Recent Articles For Pancreatobiliary Pathology Society Journal Watch

Others

Last Update on 2019-08-20

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PBPath Journal Watch Articles

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

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Recent Articles

Pancreas

- Response to the Letter to the Editor "Minimally Invasive Versus Open Distal Pancreatectomy (LEOPARD)"

Annals of surgery 2019 Aug;():

- Significance of Examined Lymph Node Number in Accurate Staging and Long-term Survival in Resected Stage I-II Pancreatic Cancer-More is Better? A Large International Population-based Cohort Study

Annals of surgery 2019 Aug;():

OBJECTIVE: This large international cohort study aimed to investigate the associations of examined lymph node (ELN) number with accurate staging and long-term survival in pancreatic adenocarcinoma (PaC) and to robustly determine the minimal and optimal ELN thresholds. SUMMARY BACKGROUND DATA: ELN number is an important quality metric in cancer care. The recommended minimal ELN number in PaC to accurately stage cancer varies greatly across guidelines, and the optimal number especially to adequately stratify patient survival has not yet been established. METHODS: Population-based data on patients with stage I to II PaC resected in 2003 to 2015 from the US Surveillance, Epidemiology, and End Results (SEER)-18 Program and Netherlands National Cancer Registry (NCR) were analyzed. Associations of ELN number with stage migration and survival were evaluated using multivariable-adjusted logistic and Cox regression models, respectively. The series of odds ratios (ORs) for negative-to-positive node stage migration and hazard ratios (HRs) for survival with more ELNs were fitted using a LOWESS smoother, and structural breakpoints were determined by Chow test. RESULTS: Overall 16,241 patients were analyzed. With increasing ELN number, both cohorts exhibited significant proportional increases from node-negative to node-positive disease [ORSEER-18=1.05, 95% confidence interval (CI) = 1.04-1.05; ORNCR = 1.10, 95% CI = 1.08-1.12] and serial improvements in survival (HRSEER-18 = 0.98, 95% CI = 0.98-0.99; HRNCR = 0.98, 95% CI = 0.97-0.99) per additional ELN after controlling for confounders. Associations for stage migration and survival remained significant in most stratifications by patient, tumor, and treatment factors. Cut-point analyses suggested a minimal threshold ELN number of 11 and an optimal number of 19, which were validated both internally in the derivative US cohort and externally in the Dutch cohort with the ability to well discriminate different probabilities of both survival and stage migration. CONCLUSIONS: In stage I to II PaC, more ELNs are associated with more precise nodal staging, which might largely explain the survival association. Our observational study does not suggest causality, and does not encourage more extended lymphadenectomy before further randomized evidence is obtained. Our results robustly conclude 11 ELNs as the minimal and suggest 19 ELNs as the optimal cut-points, for evaluating quality of lymph node examination and possibly for stratifying postoperative prognosis.

- Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

The lancet. Diabetes & endocrinology 2019 Aug;():

BACKGROUND: Glucagon-like peptide-1 (GLP-1) receptor agonists differ in their structure and duration of action and have been studied in trials of varying sizes and with different patient populations, with inconsistent effects on cardiovascular outcomes reported. We aimed to synthesise the available evidence by doing a systematic review and meta-analysis of cardiovascular outcome trials of these drugs. METHODS: We searched MEDLINE (via PubMed) and the Cochrane Central Register of Controlled Trials for eligible placebo-controlled trials reporting major adverse cardiovascular events (MACE; ie, cardiovascular death, stroke, or myocardial infarction) up to June 15, 2019. We did a meta-analysis using a random-effects model to estimate overall hazard ratios (HRs) for MACE, its components, death from any cause, hospital admission for heart failure, kidney outcomes, and key safety outcomes (severe hypoglycaemia, pancreatitis, and pancreatic cancer). We also examined MACE in several subgroups based on patient characteristics (history of cardiovascular disease, BMI, age, baseline HbA1c, and baseline estimated glomerular filtration rate), trial duration, treatment dosing interval, and structural homology. FINDINGS: Of 27 publications screened, seven trials, with a combined total of 56 004 participants, were included: ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN-6 (semaglutide), EXSCEL (exenatide), Harmony Outcomes (albiglutide), REWIND (dulaglutide), and PIONEER 6 (oral semaglutide). Overall, GLP-1 receptor agonist treatment reduced MACE by 12% (HR $0\cdot88$, 95% CI $0\cdot82$-$0\cdot94$; p<$0\cdot0001$). There was no statistically significant heterogeneity across the subgroups examined. HRs were $0\cdot88$ (95% CI $0\cdot81$-$0\cdot96$; p=$0\cdot003$) for death from cardiovascular causes, $0\cdot84$ ($0\cdot76$-$0\cdot93$; p<$0\cdot0001$) for fatal or non-fatal stroke, and $0\cdot91$ ($0\cdot84$-$1\cdot00$; p=$0\cdot043$) for fatal or non-fatal myocardial infarction. GLP-1 receptor agonist treatment reduced all-cause mortality by 12% ($0\cdot88$, $0\cdot83$-$0\cdot95$; p=$0\cdot001$), hospital admission for heart failure by 9% ($0\cdot91$, $0\cdot83$-$0\cdot99$; p=$0\cdot028$), and a broad composite kidney outcome (development of new-onset macroalbuminuria, decline in estimated glomerular filtration rate [or increase in creatinine], progression to end-stage kidney disease, or death attributable to kidney causes) by 17% ($0\cdot83$, $0\cdot78$-$0\cdot89$; p<$0\cdot0001$), mainly due to a reduction in urinary albumin excretion. There was no increase in risk of severe hypoglycaemia, pancreatitis, or pancreatic cancer. INTERPRETATION: Treatment with GLP-1 receptor agonists has beneficial effects on cardiovascular, mortality, and kidney outcomes in patients with type 2 diabetes. FUNDING: None.

- Long-term outcomes of therapeutic ERCP in pediatric patients with pancreas divisum presenting with acute recurrent or chronic pancreatitis

Pancreatology : official journal of the International Association of Pancreatology (IAP) ... [et al.] 2019 Aug;():

OBJECTIVES: The aim of this study was to evaluate the long-term outcomes of therapeutic endoscopic retrograde cholangiopancreatography (ERCP) for pediatric patients with pancreas divisum (PD) presenting with acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP). METHODS: Between May 2008 and August 2017, pediatric patients with PD who received endotherapy at Ruijin Hospital were identified and grouped according to clinical presentation, namely ARP and CP. Primary success was defined as patients' improvement in symptoms after index ERCPs, without further intervention or any analgesic. RESULTS: A total of 74 ERCPs were performed in 38 pediatric patients. The frequency of at least 1 genetic mutation identified in patients with ARP and CP was 44.4% and 68.4%, respectively. Patients with CP required more ERCPs than those with ARP (2.4 ± 1.7 vs. 1.1 ± 0.4, P = 0.005). The incidence of post-ERCP complications was 14.9%, including pancreatitis of 13.5% and hemorrhage of 1.4%. During a median follow-up duration of 41 months (range, 12-123 months), the frequency of pancreatitis episodes decreased significantly from 2.31

to 0.45 (P < 0.0001). The 25% recurrence and reintervention rates were estimated at 25 and 48 months, respectively, without significant difference between patients with ARP or CP. There was a nonsignificant trend towards a higher rate of primary success in patients with ARP than those with CP (92.9% vs. 69.6%, P = 0.123). After further endotherapy, 91.3% patients with CP improved clinically. CONCLUSIONS: Therapeutic ERCP is an effective and safe intervention for pediatric patients with symptomatic PD. Patients presenting with CP seem to achieve improvement after additional ERCPs.

doi: https://doi.org/10.1016/j.pan.2019.08.004

- First-in-human Study of Mivebresib (ABBV-075), an Oral Pan-inhibitor of Bromodomain and Extra Terminal Proteins, in Patients with Relapsed/Refractory Solid Tumors

Clinical cancer research : an official journal of the American Association for Cancer Research 2019 Aug;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31420359

PURPOSE: Bromodomain and extra-terminal (BET) proteins play important roles in transcriptional regulation relevant to cancer pathogenesis, and therapeutic targeting/inhibition of BET causes apoptosis of cancer cells in vitro In this first-in-human study of the pan-BET inhibitor mivebresib (ABBV-075) the safety profile, maximal tolerated dose (MTD), and recommended phase 2 dose (RP2D) were determined in patients with advanced solid tumors. EXPERIMENTAL DESIGN: A 3+3 dose escalation for different mivebresib dosing schedules (daily, Monday/Wednesday/Friday [M-W-F], 4 days on/3 off [4/7]) was followed by dose expansion in prostate cancer patients. Endpoints were safety, tolerability, pharmacokinetics, and preliminary antitumor activity. RESULTS: Seventy-two patients with solid tumors [14% uveal melanoma; 11% colorectal, 11% breast; 8% pancreatic; 7% head/neck; 49% others] were treated with mivebresib during dose escalation, and 12 additional patients with prostate cancer in expansion cohort. Most common TEAEs related to mivebresib were dysgeusia (49%), thrombocytopenia (48%), fatigue (26%) and nausea (25%). Most common grade 3/4 TEAEs related to mivebresib were thrombocytopenia (35%) and anemia (6%). Dose-limiting toxicities included thrombocytopenia (2mg daily; 4.5mg M-W-F), gastrointestinal bleed (2mg daily), hypertension (2-3mg 4/7), fatigue, decreased appetite, and aspartate aminotransferase elevation (4mg M-W-F). Of 61 evaluable patients from dose-escalation, 26 (43%) had stable disease and 35 (57%) had progressive disease. Median progression-free survival was 1.8 months (95%CI: 1.8,1.9). CONCLUSIONS: Based on safety and tolerability, mivebresib RP2D is 1.5mg for the daily schedule, 2.5mg for 4/7 and 3mg for M-W-F. Mivebresib has a tolerable safety profile and stable disease was observed in some patients with malignant solid tumors.

doi: https://doi.org/10.1158/1078-0432.CCR-19-0578

- Pancreatic tumor in type 1 autoimmune pancreatitis: a diagnostic challenge

BMC cancer 2019 Aug;19(1):814

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31419961

BACKGROUND: The co-occurrence of type 1 autoimmune pancreatitis (AIP) and pancreatic tumor (PaT) has been previously reported. Pure AIP cases have favorable prognosis and are primarily treated with steroids, while AIP cases with PaT are associated with poor prognosis where the primary management is pancreatic resection. However, it's a challenge to timely identify the concurrent PaT in AIP because of their similar clinical and radiological manifestations. METHODS: We retrospectively reviewed the data in two medical centers from January 2010 to April 2019. The inclusion criteria were as follows: 1) completion of abdominal CT imaging before invasive procedures to the pancreas, 2) a final diagnosis of type 1 AIP using the 2011 international consensus diagnostic criteria, 3) follow-up duration of at least one month unless AIP and PaT were identified simultaneously. The presence of PaT in AIP was made based on histopathological confirmation, and the absence of PaT in AIP was defined as no pathological or radiological evidence of

concurrent PaT. Clinical and radiological characteristics including gender, age, surveillance period, serum IgG4 and Ca-199 levels, biopsy, extrapancreatic involvement, CT and MR (if performed) imaging characteristics were compared between AIP with and without PaT. The Fisher's exact test was used for qualitative variables, and nonparametric Mann-Whitney test for quantitative variables. A p value 0.05 was considered statistically significant. RESULTS: A total of 74 patients with type 1 AIP were included, of which 5 (6.7%) had the concurrent PaT. The subtypes were pancreatic ductal adenocarcinoma (3/5), solitary extramedullary plasmacytoma in the pancreas (1/5) and cholangiocarcinoma in the pancreatic segment (1/5), respectively. Gender (p = 0.044), the pattern of pancreatic enlargement (p = 0.003), heterogeneity (p = 0.015), low-density (p = 0.004) on CT and rim enhancement on MRI (p = 0.050) differed significantly between AIP with and without PaT. None of the low-density characteristics on CT or other assessed MRI characteristics could significantly differentiate the two groups (p>0.05). CONCLUSIONS: Female, focal pancreatic enlargement, pancreatic heterogeneity, low-density on CT and rim enhancement on MRI are suggestive of the concurrent PaT in type 1 AIP. The characteristics of low-density on CT or other MRI characteristics did not provide further diagnostic values.

- **Transgenic Expression of PRSS1R122H Sensitizes Mice to Pancreatitis**

BACKGROUND & AIMS: Mutations in the trypsinogen gene (PRSS1) cause human hereditary pancreatitis. However, it is not clear how mutant forms of PRSS1 contribute to disease development. We studied the effects of expressing mutant forms of human PRSS1 in mice. METHODS: We expressed forms of PRSS1 with and without the mutation encoding R122H (PRSS1R122H) specifically in pancreatic acinar cells under control of a full-length pancreatic elastase gene promoter. Mice that did not express these transgenes were used as controls. Mice were given injections of caerulein to induce acute pancreatitis or injections of lipopolysaccharide (LPS) to induce chronic pancreatitis. Other groups of mice were fed ethanol or placed on a high-fat diet to induce pancreatitis. Pancreata were collected and analyzed by histology, immunoblots, real-time PCR, and immunohistochemistry. Trypsin enzymatic activity and chymotrypsin enzymatic activity were measured in pancreatic homogenates. Blood was collected and serum amylase activity was measured. RESULTS: Pancreata from mice expressing transgenes encoding PRSS1 or PRSS1R122H had focal areas of inflammation; these lesions were more prominent in mice that express PRSS1R122H. Pancreata from mice that express PRSS1 or PRSS1R122H had increased levels of HSP70 and NRF2 and reduced levels of chymotrypsin C (CTRC), compared with control mice. Increased expression of PRSS1 or PRSS1R122H increased focal damage in pancreatic tissues and increased the severity of acute pancreatitis after caerulein injection. Administration of LPS exacerbated inflammation in mice that express PRSS1R122H compared to mice that express PRSS1 or control mice. Mice that express PRSS1R122H developed more severe pancreatitis after ethanol feeding or a high-fat diet than mice that express PRSS1 or control mice. Pancreata from mice that express PRSS1R122H had more DNA damage, apoptosis, and collagen deposition and increased trypsin activity and infiltration by inflammatory cells than mice that express PRSS1 or control mice. CONCLUSIONS: Expression of a transgene encoding PRSS1R122H in mice promoted inflammation and increase the severity of pancreatitis, compared with mice that express PRSS1 or control mice. These mice might be used as a model for human hereditary pancreatitis and can be studied to determine mechanisms of induction of pancreatitis by LPS, ethanol, or a high-fat diet.

- Perioperative Gemcitabine + Erlotinib Plus Pancreaticoduodenectomy for Resectable Pancreatic Adenocarcinoma: ACOSOG Z5041 (Alliance) Phase II Trial

Annals of surgical oncology 2019 Aug;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31418130

BACKGROUND: There is considerable interest in a neoadjuvant approach for resectable pancreatic ductal adenocarcinoma (PDAC). This study evaluated perioperative gemcitabine + erlotinib (G+E) for resectable PDAC. METHODS: A multicenter, cooperative group, single-arm, phase II trial was conducted between April 2009 and November 2013 (ACOSOG Z5041). Patients with biopsy-confirmed PDAC in the pancreatic head without evidence of involvement of major mesenteric vessels (resectable) were eligible. Patients (n = 123) received an 8-week cycle of G+E before and after surgery. The primary endpoint was 2-year overall survival (OS), and secondary endpoints included toxicity, response, resection rate, and time to progression. Resectability was assessed retrospectively by central review. The study closed early due to slow accrual, and no formal hypothesis testing was performed. RESULTS: Overall, 114 patients were eligible, consented, and initiated protocol treatment. By central radiologic review, 97 (85%) of the 114 patients met the protocol-defined resectability criteria. Grade 3+ toxicity was reported in 60% and 79% of patients during the neoadjuvant phase and overall, respectively. Twenty-two of 114 (19%) patients did not proceed to surgery; 83 patients (73%) were successfully resected. R0 and R1 margins were obtained in 67 (81%) and 16 (19%) resected patients, respectively, and 54 patients completed postoperative G+E (65%). The 2-year OS rate for the entire cohort (n = 114) was 40% (95% confidence interval [CI] 31-50), with a median OS of 21.3 months (95% CI 17.2-25.9). The 2-year OS rate for resected patients (n = 83) was 52% (95% CI 41-63), with a median OS of 25.4 months (95% CI 21.8-29.6). CONCLUSIONS: For resectable PDAC, perioperative G+E is feasible. Further evaluation of neoadjuvant strategies in resectable PDAC is warranted with more active systemic regimens.

