Pancreatobiliary Pathology Society Journal Watch

August September 2018

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Contents

PANCREATOBILIARY PATHOLOGY SOCIETY

The Current PBPath Journal Watch Articles

Wellcome to the PBPath Journal Watch!

This bi-monthly journal watch features exciting recently published pancreas and biliary pathology articles that will provide up to date medical knowledge in our field. These articles will be showcased in several convenient categories, including surgical pathology, molecular pathology and cytopathology among others. The articles in each category are in no particular order.

Previous months' issues may be found in our *archive*.

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

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

Surgical Pathology

Pancreas

Morphology, Diagnostics, IHC

- Comparison of Tumor Regression Grading of Residual Pancreatic Ductal Adenocarcinoma Following Neoadjuvant Chemotherapy Without Radiation: Would Fewer Tier-Stratification Be Favorable Toward Standardization?

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

To assess whether the College of American Pathologists (CAP) and the Evans grading systems for neoadjuvant chemotherapy without radiation-treated pancreatectomy specimens are prognostic, and if a 3-tier stratification scheme preserves data granularity. Conducted retrospective review of 32 patients with ordinary pancreatic ductal adenocarcinoma treated with neoadjuvant therapy without radiation followed by surgical resection. Final pathologic tumor category (AJCC eighth edition) was 46.9% ypT1, 34.4% ypT2, and 18.7% ypT3. Median follow-up time was 29.8 months, median disease-free survival (DFS) was 19.6 months, and median overall survival (OS) was 34.2 months. CAP score 1, 2, 3 were present in 5 (15.6%), 18 (56.3%), and 9 (28.1%) patients, respectively. Evans grade III, IIb, IIa, and I were present in 10 (31.2%), 8 (25.0%), 7 (21.9%), and 7 (21.9%) patients, respectively. OS (CAP: P=0.005; Evans: P=0.001) and DFS (CAP: P=0.003; Evans: P=0.04) were statistically significant for both CAP and Evans. Stratified CAP scores 1 and 2 versus CAP score 3 was statistically significant for both OS (P=0.002) and DFS (P=0.002). Stratified Evans grades I, IIa, and IIb versus Evans grade III was statistically significant for both OS (P=0.04) and DFS (P=0.02). CAP, Evans, and 3-tier stratification are prognostic of OS and DFS.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30211728

- Residual Tumor Index: A Prognostically Significant Pathologic Parameter in Neoadjuvant-treated Pancreatic Ductal Adenocarcinoma

The American journal of surgical pathology 2018 Nov;42(11):1480-1487

In the setting of neoadjuvant therapy (NAT) for pancreatic ductual adenocarcinoma (PDAC), accurate measurement of tumor size, and consequently, staging based on AJCC eighth edition, is difficult. Attempts to address the limitations of tumor size in the NAT setting have included correlation of residual tumor percent with survival. However, only cases with complete pathologic response or minimal residual disease have shown better prognosis compared with all other groups. To date, no studies have simultaneously evaluated the prognostic value of tumor size and tumor regression in the setting of PDAC status post NAT (NAT-PDAC). Our aim was to study the prognostic value of residual tumor index (RTI), a metric combining residual tumor percent and tumor bed size as an interaction term (% residual tumor×tumor bed size [cm]). In a cohort of 105 cases of NAT-PDAC, we show that RTI supersedes the prognostic value of AJCC eighth edition T staging via multivariate cox regression. At a binary cutoff of 0.35 for RTI, the hazard ratio for recurrence-free survival is 3.26 (95% confidence interval, 1.51-7.04), P<0.01. We further identified cutoffs of 0.2, 0.2 to 2 and >2 that stratified our cases into 3 groups via RTI, which were statistically significant in Kaplan-Meier curve analysis of recurrence-free survival (P<0.01) and overall survival (P<0.01). RTI represents a novel metric for combining the prognostic value of tumor size and residual tumor in NAT-PDAC.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30179901

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

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

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

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

- Tumor-Infiltrating Platelets Predict Postsurgical Survival in Patients with Pancreatic Ductal Adenocarcinoma

Annals of surgical oncology 2018 Aug;():

BACKGROUND: Platelets are believed to promote tumor growth and metastasis in several tumor types. The prognostic role of blood platelets in pancreatic ductal adenocarcinoma (PDAC) remains controversial, and the prognostic value of tumor-infiltrating platelets (TIPs) remains unknown. METHODS: A total of 303 patients who underwent curative pancreatectomy for PDAC were enrolled from two independent centers in China and divided into three cohorts. Paired preoperative blood samples and surgical specimens from all patients were analyzed. The correlations between patient outcomes and preoperative blood platelet counts and the presence of TIPs, respectively, were analyzed. TIPs were identified by immunohistochemical staining of CD42b. Prognostic accuracy was estimated by concordance index (C-index) and Akaike information criterion (AIC). RESULTS: TIPs, but not preoperative blood platelet counts, were associated with overall survival (OS; all $P < 0.001$) and recurrence-free survival (RFS; all $P < 0.001$) in the training, testing, and validation sets. Positive CD42b expression predicted poor postsurgical survival. Incorporation of TIPs improved the predictive accuracy of the 8th edition American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system for OS in each of the three cohorts (C-index: 0.7164, 0.7569, and 0.7050, respectively; AIC: 472, 386, and 1019, respectively). The new predictor system was validated by incorporating TIPs with the 7th edition AJCC TNM staging system (C-index: 0.7052, 0.7623, and 0.7157; AIC: 476, 386, and 1015). CONCLUSION: TIPs were an independent prognostic factor that could be incorporated into the AJCC TNM staging system to refine risk stratification and predict surgical outcomes of patients with PDAC.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30171511

- Ki67 and P53 in Relation to Disease Progression in Metastatic Pancreatic Cancer: a Single Institution Analysis

Pathology oncology research : POR 2018 Sep;():

We investigated the expression patterns of Ki67 and p53 in metastatic pancreatic adenocarcinomas and analyzed their relationship with disease progression-free survival (PFS) and overall survival (OS) in the overall study population and in patients treated with a gemcitabine-containing chemotherapy versus FOLFIRINOX chemotherapy. Patients with histologically confirmed stage IV adenocarcinoma of the pancreas treated at AUBMC were included after obtaining institutional review board approval (IRB ID: IM.ST.05). The ROC was plotted to identify the threshold Ki-67, p53 and CA19-9 value for disease progression, the identified value was further used in Kaplan Meier curves to compare PFS for both groups (gemcitabine versus FOLFIRINOX). A value of $p < 0.05$ was considered significant in all analyses. On univariate analysis, patients who had a Ki-67 $> 12.5\%$ or a p53 $> 15\%$ had significantly shorter PFS ($p = 0.034$ and $p = 0.016$, respectively). This effect was restricted to Gemcitabine or gemcitabine-combination treated patients. A decrease in CA19-9 levels 6-8 weeks after chemotherapy of >58% had significantly longer PFS ($p = 0.027$). On multivariate analysis after controlling for grade, age and P53, Ki-67 remained significant, for every one unit increase in Ki-67 the progression risk increases by 1.017 times. Our study highlights the negative impact of high P53 expression and Ki67 proliferation index on PFS in patients with metastatic pancreatic cancer.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30187215

- Overexpression of S100A4 protein may be associated with the development and progression of pancreatic cancer

Journal of cancer research and therapeutics 2018 ;14(Supplement):S159-S166

Aim: Accumulated evidence has suggested a relationship between S100A4 protein expression and the development and progression of pancreatic cancer (PC) while its role in diagnosis and prognosis of PC still keeps inconsistent. To obtain definitive associations between S100A4 and PC, a meta-analysis was conducted. Materials and Methods: The PubMed and Chinese National Knowledge Infrastructure databases were electronically searched to identify studies reporting an association between S100A4 protein and PC. Statistical analyses were undergone with the utilization of STATA version 12.0 software. Results: Nine clinical studies with a total of 545 tumor samples were included in the meta-analysis. Results revealed that increased S100A4 expression were associated with the tumor-node-metastasis stages of PC (III-IV vs. I-II: odds ratio [OR] =5.50, 95% confidence interval [95% CI] =3.13-9.67, $P < 0.001$). Also, compared with 1-2 histologic grade of PC samples, S100A4 protein was expressed more frequently in samples with 3-4 histologic grade (grades 1-2 vs. grades 3-4: OR = 2.57, 95% CI = 1.05-6.24, P = 0.038). Conclusion: This meta-analysis showed that overexpression of S100A4 seems to be associated with tumor progression and poor prognosis of PC patients.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29578167

- Prognostic stratification of resected pancreatic ductal adenocarcinoma: Past, present, and future

Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver 2018 Oct;50(10):979-990

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30205952

Pancreatic ductal adenocarcinoma (PDAC) is the digestive cancer with the poorest prognosis, with a 5-year overall survival rate of 7%. Complete surgical resection followed by adjuvant chemotherapy is the only treatment with curative intent. However, many patients with an apparently localized disease who

may undergo primary tumor resection already have micro-metastatic disease and will promptly develop metastases. Considering the significant rate of morbidity and mortality upon pancreatic surgery, the pre-operative identification of patients with an aggressive disease is therefore a major clinical issue. Although tumor size, differentiation, margins, and lymph node invasion are the main "classical" prognostic factors, they are not sufficient to fully predict early disease recurrence. In the last decade, multi-omics high-throughput analyses have provided a new insight into PDAC biology and have led to the description of multiple molecular subtypes, with a significant prognostic value for most of them, but that have not yet been transposed to routine clinical practice, mainly due to poor availability of tumor tissue material prior to surgical resection. In this review, we provide an overview of the current status of clinico-pathological and molecular biomarkers (tumor and blood) to predict early recurrence, and their implications for clinical practice and future research development.

- Pancreatic cancer: French clinical practice guidelines for diagnosis, treatment and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, ACHBT, AFC)

Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver 2018 Aug;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30219670

BACKGROUND: This document is a summary of the French intergroup guidelines regarding the management of pancreatic adenocarcinoma (PA), updated in July 2018. DESIGN: This collaborative work was produced under the auspices of all French medical and surgical societies involved in the management of PA. It is based on the previous guidelines, recent literature review and expert opinions. Recommendations were graded in three categories, according to the level of evidence. RESULTS: Over the last seven years, significant changes in PA management have been implemented in clinical practice. Imaging/staging: diffusion magnetic resonance imaging is useful before surgery to rule out small liver metastases. SURGERY: centralization of pancreatic surgery in expert centers is associated with a decreased postoperative mortality. Adjuvant chemotherapy: modified FOLFIRINOX in fit patients, or gemcitabine, or 5-FU, or gemcitabine plus capecitabine, to be discussed on a case-by-case basis. Locally advanced PA: no survival benefit of chemoradiotherapy. Metastatic PA: FOLFIRINOX and gemcitabine plus nab-paclitaxel combination are first-line standards in fit patients; second-line with 5FU/nal-IRI or 5FU/oxaliplatin combination after first-line gemcitabine. CONCLUSION: Guidelines for management of PA are continuously evolving and need to be regularly updated. This constant progress is made possible through clinical and translational research. However, as each individual case is particular, they cannot substitute to multidisciplinary tumor board discussion.

- Associations between autoimmune conditions and hepatobiliary cancer risk among elderly US adults

International journal of cancer 2018 Aug;():

Growing evidence suggests that people with autoimmune conditions may be at increased risk of hepatobiliary tumors. In the present study, we evaluated associations between autoimmune conditions and hepatobiliary cancers among adults aged 66 in the United States. We used Surveillance, Epidemiology, and End Results (SEER)-Medicare data (1992-2013) to conduct a population-based, case-control study. Cases (n=32,443) had primary hepatobiliary cancer. Controls (n=200,000) were randomly selected, cancer-free adults frequency-matched to cases by sex, age, and year of selection. Using multivariate logistic regression, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) for associations with 39 autoimmune conditions identified via Medicare claims. We also conducted separate analyses for diagnoses obtained via inpatient versus outpatient claims. Sixteen conditions were associated with at least one hepatobiliary cancer. The strongest risk estimates were for primary biliary cholangitis with hepatocellular carcinoma (OR:

31.33 [95% CI: 23.63-41.56]) and primary sclerosing cholangitis with intrahepatic cholangiocarcinoma (7.53 [5.73-10.57]), extrahepatic cholangiocarcinoma (5.59 [4.03-7.75]), gallbladder cancer (2.06 [1.27-3.33]), and ampulla of Vater cancer (6.29 [4.29-9.22]). Associations with hepatobiliary-related conditions as a group were observed across nearly all cancer sites (ORs ranging from 4.53 [95% CI: 3.30-6.21] for extrahepatic cholangiocarcinoma to 7.18 [5.94-8.67] for hepatocellular carcinoma). Restricting to autoimmune conditions diagnosed via inpatient claims, 6 conditions remained associated with at least one hepatobiliary cancer, and several risk estimates increased. In the outpatient restricted analysis, 12 conditions remained associated. Multiple autoimmune conditions are associated with hepatobiliary cancer risk in the US Medicare population, supporting a shared immuno-inflammatory etiology to these cancers.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30155920

- Comparative outcomes of adenosquamous carcinoma of the pancreas: An analysis of the National Cancer Database

Journal of surgical oncology 2018 Jul;118(1):21-30

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29878370

BACKGROUND: A paucity of data exists regarding the natural history and outcome measures of adenosquamous carcinoma of the pancreas (ASCP), a histology distinct from pancreatic adenocarcinoma (PDAC). The aim of this study is to characterize the clinicopathological features of ASCP in a large cohort of patients comparing outcome measures of surgically resected patients to PDAC. METHODS: We identified patients diagnosed with ASCP or PDAC from the National Cancer Database from 2004 to 2012. Patient demographics, tumor characteristics, treatment regimens, and overall survival were analyzed between the groups. RESULTS: We identified 207 073 patients: 205 328 (99%) in the PDAC group and 1745 (1%) in the ASCP group. ASCP tumors were larger, located more frequently in a body/tail location (36% vs 24%, $P < 0.001$), undifferentiated/anaplastic histology (41% vs 17%, $P < 0.001$), and early stage presentation, (39% vs 32%, $P < 0.001$). There was no significant difference in OS when comparing all patients with PDAC and ASCP (6.2 months and 5.7 months, $P = 0.601$). In surgical patients ASCP histology was associated with worse OS (14.8 months vs 20.5 months, $P < 0.001$) but had lower nodal involvement (55% vs 61%, $P < 0.001$). ASCP histology was independently associated with worse OS, after adjusting for tumor characteristics, treatment, and patient demographics. In patients with only resected ASCP histology, negative lymph node status, R0 surgical resection, and receipt of chemotherapy was independently associated with improved overall survival following surgical resection. CONCLUSION: Although patients with ASCP and PDAC tumors have similar survival when non-surgical and surgical patients are combined, ASCP is associated with worse survival in stage I/II resected patients.

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

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

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

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

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

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

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Staging

Pancreas TNM staging, Margins, Survival

- Proposal of a modified American Joint Committee on Cancer staging scheme for resectable pancreatic ductal adenocarcinoma with a lymph node ratio-based N classification: A retrospective cohort study

Medicine 2018 Aug;97(34):e12094

The recently launched 8th edition of the American Joint Committee on Cancer (AJCC) staging scheme for pancreatic ductal adenocarcinoma (PDAC) did not account for the impact of the total examined lymph node count on prognostic accuracy. In this population-based cohort study, we proposed a modified AJCC staging scheme by incorporating a lymph node ratio (LNR)-based N classification for patients with resectable PDAC.We analyzed 8615 patients with resectable PDAC from the Surveillance, Epidemiology, and End Results database between 2004 and 2013. The optimal cut-off points for LNR were identified by recursive partitioning, and an LNR-based N classification was designed accordingly.The LNR-based N classification could further stratify patients with the 8th AJCC N1 and N2 disease into subgroups with significantly different overall survival (P<.001 for both). By replacing the 8th AJCC N classification with the corresponding LNR-based N classification, we further proposed a modified AJCC staging scheme. The modified AJCC staging outperformed the 8th AJCC staging in terms of the discriminatory capacity measured by the concordance index and Akaike information criterion, and the prognostic homogeneity assessed by using the likelihood ratio chi-squared test and stratified survival analysis.Replacing the 8th AJCC N classification with the LNR-based N classification can improve the prognostic performance of the 8th AJCC staging scheme for PDAC.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30142869

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

Neoplasma 2018 ;65(4):637-643

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

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

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

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

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

- Multinational validation of the American Joint Committee on Cancer 8th edition pancreatic cancer staging system in a pancreas head cancer cohort

Journal of hepato-biliary-pancreatic sciences 2018 Sep;25(9):418-427

BACKGROUND: The aim of the present study was to compare the 7th and 8th editions of the American Joint Committee on Cancer (AJCC) staging system for pancreas head cancer and to validate the 8th edition using three multinational tertiary center data. METHODS: Data of 2,864 patients with pancreas head cancer were collected from Korea (571), Japan (824), and the USA (1,469). Survival analysis was performed to compare the 7th and 8th editions. Validation was performed by log-rank tests and test for trend repeated 1,000 times with random sets. RESULTS: In the 7th edition, 4.1%, 3.1%, 18.6%, 67.5%, 3.6%, and 3.1% were stage IA, IB, IIA, IIB, III, and IV. In the 8th edition, 8.8%, 13.9%, 3.1%, 38.2%, 32.9%, and 3.1% were stage IA, IB, IIA, IIB, III, and IV, respectively. The change in T category downstaged 459 patients from IIA to the new IA and IB. The new N2 category upstaged 856 patients from the former IIB to III. The 7th edition reversely stratified IA and IB. The 8th edition corrected this mis-stratification of the 7th edition, but lacked discriminatory power between IB and IIA (P = 0.271). Validation using the log-rank showed that the 8th edition provided better discrimination in 6.387 test sets among 10 tests. The test for trend validated the 8th edition to stratify stages in correct order more often (7.815/10). CONCLUSION: The 8th edition provides more even distribution with more powerful discrimination compared to the 7th edition.

