://doi.org/10.1016/j.humpath.2018.03.018

- **MiR-21 up-regulation in ampullary adenocarcinoma and its pre-invasive lesions**

Pathology, research and practice 2018 Jun;214(6):835-839

Poor information is available on the molecular landscape characterizing the carcinogenetic process leading to ampullary carcinoma. MiR-21 is one of the most frequently up-regulated miRNAs in pancreatic adenocarcinoma, a tumor sharing similar molecular features with ampullary adenocarcinomas (AVCs), above all with the pancreatic-biliary type. We profiled, by in situ hybridization (ISH), miR-21 expression in a series of 26 AVCs, 50 ampullary dysplastic lesions (35 low-grade [LG-IEN] and 15 high-grade [HG-IEN]) and 10 normal duodenal mucosa samples. The same series was investigated by immunohistochemistry for -catenin, p53 and HER2 expression. HER2 gene amplification was evaluated by chromogenic in situ hybridization. To validate miR-21 ISH results we performed miR-21 qRT-PCR analysis in a series of 10 AVCs and their matched normal samples. All the normal control samples showed a negative or faint miR-21 expression, whereas a significant miR-21 up-regulation was observed during the carcinogenetic cascade ($p < 0.001$), with 21/26 (80.8%) of cancer samples showing a miR-21 overexpression. In comparison to control samples, a significant overexpression was found in samples of LG-IEN ($p = .0003$), HG-IEN ($p = .0001$), and AVCs ($p < 0.0001$). No significant difference in miR-21 overexpression was observed between LG-IEN, HG-IEN and AVCs. By qRT-PCR analysis, AVCs showed a 1.7-fold increase over the controls ($p = .003$). P53 was frequently dysregulated in both dysplastic and carcinoma samples (44 out of 76; 57.9%). A 20% (10/50) of dysplastic lesions and 11% (3/26) of carcinomas were characterized by a nuclear localization of -catenin. Only 2 AVCs (7.7%; both intestinal-type) showed a HER2 overexpression (both 2+), which corresponded to a HER2 gene amplification at CISH analysis. This is the first study demonstrating a miRNA dysregulation in the whole spectrum of ampullary carcinogenesis. MiR-21 overexpression is an early molecular event during ampullary carcinogenesis and its levels increase with the neoplastic progression.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29731265

doi: https://doi.org/10.1016/j.prp.2018.04.018

- **Simple Detection of Telomere Fusions in Pancreatic Cancer, Intraductal Papillary Mucinous Neoplasm, and Pancreatic Cyst Fluid**

The Journal of molecular diagnostics : JMD 2018 Jan;20(1):46-55

Telomere end-to-end fusions are an important source of chromosomal instability that arise in cells with critically shortened telomeres. We developed a nested real-time quantitative PCR method for telomere fusion detection in pancreatic ductal adenocarcinomas, intraductal papillary mucinous neoplasms (IPMNs), and IPMN cyst fluids. Ninety-one pancreatic cancer cell lines and xenograft samples, 93 IPMNs, and 93 surgically aspirated IPMN cyst fluid samples were analyzed. The association between telomere shortening, telomerase activity, and telomere fusion detection was evaluated. Telomere fusions were detected in 56 of 91 pancreatic cancers (61.5%). Telomere fusion-positive cell lines had significantly shorter telomere lengths than fusion-negative lines ($P = 0.003$). Telomere fusions were undetectable in normal pancreas or IPMNs with low-grade dysplasia (0.0%) and were detected in IPMN with high-grade dysplasia (HGD; 48.0%) ($P < 0.001$). In IPMN

cyst fluids, telomere fusions were more frequent in IPMNs with HGD (26.9%) or associated invasive cancer (42.9%) than IPMN with intermediate-grade dysplasia (15.4%) or low-grade dysplasia (0%) (P = 0.025). Telomerase activity levels were higher in cyst fluids with fusions than in those without (P = 0.0414). Cyst fluid telomere fusion status was an independent predictor of HGD/invasive cancer by multivariate analysis (odds ratio, 6.23; 95% CI, 1.61-28.0). Telomere fusions are detected in later stages of IPMN progression and can serve as a marker for predicting the presence of HGD and/or invasive cancer.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29229290

doi: https://doi.org/10.1016/j.jmoldx.2017.09.006

- **Genomic testing for pancreatic cancer in clinical practice as real-world evidence**

https://www.pancreatology.net/article/S1424-3903(18)30633-1/abstract

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Others

- **VEGF receptor-2/neuropilin1 trans-complex formation between endothelial and tumor cells is an independent predictor of pancreatic cancer survival**

