Pancreatobiliary Pathology Society Journal Watch

January-March 2020

Last Update on 2020-04-28

Contents

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1 PBPath Journal Watch Articles

Welcome 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, molecular pathology, pancreas, gallbladder, bile ducts, and ampulla 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 drafts of the 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!

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The *journal watch* articles are collected in zenodo and OSF.

To see these selected articles in PubMed click here

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Below is the content based groupings via openknowledgemaps.

1.1 Pancreas

- A 15-gene immune, stromal and proliferation gene signature that significantly associates with poor survival in patients with pancreatic ductal adenocarcinoma

Clinical cancer research : an official journal of the American Association for Cancer Research 2020 Mar;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=32234757

PURPOSE: Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease with dismal survival rates. Tumor microenvironment (TME), comprising of immune cells and cancer-associated fibroblasts, plays a key role in driving poor prognosis and resistance to chemotherapy. Herein, we aimed to identify a TME-associated, risk-stratification gene biomarker signature in PDAC. EXPERIMENTAL DESIGN: The initial biomarker discovery was performed in The Cancer Genome Atlas (TCGA, n=163) transcriptomic data. This was followed by independent validation of the gene signature in The International Cancer Genome Consortium (ICGC, n=95), E-MTAB-6134 (n=288), and GSE71729 (n=123) datasets for predicting overall survival (OS), and for its ability to detect poor molecular subtypes. Clinical validation and nomogram establishment was undertaken by performing multivariate cox regression analysis. RESULTS: Our biomarker discovery effort identified a 15-gene immune, stromal and proliferation (ISP) gene signature that significantly associated with poor OS (HR: 3.90, 95% CI, 2.36-6.41, p<0.0001). This signature also robustly predicted survival in 3 independent validation cohorts ICGC (HR:2.63 [1.56-4.41], p<0.0001), E-MTAB-6134 (HR:1.53 [1.14-2.04], p=0.004), and GSE71729 (HR:2.33 [1.49-3.63], p<0.0001). Interestingly, the ISP signature also permitted identification of poor molecular PDAC subtypes with excellent accuracy in all 4 cohorts; TCGA (AUC=0.94), ICGC (AUC=0.91), E-MTAB-6134 (AUC=0.80), and GSE71729 (AUC=0.83). The ISP-derived high-risk patients exhibited significantly poor OS in a clinical validation cohort (n=119; HR:2.62 [1.50-4.56], p=0.0004). A nomogram was established which included the ISP, CA19-9, T and N-stage for eventual clinical translation. CONCLUSIONS: We report a novel gene signature for risk-stratification and robust identification of PDAC patients with poor molecular subtypes.

doi: https://doi.org/10.1158/1078-0432.CCR-19-4044

- Expression Patterns and Prognostic Value of DNA Damage Repair Proteins in Resected Pancreatic Neuroendocrine Neoplasms

Annals of surgery 2020 Mar;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=32209898

OBJECTIVE: This study aimed to examine the expression profiles and prognostic value of multiple DDR proteins in resected PanNENs. BACKGROUND: DDR proteins play important roles in various cancers, including pancreatic ductal adenocarcinoma. However, the expression patterns and prognostic value of DDR proteins in PanNENs remain unclear. METHODS: This retrospective analysis included PanNEN patients who underwent resection at the Fudan University Shanghai Cancer Center from 2012 to 2018. Immunohistochemical staining was performed for 12 DDR proteins in tissue microarrays. The associations of DDR protein expression and clinicopathological features with recurrence-free survival (RFS) were examined via a Cox regression model and random survival forest. A recurrence signature was constructed using recursive partitioning analysis. RESULTS: In total, 131 PanNEN patients were included, with 32 (24.4%) cases of recurrence. Among the 12 DDR proteins, low checkpoint kinase 2 (CHK2) expression (P = 0.020) and loss of ataxia-telangiectasia-mutated (ATM) (P = 0.0007) significantly correlated with recurrence. Multivariable Cox regression analysis identified tumor size 3cm, lymph node (LN) metastasis, high tumor grade, low CHK2 expression, and ATM loss as independent risk factors for recurrence. A recurrence signature was established

based on the importance of recurrence-specific risk factors; patients with the LNnegTumorSize<3cm signature had a 5-year RFS rate of 96.8%, whereas patients with the LNposCHK2low signature had the worst 5-year RFS rate (0%). Discrimination (concordance index: 0.770) and calibration plots indicated that the recurrence signature had a good ability to identify patients at risk for recurrence. CONCLUSIONS: By analyzing large-scale tissue microarrays of PanNENs, we evaluated 12 DDR protein expression profiles. We developed a recurrence signature that can identify distinct subpopulations according to RFS, which may help refine individual follow-up.

doi: https://doi.org/10.1097/SLA.0000000000003884

- DETECTION OF CIRCULATING TUMOR DNA IN PATIENTS WITH PANCREATIC CANCER USING DIGITAL NEXT-GENERATION SEQUENCING

The Journal of molecular diagnostics : JMD 2020 Mar;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=32205290

Circulating tumor DNA (ctDNA) measurements can be used to estimate tumor burden, but avoiding false-positives is a challenge. We evaluated digital next-generation sequencing (NGS) as a ctDNA detection method. Plasma KRAS and GNAS hotspot mutation levels were measured in 140 subjects including 67 with pancreatic ductal adenocarcinoma, and 73 healthy and disease controls. To limit chemical modifications of DNA that yield false-positive mutation calls, plasma DNA was enzymatically pre-treated, after which DNA was aliquoted for digital detection of mutations (up to 384 aliquots/sample) by PCR and NGS. A digital NGS score of two standard deviations above the mean in controls was considered positive. 37% of patients with pancreatic cancer, including 31% of patients with Stage I/II disease had positive KRAS codon 12 ctDNA scores; only one patient had a positive GNAS mutation score. Two disease control patients had positive ctDNA scores. Low normal-range digital NGS scores at mutation hot-spots were found at similar levels in healthy and disease controls, usually at sites of cytosine deamination, and were likely the result of chemical modification of plasma DNA and NGS error, rather than true mutations. Digital NGS detects mutated ctDNA in patients with pancreatic cancer with similar yield to other methods. The detection of low-level, true-positive ctDNA is limited by frequent low-level detection of false-positive mutation cells in plasma DNA from controls.

doi: https://doi.org/10.1016/j.jmoldx.2020.02.010

- GATA6 expression distinguishes classical and basal-like subtypes in advanced pancreatic cancer

Clinical cancer research : an official journal of the American Association for Cancer Research 2020 Mar;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=32156747

PURPOSE: To determine the impact of basal-like and classical subtypes in advanced PDAC and to explore GATA6 expression as a surrogate biomarker. EXPERIMENTAL DESIGN: Within the COMPASS trial patients proceeding to chemotherapy for advanced PDAC undergo tumour biopsy for RNA sequencing. Overall response rate (ORR) and overall survival (OS) were stratified by subtypes and according to chemotherapy received. Correlation of GATA6 with the subtypes using gene expression profiling, in situ hybridization (ISH) were explored. RESULTS: Between December 2015-May 2019, 195 patients (95%) had enough tissue for RNA sequencing; 39 (20%) were classified as basal-like and 156 (80%) as classical. RECIST response data were available for 157 patients; 29 basal-like and 128 classical where the ORR was 10% vs. 33% respectively (p=0.02). In patients with basal-like tumours treated with modified FOLFIRINOX (mFFX) (n=22) the progression rate was 60% compared to 15% in classical PDAC (p= 0.0002). Median OS in the intention to treat population (n=195) was 9.3 months for classical vs. 5.9 months for basal-like PDAC (HR 0.47 95% CI