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

- Clinical Implications of Extensive Lymph Node Metastases for Resected Pancreatic Cancer

Annals of surgical oncology 2018 Sep;():

BACKGROUND: Outcomes of patients with resected pancreatic ductal adenocarcinoma (PDA) and extensive lymph node metastases have not been fully characterized. METHODS: A total of 637 patients underwent resection for pancreatic ductal adenocarcinoma (PDA) between 2002 and 2014 at the Thomas Jefferson University. Positive lymph node count (LNC) and positive lymph node ratio (LNR) were analyzed as predictors of cancer-specific outcomes, with a focus on outcomes of patients with extensive lymph node burden. RESULTS: Resected patients with regional lymph node metastases had a median survival of 17.1 months (n = 425, 70%) compared with 25.5 months (n = 185, 30%) for patients without lymph node spread (N0) (hazard ratio [HR] = 1.9, $p < 0.001$). Overall survival decremented with increased lymph node spread, but plateaued for LNC 4 (HR 2.4 vs. N0, $p < 0.001$) and LNR 0.4 (HR 2.2, $p < 0.001$). Compared with historical cohorts with macroscopic metastatic disease, as opposed to microscopic, superior long-term survival was achieved in patients with extensive lymph node metastases (LNC 4); 24- and 36-month survivals were 25% (vs. 16%, $p < 0.001$) and 12% (vs. 6%, $p < 0.001$), respectively. Extensive lymph node burden was associated with increased baseline postoperative serum CA 19-9 ($p = 0.044$) and systemic recurrence ($p < 0.001$). CONCLUSIONS: The prognostic impact of extensive lymph node spread after resection for PDA plateaus above a specific threshold (LNC 4 or LNR 0.4), supporting the new 8th edition AJCC criteria for N2 disease. Clinically, lymph node spread above this threshold seems to correlate with occult systemic disease (elevated postoperative CA 19-9 and systemic pattern of failure).

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30225835

- The Prognostic Significance of Resection Margins After Pancreaticoduodenectomy

Annals of surgical oncology 2018 Sep;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30264255

- Proposal of a modified American Joint Committee on Cancer staging scheme for resectable pancreatic ductal adenocarcinoma with a lymph node ratio-based N classification: A retrospective cohort study

Medicine 2018 Aug;97(34):e12094

The recently launched 8th edition of the American Joint Committee on Cancer (AJCC) staging scheme for pancreatic ductal adenocarcinoma (PDAC) did not account for the impact of the total examined lymph node count on prognostic accuracy. In this population-based cohort study, we proposed a modified AJCC staging scheme by incorporating a lymph node ratio (LNR)-based N classification for patients with resectable PDAC.We analyzed 8615 patients with resectable PDAC from the Surveillance, Epidemiology, and End Results database between 2004 and 2013. The optimal cut-off points for LNR were identified by recursive partitioning, and an LNR-based N classification was designed accordingly.The LNR-based N classification could further stratify patients with the 8th AJCC N1 and N2 disease into subgroups with significantly different overall survival ($P<.001$ for both). By replacing the 8th AJCC N classification with the corresponding LNR-based N classification, we further proposed a modified AJCC staging scheme. The modified AJCC staging outperformed the 8th AJCC staging in terms of the discriminatory capacity measured by the concordance index and Akaike information criterion, and the prognostic homogeneity assessed by using the likelihood ratio chi-squared test and stratified survival analysis.Replacing the 8th AJCC N classification with the LNR-based N classification can improve the prognostic performance of the 8th AJCC staging scheme for PDAC.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30142869

- A Prognostic Nomogram for Disease-Specific Survival in Patients with Pancreatic Ductal Adenocarcinoma of the Head of the Pancreas Following Pancreaticoduodenectomy

Medical science monitor : international medical journal of experimental and clinical research 2018 Sep;24():6313-6321

BACKGROUND This study developed and validated a nomogram to predict patient prognosis for pancreatic ductal adenocarcinoma (PDAC) of the head of the pancreas following pancreaticoduodenectomy. MATERIAL AND METHODS Retrospective data were obtained from 4,383 patients with PDAC of the head of the pancreas who underwent pancreaticoduodenectomy between 2004-2013 from 11 Registries Research Data of the Surveillance, Epidemiology,and End Results (SEER) database. Cox proportional hazards model was used to identify independent risk factors. The predictive accuracy of the nomogram was determined by the concordance index (C-index) and calibration curve. The results were externally validated by comparison with data from 1,743 patients from 7 other Registries Research Data. RESULTS Of the 4,383 patients in the training dataset, median disease-specific survival (DSS) was 17.0 months (range, 1.0-131 months), and postoperative 1-year, 3-year, and 5-year DSS rates were 70.3%, 26.1%, and 16.8%, respectively. Multivariate analysis showed that patient sex, age, tumor grade, regional lymph nodes examined, positive regional lymph nodes, tumor size, extent of local invasion, and tumor metastases were independent risk factors for DSS. The C-index of the internal validation dataset for prediction of DSS was 0.64 (95% CI, 0.63-0.65), which was superior to the American Joint Committee on Cancer (AJCC) staging, 0.57 (95% CI, 0.56-0.58) ($P<0.001$). The 5-year DSS rates and median DSS time for patients in the low-risk group were significantly greater compared with high-risk group ($P<0.001$). CONCLUSIONS A validated prognostic disease-specific

nomogram for patient survival in PDAC of the head of the pancreas following pancreaticoduodenectomy was developed.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30198517

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

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

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

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

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

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

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

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

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

Journal of Cancer 2018 ;9(17):3156-3167

Background: The objective of this study was to estimate probabilities of overall survival (OS) and cancer-specific survival (CSS) in patients with pancreatic head adenocarcinoma after surgery. In addition, we attempted to build nomograms to predict prognosis of these patients. Methods: Patients diagnosed with surgically resected pancreatic head adenocarcinoma between 2004 and 2014 were selected for the study from the Surveillance, Epidemiology, and End Results (SEER) database. Nomograms were established for estimating 1-, 2- and 3-year OS and CSS based on Cox regression model and Fine and Grey's model. The performance of the nomogram was measured by concordance index (C-index) and the area under receiver operating characteristic (ROC) curve (AUC). Results: A total of 2374 patients were retrospectively collected from the SEER database. The discrimination of nomogram for OS prediction was superior to that of the Tumor-Node-Metastasis (TNM) 7th or 8th edition stage systems (C-index = 0.640, 95% CI, 0.618 - 0.662 vs 0.573, 95% CI, 0.554 - 0.593, $P < 0.001$; 0.640, 95% CI, 0.618 - 0.662 vs 0.596, 95% CI, 0.586 - 0.607, $P < 0.001$, respectively). The comparisons of values of AUC showed that the established nomograms displayed better discrimination power than TNM 7th or 8th stage systems for predicting both OS and CSS. Conclusions: The nomograms which could predict 1-, 2- and 3-year OS and CSS were established in this study. Our nomograms showed a relatively good performance and could be served as an effective tool for prognostic evaluation of patients with pancreatic head adenocarcinoma after surgery.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30210639

- **A Prognostic Nomogram for Disease-Specific Survival in Patients with Pancreatic Ductal Adenocarcinoma of the Head of the Pancreas Following Pancreaticoduodenectomy**

https://www.medscimonit.com/abstract/index/idArt/909649/act/2

- **A Refined Staging Model for Resectable Pancreatic Ductal Adenocarcinoma Incorporating Examined Lymph Nodes, Location of Tumor and Positive Lymph Nodes Ratio**

https://www.researchgate.net/profile/Chaobin_He/publication/327545050_A_Refined_Staging_Model_for_Resectable_Pancreatic_Ductal_Adenocarcinoma_Incorporating_Examined_Lymph_Nodes_Location_of_Tumor_and_Positive_Lymph_Nodes_Ratio/links/5b952e98299bf14739317b7e/A-Refined-Staging-Model-for
pdf

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

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

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

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

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

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

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

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

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

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

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

- **Lymph Node Ratio in Pancreatic Adenocarcinoma After Preoperative Chemotherapy vs. Preoperative Chemoradiation and Its Utility in Decisions About Postoperative Chemotherapy**

https://link.springer.com/article/10.1007/s11605-018-3953-0

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Macroscopy

Macroscopy / Grossing

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

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

OBJECTIVES: Processing of pancreatoduodenectomy specimens is not standardized; the clinical impact of pathologic surgical margins remains controversial. We used the color-coding method using tissue-marking dyes to evaluate margin status of resected specimens to assess its association with postoperative recurrence. METHODS: We developed a unified processing approach to assess pancreatoduodenectomy specimens. Five surgical margins of resected pancreatic specimens were marked with 5 colors. Microscopic resection margin distance (RMD) from margin closest to the tumor was evaluated for each surgical margin. Forty patients assessed using nonunified protocols, and 98 patients assessed using unified protocols were included. RESULTS: The frequency of tumors with RMD of 1 mm or less in posterior margin was significantly lower and that in portal vein/superior mesenteric vein margin was significantly higher in unified protocol group than in nonunified protocol group ($P < 0.001$). In unified protocol group, tumors with RMD of 1 mm or less correlated with locoregional recurrence ($P = 0.025$) and recurrence-free survival ($P = 0.030$). Multivariate analysis revealed that tumor size and lymph node metastasis were independent indicators for disease recurrence. CONCLUSIONS: Resection margin distance of 1 mm or less was a predictor for disease recurrence, particularly for locoregional recurrence. Early detection of small-sized tumors without lymph node metastasis is necessary for improved clinical outcomes in pancreas cancers.

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

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

Virchows Archiv : an international journal of pathology 2018 Sep;473(3):293-303

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

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

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

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Preneoplastic and Preinvasive Lesions

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

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

The American journal of surgical pathology 2018 Nov;42(11):1556-1561

Invasive pancreatic ductal adenocarcinoma (PDAC) can infiltrate back into and spread along preexisting pancreatic ducts and ductules in a process known as cancerization of ducts (COD). Histologically COD can mimic high-grade pancreatic intraepithelial neoplasia (HG-PanIN). We reviewed pancreatic resections from 100 patients with PDAC for the presence or absence of ducts with histologic features of COD. Features supporting COD included adjacent histologically similar invasive PDAC and an abrupt transition between markedly atypical intraductal epithelium and normal duct epithelium or circumferential involvement of a duct. As the TP53 and SMAD4 genes are frequently targeted in invasive PDAC but not HG-PanIN, paired PDAC and histologically suspected COD lesions were immunolabeled with antibodies to the p53 and Smad4 proteins. Suspected COD was identified on hematoxylin and eosin sections in 89 (89%) of the cases. Immunolabeling for p53 and Smad4 was performed in 68 (76%) of 89 cases. p53 was interpretable in 55 cases and all 55 (100%) cases showed concordant labeling between COD and invasive PDAC. There was matched aberrant p53 immunolabeling in 37 (67%) cases including overexpression in 30 (55%) cases and lack of expression in 7 (13%) cases. Smad4 immunolabeling was interpretable in 61 cases and 59 (97%) cases showed concordant labeling between COD and invasive PDAC. Matched loss of Smad4 was seen in 28 (46%) cases. The immunolabeling of invasive PDAC and COD for p53 and Smad4 supports the high prevalence of COD observed on hematoxylin and eosin and highlights the utility of p53 and Smad4 immunolabeling in differentiating COD and HG-PanIN.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30212393

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

Pathology international 2018 Apr;():

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

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

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

AIMS: This study aimed to identify the pathological features of high-grade PanIN that presents with imaging-detectable abnormalities. METHODS AND RESULTS: Ten cases of isolated, main-duct, high-grade PanIN as the primary clinical presentation were identified. All patients presented with stenosis of the main pancreatic duct, with two being associated with extensive upstream duct dilatation (>5 mm in diameter). Pancreatic juice cytology suggested adenocarcinoma in all seven cases examined. In resected specimens, high-grade PanIN was present chiefly in the main pancreatic duct, with longitudinal extension ranging between 3 and 40 mm in length (median = 18 mm). In four cases, in which hypoechoic or hypovascular masses

were observed on imaging, radiopathology correlations suggested that they represented parenchymal atrophy and subsequent fibrosis around affected ducts, but not invasive malignancy. On immunohistochemistry, the loss of p16 expression was found in five (50%), p53 overexpression in two (20%) and loss of SMAD4 expression in none (0%). KRAS mutations were detected in nine cases, with two dominant clones being found in three by ultrasensitive droplet digital polymerase chain reaction, suggesting the genetic heterogeneity of dysplastic cells composing individual lesions. Mutant GNAS was also observed in one case. CONCLUSIONS: Isolated high-grade PanIN may present with pancreatic duct stenosis. Therefore, intensive investigations including pancreatic juice cytology will be required for patients with unexplained pancreatic duct stenosis. The abnormal expression of p53 and SMAD4 is infrequent, while GNAS may be mutated in premalignant lesions mainly affecting the main pancreatic duct, similar to KRAS.

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

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

The Journal of pathology 2018 Aug;():

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- **Surgical overtreatment of pancreatic intraductal papillary mucinous neoplasms: Do the 2017 International Consensus Guidelines improve clinical decision making?**

https://www.surgjournal.com/article/S0039-6060(18)30459-8/fulltext

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- **Management of Intraductal Papillary Mucinous Neoplasms: Controversies in Guidelines and Future Perspectives**

https://link.springer.com/article/10.1007/s11938-018-0190-2

- **Clinical utility of the guidelines for intraductal papillary mucinous neoplasm: A case series from a medical center in central Taiwan**

https://onlinelibrary.wiley.com/doi/abs/10.1002/aid2.13095

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

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

OBJECTIVES: To gain insight into the natural history and carcinogenesis pathway of Pancreatic Intraepithelial Neoplasia (PanIN) lesions by building a calibrated simulation model of PanIN progression to pancreatic ductal adenocarcinoma (PDAC) METHODS: We revised a previously validated simulation model of solid PDAC, calibrating the model to fit data from the National Cancer Institute's Surveillance, Epidemiology, and End Results program and published literature on PanIN prevalence by age. We estimated the likelihood of progression from PanIN states (1, 2, and 3) to PDAC and the time between PanIN onset and PDAC (dwell time). We evaluated a hypothetical intervention to test for and treat PanIN 3 lesions to estimate the potential benefits from PanIN detection. RESULTS: We estimated the lifetime probability of progressing from PanIN 1 to PDAC to be 1.5% (men), 1.3% (women). Progression from PanIN 1 to PDAC took 33.6 years and 35.3 years, respectively, and from PanIN 3 to PDAC took 11.3 years and 12.3 years. A hypothetical test for PanIN 3 detection and treatment could provide a maximum, average life expectancy gain of 40 days. CONCLUSIONS: Our modeling analysis estimates PanINs have a relatively indolent course to PDAC, supporting the feasibility of potential future early detection strategies.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30143405

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

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

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

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

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

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

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

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

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

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

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Microenvironment

Tumor Stroma Interactions, Microenvironment, Inflammatory Response

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

Gastroenterology 2018 Aug;():

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

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

- Stromal biology and therapy in pancreatic cancer: ready for clinical translation?

Gut 2018 Sep;():

Pancreatic ductal adenocarcinoma (PDA) is notoriously aggressive and hard to treat. The tumour microenvironment (TME) in PDA is highly dynamic and has been found to promote tumour progression, metastasis niche formation and therapeutic resistance. Intensive research of recent years has revealed an incredible heterogeneity and complexity of the different components of the TME, including cancer-associated fibroblasts, immune cells, extracellular matrix components, tumour vessels and nerves. It has been hypothesised that paracrine interactions between neoplastic epithelial cells and TME compartments may result in either tumour-promoting or tumour-restraining consequences. A better preclinical understanding of such complex and dynamic network systems is required to develop more powerful treatment strategies for patients. Scientific activity and the number of compelling findings has virtually exploded during recent years. Here, we provide an update of the most recent findings in this area and discuss their translational and clinical implications for basic scientists and clinicians alike.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30177543

- **Epithelial-Mesenchymal Transition in Pancreatic Cancer: A Review**

BioMed research international 2017 ;2017():2646148

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

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

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

Pancreatology : official journal of the International Association of Pancreatology (IAP) … [et al.] 2018 Oct;18(7):705-716

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

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

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

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

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- **p21-activated kinase signalling in pancreatic cancer: New insights into tumour biology and immune modulation**

World journal of gastroenterology 2018 Sep;24(33):3709-3723

Pancreatic cancer is one of the most aggressive and lethal malignancies worldwide, with a very poor prognosis and a five-year survival rate less than 8%. This dismal outcome is largely due to delayed diagnosis, early distant dissemination and resistance to conventional chemo-therapies. Kras mutation is a well-defined hallmark of pancreatic cancer, with over 95% of cases harbouring Kras mutations that give rise to constitutively active forms of Kras. As important down-stream effectors of Kras, p21-activated kinases (PAKs) are involved in regulating cell proliferation, apoptosis, invasion/migration and chemo-resistance. Immunotherapy is now emerging as a promising treatment modality in the era of personalized anti-cancer therapeutics. In this review, basic knowledge of PAK structure and regulation is briefly summarised and the pivotal role of PAKs in Kras-driven pancreatic cancer is highlighted in terms of tumour biology and chemo-resistance. Finally, the involvement of PAKs in immune modulation in the tumour microenvironment is discussed and the potential advantages of targeting PAKs are explored.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30197477

- **The Gut Microbiome in Pancreatic Disease**

https://www.sciencedirect.com/science/article/pii/S1542356518308838

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SPN

Solid Pseudopapillary Neoplasm

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

Human pathology 2018 Aug;():

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

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

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

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

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

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

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

Current problems in cancer 2018 Jul;():

PURPOSE: Solid pseudopapillary neoplasm (SPN) is a rare, low-grade neoplasm with excellent prognosis. In this study, we evaluated clinicopathological characteristics of patients diagnosed with SPN retrospectively.

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

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

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Analogue Tumors

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

The American journal of surgical pathology 2018 Nov;42(11):1419-1428

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

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

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

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

BACKGROUND: Recently, we came with the theory of a possible relationship between a group of testicular and pancreatic tumors. We used one case of a pancreatic analogue solid pseudopapillary neoplasm of the testis composed partially of areas reminiscent of solid pseudopapillary neoplasm (SPN) of the pancreas and partially of structures identical to primary signet ring stromal tumor of the testis (PSRSTT) as a connecting link between these two entities. After demonstrating that PSRSTT and pancreatic analogue SPN of the testis share the same immunoprofile and genetic features characteristic for pancreatic SPN, we came to the conclusion that pancreatic analogue SPN of the testis and PSRSTT represent a morphological spectrum of a single entity and that both are related to the pancreatic SPN. DESIGN: The aim of this study is to present a series of 6 cases of testicular tumors, which lacked the signet ring cell component and were thus morphologically very similar to the SPN of the pancreas. The goal of this study is to compare the genetic background of these testicular tumors that are obviously related to the PSRSTT/pancreatic analogue SPN of the testis with the series of 8 pancreatic SPN. RESULTS: The mutational analysis revealed an oncogenic somatic mutation in the exon 3 of the CTNNB1 (-catenin) gene in all analyzable (5/6) testicular and all pancreatic (8/8) tumors. The immunoprofile (positivity with -catenin, CD10, vimentin, NSE, CD56, and negativity with inhibin, calretinin, chromogranin) was identical in all testicular and pancreatic tumors. CONCLUSION: This study expanded the morphological spectrum of the PSRSTT/pancreatic analogue SPN

of the testis by adding 6 cases without the signet ring cell component. Considering the obvious analogy of PSRSTT/pancreatic analogue SPN of the testis/SPN of the testis and their relationship to the pancreatic SPN we propose the collective term "solid pseudopapillary neoplasm of the testis" for these tumors. The mutational profile of the SPN of the testis and pancreas was the same in both groups of tumors which we consider as a final proof that SPN of the testis is identical to the SPN of the pancreas.