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- Cell phenotypic plasticity requires autophagic flux driven by YAP/TAZ mechanotransduction

Proceedings of the National Academy of Sciences of the United States of America 2019 Aug;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31416916

Autophagy, besides ensuring energy metabolism and organelle renewal, is crucial for the biology of adult normal and cancer stem cells. However, it remains incompletely understood how autophagy connects to stemness factors and the nature of the microenvironmental signals that pattern autophagy in different cell types. Here we advance in these directions by reporting that YAP/TAZ transcriptionally control autophagy, being critical for autophagosomal degradation into autolysosomes. YAP/TAZ are downstream effectors of cellular mechanotransduction and indeed we found that cell mechanics, dictated by the physical property of the ECM and cytoskeletal tension, profoundly impact on autophagic flux in a YAP/TAZ-mediated manner. Functionally, by using pancreatic and mammary organoid cultures, we found that YAP/TAZ-regulated autophagy is essential in normal cells for YAP/TAZ-mediated dedifferentiation and acquisition of self-renewing properties. In tumor cells, the YAP/TAZ-autophagy connection is key to sustain transformed traits and for acquisition of a cancer stem cell state by otherwise more benign cells. Mechanistically, YAP/TAZ promote autophagic flux by directly promoting the expression of Armus, a RAB7-GAP required for autophagosome turnover and whose add-back rescues autophagy in YAP/TAZ-depleted cells. These findings expand the influence of YAP/TAZ mechanotransduction to the control of autophagy and, vice versa, the role of autophagy in YAP/TAZ biology, and suggest a mechanism to coordinate transcriptional rewiring with cytoplasmic restructuring during cell reprogramming.

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- A multicenter, open-label, single-arm study of anamorelin (ONO-7643) in advanced gastrointestinal cancer patients with cancer cachexia

Cancer 2019 Aug;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31415709

BACKGROUND: Cancer cachexia is characterized by weight loss and is associated with increased morbidity and mortality in patients with cancer. Anamorelin (ONO-7643; ANAM) is a novel and selective ghrelin receptor agonist that improves appetite, lean body mass (LBM), body weight, and anorexia. METHODS: This multicenter, open-label, single-arm study investigated the efficacy and safety of 100 mg anamorelin in 50 Japanese patients with advanced and unresectable gastrointestinal (colorectal, gastric, or pancreatic) cancer. ANAM was administered once daily over 12 weeks. The primary endpoint was the proportion of patients that maintained or gained LBM over the course of the study. Secondary endpoints included changes in LBM, body weight, quality of life (QoL), and nutritional status biomarkers. RESULTS: The proportion of patients who responded to treatment was 63.3% (95% CI, 48.3%-76.6%), with a least square mean $\pm$ SE change in LBM and body weight from baseline of 1.89 ± 0.36 kg and 1.41 ± 0.61 kg, respectively. Appetite-related questions on the QoL questionnaire showed that ANAM improved appetite. Adverse events occurred in 79.6% of patients, and the most common treatment-related adverse events were increased -glutamyl transpeptidase (8.2%), diabetes mellitus (6.1%), hyperglycemia (6.1%), and prolonged QRS complex (6.1%). CONCLUSIONS: ANAM improved anorexia and patients' nutritional status, resulting in rapid increases in LBM and body weight in patients with advanced gastrointestinal cancer who had cancer cachexia. ANAM treatment was well tolerated over 12 weeks. ANAM is a potential clinically beneficial pharmacotherapeutic option for patients with advanced gastrointestinal cancer who have cancer cachexia.

doi: https://doi.org/10.1002/cncr.32406

- Grading Pancreatic Neuroendocrine Tumors by Ki-67 Index Evaluated on Fine-Needle Aspiration Cell Block Material

American journal of clinical pathology 2019 Aug;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31415691

OBJECTIVES: This study aimed to determine whether Ki-67 index evaluated on cytologic material could reliably grade pancreatic neuroendocrine tumors (PanNETs). METHODS: Cases with adequate cell block and available surgical specimens were included. Ki-67 index was calculated using "eyeballing," "hot spot," and "complete" counting methods. RESULTS: The overall concordance rates between cytology and surgical specimens were 71%, 73%, and 59%, respectively, by using eyeballing, hot spot, and complete counting approaches. All grade 1 tumors were correctly graded on cytology, but in grade 2 tumors concordance rates were only 36%, 41%, and 9%, respectively. All grade 2 tumors were undergraded when cell blocks contained fewer than 1,000 cells, while concordance rate increased to 57%, 64%, and 14%, respectively, in cases with 1,000 cells or more. CONCLUSIONS: Grade 2 PanNETs can be significantly undergraded when Ki-67 index is evaluated on cell block material. In cases with 1,000 or more cells, the hot spot counting method has better correlation with surgical specimens.

doi: https://doi.org/10.1093/ajcp/aqz110

- Randomized Comparison of Gastric Tube Reconstruction With and Without Duodenal Diversion Plus Roux-en-Y Anastomosis After Esophagectomy

Annals of surgery 2019 Aug;():

OBJECTIVE: This prospective randomized phase-II trial examined whether gastric reconstruction with duodenal diversion plus Roux-en-Y anastomosis(RY) minimized gastroduodenal reflux and delayed gastric emptying compared with standard gastric reconstruction. SUMMARY BACKGROUND DATA: There is no established standard surgical procedure to prevent both gastroduodenal reflux and delayed gastric emptying simultaneously. METHODS: Sixty patients with thoracic esophageal cancer scheduled to undergo esophagectomy with retrosternal gastric tube reconstruction were randomly allocated to standard gastric reconstruction (non-RY, n = 31) or gastric reconstruction with duodenal diversion plus RY (n = 29) groups. Primary endpoint was quality of life assessed by DAUGS-32 score 1 year after surgery. Secondary endpoints were the extent of postoperative duodenal juice reflux into the gastric tube, postoperative morbidity, endoscopic findings, body weight changes, and nutritional status. RESULTS: Preoperative clinicopathological characteristics and postoperative morbidity did not differ significantly between groups. However, operation time and blood loss volume were significantly higher in the RY group. Pancreatic amylase concentrations in the gastric conduit on postoperative days 2, 3, and 7 were higher in the non-RY group. Postoperative endoscopic examination showed residual gastric content in 7 of 17 patients in the non-RY group but in none in the RY group (P = 0.012). Quality of life was significantly favorable in the RY group with regard to reflux symptoms and food passage dysfunction. Postoperative body weight changes, serum albumin levels, and peripheral blood lymphocyte counts were not significantly different between groups. CONCLUSION: Gastric reconstruction with duodenal diversion plus RY is effective in improving both gastroduodenal reflux and delayed gastric emptying.

- Rosai-Dorfman Disease of the Digestive System-Beware Vasculopathy: A Clinicopathologic Analysis

Rosai-Dorfman disease (RDD) is a rare non-Langerhans cell histiocytic proliferation that occurs in nodal and extranodal sites. Rare examples of the disease involving the digestive system have been described. To characterize the digestive tract manifestations of this disease, 12 specimens from 11 patients with extranodal RDD affecting the digestive organs were analyzed. Hematoxylin and eosin sections and available immunohistochemical stains were reviewed, and the clinical information was obtained from patients' electronic or submitted records. Eight patients were female and 3 male (median age, 65 y; range, 17 to 76 y). Abdominal pain was the most frequent symptom. Six patients had an associated immunologic or malignant disease. Nine lesions arose in the gastrointestinal tract (1 involving the appendix, 2 right colon, 6 left colon), 2 in the pancreas, and 1 in the liver. Two patients had the coexistent nodal disease, and 1 had bone and soft-tissue involvement. The lesions were generally composed of polygonal to spindle-shaped histiocytes with eosinophilic to clear cytoplasm admixed with lymphoplasmacytic cells. The inflammatory cells formed lymphoid aggregates in 7 cases and included focally scattered or small collections of neutrophils in 6 cases. Fibrosis was variable, and 4 cases had a storiform pattern. Vasculopathy in the form of a thickened capillary wall, medium-sized arterial wall infiltration by lesional and inflammatory cells and phlebitis was seen in 10, 5, and 2 cases, respectively. All cases were reactive for S100-protein. Of the 5 patients with follow-up, 1 developed immunoglobulin A nephropathy and died of renal failure.

- The applications of metabolomics in the molecular diagnostics of cancer

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31414918

Introduction: Metabolomics, the study of metabolites, is a promising research field for cancers. The metabolic pathway in a tumor cell is different from a normal tissue cell. There are two approaches to study the metabolism, targeted and untargeted. The general approach is that metabolomic data are interpreted by bioinformatics tools correlating with metabolomic databases to obtain significant findings. With the use of specific analysis tools, such as nuclear magnetic resonance (NMR) and mass spectrometer (MS) combined with chromatography, metabolic profile or metabolic fingerprint of various biological specimens could be obtained. The applications of metabolomics are used to discover potential cancer biomarkers and monitor the metastatic state, therapeutic and drug response for better patient management. Areas covered: In this review, the author introduce metabolomics and discuss the use of metabolomics approaches in different cancers, including the study of colorectal cancer, prostate cancer, liver cancer, pancreatic cancer and breast cancer using NMR and MS. Expert opinion: Knowledge on the molecular basis of cancer metabolism and its potential clinical applications has been improving recently. However, there are still many challenges for the technological development and integration of metabolomics with other omics spaces such as genomics. In the near future, it is expected that metabolomics will play an important role in cancer molecular diagnostics.

doi: https://doi.org/10.1080/14737159.2019.1656530

- Lipid droplet velocity is a microenvironmental sensor of aggressive tumors regulated by V-ATPase and PEDF

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31409893

Lipid droplets (LDs) utilize microtubules (MTs) to participate in intracellular trafficking of cargo proteins. Cancer cells accumulate LDs and acidify their tumor microenvironment (TME) by increasing the proton pump V-ATPase. However, it is not known whether these two metabolic changes are mechanistically related or influence LD movement. We postulated that LD density and velocity are progressively increased with tumor aggressiveness and are dependent on V-ATPase and the lipolysis regulator pigment epithelium-derived factor (PEDF). LD density was assessed in human prostate cancer (PCa) specimens across Gleason scores (GS) 6-8. LD distribution and velocity were analyzed in low and highly aggressive tumors using live-cell imaging and in cells exposed to low pH and/or treated with V-ATPase inhibitors. The MT network was disrupted and analyzed by -tubulin staining. LD density positively correlated with advancing GS in human tumors. Acidification promoted peripheral localization and clustering of LDs. Highly aggressive prostate, breast, and pancreatic cell lines had significantly higher maximum LD velocity (LDVmax) than less aggressive and benign cells. LDVmax was MT-dependent and suppressed by blocking V-ATPase directly or indirectly with PEDF. Upon lowering pH, LDs moved to the cell periphery and carried metalloproteinases. These results suggest that acidification of the TME can alter intracellular LD movement and augment velocity in cancer. Restoration of PEDF or blockade of V-ATPase can normalize LD distribution and decrease velocity. This study identifies V-ATPase and PEDF as new modulators of LD trafficking in the cancer microenvironment.

doi: https://doi.org/10.1038/s41374-019-0296-8

- Mouse pancreatic ductal organoid culture as a relevant model to study exocrine pancreatic ion secretion

Pancreatic exocrine secretory processes are challenging to investigate on primary epithelial cells. Pancreatic organoid cultures may help to overcome shortcomings of the current models, however the ion secretory processes in pancreatic organoids-and therefore their physiological relevance or their utility in disease modeling-are not known. To answer these questions, we provide side-by-side comparison of gene expression, morphology, and function of epithelial cells in primary isolated pancreatic ducts and organoids. We used mouse pancreatic ductal fragments for experiments or were grown in Matrigel to obtain organoid cultures. Using PCR analysis we showed that gene expression of ion channels and transporters remarkably overlap in primary ductal cells and organoids. Morphological analysis with scanning electron microscopy revealed that pancreatic organoids form polarized monolayers with brush border on the apical membrane. Whereas the expression and localization of key proteins involved in ductal secretion (cystic fibrosis transmembrane conductance regulator, Na+/H+ exchanger 1 and electrogenic Na+/HCO3- cotransporter 1) are equivalent to the primary ductal fragments. Measurements of intracellular pH and Cl- levels revealed no significant difference in the activities of the apical Cl-/HCO3- exchange, or in the basolateral Na+ dependent HCO3- uptake. In summary we found that ion transport activities in the mouse pancreatic organoids are remarkably similar to those observed in freshly isolated primary ductal fragments. These results suggest that organoids can be suitable and robust model to study pancreatic ductal epithelial ion transport in health and diseases and facilitate drug development for secretory pancreatic disorders like cystic fibrosis, or chronic pancreatitis.

- **Prognostic significance of neutrophil-lymphocyte ratio in resectable pancreatic neuroendocrine tumors with special reference to tumor-associated macrophages**

BACKGROUND: Recent studies have shown that the systemic inflammatory response induced by cancer leads to cancer progression. Neutrophil-to-lymphocyte ratio (NLR) is the most reliable marker to detect systemic inflammation. In this study, we investigated the significance of NLR in patients with well-differentiated pancreatic neuroendocrine tumors (PanNETs) according to the World Health Organization 2017 classification. METHODS: We retrospectively collected data for patients with PanNET who underwent pancreatic resection with curative intent between January 2008 and December 2017 at six institutions. Clinicopathological factors, recurrence, and immunohistochemical staining of tumor-associated macrophages (TAMs) were analyzed in a total of 55 patients in this study. RESULTS: High NLR (>3.41) in patients was significantly associated with higher white blood cell count, higher Ki-67 index, higher mitotic count, higher grade, higher incidence of lymph node metastasis, higher incidence of lymphatic and neural invasion, massive blood loss, and a large number of CD163-expressing TAMs. Recurrence-free survival of patients with high NLR was significantly poorer than that of patients with low NLR. Multivariate analysis identified high NLR, NET Grade 2 (G2) or Grade 3 (G3), and synchronous hepatic resection as independent risk factors for recurrence after curative resection. CONCLUSIONS: NLR is a promising predictor of recurrence after pancreatectomy that needs to be further investigated and that accumulation of TAMs in the tumor could be one of the causes of NLR elevation.