0.32-0.69, p=0.0001). GATA6 expression by RNAseq highly correlated with the classifier (p<0.001) and ISH predicted the subtypes with sensitivity of 89% and specificity of 83%. In a multivariable analysis, GATA6 expression was prognostic (p=0.02). In exploratory analyses, basal-like tumours, could be identified by keratin 5, were more hypoxic and enriched for a T cell inflamed gene expression signature. CONCLUSIONS: The basal-like subtype is chemoresistant and can be distinguished from classical PDAC by GATA6 expression.

doi: https://doi.org/10.1158/1078-0432.CCR-19-3724

- Validation and modification of staging Systems for Poorly Differentiated Pancreatic Neuroendocrine Carcinoma

BMC cancer 2020 Mar;20(1):188

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=32138704

BACKGROUND: The American Joint Committee on Cancer (AJCC) and the European Neuroendocrine Tumor Society (ENETS) staging classifications are two broadly used systems for pancreatic neuroendocrine tumors. This study aims to identify the most accurate and useful tumor-node-metastasis (TNM) staging system for poorly differentiated pancreatic neuroendocrine carcinomas (pNECs). METHODS: An analysis was performed to evaluate the application of the ENETS, 7th edition (7th) AJCC and 8th edition (8th) AJCC staging classifications using the Surveillance, Epidemiology, and End Results (SEER) registry (N = 568 patients), and a modified system based on the analysis of the 7th AJCC classification was proposed. RESULTS: In multivariable analyses, only the 7th AJCC staging system allocated patients into four different risk groups, although there was no significant difference. We modified the staging classification by maintaining the T and M definitions of the 7th AJCC staging and adopting new staging definitions. An increased hazard ratio (HR) of death was also observed from class I to class IV for the modified 7th (m7th) staging system (compared with stage I disease; HR for stage II =1.23, 95% confidence interval (CI) = 0.73-2.06, P = 0.44; HR for stage III =2.20, 95% CI =1.06-4.56, P = 0.03; HR for stage IV =4.95, 95% CI =3.20-7.65, P < 0.001). The concordance index (C-index) was higher for local disease with the m7th AJCC staging system than with the 7th AJCC staging system. CONCLUSIONS: The m7th AJCC staging system for pNECs proposed in this study provides improvements and may be assessed for potential adoption in the next edition.

doi: https://doi.org/10.1186/s12885-020-6634-9

- INSM1 Is a Highly Specific Marker of Neuroendocrine Differentiation in Primary Neoplasms of the Gastrointestinal Tract, Appendix, and Pancreas

American journal of clinical pathology 2020 Mar;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=32128564

OBJECTIVES: INSM1 has been described as a sensitive and specific neuroendocrine marker. This study aims to compare INSM1 with traditional neuroendocrine markers in gastrointestinal neuroendocrine neoplasms. METHODS: Retrospective review (2008-2018) was used to retrieve paraffin-embedded tissue from 110 gastrointestinal neuroendocrine neoplasms and controls that was subsequently stained with INSM1, synaptophysin, chromogranin, CD56, and Ki-67. RESULTS: INSM1 was positive in 16 of 17 (94.1%) gastric, 17 of 18 (94.4%) pancreatic, 13 of 18 (72.2%) small bowel, 17 of 21 (81.0%) colonic, and 26 of 36 (72.2%) appendiceal tumors. INSM1 was positive in 58 of 70 (82.9%) well-differentiated neuroendocrine tumors, 17 of 20 (85.0%) poorly differentiated neuroendocrine carcinomas, 8 of 11 (72.7%) low-grade goblet cell adenocarcinomas (grade 1), and 6 of 9 (66.7%) high-grade goblet cell adenocarcinomas (grade 2/3). INSM1 sensitivity for neuroendocrine neoplasms (80.9%) was less than that of synaptophysin (99.1%), chromogranin (88%), and CD56 (95.3%); specificity was higher (95.7% vs 86.0%, 87.3%, and 86.0%, respectively). CONCLUSIONS: INSM1 is a useful marker of neuroendocrine differentiation in gastrointestinal neuroendocrine

and mixed neuroendocrine neoplasms. Compared with traditional neuroendocrine markers, INSM1 is less sensitive but more specific.

doi: https://doi.org/10.1093/ajcp/aqaa014

- Global, regional and national burden of pancreatic cancer, 1990 to 2017: Results from the Global Burden of Disease Study 2017

Pancreatology : official journal of the International Association of Pancreatology (IAP) … [et al.] 2020 Apr;20(3):462-469

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=32113937

BACKGROUND: The global burden of pancreatic cancer (PCa) continues to grow. Detailed data on PCa epidemiology are essential for policy-making and appropriate healthcare resource allocation. METHODS: Estimates of incidence, death and disability-adjusted life years (DALYs) of PCa from 1990 to 2017 were collected from the Global Burden of Disease Study 2017. Decomposition analysis was conducted to detect the contributing factors related to PCa incidence variation. The estimated annual percentage change (EAPC) was calculated to quantify the PCa epidemiology trends over a specified interval. RESULTS: Globally, the incidence of PCa cases increased by 129.1% to 447 664 664 (95% uncertainty interval (UI) 438 597-456 295), death increased by 125.2% to 441 082 082 (95% UI 448 960-432 833), and DALYs increased by 107.3% to 9 080 004 (95% UI 8 894 128-9 256 346) between 1990 and 2017. Relatively higher sociodemographic index (SDI) regions were observed with greater incidences, more deaths and a greater number of DALYs of PCa, but relatively lower SDI regions experienced a sharply increasing trend in these measures. Decomposition analysis indicated that the global increase in PCa incidence was driven by the aging population from 2007 to 2017, especially in higher SDI regions. In addition, a significant negative correlation was found between EAPC and ASIR (in 1990) ($r = -0.56$, $P < 0.001$). CONCLUSIONS: PCa remains a major public health burden globally. The unfavorable trend in PCa suggesting that further study for prevention should be conducted to forestall the increase in pancreatic cancer.

doi: https://doi.org/10.1016/j.pan.2020.02.011

- Pancreatic acinar cell carcinomas and mixed acinar-neuroendocrine carcinomas are more clinically aggressive than grade 1 pancreatic neuroendocrine tumours

Pathology 2020 Apr;52(3):336-347

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=32111396

Acinar cell carcinomas (ACCs) and mixed acinar-neuroendocrine carcinomas (MAcNECs) of the pancreas are extremely rare carcinomas with a significant component with acinar differentiation. To date, the clinicopathological behaviours of these neoplasms remain unclear. In this study, we evaluated the histopathological and molecular characteristics of 20 ACCs and 13 MAcNECs and compared them to a cohort of 269 well-differentiated pancreatic neuroendocrine tumours (PanNETs). Compared to PanNETs, both ACCs and MAcNECs had an advanced pT classification ($p<0.001$), as well as more prevalent lymphovascular and perineural invasion ($p=0.002$) and lymph node and distant metastases ($p<0.001$). Patients with MAcNECs had worse overall ($p<0.001$) and recurrence-free survival ($p<0.001$) than those with PanNETs, but no significant difference with those with ACCs. Subgroup analyses revealed that patients with ACCs and MAcNECs had significantly worse recurrence-free survival than those with grade 1 PanNET ($p<0.001$), and patients with MAcNECs also had worse overall survival than those with grade 1 and 2 PanNETs ($p<0.001$, and $p=0.001$). ACCs presented more commonly with intraductal growth ($p=0.014$) than MAcNECs, while MAcNECs more often had lymph node metastasis ($p=0.012$) than ACCs. The telomere maintenance mechanism Alternative Lengthening of Telomeres (ALT) was assessed by telomere-specific FISH, and ALT was detected in 1 of 20

ACCs and in three of the 13 MAcNECs. Patients with MAcNECs and ACCs had worse survival and more aggressive behaviour than those with grade 1 PanNETs; thus, the clinicopathological behaviour of MAcNECs resembles ACCs rather than PanNETs. Combined neuroendocrine and acinar cell immunohistochemical markers are helpful for differentiating these different tumour types.