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

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

Human pathology 2018 Aug;():

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

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

Human pathology 2018 Aug;():

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

- Systems Oncology: Bridging Pancreatic and Castrate Resistant Prostate Cancer

Pathology oncology research : POR 2018 Sep;():

Large investments by pharmaceutical companies in the development of new antineoplastic drugs have not been resulting in adequate advances of new therapies. Despite the introduction of new methods, technologies, translational medicine and bioinformatics, the usage of collected knowledge is unsatisfactory. In this paper, using examples of pancreatic ductal adenocarcinoma (PaC) and castrate-resistant prostate cancer (CRPC), we proposed a concept showing that, in order to improve applicability of current knowledge in oncology, the re-clustering of clinical and scientific data is crucial. Such an approach, based on systems oncology, would include bridging of data on biomarkers and pathways between different cancer types. Proposed concept would introduce a new matrix, which enables combining of already approved therapies between cancer types. Paper provides a (a) detailed analysis of similarities in mechanisms of etiology and progression between PaC and CRPC, (b) diabetes as common hallmark of both cancer types and (c) knowledge gaps and directions of future investigations. Proposed horizontal and vertical matrix in cancer profiling has potency to improve current antineoplastic therapy efficacy. Systems biology map using Systems Biology Graphical Notation Language is used for summarizing complex interactions and similarities of mechanisms in biology of PaC and CRPC.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30220022

- Primordial germ cells as a potential shared cell of origin for mucinous cystic neoplasms of the pancreas and mucinous ovarian tumors

The Journal of pathology 2018 Sep;():

Mucinous ovarian tumors (MOTs) morphologically and epidemiologically resemble mucinous cystic neoplasms (MCNs) of the pancreas, sharing a similar stroma and both occurring disproportionately among young females. Additionally, MOTs and MCNs share similar clinical characteristics and immunohistochemical

phenotypes. Exome sequencing has revealed frequent recurrent mutations in KRAS and RNF43 in both MOTs and MCNs. The cell of origin for these tumors remains unclear, but MOTs sometimes arise in the context of mature cystic teratomas and other primordial germ cell (PGC) tumors. We undertook the present study to investigate whether non-teratoma-associated MOTs and MCNs share a common cell of origin. Comparisons of the gene expression profiles of MOTs [including both the mucinous borderline ovarian tumors (MBOTs) and invasive mucinous ovarian carcinomas (MOCs)], high-grade serous ovarian carcinomas, ovarian surface epithelium, Fallopian tube epithelium, normal pancreatic tissue, pancreatic duct adenocarcinomas, MCNs, and single-cell RNA-sequencing of PGCs revealed that both MOTs and MCNs are more closely related to PGCs than to either eutopic epithelial tumors or normal epithelia. We hypothesize that MCNs may arise from PGCs that stopped in the dorsal pancreas during their descent to the gonads during early human embryogenesis, while MOTs arise from PGCs in the ovary. Together, these data suggest a common pathway for the development of MCNs and MOTs, and suggest that these tumors may be more properly classified as germ cell tumor variants.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30229909

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SCA

- Serous Neoplasms of the Pancreas: A Comprehensive Review

Archives of pathology & laboratory medicine 2018 Sep;142(9):1134-1140

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30141993

Serous neoplasms are uncommon, usually cystic tumors that account for less than 1% of all primary pancreatic lesions. They consist predominantly of a monomorphic epithelial cell population with a glycogen-rich, clear cytoplasm, reminiscent of clear cell renal cell carcinoma, with which serous neoplasms share an association with underlying VHL loss-of-function mutations. Serous neoplasms have no metastatic potential. Accurate recognition of this entity, including its various architectural subtypes, is critical to appropriate prognostication and treatment. Immunohistochemical detection of inhibin and calponin expression, along with the absence of both estrogen and progesterone receptors and nuclear -catenin, can help to distinguish serous neoplasms from mimics. With the advent of minimally invasive and molecularly driven diagnostic techniques, the pathologist's role in the assessment and management of serous neoplasms has become increasingly complex and important. We provide an update on the histologic, immunohistochemical, and molecular features of pancreatic serous neoplasms for the practicing pathologist.

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

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

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

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

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- Is It Acute Pancreatitis or Recurrent Acute Pancreatitis Leading to Chronic Pancreatitis that Increases Pancreatic Cancer Risk?

Gastroenterology 2018 10;155(4):1279-1280

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30236555

- Spatial Distribution of Pancreatic Stones in Chronic Pancreatitis

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

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

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

- Vanishing Pancreas

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

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

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

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

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

- Pancreatic cystosis in patients with cystic fibrosis: A qualitative systematic review

Pancreatology : official journal of the International Association of Pancreatology (IAP) ... [et al.] 2018 Oct;18(7):700-704

BACKGROUND: Patients with cystic fibrosis (CF) and a CFTR gene mutation may present with a variety of pancreatic disorders. The presence of multiple macrocysts (>1 cm) replacing the entire pancreatic parenchyma is termed pancreatic cystosis. Lack of clear data makes clinical decision making challenging and controversial. The aim of this review is to perform a qualitative systematic analysis of the literature with intention to evaluate management plans. METHODS: Electronic databases MEDLINE, Embase, and Scopus were searched for relevant studies, and 19 studies describing patients with pancreatic cystosis were included and analyzed for clinical features and therapy offered. RESULTS: The data of 24 patients were collected from included studies. Eight cases (33%) had a documented CFTR gene mutation and 10 (42%) were symptomatic at presentation. Imaging modalities included ultrasound in 18 (75%), CT in 12 (50%), and MRI in 8 (33%) cases. An average size of the largest cyst was 5.4 cm. 6 (25%) patients were offered therapy that described surgical (3), endoscopic (1), or medical therapy (2). Surgeries offered included total pancreatectomy, partial pancreatic resection of uncertain extent, and complex cyst resection. Endoscopic treatment was cystogastrostomy. Novel medical treatment was utilized with Doxepin, Propantheline, and Clonidine, resulting in reduction in cyst size and overall clinical improvement. CONCLUSION: Patients with pancreatic cystosis should not be denied treatment when necessary. This literature review is the most comprehensive thus far of cystic fibrosis and pancreatic cystosis, and it did not provide identification of a definitive treatment plan or demonstrate contraindication to specific therapies.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30139657

- Does Autophagy Promote or Protect Against the Pathogenesis of Pancreatitis?

Gastroenterology 2018 10;155(4):1273-1274

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30222940

- Diagnosis, treatment and long-term outcome of autoimmune pancreatitis in Sweden

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

INTRODUCTION: Autoimmune pancreatitis (AIP) is a pancreatic inflammatory process characterized by a strong inflammatory cell infiltration and two histopathologically distinct subtypes: type 1 and type 2. Diagnosis is often challenging and requires a combination of clinical, laboratory and imaging data. AIP can mimic pancreatic tumours leading to unnecessary resections if not correctly diagnosed. Short- and long-term outcomes of AIP have been poorly investigated so far and no large series have been previously reported from Sweden. METHODS: A single-centre, retrospective, cohort study of patients with histologically confirmed or highly probable diagnosis of AIP according to ICDC criteria. Demographic, clinical and radiological characteristics, type of treatment and its outcomes were collected and analysed. RESULTS: Seventy-one patients with AIP (87% with type 1), were evaluated at Karolinska University Hospital between 2004 and 2018; 49% males, mean age 49 years (range 44-53). Among them, 28% were histologically confirmed, 35% presented with jaundice, 22% with acute pancreatitis, 39% had non-specific symptoms such as weight loss or abdominal pain, 84% showed other organ involvement (OOI). Radiologically, 76% showed a focal pancreatic enlargement, 27% diffuse enlargement, 27% signs of acute pancreatitis and 10% of chronic pancreatitis. Overall, 58 patients (81%) underwent treatment with different medications: 46 (79%) cortisone, 7 (12%) azathioprine, 5 (8%) other immunosuppressive drugs. Twenty-six (36%) underwent biliary stenting and 12 (16%) were given surgery. In total, 47% of patients developed pancreatic exocrine insufficiency (PEI), of whom 76% had a severe form (faecal elastase-1 < 100 g/g) and 21% of patients developed diabetes mellitus (pancreatic endocrine insufficiency), of whom 73% required insulin. CONCLUSIONS: AIP is a challenging disease for diagnosis and treatment. Cortisone treatment is generally successful and provides clinical remission in the large majority of patients (>90%). In the further course of the disease, a considerable number of patients develop PEI and diabetes. Only one-quarter of patients exhibit on imaging the characteristic “sausage-like”

pancreas (diffuse enlargement), approximately three-quarters had a focal mass that could be misdiagnosed as pancreatic malignancy.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30236651

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Techniques & Research Methods

- A "Clearer" View of Pancreatic Pathology: A Review of Tissue Clearing and Advanced Microscopy Techniques

Advances in anatomic pathology 2018 Sep;():

Although pathologic lesions in the pancreas are 3-dimensional (3D) complex structures, we currently use thin 2D hematoxylin and eosin stained slides to study and diagnose pancreatic pathology. Two technologies, tissue clearing and advanced microscopy, have recently converged, and when used together they open the remarkable world of 3D anatomy and pathology to pathologists. Advances in tissue clearing and antibody penetration now make even dense fibrotic tissues amenable to clearing, and light sheet and confocal microscopies allow labeled cells deep within these cleared tissues to be visualized. Clearing techniques can be categorized as solvent-based or aqueous-based techniques, but both clearing methods consist of 4 fundamental steps, including pretreatment of specimens, permeabilization and/or removal of lipid, immunolabeling with antibody penetration, and clearing by refractive index matching. Specialized microscopes, including the light sheet microscope, the 2-photon microscope, and the confocal microscope, can then be used to visualize and evaluate the 3D histology. Both endocrine and exocrine pancreas pathology can then be visualized. The application of labeling and clearing to surgically resected human pancreatic parenchyma can provide detailed visualization of the complexities of normal pancreatic anatomy. It also can be used to characterize the 3D architecture of disease processes ranging from precursor lesions, such as pancreatic intraepithelial neoplasia lesions and intraductal papillary mucinous neoplasms, to infiltrating pancreatic ductal adenocarcinomas. The evaluation of 3D histopathology, including pathology of the pancreatic lesions, will provide new insights into lesions that previously were seen, and thought of, only in 2 dimensions.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30256228

- **Accurate 3D Reconstruction of a Whole Pancreatic Cancer Tumor from Pathology Images with Different Stains**

https://link.springer.com/chapter/10.1007/978-3-030-00949-6_5

- **Construction of a Generative Model of H&E Stained Pathology Images of Pancreas Tumors Conditioned by a Voxel Value of MRI Image**

https://link.springer.com/chapter/10.1007/978-3-030-00949-6_4

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

Nature reviews. Gastroenterology & hepatology 2018 Oct;15(10):586-587

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

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

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

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

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

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

Biochimica et biophysica acta. General subjects 2018 Jul;1862(7):1537-1546

BACKGROUND: Tumor microenvironment consists of the extracellular matrix (ECM), stromal cells, such as fibroblasts (FBs) and cancer associated fibroblasts (CAFs), and a myriad of soluble factors. In many tumor types, including pancreatic tumors, the interplay between stromal cells and the other tumor microenvironment components leads to desmoplasia, a cancer-specific type of fibrosis that hinders treatment. Transforming growth factor beta (TGF-) and CAFs are thought to play a crucial role in this tumor desmoplastic reaction, although the involved mechanisms are unknown. METHODS: Optical/fluorescence microscopy, atomic force microscopy, image processing techniques, invasion assay in 3D collagen I gels and real-time PCR were employed to investigate the effect of TGF- on normal pancreatic FBs and CAFs with regard to crucial cellular morphodynamic characteristics and relevant gene expression involved in tumor progression and metastasis. RESULTS: CAFs present specific myofibroblast-like characteristics, such as -smooth muscle actin expression and cell elongation, they also form more lamellipodia and are softer than FBs. TGF- treatment increases cell stiffness (Young's modulus) of both FBs and CAFs and increases CAF's (but not FB's) elongation, cell spreading, lamellipodia formation and spheroid invasion. Gene expression analysis shows that these morphodynamic characteristics are mediated by Rac, RhoA and ROCK expression in CAFs treated with TGF- . CONCLUSIONS: TGF- modulates CAFs', but not FBs', cell shape, stiffness and invasion. GENERAL SIGNIFICANCE: Our findings elucidate on the effects of TGF- on CAFs' behavior and stiffness providing new insights into the mechanisms involved.

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

- Human Organoids Share Structural and Genetic Features with Primary Pancreatic Adenocarcinoma Tumors

Molecular cancer research : MCR 2018 Aug;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30171177

Patient-derived pancreatic ductal adenocarcinoma (PDAC) organoid systems show great promise for understanding the biological underpinnings of disease and advancing therapeutic precision medicine. Despite the increased use of organoids, the fidelity of molecular features, genetic heterogeneity, and drug response to the tumor of origin remain important unanswered questions limiting their utility. To address this gap in knowledge, primary tumor- and PDX-derived organoids, and 2D cultures for in-depth genomic and histopathological comparisons to the primary tumor were created. Histopathological features and PDAC representative protein markers (e.g., claudin 4 and CA19-9) showed strong concordance. DNA- and RNA-sequencing (RNAseq) of single organoids revealed patient-specific genomic and transcriptomic consistency. Single-cell RNAseq demonstrated that organoids are primarily a clonal population. In drug response assays, organoids displayed patient-specific sensitivities. Additionally, the in vivo PDX response to FOLFIRINOX and Gemcitabine/Abraxane treatments were examined, which was recapitulated in vitro with organoids. This study has demonstrated that organoids are potentially invaluable for precision medicine as well as pre-clinical drug treatment studies because they maintain distinct patient phenotypes and respond differently to drug combinations and dosage. The patient-specific molecular and histopathological fidelity of organoids indicate that they can be used to understand the etiology of the patient's tumor and the differential response to therapies and suggests utility for predicting drug responses.

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

Journal of gastrointestinal cancer 2018 Aug;():

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

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

- **Fluorescent-guided surgery for sentinel lymph node detection in gastric cancer and carcinoembryonic antigen targeted fluorescent-guided surgery in colorectal and pancreatic cancer**

https://onlinelibrary.wiley.com/doi/10.1002/jso.25139

- A Hypervascular Pancreatic Tumor

Gastroenterology 2018 Sep;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30240665

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Animal Studies

- Inverse Correlation of STAT3 and MEK Signaling Mediates Resistance to RAS Pathway Inhibition in Pancreatic Cancer

Cancer research 2018 Aug;():

Major contributors to therapeutic resistance in pancreatic cancer (PDAC) include Kras mutations, a dense desmoplastic stroma that prevents drug delivery to the tumor, and activation of redundant signaling pathways. We have previously identified a mechanistic rationale for targeting STAT3 signaling to overcome therapeutic resistance in PDAC. In this study, we investigate the molecular mechanisms underlying the heterogeneous response to STAT3 and RAS pathway inhibition in PDAC. Effects of JAK/STAT3 inhibition (STAT3i) or MEK inhibition (MEKi) were established in Ptf1acre/+;LSL-KrasG12D/+;Tgfbr2flox/flox (PKT) mice and patient-derived xenografts (PDX). Amphiregulin (AREG) levels were determined in serum from human PDAC patients, LSL-KrasG12D/+;Trp53R172H/+;Pdx1Cre/+ (KPC), and PKT mice. MEKi/STAT3i-treated tumors were analyzed for integrity of the pancreas and the presence of cancer stem cells (CSC). We observed an inverse correlation between ERK and STAT3 phosphorylation. MEKi resulted in immediate activation of STAT3, while STAT3i resulted in TACE-induced, AREG-dependent activation of EGFR and ERK. Combined MEKi/STAT3i sustained blockade of ERK, EGFR, and STAT3 signaling, overcoming resistance to individual MEKi or STAT3i. This combined inhibition attenuated tumor growth in PDX and increased survival of PKT mice while reducing serum AREG levels. Furthermore, MEKi/STAT3i altered the PDAC tumor microenvironment by depleting tumor fibrosis, maintaining pancreatic integrity, and downregulating CD44+ and CD133+ CSC. These results demonstrate that resistance to MEKi is mediated through activation of STAT3, while TACE-AREG-EGFR-dependent activation of RAS pathway signaling confers resistance to STAT3 inhibition. Combined MEKi/STAT3i overcomes these resistances and provides a novel therapeutic strategy to target the RAS and STAT3 pathway in PDAC.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30154150

- GNASR201C Induces Pancreatic Cystic Neoplasms in Mice That Express Activated KRAS by Inhibiting YAP1 Signaling

Gastroenterology 2018 Aug;():

BACKGROUND & AIMS: Mutations at hotspots in GNAS, which encodes stimulatory G-protein, subunits, are detected in approximately 60% of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas. We generated mice with KRAS-induced IPMNs that also express a constitutively active form of GNAS in pancreas and studied tumor development. METHODS: We generated p48-Cre; LSL-KrasG12D; Rosa26R-LSL-rtTA-TetO-GnasR201C mice (Kras;Gnas mice); pancreatic tissues of these mice express activated KRAS and also express a mutant form of GNAS (GNASR201C) upon doxycycline administration. Mice that were not given doxycycline were used as controls, and survival times were compared by Kaplan-Meier analysis. Pancreata were collected at different time points after doxycycline administration and analyzed by histology. Pancreatic ductal adenocarcinomas (PDACs) were isolated from mice and used to generate cell lines, which were analyzed by reverse transcription polymerase chain reaction, immunoblotting, immunohistochemistry, and colony formation and invasion assays. Full-length and mutant forms of yes-associated protein (YAP) were expressed in PDAC cells. IPMN specimens were obtained from 13 patients with IPMN undergoing surgery and analyzed by immunohistochemistry. RESULTS: All Kras;Gnas mice developed pancreatic cystic lesions that resemble human IPMNs; the grade of epithelial dysplasia increased with time. None of the control mice developed cystic lesions. Approximately one third of Kras;Gnas mice developed PDACs at a median of 30 weeks after doxycycline administration, whereas 33% of control mice developed PDACs. Expression of GNASR201C did not accelerate the development of PDACs compared with control mice. However, the neoplasms observed in Kras;Gnas mice were more differentiated, and expressed more genes associated with

ductal phenotypes, than in control mice. PDACs isolated from Kras;Gnas mice had activation of the Hippo pathway; in cells from these tumors, phosphorylated YAP1 was sequestered in the cytoplasm, and this was also observed in human IPMNs with GNAS mutations. Sequestration of YAP1 was not observed in PDAC cells from control mice. CONCLUSIONS: In mice that express activated KRAS in the pancreas, we found expression of GNASR201C to cause development of more differentiated tumors, with gene expression pattern associated with the ductal phenotype. Expression of mutant GNAS caused phosphorylated YAP1 to be sequestered in the cytoplasm, altering tumor progression.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30142336