- **Dissecting the presence of malignant squamous cells in pancreatic cytopathology: A case series**

The presence of malignant squamous cells in pancreatic cytopathology is a rare phenomenon that results either from a primary or a metastatic process. Pancreatic adenosquamous carcinoma (PASC) represents the most common variant of pancreatic ductal adenocarcinoma and is associated with a dismal prognosis. Within the period of 2013-2018, the archives of "Hygeia and Mitera Hospital" were searched for pancreatic cytopathology-related diagnoses that included the interpretation of "malignant squamous cells present." All fine needle aspirations (FNAs) of pancreatic lesions, including liver metastases in patients with known pancreatic primaries, were retrieved along with their relevant clinical information. Five pancreatic and two liver FNAs acquired from a total of six patients were reexamined. None of these patients had any documented history of primary squamous malignancy elsewhere. All pancreatic and one of the two liver FNAs showed malignant squamous cells, identified based on either morphology or immunochemistry. The other liver FNA represented a metastatic deposit which comprised of only a glandular component, whereas the associated pancreatic FNA exhibited both squamous and glandular counterparts. Most cases characteristically showed necrosis and keratinization. Of interest, two cases revealed the presence of tumor-associated giant cells. In conclusion, the presence of malignant squamous cells in pancreatic FNAs could mean the presence of PASC, especially when there is no documented history of a primary malignancy and a complete clinical and imaging workup has been performed. Immunochemistry on cell block material could help to confirm squamous differentiation in the absence of overt keratinization.
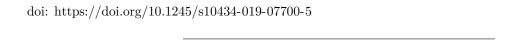

- Laparoscopic Suprapancreatic Lymph Node Dissection Using a Systematic Mesogastric Excision Concept for Gastric Cancer

BACKGROUND: Gastrointestinal cancer surgery requires en bloc removal of the primary tumor and organ-specific mesentery1,2. However, this surgical concept for gastric cancer has not yet been applied because of the morphological complexity of the mesenteries of the stomach. Lymph node dissection in gastric cancer surgery can be roughly performed into three regions: lesser curvature, grater curvature, and suprapancreatic region. In this video, we introduced laparoscopic lymphadenectomy in the suprapancreatic region using a systematic mesogastric excision (SME), which has been reported as a concept to perform en bloc resection3. METHODS: This procedure was divided into three steps. First, mesenterization of the mesogastrium was performed by dissecting the embryological planes, and the mesogastrium was dissected from the retroperitoneal surface (Fig. 1a). Second, soft tissue, including the lymph node, was separated from the pancreas and the splenic artery by tracing the inner dissectable layer (Fig. 1b). Finally, the tumor-specific mesentery was transected according to the extent of the lymphadenectomy (Fig. 1c). Fig. 1 Intraoperative findings during the stepwise procedure in dissecting the lymph node in the suprapancreatic region. The red broken line indicates the surgical outline. a The mesogastrium is dissected from the retroperitoneal tissue. b The mesogastrium is separated from the pancreas and splenic artery. c The mesogastric transection line is determined on the basis of the extent of the lymphadenectomy. Inf. phrenic a. inferior phrenic artery; PGA posterior gastric artery; Post. epiploic a. posterior epiploic artery; RV renal vein; SA splenic artery; SV splenic vein RESULTS: Between January 2017 and December 2017, six patients underwent laparoscopic distal gastrectomy with D2 lymphadenectomy using SME. The median time required to complete the suprapancreatic lymphadenectomy was 48 min. No patient underwent conversion to open surgery or experienced intraoperative complications. CONCLUSIONS: We believe that this laparoscopic suprapancreatic lymphadenectomy using SME takes advantage of the surgical anatomy and achieves en bloc removal of the primary tumor and gastric mesentery. This series is a proof of concept that this procedure can be performed in a timely manner and is feasible.

- Extended Laparoscopic Central Pancreatectomy with Clamping of the Mesentericoportal Vein and Resection of the Splenic Vessels for a Large Solid Pseudopapillary Tumor

BACKGROUND: Solid pseudopapillary tumors (SPPTs) are low malignant potential entities found mainly in young females.1,2 Pancreatectomy without tumor rupture is the treatment of choice, and the laparoscopic approach is indicated.3,4 Limited pancreatectomy is possible due to the low risk of malignancy ($< 10\%$) based on the low risk of lymph node invasion or true vascular invasion.1,2 Centrally located large SPPTs can be treated by extended central pancreatectomy with or without vascular resection to avoid pancreato-duodenectomy or distal pancreatectomy. METHODS: A 24-year-old woman was admitted with abdominal pain. A 6-cm SPPT was discovered at the neck-body junction in close contact with the anterior aspect of the mesentericoportal vein (MPV) and the splenic vessels, with signs of segmental portal hypertension. To avoid an extended pancreatectomy for this young patient, an extended central pancreatectomy was performed, with resection of the splenic vessels, and the MPV was freed from the tumor under clamping for 10 min, with no need for vascular reconstruction. The duration of the surgery was 260 min, with 200 ml of blood loss and no transfusion. RESULTS: The woman's postoperative course was uneventful, with a hospital stay of 16 days. Histology confirmed the diagnosis of a 6-cm SPPT tumor (R0 and N0). The patient was asymptomatic 1 year later, with no tumor recurrence and no pancreatic insufficiency. Between 2011 and 2018 the authors performed 72 laparoscopic central pancreatectomies, with SPPT performed for 13 patients (18%). Laparoscopic central pancreatectomy was extended (n = 5) or standard (n = 8) with no conversion, no recurrence, and no pancreatic insufficiency. CONCLUSION: An SPPT tumor is a good indication for the laparoscopic approach because this entity is found in young patients with a low risk of malignancy. Large centrally located tumors can be treated by extended central pancreatectomy to avoid a large pancreatectomy with greater early and long-term disadvantages.

- Robotic Extended Right Hemicolectomy with Complete Mesocolic Excision and D3 Lymph Node Dissection

BACKGROUND: Recent studies have shown the benefits of complete mesocolic excision and extended lymphadenectomy (D3 lymph node dissection) in patients with colon cancer.1-3 METHODS: We present the case of a 62-year-old male with hepatic flexure adenocarcinoma. No metastatic disease was identified by computed tomography. A robot-assisted extended right hemicolectomy with complete mesocolic excision, D3 lymph node dissection, and resection of the mesentery with intact visceral peritoneum was performed. RESULTS: The trocars are placed in the right lower (8 mm), lower midline (8 mm), and left upper (12 mm) quadrants. The camera port is placed superior to the umbilicus, and the assistant port is placed in the left lower quadrant. The robotic right lower port is used to place the cecum on tension in order to outline the ileocolic pedicle. The assistant retracts the transverse colon cephalad to outline the superior mesenteric artery and vein. Using two robotic arms, the surgeon begins dissection over the superior mesenteric vein inferior to the ileocolic pedicle. Cephalad dissection along the superior mesenteric vein proceeds with reflection of the mesentery and D3 lymph nodes laterally to allow en bloc resection. The ileocolic and middle colic vessels are identified, ligated and divided at their origins. The plane is then developed between the

right colon mesentery and the retroperitoneum, including Gerota's fascia, duodenum, and head of the pancreas, in a medial-to-lateral fashion, with care taken to ensure an intact visceral peritoneum is maintained. The proximal transverse colon, hepatic flexure, and ascending colon are mobilized by taking down lateral attachments. The intervening mesentery is transected, and perfusion is assessed with indocyanine green fluorescence imaging. An intracorporeal, isoperistaltic, side-to-side anastomosis is performed using the 45-mm robotic stapler. The common enterotomy is sewn closed in two layers. Pathology showed T3N0 adenocarcinoma with all negative margins. CONCLUSION: Extended right hemicolectomy with complete mesocolic excision and D3 lymph node dissection is facilitated by a robotic approach, which improves visualization and instrument dexterity.

doi: https://doi.org/10.1245/s10434-019-07692-2

- Short-Term Outcomes of Laparoscopic and Open Total Gastrectomy for Gastric Cancer: A Nationwide Retrospective Cohort Analysis

Annals of surgical oncology 2019 Aug;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31407172

BACKGROUND: Laparoscopic total gastrectomy is gradually gaining popularity; however, previous studies have produced conflicting results regarding the safety and advantages of the procedure, partly because of small sample sizes. The purpose of this study was to compare short-term outcomes between laparoscopic and open total gastrectomy for gastric cancer. METHODS: We analyzed data for patients undergoing laparoscopic or open total gastrectomy for clinical stage I-III gastric cancer from July 2010 to March 2017, using a Japanese nationwide inpatient database. We performed propensity-matched analyses to compare in-hospital mortality, morbidity, duration of anesthesia, time to first oral intake, and length of postoperative stay between the two groups. RESULTS: Among 58,689 eligible patients, propensity-score matching created 12,229 pairs. Laparoscopic total gastrectomy was associated with higher incidences of anastomotic leakage (2.9% vs. 1.7%, $p < 0.001$) and stenosis (0.9% vs. 0.6%, $p = 0.02$), lower incidences of pancreatic injury (1.4% vs. 1.8%, $p = 0.01$), endoscopic hemostasis (0.9% vs. 1.7%, $p < 0.001$), blood transfusion (9.9% vs. 17.7%, $p < 0.001$) and 30-day readmission, a shorter interval from surgery to first oral intake (4 vs. 5 days, $p < 0.001$), shorter postoperative hospital stay (14 vs. 15 days, $p < 0.001$), and a longer duration of anesthesia (323 vs. 304 min, $p < 0.001$). There was no significant difference in in-hospital mortality (0.6% vs. 0.8%, $p = 0.58$). CONCLUSIONS: Laparoscopic total gastrectomy has some advantages over open surgery for gastric cancer in terms of time to first oral intake and postoperative length of stay, but the incidence of anastomotic leakage was higher than that of open total gastrectomy.

doi: https://doi.org/10.1245/s10434-019-07688-y

- Pancreas FNA

Cytopathology : official journal of the British Society for Clinical Cytology 2019 Aug;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31400170

67-year-old lady diagnosed with right breast invasive ductal carcinoma with axillary node involvement. Staging FDG PET identified a small enhancing 1.2cm 'indeterminate' nodule within pancreatic tail, which CT pancreas with contrast revealed to be hypervascular. This article is protected by copyright. All rights reserved.

doi: https://doi.org/10.1111/cyt.12767

- Comparison of Tissue and Blood Concentrations of Oxaliplatin Administered by Different Modalities of Intraperitoneal Chemotherapy

Annals of surgical oncology 2019 Aug;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31399820

BACKGROUND: Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a new technology for delivering intraperitoneal chemotherapy. It is generally assumed that with PIPAC, the ratio of peritoneal to systemic drug concentration is superior to liquid hyperthermic intraperitoneal chemotherapy (HIPEC). To date, no direct comparative data are available supporting such an assumption. MATERIALS AND METHODS: Twelve 65-day-old pigs were randomly separated into three groups of four pigs each, all of which received intraperitoneal chemotherapy using the following administration methods: PIPAC with oxaliplatin 92 mg in 150 ml dextrose 5% (Group 1); PIPAC with electrostatic aerosol precipitation (ePIPAC; Group 2); or laparoscopic HIPEC (L-HIPEC) with oxaliplatin 400 mg in 4 L dextrose 5% at 42 °C (Group 3). Serial blood and peritoneal tissue concentrations of oxaliplatin were determined by spectrometry. RESULTS: In all three groups, the maximum concentration of oxaliplatin in blood was detected 50-60 min after onset of the chemotherapy experiments, with no significant differences among the three groups (p = 0.7994). Blood oxaliplatin concentrations (0-30 min) were significantly higher in the L-HIPEC group compared with the ePIPAC group (p < 0.05). No difference was found for the overall systemic oxaliplatin absorption (area under the curve). Overall concentrations in the peritoneum were not different among the three groups (p = 0.4725), but were significantly higher in the visceral peritoneum in the PIPAC group (p = 0.0242). CONCLUSIONS: Blood and tissue concentrations were comparable between all groups; however, depending on the intraperitoneal area examined and the time points of drug delivery, the concentrations differed significantly between the three groups.

doi: https://doi.org/10.1245/s10434-019-07695-z

- ARF6 and AMAP1 are major targets of KRAS and TP53 mutations to promote invasion, PD-L1 dynamics, and immune evasion of pancreatic cancer

Proceedings of the National Academy of Sciences of the United States of America 2019 Aug;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31399545

Although KRAS and TP53 mutations are major drivers of pancreatic ductal adenocarcinoma (PDAC), the incurable nature of this cancer still remains largely elusive. ARF6 and its effector AMAP1 are often overexpressed in different cancers and regulate the intracellular dynamics of integrins and E-cadherin, thus promoting tumor invasion and metastasis when ARF6 is activated. Here we show that the ARF6-AMAP1 pathway is a major target by which KRAS and TP53 cooperatively promote malignancy. KRAS was identified to promote eIF4A-dependent ARF6 mRNA translation, which contains a quadruplex structure at its 5'-untranslated region, by inducing TEAD3 and ETV4 to suppress PDCD4; and also eIF4E-dependent AMAP1 mRNA translation, which contains a 5'-terminal oligopyrimidine-like sequence, via up-regulating mTORC1. TP53 facilitated ARF6 activation by platelet-derived growth factor (PDGF), via its known function to promote the expression of PDGF receptor (PDGFR) and enzymes of the mevalonate pathway (MVP). The ARF6-AMAP1 pathway was moreover essential for PDGF-driven recycling of PD-L1, in which KRAS, TP53, eIF4A/4E-dependent translation, mTOR, and MVP were all integral. We moreover demonstrated that the mouse PDAC model KPC cells, bearing KRAS/TP53 mutations, express ARF6 and AMAP1 at high levels and that the ARF6-based pathway is closely associated with immune evasion of KPC cells. Expression of ARF6 pathway components statistically correlated with poor patient outcomes. Thus, the cooperation among eIF4A/4E-dependent mRNA translation and MVP has emerged as a link by which pancreatic driver mutations may promote tumor cell motility, PD-L1 dynamics, and immune evasion, via empowering the ARF6-based pathway and its activation by external ligands.

- Second harmonic generation detection of Ras conformational changes and discovery of a small molecule binder

Proceedings of the National Academy of Sciences of the United States of America 2019 Aug;():

Second harmonic generation (SHG) is an emergent biophysical method that sensitively measures real-time conformational change of biomolecules in the presence of biological ligands and small molecules. This study describes the successful implementation of SHG as a primary screening platform to identify fragment ligands to oncogenic Kirsten rat sarcoma (KRas). KRas is the most frequently mutated driver of pancreatic, colon, and lung cancers; however, there are few well-characterized small molecule ligands due to a lack of deep binding pockets. Using SHG, we identified a fragment binder to KRasG12D and used 1H 15N transverse relaxation optimized spectroscopy (TROSY) heteronuclear single-quantum coherence (HSQC) NMR to characterize its binding site as a pocket adjacent to the switch 2 region. The unique sensitivity of SHG furthered our study by revealing distinct conformations induced by our hit fragment compared with 4,6-dichloro-2-methyl-3-aminoethyl-indole (DCAI), a Ras ligand previously described to bind the same pocket. This study highlights SHG as a high-throughput screening platform that reveals structural insights in addition to ligand binding.

- Tumor Microbiome Diversity and Composition Influence Pancreatic Cancer Outcomes

Cell 2019 Aug;178(4):795-806.e12

Most patients diagnosed with resected pancreatic adenocarcinoma (PDAC) survive less than 5 years, but a minor subset survives longer. Here, we dissect the role of the tumor microbiota and the immune system in influencing long-term survival. Using 16S rRNA gene sequencing, we analyzed the tumor microbiome composition in PDAC patients with short-term survival (STS) and long-term survival (LTS). We found higher alpha-diversity in the tumor microbiome of LTS patients and identified an intra-tumoral microbiome signature (Pseudoxanthomonas-Streptomyces-Saccharopolyspora-Bacillus clausii) highly predictive of long-term survivorship in both discovery and validation cohorts. Through human-into-mice fecal microbiota transplantation (FMT) experiments from STS, LTS, or control donors, we were able to differentially modulate the tumor microbiome and affect tumor growth as well as tumor immune infiltration. Our study demonstrates that PDAC microbiome composition, which cross-talks to the gut microbiome, influences the host immune response and natural history of the disease.