doi: https://doi.org/10.1016/j.pathol.2020.01.437

- MMR Deficiency is Homogeneous in Pancreatic Carcinoma and Associated with High Density of Cd8-Positive Lymphocytes

Annals of surgical oncology 2020 Feb;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=32108923

BACKGROUND: Microsatellite instability (MSI) has emerged as a predictive biomarker for immune checkpoint inhibitor therapy. Cancer heterogeneity represents a potential obstacle for the analysis of predicitive biomarkers. MSI has been reported in pancreatic cancer, but data on the possible extent of intratumoral heterogeneity are lacking. METHODS: To study MSI heterogeneity in pancreatic cancer, a tissue microarray (TMA) comprising 597 tumors was screened by immunohistochemistry with antibodies for the mismatch repair (MMR) proteins MLH1, PMS2, MSH2, and MSH6. RESULTS: In six suspicious cases, large section immunohistochemistry and microsatellite analysis (Bethesda panel) resulted in the identification of 4 (0.8%) validated MSI cases out of 480 interpretable pancreatic ductal adenocarcinomas. MSI was absent in 55 adenocarcinomas of the ampulla of Vater and 7 acinar cell carcinomas. MMR deficiency always involved MSH6 loss, in three cases with additional loss of MSH2 expression. Three cancers were MSI-high and one case with isolated MSH6 loss was MSS in PCR analysis. The analysis of 44 cancer-containing tumor blocks revealed that the loss of MMR protein expression was always homogeneous in affected tumors. Automated digital image analysis of CD8 immunostaining demonstrated markedly higher CD8 + tumor infiltrating lymphocytes in tumors with (mean = 685, median = 626) than without (mean = 227; median = 124) MMR deficiency ($p < 0.0001$), suggesting a role of MSI for immune response. CONCLUSIONS: Our data suggest that MSI occurs early in a small subset of ductal adenocarcinomas of the pancreas and that immunohistochemical MMR analysis on limited biopsy or cytology material may be sufficient to estimate MMR status of the entire cancer mass.

doi: https://doi.org/10.1245/s10434-020-08209-y

- Tumor-Insular Complex in Neoadjuvant Treated Pancreatic Ductal Adenocarcinoma Is Associated With Higher Residual Tumor

The American journal of surgical pathology 2020 Feb;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=32091434

The tumor microenvironment in pancreatic ductal adenocarcinoma (PDAC) plays a vital role in treatment response, and therefore, patient survival. We and others have observed an intimate association of neoplastic ductal cells with non-neoplastic islet cells, recapitulating the ductoinsular complex. We define this phenomenon as tumor-insular complex (TIC). Herein, we describe the clinicopathologic characteristics of TIC in neoadjuvant treated PDAC cases for the first time. We retrospectively reviewed the pathology of 105 cases of neoadjuvant treated PDAC resected at our institution. TIC was noted in 35 cases (33.3%), the mean tumor bed size was 2.7±1.0 cm, mean percentage of residual tumor 40±28% and mean Residual Tumor Index (RTI) (an index previously established as a prognostic parameter by our group) was 1.1±1.0. TIC was significantly associated with perineural invasion (P=0.001), higher tumor bed size (P=0.007), percentage of residual tumor (P=0.009), RTI (P=0.001), ypT stage (P=0.045), and poor treatment response, grouped by a previously established criteria (P=0.010). Using our prior binary reported prognostic cutoff for RTI of

0.35 and >0.35, TIC was associated with a RTI >0.35 (P=0.002). Moreover, patients who did not receive neoadjuvant radiation were associated with a higher frequency of TIC (P=0.003). In this cohort, RTI but not TIC was also shown to be a significant independent prognosticator for recurrence-free survival and overall survival on multivariate analysis. In conclusion, TIC is significantly associated with a more aggressive neoplasm which shows a poor treatment response. Further studies will be needed to better understand the tumor biology of TICs.

doi: https://doi.org/10.1097/PAS.0000000000001454

- Insulinoma-associated protein 1 (INSM1) is a robust marker for identifying and grading pancreatic neuroendocrine tumors

Cancer cytopathology 2020 Apr;128(4):269-277

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31977134

BACKGROUND: Pancreatic neuroendocrine tumor (PNET) is a diagnostic challenge with limited samples in not only identification but grading. Prior studies have shown insulinoma-associated protein 1 (INSM1) to be a robust marker in identifying PNETs from other solid pancreatic tumors on resection specimens. In this study, we investigated the utility of INSM1 not only for identifying PNETs but also for grading in cell blocks (CBs) and surgical resections (SRs). METHODS: A search for PNET cases between 2000 and 2019 identified 55 samples (26 CBs and 29 SRs) that were further separated into high (2 CBs, 3 SRs), intermediate (4 CBs, 7 SRs), and low (20 CBs, 19 SRs) grades based on their final pathology report and Ki-67 level. Immunohistochemical (IHC) staining for INSM1 (C-8, Santa Cruz Biotechnology [1:100]) was performed and quantified using an H score of 0 to 300. Non-PNET solid pancreatic tumors were compared and included acinar cell carcinoma, solid pseudopapillary neoplasm, and ductal adenocarcinoma. RESULTS: All 55 cases of PNET demonstrated nuclear INSM1 staining. The average H scores for INSM1 staining of PNET were 254 and 252 in CB and SR, respectively. The H scores decreased with increasing tumor grade, with low-grade (G1), intermediate-grade (G2), and high-grade (G3) tumors showing average INSM1 H scores of 229 and 253, 266 and 253, and 30 and 33 in both CB and SR, respectively. CONCLUSION: IHC with INSM1 plays a role in identifying and potentially grading PNETs.

doi: https://doi.org/10.1002/cncy.22242

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

Histopathology 2020 Jan;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31965618

BACKGROUND: Pancreatic ductal adenocarcinomas (PDACs) are increasingly treated with neoadjuvant therapy. However, the American Joint Committee on Cancer (AJCC) 8th Edition T staging based on tumor size does not reflect treatment effect, which often results in multiple, small foci of residual tumor in a background of mass-forming fibrosis. Thus, we evaluated the performance of AJCC 8th Edition T staging in predicting patient outcomes using a microscopic tumor size measurement method. METHODS AND RESULTS: 106 post-neoadjuvant therapy pancreatectomies were reviewed, and all individual tumor foci were measured. T stages based on gross size (GS) and the largest single microscopic focus size (MFS) were examined in association with clinicopathologic variables and patient outcomes. 63/106 (59%) were locally advanced; 78% received FOLFIRINOX treatment. Average GS and MFS were 2.5cm and 1.1cm, respectively; 9 cases each were classified as T0, 35 and 85 cases as T1, 42 and 12 cases as T2, and 20 and 0 cases as T3, based on the GS and MFS, respectively. Higher GS- and MFS-based T stages were significantly associated with higher tumor regression grade, lymphovascular and perineural invasion, and

higher N stage. Furthermore, higher MFS-based T stage was significantly associated with shorter disease-free survival (DFS) (p<0.001) and shorter overall survival (OS) (p=0.002). GS was significantly associated with OS (p=0.046), but not with DFS. CONCLUSIONS: In post-neoadjuvant PDAC resections, MFS-based T staging is superior to GS-based T staging for predicting patient outcomes, suggesting that microscopic measurements have clinical utility beyond the conventional use of GS measurements alone.

doi: https://doi.org/10.1111/his.14067

- DNAJB1-PRKACA fusions occur in oncocytic pancreatic and biliary neoplasms and are not specific for fibrolamellar hepatocellular carcinoma

Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc 2020 04;33(4):648-656

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31676785

Recently discovered DNAJB1-PRKACA oncogenic fusions have been considered diagnostic for fibrolamellar hepatocellular carcinoma. In this study, we describe six pancreatobiliary neoplasms with PRKACA fusions, five of which harbor the DNAJB1-PRKACA fusion. All neoplasms were subjected to a hybridization capture-based next-generation sequencing assay (MSK-IMPACT), which enables the identification of sequence mutations, copy number alterations, and selected structural rearrangements involving 410 genes (n = 6) and/or to a custom targeted, RNA-based panel (MSK-Fusion) that utilizes Archer Anchored Multiplex PCR technology and next-generation sequencing to detect gene fusions in 62 genes (n = 2). Selected neoplasms also underwent FISH analysis, albumin mRNA in-situ hybridization, and arginase-1 immunohistochemical labeling (n = 3). Five neoplasms were pancreatic, and one arose in the intrahepatic bile ducts. All revealed at least focal oncocytic morphology: three cases were diagnosed as intraductal oncocytic papillary neoplasms, and three as intraductal papillary mucinous neoplasms with mixed oncocytic and pancreatobiliary or gastric features. Four cases had an invasive carcinoma component composed of oncocytic cells. Five cases revealed DNAJB1-PRKACA fusions and one revealed an ATP1B1-PRKACA fusion. None of the cases tested were positive for albumin or arginase-1. Our data prove that DNAJB1-PRKACA fusion is neither exclusive nor diagnostic for fibrolamellar hepatocellular carcinoma, and caution should be exercised in diagnosing liver tumors with DNAJB1-PRKACA fusions as fibrolamellar hepatocellular carcinoma, particularly if a pancreatic lesion is present. Moreover, considering DNAJB1-PRKACA fusions lead to upregulated protein kinase activity and that this upregulated protein kinase activity has a significant role in tumorigenesis of fibrolamellar hepatocellular carcinoma, protein kinase inhibition could have therapeutic potential in the treatment of these pancreatobiliary neoplasms as well, once a suitable drug is developed.

doi: https://doi.org/10.1038/s41379-019-0398-2

- RET gene rearrangements occur in a subset of pancreatic acinar cell carcinomas

Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc 2020 04;33(4):657-664

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31558784

Pancreatic acinar cell carcinoma is relatively rare (1 to 2% of pancreatic malignancies) but may be underrecognized. In contrast to pancreatic ductal adenocarcinoma, most acinar cell carcinomas lack mutations in KRAS, DPC, CDKN2A or TP53, but appear to have a high incidence of gene rearrangements, with up to 20% reported to be driven by BRAF fusions. With the development of a new class of RET-specific tyrosine kinase inhibitors, which appear to have particularly strong activity against RET gene rearranged tumours, there is now considerable interest in identifying RET gene rearrangements across a wide range of cancers. RET rearrangements have been reported to occur at a very low incidence (<1%) in all pancreatic

carcinomas. We postulated that given its unique molecular profile, RET gene rearrangements may be common in acinar cell carcinomas. We performed fluorescent in-situ hybridization (FISH) studies on a cohort of 40 acinar cell spectrum tumours comprising 36 pure acinar cell carcinomas, three pancreatoblastomas and one mixed acinar-pancreatic neuroendocrine tumour. RET gene rearrangements were identified in 3 (7.5%) cases and BRAF gene rearrangements in 5 (12.5%). All gene rearranged tumours were pure acinar cell carcinomas. Our findings indicate that amongst all pancreatic carcinomas, acinar carcinomas are highly enriched for potentially actionable gene rearrangements in RET or BRAF. FISH testing is inexpensive and readily available in the routine clinical setting and may have a role in the assessment of all acinar cell carcinomas-at this stage to recruit patients for clinical trials of new targeted therapies, but perhaps in the near future as part of routine care.

doi: https://doi.org/10.1038/s41379-019-0373-y

- Elucidating the roles of ASPM isoforms reveals a novel prognostic marker for pancreatic cancer

The Journal of pathology 2020 Feb;250(2):123-125

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31595972

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest cancers worldwide. Late diagnosis, desmoplastic tissue and intrinsic resistance to therapy are among the main reasons for its aggressive phenotype. In addition, it is now appreciated that cancer stem cells - a rare subpopulation of tumor cells highly resistant to therapy - are crucial players in PDAC initiation, progression and resistance to therapy. In a recent article in The Journal of Pathology, Hsu et al elucidated the specific roles of abnormal spindle-like, microcephaly-associated protein (ASPM) isoforms in PDAC. The authors reported that ASPM isoform I (ASPM-iI) is mainly expressed in the cytoplasm of PDAC cells. Its expression is associated with the Wnt signaling pathway, which promotes stemness and maintains the cancer stem cell niche. Clinically, expression of ASPM-iI correlates with poor survival in PDAC patients. Thus, this study revealed a novel prognostic marker as well as a potential therapeutic target for PDAC.

doi: https://doi.org/10.1002/path.5355

- Sclerosing epithelioid mesenchymal neoplasm of the pancreas - a proposed new entity

Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc 2020 03;33(3):456-467

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31383964

We have encountered pancreatic tumors with unique histologic features, which do not conform to any of the known tumors of the pancreas or other anatomical sites. We aimed to define their clinicopathologic features and whether they are characterized by recurrent molecular signatures. Eight cases were identified; studied histologically and by immunohistochemistry. Selected cases were also subjected to whole-exome sequencing (WES; n = 4), RNA-sequencing (n = 6), Archer FusionPlex assay (n = 5), methylation profiling using the Illumina MethylationEPIC (850k) array platform (n = 6), and TERT promoter sequencing (n = 5). Six neoplasms occurred in females. The mean age was 43 years (range: 26-75). Five occurred in the head/neck of the pancreas. All patients were treated surgically; none received neoadjuvant/adjuvant therapy. All patients are free of disease after 53 months of median follow-up (range: 8-94). The tumors were well-circumscribed, and the median size was 1.8 cm (range: 1.3-5.8). Microscopically, the unencapsulated tumors had a geographic pattern of epithelioid cell nests alternating with spindle cell fascicles. Some areas showed dense fibrosis, in which enmeshed tumor cells imparted a slit-like pattern. The predominant epithelioid cells had

scant cytoplasm and round-oval nuclei with open chromatin. The spindle cells displayed irregular, hyperchromatic nuclei. Mitoses were rare. No lymph node metastases were identified. All tumors were positive for vimentin, CD99 and cytokeratin (patchy), while negative for markers of solid pseudopapillary neoplasm, neuroendocrine, acinar, myogenic/rhabdoid, vascular, melanocytic, or lymphoid differentiation, gastrointestinal stromal tumor as well as MUC4. Whole-exome sequencing revealed no recurrent somatic mutations or amplifications/homozygous deletions in any known oncogenes or tumor suppressor genes. RNA-sequencing and the Archer FusionPlex assay did not detect any recurrent likely pathogenic gene fusions. Single sample gene set enrichment analysis revealed that these tumors display a likely mesenchymal transcriptomic program. Unsupervised analysis (t-SNE) of their methylation profiles against a set of different mesenchymal neoplasms demonstrated a distinct methylation pattern. Here, we describe pancreatic neoplasms with unique morphologic/immunophenotypic features and a distinct methylation pattern, along with a lack of abnormalities in any of key genetic drivers, supporting that these neoplasms represent a novel entity with an indolent clinical course. Given their mesenchymal transcriptomic features, we propose the designation of "sclerosing epithelioid mesenchymal neoplasm" of the pancreas.

doi: https://doi.org/10.1038/s41379-019-0334-5

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1.2 Gallbladder

- Long-term outcomes of surgical resection for T1b gallbladder cancer: an institutional evaluation