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

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

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

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

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

Gastroenterology 2018 Aug;():

BACKGROUND & AIMS: Pancreatic ductal adenocarcinomas (PDACs) produce higher levels of truncated O-glycan structures (such as Tn and sTn) than normal pancreata. Dysregulated activity of core 1 synthase glycoprotein-N-acetylgalactosamine 3- -galactosyltransferase 1 (C1GALT1) leads to increased expression of these truncated O-glycans. We investigated whether and how truncated O-glycans contributes to the development and progression of PDAC using mice with disruption of C1galt1. METHODS: We crossed C1galt1 floxed mice (C1galt1loxP/loxP) with KrasG12D/+; Trp53R172H/+; Pdx1-Cre (KPC) mice to create KPCC mice. Growth and progression of pancreatic tumors were compared between KPC and KPCC mice; pancreatic tissues were collected and analyzed by immunohistochemistry; immunofluorescence; and Sirius red, alcian blue, and lectin staining. We used the CRISPR/Cas9 system to disrupt C1galt1 in human PDAC cells (T3M4 and CD18/HPAF) and levels of O-glycans were analyzed by lectin blotting, mass spectrometry, and lectin pulldown assay. Orthotopic studies and RNA sequencing analyses were performed with control and C1galt1 knockout PDAC cells. C1galt1 expression was analyzed in well-differentiated (n = 36) and poorly differentiated (n = 23) PDAC samples by immunohistochemistry. RESULTS: KPCC mice had significantly shorter survival times (median 102 days) than KPC mice (median 200 days) and developed early pancreatic

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

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

- Local Phototherapy Synergizes with Immunoadjuvant for Treatment of Pancreatic Cancer through Induced Immunogenic Tumor Vaccine

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

Purpose: To develop a synergistic combination therapy for advanced pancreatic cancer, using local phototherapy and immunotherapy, and to determine the efficacy and mechanism of the novel combination therapy using a highly metastatic pancreatic tumor model in mice.Experimental Design: Mice bearing Panc02-H7 pancreatic tumors (both subcutaneous and orthotopic) were treated with noninvasive or interventional photothermal therapy, followed by local application of an immunoadjuvant. Tumor growth and animal survival were assessed. Immune cell populations within spleen and tumors were evaluated by FACS and IHC, and cytokine levels were determined by ELISA.Results: Up to 75% of mice bearing subcutaneous tumors treated with combination therapy had complete tumor regression. Local photothermal therapy exposed/released damage-associated molecular patterns, which initiated an immunogenic tumor cell death, resulting in infiltration of antigen-presenting cells and Th1 immunity. Concomitant application of immunoadjuvant amplified Th1 immunity, especially the tumor-specific cytotoxic T lymphocyte response, with increased quantity and quality of T cells. Combination therapy also induced tumor-specific immune memory, as demonstrated by resistance to tumor rechallenge and production of memory T cells. For the treatment of orthotopic tumor, the combination therapy significantly reduced the primary tumors and metastases, and prolonged the animal survival time.Conclusions: This study indicated that combination of local phototherapy and immunotherapy induced a systemic immunity against established tumors and metastases in an aggressive, preclinical pancreatic tumor model, leading to a potential clinical method for patients with advanced pancreatic cancer. Clin Cancer Res; 1-12. ©2018 AACR.

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

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

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

OBJECTIVES: In patients with pancreatic ductal adenocarcinoma (PDAC), increased expression of proinflammatory neurotrophic growth factors (eg, nerve growth factor [NGF]) correlates with a poorer prognosis, perineural invasion, and, with regard to NGF, pain severity. We hypothesized that NGF sequestration would reduce inflammation and disease in the KPC mouse model of PDAC. METHODS: Following biweekly injections of NGF antibody or control immunoglobulin G, beginning at 4 or 8 weeks of age, inflammation and disease stage were assessed using histological, protein expression, and quantitative polymerase chain reaction analyses. RESULTS: In the 8-week anti-NGF group, indicators of neurogenic inflammation in the dorsal root ganglia (substance P and calcitonin gene-related peptide) and spinal cord (glial fibrillary acidic protein) were significantly reduced. In the 4-week anti-NGF group, TRPA1 mRNA in dorsal root ganglia and spinal

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

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

- ARID1A, a SWI/SNF subunit, is critical to acinar cell homeostasis and regeneration and is a barrier to transformation and epithelial-mesenchymal transition in the pancreas

Gut 2018 Sep;():

OBJECTIVE: Here, we evaluate the contribution of AT-rich interaction domain-containing protein 1A (ARID1A), the most frequently mutated member of the SWItch/sucrose non-fermentable (SWI/SNF) complex, in pancreatic homeostasis and pancreatic ductal adenocarcinoma (PDAC) pathogenesis using mouse models. DESIGN: Mice with a targeted deletion of Arid1a in the pancreas by itself and in the context of two common genetic alterations in PDAC, Kras and p53, were followed longitudinally. Pancreases were examined and analysed for proliferation, response to injury and tumourigenesis. Cancer cell lines derived from these models were analysed for clonogenic, migratory, invasive and transcriptomic changes. RESULTS: Arid1a deletion in the pancreas results in progressive acinar-to-ductal metaplasia (ADM), loss of acinar mass, diminished acinar regeneration in response to injury and ductal cell expansion. Mutant Kras cooperates with homozygous deletion of Arid1a, leading to intraductal papillary mucinous neoplasm (IPMN). Arid1a loss in the context of mutant Kras and p53 leads to shorter tumour latency, with the resulting tumours being poorly differentiated. Cancer cell lines derived from Arid1a-mutant tumours are more mesenchymal, migratory, invasive and capable of anchorage-independent growth; gene expression analysis showed activation of epithelial-mesenchymal transition (EMT) and stem cell identity pathways that are partially dependent on Arid1a loss for dysregulation. CONCLUSIONS: ARID1A plays a key role in pancreatic acinar homeostasis and response to injury. Furthermore, ARID1A restrains oncogenic KRAS-driven formation of premalignant proliferative IPMN. Arid1a-deficient PDACs are poorly differentiated and have mesenchymal features conferring migratory/invasive and stem-like properties.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30228219

- **The loss of ATRX increases susceptibility to pancreatic injury and oncogenic KRAS in female but not male mice**

https://www.sciencedirect.com/science/article/pii/S2352345X18301255

- **Hmga2 is dispensable for pancreatic cancer development, metastasis, and therapy resistance**

https://www.nature.com/articles/s41598-018-32159-x

- Inhibition of 15-PGDH causes Kras-driven tumor expansion through prostaglandin E2-ALDH1 signaling in the pancreas

Oncogene 2018 Sep;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30250298

The accumulation of prostaglandin E2 (PGE2) during chronic inflammation has been implicated in the progression of several cancers. Cyclooxygenase is the key synthesizing enzyme of PGE2, although the degradation enzyme 15-hydroxyprostaglandin dehydrogenase (15-PGDH) has received considerable attention recently. We investigated the molecular mechanisms of pancreatic ductal adenocarcinoma (PDAC) progression via 15-PGDH downregulation. Here, we found that 15-PGDH expression was inversely correlated with ALDH1, an important cancer stem cell-associated marker indicative of poor prognosis in humans. Moreover, we demonstrated that pharmacological inhibition of 15-PGDH enhanced CYP26A1 expression, leading to depletion of all-trans retinoic acid (ATRA) and expansion of the ALDH1-positive subset in both human PDAC cells and tumor cells of KrasLSL-G12D/+; Ptf1aCre/+ (KC) mice. Furthermore, genetic deletion of 15-Pgdh in KC mice showed PGE2 accumulation and ATRA depletion in the pancreas, resulting in PDAC with high levels of Aldh1 and Ki-67. Finally, ATRA replacement suppressed 15-PGDH inhibition-induced tumor progression in KC mice, and ATRA treatment attenuated Aldh1 activity in tumor cells isolated from the pancreas of 15-Pgdh-/- KC mice. These findings provide evidence that 15-PGDH inhibition enhances KRAS-driven tumor progression via ATRA depletion in the pancreas. Therefore, ATRA replacement could be a potential strategy for PDAC treatment.

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

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

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

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

- Gut microbiome-immune crosstalk affects progression of cancer

Translational gastroenterology and hepatology 2018 ;3():34

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

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Bile Ducts

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

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

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

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

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

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

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

- Postradiation Synovial Sarcoma of the Common Bile Duct: A Previously Unreported Anatomic Site

International journal of surgical pathology 2018 Aug;26(5):469-474

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

previously, and this is the first report of a radiotherapy-related synovial sarcoma arising from the extrahepatic biliary tree, and the second case described in this anatomic region.

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

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

- Mucinous intrahepatic cholangiocarcinoma: a distinct variant

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

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

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

- Biliary Tract Cancer: State of the Art and potential role of DNA Damage Repair

Cancer treatment reviews 2018 Sep;70():168-177

Biliary tract cancers (BTCs), including cholangiocarcinoma, gallbladder cancer and ampullary cancers, are poor-prognosis malignancies. Most patients are diagnosed with advanced disease, when treatment is limited to palliative chemotherapy. First line chemotherapy is usually administered in the form of cisplatin and gemcitabine. Benefit from second line chemotherapy is still to be confirmed. Even though new systemic treatment targets have been recognised, especially in patients with intrahepatic cholangiocarcinoma (e.g. IDH and FGFR), there is an urgent need for novel treatment strategies. Genomic profiling of BTC is progressively becoming a reality which allows a better understanding of their biology and potential new targets. This review provides an insight into DNA Damage Repair (DDR) mechanisms, prevalence of DDR-deficient tumours in BTC, and the potential role of DDR in cancer development. Some form of DDR deficiency is expected to be present in around 25% of patients with BTC, and this knowledge could be exploited to potentially increase response to currently-available treatment strategies (chemotherapy, radiotherapy or immunotherapy). For patients with DDR-proficient tumours, drug inhibition of DDR could be instituted.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30218788

- **Combined CDK4/6 and Pan-mTOR Inhibition Is Synergistic Against Intrahepatic Cholangiocarcinoma**

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

Purpose: Intrahepatic cholangiocarcinoma (ICC) is an aggressive cancer type, lacking effective therapies and associated with a dismal prognosis. Palbociclib is a selective CDK4/6 inhibitor, which has been shown to suppress cell proliferation in many experimental cancer models. Recently, we demonstrated that pan-mTOR inhibitors, such as MLN0128, effectively induce apoptosis, although have limited efficacy in restraining proliferation of ICC cells. Here, we tested the hypothesis that palbociclib, due to its antproliferative properties in many cancer types, might synergize with MLN0128 to impair ICC growth.Experimental Design: Human ICC cell lines and the AKT/YapS127A ICC mouse model were used to test the therapeutic efficacy of palbociclib and MLN0128, either alone or in combination.Results: Administration of palbociclib suppressed in vitro ICC cell growth by inhibiting cell-cycle progression. Concomitant administration of palbociclib and MLN0128 led to a pronounced, synergistic growth constraint of ICC cell lines. Furthermore, while treatment with palbociclib or MLN0128 alone resulted in tumor growth reduction in AKT/YapS127A mice, a remarkable tumor regression was achieved when the two drugs were administered simultaneously. Mechanistically, palbociclib was found to potentiate MLN0128 mTOR inhibition activity, whereas MLN0128 prevented the upregulation of cyclin D1 induced by palbociclib treatment.Conclusions: Our study indicates the synergistic activity of palbociclib and MLN0128 in inhibiting ICC cell proliferation. Thus, combination of CDK4/6 and mTOR inhibitors might represent a novel, promising, and effective therapeutic approach against human ICC. Clin Cancer Res; 1-11. ©2018 AACR.

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

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

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

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

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

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

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

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

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

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

- **Intrahepatic cholangiocarcinoma: the AJCC/UICC 8th edition updates**

Chinese clinical oncology 2018 Jul;():

Intrahepatic cholangiocarcinoma accounts for 5% to 30% of all primary liver cancers, and its incidence has increased in the last 3 decades. Surgical resection remains the only potentially curative treatment but is associated with high tumor recurrence rates. The 7th edition of the American Joint Committee on Cancer (AJCC) Staging Manual introduced a new staging system for intrahepatic cholangiocarcinoma, which was previously staged the same as hepatocellular carcinoma. The recently published 8th edition has subdivided the T1 category to T1a and T1b based on a size cutoff of 5 cm, removed periductal invasion from the T4 category, and downstaged T4 tumors and regional lymph node metastasis from stage IV to IIIB. Continued international efforts to accurately stratify prognosis are important to counsel patients and guide treatment decisions.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30180751

- **Novel targeted treatment options for advanced cholangiocarcinoma**

https://www.tandfonline.com/doi/abs/10.1080/13543784.2018.1512581

- **Biliary Tract Cancer: State of the Art and potential role of DNA Damage Repair**

https://www.cancertreatmentreviews.com/article/S0305-7372(18)30156-7/fulltext

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- Tumor grade and sex should influence the utilization of portal lymphadenectomy for early stage intrahepatic cholangiocarcinoma

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

BACKGROUND: Portal lymphadenectomy for intrahepatic cholangiocarcinoma (ICC) is encouraged for staging purposes, though it is under-utilized for clinically early-stage tumors. We sought to determine if any factor knowable prior to resection influences rates of portal lymph node metastases. METHODS: The Surveillance, Epidemiology, and End Results (SEER) Program (1973-2014) database was queried to identify patients with T1/T2 ICC undergoing resection. Patients were stratified by lymph node (LN) status. Patients deemed LN negative required examination of six or more LNs (AJCC guidelines). RESULTS: One-hundred and fifty-two patients were included in the analysis (LN negative: 38, LN positive: 114). Patients with LN negative cancers experienced prolonged overall survival as compared to patients with positive LNs (median 77 months vs 19 months, respectively $p < 0.001$). Twelve patients had well-differentiated tumors (G1), 92 patients had moderately-differentiated tumors (G2) and 58 patients had poorly-differentiated tumors (G3). Tumor grade (OR 3.9, CI 1.1-13.7, $p = 0.031$) and male sex (OR 2.6, CI 1.1-6.1, $p = 0.022$) were associated with positive LNs on multivariable logistic regression analysis. CONCLUSION: Intermediate/High grade and male sex are associated with high rates of lymph node metastasis for patients with early-stage ICC, which portends abbreviated overall survival.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30139566

- Prognostic value of retrieved lymph node counts in patients with node-negative perihilar cholangiocarcinomas

ANZ journal of surgery 2018 Sep;():

BACKGROUND: This study aimed to find out the prognostic value and optimal cut-off value of retrieved lymph node (LN) counts in patients with node-negative perihilar cholangiocarcinomas. METHODS: The Surveillance, Epidemiology and End Results (SEER) database was used to screen out patients with perihilar cholangiocarcinoma. The cut-off number of retrieved LNs was determined by the X-tile programme. Kaplan-Meier methods with log-rank tests and Cox regression analysis were used for survival analysis. RESULTS: A total of 778 patients with perihilar cholangiocarcinoma (2004-2014) met the inclusion criteria for this research, and there were 403 patients without LN metastases (N0) among them. The cut-off numbers of retrieved LNs, which were determined using the X-tile programme, were 8 and 18. Both results of univariate and multivariate survival analyses in N0 patients showed that patients with 18 retrieved LNs had a significantly better survival rate than patients with 1-7 retrieved LNs and patients with 8-17 retrieved LNs. In the subgroup of patients with early-stage tumours, patients with at least 13 retrieved LNs had a significantly better overall and cancer-specific survival than patients with fewer retrieved LNs. CONCLUSIONS: The retrieved LN counts are an independent prognostic factor for patients with node-negative perihilar cholangiocarcinoma. Patients with at least 18 retrieved LNs had a better overall and cancer-specific survival than patients with fewer retrieved LNs. The minimum requirement for retrieving of LNs should reach 18 in perihilar cholangiocarcinoma.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30207026

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Gallbladder

- Gallbladder carcinoma and epithelial dysplasia: Appropriate sampling for histopathology

Annals of diagnostic pathology 2018 Sep;37():7-11

Gallbladder carcinoma (GC) is an uncommon malignancy with an overall 5-year survival of <5%. Due to overlap of clinical presentation with the more common cholecystitis, an estimated 50-65% of all GCs are found incidentally. Epithelial dysplasia is identified in ~50% of specimens with invasive carcinoma. Recent expert panel guidelines have recommended histologic examination of the entire gallbladder in cases where initial sampling reveals dysplasia. 89 cases of GC, 34 high grade dysplasia (HGD), and 60 low grade dysplasia (LGD) were identified in cholecystectomy specimens assessed at our institution over the last 15 years. Pre-operative imaging (either ultrasound or CT) only identified 52% of mass lesions in GC cases. Among gallbladder specimens with epithelial dysplasia only at initial sampling, additional sectioning was performed in 59% of HGD and 55% of LGD. Additional sectioning of gallbladder specimens with HGD had a higher yield (10%) for identifying invasive carcinoma than those with LGD (0 of 28). The diagnostic yield of additional sectioning is significantly higher in the setting of high grade as compared to low grade dysplasia, suggesting that sampling at the discretion of the pathologist may be sufficient for the latter.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30216818

- **Significance of HER2 and Ki-67 in Preneoplastic Lesions and Carcinoma of Gallbladder**

https://link.springer.com/article/10.1007/s12029-018-0162-8

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

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

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

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

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

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

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

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

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

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

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

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- Prognostic validation of the updated 8th edition Tumor-Node-Metastasis classification by the Union for International Cancer Control: Survival analyses of 307 patients with surgically treated gallbladder carcinoma

Oncology letters 2018 Oct;16(4):4427-4433

In December 2016, the Union for International Cancer Control (UICC) published the 8th edition of the Tumor-Node-Metastasis (TNM) classification of malignant tumors, including a number of vital changes in the definitions of the T2 category, the N category and the stages of gallbladder cancer (GBC). The clinical value of this newly updated classification in patients with surgically treated GBC has not been rigorously validated. The present study aimed to analyze the prognosis of patients with GBC in a high-volume surgical unit, and to validate the prognostic value of the new UICC TNM classification, particularly the main changes in the stages of GBC. Data from 307 patients who were surgically treated and histopathologically diagnosed with GBC between January 2011 and July 2016 in The West China Hospital (Chengdu, Sichuan, China) were retrospectively collected and analyzed. The new UICC criteria distributed 32, 60, 99 and 116 eligible patients in stages I, II, III and IV, respectively. The differences in overall survival time between each stage (I-IV) demonstrated statistical significance ($P<0.05$). As a result of the main change of this classification, the novel definitions of T2a and T2b effectively stratified the prognosis of patients with T2