- Variation in use of open and laparoscopic distal pancreatectomy and associated outcome metrics in a universal health care system

Pancreatology : official journal of the International Association of Pancreatology (IAP) … [et al.] 2019 Aug;():

BACKGROUND: Universal health care (UHC) should ensure equal access to and use of surgery, but few studies have explored variation in UHC systems. The objective was to describe practice of distal pancreatectomy in Norway covered exclusively by an UHC. METHODS: Data on all patients undergoing distal pancreatectomy from the Norwegian Patient Register over a 5-year period. Age- and gender-adjusted population-based resection rates (adj. per million/yr) for distal pancreatectomy were analysed across 4 regions and outcomes related to splenic salvage rate, hospital stay, reoperation, readmissions and 90-day mortality risk between regions. Risk is reported as odds ratio (OR) with 95% confidence interval (c.i.). RESULTS: Regional difference exist in terms of absolute numbers, with the majority of procedures done in one region (n = 331; 59.7%). Regional variation persisted for age- and gender-adjusted population-rates, with highest rate at 23.8/million/yr and lowest rate at 13.5/mill/yr (for a 176% relative difference; or an absolute difference of +10.3 resections/million/yr). Overall, a lapDP instead of an open DP was 3.5 times more likely in SouthEast compared to all other regions combined (lapDP rate: 83% vrs 24%, respectively; OR 15.4, 95% c.i. 10.1-23.5; P < 0.001). The splenic salvage rate was lower in SouthEast (19.9%) compared to all other regions (average 26.5%; highest in Central-region at 37.0%; P = 0.010 for trend). Controlled for other factors in multivariate regression, 'region' of surgery remained significantly associated with laparoscopic access. CONCLUSION: Despite a universal health care system, considerable variation exists in resection rates, use of laparoscopy and splenic salvage rates across regions.

doi: https://doi.org/10.1016/j.pan.2019.07.047

- Comparison of overall survival and perioperative outcomes of laparoscopic pancreaticoduodenectomy and open pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: a systematic review and meta-analysis

BMC cancer 2019 Aug;19(1):781

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31391085

BACKGROUND: The aim of this study was to compare the oncological outcomes and clinical efficacy of laparoscopic pancreaticoduodenectomy (LPD) and open pancreaticoduodenectomy (OPD) in patients with pancreatic ductal adenocarcinoma (PDAC). METHODS: We systematically searched PubMed, EMBASE, Web of Science, ClinicalTrials.gov and the Cochrane Central Register for studies published between May 1998 and May 2018. The included studies compared LPD and OPD for the treatment of PDAC. The oncological outcomes and perioperative data were analyzed. RESULTS: Eight studies involving 15,278 patients were included in our meta-analysis. No significant difference was found in the 5-year overall survival (OS) between patients undergoing the two types of surgery (HR: 0.97, 95% CI 0.82-1.15, p = 0.76). LPD resulted in a higher rate of R0 resection than OPD (OR: 1.16, 95% CI 0.85-1.57, p > 0.05). This study showed that compared with OPD, LPD resulted in comparable rates of postoperative pancreatic fistulas (POPFs) (OR: 1.07, 95% CI: 0.68-1.68, p = 0.77) and postoperative hemorrhage (OR: 1.74, 95% CI 0.96-3.71, p = 0.07), more harvested lymph nodes (WMD: 1.84, 95% CI: 0.95-2.72, p < 0.05), shorter hospital stays (WMD: -2.45, 95% CI: - 3.33- -1.56, p < 0.05), and less estimated blood loss (WMD: -374.30, 95% CI: - 513.06- -235.54, p < 0.05). CONCLUSIONS: LPD is equivalent to OPD with respect to 5-year OS and results in better perioperative clinical outcomes for patients with PDAC.

doi: https://doi.org/10.1186/s12885-019-6001-x

- A 12-year trend analysis of the incidence of gastrointestinal cancers in East Azerbaijan: last updated results of an ongoing population-based cancer registry

BMC cancer 2019 Aug;19(1):782

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31391032

BACKGROUND: The most recent results of Global Cancer Statistics indicated that gastrointestinal cancers, including gastric, colorectal, esophageal, and liver cancers, are among the most commonly diagnosed cancers worldwide. Previous reports from cancer registries in East Azerbaijan have shown that there is a high incidence of gastrointestinal cancer in this region, so we performed a trend analysis to determine the pattern of change over the last decade. METHODS: In total, 12 years of cancer registry data were collected from different sources in East Azerbaijan, and a data quality check was performed to ensure clean data. Using the 2000 World Health Organization standard population, we then generated age-standardized incidence rates (ASRs) for different cancers, and for each year from 1383 to 1394 of the Persian calendar (i.e., 19 March 2004 to 20 March 2015). Annual percent changes (APCs) and Average annual percent changes (AAPCs) in the ASRs for esophageal, gastric, small intestine, colorectal, anal, liver, gallbladder, and pancreatic cancers were calculated using Joinpoint Software (Version 4.5.0.1, June 2017). RESULTS: An increase in most types of cancer was observed during the study period. The ASR for colorectal cancer increased from 2.9 to 13.6 per 100,000 women (APC, 9.7%) and from 2.2 to 17.8 per 100,000 men (APC, 10.2%). The ASR for gastric cancer showed a slight increasing trend from 10.5 to 13.5 per 100,000 women (APC, 1.3%) and from 3.1 to 29.9 per 100,000 men (APC, 3.2%). However, trend analysis showed a decreasing pattern for the ASR of esophageal cancer in both genders (APC,- 3%), with APCs of - 1.1% in females and - 0.4% in males. CONCLUSIONS: The latest results of the East Azerbaijan Population-Based Cancer Registry indicate that gastrointestinal cancers remain common, with significant increasing trends in their ASRs. Improved screening and early detection are needed in this region.

- The prognostic value of lncRNA SNHG1 in cancer patients: a meta-analysis

BMC cancer 2019 Aug;19(1):780

BACKGROUND: Increasing evidence revealed that high expression level of lncRNA SNHG1 was associated with the unfavorable prognosis of cancer and maybe used as a valuable biomarker for cancer patients. The present meta->analysis is to analyze existing data to reveal potential clinical application of SNHG1 on cancer prognosis and tumor progression. All of the included studies were collected through a variety of retrieval strategies. And the articles were qualified by MOOSE and PRISMA checklists. METHODS: Up to Mar 20, 2018, literature collection was performed by comprehensive search through electronic databases, including the Cochrane library, PubMed, Embase, Web of science, Springer, Science direct, and three Chinese databases: CNKI, Weipu, and Wanfang. We analyzed 14 studies that met the criteria, and concluded that the increased SHNG1 level was correlated with poor OS and tumor progression. RESULTS: The combined results indicated that elevated SNHG1 expression level was significantly associated with poor OS (HR = 2.06, 95% CI: 1.69-2.52, P < 0.01) and PFS (HR = 2.78, 95% CI: 1.69-4.55, P < 0.01) in various cancers. Moreover, the promoted SNHG1 expression was also associated with tumor progression ((III/IV vs. I/II: HR = 1.89, 95% CI: 1.53-2.34, P < 0.01). In stratified analyses, a significantly unfavorable association of elevated lncRNA SNHG1 and OS was observed in both digestive system (HR = 2.04, 95% CI: 1.56-2.68, P < 0.01) and non-digestive system (HR = 2.09, 95% CI: 1.55-2.83, P < 0.01) cancer patients. CONCLUSIONS: The present analysis indicated that the increased SNHG1 is associated with poor OS in patients with general tumors and may be served as a useful prognostic biomarker.

- Dynamic serum alkaline phosphatase is an indicator of overall survival in pancreatic cancer

BMC cancer 2019 Aug;19(1):785

BACKGROUND: The prognostic role of serum alkaline phosphatase (ALP) has been found in several kinds of solid malignant tumor, but has never been extensively discussed in pancreatic cancer, especially through the application of dynamic survival model which incorporates the varying nature of ALP measurements. METHODS: We conducted a retrospective study which successfully collected 551 histopathologically confirmed pancreatic ductal adenocarcinoma (PDAC) patients from a cancer specialized hospital in southwest China. The association between variant ALP which measured during the whole survival period and the overall survival (OS) of PDAC patients was evaluated by using dynamic Anderson-Gill (AG) model. Exhaustive sensitivity analysis was performed by adopting continuous cut-offs of ALP. RESULTS: After adjusted for possible confounding of serum albumin, total bilirubin and leukocyte counts, AG model revealed that, serum ALP during the survival period was nonlinearly associated with the OS of PDAC: for resected patients, compared with those whose ALP results ranged within the first quartile (<P25), patients whose ALP measurements belonged to the second (P25-P50), the third (P50-P75), and the forth (>P75) quartiles were observed 1.14 (95% CI: 0.29-4.56), 3.93 (95% CI: 1.23-12.60), 3.87 (95% CI: 1.32-11.36) folds of death hazard; whereas in un-resected PDAC patients, the hazard ratios (HRs) were 1.15 (95% CI: 0.79-1.68), 1.92 (95% CI: 1.32-2.78), and 1.97 (95% CI: 1.30-2.98), respectively. Sensitivity analysis revealed that, for both resected and un-resected patients, the results of AG model were robust with regard to various cut-offs of ALP, and an increased ALP was in general associated with significantly increased hazard of death. CONCLUSION: Serum ALP during the survival period was significantly associated with the OS of PDAC patients, especially for resected early stage PDAC patients. Future studies with expanded sample size and refined prospective design should be implemented to corroborate our major findings. Besides, the underlying mechanism for this possible hazardous role of ALP should also be investigated.

- **Corrigendum to "Cystic pancreatic neuroendocrine tumors: A more favorable lesion?" [Pancreatology 19 (2) (March 2019) 372-376]**

Pancreatology : official journal of the International Association of Pancreatology (IAP) … [et al.] 2019 Aug;():

- **Classification of Complication Clusters Might Vary in Different Populations With Chronic Pancreatitis**

The American journal of gastroenterology 2019 Aug;114(8):1351-1352

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

Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc 2019 Aug;():

We have encountered pancreatic tumors with unique histologic features, which do not conform to any of the known tumors of the pancreas or other anatomical sites. We aimed to define their clinicopathologic features and whether they are characterized by recurrent molecular signatures. Eight cases were identified; studied histologically and by immunohistochemistry. Selected cases were also subjected to whole-exome sequencing (WES; n = 4), RNA-sequencing (n = 6), Archer FusionPlex assay (n = 5), methylation profiling using the Illumina MethylationEPIC (850k) array platform (n = 6), and TERT promoter sequencing (n = 5). Six neoplasms occurred in females. The mean age was 43 years (range: 26-75). Five occurred in the head/neck of the pancreas. All patients were treated surgically; none received neoadjuvant/adjuvant therapy. All patients are free of disease after 53 months of median follow-up (range: 8-94). The tumors were well-circumscribed, and the median size was 1.8 cm (range: 1.3-5.8). Microscopically, the unencapsulated tumors had a geographic pattern of epithelioid cell nests alternating with spindle cell fascicles. Some areas showed dense fibrosis, in which enmeshed tumor cells imparted a slit-like pattern. The predominant epithelioid cells had scant cytoplasm and round-oval nuclei with open chromatin. The spindle cells displayed irregular, hyperchromatic nuclei. Mitoses were rare. No lymph node metastases were identified. All tumors were positive for vimentin, CD99 and cytokeratin (patchy), while negative for markers of solid pseudopapillary neoplasm, neuroendocrine, acinar, myogenic/rhabdoid, vascular, melanocytic, or lymphoid differentiation, gastrointestinal stromal tumor as well as MUC4. Whole-exome sequencing revealed no recurrent somatic mutations or amplifications/homozygous deletions in any known oncogenes or tumor suppressor genes. RNA-sequencing and the Archer FusionPlex assay did not detect any recurrent likely pathogenic gene fusions. Single sample gene set enrichment analysis revealed that these tumors display a likely mesenchymal transcriptomic program. Unsupervised analysis (t-SNE) of their methylation profiles against a set of different mesenchymal neoplasms demonstrated a distinct methylation pattern. Here, we describe pancreatic neoplasms with unique morphologic/immunophenotypic features and a distinct methylation pattern, along with a lack of abnormalities in any of key genetic drivers, supporting that these neoplasms represent a novel entity with an indolent clinical course. Given their mesenchymal transcriptomic features, we propose the designation of "sclerosing epithelioid mesenchymal neoplasm" of the pancreas.

- **The cost of endoscopic treatment for walled-off pancreatic necrosis**

BACKGROUND: Use of minimally invasive techniques has reduced mortality in walled-off pancreatic necrosis (WON) but may be costly. The aim of this study was to evaluate the actual costs associated with the endoscopic management of patients with WON. METHODS: We included a retrospective cohort of WON patients treated with endoscopic, transgastric drainage and necrosectomy (ETDN) during 2013-2014. Costs were calculated for six sub-areas based on a micro-costing model. Students T-test and non-parametric analysis of variance were performed to evaluate costs in relation to disease etiology and outcome. RESULTS: We included 58 patients (50% men, median age 57 years). The most common etiologies were gallstones (57%) and alcohol (19%). Nine patients (16%) died during admission. The median length of stay was 50 days (IQR 31 days). Eighteen patients (31%) needed treatment in our intensive care unit with a median length of stay of 16 days (IQR 31 days). The mean costs and standard deviation of costs (SD) per patient were: diagnostic imaging $2,431 ($2,301), laboratory tests $3,579 ($2,477), blood products $982 ($1,734), endoscopic treatment $3,794 ($1,777), medicine $5,440 ($6,656), and ward cost $41,260 ($35,854). The mean total cost was $57,486 ($46,739). Post-ERCP pancreatitis and mortality predicted higher costs. CONCLUSIONS: This study sheds light on the different costs associated with endoscopic treatment of WON. As nearly three quarters of the costs are related to ward care, initiatives aimed at reducing the length of hospital stay may have a great impact on making endoscopic treatment more cost effective.

- **Coexisting pancreatic serous cystadenoma and pancreatic ductal adenocarcinoma: A cytological-pathologic correlation with literature review**

Annals of diagnostic pathology 2019 Jul;42():87-91

Pancreatic serous cystadenoma (SCA) is a benign neoplastic lesion with a distinctive gross and microscopic appearance consisting of numerous thin-walled cysts lined by uniform epithelial cells with clear cytoplasm and small nuclei. The vast majority of serous cystadenomas are benign. Pancreatic SCA has rarely been reported in association with other pancreatic lesions. We present a challenging case in which a cystic and solid pancreatic mass was identified on imaging studies. FNA was performed and showed clusters of atypical cells with significant nuclear pleomorphism ($>4:1$), disorganized, overlapping nuclei, and prominent nucleoli. The FNA diagnosis was positive for malignancy, consistent with adenocarcinoma. The patient underwent neoadjuvant therapy and pancreaticoduodenectomy. Final pathology showed a serous cystadenoma associated with small foci of high-grade PanIN. The lack of invasive adenocarcinoma in the resection specimen was most likely due to complete response of the tumor to neoadjuvant chemoradiation therapy, but it is also possible that only high-grade PanIN was present initially. To our knowledge, this is the first reported case of SCA and high grade PanIN/PDAC that was assessed by FNA. We discuss the cytologic differential diagnosis and how to avoid potential pitfalls highlighted by this case.

- **Pancreatic cancer-A disease in need: Optimizing and integrating supportive care**

Cancer 2019 Aug;():

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy that continues to be challenging to treat. PDAC has the lowest 5-year relative survival rate compared with all other solid tumor malignancies and is expected to become the second-leading cause of cancer-related death in the United States by 2030. Given the high mortality, there is an increasing role for concurrent anticancer and supportive care in the management of patients with PDAC with the aims of maximizing length of life, quality of life, and symptom control. Emerging trends in supportive care that can be integrated into the clinical management of patients with PDAC include standardized supportive care screening, early integration of supportive care into routine cancer care, early implementation of outpatient-based advance care planning, and utilization of electronic patient-reported outcomes for improved symptom management and quality of life. The most common symptoms experienced are nausea, constipation, weight loss, diarrhea, anorexia, and abdominal and back pain. This review article includes current supportive management strategies for these and others. Common disease-related complications include biliary and duodenal obstruction requiring endoscopic procedures and venous thromboembolic events. Patients with PDAC continue to have a poor prognosis. Systemic therapy options are able to palliate the high symptom burden but have a modest impact on overall survival. Early integration of supportive care can lead to improved outcomes.