The Journal of pathology 2018 Jul;():

Unstable and dysfunctional tumor vasculature promotes cancer progression and spread. Signal transduction by the pro-angiogenic vascular endothelial growth factor (VEGF) receptor-2 (VEGFR2) is modulated by VEGFA-dependent complex formation with Neuropilin-1 (NRP1). NRP1 expressed on tumor cells can form VEGFR2/NRP1 trans-complexes between tumor cells and endothelial cells which arrests VEGFR2 on the endothelial surface, thus interfering with productive VEGFR2 signaling. In mouse fibrosarcoma, VEGFR2/NRP1 trans-complexes correlated with reduced tumor vessel branching and reduced tumor cell proliferation. Pancreatic ductal adenocarcinoma (PDAC) strongly expressed NRP1 on both tumor cells and endothelial cells in contrast to other common cancer forms. Using proximity ligation assay, VEGFR2/NRP1 trans-complexes were identified in human PDAC tumor tissue, and its presence was associated with reduced tumor vessel branching, reduced tumor cell proliferation and improved patient survival after adjusting for other known survival predictors. We conclude that VEGFR2/NRP1 trans-complex formation is an independent predictor of PDAC patient survival.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30027561

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- **Immunolabeling of Cleared Human Pancreata Provides Insights into Three-Dimensional Pancreatic Anatomy and Pathology**

The American journal of pathology 2018 Jul;188(7):1530-1535

Visualizing pathologies in three dimensions can provide unique insights into the biology of human diseases. A rapid and easy-to-implement dibenzyl ether-based technique was used to clear thick sections of surgically resected human pancreatic parenchyma. Protocols were applicable to both fresh and formalin-fixed, paraffin-embedded tissue. The penetration of antibodies into dense pancreatic parenchyma was optimized using

both gradually increasing antibody concentrations and centrifugal flow. Immunolabeling with antibodies against cytokeratin 19 was visualized using both light sheet and confocal laser scanning microscopy. The technique was applied successfully to 26 sections of pancreas, providing three-dimensional (3D) images of normal pancreatic tissue, pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasms, and infiltrating pancreatic ductal adenocarcinomas. 3D visualization highlighted processes that are hard to conceptualize in two dimensions, such as invasive carcinoma growing into what appeared to be pre-existing pancreatic ducts and within venules, and the tracking of long cords of neoplastic cells parallel to blood vessels. Expanding this technique to formalin-fixed, paraffin-embedded tissue opens pathology archives to 3D visualization of unique biosamples and rare diseases. The application of immunolabeling and clearing to human pancreatic parenchyma provides detailed visualization of normal pancreatic anatomy, and can be used to characterize the 3D architecture of diseases including pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasm, and pancreatic ductal adenocarcinomas.

https://www.sciencedirect.com/science/article/pii/S0002944018300014

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29684363

doi: https://doi.org/10.1016/j.ajpath.2018.04.002

- **The BRG1/SOX9 axis is critical for acinar cell-derived pancreatic tumorigenesis**

The Journal of clinical investigation 2018 Jul;():

Chromatin remodeler Brahma related gene 1 (BRG1) is silenced in approximately 10% of human pancreatic ductal adenocarcinomas (PDAs). We previously showed that BRG1 inhibits the formation of intraductal pancreatic mucinous neoplasm (IPMN) and that IPMN-derived PDA originated from ductal cells. However, the role of BRG1 in pancreatic intraepithelial neoplasia-derived (PanIN-derived) PDA that originated from acinar cells remains elusive. Here, we found that exclusive elimination of Brg1 in acinar cells of Ptf1a-CreER; KrasG12D; Brg1fl/fl mice impaired the formation of acinar-to-ductal metaplasia (ADM) and PanIN independently of p53 mutation, while PDA formation was inhibited in the presence of p53 mutation. BRG1 bound to regions of the Sox9 promoter to regulate its expression and was critical for recruitment of upstream regulators, including PDX1, to the Sox9 promoter and enhancer in acinar cells. SOX9 expression was downregulated in BRG1-depleted ADMs/PanINs. Notably, Sox9 overexpression canceled this PanIN-attenuated phenotype in KBC mice. Furthermore, Brg1 deletion in established PanIN by using a dual recombinase system resulted in regression of the lesions in mice. Finally, BRG1 expression correlated with SOX9 expression in human PDAs. In summary, BRG1 is critical for PanIN initiation and progression through positive regulation of SOX9. Thus, the BRG1/SOX9 axis is a potential target for PanIN-derived PDA.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30010625

doi: https://doi.org/10.1172/JCI94287

- **Pancreatic Effects of a Bruton's Tyrosine Kinase Small-molecule Inhibitor in Rats Are Strain-dependent**