GBC (P<0.001). Furthermore, patients with stage IIa tumors also obtained significantly improved overall survival time compared with patients with stage IIb tumors (P=0.04), whereas the comparison between patients with stage IIb and IIIa tumors did not present any notable difference (P=0.20). Additionally, the new N category stratified the survival of the patients effectively (P<0.001). Together with curative resection, this latest classification was indicated to be an independent predictor of survival via multivariate analysis (hazard ratio, 6.25; 95% confidence interval, 3.81-10.26; P<0.001). In conclusion, the newly updated UICC TNM classification could effectively reflect the clinical outcome of patients with surgically treated GBC. Furthermore, tumor location could predict the survival of surgically treated T2 GBC. The novel classification of the N category by the number of lymph nodes involved was also demonstrated to be valid.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30214577

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

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

- **The association between preoperative serum interleukin-6 levels and postoperative prognosis in patients with T2 gallbladder cancer**

https://onlinelibrary.wiley.com/doi/10.1002/jso.25085

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

Journal of cutaneous pathology 2018 Nov;45(11):870-873

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

- Incidental gallbladder cancer at cholecystectomy

Annali italiani di chirurgia 2017 ;6():399-402

BACKGROUND: Gallbladder tumours rank fifth in the world among gastrointestinal system tumours. Coincidental gallbladder tumours are diagnosed during cholecystectomies, or by examining the cholecystectomy material. AIMS: In this study, we aimed to evaluate the incidence of gallbladder cancer among patients undergoing cholecystectomies due to gallbladder disease. STUDY DESIGN: Retrospective study METHODS: The files of 341 patients who had undergone routine cholecystectomy operations between January 2013 and March 2016 were reviewed, and their pathology results were recorded. Those patients with gallbladder carcinomas were evaluated in terms of age, gender, preoperative findings, existing symptoms, radiological findings, surgical findings and follow-up. The cancer invasion depth was classified according to the American Joint Commission on Cancer (AJCC) atlas, and this study was approved by the ethical committee of our university. RESULTS: Among the 341 patients who participated in this study, 253 (74.41%) were female, 88 (25.80%) were male, and their average age was 49.61 years old (17-86). Seven of the patients (2.05%) had gallbladder tumours; six of which were female, one was male and their average age was 67.71 years old (62-76). One tumour was diagnosed as a frozen specimen during the operation, while the others were diagnosed

during the postoperation phase. Three of the patients had T1b and four had T2 tumours. CONCLUSION: Gallbladder tumours detected incidentally could extend survival rates with proper surgical intervention and chemotherapy. The possibility of a tumour should not be dismissed in those patients with advanced age, females or patients with gallbladder stones. Frozen specimens should be created during a cholecystectomy, and if there is any doubt about the diagnosis, a postoperative histopathological examination of the gallbladder should be conducted. KEY WORDS: Cholecystectomy, Gall bladder stone, Incidental gallbladder carcinoma.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29197189

- **Gallbladder Cancer in Eastern Province of Saudi Arabia: A Retrospective Cohort Study**

https://www.sciencedirect.com/science/article/pii/S2049080118301845

- **Gallbladder carcinoma: An analysis of the national cancer data base to examine hispanic influence**

https://onlinelibrary.wiley.com/doi/10.1002/jso.25050

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Ampulla of Vater

- High-grade precursor lesions can be used as surrogate markers to identify the epicenter of periampullary carcinomas

Human pathology 2018 Sep;():

Identifying the accurate origin of periampullary cancers is important, because different origins may trigger different clinicopathologic behaviors. The presence of intraepithelial precursor lesions, including high-grade pancreatic intraepithelial neoplasias (PanINs) and/or high-grade biliary intraepithelial neoplasias (BilINs), may be suggestive of the origin of the periampullary carcinoma in challenging cases. To prove the usefulness of high-grade intraepithelial precursor lesions to identify the origin of ambiguous periampullary cancers, the status and grades of PanINs and BilINs were evaluated in 256 periampullary carcinomas with a well-defined cancer origin as a test set, including 114 pancreatic cancers, 82 distal bile duct cancers, 54 ampullary cancers, and 6 duodenal cancers, and 112 periampullary carcinomas with clinically equivocal epicenter either by radiologic imaging used as a validation set. High-grade PanINs were found more commonly in pancreatic cancers than in distal bile duct, ampullary, and duodenal cancers both in test (P=.002) and validation sets (P<.001). Similarly, high-grade BilINs were identified more frequently in distal bile duct cancers than in ampullary, pancreatic, and duodenal cancers both in test (P<.001) and validation sets (P=.039). High-grade PanINs were found most commonly in pancreatic cancers, while high-grade BilINs were seen most frequently in distal bile duct cancers. In addition, both high-grade PanINs and high-grade BilINs are uncommonly noted in ampullary or duodenal cancers. The recognition of high-grade intraepithelial lesions can help identify the primary origin of periampullary cancers, especially when the epicenter of the periampullary cancer is ambiguous.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30261192

- Intraobserver and Interobserver Variability in the Assessment of Dysplasia in Ampullary Mucosal Biopsies

The American journal of surgical pathology 2018 Aug;42(8):1095-1100

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

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

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

- Clinicopathological features related to survival in adenocarcinoma of the vaterian system in a Mexican population

Human pathology 2018 Sep;():

Adenocarcinomas of the ampulla of Vater account for 0.5% of malignant neoplasms of the gastrointestinal tract, and 6-20% of malignant periampullary neoplasms, the majority of patients being candidates to elective surgery. Our objective was to evaluate the clinicopathological prognostic factors of ampullary adenocarcinomas after surgical resection, in the Mexican population. From the records of the Department of Pathology at the Instituto Nacional de Cancerología, México, cases diagnosed as adenocarcinomas of the ampulla of Vater were selected over a period of 11years, from January 2005 to September 2015. Cases with a pancreaticoduodenectomy report were included, and from each case, demographic and pathological data of the surgical specimen, were obtained. Univariate and multivariate statistical analyses were performed using the Log-rank test and Cox regression.Of 157 cases diagnosed as ampullary adenocarcinomas, 104 patients were excluded as not elegible for surgical treatment at the time of diagnosis. In the remaining 53 patients, a pancreaticoduodenectomy was performed. The mean age of the entire group was 55.4years and the majority were men. Intestinal-type adenocarcinomas were more frequent (77.4%) than pancreatobiliary-type (15.1%), most without perineural invasion, well to moderately differentiated, and less than 3cm in size. Lymph node metastasis and age over 65years, had a negative impact on overall survival of the patients.The most convenient classification of malignant epithelial tumors of the Vaterian system, is according to the histopathological phenotype into intestinal-, pancreatobiliary and mixed-type adenocarcinomas, as well as uncommon variants.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30179685

- 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

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

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

BACKGROUND AND AIMS: Duodenal collections of pancreatic fluid can be used as a source of mutations and other markers of pancreatic ductal neoplasia, but admixing pancreatic juice with duodenal contents lowers the concentrations of mutations. Collecting pancreatic fluid directly from the ampulla could yield a purer

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

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

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

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

BACKGROUND: Duodenal adenocarcinoma (DA) is a rare tumor for which survival data per treatment modality and disease stage are unclear. This systematic review and meta-analysis aims to summarize the current literature on patient outcome after surgical, (neo)adjuvant, and palliative treatment in patients with DA. METHODS: A systematic search was performed according to the preferred reporting items for systematic reviews and meta-analyses guidelines, to 25 April 2017. Primary outcome was overall survival (OS), specified for treatment strategy or disease stage. Random-effects models were used for the calculation of pooled odds ratios per treatment modality. Included papers were also screened for prognostic factors. RESULTS: A total of 26 observational studies, comprising 6438 patients with DA, were included. Of these, resection with curative intent was performed in 71% (range 53-100%) of patients, and 29% received palliative treatment (range 0-61%). The pooled 5-year OS rate was 46% after curative resection, compared with 1% in palliative-treated patients (OR 0.04, 95% confidence interval [CI] 0.02-0.09, $p < 0.0001$). Both segmental resection and pancreaticoduodenectomy allowed adequate assessment of lymph node involvement and resulted in similar OS. Lymph node involvement correlated with worse OS (pooled 5-year survival rate 21% for nodal metastases vs. 65% for node-negative disease; OR 0.17, 95% CI 0.11-0.27, $p < 0.0001$). In the current literature, no survival benefit for adjuvant therapy after curative resection was found. CONCLUSION: Resection with curative intent, either pancreaticoduodenectomy or segmental resection, and lack of nodal metastases, favors survival for DA. Further studies exploring multimodality (neo)adjuvant therapy are warranted to investigate their benefit.

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

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

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

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

- Clinicopathological Stratification and Long-term Follow-up of Patients with Periampullary Carcinomas

Anticancer research 2018 Sep;38(9):5379-5386

BACKGROUND: Periampullary carcinomas generally confer a poor outcome. Choosing the most effective treatment regimen for each sub-entity proves challenging and is usually based on experience from pancreatic adenocarcinoma (PDAC). PATIENTS AND METHODS: The long-term follow-up is presented of 472 patients with periampullary tumors [PDAC, distal cholangiocarcinoma (dCC) and ampullary carcinomas (AC)] who underwent radical resection considering clinical characteristics, paraclinical findings and histopathological features in order to define factors of prognostic relevance. RESULTS: Patients with PDACs presented with larger tumor sizes, more frequent R1 resection, higher rate of nodal and perineural invasion, higher tumor stage according to the classification of tumors of the Union Internationale contre le Cancer when compared to those with dCCs and ACs. In a multivariate analysis, age >65 years, postoperative complications and higher grading of the tumor proved to be independent prognostic factors for survival. CONCLUSION: Patients suffering from PDAC have the worst prognosis and greatest benefit from radical resection of all patients with periampullary tumors. More detailed studies are warranted to better distinguish between the different entities.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30194192

- Pancreaticoduodenectomy for periampullary cancer: does the tumour entity influence perioperative morbidity and long-term outcome?

Acta chirurgica Belgica 2018 Sep;():1-7

BACKGROUND: Malignant tumours of the periampullary region include ductal adenocarcinoma of the pancreas (Pan-Ca), distal bile duct cancer (DBDC) and adenocarcinoma of the ampulla (Amp-Ca). The present retrospective clinical study was designed to evaluate the influence of tumour entity on postoperative complications and identify risk factors predicting survival and morbidity. METHODS: We retrospectively analysed data from all patients who underwent pancreatic resection for periampullary cancer with curative intent (R0 or R1). Demographic data, risk factors, perioperative complications and survival rates for the different subtypes were assessed. RESULTS: A total of 225 patients with periampullary cancer were identified: 124 (55.1%) had Pan-Ca, 55 (24.4%) had DBDC and 46 had (20.4%) Amp-Ca. Sixty-nine patients (30.7%) had major complications (grade IIIb-V). Patients with DBDC had significantly more grade C pancreatic fistulas. Univariate analysis revealed male gender, BMI >30, R1-status, and low-grade tumour differentiation as risk factors for major complications. Overall in-hospital-mortality was 6.7%. CONCLUSIONS: Further research will be needed to implement more individualized therapy.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30203717

- Obstructive jaundice caused by myeloid sarcoma in duodenal ampulla

Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver 2018 Sep;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30253977

- 'Bleeding Dilemma': The Story of a Periampullary Mass

Cureus 2018 Jul;10(7):e3035

Periampullary malignancies arise in the vicinity of the ampulla of Vater, a common passage for biliary and pancreatic secretions. Determining the anatomical origin of these tumors represents a diagnostic challenge. This is especially true for large tumors due to the transitional nature of this region, proximity to

different structures, anatomical variations, and overlapping features among constituting structures. This determination has significant prognostic and therapeutic implications. Among them, primary ampullary adenocarcinoma is a rare malignancy that has the best overall prognosis with high rates of potentially curative resection and possible survival even in advanced disease. Due to its rarity, it is also a vague territory with no definitive guidelines regarding management and surveillance currently available. Acute gastrointestinal hemorrhage is a rare presentation of ampullary carcinoma that occurs secondary to tumor ulceration. We report an elderly male with a previously known large, initially asymptomatic periampullary mass who came for evaluation of melena and was noted to be hypotensive secondary to acute blood loss from the large tumor, later determined to be adenocarcinoma of the ampulla of Vater.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30254824

- Underutilization of Surgery in Periampullary Cancer Treatment

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

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

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

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Neuroendocrine

PanNet

PanNET, Pancreatic Neuroendocrine Tumors and related neuroendocrine neoplasms

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- **The expression of TTF1, CDX2 and ISL1 in 74 poorly differentiated neuroendocrine carcinomas**

https://www.sciencedirect.com/science/article/pii/S1092913418302272

- **Unmet needs in high-grade gastroenteropancreatic neuroendocrine neoplasms (WHO G3).**

https://www.karger.com/Article/Abstract/493318

- A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal

Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc 2018 Aug;():

The classification of neuroendocrine neoplasms (NENs) differs between organ systems and currently causes considerable confusion. A uniform classification framework for NENs at any anatomical location may reduce inconsistencies and contradictions among the various systems currently in use. The classification suggested here is intended to allow pathologists and clinicians to manage their patients with NENs consistently, while acknowledging organ-specific differences in classification criteria, tumor biology, and prognostic factors. The classification suggested is based on a consensus conference held at the International Agency for Research on Cancer (IARC) in November 2017 and subsequent discussion with additional experts. The key feature of the new classification is a distinction between differentiated neuroendocrine tumors (NETs), also designated carcinoid tumors in some systems, and poorly differentiated NECs, as they both share common expression of neuroendocrine markers. This dichotomous morphological subdivision into NETs and NECs is supported by genetic evidence at specific anatomic sites as well as clinical, epidemiologic, histologic, and prognostic differences. In many organ systems, NETs are graded as G1, G2, or G3 based on mitotic count and/or Ki-67 labeling index, and/or the presence of necrosis; NECs are considered high grade by definition. We believe this conceptual approach can form the basis for the next generation of NEN classifications and will allow more consistent taxonomy to understand how neoplasms from different organ systems inter-relate clinically and genetically.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30140036

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

Human pathology 2018 Aug;():

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

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

- Recurrence of Pancreatic Neuroendocrine Tumors and Survival Predicted by Ki67

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

BACKGROUND: Despite evidence of different malignant potentials, postoperative follow-up assessment is similar for G1 and G2 pancreatic neuroendocrine tumors (panNETs) and adjuvant treatment currently is not indicated. This study investigated the role of Ki67 with regard to recurrence and survival after curative resection of panNET. METHODS: Patients with resected non-functioning panNET diagnosed between 1992 and 2016 from three institutions were retrospectively analyzed. Patients who had G1 or G2 tumor without distant metastases or hereditary syndromes were included in the study. The patients were re-categorized into Ki67 0-5 and Ki67 6-20%. Cox regression analysis with log-rank testing for recurrence and survival was performed. RESULTS: The study enrolled 241 patients (86%) with Ki67 0-5% and 39 patients (14%) with Ki67 6-20%. Recurrence was seen in 34 patients (14%) with Ki67 0-5% after a median period of 34 months and in 16 patients (41%) with Ki67 6-20% after a median period of 16 months ($p < 0.001$). The 5-year recurrence-free and 10-year disease-specific survival periods were respectively 90 and 91% for Ki67 0-5% and respectively 55 and 26% for Ki67 6-20% ($p < 0.001$). The overall survival period after recurrence was 44.9 months, which was comparable between the two groups ($p = 0.283$). In addition to a Ki67 rate higher than 5%, tumor larger than 4 cm and lymph node metastases were independently associated with recurrence. CONCLUSIONS: Patients at high risk for recurrence after curative resection of G1 or G2 panNET can be identified by a Ki67 rate higher than 5%. These patients should be more closely monitored postoperatively to detect recurrence early and might benefit from adjuvant treatment. A clear postoperative follow-up regimen is proposed.

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

- Neuroendocrine tumor of the pancreas with rhabdoid feature

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

Imaging of a 53-year-old Japanese man revealed two tumors in the liver and a tumor in the head of the pancreas with a swelling lymph node. A needle biopsy for the liver tumors was performed, revealing a neuroendocrine tumor. Enucleation, lymphadenectomy, and partial hepatectomy were performed. The microscopic examination identified many tumor cells with intracytoplasmic inclusions arranged in a nested, cord,

or tubular fashion. The intracytoplasmic inclusions displayed densely eosinophilic globules and displaced the nuclei toward the periphery, which constitutes “rhabdoid” features. The tumor cells were positive for synaptophysin and weakly positive for NCAM, but negative for chromogranin A. Epithelial markers (AE1/AE3 and CAM5.2) accentuated intracytoplasmic globules. Pancreatic neuroendocrine tumors with rhabdoid features are very rare. Generally, rhabdoid features are aggressive and dedifferentiated characteristics of various types of tumor. Pancreatic neuroendocrine tumors containing rhabdoid cells tend to display extrapancreatic spread at the time of presentation, although some of these tumors with rhabdoid features are not always associated with aggressive behavior.

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

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

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

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

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

- Variability of the Ki-67 proliferation index in gastroenteropancreatic neuroendocrine neoplasms - a single-center retrospective study

https://link.springer.com/article/10.1186/s12902-018-0274-y

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

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

PURPOSE: Apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3B (APOBEC3B) is known as a source of mutations in multiple cancers. Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are a group of heterogeneous tumors. However, the expression and significance of APOBEC3B in

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

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

- **The expression of TTF1, CDX2 and ISL1 in 74 poorly differentiated neuroendocrine carcinomas**

Annals of diagnostic pathology 2018 Sep;37():30-34

BACKGROUND: The expression profile of immunohistochemical markers of origin in poorly differentiated neuroendocrine carcinoma (PDNEC) is not well studied. MATERIALS AND METHODS: Seventy-four PDNECs from gastroenteropancreatic (GEP) organs and the lung, including 48 large cell NEC (LCNEC) and 26 small cell carcinomas (SmCC), were subject to immunohistochemical staining for CDX2, TTF1 and ISL1. The staining intensity (1 to 3) and percentage of positive tumor cells [0 (negative), 1 (<50%) and 2 (50%)] were assessed. The multiplicative index (maximum 6) was calculated and the average total score (aTS) was determined for each primary site and histologic subtype. RESULTS: In the 38 GEP and 36 lung PDNECs, CDX2, TTF1 and ISL1 staining was observed in 71% (aTS 2.8), 16% (aTS 0.4), 63% (aTS 1.9), and 22% (aTS 0.6), 72% (aTS 2.9) and 92% (aTS 3.8), respectively. GEP PDNECs showed a higher aTS for CDX2 and lower aTS for TTF1 and ISL1, compared to that of lung PDNECs (Student's t-test, $p < 0.001$). SmCC had a higher aTS for TTF1 and ISL1 ($p < 0.001$) and lower aTS for CDX2 ($p < 0.002$) than that of LCNEC. CONCLUSIONS: CDX2 and TTF1 demonstrate potential utility in suggesting the primary site of PDNEC. In addition, CDX2 may be useful in supporting the diagnosis of LCNEC in cases with overlapping or borderline morphology. Utility of ISL1 as an adjunctive diagnostic marker of SmCC remains to be studied.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30236546

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

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

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

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

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

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

Annals of surgical oncology 2018 Aug;():

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

- **Tissue heterogeneity contributes to suboptimal precision of WHO 2010 scoring criteria for Ki67 labeling index in a subset of neuroendocrine neoplasms of the pancreas**

https://www.termedia.pl/Tissue-heterogeneity-contributes-to-suboptimal-precision-of-WHO-2010-scoring-criteria-for-Ki67-55,29474,1,1.html

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- ASO Author Reflections: Heterogeneity of Duodenal Neuroendocrine Tumors

Annals of surgical oncology 2018 Aug;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30145647

- **Pancreatic islet of Langerhans' cytoarchitecture and ultrastructure in normal glucose tolerance and in type 2 diabetes mellitus**

https://onlinelibrary.wiley.com/doi/pdf/10.1111/dom.13380

- Lymphadenectomy in pancreatic neuroendocrine neoplasms: Why are we still debating?