- **The role of abdominal drainage in pancreatic resection - A multicenter validation study for early drain removal**

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31378583

BACKGROUND: Abdominal drainage and the timing of drain removal in patients undergoing pancreatic resection are under debate. Early drain removal after pancreatic resection has been reported to be safe with a low risk for clinical relevant postoperative pancreatic fistula (CR-POPF) when drain amylase on POD1 is $< 5000U/L$. The aim of this study was to validate this algorithm in a large national cohort. METHODS: Patients registered in the Dutch Pancreatic Cancer Audit (2014-2016) who underwent pancreatoduodenectomy, distal pancreatectomy or enucleation were analysed. Data on post-operative drain amylase levels, drain removal, postoperative pancreatic fistulae were collected. Univariate and multivariate analysis using a logistic regression model were performed. The primary outcome measure was grade B/C pancreatic fistula (CR-POPF). RESULTS: Among 1402 included patients, 433 patients with a drain fluid amylase level of <5000U/L on POD1, 7% developed a CR-POPF. For patients with an amylase level >5000U/L the CR-POPF rate was 28%. When using a cut-off point of 2000U/L or 1000U/L during POD1-3, the CR-POPF rates were 6% and 5% respectively. For patients with an amylase level of >2000U/L and >1000UL during POD 1-3 the CR-POPF rates were 26% and 22% respectively (n = 223). Drain removal on POD4 or thereafter was associated with more complications (p = 0.004). Drain amylase level was shown to be the most statistically significant predicting factor for CR-POPF (Wald = 49.7; p < 0.001). CONCLUSION: Our data support early drain removal after pancreatic resection. However, a cut-off of 5000U/L drain amylase on POD1 was associated with a relatively high CR-POPF rate of 7%. A cut-off point of 1000U/L during POD1-3 resulted in 5% CR-POPF and might be a safer alternative.

- Factors predicting readmission within 30 days of acute pancreatitis attack: A prospective study

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31378581

- The Impact of Dedicated Cancer Centers on Outcomes Among Medicare Beneficiaries Undergoing Liver and Pancreatic Cancer Surgery

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31376033

BACKGROUND: The Alliance of Dedicated Cancer Centers (DCCs) is comprised of 11 institutions that are exempt from the prospective payment system utilized by Medicare for hospital reimbursement. OBJECTIVE: The aim of this study was to compare short- and long-term outcomes of patients undergoing liver and pancreatic surgery for cancer at DCCs versus non-DCCs. METHODS: Patients who underwent a liver or pancreatic operation for a malignant indication between 2013 and 2015 were identified using the Medicare Inpatient Standard Analytic Files. Regression analyses and the Kaplan-Meier method were used to assess short- and long-term outcomes of patients at DCCs versus non-DCCs. RESULTS: Among 13,256 patients, 7.0% of patients were treated at a DCC. Median patient age and complexity of surgical procedures were comparable among DCCs and non-DCCs (all p > 0.05). Overall complications (16.5% vs. 23.6%), 90-day readmission (26.2% vs. 30.2%), and 90-day mortality (3.0% vs. 8.7%) were lower at DCCs compared with

non-DCCs (all p < 0.001). In addition, long-term hazards of death among patients undergoing hepatectomy [hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.54-0.75] and pancreatectomy (HR 0.66, 95% CI 0.56-0.78) were lower among patients treated at DCCs (both p < 0.05). While Medicare payments for patients undergoing pancreatic surgery (DCC: $22,200 vs. non-DCC: $22,100; p = 0.772) were comparable among DCC and non-DCC hospitals, Medicare payments for liver resection at DCCs were 13.9% lower than non-DCCs (DCC: $16,700 vs. non-DCC: $19,400; p < 0.001). CONCLUSIONS: Patients undergoing hepatopancreatic surgery at DCCs had better short- and long-term outcomes for the same/lower level of Medicare expenditure as non-DCC hospitals. DCCs provide higher-value surgical care for patients undergoing liver and pancreatic cancer operations.

- NTRK fusion detection across multiple assays and 33,997 cases: diagnostic implications and pitfalls

With the FDA approval of larotrectinib, NTRK fusion assessment has recently become a standard part of management for patients with locally advanced or metastatic cancers. Unlike somatic mutation assessment, the detection of NTRK fusions is not straightforward, and various assays exist at the DNA, RNA, and protein level. Here, we investigate the performance of immunohistochemistry and DNA-based next-generation sequencing to indirectly or directly detect NTRK fusions relative to an RNA-based next-generation sequencing approach in the largest cohort of NTRK fusion positive solid tumors to date. A retrospective analysis of 38,095 samples from 33,997 patients sequenced by a targeted DNA-based next-generation sequencing panel (MSK-IMPACT), 2189 of which were also examined by an RNA-based sequencing assay (MSK-Fusion), identified 87 patients with oncogenic NTRK1-3 fusions. All available institutional NTRK fusion positive cases were assessed by pan-Trk immunohistochemistry along with a cohort of control cases negative for NTRK fusions by next-generation sequencing. DNA-based sequencing showed an overall sensitivity and specificity of 81.1% and 99.9%, respectively, for the detection of NTRK fusions when compared to RNA-based sequencing. False negatives occurred when fusions involved breakpoints not covered by the assay. Immunohistochemistry showed overall sensitivity of 87.9% and specificity of 81.1%, with high sensitivity for NTRK1 (96%) and NTRK2 (100%) fusions and lower sensitivity for NTRK3 fusions (79%). Specificity was 100% for carcinomas of the colon, lung, thyroid, pancreas, and biliary tract. Decreased specificity was seen in breast and salivary gland carcinomas (82% and 52%, respectively), and positive staining was often seen in tumors with neural differentiation. Both sensitivity and specificity were poor in sarcomas. Selection of the appropriate assay for NTRK fusion detection therefore depends on tumor type and genes involved, as well as consideration of other factors such as available material, accessibility of various clinical assays, and whether comprehensive genomic testing is needed concurrently.

- Tumour Growth Rate as a validated early radiological biomarker able to reflect treatment-induced changes in Neuroendocrine Tumours; the GREPONET-2 study

PURPOSE: TGR represents the percentage change in tumour volume per month (%/m). Previous results from the GREPONET study showed that TGR measured after 3 months (TGR3m) of starting systemic

treatment (ST) or watch and wait (WW) was an early biomarker predicting progression-free survival (PFS) in NETs. EXPERIMENTAL DESIGN: Pts from7 centres with advanced grade(G) 1/2 NETs from the pancreas(P)/small bowel(SB) initiating ST/WW were eligible. Computed tomography (CT) / magnetic resonance imaging (MRI) performed at pre-baseline, baseline and 3(+/-1) months of study entry were retrospectively reviewed. Aim-1: explore treatment-induced changes in TGR (ΔTGR3m-BL) (paired T-test) and Aim-2: validate TGR3m (<0.8%/m vs 0.8%/m) as an early biomarker in an independent cohort (Kaplan-Meier/Cox Regression). RESULTS: Out of 785 pts screened, 127 were eligible. Mean (SD) TGR0 and TGR3m were 5.4%/m (14.9) and -1.4%/m (11.8), respectively. Mean(SD) ΔTGR3m-BL paired-difference was -6.8%/m(19.3) (p<0.001). Most marked ΔTGR3m-BL (mean (SD);p) were identified with targeted therapies (-11.3%/m(4.7);0.0237) and chemotherapy (-7.9%/m(3.4);0.0261). Multivariable analysis confirmed the absence of previous treatment (Odds Ratio (OR) 4.65 (95%CI 1.31-16.52); p-value0.018) and low TGR3m (continuous variable; OR 1.09 (95%CI 1.01-1.19); p-value0.042) to be independent predictors of radiological objective response. When the multivariable Cox Regression was adjusted to grade (p-value 0.004) and stage (p-value0.017), TGR3m 0.8 (vs.<0.8) maintained its significance (p<0.001), while TGR0 and ΔTGR3m-BL did not. TGR3m was confirmed as an independent prognosis factor for PFS (external validation; Aim-2) (multivariable HR 2.21 (95%CI 1.21-3.70); p-value0.003). CONCLUSIONS: TGR has a role as biomarker for monitoring response to therapy for early prediction of PFS and radiological objective response.

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- **Intraductal oncocytic papillary neoplasm of the pancreas: A systematic review**

Pancreatology : official journal of the International Association of Pancreatology (IAP) ... [et al.] 2019 Jul;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31375434

BACKGROUND: Intraductal oncocytic papillary neoplasm of the pancreas (IOPN-P) is a rare subtype of intraductal papillary mucinous neoplasm (IPMN). This study was performed to summarize the clinicopathological features and management of IOPN-P. METHODS: English-language articles were searched from MEDLINE and EMBASE from the first report of IOPN-P in 1996 until 1 May 2019 following the methodology in the PRISMA guidelines. RESULTS: In total, 66 patients from 24 full articles were included in the final data analysis. The patients' average age was 61 years, and the male/female ratio was 1. Most lesions were large (average size, 5.50 cm), located in the pancreatic head, and found either incidentally or by uncharacteristic abdominal symptoms. IOPN-P was usually a cystic and solid lesion with or without mural nodules on radiological examination. A definitive diagnosis was often acquired from fine needle aspiration biopsy or postoperative pathology. All tumors were diagnosed as carcinoma in situ or minimally invasive carcinoma, necessitating surgical resection. The prognosis of IOPN-P was better than that of other IPMN subtypes, even when metastasis occurred. Recurrence after surgical resection of IOPN-P was rare. CONCLUSIONS: IOPN-P is rare among IPMN subtypes with unique pathological characteristics. Because of the nontypical symptoms and radiological findings, a definitive preoperative diagnosis usually depends on multimodal examinations. Management and surveillance of IOPN-P after surgical resection should be differentiated from those of other pancreatic benign cystic lesions because of its relative malignancy, but IOPN-P should also be differentiated from other IPMN subtypes and malignant cystic tumors because of its favorable prognosis.

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- **Response to repeat echoendoscopic celiac plexus neurolysis in pancreatic cancer patients: A machine learning approach**

BACKGROUND: /Objectives: Efficacy of repeat echoendoscopic celiac plexus neurolysis is still unclear. Aim of the study was to assess the efficacy of repeat celiac plexus neurolysis and to build an artificial neural network model able to predict pain response. METHODS: Data regarding 156 patients treated with repeat celiac plexus neurolysis between 2004 and 2019 were reviewed. Artificial neural network and logistic regression models were built to predict pain response after treatment. Performance of the models was expressed in terms of accuracy, positive predictive value, and positive likelihood ratio. RESULTS: Median age was 62 years (range 39-86) and most patients were male (66%) with pre-procedural visual analogue score 7. Fifty-one patients (32.6%) experienced treatment response, of which 6 (3.8%) complete pain suppression. Median duration of pain relief was 6 (2-8) weeks. Tumoral stage, interval from initial to repeat treatment, response to initial neurolysis, and tumor progression between the two treatments resulted as significant predictors of pain response. The performance of the artificial neural network in predicting treatment response was higher than regression model (area under the curve: 0.94, 0.89-0.97 versus 0.85, 0.78-0.89; $p < 0.001$). Positive predictive value and positive likelihood ratio resulted 90.3% and 19.35, respectively. Classification error rate was 5.7% with the artificial neural network compared to 14.7% of regression model ($p < 0.001$). These findings were confirmed through ten-fold cross validation. CONCLUSIONS: Pain response following repeat neurolysis is generally less pronounced than after initial treatment. Artificial neural network may help to identify those subjects likely to benefit from repeat neurolysis.

- Facility Type is Another Factor in the Volume-Outcome Relationship for Complex Hepatopancreatobiliary Procedures

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- Disruption of IRE1 through its kinase domain attenuates multiple myeloma

Multiple myeloma (MM) arises from malignant immunoglobulin (Ig)-secreting plasma cells and remains an incurable, often lethal disease despite therapeutic advances. The unfolded-protein response sensor IRE1 supports protein secretion by deploying a kinase-endoribonuclease module to activate the transcription factor XBP1s. MM cells may co-opt the IRE1-XBP1s pathway; however, the validity of IRE1 as a potential MM therapeutic target is controversial. Genetic disruption of IRE1 or XBP1s, or pharmacologic IRE1 kinase inhibition, attenuated subcutaneous or orthometastatic growth of MM tumors in mice and augmented efficacy of two established frontline antimyeloma agents, bortezomib and lenalidomide. Mechanistically, IRE1 perturbation inhibited expression of key components of the endoplasmic reticulum-associated degradation machinery, as well as secretion of Ig light chains and of cytokines and chemokines known to promote MM growth. Selective IRE1 kinase inhibition reduced viability of CD138+ plasma cells while sparing CD138- cells derived from bone marrows of newly diagnosed or posttreatment-relapsed MM patients, in both US- and European Union-based cohorts. Effective IRE1 inhibition preserved glucose-induced insulin secretion

by pancreatic microislets and viability of primary hepatocytes in vitro, as well as normal tissue homeostasis in mice. These results establish a strong rationale for developing kinase-directed inhibitors of IRE1 for MM therapy.

- Comparative effectiveness of primary tumor resection in patients with stage III pancreatic adenocarcinoma

BMC cancer 2019 Aug;19(1):761

BACKGROUND: Previous studies comparing primary tumor resection (PTR) to palliative treatment for advanced-stage pancreatic ductal adenocarcinoma (PDA) were limited by strong selection bias. We used multiple methods to control for confounding and selection bias to estimate the effect of PTR on survival for late-stage PDA. METHODS: Surveillance, Epidemiology, and End Results (SEER) 18 registry database for 2004 through 2014 was retrieved for the present study. A total of 4322 patients with stage III (AJCC, 6th) PDA were included in this study. Propensity score matching (PSM) was performed to eliminate possible bias. In addition, instrumental variable (IV) analysis was utilized to adjust for both measured and unmeasured confounders. RESULTS: A total of 4322 patients with stage III PDA including 552 (12.8%) who underwent PTR, 3770 (87.2%) without PTR, were identified. In the multivariable cohort, a clear prognostic advantage of PTR was observed in overall survival (OS) (P < 0.001) and disease-specific survival (DSS) (P < 0.001) compared to patients after non-surgery therapy. In the PSM cohort, patients in PTR group showed a better OS and DSS (both P values < 0.001) compared to patients in non-surgery group. The survival benefit of PTR for stage III PDA was not observed in the two-stage residual inclusion (2SRI) model. Estimates based on this instrument indicated that patients treated with PTR had similar OS (P = 0.448) and DSS (P = 0.719). In IV analyses stratified by chemotherapy and tumor location, patients undergoing PTR had similar OS and DSS compared to patients in non-surgery group across all subgroups. CONCLUSIONS: Survival with PTR did not differ significantly from palliative treatment in marginal patients with stage III pancreatic adenocarcinoma. High-quality randomized trials are needed to validate these results.