BMC cancer 2020 Jan;20(1):20

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31907021

BACKGROUND: There is no comprehensive agreement concerning the overall performance of radical resection for T1b gallbladder cancer (GBC). This research focused on addressing whether T1b GBC may spread loco-regionally and whether radical resection is necessary. METHODS: A retrospective analysis was conducted of 1032 patients with GBC who underwent surgical resection at our centre and its affiliated institutions between January 1982 and December 2018. A total of 47 patients with T1b GBC, 29 (62%) of whom underwent simple cholecystectomy and 18 (38%) of whom underwent radical resection with regional lymph node dissection, were enrolled in the study. RESULTS: GBC was diagnosed pre-operatively in 16 patients (34%), whereas 31 patients (66%) had incidental GBC. There was no blood venous or perineural invasion in any patient on histology evaluation, except for lymphatic vessel invasion in a single patient. There were no metastases in any analysed lymph nodes. The open surgical approach was more prevalent among the 18 patients who underwent radical resection (open in all 18 patients) than among the 29 patients who underwent simple cholecystectomy (open in 21; laparoscopic in 8) ($P = 0.017$). The cumulative 10- and 20-year overall survival rates were 65 and 25%, respectively. The outcome following simple cholecystectomy (10-year overall survival rate of 66%) was akin to that following radical resection (64%, $P = 0.618$). The cumulative 10- and 20-year disease-specific survival rates were 93 and 93%, respectively. The outcome following simple cholecystectomy (10-year disease-specific survival rate of 100%) was equivalent to that following radical resection (that of 86%, $P = 0.151$). While age (> 70 years, hazard ratio 5.285, $P = 0.003$) and gender (female, hazard ratio 0.272, $P = 0.007$) had a strong effect on patient overall survival, surgical procedure (simple cholecystectomy vs. radical resection) and surgical approach (open vs. laparoscopic) did not. CONCLUSIONS: Most T1b GBCs represent local disease. As pre-operative diagnosis, including tumour penetration of T1b GBC, is difficult, the decision of radical resection is justified. Additional radical resection is not required following simple cholecystectomy provided that the penetration depth is restricted towards the muscular layer and that surgical margins are uninvolved.

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- TRAIL receptors are differentially regulated and clinically significant in gallbladder cancer

Pathology 2020 Apr;52(3):348-358

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=32111400

Deregulation of the receptors of TNF-related apoptosis inducing ligand (TRAIL) has been reported in various cancers. In an effort to define the role of these receptors we profiled their expression in gallbladder cancer (GBC) and explored their clinical significance. Expression of TRAIL receptors' mRNA in GBC was analysed through reverse transcriptase polymerase chain reaction (RT-PCR), and protein through western blotting, immunohistochemistry and enzyme-linked immunosorbent assay (ELISA). mRNA data show frequent higher expression of TRAIL receptors in GBC samples. Death receptors DR4 and DR5 showed significant negative correlation with tumour stage, T stage and tumour grade; DcR1 transcript showed positive correlation with tumour stage, N stage, M stage and tumour grade. Similarly, IHC showed frequent positive staining for DR4, DR5 and DcR1in GBC samples. Cytoplasmic and nuclear DR4 protein showed negative correlation with T stage and tumour grade, whereas cytoplasmic DcR1 protein showed positive correlation with tumour stage and N stage. Nuclear DcR1 showed positive correlation with N stage. ELISA results showed significantly

higher expression of secretory DcR1 in GBC patients. Kaplan-Meier analysis demonstrated significantly decreased mean survival of patients with positive staining of cytoplasmic DcR1. High level of death receptors identified the patients with early gallbladder cancer, whereas high DcR1 expression served as a prognostic factor for poor outcome.

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- Non-neoplastic Polyps of the Gallbladder: A Clinicopathologic Analysis of 447 Cases

The American journal of surgical pathology 2020 Apr;44(4):467-476

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31725469

There is no systematic histopathologic analysis of non-neoplastic polyps in the gallbladder. In this study, in addition to a computer search for cases designated as "polyp," a systematic review of 2533 consecutive routinely sampled archival and 203 totally submitted prospective cholecystectomies were analyzed for >2 mm polyps (cut-off was based on radiologic sensitivity). A total of 447 non-neoplastic polyps were identified. The frequency was 3% in archival cases and 5% in totally submitted cases. Only 21 (5%) were 1 cm. The average age was 52 years, and the female to male ratio was 3.1. Two distinct categories were delineated: (1) injury-related polyps (n=273): (a) Fibro(myo)glandular polyps (n=214) were small (mean=0.4 cm), broad-based, often multiple (45%), almost always (98%) gallstone-associated, and were composed of a mixture of (myo)fibroblastic tissue/lobular glandular units with chronic cholecystitis. Dysplasia seen in 9% seemed to be secondary involvement. (b) Metaplastic pyloric glands forming polypoid collections (n=42). (c) Inflammatory-type polyps associated with acute/subacute injury (11 granulation tissue, 3 xanthogranulomatous, 3 lymphoid). (2) Cholesterol polyps (n=174) occurred in uninjured gallbladders, revealing a very thin stalk, edematous cores devoid of glands but with cholesterol-laden macrophages in 85%, and cholesterolosis in the uninvolved mucosa in 60%. Focal low-grade dysplasia was seen in 3%, always confined to the polyp, unaccompanied by carcinoma. In conclusion, non-neoplastic polyps are seen in 3% of cholecystectomies and are often small. Injury-related fibromyoglandular polyps are the most common. Cholesterol polyps have distinctive cauliflower architecture, often in a background of uninjured gallbladders with cholesterolosis and may lack the cholesterol-laden macrophages in the polyp itself. Although dysplastic changes can involve non-neoplastic polyps, they do not seem to be the cause of invasive carcinoma by themselves.

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- Clinicopathologic and Prognostic Significance of Gallbladder and Cystic Duct Invasion in Distal Bile Duct Carcinoma

Archives of pathology & laboratory medicine 2019 Nov;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31755778

CONTEXT.—: The roles of the gallbladder and cystic duct (CD) invasions in distal bile duct carcinoma (DBDC) have not been well elucidated. OBJECTIVE.—: To define the characteristics and prognostic significance of gallbladder or CD invasions in patients with DBDC. DESIGN.—: Organ invasion patterns with clinicopathologic features were assessed in 258 resected DBDCs. RESULTS.—: CD invasions (N = 31) were associated with frequent concomitant pancreatic and/or duodenal invasions (23 of 31, 74%) and showed stromal infiltration (16 of 31, 52%) and intraductal cancerization (15 of 31, 48%) patterns. In only 2 cases, invasions with intraductal cancerization were observed in the gallbladder neck. Conversely, all pancreatic (N = 175) and duodenal (83) invasions developed through stromal infiltration. CD invasions were associated with larger tumor size (P = .001), bile duct margin positivity (P = .001), perineural invasions (P = .04), and higher N categories (P = .007). Patients with pancreatic or duodenal invasions had significantly lower survival rates than those without pancreatic (median, 31.0 versus 93.9 months) or duodenal (27.5

versus 56.8 months, P < .001, both) invasions. However, those with gallbladder or CD invasions did not have different survival times (P = .13). Patients with concomitant gallbladder/CD and pancreatic/duodenal invasions demonstrated significantly lower survival rates than those without organ invasions (P < .001). CONCLUSIONS.—: Gallbladder invasions were rare in DBDCs as neck invasions with intraductal cancerization. CD invasions occurred by stromal infiltrations and intraductal cancerization, whereas all pancreatic and duodenal invasions had stromal infiltration patterns. Gallbladder and/or CD invasions did not affect survival rates of patients with DBDC, while pancreatic and duodenal invasions affected survival rates. Therefore, these differences in survival rates may originate from the different invasive patterns of DBDCs.

doi: https://doi.org/10.5858/arpa.2019-0218-OA

- Ultrastructural Characteristics of Gallbladder Epithelial Inclusions Mimicking Cystoisospora

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PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31600399