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

Pancreatic Neuroendocrine Neoplasms (PNEN) are rare tumours exhibiting very heterogeneous behaviour. For these reasons, studies with high level of evidence are lacking. Whether lymphadenectomy should be performed for PNEN is a matter of debate. In this review, we perform a critical analysis of the available literature regarding the clinical significance of lymphnode metastases, the importance of lymphadenectomy, and the implications on disease-specific survival.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30253923

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

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

- Pancreaticoduodenectomy and metastasectomy for metastatic pancreatic neuroendocrine tumors

Journal of surgical oncology 2018 Nov;118(6):983-990

BACKGROUND AND OBJECTIVES: Various treatment options exist for patients with metastatic pancreatic neuroendocrine tumors (PNETs). Surgical resection with pancreaticoduodenectomy (PD) typically reserved for patients with limited disease. Definitive data are lacking to support either the resection of primary PNET in the metastatic setting or for surgical debulking of metastatic lesions. METHODS: We conducted an analysis of the National Cancer Database (NCDB) using the pancreatic cancer Participant User File. Thirty- and 90-day mortality rates and survival rates were determined for patients undergoing PD for primary tumor resection and compared with patients who had no surgery or metastasectomy. The Kaplan-Meier method was used to compare survival time. Cox regression models were used to assess factors independently associated with overall survival time. RESULTS: Resection of the primary tumor or metastatic disease each significantly improved overall survival time compared with no resection. Adding metastasectomy to PD resulted in an incremental increase in overall survival time. Both PD and metastasectomy are independently associated with overall survival time. CONCLUSIONS: Our report highlights the potential for survival time benefit in appropriately selected patients who undergo PD in the setting of metastatic PNET.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30212595

- Life expectancy in pancreatic neuroendocrine cancer

Clinics and research in hepatology and gastroenterology 2018 Sep;():

BACKGROUND: The prognoses widely reported for pancreatic cancer reflect the very poor survival associated with the most common histological type, exocrine adenocarcinoma. We calculated life expectancies for patients with less common pancreatic neuroendocrine tumors (PNETs), and also for the subsets of these patients who survive 1 and 5 years post-diagnosis, all of which carry a significantly better prognosis. Results for 1- and 5-year PNET survivors appear not to have been previously reported, nor have life expectancies (average long-term survival times) been given. METHODS: We identified 5287 cases of PNET in the SEER US national database, 1973-2013. The Kaplan-Meier estimator was used to compute empirical survival probabilities and median survival times for functioning ($n = 279$) and non-functioning PNET ($n = 5008$) cases. The Cox proportional hazards regression model was used to examine univariate associations of survival with covariates including patient age, sex, race, cancer stage, tumor grade, surgical treatment, and calendar year. A multivariate multiplicative hazard Poisson regression model estimated mortality rates for all combinations of the covariates. The rates were used to construct actuarial life tables, which gave life expectancies for male and female patients according to age, cancer stage, tumor grade, histology (functioning versus non-functioning), surgical treatment status, and time since diagnosis. These life expectancies were compared with age- and sex-specific figures from the US general population. RESULTS: Life expectancy in PNET is lower than that of the US general population and varies significantly according to patient age, cancer stage, tumor grade, mode of treatment, and time since diagnosis. For example, it is near normal for persons aged 70 and older who undergo surgical resection of localized well-differentiated (i.e., grade I) tumors. By contrast, persons with metastatic high-grade tumors not amenable to surgery have life expectancies of only 1 to 4 years depending on patient age. Functioning PNETs were associated with somewhat lower mortality than non-functioning within the first few years after diagnosis, though no major differences were observed long-term. Positive factors for survival were younger age, localized stage, low tumor grade, and surgical treatment. Survival improved over the 1973-2013 study period: on average mortality rates fell by 1.2% per year after controlling for changes in the patient population. Life expectancy increased markedly with time since diagnosis: those surviving 1 and 5 years post-diagnosis had longer additional life expectancies. CONCLUSIONS: Life expectancies of patients with PNETs may be markedly reduced from normal, but even

in the worst cases their prognoses remain significantly better than that of patients with the more common pancreatic adenocarcinomas. In some very favorable cases, the life expectancy is near-normal, especially amongst 1- and 5-year survivors. This information can be used to counsel patients.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30220478

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Microenvironment

Neuroendocrine Tumor Stroma Interactions, Microenvironment, Inflammatory Response

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- Profiling the Tumour Immune Microenvironment in Pancreatic Neuroendocrine Neoplasms with Multispectral Imaging Indicates Distinct Subpopulation Characteristics Concordant with WHO 2017 Classification

Scientific reports 2018 Sep;8(1):13166

We successfully determined the difference of immune microenvironments between pNENs and pancreatic ductal adenocarcinomas (PDACs), and the histology-dependent variability among pNENs using multispectral fluorescent imaging system. Tumour tissue samples including 52 pNENs and 18 PDACs were investigated. The tumour-infiltrating lymphocytes (TILs), their PD-1 and PD-L1 expression in the pNENs were comprehensively and quantitatively analysed and were subsequently compared with those in PDACs. A principal component analysis revealed that the tissue immune profile is related to tumour histology, with distinct groups being observed for NETs, NECs, and PDACs. While NECs and some PDACs had hot immune microenvironments with abundant TILs, NETs had a cold immune microenvironment with few TILs. Moreover, in NETs, the numbers of intraepithelial PD-1high T cells and PD-L1high Type-II macrophages were elevated according to the grade. Univariate analysis revealed that lymph node metastasis, grade, stage, PD-1high T cells, and PD-L1high Type-II macrophages were predictors for recurrence-free survival (RFS), while grade and PD-1high T cells were prognostic factors for overall survival (OS). We also showed that PD-1high T cells and PD-L1high Type-II macrophages were associated with worse outcome in pNENs. Our results support the WHO 2017 tumour classification criteria, which distinguish between G3 NETs and NECs.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30177687

- Characterization of the Neuroendocrine Tumor Immune Microenvironment

Pancreas 2018 Oct;47(9):1123-1129

OBJECTIVES: The immune environment and the potential for neuroendocrine tumors (NETs) to respond to immune checkpoint inhibitors remain largely unexplored. We assessed immune checkpoint marker expression, lymphocytic infiltrate, and associated mutational profiles in a cohort of small intestine and pancreatic NETs. METHODS: We assessed expression of PDCD1 (PD-1), CD274 (PD-L1), and PDCD1LG2 (PD-L2) in archival tissue from 64 small intestine (SINETs) and 31 pancreatic NETs (pNET). We additionally assessed T-cell infiltrates, categorizing T-cell subsets based on expression of the T-cell markers CD3, CD8, CD45RO (PTPRC), or FOXP3. Finally, we explored associations between immune checkpoint marker expression, lymphocytic infiltrate, and tumor mutational profiles. RESULTS: Expression of PD-1 or PD-L1 in small intestine or pancreatic NET was rare, whereas expression of PD-L2 was common in both NET subtypes. T-cell infiltrates were more abundant in pNET than in SINET. We found no clear associations between immune checkpoint marker expression, immune infiltrates, and specific mutational profile within each tumor type. CONCLUSIONS: Our findings provide an initial assessment of the immune environment of well-differentiated NETs. Further studies to define the immunologic differences between pNET and SINET, as well as the role of PD-L2 in these tumors, are warranted.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30153220

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

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

Tissue-specific autoimmunity occurs when selected antigens presented by susceptible alleles of the major histocompatibility complex are recognized by T cells. However, the reason why certain specific self-antigens dominate the response and are indispensable for triggering autoreactivity is unclear. Spontaneous presentation of insulin is essential for initiating autoimmune type 1 diabetes in non-obese diabetic mice1,2. A major set of pathogenic CD4 T cells specifically recognizes the 12-20 segment of the insulin B-chain (B:12-20), an epitope that is generated from direct presentation of insulin peptides by antigen-presenting cells3,4. These T cells do not respond to antigen-presenting cells that have taken up insulin that, after processing, leads to presentation of a different segment representing a one-residue shift, B:13-214. CD4 T cells that recognize B:12-20 escape negative selection in the thymus and cause diabetes, whereas those that recognize B:13-21 have only a minor role in autoimmunity3-5. Although presentation of B:12-20 is evident in the islets3,6, insulin-specific germinal centres can be formed in various lymphoid tissues, suggesting that insulin presentation is widespread7,8. Here we use live imaging to document the distribution of insulin recognition by CD4 T cells throughout various lymph nodes. Furthermore, we identify catabolized insulin peptide fragments containing defined pathogenic epitopes in -cell granules from mice and humans. Upon glucose challenge, these fragments are released into the circulation and are recognized by CD4 T cells, leading to an activation state that results in transcriptional reprogramming and enhanced diabetogenicity. Therefore, a tissue such as pancreatic islets, by releasing catabolized products, imposes a constant threat to self-tolerance. These findings reveal a self-recognition pathway underlying a primary autoantigen and provide a foundation for assessing antigenic targets that precipitate pathogenic outcomes by systemically sensitizing lymphoid tissues.

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

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Techniques & Research Methods

Neuroendocrine Techniques & Research Methods

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

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

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

- Surfactants Improve Live Cell Imaging of Human Pancreatic Islets

Pancreas 2018 Oct;47(9):1093-1100

OBJECTIVES: Newport Green is a zinc-specific fluorescent dye developed to monitor cellular zinc transport. In pancreatic islets with zinc-rich -cells, Newport Green is expected to be useful as an islet-specific indicator for live imaging. However, the low penetration of Newport Green into islets hinders clear detection. The aim of this study was to develop a practical method of live islet imaging by using surfactants to enhance the penetration efficiency. METHODS: Surfactants (F127, Tween 20, and Triton X-100) were co-incubated with Newport Green for fluorescent imaging of live isolated human islet and nonislet tissues. Toxicity, enhancement of Newport Green fluorescence, and effects on specificity to islets were examined. RESULTS: Newport Green fluorescent intensity was increased after co-incubation with all surfactants tested (0.2-3.2 mM); however, surfactants were toxic to islets at high concentrations. Within the nontoxic range, high specificity to islets was observed when co-incubated with Tween 20 at 0.2-0.4 mM, compared with F127 and Triton X-100. This optimized range successfully distinguished islets from nonislet tissues using statistically calculated cutoff value of Newport Green fluorescent intensity. CONCLUSIONS: Surfactants, particularly Tween 20 in the optimized range, effectively and selectively enhanced Newport Green fluorescence in live islets without increasing islet toxicity.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30142118

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Cytopathology

Pancreas

- Pancreatic Cytology

Surgical pathology clinics 2018 Sep;11(3):563-588

The diagnostic approach to pancreaticobiliary disease requires a multidisciplinary team in which the cytopathologist plays a crucial role. Fine-needle aspiration, obtained by endoscopic ultrasound, is the diagnostic test of choice for pancreatic lesions. Preoperative clinical management depends on many factors, many of which rely on accurate cytologic assessment. Pancreaticobiliary cytology is wrought with diagnostic pitfalls. Clinical history, imaging studies, cytology samples, and ancillary tests, including immunohistochemistry, biochemical analysis, and genetic sequencing, are integral to forming a complete diagnosis and guiding optimal patient management. This article reviews clinical aspects and the diagnostic work-up of commonly encountered diagnostic entities within the field of pancreatic cytology.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30190141

https://www.surgpath.theclinics.com/article/S1875-9181(18)30029-1/fulltext

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

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

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

- Cystic pancreatic schwannoma diagnosed by endoscopic ultrasound-guided fine needle aspiration

Diagnostic cytopathology 2018 Oct;46(10):883-885

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30146793

- Ancillary tests in the diagnosis of liver and pancreatic neoplasms

Cancer cytopathology 2018 Aug;126 Suppl 8():672-690

Ancillary tests in the diagnosis of liver and pancreatic neoplasms include a wide array of immunostains and molecular diagnostic tests, and the selection of tests is based on the differential diagnosis. This review discusses ancillary tests in the diagnosis of liver tumors, including benign and malignant primary tumors as well as metastatic tumors to the liver. In addition, ancillary tests for the diagnosis of both solid and cystic pancreatic neoplasms, including molecular tests in these lesions are also reviewed.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30156777

- Synchronous pancreatic tumors in a patient with history of Wilms tumor: A case of pancreatic adenocarcinoma and lipid-rich neuroendocrine tumor diagnosed by cytopathology

Diagnostic cytopathology 2018 Oct;46(10):864-869

Synchronous tumors represent a very small portion of pancreatic tumors. Although there is a higher incidence of secondary malignant neoplasms (SMN) in patients with history of Wilms tumor (WT), pancreatic tumors are very infrequent SMNs in this population. We report the first case of synchronous pancreatic tumors in a patient with history of WT. Two separated pancreatic lesions were identified by abdominal computerized tomography (CT) scan. Fine-needle aspiration of both lesions was performed for cytopathology examination. A pancreatic adenocarcinoma was diagnosed in the head of pancreas, and the pancreatic body lesion was found to be a neuroendocrine tumor (NET). The NET had characteristic vacuolated lipid-rich cytoplasm. Further molecular testing was done on both tumors, but no common cancer-associated mutation was found.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30194916

- Comparison between groove carcinoma and groove pancreatitis

Pancreatology : official journal of the International Association of Pancreatology (IAP) … [et al.] 2018 Oct;18(7):805-811

BACKGROUND/OBJECTIVES: The pancreatoduodenal groove (anatomical groove) is a potential space bordered by the head of the pancreas, duodenum, and common bile duct. Discerning between groove carcinoma (GC) and groove pancreatitis (GP) is often difficult, but clinically important. We retrospectively analyzed and compared the findings of computed tomography (CT), laboratory tests, and endoscopic ultrasound-fine needle aspiration (EUS-FNA) for GC and GP. METHODS: GC (n = 36) and GP (n = 44) patients at Asan Medical Center from January 1, 2000, to May 31, 2017 were retrospectively reviewed. MDCT findings, baseline characteristics, laboratory test results, and EUS and EUS-FNA findings of GC and GP patients were compared. RESULTS: CT showed no significant difference in groove enhancement between the groups. Mass-like lesions, cystic groove lesions, and calcification were observed in 86.1% and 15.9%, 38.9% and 75%, and 2.8% and 29.5% of GC and GP patients, respectively. Patients were tested for total bilirubin (GC: 2.0 vs. GP: 0.6 mg/dL), cancer antigen 19-9 (CA19-9) (GC: 76 vs. GP: 12.5 U/mL), and carcinoembryonic antigen (GC: 2.4 vs. GP: 2 ng/mL). Three GP patients died, and one GP patient was diagnosed with GC. However, among 30 GC patients with at least 1-year follow-up, 20 died. In multivariate logistic regression, CA19-9, and mass-like lesion on multidetector CT (MDCT) were discriminating factors between GC and GP. Among 23 (10 GC, 13 GP) patients who underwent EUS-FNA, the diagnostic sensitivity, specificity, positive predictive value, negative predictive value, accuracy of EUS-FNA were 90%, 100%, 100%, 92.86%, and 95.65%, respectively. CONCLUSIONS: Several MDCT and laboratory findings favor GC over GP. EUS-FNA should be considered in patients with elevated CA19-9 levels and mass-like lesions on MDCT.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30224296

- Risk of malignancy in pancreatic cysts with cytology of high-grade epithelial atypia

Cancer cytopathology 2018 Sep;126(9):773-781

BACKGROUND: The risk of malignancy is weighed against the attendant risks of surgery in the clinical management of pancreatic cysts. The latter are a group of histologically diverse and prognostically variable entities, and the risk of malignancy therein is primarily based on imaging characteristics-with or without high-grade atypia. Cytologic criteria for high-grade atypia in intraductal papillary mucinous neoplasms have

recently been defined, and its recognition in all pancreatic cysts may help to guide management. METHODS: All patients who underwent endoscopic ultrasound-guided fine-needle aspiration for a pancreatic cyst at Massachusetts General Hospital from June 2015 to October 2016 were prospectively evaluated. Clinical data, radiographic impressions, biochemical analyses, and cytologic diagnoses of 118 pancreatic cyst fine-needle aspiration biopsy specimens from 106 patients were reviewed. Clinical and radiologic data were used as follow-up for 86 patients, and histology was obtained in 20 cases. Cysts were classified by imaging as high-risk, worrisome, or low-risk as defined by the 2012 Fukuoka consensus guidelines. Cytology was categorized as low-grade or high-grade. Malignant histology included mucinous cysts with high-grade dysplasia, invasive adenocarcinomas, and neuroendocrine tumors. The risk of malignancy (ROM) was determined by histological outcome. RESULTS: The presence of high-grade cytology ($P < .01$) was the only statistically significant predictor of malignancy and was 89% sensitive and 98% specific for malignancy. The positive predictive value (ie, ROM) of high-grade atypia on cytology was 80%. CONCLUSIONS: High-grade atypia is both sensitive and specific for identifying high-risk pancreatic cysts and is associated with a high risk of malignancy, and thus resection is warranted.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30257067

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

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

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

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

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

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

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

Annals of surgery 2018 Oct;268(4):610-619

OBJECTIVES: One facet of precision medicine is the use of tumor molecular profiling to guide chemotherapeutic selection. We conducted the first prospective clinical trial of molecular profiling to guide neoadjuvant therapy in patients with operable pancreatic ductal adenocarcinoma (PDAC). We hypothesized that more effective systemic therapy would prevent disease progression during neoadjuvant therapy and, therefore, allow more patients to undergo surgery. METHODS: In patients with resectable and borderline resectable (BLR) PDAC, molecular profiling consisted of immunocytochemical staining of pretreatment endoscopic ultrasound-guided fine needle aspiration tumor biopsies using 6 biomarkers. Neoadjuvant systemic therapy was selected based on the molecular profiling results. The primary endpoint was the completion of all intended neoadjuvant therapy and surgery. RESULTS: The trial enrolled 130 patients; 61 (47%) resectable and 69 (53%) BLR. Molecular profiling was reported within a median of 5 business days (IQR: 3). Of the

130 patient samples, 95 (73%) had adequate cellularity for molecular profiling and 92 (71%) patients received molecular profile-directed therapy. Of the 92 patients who had predictive profiling, 74 (80%) received fluoropyrimidine-based therapy and 18 (20%) received gemcitabine-based therapies. Of the 130 patients, 107 (82%) completed all intended neoadjuvant therapy and surgery; 56 (92%) of the 61 with resectable PDAC and 51 (74%) of 69 with BLR PDAC. CONCLUSIONS: We report the first prospective clinical trial that utilized molecular profiling to select neoadjuvant therapy in patients with operable PDAC. Such high resectability rates have not been observed in prior neoadjuvant trials, suggesting that molecular profiling may improve the efficacy of chemotherapy in these patients.