- Rosai-Dorfman Disease of the Pancreas Shows Significant Histologic Overlap With IgG4-related Disease

The American journal of surgical pathology 2019 Jul;():

Rosai-Dorfman disease (RDD) is a rare entity characterized by proliferating S100-positive histiocytes. Originally described in lymph nodes, it can involve extranodal sites. Pancreatic involvement is rare, with <10 cases previously reported. Recent studies demonstrate a possible overlap between RDD and the more common IgG4-related disease (IRD), which could further complicate pathologic diagnosis. We describe distinct morphologic characteristics as well as overlapping histologic features of IRD in 5 cases of pancreatic RDD at our institution and compare these to a cohort of nonpancreatic extranodal RDD cases. All pancreatic cases were mass forming and had spindled patterns of elongated histiocytes with smaller areas of more classical appearing RDD; all cases had areas of storiform fibrosis and dense lymphoplasmacytic infiltrates with no increase in IgG4-positive plasma cells, and all cases had some degree of vasculitis (4 cases had obliterative vasculitis). Thirteen nonpancreatic extranodal RDD cases had dense lymphoplasmacytic infiltrates; most (85%) had some fibrosis with 46% showing storiform fibrosis, 85% had vasculitis with 31% demonstrating obliterative vasculitis and 2 cases had increased IgG4 staining. Extranodal (pancreatic and nonpancreatic)

RDD often shows overlapping morphologic features with IRD, including lymphoplasmacytic inflammation, storiform fibrosis with elongated histiocytes and vasculitis. This can create a diagnostic challenge in the pancreas where IRD is more commonly encountered. Pathologists need to be aware that RDD can occur in the pancreas and should include RDD in the differential of any mass forming pancreatic lesion in which morphologic features of IRD are present.

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- ZEB1 promotes inflammation and progression towards inflammation-driven carcinoma through repression of the DNA repair glycosylase MPG in epithelial cells

Gut 2019 Jul;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31366457

OBJECTIVE: Chronic inflammation is a risk factor in colorectal cancer (CRC) and reactive oxygen species (ROS) released by the inflamed stroma elicit DNA damage in epithelial cells. We sought to identify new drivers of UC and inflammatory CRC. DESIGN: The study uses samples from patients with UC, mouse models of colitis and CRC and mice deficient for the epithelial-to-mesenchymal transition factor ZEB1 and the DNA repair glycosylase N-methyl-purine glycosylase (MPG). Samples were analysed by immunostaining, qRT-PCR, chromatin immunoprecipitation assays, microbiota next-generation sequencing and ROS determination. RESULTS: ZEB1 was induced in the colonic epithelium of UC and of mouse models of colitis. Compared with wild-type counterparts, Zeb1-deficient mice were partially protected from experimental colitis and, in a model of inflammatory CRC, they developed fewer tumours and exhibited lower levels of DNA damage (8-oxo-dG) and higher expression of MPG. Knockdown of ZEB1 in CRC cells inhibited 8-oxo-dG induction by oxidative stress (H2O2) and inflammatory cytokines (interleukin (IL)1). ZEB1 bound directly to the MPG promoter whose expression inhibited. This molecular mechanism was validated at the genetic level and the crossing of Zeb1-deficient and Mpg-deficient mice reverted the reduced inflammation and tumourigenesis in the former. ZEB1 expression in CRC cells induced ROS and IL1 production by macrophages that, in turn, lowered MPG in CRC cells thus amplifying a positive loop between both cells to promote DNA damage and inhibit DNA repair. CONCLUSIONS: ZEB1 promotes colitis and inflammatory CRC through the inhibition of MPG in epithelial cells, thus offering new therapeutic strategies to modulate inflammation and inflammatory cancer.

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- Characterising the impact of body composition change during neoadjuvant chemotherapy for pancreatic cancer

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31362865

BACKGROUND: Pancreatic Cancer remains a lethal disease for the majority of patients. New chemotherapy agents such as Folfirinox offer therapeutic potential for patients who present with Borderline Resectable disease (BRPC). However, results to date are inconsistent, with factors such as malnutrition limiting successful drug delivery. We sought to determine the prevalence of sarcopenia in BRPC patients at diagnosis, and to quantify body composition change during chemotherapy. METHODS: The diagnostic/restaging CT scans of BRPC patients were analysed. Body composition was measured at L3 using Tomovision Slice-O-Matic™. Total muscle and adipose tissue mass were estimated using validated regression equations. Sarcopenia was defined as per gender- and body mass index (BMI)-specific lumbar skeletal muscle index (LSMI) and muscle attenuation reference values. RESULTS: Seventy-eight patients received neo-adjuvant chemotherapy, and

67 patients underwent restaging CT, at which point a third were deemed resectable. Half were sarcopenic at diagnosis, and sarcopenia was equally prevalent across all BMI categories.. Skeletal muscle and adipose tissue (intra-muscular, visceral and sub-cutaneous) area decreased during chemotherapy ($p < 0.0001$). Low muscle attenuation was observed in half of patients at diagnosis, and was associated with increased mortality risk. Loss of lean tissue parameters during chemotherapy was associated with an increased mortality risk; specifically fat-free mass, HR 1.1 (95% CI 1.03-1.17, $p = 0.003$) and skeletal muscle mass, HR 1.21 (95%CI 1.08-1.35, $p = 0.001$). CONCLUSIONS: Sarcopenia was prevalent in half of patients at the time of diagnosis with BRPC. Low muscle attenuation at diagnosis, coupled with lean tissue loss during chemotherapy, independently increased mortality risk.

- Actual 10-Year Survival After Surgical Microwave Ablation for Hepatocellular Carcinoma: A Single-Center Experience in Japan

BACKGROUND: Little evidence exists regarding long-term survival after microwave ablation for hepatocellular carcinoma (HCC). The aim of this study is to determine actual 10-year survival and clarify the clinicopathological features of patients surviving 10 years after surgical microwave ablation. PATIENTS AND METHODS: This retrospective study identified 459 patients who underwent surgical microwave ablation for HCC with curative intent between 2001 and 2008. We compared 100 patients who survived 10 years with 321 patients who died within 10 years. RESULTS: Median overall survival and recurrence-free survival rates were 5.5 and 2.4 years, respectively. The actual 10-year overall survival rate was 23.8%, and the actual 10-year recurrence-free survival rate was 8.1%. Multivariate analysis showed that age > 70 years [odds ratio 1.87, $P = 0.029$], hepatitis C virus positivity (OR 2.30, $P = 0.004$), Child-Pugh class B (OR 3.28, $P = 0.003$), and platelet count $< 10 \times 104$ /µL (OR 1.93, $P = 0.033$) were independent risk factors for actual 10-year survival. During 10-year follow-up, 66% of the 10-year survivors developed recurrence, and 91% of these patients underwent further curative treatment, including hepatic resection or local ablation, for HCC recurrence. CONCLUSION: Ten-year survival after surgical microwave ablation for HCC can be expected in approximately 24% of patients, even though nearly 2/3 of our 10-year survival patients experienced recurrence. Close postoperative follow-up and further curative treatment for recurrence are important for improving long-term survival.

- Characterization and comparison of GITR expression in solid tumors

PURPOSE: Determine the differential effect of a FcgR-binding, mIgG2a anti-GITR antibody in mouse tumor modelsand characterize the tumor microenvironment for the frequency of GITR expression in T cell subsets from seven different human solid tumors. EXPERIMENTAL DESIGN: For mouse experiments, wildtype C57BL/6 mice were subcutaneously injected with MC38 cells or B16 cells, and BALB/c mice were injected with CT26 cells. Mice were treated with the anti-mouse GITR agonist antibody 21B6, and tumor burden and survival were monitored. GITR expression was evaluated at the single cell level using flow cytometry (FC). 213 samples were evaluated for GITR expression by immunohistochemistry (IHC), 63 by FC and 170 by both in seven human solid tumors: advanced hepatocellular carcinoma, non-small cell lung cancer, renal cell carcinoma, pancreatic carcinoma, head and neck carcinoma, melanoma, and ovarian carcinoma.

RESULTS: The therapeutic benefit of 21B6 was greatest in CT26 followed by MC38, and was least in the B16 tumor model. The frequency of CD8 T cells and effector CD4 T cells within the immune infiltrate correlated with response to treatment with GITR antibody. Analysis of clinical tumor samples showed that non-small cell lung cancer, renal cell carcinoma, and melanoma had the highest proportions of GITR-expressing cells and highest per-cell density of GITR expression on CD4-positive Foxp3 positive Tregs. IHC and FC data showed similar trends with a good correlation between both techniques. CONCLUSIONS: Human tumor data suggest that NSCLC, RCC, and melanoma should be the tumor subtypes prioritized for anti-GITR therapy development.

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- Fungal sinusitis in simultaneous pancreas-kidney transplant

Journal of clinical pathology 2019 Jul;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31358535

doi: https://doi.org/10.1136/jclinpath-2018-205258

- New Nodal Staging for Primary Pancreatic Neuroendocrine Tumors: A Multi-institutional and National Data Analysis

Annals of surgery 2019 Jul;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31356277

OBJECTIVE: To determine the prognostic role of metastatic lymph node (LN) number and the minimal number of LNs for optimal staging of patients with pancreatic neuroendocrine tumors (pNETs). BACK-GROUND: Prognosis relative to number of LN metastasis (LNM), and minimal number of LNs needed to evaluate for accurate staging, have been poorly defined for pNETs. METHODS: Number of LNM and total number of LN evaluated (TNLE) were assessed relative to recurrence-free survival (RFS) and overall survival (OS) in a multi-institutional database. External validation was performed using Surveillance, Epidemiology and End Results (SEER) registry. RESULTS: Among 854 patients who underwent resection, 233 (27.3%) had at least 1 LNM. Patients with 1, 2, or 3 LNM had a comparable worse RFS versus patients with no nodal metastasis (5-year RFS, 1 LNM 65.6%, 2 LNM 68.2%, 3 LNM 63.2% vs 0 LNM 82.6%; all P < 0.001). In contrast, patients with 4 LNM (proposed N2) had a worse RFS versus patients who either had 1 to 3 LNM (proposed N1) or node-negative disease (5-year RFS, 4 LNM 43.5% vs 1-3 LNM 66.3%, 0 LNM 82.6%; all P < 0.05) [C-statistics area under the curve (AUC) 0.650]. TNLE 8 had the highest discriminatory power relative to RFS (AUC 0.713) and OS (AUC 0.726) among patients who had 1 to 3 LNM, and patients who had 4 LNM in the multi-institutional and SEER database (n = 2764). CONCLUSIONS: Regional lymphadenectomy of at least 8 lymph nodes was necessary to stage patients accurately. The proposed nodal staging of N0, N1, and N2 optimally staged patients.

doi: https://doi.org/10.1097/SLA.0000000000003478

- Left-sided Portal Hypertension After Pancreaticoduodenectomy With Resection of the Portal Vein/Superior Mesenteric Vein Confluence in Patients With Pancreatic Cancer: A Project Study by the Japanese Society of Hepato-Biliary-Pancreatic Surgery

Annals of surgery 2019 Jul;():

OBJECTIVE: The aim of this study was to evaluate how often left-sided portal hypertension (LPH) develops and how LPH affects the long-term outcomes of patients with pancreatic cancer treated with pancreaticoduodenectomy (PD) and resection of the portal vein (PV)/superior mesenteric vein (SMV) confluence. SUMMARY BACKGROUND DATA: Little is known about LPH after PD with resection of the PV/SMV confluence. METHODS: Overall, 536 patients who underwent PD with PV/SMV resection were enrolled. Among them, we mainly compared the SVp group [n=285; the splenic vein (SV) was preserved] and the SVr group (n = 227; the SV was divided and not reconstructed). RESULTS: The incidence of variceal formation in the SVr group increased until 3 years after PD compared with that in the SVp group (38.7% vs 8.3%, P < 0.001). Variceal bleeding occurred in the SVr group (n = 9: 4.0%) but not in the SVp group (P < 0.001). In the multivariate analysis, the risk factors for variceal formation were liver disease, N factor, conventional PD, middle colic artery resection, and SV division. The only risk factor for variceal bleeding was SV division. The platelet count ratio at 6 months after PD was significantly lower in the SVr group than in the SVp group (0.97 vs 0.82, P < 0.001), and the spleen-volume ratios at 6 and 12 months were significantly higher in the SVr group than in the SVp group (1.38 vs 1.00 and 1.54 vs 1.09; P < 0.001 and P < 0.001, respectively). CONCLUSIONS: PD with SV division causes variceal formation, bleeding, and thrombocytopenia.

- **Cytology with rapid on-site examination (ROSE) does not improve diagnostic yield of EUS-FNA of pancreatic cystic lesions**

BACKGROUND: Cytology with rapid on-site evaluation (ROSE) has been shown to increase the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) for solid pancreatic lesions. No data exists on the need for rapid onsite cytology in the evaluation of pancreatic cystic lesions (PCLs). The purpose of this study is to determine whether onsite cytology impacts the diagnostic yield of EUS-FNA of PCLs. METHODS: We prospectively examined all patients with PCLs who underwent EUS-FNA without onsite cytology over a 6-month period and compared this to a historical cohort of patients with PCLs who underwent EUS-FNA with ROSE in the previous 6 months. Comparison was made between the two groups based upon patient demographics, EUS cyst characteristics, and FNA fluid & cytopathology results. RESULTS: A total of 100 EUS-FNA exams for PCLs were identified: 46 with ROSE and 54 without onsite cytology. The majority of cytology findings were negative or nondiagnostic, 87.0% in the ROSE group, 77.8% in the group without onsite cytology. There was no difference using EUS-FNA without onsite cytology compared to ROSE when measuring total diagnostic yield (22.2% vs 13.0%, P = .30), number of nondiagnostic specimens (50% vs 54%, P = .69), and number of needle passes (1.51 vs 1.57, P = .68). CONCLUSIONS: (a) The majority of cytology results from EUS-FNA of cystic lesions are negative or nondiagnostic. (b) Having rapid onsite cytology evaluation of cystic lesions does not affect the number of needle passes nor diagnostic yield and is thus not recommended.