OBJECTIVES: There is recently reported increased prevalence of Isospora organisms in cholecystectomy specimens from immunocompetent patients, especially in acalculous cholecystectomies. We performed an ultrastructural and molecular evaluation of these specimens. METHODS: From 28 gallbladders with intraepithelial inclusions, two specimens with diffuse involvement of the gallbladder epithelium were analyzed by electron microscopy. Polymerase chain reaction was performed on five samples for the ITS2 region of C belli and eukaryotic 18S region. The 18S products were sequenced by next-generation sequencing. RESULTS: Electron microscopic analysis showed cytoplasmic condensations leading to vacuole formation. In contrast with true C belli, there were no identifiable organelles or organization. None of these cases showed amplified products other than human on molecular analysis. CONCLUSIONS: Electron microscopic analysis demonstrates that the inclusions are condensed cytoplasmic material and not true organisms.

doi: https://doi.org/10.1093/ajcp/aqz137

- Gallbladder and extrahepatic bile duct cancers in the Americas: Incidence and mortality patterns and trends

International journal of cancer 2020 Jan;():

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Trends in gallbladder cancer incidence and mortality in populations across the Americas can provide insight into shifting epidemiologic patterns and the current and potential impact of preventative and curative programs. Estimates of gallbladder and extrahepatic bile duct cancer incidence and mortality for the year 2018 were extracted from International Agency for Research on Cancer (IARC) GLOBOCAN database for 185 countries. Recorded registry-based incidence from 13 countries was extracted from IARCs Cancer Incidence in Five Continents series and corresponding national deaths from the WHO mortality database. Among females, the highest estimated incidence for gallbladder and extrahepatic bile duct cancer in the Americas were found in Bolivia (21.0 per 100,000), Chile (11.7) and Peru (6.0). In the US, the highest incidence rates were observed among Hispanics (1.8). In the Chilean population, gallbladder cancer rates declined in both females and males between 1998 and 2012. Rates dropped slightly in Canada, Costa Rica, US Whites and Hispanics in Los Angeles. Gallbladder cancer mortality rates also decreased across the studied countries, although rising trends were observed in Colombia and Canada after 2010. Countries within Southern and Central America tended to have a higher proportion of unspecified biliary tract cancers. In public health terms, the decline in gallbladder cancer incidence and mortality rates is encouraging. However, the slight increase in mortality rates during recent years in Colombia and Canada warrant further attention. Higher

proportions of unspecified biliary tract cancers (with correspondingly higher mortality rates) suggest more rigorous pathology procedures may be needed after surgery.

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1.3 Bile Ducts

- Germline alterations in patients with biliary tract cancers: A spectrum of significant and previously underappreciated findings

Cancer 2020 Jan;126(9):1995-2002

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=32012241

BACKGROUND: With limited information on germline mutations in biliary tract cancers, this study performed somatic and germline testing for patients at Memorial Sloan Kettering Cancer Center with known biliary tract carcinoma with the aim of determining the frequency and range of pathogenic germline alterations (PGAs). METHODS: Patients with biliary tract carcinoma were consented for somatic tumor and matched blood testing of up to 468 genes via the Memorial Sloan Kettering Cancer Center Integrated Mutation Profiling of Actionable Cancer Targets next-generation sequencing platform. A germline variant analysis was performed on a panel of up to 88 genes associated with an increased predisposition for cancer. Demographic and diagnostic details were collected. RESULTS: Germline mutations were tested in 131 patients. Intrahepatic cholangiocarcinoma was the most common cancer (63.4%), and it was followed by gallbladder adenocarcinoma (16.8%), extrahepatic cholangiocarcinoma (16%), and otherwise unspecified biliary tract cancer (3.8%). Known and likely PGAs were present in 21 patients (16.0%), with 9.9% harboring a PGA in a high/moderate-penetrance cancer predisposition gene. Among high-penetrance cancer susceptibility genes, PGAs were most commonly observed in BRCA1 and BRCA2 (33.3%), which made up 5.3% of the entire cohort, and they were followed by PALB2, BAP1, and PMS2. Mutations in ATM, MITF, and NBN, moderate-penetrance cancer susceptibility genes, were identified in 1 patient each. There was no observed difference in the types of mutations among the subtypes of biliary tract cancer. CONCLUSIONS: The frequency of PGAs found was comparable to existing data on the prevalence of germline mutations in other solid tumor types with matched tumor analysis. This provides support for the role of the BRCA1/2, ATM, and BAP1 genes in biliary tract cancer susceptibility.

doi: https://doi.org/10.1002/cncr.32740

- DNA Flow Cytometric Analysis of Paraffin-Embedded Tissue for the Diagnosis of Malignancy in Bile Duct Biopsies

Human pathology 2020 Apr;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=32272125

Differentiation of reactive versus neoplastic epithelial changes can be challenging in bile duct biopsies. The samples are often scant, distorted, and mixed with significant inflammation, ulceration, and/or debris. Histological confirmation of malignancy is often required before the initiation of surgical therapy, while an erroneous diagnosis of malignancy can lead to unnecessary clinical management. Aneuploidy assessment by DNA flow cytometry was performed on formalin-fixed paraffin-embedded (FFPE) tissue from 63 bile duct biopsies: 10 with a malignant diagnosis (7 adenocarcinoma and 3 at least high-grade dysplasia [HGD]); 3 with an "atypical" diagnosis showing rare atypical glands/cells, concerning but not definite for malignancy; 28 likely "reactive" biopsies with acute/chronic inflammation, ulceration, and/or mild nuclear atypia; and 22 additional benign biopsies without significant inflammation, ulceration, or nuclear atypia. Aneuploidy was detected in 7 (70%) of the 10 biopsies with definite neoplasia (5 of 7 adenocarcinoma and 2 of 3 at least HGD), all 3 (100%) "atypical" biopsies, and none of the 50 benign biopsies. All 3 "atypical" cases with aneuploidy were subsequently found to have adenocarcinoma (n = 2) or HGD (n = 1). Among the 2 cases of at least HGD with aneuploidy, 1 case developed adenocarcinoma, but no follow-up information was available in the other case. The remaining 1 case of at least HGD, despite having normal DNA content,

was found to have adenocarcinoma on follow-up. None of the 50 benign cases (further supported by normal DNA content) developed adenocarcinoma within a mean follow-up time of 37 months (range: 0-282 months). The estimated sensitivity of aneuploidy as a diagnostic marker of malignancy (adenocarcinoma and HGD) was 70% with the specificity of 100%, positive predictive value of 100%, and negative predictive value of 94%. In conclusion, DNA flow cytometry using FFPE tissue from bile duct biopsies demonstrates a high rate of aneuploidy (70%) in malignant cases, and normal DNA content in all benign biopsies. Although the sample size is small, the results indicate that this assay can be potentially useful in challenging "atypical" cases, where morphological evaluation is limited by scarcity of atypical glands/cells, inflammation, and/or ulceration.

doi: https://doi.org/10.1016/j.humpath.2020.04.002

- Biliary intraductal tubule-forming neoplasm: A whole exome sequencing study of MUC5AC-positive and -negative cases

Histopathology 2020 Mar;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=32181510