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

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Bile Ducts

- Cytologic diagnosis of adenocarcinoma on bile duct brushings in the presence of stent associated changes: A retrospective analysis

Diagnostic cytopathology 2018 Oct;46(10):826-832

BACKGROUND: Bile duct brushing (BDB) cytology, for the characterization of bile duct strictures, can be challenging to interpret when associated with a stent. Our study aims to identify the cytologic criteria for the diagnosis of adenocarcinoma in BDBs in the presence of a stent. METHODS: A database search (January 2010-December 2015) identified three groups of BDBs-negative with stent, malignant with stent, malignant without stent. All malignant cases had histologic and/or cytologic evidence of malignancy within 1 month of the brushing sample. All reactive cases had 6 months of benign clinical follow-up. ThinPrep slides were reviewed by two cytopathologists and cytologic features were recorded. Statistical analysis was performed using Fisher's exact test. RESULTS: The study cohort included 12 reactive cases with stent, 17 malignant cases with stent and 32 malignant cases without stent. Among the stented cases, the cytologic features that reached statistical significance were 3D architecture, anisonucleosis to the extent of 1:6, coarse chromatin distribution and the presence of single atypical cells in the malignant group in contrast to the benign group. Cases that were diagnosed malignant in the presence of a stent revealed a spectrum of cell populations more frequently as compared with the malignant cases without stent (76% vs 16%). CONCLUSION: Our findings reveal that the cytologic features of malignancy in non-stented BDBs mostly hold true for stented specimens as well. Application of these criteria in the presence of a stent can improve diagnostic accuracy and thereby patient care.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30144340

- Cytological diagnosis of cryptococcosis in a biliary specimen: Report of a rare case with brief review of literature

Cytopathology : official journal of the British Society for Clinical Cytology 2018 Aug;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30153349

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Ampulla of Vater

- Cytological features of mixed adenoneuroendocrine carcinoma of the ampulla of Vater: A case report with immunocytochemical analyses

Diagnostic cytopathology 2018 Jun;46(6):540-546

Mixed adenoneuroendocrine carcinoma (MANEC) is defined as a tumor that has morphologically recognizable both adenocarcinoma and neuroendocrine carcinoma components comprising at least 30% of either components. MANEC occurring in the ampulla of Vater is extremely rare, and only 16 cases have been reported in the English language literature. In the present report, we describe the first case of MANEC of the ampulla of Vater with immunocytochemical analyses. An 82-year-old Japanese male was incidentally found to have a tumorous lesion in the ampulla of Vater. Endoscopic ultrasound-fine needle aspiration (EUS-FNA) of the tumor was performed. The Papanicolaou smear demonstrated the presence of different three components. The most dominant component was cohesive clusters of small round cells with round to oval nuclei with powdery chromatin and scant cytoplasm, which corresponded to small cell carcinoma. The second component was an adenocarcinoma, which was composed of irregularly overlapping clusters of tall columnar cells with large round to oval nuclei containing conspicuous nucleoli. The third component was an adenoma, which was comprised of flat cohesive clusters of columnar cells without atypia. Immunocytochemical analyses demonstrated that synaptophysin was expressed in the small round cells, and cdx-2 was expressed in all three components. Accordingly, a cytodiagnosis of MANEC with adenoma component was made. Preoperative diagnosis of ampullary MANEC is difficult. However, this report clearly demonstrates three different components in the EUS-FNA cytological specimen. Therefore, we suggest that cytological examination is a useful method for diagnosis of MANEC of the ampulla of Vater.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29341470

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Neuroendocrine

- **Grading by the Ki-67 Labeling Index of Endoscopic Ultrasound-Guided Fine Needle Aspiration Biopsy Specimens of Pancreatic Neuroendocrine Tumors Can Be Underestimated.**

Pancreas. 2018 Nov/Dec;47(10):1296-1303.

https://www.ncbi.nlm.nih.gov/pubmed/?term=30211805

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Molecular Pathology

Pancreas

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

The Journal of pathology 2018 Nov;246(3):352-365

Pancreatic ductal adenocarcinoma (PDAC), which is the primary cause of pancreatic cancer mortality, is poorly responsive to currently available interventions. Identifying new targets that drive PDAC formation and progression is critical for developing alternative therapeutic strategies to treat this lethal malignancy. Using genetic and pharmacological approaches, we investigated in vivo and in vitro whether uptake of the monoamine serotonin [5-hydroxytryptamine (5-HT)] is required for PDAC development. We demonstrated that pancreatic acinar cells have the ability to readily take up 5-HT in a transport-mediated manner. 5-HT uptake promoted activation of the small GTPase Ras-related C3 botulinum toxin substrate 1 (Rac1), which is required for transdifferentiation of acinar cells into acinar-to-ductal metaplasia (ADM), a key determinant in PDAC development. Consistent with the central role played by Rac1 in ADM formation, inhibition of the 5-HT transporter Sert (Slc6a4) with fluoxetine reduced ADM formation both in vitro and in vivo in a cell-autonomous manner. In addition, fluoxetine treatment profoundly compromised the stromal reaction and affected the proliferation and lipid metabolism of malignant PDAC cells. We propose that Sert is a promising therapeutic target to counteract the early event of ADM, with the potential to stall the initiation and progression of pancreatic carcinogenesis.

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

- Precancerous neoplastic cells can move through the pancreatic ductal system

Nature 2018 Sep;561(7722):201-205

Most adult carcinomas develop from noninvasive precursor lesions, a progression that is supported by genetic analysis. However, the evolutionary and genetic relationships among co-existing lesions are unclear. Here we analysed the somatic variants of pancreatic cancers and precursor lesions sampled from distinct regions of the same pancreas. After inferring evolutionary relationships, we found that the ancestral cell had initiated and clonally expanded to form one or more lesions, and that subsequent driver gene mutations eventually led to invasive pancreatic cancer. We estimate that this multi-step progression generally spans many years. These new data reframe the step-wise progression model of pancreatic cancer by illustrating that independent, high-grade pancreatic precursor lesions observed in a single pancreas often represent a single neoplasm that has colonized the ductal system, accumulating spatial and genetic divergence over time.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30177826

- Stratification of Pancreatic Ductal Adenocarcinomas Based on Tumor and Microenvironment Features

Gastroenterology 2018 Aug;():

BACKGROUND & AIMS: Genomic studies have revealed subtypes of pancreatic ductal adenocarcinoma (PDA) based on their molecular features, but different studies have reported different classification systems. It is a challenge to obtain high-quality, freshly frozen tissue for clinical analysis and determination of PDA subtypes. We aimed to redefine subtypes of PDA using a large number of formalin-fixed and paraffin-embedded PDA samples, which are more amenable to routine clinical evaluation. METHODS: We collected PDA samples from 309 consecutive patients who underwent surgery from September 1996 through December 2010 at 4 academic hospitals in Europe; non-tumor tissue samples were not included. Samples were formalin fixed and paraffin embedded. DNA and RNA were isolated; gene expression, targeted DNA sequencing, and immunohistochemical analyses were performed. We used independent component analysis to deconvolute normal, tumor, and microenvironment transcriptome patterns in samples. We devised classification systems from an unsupervised analysis using a consensus clustering approach of our dataset after removal of normal contamination components. We associated subtypes with overall survival and disease-free survival of patients using Cox proportional hazards regression with estimation of hazard ratios and 95% CIs. We used The Cancer Genome Consortium (TCGA) and International Cancer Genome Consortium (ICGC) PDA datasets as validation cohorts. RESULTS: We validated the previously reported basal-like and classical tumor-specific subtypes of PDAs. We identified features of the PDA, including microenvironment gene expression patterns, that allowed tumors to be categorized into 5 subtypes, called pure basal like, stroma activated, desmoplastic, pure classical, and immune classical. These PDA subtypes have features of cancer cells and immune cells that could be targeted by pharmacologic agents. Tumor subtypes associated with patient outcomes, based on analysis of our dataset and the ICGC and TCGA PDA datasets. We also observed an exocrine signal associated with acinar cell contamination (from pancreatic tissue). CONCLUSIONS: We identified a classification system based on gene expression analysis of formalin-fixed PDA samples. We identified 5 PDA subtypes, based on features of cancer cells and the tumor microenvironment. This system might be used to select therapies and predict patient outcomes. We found evidence that the previously reported exocrine-like (called ADEX) tumor subtype resulted from contamination with pancreatic acinar cells.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30165049

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

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

We have also defined the miR-141/200c-WIPF1-YAP/TAZ as a novel signaling pathway that is involved in the regulation of the invasion and metastasis of human PDAC cells.

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

- Liquid Biopsies for Management of Pancreatic Cancer

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

- Smad4/DPC4

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

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

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

- Prospective study of germline genetic testing in incident cases of pancreatic adenocarcinoma

Cancer 2018 Sep;124(17):3520-3527

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

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

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

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

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

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

- Regulation of Epithelial Plasticity Determines Metastatic Organotropism in Pancreatic Cancer

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pancreatic cancer requires many genetic mutations. Combinations of underlying germline variants and environmental factors may increase the risk of cancer and accelerate the oncogenic process. We systematically reviewed, annotated, and classified previously reported pancreatic cancer-associated germline variants in established risk genes. Variants were scored using multiple criteria and binned by evidence for pathogenicity, then annotated with published functional studies and associated biological systems/pathways. Twenty-two

previously identified pancreatic cancer risk genes and 337 germline variants were identified from 97 informative studies that met our inclusion criteria. Fifteen of these genes contained 66 variants predicted to be pathogenic (APC, ATM, BRCA1, BRCA2, CDKN2A, CFTR, CHEK2, MLH1, MSH2, NBN, PALB2, PALLD, PRSS1, SPINK1, TP53). Pancreatic cancer risk genes were organized into key biological mechanisms that promote pancreatic oncogenesis within an oncogenic model. Development of precision medicine approaches requires updated variant information within the framework of an oncogenic progression model. Complex risk modeling may improve interpretation of early biomarkers and guide pathway-specific treatment for pancreatic cancer in the future. Precision medicine is within reach.

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

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

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

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

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

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

Pancreas 2018 Oct;47(9):1078-1086

OBJECTIVE: The aim of this study was to evaluate the connection between pancreatic cancer (PC) and genetic variants associated with chronic pancreatitis via systematic review and meta-analysis. METHODS: The data search was performed in 3 major databases (PubMed, Embase, and Cochrane Library). The selected studies have looked into the presence of the pancreatitis-associated genes in patients with PC and in control subjects, the outcome being the frequency of the mutations in the 2 groups. For the binary outcomes, pooled odds ratio (OR) and 95% confidence interval (CI) were calculated. RESULTS: Ten articles proved to be eligible for the qualitative synthesis, and 8 articles were suitable for statistical analysis. Six case-control studies, comprising 929 PC cases and 1890 control subjects for serine protease inhibitor Kazal type 1 (SPINK1) mutations, and 5 case-control studies, comprising 1674 PC cases and 19,036 control subjects for CFTR mutations, were enrolled in our analysis. SPINK1 mutations showed no association with PC (OR, 1.52; 95% CI, 0.67-3.45; P = 0.315), whereas mutations in CFTR modestly increased the risk of PC (OR, 1.41; 95% CI, 1.07-1.84; P = 0.013). CONCLUSION: Our meta-analysis showed that mutations in CFTR modestly increase the risk of PC, whereas no association was found between SPINK1 and PC.

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

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

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

Purpose: Pancreatic ductal adenocarcinoma (PDAC) is a lethal cancer with lack of predictive biomarkers. We conducted a study to assess DNA damage repair (DDR) gene mutations as a predictive biomarker in PDAC patients treated with FOLFIRINOX.Experimental Design: Indiana University Simon Cancer Center pancreatic cancer database was used to identify patients with metastatic PDAC, treated with FOLFIRINOX and had tissue available for DNA sequencing. Baseline demographic, clinical, and pathologic information was gathered. DNA isolation and targeted sequencing was performed using the Ion AmpliSeq protocol. Overall survival (OS) analysis was conducted using Kaplan-Meier, logistic regression and Cox proportional hazard methods. Multivariate models were adjusted for age, gender, margin status, CA 19-9, adjuvant chemotherapy, tumor and nodal stage.Results: Overall, 36 patients were sequenced. DDR gene mutations were found in 12 patients. Mutations were seen in BRCA1 (N = 7), BRCA2 (N = 5), PALB2 (N = 3), MSH2 (N = 1), and FANCF (N = 1) of all the DDR genes sequenced. Median age was 65.5 years, 58% were male, 97.2% were Caucasian and 51.4% had any family history of cancer. The median OS was near significantly superior in those with DDR gene mutations present vs. absent [14 vs. 5 months; HR, 0.58; 95% confidence interval (CI), 0.29-1.14; log-rank P = 0.08]. Multivariate logistic (OR, 1.47; 95% CI, 1.04-2.06; P = 0.04) and Cox regression (HR, 0.37; 95% CI, 0.15-0.94; P = 0.04) showed presence of DDR gene mutations was associated with improved OS.Conclusions: In a single institution, retrospective study, we found that the presence of DDR gene mutations are associated with improved OS in PDAC patients treated with FOLFIRINOX. Clin Cancer Res; 1-8. ©2018 AACR.

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

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

https://www.sciencedirect.com/science/article/pii/S1424390318306331

- **Improving the accuracy of pancreatic cancer clinical staging by exploitation of nanoparticle-blood interactions: A pilot study**

https://www.sciencedirect.com/science/article/pii/S1424390318306070

- **DNA profile components predict malignant outcomes in select cases of intraductal papillary mucinous neoplasm with negative cytology**

https://www.sciencedirect.com/science/article/pii/S0039606018302836

- **Stratification of Pancreatic Ductal Adenocarcinomas Based on Tumor and Microenvironment Features**

https://www.sciencedirect.com/science/article/pii/S0016508518349199

- Galectin-3 Mediates Tumor Cell-Stroma Interactions by Activating Pancreatic Stellate Cells to Produce Cytokines via Integrin Signaling

Gastroenterology 2018 04;154(5):1524-1537.e6

BACKGROUND & AIMS: Pancreatic ductal adenocarcinoma (PDAC) is characterized by activated pancreatic stellate cells (PSCs), abundance of extracellular matrix (ECM), and production of cytokines and chemokines. Galectin 3 (GAL3), a -galactoside-specific lectin, contributes to PDAC development but its effects on the stroma and cytokine production are unclear. METHODS: The effect of recombinant human GAL3 (rGAL3) on activation of PSCs, production of cytokines, and ECM proteins was determined by proliferation, invasion, cytokine array, and quantitative polymerase chain reaction. We assessed co-cultures of PDAC cells with GAL3 genetic alterations with PSCs. Production of interleukin 8 (IL8) and activities of nuclear factor (NF)- B were determined by enzyme-linked immunosorbent assay and luciferase reporter analyses. We studied the effects of inhibitors of NF- B and integrin-linked kinase (ILK) on pathways activated by rGAL3. RESULTS: In analyses of the Gene Expression Omnibus database and our dataset, we observed higher levels of GAL3, IL8, and other cytokines in PDAC than in nontumor tissues. Production of IL8, granulocyte-macrophage colony-stimulating factor, chemokine ligand 1, and C-C motif chemokine ligand 2 increased in PSCs exposed to rGAL3 compared with controls. Culture of PSCs with PDAC cells that express different levels of GAL3 resulted in proliferation and invasion of PSCs that increased with level of GAL3. GAL3 stimulated transcription of IL8 through integrin subunit beta 1 (ITGB1) on PSCs, which activates NF- B through ILK. Inhibitors of ILK or NF- B or a neutralizing antibody against ITGB1 blocked transcription and production of IL8 from PSCs induced by rGAL3. The GAL3 inhibitor significantly reduced growth and metastases of orthotopic tumors that formed from PDAC and PSC cells co-implanted in mice. CONCLUSION: GAL3 activates PSC cells to produce inflammatory cytokines via ITGB1signaling to ILK and activation of NF- B. Inhibition of this pathway reduced growth and metastases of pancreatic orthotopic tumors in mice.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29274868

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

Gastroenterology 2018 09;155(3):933-934

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

- Reply

Gastroenterology 2018 09;155(3):934-935

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30098926

- Circulating Tumor Cells are an Independent Predictor of Shorter Survival in Patients Undergoing Resection for Pancreatic and Periampullary Adenocarcinoma

Annals of surgery 2018 Sep;():

OBJECTIVE: We evaluated the prognostic impact of circulating tumor cells (CTCs) for patients with presumed resectable pancreatic and periampullary cancers. SUMMARY OF BACKGROUND DATA: Initial treatment decisions for this group are currently taken without a reliable prognostic marker. The CellSearch

system allows standardized CTC-testing and has shown excellent specificity and prognostic value in other applications. METHODS: Preoperative blood samples from 242 patients between September 2009 and December 2014 were analyzed. One hundred seventy-nine patients underwent tumor resection, of whom 30 with stage-I tumors and duodenal cancer were assigned to the low-risk group, and the others to the high-risk group. Further 33 had advanced disease, 30 benign histology. Observation ended in December 2016. Cancer-specific survival (CSS) and disease-free survival (DFS) were calculated by log-rank and Cox regression. RESULTS: CTCs (CTC-positive; 1 CTC/7.5mL) were detected in 6.8% (10/147) of the high-risk patients and 6.2% (2/33) with advanced disease. No CTCs (CTC-negative) were detected in the low-risk patients or benign disease. In high-risk patients, median CSS for CTC-positive versus CTC-negative was 8.1 versus 20.0 months ($P < 0.0001$), and DFS 4.0 versus 10.5 months ($P < 0.001$). Median CSS in advanced disease was 7.7 months. Univariate hazard ratio (HR) of CTC-positivity was 3.4 ($P < 0.001$). In multivariable analysis, CTC-status remained independent (HR: 2.4, $P = 0.009$) when corrected for histological type (HR: 2.7, $P = 0.030$), nodal status (HR: 1.7, $P = 0.016$), and vascular infiltration (HR: 1.7, $P = 0.001$). CONCLUSION: Patients testing CTC-positive preoperatively showed a detrimental outcome despite successful tumor resections. Although the low CTC-rate seems a limiting factor, results indicate high specificity. Thus, preoperative analysis of CTCs by this test may guide treatment decisions and warrants further testing in clinical trials.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30216219