- **African American women with gum disease and tooth loss face higher pancreatic cancer risk**

- **Oncogenic KRAS Reduces Expression of FGF21 in Acinar Cells to Promote Pancreatic Tumorigenesis in Mice on a High-Fat Diet**

Gastroenterology 2019 Jul;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31352001

BACKGROUND & AIMS: Obesity is a risk factor for pancreatic cancer. In mice, a high-fat diet (HFD) and expression of oncogenic KRAS lead to development of invasive pancreatic ductal adenocarcinoma (PDAC) by unknown mechanisms. We investigated how oncogenic KRAS regulates the expression of fibroblast growth factor 21 (FGF21), a metabolic regulator that prevents obesity, and the effects of recombinant human FGF21 (rhFGF21) on pancreatic tumorigenesis. METHODS: We performed immunohistochemical analyses of FGF21 levels in human pancreatic tissue arrays, comprising 59 PDAC specimens and 45 non-tumor tissues. We also studied mice with tamoxifen-inducible expression of oncogenic KRAS in acinar cells (KrasG12D/+ mice) and fElasCreERT mice (controls). KrasG12D/+ mice were placed on a HFD or regular chow diet (control) and given injections of rhFGF21 or vehicle; pancreata were collected and analyzed by histology, immunoblots, quantitative PCR, and immunohistochemistry. We measured markers of inflammation in the pancreas, liver, and adipose tissue. Activity of RAS was measured based on the amount of bound GTP. RESULTS: Pancreatic tissues of mice expressed high levels of FGF21 compared with liver. FGF21 and its receptor proteins were expressed by acinar cells. Acinar cells that expressed KrasG12D/+ had significantly lower expression of Fgf21 mRNA, compared with acinar cells from control mice, partly due to downregulation of PPARG expression-a transcription factor that activates Fgf21 transcription. Pancreata from KrasG12D/+ mice on a control diet and given injections of rhFGF21 had reduced pancreatic inflammation, infiltration by immune cells, and acinar-to-ductal metaplasia compared with mice given injections of vehicle. HFD-fed KrasG12D/+ mice given injections of vehicle accumulated abdominal fat, developed extensive inflammation, pancreatic cysts, and high-grade pancreatic intraepithelial neoplasias (PanINs); half the mice developed PDAC with liver metastases. HFD-fed KrasG12D/+ mice given injections of rhFGF21 had reduced accumulation of abdominal fat and pancreatic triglycerides, fewer pancreatic cysts, reduced systemic and pancreatic markers of inflammation, fewer PanINs, and longer survival-only about 12% of mice developed PDACs and none of the mice had metastases. Pancreata from HFD-fed KrasG12D/+ mice given injections of rhFGF21 had lower levels of active RAS than from mice given vehicle. CONCLUSIONS: Normal acinar cells from mice and humans express high levels of FGF21. In mice, acinar expression of oncogenic KRAS significantly reduces FGF21 expression. When these mice are placed on a HFD, they develop extensive inflammation, pancreatic cysts, PanINs, and PDACs, which are reduced by injection of FGF21. FGF21 also reduces the GTP binding capacity of RAS. FGF21 might be used in prevention or treatment of pancreatic cancer.

doi: https://doi.org/10.1053/j.gastro.2019.07.030

- **Fine needle aspiration of the liver: a ten-year single institution retrospective review**

Human pathology 2019 Jul;():

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Fine-needle aspiration (FNA) of liver masses is a minimally invasive means of evaluation, with diagnostic accuracy over 85%. Given that most of the recent literature on sampling hepatic tumors was published by radiologists and gastroenterologists, we herein conduct a 10-year retrospective review of a single institution's cytopathology experience with the diagnosis of liver lesions. Electronic record review of the cytopathology files (CoPathPlus; Cerner Corp.) was conducted for the 10-year interval January 2007 through December 2016. All cytology specimens designated as "liver" and "FNA" were included. Associated concurrent and subsequent surgical pathology and cytopathology cases were identified. All FNA cases were organized into

four diagnostic categories: positive for malignancy, atypical, negative for malignancy, and non-diagnostic. There were 713 hepatic FNAs that were categorized as follows: positive for malignancy 467 (65.5%), atypical 49 (6.9%), negative 171 (24.0%) and non-diagnostic 26 (3.6%). Metastatic tumors (95.7%) were more common that primary (4.3%). The top two metastatic primary sites were pancreas (30.1%) and colon (12.7%). A total of 166 (23.2%) cases had concurrent core needle biopsies (CNB). 111 (66.9%) were concordant with the FNA diagnosis. Of the 55 discordant cases, 43 (25.9%) had diagnostic material only on CNB and 12 (7.2%) had diagnostic material only on FNA. The sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy were 93.4%, 96.7%, 98.2%, 84.3%, and 89.3% respectively. Irrespective of endoscopic versus percutaneous approach, hepatic FNA is a sensitive and specific means of identifying metastatic and primary malignancies of the liver.

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- Morphologic Factors Predict Pain Relief Following Pancreatic Head Resection in Chronic Pancreatitis Description of the Chronic Pancreatitis Pain Relief (CPPR) Score

Annals of surgery 2019 Jul;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31348039

OBJECTIVE: This study analyzes the clinicopathologic findings and their impact on outcome of patients so as to identify which patients benefit most from surgical treatment in chronic pancreatitis, especially in regard to pain relief. SUMMARY BACKGROUND DATA: The predominant symptom of chronic pancreatitis is chronic pain resulting in reduced quality of life. It is well known that the main reason for development of the disease is abuse of alcohol and nicotine, but only little data on factors influencing outcome are available. METHODS: One thousand one hundred forty-six consecutive patients who underwent surgery for chronic pancreatitis were included. Clinicopathologic data, including morphology of the pancreas in preoperative diagnostics and the histopathologic results, were evaluated. A long-term follow-up including Quality of Life and pain scores was performed. Additionally, we describe the novel Chronic Pancreatitis Pain Relief Score (CPPR-Score) as a tool for prediction of pain relief. RESULTS: Overall the rate of pain relief was 79.8% after surgery. The presence of an inflammatory mass in the pancreatic head larger than 4cm (P < 0.001), presence of a dilated main pancreatic duct of over 4mm (P < 0.001), histopathologically detected severe calcifications (P = 0.001) and severe fibrosis (P < 0.001) as well as ethanol induced disease (P < 0.001) found to be strong independent prognostic factors for pain relief. The CPPR-Score (0-5 points) proved to be a very good predictive score for pain-relief (P < 0.001). CONCLUSIONS: The rate of pain relief after surgical treatment in chronic pancreatitis is high and the commonly used procedures can be performed with acceptable morbidity and mortality. The Chronic Pancreatitis Pain Relief Score allows identifying patients who will benefit most from surgery.

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- Reappraisal of a 2-Cm Cut-Off Size for the Management of Cystic Pancreatic Neuroendocrine Neoplasms: A Multicenter International Study

Annals of surgery 2019 Jul;():

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MINI: The characteristics of cystic pancreatic neuroendocrine neoplasms (cPanNENs) are largely unknown, and their clinical management remains unclear; specifically, an observational strategy for asymptomatic cPanNENs 2cm has been proposed by recent guidelines, but evidence is scarce and limited to single institutional series. In this international cohort study of 263 resected cPanNENs from 16 institutions worldwide, a preoperative size >2cm was independently associated with aggressive behavior both in the whole cohort and

in the subset of asymptomatic patients; notably, only 1 of 61 asymptomatic cPanNENs 2cm was aggressive. Based on these results, a watch-and-wait policy for sporadic asymptomatic cPanNENs 2cm seems justified and safe. The aim of this study was to characterize an international cohort of resected cystic pancreatic neuroendocrine neoplasms (cPanNENs) and identify preoperative predictors of aggressive behavior. The characteristics of cPanNENs are unknown and their clinical management remains unclear. An observational strategy for asymptomatic cPanNENs 2cm has been proposed by recent guidelines, but evidence is scarce and limited to single-institutional series. Resected cPanNENs (1995-2017) from 16 institutions worldwide were included. Solid lesions (>50% solid component), functional tumors, and MEN-1 patients were excluded. Aggressiveness was defined as lymph node (LN) involvement, G3 grading, distant metastases, and/or recurrence. Overall, 263 resected cPanNENs were included, among which 177 (63.5%) were >2cm preoperatively. A preoperative diagnosis of cPanNEN was established in 162 cases (61.6%) and was more frequent when patients underwent endoscopic ultrasound [EUS, odds ratio (OR) 2.69, 95% confidence interval (CI) 1.52-4.77] and somatostatin-receptor imaging (OR 3.681, 95% CI 1.809-7.490), and for those managed in specialized institutions (OR 3.12, 95% CI 1.57-6.21). Forty-one cPanNENs (15.6%) were considered aggressive. In the whole cohort, LN involvement on imaging, age >65 years, preoperative size >2cm, and pancreatic duct dilation were independently associated with aggressive behavior. In asymptomatic patients, older age and a preoperative size >2cm remained independently associated with aggressiveness. Only 1 of 61 asymptomatic cPanNENs 2cm displayed an aggressive behavior. The diagnostic accuracy of cPanNENs is increased by the use of EUS and somatostatin-receptor imaging and is higher in specialized institutions. Preoperative size >2cm is independently associated with aggressive behavior. Consequently, a watch-and-wait policy for sporadic asymptomatic cPanNENs 2cm seems justified and safe for most patients.

- **Long non-coding RNA PTTG3P functions as an oncogene by sponging miR-383 and up-regulating CCND1 and PARP2 in hepatocellular carcinoma**

BACKGROUND: Emerging evidence indicates that Long non-coding RNAs (LncRNAs) and microRNAs (miRNAs) play crucial roles in tumor progression, including hepatocellular carcinoma (HCC). However, whether there is a crosstalk between LncRNA pituitary tumor-transforming 3 (PTTG3P) and miR-383 in HCC remains unknown. This study is designed to explore the underlying mechanism by which LncRNA PTTG3P sponges miR-383 during HCC progression. METHODS: qPCR and Western blot were used to analyze LncRNA PTTG3P, miR-383 and other target genes' expression. CCK-8 assay was performed to examine cell proliferation. Annexin V-PE/PI and PI staining were used to analyze cell apoptosis and cell cycle distribution by flow cytometry, respectively. Transwell migration and invasion assays were used to examine cell migration and invasion abilities. An in vivo xenograft study was performed to detect tumor growth. Luciferase reporter assay and RNA pull-down assay were carried out to detect the interaction between miR-383 and LncRNA PTTG3P. RIP was carried out to detect whether PTTG3P and miR-383 were enriched in Ago2-immunoprecipitated complex. RESULTS: In this study, we found that PTTG3P was up-regulated in HCC tissues and cells. Functional experiments demonstrated that knockdown of PTTG3P inhibited cell proliferation, migration and invasion, and promoted cell apoptosis, acting as an oncogene. Mechanistically, PTTG3P upregulated the expression of miR-383 targets Cyclin D1 (CCND1) and poly ADP-ribose polymerase 2 (PARP2) by sponging miR-383, acting as a competing endogenous RNA (ceRNA). The PTTG3P-miR-383-CCND1/PARP2 axis modulated HCC phenotypes. Moreover, PTTG3P also affected the PI3K/Akt signaling pathway. CONCLUSION: The data indicate a novel PTTG3P-miR-383-CCND1/PARP2 axis in HCC tumorigenesis, suggesting that PTTG3P may be used as a potential therapeutic target in HCC.

- Age-related morphological changes in the pancreas and their association with pancreatic carcinogenesis

Pathology international 2019 Jul;():

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Age-related pathological changes in the pancreas have been unclear because they are often minor and non-specific. However, recent studies have shown that they are closely related to various pathological conditions such as pancreatic cancer and diabetes mellitus. Knowledge of age-related changes is important to determine appropriate prevention, detection, and treatment strategies for various diseases observed in elderly patients. We present a review of the pathological age-related non-neoplastic changes in the exocrine pancreas such as pancreatic fatty replacement, lobulocentric pancreatic atrophy, pancreatic duct ectasia, and metaplasia of exocrine pancreas, as well as changes in islet cells. We have discussed common pancreatic neoplasms in elderly patients, such as pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasms (IPMNs), and pancreatic ductal adenocarcinoma (PDAC). Age-related pathological changes play a key role in pancreatic carcinogenesis via telomere dysfunction. Further studies are warranted to clarify molecular mechanisms of pancreatic carcinogenesis in elderly patients.

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- Acinar cell carcinoma of the pancreas with thyroid-like follicular features: first description of a new diagnostic challenging subtype

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Acinar cell carcinomas (ACCs) of the pancreas are a heterogeneous group of neoplasms showing a wide spectrum of morphological features including acinar, solid, glandular, and trabecular architecture. In addition, uncommon cytological aspects have recently been described and include oncocytic, spindle, clear, and pleomorphic cell types. This wide histological spectrum represents a challenge in the diagnostic task for pathologists. Molecular mechanisms involved in the onset and progression of ACCs are not completely known, but, in general, they differ from those observed in ductal adenocarcinomas or neuroendocrine neoplasms of the pancreas and frequently include alterations in the APC/ -catenin pathway. In the present paper, we describe a new variant of ACC showing thyroid-like follicular features and CTNNB1 mutation. This phenotype needs to be included in the spectrum of morphological presentation of ACC.

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- Overall survival in patients over 40 years old with surgically resected pancreatic carcinoma: a SEER-based nomogram analysis

BMC cancer 2019 Jul;19(1):726

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BACKGROUND: The aim of this study was to identify the determinants of overall survival (OS) within patients over 40 years old with surgically resected pancreatic carcinoma (PC), and to develop a nomogram with the intention of OS predicting. METHODS: A total of 6341 patients of 40 years of age or later with surgically resected PC between 2010 and 2015 were enrolled from the Surveillance, Epidemiology, and End Results (SEER) program and randomly assigned into training set (4242 cases) and validation set (2099 cases). A nomogram was constructed for predicting 1-, 2- and 3-years OS based on univairate and multivariate Cox

regression. The C-index and calibration plot were adopted to assess the nomogram performance. RESULTS: Our analysis showed that age, location of carcinoma in pancreas, tumor grade, TNM stage, size of carcinoma together with lymph node ratio (LNR) were considered to be independent overall survival predictors. A nomogram based on these six factors was developed with C-index being 0.680 (95%CI: 0.667-0.693). All calibration curves of OS fitted well. The OS curves stratified by nomogram-predicted probability score (20, 10-19 and < 10) demonstrated statistically significant difference not only within training set but also in validation set. CONCLUSIONS: The present nomogram for OS predicting can serve as the efficacious survival-predicting model and assist in accurate decision-making for patients over 40 years old with surgically resected PC.

doi: https://doi.org/10.1186/s12885-019-5958-9

- **Anticancer immunotherapy by MFAP5 blockade inhibits fibrosis and enhances chemosensitivity in ovarian and pancreatic cancer**

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PURPOSE: Recent studies demonstrate the role of the tumor microenvironment in tumor progression. However, strategies used to overcome the malignant phenotypes of cancer cells modulated by the microenvironment have not been thoroughly explored. In this study, we evaluated the therapeutic efficacy of a newly developed monoclonal antibody targeting microfibril associated protein 5 (MFAP5), which is secreted predominately by CAFs, in ovarian and pancreatic cancer models. EXPERIMENTAL DESIGN: Monoclonal antibodies were developed using human MFAP5 recombinant protein as an antigen in mice and antibodies from hybridoma clones were evaluated for their specificity to human and murine MFAP5. An Octet RED384 system was used to determine the kinetics of binding affinity and the specificity of the antibody clones, which were followed by epitope mapping and functional characterization by in vitro assays. The therapeutic efficacy of a lead anti-MFAP5 antibody clone 130A in tumor suppression was evaluated by ovarian tumor- and pancreatic tumor-bearing mouse models. RESULTS: Three hybridoma clones, which produced antibodies with high affinity and specificity to MFAP5, were selected for functional studies. Antibody clone 130A, which recognizes a common epitope shared between human and murine MFAP5 protein, were further selected for in vivo studies. Results showed that clone 130A down-regulated MFAP5-induced collagen production in CAFs, suppressed intratumoral microvessel leakiness, and enhanced paclitaxel bioavailability in both ovarian and pancreatic cancer mouse models. CONCLUSIONS: These data suggest that MFAP5 blockade using an immunologic approach inhibits fibrosis, induces tumor vessel normalization and enhances chemosensitivity in ovarian and pancreatic cancer, and can be used as a novel therapeutic agent.

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- **Mild maternal hyperglycemia in INSC93S transgenic pigs causes impaired glucose tolerance and metabolic alterations in neonatal offspring**

Disease models & mechanisms 2019 Aug;12(8):

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Alongside the obesity epidemic, the prevalence of maternal diabetes is rising worldwide, and adverse effects on fetal development and metabolic disturbances in the offspring's later life have been described. To clarify whether metabolic programming effects are due to mild maternal hyperglycemia without confounding obesity, we investigated wild-type offspring of INSC93S transgenic pigs, which are a novel genetically modified large-animal model expressing mutant insulin (INS) C93S in pancreatic -cells. This mutation results in impaired glucose tolerance, mild fasting hyperglycemia and insulin resistance during late pregnancy. Compared with

offspring from wild-type sows, piglets from hyperglycemic mothers showed impaired glucose tolerance and insulin resistance (homeostatic model assessment of insulin resistance: +3-fold in males; +4.4-fold in females) prior to colostrum uptake. Targeted metabolomics in the fasting and insulin-stimulated state revealed distinct alterations in the plasma metabolic profile of piglets from hyperglycemic mothers. They showed increased levels of acylcarnitines, gluconeogenic precursors such as alanine, phospholipids (in particular lyso-phosphatidylcholines) and -aminoadipic acid, a potential biomarker for type 2 diabetes. These observations indicate that mild gestational hyperglycemia can cause impaired glucose tolerance, insulin resistance and associated metabolic alterations in neonatal offspring of a large-animal model born at a developmental maturation status comparable to human babies.