AIMS: Biliary intraductal tubular neoplasms that are non-mucinous and negative for MUC5AC are called intraductal tubulopapillary neoplasm (ITPNs). Intraductal tubular neoplasms with mucinous cytoplasm and MUC5AC positivity also occur, and their nature remains unclear although some pathologists may classify these as "IPNBs of gastric type". This study aimed to elucidate genetic features of biliary intraductal tubular neoplasms. METHODS: Six resected cases of biliary intraductal neoplasm with >70% tubular configuration were characterized by the clinicopathological examination and whole exome sequencing, and obtained findings were compared between MUC5AC-positive (n=2) and -negative cases (n=4). RESULTS: The intraductal tumours consisted of the pancreatobiliary-type epithelium with high-grade dysplasia arranged in back-to-back tubules. Both two MUC5AC-negative cases were non-invasive neoplasms developed in the liver, whereas all MUC5AC-positive cases had invasive carcinoma and were present in the intrahepatic (n=2), perihilar (n=1), and distal bile ducts (n=1). In an exome-sequencing study, MUC5AC-negative cases harboured mutations in CTNNB1, SF3B1, BAP1, and BRCA1 (one case each). KRAS mutations were observed in 3/4 MUC5AC-positive cases (75%) but none of MUC5AC-negative neoplasms. Compared to published data, known driver genes of other intraductal neoplasms of the pancreatobiliary systems (e.g., APC, CTNNB1, STK11, GNAS, and PIK3CA) were wild-type in all but one MUC5AC-negative case with CTNNB1 mutation. Chromatin modifiers (ARID1A, BAP1, and KMT2C) were also altered in MUC5AC-positive cases, similar to usual cholangiocarcinomas. CONCLUSIONS: This exome-sequencing study suggested that MUC5AC-negative biliary ITPNs are genetically distinct from pancreatic ITPNs and IPNBs. They may also biologically differ from MUC5AC-positive tubular neoplasms despite morphological resemblance.

doi: https://doi.org/10.1111/his.14103

- Validation of the T category for distal cholangiocarcinoma: Measuring the depth of invasion is complex but correlates with survival

Annals of diagnostic pathology 2020 Mar;46():151489

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=32169826

According to the current 8th edition of the American Joint Committee of Cancer (AJCC), the T category of distal cholangiocarcinomas is classified based on the depth of invasion (DOI) (T1, < 5 mm; T2, between 5 and 12 mm; T3, > 12 mm). In consideration of the discrepancies between previous studies about the prognostic significance, we aimed to validate the current AJCC T staging system of distal cholangiocarcinomas. DOI was measured using three different methods: DOI1, DOI2, and DOI3. DOI1 was defined and stratified

according to the AJCC 8th edition. DOI2 was measured as the distance from an imaginary curved line approximated along the distorted mucosal surface to the deepest invasive tumor cells. DOI3 was defined as the total tumor thickness. DOI2 and DOI3 were also divided into three categories using the same cut-off points as in the AJCC 8th edition. We compared these three DOI methods to the AJCC 7th edition as well. In contrast with the AJCC 7th edition, all three groups showed a correlation with patients' overall survival. Above all, the DOI2 group demonstrated the best significance in multivariate analysis. However, when the C indices were compared between these groups, differential significance proved to be negligible (DOI1 vs DOI2, $p = 0.915$; DOI2 vs DOI3, $p = 0.057$). Therefore, the measurement of DOI does not need to be rigorously and stringently performed. In conclusion, we showed that the current T classification system better correlates with the overall survival of patients with distal cholangiocarcinomas than the previous system.

doi: https://doi.org/10.1016/j.anndiagpath.2020.151489

- Global trends in intrahepatic and extrahepatic cholangiocarcinoma incidence from 1993 to 2012

Cancer 2020 Mar;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=32129902

BACKGROUND: Intrahepatic cholangiocarcinomas (ICCs) and extrahepatic cholangiocarcinomas (ECCs) are highly lethal bile duct tumors. Their incidence can be difficult to estimate because of changes in cancer coding over time. No studies to date have examined their global incidence and trends with high-quality topography- and histology-specific cancer registry data. Therefore, this study examined ICC and ECC incidence with the Cancer Incidence in Five Continents Plus database. METHODS: Regional and national cancer registry data were used to estimate age-standardized incidence rates (ASRs) per 100,000 person-years, 95% confidence intervals, and average annual percent changes (AAPCs) for ICC in 38 countries and for ECC in 33 countries from 1993 to 2012. ICC and ECC trends were tabulated and plotted by country. Rates versus birth cohort by age were plotted, and an age-period-cohort analysis was performed to assess age and cohort incidence rate ratios. RESULTS: The highest rates of ICC and ECC were in Asia, specifically South Korea (ASR for ICC, 2.80; ASR for ECC, 2.24), Thailand (ASR for ICC, 2.19; ASR for ECC, 0.71), and Japan (ASR for ICC, 0.95; ASR for ECC, 0.83). Between 1993 and 2012, incidence rates of both ICC and ECC increased in most countries. The largest ASR increases over the study period occurred in Latvia (AAPC, 20.1%) and China (AAPC, 11.1%) for ICC and in Thailand (AAPC, 8.8%) and Colombia (AAPC, 8.5%) for ECC. CONCLUSIONS: In the 20 years examined, ICC and ECC incidence increased in the majority of countries worldwide. ICC and ECC incidence may continue to increase because of metabolic and infectious etiologic factors. Efforts to further elucidate risk factors contributing to these increases in incidence are warranted.

doi: https://doi.org/10.1002/cncr.32803

- Intraductal papillary neoplasms of the bile duct consist of two distinct types specifically associated with clinicopathological features and molecular phenotypes

The Journal of pathology 2020 Feb;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=32100878

Intraductal papillary neoplasm of the bile duct (IPNB) is a grossly visible papillary biliary neoplasm with morphological variations and occasional invasion. Recently a new classification of IPNB into type 1 and type 2 was proposed in which the type 1 IPNBs consist of fine papillary neoplastic glands and the type 2 IPNBs consist of complex branching glands, seldom with foci of solid-tubular components. However, clinicopathological and molecular characteristics of these types of IPNBs are yet to be identified. We aimed

to uncover clinicopathological and molecular characteristics of the types of IPNBs. Thirty-six IPNBs were studied retrospectively. Clinicopathological features as well as molecular alterations of 31 genes were evaluated by means of targeted next-generation sequencing and immunohistochemical examination of expression of mucin and cancer-associated molecules. The 36 IPNBs were classified into 22 of type 1 and 14 of type 2. The type 1 IPNBs were associated with a non-invasive phenotype, intestinal and oncocytic subtypes, development in the intrahepatic bile duct, overt mucin production, and a relatively good prognosis. The type 2 IPNBs were associated with an invasive phenotype, the pancreatobiliary subtype, development within the extrahepatic bile duct, and worse prognosis compared with the type 1 IPNBs. In the molecular analysis, recurrent mutations were found in TP53 (34.3%), KRAS (31.4%), STK11 (25.7%), CTNNB1 (17.1%), APC (14.3%), SMAD4 (14.3%), GNAS (11.4%), PBRM1 (11.4%), ELF3 (8.6%), KMT2C (8.6%), NF1 (8.6%), PIK3CA (8.6%), ARID1A (5.7%), ARID2 (5.7%), BAP1 (5.7%), BRAF (5.7%), EPHA6 (5.7%), ERBB2 (5.7%), ERBB3 (5.7%), KMT2D (5.7%), and RNF43 (5.7%). Mutations in KRAS and GNAS were enriched in the type 1 IPNBs, whereas mutations in TP53, SMAD4, and KMT2C were enriched in the type 2 IPNBs. These results indicate that IPNBs consist of two distinct types of neoplasms specifically associated with clinicopathological features and molecular phenotypes.