- Early Loss of Forkhead Transcription Factor, O Subgroup, Member 1 Protein in the Development of Pancreatic Ductal Adenocarcinoma

Pathobiology : journal of immunopathology, molecular and cellular biology 2018 Sep;():1-6

OBJECTIVES: Forkhead transcription factor, O subgroup, member 1 (FOXO1) is a regulatory protein that plays an essential role in cellular homeostasis. A biological function as a tumor suppressor has been proposed. Here, we examined FOXO1 expression in human pancreatic ductal adenocarcinoma (PDAC) and its precursor lesions. METHODS: We immunohistochemically labeled tissue samples from 47 patients with PDAC for FOXO1 protein. In addition, we extracted data from the Cancer Genome Atlas and the Cancer Cell Line Encyclopedia and studied a potential association with well-established genetic variants. A publicly available microarray dataset of 102 PDAC samples was used to explore the influence of FOXO1 expression on patients' clinical outcome. RESULTS: Normal ductal epithelium universally expressed nuclear and cytoplasmic FOXO1. Reduced expression was observed in PanIN lesions and PDAC of all cases. Analysis of several datasets showed that the FOXO1 gene transcript levels do not correlate with KRAS, TP53, SMAD4, or CDKN2A mutation status, but positively correlate with patients' outcomes. CONCLUSIONS: Loss of FOXO1 protein is identified as an early event during PDAC development and may be independent of the top 4 mutated cancer genes. Because of its strong expression in normal ductal cells, immunohistochemical detection of FOXO1 can function as a valuable test to establish the diagnosis of transformation and malignancy in pancreatic tissues.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30227407

- Circulating Nucleic Acids Associate with Outcomes of Patients with Pancreatic Cancer

Gastroenterology 2018 Sep;():

BACKGROUND & AIMS: We aimed to investigate the clinical utility of circulating tumor cell DNA (ctDNA) and exosome DNA (exoDNA) in pancreatic cancer. METHODS: We collected liquid biopsies from 194 patients undergoing treatment for localized or metastatic pancreatic adenocarcinoma from April 7, 2015 through October 13, 2017 (425 blood samples collected before (baseline) and during therapy). Additional liquid biopsies were collected from 37 disease controls. Droplet digital PCR was used to determine KRAS mutant allele fraction (MAF) from ctDNA and exoDNA purified from plasma. For the longitudinal analysis,

we analyzed exoDNA and ctDNA in 123 serial blood samples, from 34 patients. We performed analysis including cox regression, Fisher exact test, and Bayesian inference to associate KRAS MAFs in exoDNA and ctDNA with prognostic and predictive outcomes. RESULTS: In the 34 patients with potentially resectable tumors, an increase level of exoDNA following neoadjuvant therapy significantly associated with disease progression (P=.003), while ctDNA did not reveal correlations with outcomes. Concordance rates of KRAS mutations present in surgically resected tissue and detected in liquid biopsies was over 95%. On univariate analysis, patients with metastases and detectable ctDNA at baseline status had significantly shorter times of progression-free survival (hazard ratio [HR] for death, 1.8; 95% CI, 1.1-3.0; P=.019), and overall survival (OS) (HR, 2.8; 95% CI, 1.4-5.7; P=.0045) compared to patients without detectable ctDNA. On multivariate analysis, MAFs 5% in exoDNA was a significant predictor of progression-free survival (HR, 2.28; 95% CI 1.18-4.40; P=.014) and OS (HR, 3.46; 95% CI, 1.40-8.50; P=.007). A multi-analyte approach revealed detection of both ctDNA and exoDNA MAF 5% at baseline status as a significant predictor of OS (HR 7.73, 95% CI 2.61-22.91, P=0.00002) on multivariate analysis. In the longitudinal analysis, a MAF peak above 1% in exoDNA was significantly associated with radiological progression (P=.0003). CONCLUSIONS: In a prospective cohort of pancreatic cancer patients, we demonstrate how longitudinal monitoring using liquid biopsies through exoDNA and ctDNA, provides both predictive and prognostic information relevant towards therapeutic stratification.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30240661

- **Next Generation Sequencing of the cellular and liquid fraction of pancreatic cyst fluid supports discrimination of IPMN from pseudocysts and reveals cases with multiple mutated driver clones - first findings from the prospective ZYSTEUS biomarker study**

https://onlinelibrary.wiley.com/doi/abs/10.1002/gcc.22682

- **ARID1A, a SWI/SNF subunit, is critical to acinar cell homeostasis and regeneration and is a barrier to transformation and epithelial-mesenchymal transition in the pancreas**

https://gut.bmj.com/content/early/2018/09/18/gutjnl-2017-315541

- **Gene expression analysis of embryonic pancreas development master regulators and terminal cell fate markers in resected pancreatic cancer: A correlation with clinical outcome**

https://www.sciencedirect.com/science/article/pii/S1424390318306835

- Elevated expression of NFE2L3 predicts the poor prognosis of pancreatic cancer patients

Cell cycle (Georgetown, Tex.) 2018 ;17(17):2164-2174

The highly malignant feature and difficulties for early diagnosis are the key reasons contributing to the poor prognosis of pancreatic cancer (PC) patients. NFE2L3 is a nuclear transcription factor, which has been reported an important biomarker of several tumors. But the role of NFE2L3 in PC remained undefined. Herein, through qPCR and immunohistochemistry, we found a significantly increased NFE2L3 in PC tissues

as compared with adjacent non-tumor tissues. While reducing NFE2L3 expression suppressed the invasion abilities of PC cells, elevated NFE2L3 was found associated with lymph node metastasis (P = 0.001; HR = 3.95; 95% CI: 1.70 - 9.17) and advanced TNM stages (P < 0.001; HR = 4.06; 95% CI: 1.74 - 9.46). Consistently, data from both our two cohorts and the TCGA database revealed that higher NFE2L3 PC carriers had worse outcomes than those lower NFE2L3 expressers. Lastly, we confirmed the regulatory role of NFE2L3 on VEGFA, an important player involved in tumor angiogenesis. Collectively, our investigations suggested the oncogenic role of NFE2L3 in PC development and provided the rational for future adding NFE2L3 for the risk assessment of PC patients. NFE2L3: NF-E2-related factor 3; UHMK1: U2AF homology motif kinase 1; VEGFA: vascular endothelial growth factor A; GEO: gene expression omnibus; TCGA: The Cancer Genome Atlas; HPDE: human pancreas duct cells; OS: overall survival; IHC: immunohistochemistry; FFPE: formalin-fixed and paraffin-embedded; SEM: standard error of mean.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30196752

- Integrating MicroRNA Expression Profiling Studies to Systematically Evaluate the Diagnostic Value of MicroRNAs in Pancreatic Cancer and Validate Their Prognostic Significance with the Cancer Genome Atlas Data

Cellular physiology and biochemistry : international journal of experimental cellular physiology, biochemistry, and pharmacology 2018 ;49(2):678-695

BACKGROUND/AIMS: MicroRNAs (miRNAs) are promising biomarkers for pancreatic cancer (PaCa). However, systemic and unified evaluations of the diagnostic value of miRNAs are lacking. Therefore, we performed a systematic evaluation based on miRNA expression profiling studies. METHODS: We obtained miRNA expression profiling studies from Gene Expression Omnibus (GEO) and ArrayExpress (AE) databases and calculated the pooled sensitivity, specificity, and summary area under a receiver operating characteristic (ROC) curve for every miRNA. According to the area under the curve (AUC), we identified the miRNAs with diagnostic potentiality and validated their prognostic role in The Cancer Genome Atlas (TCGA) data. Gene Ontology (GO) annotations and pathway enrichments of the target genes of the miRNAs were evaluated using bioinformatics tools. RESULTS: Ten miRNA expression profiling studies including 958 patients were used in this diagnostic meta-analysis. A total of 693 miRNAs were measured in more than 9 studies. The top 50 miRNAs with high predictive values for PaCa were identified. Among them, miR-130b had the best predictive value for PaCa (pooled sensitivity: 0.73 [95% confidence intervals (CI) 0.44-0.91], specificity: 0.81 [95% CI 0.59-0.93], and AUC: 0.84 [95% CI 0.73-0.95]). We identified nine miRNAs (miR-23a, miR-30a, miR-125a, miR-129-1, miR-181b-1, miR-203, miR-221, miR-222, and miR-1301) associated with overall survival in PaCa patients by combining our results with TCGA data. The results of a Cox model revealed that two miRNAs (miR-30a [hazard ratio (HR)=2.43, 95% CI 1.05-5.59; p=0.037] and miR-203 [HR=3.14, 95% CI 1.28-7.71; p=0.012]) were independent risk factors for prognosis in PaCa patients. In total, 405 target genes of the nine miRNAs were enriched with Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways, and cancer-associated pathways such as Ras signaling pathways, phospholipase D signaling pathway, and AMP-activated protein kinase (AMPK) signaling pathway were revealed among the top 20 enriched pathways. There were significant negative correlations between miR-181b-1 and miR-125a expression levels and the methylation status of their promoter region. CONCLUSION: Our study performed a systematic evaluation of the diagnostic value of miRNAs based on miRNA expression profiling studies. We identified that miR-23a, miR-30a, miR-125a, miR-129-1, miR-181b-1, miR-203, miR-221, miR-222, and miR-1301 had moderate diagnostic value for PaCa and predicted overall survival in PaCa patients.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30165365

- Pancreatic cancer survival analysis defines a signature that predicts outcome

PloS one 2018 ;13(8):e0201751

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

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

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

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

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

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

- Prognostic value of minichromosome maintenance mRNA expression in early-stage pancreatic ductal adenocarcinoma patients after pancreaticoduodenectomy

Cancer management and research 2018 ;10():3255-3271

Background: The aim of the current study was to investigate the potential prognostic value of minichromosome maintenance (MCM) genes in patients with early-stage pancreatic ductal adenocarcinoma (PDAC) after pancreaticoduodenectomy by using the RNA-sequencing dataset from The Cancer Genome Atlas (TCGA). Methods: An RNA-sequencing dataset of 112 early-stage PDAC patients who received a pancreaticoduodenectomy was obtained from TCGA. Survival analysis was used to identify potential prognostic values of MCM genes in PDAC overall survival (OS). Results: Through mining public databases, we observed that MCM genes (MCM2, MCM3, MCM4, MCM5, MCM6, and MCM7) were upregulated in pancreatic cancer tumor tissue and have a strong positive coexpression with each other. Multivariate survival analysis indicated that a high expression of MCM4 significantly increased the risk of death in patients with PDAC, and time-dependent receiver operating characteristic analysis showed an area under the curve of 0.655, 0.587, and 0.509 for a 1-, 2-, and 3-year PDAC OS prediction, respectively. Comprehensive survival analysis of MCM4 using stratified and joint effects survival analysis suggests that MCM4 may be an independent prognostic indicator for PDAC OS. Gene set enrichment analysis indicated that MCM4 may participate in multiple biologic processes and pathways, including DNA replication, cell cycle, tumor protein p53, and Notch signaling pathways, thereby affecting prognosis of PDAC patients. Conclusions: Our study indicates that MCM2-7 were upregulated in pancreatic cancer tumor tissues, and mRNA expression of MCM4 may serve as an independent prognostic indicator for PDAC OS prediction after pancreaticoduodenectomy.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30233242

- Subgroup analysis reveals molecular heterogeneity and provides potential precise treatment for pancreatic cancers

OncoTargets and therapy 2018 ;11():5811-5819

Background: The relationship between molecular heterogeneity and clinical features of pancreatic cancer remains unclear. In this study, pancreatic cancer was divided into different subgroups to explore its specific molecular characteristics and potential therapeutic targets. Patients and methods: Expression profiling data were downloaded from The Cancer Genome Atlas database and standardized. Bioinformatics techniques such as unsupervised hierarchical clustering was used to explore the optimal molecular subgroups in pancreatic cancer. Clinical pathological features and pathways in each subgroup were also analyzed to find out the potential clinical applications and initial promotive mechanisms of pancreatic cancer. Results: Pancreatic cancer was divided into three subgroups based on different gene expression features. Patients included in each subgroup had specific biological features and responded significantly different to chemotherapy. Conclusion: Three distinct subgroups of pancreatic cancer were identified, which means that patients in each subgroup might benefit from targeted individual management.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30254473

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

BMC cancer 2018 Jul;18(1):772

BACKGROUND: Label-retaining cancer cells (LRCC) have been proposed as a model of slowly cycling cancer stem cells (CSC) which mediate resistance to chemotherapy, tumor recurrence, and metastasis. The molecular mechanisms of chemoresistance in LRCC remain to-date incompletely understood. This study aims to identify molecular targets in LRCC that can be exploited to overcome resistance to gemcitabine, a standard chemotherapy agent for the treatment of pancreas cancer. METHODS: LRCC were isolated

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

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

- HNF1A is a novel oncogene that regulates human pancreatic cancer stem cell properties

eLife 2018 Aug;7():

The biological properties of pancreatic cancer stem cells (PCSCs) remain incompletely defined and the central regulators are unknown. By bioinformatic analysis of a human PCSC-enriched gene signature, we identified the transcription factor HNF1A as a putative central regulator of PCSC function. Levels of HNF1A and its target genes were found to be elevated in PCSCs and tumorspheres, and depletion of HNF1A resulted in growth inhibition, apoptosis, impaired tumorsphere formation, decreased PCSC marker expression, and downregulation of POU5F1/OCT4 expression. Conversely, HNF1A overexpression increased PCSC marker expression and tumorsphere formation in pancreatic cancer cells and drove pancreatic ductal adenocarcinoma (PDA) cell growth. Importantly, depletion of HNF1A in xenografts impaired tumor growth and depleted PCSC marker-positive cells in vivo. Finally, we established an HNF1A-dependent gene signature in PDA cells that significantly correlated with reduced survivability in patients. These findings identify HNF1A as a central transcriptional regulator of PCSC properties and novel oncogene in PDA.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30074477

- **Genomic Profiling and Potentially Targetable Alterations in Pancreatic Ductal Adenocarcinoma**

https://link.springer.com/article/10.1007/s11938-018-0195-x

- **Real-time Genomic Characterization of Advanced Pancreatic Cancer to Enable Precision Medicine**

http://cancerdiscovery.aacrjournals.org/content/8/9/1096?iss=9

- **Organoid Profiling Identifies Common Responders to Chemotherapy in Pancreatic Cancer**

http://cancerdiscovery.aacrjournals.org/content/8/9/1112?iss=9

- **Pentose conversions support the tumorigenesis of pancreatic cancer distant metastases**
  Oncogene volume 37, pages 5248–5256 (2018)

https://www.nature.com/articles/s41388-018-0346-5

- Complex HuR function in pancreatic cancer cells

Wiley interdisciplinary reviews. RNA 2018 05;9(3):e1469

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers with dismal patient outcomes. The underlying core genetic drivers of disease have been identified in human tumor specimens and described in genetically engineered mouse models. These genetic drivers of PDAC include KRAS signaling, TP53 mutations, and genetic loss of the SMAD4 tumor suppressor protein. Beyond the known mutational landscape of PDAC genomes, alternative disrupted targets that extend beyond conventional genetic mutations have been elusive and understudied in the context of PDAC cell therapeutic resistance and survival. This last point is important because PDAC tumors have a unique and complex tumor microenvironment that includes hypoxic and nutrient-deprived niches that could select for cell populations that garner therapeutic resistance, explaining tumor heterogeneity in regards to response to different therapies. We and others have embarked in a line of investigation focused on the key molecular mechanism of posttranscriptional gene regulation that is altered in PDAC cells and supports this pro-survival phenotype intrinsic to PDAC cells. Specifically, the key regulator of this mechanism is a RNA-binding protein, HuR (ELAVL1), first described in cancer nearly two decades ago. Herein, we will provide a brief overview of the work demonstrating the importance of this RNA-binding protein in PDAC biology and then provide insight into ongoing work developing therapeutic strategies aimed at targeting this molecule in PDAC cells. This article is categorized under: RNA in Disease and Development > RNA in Disease.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29452455

- **Norepinephrine enhances cell viability and invasion, and inhibits apoptosis of pancreatic cancer cells in a Notch-1-dependent manner**

https://www.spandidos-publications.com/or/40/5/3015

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Bile Ducts

- Recurrent Mutations in APC and CTNNB1 and Activated Wnt/ -catenin Signaling in Intraductal Papillary Neoplasms of the Bile Duct: A Whole Exome Sequencing Study

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

This study aimed to elucidate the genetic landscape of biliary papillary neoplasms. Of 28 cases examined, 7 underwent whole exome sequencing, while the remaining 21 were used for validation studies with targeted sequencing. In the whole exome sequencing study, 4/7 cases had mutations in either APC or CTNNB1, both of which belong to the Wnt/ -catenin pathway. Somatic mutations were also identified in genes involved in RAS signaling (KRAS, BRAF), a cell cycle regulator (CDC27), histone methyltransferase (KMT2C, KMT2D), and DNA mismatch repair (MSH3, MSH6, PMS1). Combined with discovery and validation cohorts, mutations in APC or CTNNB1 were observed in 6/28 subjects (21%) and were mutually exclusive. When the cases were classified into intraductal papillary neoplasms of the bile duct (IPNBs, n=14) and papillary cholangiocarcinomas (n=14) based on the recently proposed classification criteria, mutations in APC and CTNNB1 appeared to be entirely restricted to IPNBs with 6/14 cases (43%) harboring mutations in either gene. These genetic alterations were detected across the 3 nonintestinal histologic types. In immunohistochemistry, the aberrant cytoplasmic and/or nuclear expression of -catenin was found in not only 5/6 IPNBs with APC or CTNNB1 mutations, but also 6/8 cases with wild-type APC and CTNNB1 (total 79%). In addition, APC and CTNNB1 alterations were exceptional in nonpapillary cholangiocarcinomas (n=29) with a single case harboring CTNNB1 mutation (3%). This study demonstrated recurrent mutations in APC and CTNNB1 in nonintestinal-type IPNBs, suggesting that activation of the Wnt/ -catenin signaling pathway is relevant to the development and progression of IPNBs.

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30212390

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

Annals of surgical oncology 2018 Nov;25(12):3728-3737

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

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

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Neuroendocrine

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

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

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