Toxicologic pathology 2018 Jun;46(4):460-472

Inhibitors of Bruton's tyrosine kinase (BTK) are under development as potential therapies for various autoimmune diseases. In repeat-dose toxicity studies, small-molecule BTK inhibitors (BTKi) have been reported to cause a constellation of histologic effects at the pancreatic endocrine-exocrine interface in male rats; however, similar findings were not reported in other species. Since the BTKi-induced pancreatic effect is morphologically similar to well-documented spontaneous changes (predominantly characterized by insular/peri-insular

hemorrhage, pigment deposition, chronic inflammation, and fibrosis) that are known to vary by rat strain, we investigated potential strain-dependent differences in the pancreatic effects of a small-molecule BTKi, LY3337641. Following 13 weeks of LY3337641 treatment, Crl:CD(SD) rats were most sensitive, Crl:WI(Han) rats were of intermediate sensitivity, and Hsd:SD rats were least sensitive. These strain differences appear to be related to differences in rate of weight gain across strains and sexes; however, a definitive mechanism was not determined. This study demonstrated that BTKi-induced pancreatic effects were highly dependent on rat strain and correlated with differences in the incidence and severity of the spontaneous background change. When considered with the lack of pancreas effects in nonrat species, these changes in rats are unlikely predictive of similar changes in humans administered a BTK inhibitor.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29699458

doi: https://doi.org/10.1177/0192623318770163

- **Orthotopic and heterotopic murine models of pancreatic cancer and their different responses to FOLFIRINOX chemotherapy**

Disease models & mechanisms 2018 Jun;():

INTRODUCTION: Syngeneic, immunocompetent allograft tumor models recapitulate important aspects of the tumor microenvironment and have short tumor latency with predictable growth kinetics, making them useful for trialing novel therapeutics. We describe surgical techniques for orthotopic and heterotopic PDAC tumor implantation and characterize phenotypes based on implantation site. METHODS: Mice (n=8 per group) were implanted with 104 cells in the pancreas or flank. Hy15549 and Han4.13 cell lines were derived from primary murine PDAC (Ptf1-Cre; LSL-KRAS-G12D; p53 Lox/+) on C57BL/6 and FVB strains, respectively. Single cell suspension and solid tumor implants were compared. Tumors were treated with two intravenous doses of FOLFIRINOX and responses evaluated. RESULTS: All mice developed pancreatic tumors within 7 days. Orthotopic tumors grew faster and larger than heterotopic tumors. By 3 weeks, orthotopic mice began losing weight, and showed declines in body condition requiring euthanasia starting at 4 weeks. Single cell injection into the pancreas had near 100% engraftment, but solid tumor implant engraftment was approximately 50% and was associated with growth restriction. Orthotopic tumors were significantly more responsive to IV FOLFIRINOX compared to heterotopic tumors, with greater reductions in size and increased apoptosis. Heterotopic tumors were more desmoplastic and hypovascular. However, drug uptake into tumor tissue was equivalent regardless of tumor location or degree of fibrosis, indicating that microenvironment differences between heterotopic and orthotopic tumors influenced response to therapy. CONCLUSION: Orthotopic and heterotopic allograft locations confer unique microenvironments that influence growth kinetics, desmoplastic response, and angiogenesis. Tumor location influences chemosensitivity to FOLFIRINOX and should inform future preclinical trials.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29903803

doi: https://doi.org/10.1242/dmm.034793

Journals Reviewed

Advances in Anatomic Pathology

American Journal of Clinical Pathology

The American Journal of Gastroenterology

The American Journal of Pathology

American Journal of Clinical Pathology

American Journal of Pathology

American Journal of Surgical Pathology

Annals of Diagnostic Pathology

Annals of Surgery

Annals of Surgical Oncology

Annual Review of Pathology-Mechanisms of Disease

APMIS

Applied Immunohistochemistry & Molecular Morphology

Archives of Pathology & Laboratory Medicine

Cancer

Cancer Cell

Cancer Cytopathology

Cellular Oncology

Clinical Cancer Research

Cochrane Reviews

Cytojournal

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International Journal of Clinical and Experimental Pathology

Journal of Clinical Pathology

Journal of Molecular Diagnostics

Journal of Pathology

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The Journal of Pathology

Tissue Antigens

Virchows Archiv