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- DNAJB1-PRKACA fusions occur in oncocytic pancreatic and biliary neoplasms and are not specific for fibrolamellar hepatocellular carcinoma

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Recently discovered DNAJB1-PRKACA oncogenic fusions have been considered diagnostic for fibrolamellar hepatocellular carcinoma. In this study, we describe six pancreatobiliary neoplasms with PRKACA fusions, five of which harbor the DNAJB1-PRKACA fusion. All neoplasms were subjected to a hybridization capture-based next-generation sequencing assay (MSK-IMPACT), which enables the identification of sequence mutations, copy number alterations, and selected structural rearrangements involving 410 genes (n = 6) and/or to a custom targeted, RNA-based panel (MSK-Fusion) that utilizes Archer Anchored Multiplex PCR technology and next-generation sequencing to detect gene fusions in 62 genes (n = 2). Selected neoplasms also underwent FISH analysis, albumin mRNA in-situ hybridization, and arginase-1 immunohistochemical labeling (n = 3). Five neoplasms were pancreatic, and one arose in the intrahepatic bile ducts. All revealed at least focal oncocytic morphology: three cases were diagnosed as intraductal oncocytic papillary neoplasms, and three as intraductal papillary mucinous neoplasms with mixed oncocytic and pancreatobiliary or gastric features. Four cases had an invasive carcinoma component composed of oncocytic cells. Five cases revealed DNAJB1-PRKACA fusions and one revealed an ATP1B1-PRKACA fusion. None of the cases tested were positive for albumin or arginase-1. Our data prove that DNAJB1-PRKACA fusion is neither exclusive nor diagnostic for fibrolamellar hepatocellular carcinoma, and caution should be exercised in diagnosing liver tumors with DNAJB1-PRKACA fusions as fibrolamellar hepatocellular carcinoma, particularly if a pancreatic lesion is present. Moreover, considering DNAJB1-PRKACA fusions lead to upregulated protein kinase activity and that this upregulated protein kinase activity has a significant role in tumorigenesis of fibrolamellar hepatocellular carcinoma, protein kinase inhibition could have therapeutic potential in the treatment of these pancreatobiliary neoplasms as well, once a suitable drug is developed.

doi: https://doi.org/10.1038/s41379-019-0398-2

- Clinicopathologic and Prognostic Significance of Gallbladder and Cystic Duct Invasion in Distal Bile Duct Carcinoma

Archives of pathology & laboratory medicine 2019 Nov;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31755778

CONTEXT.—: The roles of the gallbladder and cystic duct (CD) invasions in distal bile duct carcinoma (DBDC) have not been well elucidated. OBJECTIVE.—: To define the characteristics and prognostic significance of gallbladder or CD invasions in patients with DBDC. DESIGN.—: Organ invasion patterns with clinicopathologic features were assessed in 258 resected DBDCs. RESULTS.—: CD invasions (N = 31) were associated with frequent concomitant pancreatic and/or duodenal invasions (23 of 31, 74%) and showed stromal infiltration (16 of 31, 52%) and intraductal cancerization (15 of 31, 48%) patterns. In only 2 cases, invasions with intraductal cancerization were observed in the gallbladder neck. Conversely, all pancreatic (N = 175) and duodenal (83) invasions developed through stromal infiltration. CD invasions were associated with larger tumor size (P = .001), bile duct margin positivity (P = .001), perineural invasions (P = .04), and higher N categories (P = .007). Patients with pancreatic or duodenal invasions had significantly lower survival rates than those without pancreatic (median, 31.0 versus 93.9 months) or duodenal (27.5 versus 56.8 months, P < .001, both) invasions. However, those with gallbladder or CD invasions did not have different survival times (P = .13). Patients with concomitant gallbladder/CD and pancreatic/duodenal invasions demonstrated significantly lower survival rates than those without organ invasions (P < .001). CONCLUSIONS.—: Gallbladder invasions were rare in DBDCs as neck invasions with intraductal cancerization. CD invasions occurred by stromal infiltrations and intraductal cancerization, whereas all pancreatic and duodenal invasions had stromal infiltration patterns. Gallbladder and/or CD invasions did not affect survival rates of patients with DBDC, while pancreatic and duodenal invasions affected survival rates. Therefore, these differences in survival rates may originate from the different invasive patterns of DBDCs.

doi: https://doi.org/10.5858/arpa.2019-0218-OA

- Recurrent Rearrangements in PRKACA and PRKACB in Intraductal Oncocytic Papillary Neoplasms of the Pancreas and Bile Duct

Gastroenterology 2020 02;158(3):573-582.e2

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31678302

BACKGROUND & AIMS: Intraductal oncocytic papillary neoplasms (IOPNs) of the pancreas and bile duct contain epithelial cells with numerous, large mitochondria and are cystic precursors to pancreatic ductal adenocarcinoma (PDAC) and cholangiocarcinoma (CCA), respectively. However, IOPNs do not have the genomic alterations found in other pancreatobiliary neoplasms. In fact, no recurrent genomic alterations have been described in IOPNs. PDACs without activating mutations in KRAS contain gene rearrangements, so we investigated whether IOPNs have recurrent fusions in genes. METHODS: We analyzed 20 resected pancreatic IOPNs and 3 resected biliary IOPNs using a broad RNA-based targeted sequencing panel to detect cancer-related fusion genes. Four invasive PDACs and 2 intrahepatic CCAs from the same patients as the IOPNs, were also available for analysis. Samples of pancreatic cyst fluid (n = 5, collected before surgery) and bile duct brushings (n = 2) were analyzed for translocations. For comparison, we analyzed pancreatobiliary lesions from 126 patients without IOPN (controls). RESULTS: All IOPNs evaluated were found to have recurring fusions of ATP1B1-PRKACB (n = 13), DNAJB1-PRKACA (n = 6), or ATP1B1-PRKACA (n = 4). These fusions also were found in corresponding invasive PDACs and intrahepatic CCAs, as well as in matched pancreatic cyst fluid and bile duct brushings. These gene rearrangements were absent from all 126 control pancreatobiliary lesions. CONCLUSIONS: We identified fusions in PRKACA and PRKACB genes in pancreatic and biliary IOPNs, as well as in PDACs and pancreatic cyst fluid and bile duct cells from the same patients. We did not identify these gene fusions in 126 control pancreatobiliary lesions. These fusions might be used to identify patients at risk for IOPNs and their associated invasive carcinomas.

doi: https://doi.org/10.1053/j.gastro.2019.10.028

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1.4 Ampulla

- Prognostic significance of stem cell/ epithelial-mesenchymal transition markers in periampullary/pancreatic cancers: FGFR1 is a promising prognostic marker

BMC cancer 2020 Mar;20(1):216

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=32171280

BACKGROUND: Periampullary cancers (PAC) including pancreatic, ampulla of Vater (AOV), and common bile duct (CBD) cancers are highly aggressive with a lack of useful prognostic markers beyond T stage. However, T staging can be biased due to the anatomic complexity of this region. Recently, several markers related to cancer stem cells and epithelial-mesenchymal transition (EMT) such as octamer transcription factor-4 (Oct4) and fibroblast growth factor receptor 1 (FGFR1) respectively, have been proposed as new promising markers in other solid cancers. The aim of this study was to assess the expression and prognostic significance of stem cell/EMT markers in PACs. METHODS: Formalin-fixed, paraffin-embedded tissues of surgically excised PACs from the laboratory archives from 1998 to 2014 were evaluated by immunohistochemical staining for stem cell/EMT markers using tissue microarray. The clinicopathologic parameters were documented and statistically analyzed with the immunohistochemical findings. Survival and recurrence data were collected and analyzed. RESULTS: A total of 126 PAC cases were evaluated. The average age was 63 years, with 76 male and 50 female patient samples. Age less than 74 years, AOV cancers, lower T & N stage, lower tumor size, no lymphatic, vascular, perineural invasion and histologic well differentiation, intestinal type, no fibrosis, severe inflammation were significantly associated with the better overall survival High expression levels of FGFR1 as well as CK20, CDX2, and VEGF were significantly related to better overall survival, while other stem cell markers were not related. Similar findings were observed for tumor recurrence using disease-free survival. CONCLUSIONS: In addition to other clinicopathologic parameters, severe fibrosis was related to frequent tumor recurrence, and high FGFR1 expression was associated with better overall survival. Histologic changes such as extensive fibrosis need to be investigated further in relation to EMT of PACs.

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