- **Reply to Comment on Zeng et al, Spatial Distribution of Pancreatic Stones in Chronic Pancreatitis**

Pancreas 2019 Aug;48(7):e59

- **Mathematical Model and Study Design Could Be Optimized in Spatial Distribution Analysis of Pancreatic Stones**

Pancreas 2019 Aug;48(7):e58

- **Reply to: The Relationship of Acute Pancreatitis and Pancreatic Cancer**

Pancreas 2019 Aug;48(7):e57-e58

- **The Relationship of Acute Pancreatitis and Pancreatic Cancer**

Pancreas 2019 Aug;48(7):e57

- Surgical and Oncological Outcomes of Laparoscopic Versus Open Pancreaticoduodenectomy in Patients With Pancreatic Duct Adenocarcinoma

It is not clear which of the 2 principal treatments for patients with pancreatic duct adenocarcinoma (PDAC), laparoscopic pancreaticoduodenectomy (LPD) and open pancreaticoduodenectomy (OPD), has greater safety and efficacy. We performed the present meta-analysis to assess the efficacy of both treatments for PDAC patients undergoing LPD. Multiple electronic databases were systematically searched to identify studies (up to October 2018) comparing LPD with OPD for PDAC. Short- and long-term oncological outcomes were evaluated. Six studies were qualified for inclusion criteria in this meta-analysis with a total of 9144 PDAC participants. Regarding safety, there were fewer overall postoperative complications associated with LPD (P = 0.005), but the results were similar in terms of pancreatic fistula and mortality. Laparoscopic pancreaticoduodenectomy was associated with a better trend of performance both in R0 resection (relative risk, 1.03; 95% confidence interval [CI], 1.00-1.07; P = 0.07) and preserved lymph nodes (median, 2.14; 95% CI, -0.21 to 4.49; P = 0.07). Long-term overall survival was comparable between LPD and OPD (hazard ratio, 1.03; 95% CI, 0.95-1.13; P = 0.49). In conclusion, LPD was found to be a suitable alternative to OPD in selected PDAC patients with respect to both surgical and oncological outcomes.

- Excess body weight at age <50 years is linked to pancreatic cancer mortality

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- Impact of Changes in the American Joint Committee on Cancer Staging Manual, Eighth Edition, for Pancreatic Ductal Adenocarcinoma

OBJECTIVE: Consistent and reliable tumor staging is a critical factor in determining treatment strategy, selection of patients for adjuvant therapy, and for therapeutic clinical trials. The aim of this study was to evaluate the number and extent of pancreatic ductal adenocarcinoma (PDAC) cases that would have a different pT, pN, and overall stages based on the new eighth edition American Joint Committee on Cancer staging system when compared with the seventh edition. METHODS: Patients diagnosed with PDAC who underwent pancreaticoduodenectomy, total pancreatectomy, or distal pancreatectomy from 2007 to 2017 were retrospectively reviewed. A total of 340 cases were included. RESULTS: According to the seventh edition, the vast majority of tumors in our cohort were staged as pT3 tumors (88.2%). Restaging these cases with the new size-based pT system resulted in a more equal distribution among the 3 pT categories, with higher percentage of pT2 cases (55%). CONCLUSIONS: The newly adopted pT stage protocol for PDAC is clinically relevant, ensures a more equal distribution among different stages, and allows for a significant prognostic stratification. In contrast, the new pN classification (pN1 and pN2) based on the number of positive lymph nodes failed to show survival differences and remains controversial.

- The Surveillance Patterns of Incidentally Detected Pancreatic Cysts Vary Widely and Infrequently Adhere to Guidelines

OBJECTIVES: We aimed to determine incidental pancreatic cyst ("cyst") surveillance patterns, predictors of receiving surveillance, and guideline adherence. METHODS: We performed a retrospective cohort study of all patients receiving longitudinal care at a single tertiary care center with a newly diagnosed incidental pancreatic cyst over a 2-year period (2010-2011). All follow-up care was abstracted over a 5-year period. RESULTS: Of 3241 eligible imaging studies reviewed, 100 patients with newly diagnosed incidental cysts eligible for surveillance were identified. A majority (53%) received no follow-up. We identified 4 predictors of cyst surveillance: radiology report conclusion mentioning the cyst (odds ratio [OR], 14.9; 95% confidence interval [CI], 1.9-119) and recommending follow-up (OR, 5.5; 95% CI, 2.1-13.9), pancreas main duct dilation (OR, 10.7; 95% CI, 1.3-89), and absence of multiple cysts (OR, 2.5; 95% CI, 1.1-10.0). Of the 47 patients who received surveillance, 66% met minimum surveillance imaging intervals of at least one guideline. Conversely, 21% of patients met the criteria for overutilization in at least one guideline. CONCLUSIONS: Although guidelines recommend that surgically fit patients with incidental cysts undergo surveillance, most patients receive no follow-up. When follow-up occurs, surveillance patterns vary widely and infrequently conform to guidelines. Interventions to reduce care variation require study.

- Alternate Week Gemcitabine and Capecitabine: An Effective Treatment for Patients With Pancreatic Adenocarcinoma

OBJECTIVE: Determine whether a regimen of fixed dose rate gemcitabine plus capecitabine is effective and tolerable for advanced pancreatic adenocarcinoma. METHODS: We performed a retrospective analysis of 62 patients with locally advanced or metastatic pancreatic adenocarcinoma treated at the University of California San Francisco between 2008 and 2016. Treatment was an alternate week schedule of fixed dose rate 1000 mg/m gemcitabine and capecitabine 1000 mg/m (58 patients), 1200 mg/m (12 patients), or 650 mg/m (1 patient) for intended 12 cycles. We evaluated overall survival (OS), progression-free survival (PFS), radiologic response, and adverse events necessitating treatment modification. RESULTS: For metastatic patients, median OS was 10.3 months (95% confidence interval [CI], 6.7-12.1 months), and PFS was 5.6 months (95% CI, 2.6-7.7 months). In locally advanced patients, OS was 12.0 months (95% CI, 4.9-17.1 months), and PFS was 5.4 months (95% CI, 2.5-9.4 months). Radiologic response for metastatic disease (42 patients) was 19% objective response, 45% stable disease, and 36% progressive disease. Treatment required modification for 22 patients due to adverse events, most frequently hand-foot syndrome (18 patients). CONCLUSIONS: Alternate week schedule of fixed dose rate gemcitabine and capecitabine was active and tolerable for advanced pancreatic adenocarcinoma. Overall survival and PFS were comparable to first-line treatments. Importantly, adverse effects appear less severe than first-line treatments.

- Induction Therapy in Localized Pancreatic Cancer

OBJECTIVES: Pancreatic cancer (PDAC) with localized stage includes resectable (RPC), borderline resectable (BRPC), or locally advanced unresectable (LAPC). Standard of care for RPC is adjuvant chemotherapy. There are no prospective randomized trials for best treatment of BRPC and LAPC. We evaluate the impact of induction chemotherapy on localized PDAC. METHODS: Charts of PDAC patients treated at Emory University between 2009 and 2016 were reviewed. The primary end point was overall survival (OS). RESULTS: A total of 409 localized PDACs were identified. Resectability was prospectively determined at a multidisciplinary tumor conference. Median age was 67 years (range, 30-92 years), 49% were male, 66% were white, 171 had RPC, 131 had BRPC, and 107 had LAPC. Median OSs for RPC, BRPC, and LAPC were 19.5, 16.1, and 12.7 months, respectively. Type of chemotherapy and age were predictors of OS. Induction chemotherapy was used in 106 with BRPC (81%) and 74 with RPC (56.5%); patients with BRPC who received combination chemotherapy and resection had a median OS of 31.5 compared with 19.5 months in patients with RPC (P = 0.0049). Patients with LAPC had a median OS of 12.7 months. CONCLUSIONS: In patients with BRPC who undergo resection after induction treatment, the OS was significantly better than in patients with RPC. Neoadjuvant treatment should be considered for all localized PDACs.

- Acute Recurrent and Chronic Pancreatitis as Initial Manifestations of Cystic Fibrosis and Cystic Fibrosis Transmembrane Conductance Regulator-Related Disorders

OBJECTIVES: Recurrent pancreatitis is considered a rare manifestation of cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction; this case series highlights that pancreatitis can be a presenting symptoms of cystic fibrosis (CF) or a CFTR-related disorder (CFTR-RD). METHODS: Retrospective review of patients younger than 30 years diagnosed as having acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP) and subsequently diagnosed as having CF or CFTR-RD. RESULTS: Among 18 patients, median time from diagnosis of ARP/CP to diagnosis of CF was 0.4 years (range, 0-33 years). Eight were classified as having CF by elevated sweat chloride testing (SCT). Five had intermediate SCT (30-59 mmol/L) with 2 pathogenic mutations. Five had CFTR-RD with intermediate SCT and 0 to 1 pathogenic mutations. Eight patients (44%) had exocrine pancreatic insufficiency, and pancreatic fluid collections were more common in this group. Based on the CFTR mutation, 6 patients were eligible for CFTR potentiator therapy, although none received it during the study period. Nine of the 18 had 1 other likely CF manifestations, including sinusitis (33%), nasal polyps (11%), pneumonia (22%), and gallbladder disease (22%). CONCLUSIONS: Cystic fibrosis or CFTR-RD can present as ARP/CP. Complete diagnostic testing for CFTR-RD in patients with ARP/CP will broaden treatment options and help to identify comorbid illness.

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

OBJECTIVES: Understanding the effect of lymph node metastasis (LNM) on prognosis in pancreatic neuroendocrine neoplasm is helpful for surgery and follow-up. In this study, we investigated the significance of LNM in well-differentiated pancreatic neuroendocrine tumors (PanNETs) according to the World Health

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

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- **Gastric Emptying and Distal Gastrectomy Independently Enhance Postprandial Glucagon-Like Peptide-1 Release After a Mixed Meal and Improve Glycemic Control in Subjects Having Undergone Pancreaticoduodenectomy**

Pancreas 2019 Aug;48(7):953-957

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31268979

OBJECTIVES: New-onset diabetes frequently resolves after pancreaticoduodenectomy (PD). Glucagon-like peptide-1 (GLP-1) conceivably is involved as its release is enhanced by rapid gastric emptying and distal bowel exposure to nutrients. We aimed at studying factors associated with GLP-1 release after PD. METHODS: Fifteen PD subjects with distal gastrectomy (Whipple) and 15 with pylorus preservation were evaluated. A test meal containing 1 g paracetamol to measure gastric emptying was ingested. Blood for the measurement of paracetamol, glucose, insulin, and GLP-1 was drawn at baseline and 10, 20, 30, 60, 90, 120, 150, and 180 minutes thereafter. The Matsuda index of insulin sensitivity was calculated. RESULTS: In univariate analysis, gastric emptying correlated with GLP-1. Glucagon-like peptide-1 responses to the modes of operation did not differ. Multiple regression analysis confirmed gastric emptying and Whipple versus pylorus-preserving pancreaticoduodenectomy as independent predictors of GLP-1 release. The Matsuda index of insulin sensitivity correlated with GLP-1 concentrations and inversely with body mass index. Patients after Whipple procedure revealed lower glycated hemoglobin as compared with pylorus-preserving pancreaticoduodenectomy. CONCLUSIONS: Following PD, the postprandial GLP-1 release seems to be enhanced by rapid gastric emptying and to improve insulin sensitivity. Partial gastrectomy versus pylorus preservation enhanced the release of GLP-1, conceivably because of greater distal bowel exposure to undigested nutrients.

doi: https://doi.org/10.1097/MPA.0000000000001361

- **Endogenous Gastrin Collaborates With Mutant KRAS in Pancreatic Carcinogenesis**

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

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OBJECTIVE: The KRAS gene is the most frequently mutated gene in pancreatic cancer, and no successful anti-Ras therapy has been developed. Gastrin has been shown to stimulate pancreatic cancer in an autocrine fashion. We hypothesized that reactivation of the peptide gastrin collaborates with KRAS during pancreatic carcinogenesis. METHODS: LSL-Kras; P48-Cre (KC) mutant KRAS transgenic mice were crossed with gastrin-KO (GKO) mice to develop GKO/KC mice. Pancreata were examined for 8 months for stage of pancreatic intraepithelial neoplasia lesions, inflammation, fibrosis, gastrin peptide, and microRNA expression. Pancreatic intraepithelial neoplasias from mice were collected by laser capture microdissection and subjected to reverse-phase protein microarray, for gastrin and protein kinases associated with signal

transduction. Gastrin mRNA was measured by RNAseq in human pancreatic cancer tissues and compared to that in normal pancreas. RESULTS: In the absence of gastrin, PanIN progression, inflammation, and fibrosis were significantly decreased and signal transduction was reversed to the canonical pathway with decreased KRAS. Gastrin re-expression in the PanINs was mediated by miR-27a. Gastrin mRNA expression was significantly increased in human pancreatic cancer samples compared to normal human pancreas controls. CONCLUSIONS: This study supports the mitogenic role of gastrin in activation of KRAS during pancreatic carcinogenesis.

- New-Onset Diabetes Mellitus After Chronic Pancreatitis Diagnosis: A Systematic Review and Meta-analysis

OBJECTIVES: The aim of this study was to assess the occurrence of new-onset diabetes mellitus (DM) after chronic pancreatitis (CP) diagnosis via systematic review and meta-analysis. METHODS: A systematic review of literature and meta-analysis of relevant reports were performed. The primary outcome measures studied were newly diagnosed DM and DM treated with insulin. For the binary outcomes, pooled prevalence and 95% confidence interval (CI) were calculated. METHODS: Fifteen studies involving 8970 patients were eligible. The incidence of new-onset DM after CP diagnosis was 30% (95% CI, 27%-33%). Among all patients, 17% (95% CI, 13%-22%) developed insulin-dependent new-onset DM. The prevalence of newly diagnosed DM after CP diagnosis increased from 15% within 36 months to 33% after 60 months. The proportion of alcoholic CP, sex, age, and body mass index had minimal effect on the studied outcomes. CONCLUSIONS: This systematic review identified a clinically relevant risk of new-onset DM after CP diagnosis. Therefore, patients should be informed of the risk of DM and monitored.

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

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

- Correlation of DOTATOC Uptake and Pathologic Grade in Neuroendocrine Tumors

OBJECTIVES: Gallium (Ga)-DOTATOC is a somatostatin analog used to detect neuroendocrine tumors (NETs). Ki-67 proliferation index (Ki-67 PI) has been established as a prognostic factor in NETs. We aimed to evaluate whether a correlation exists between Ki-67 PI and somatostatin receptor positron emission tomography (SSTR-PET) uptake. METHODS: We retrospectively reviewed 238 DOTATOC PET scans between 2014 and 2016. Patients were excluded if DOTATOC PET was performed more than 365 days from the date of biopsy. Maximum standardized uptake values (SUVmax) of SSTR-PET from biopsied lesions were measured and correlated with Ki-67 PI using the Pearson correlation coefficient. RESULTS: Among 110 lesions from 90 patients, DOTATOC PET had 92.7% sensitivity and 100% specificity (102 true positives, 8 false negatives) for detection of NETs. Among 63 lesions from 54 patients with Ki-67 PI available, there were 27 grade 1 lesions [median Ki-67 PI, 1.0%; interquartile range (IQR), 1.0-2.0], 30 grade 2 lesions (median, Ki-67 PI 7.5%; IQR, 5-10), and 6 grade 3 lesions (median Ki-67 PI, 30%; IQR, 26-34). There was a correlation between Ki-67 PI and SUVmax (r = -0.3, P = 0.018). CONCLUSIONS: Our analysis demonstrates an inverse correlation between Ki-67 PI and SUVmax in NETs. Somatostatin receptor-PET provides additional information that can help guide management of NETs.

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

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

- Complications to Chronic Pancreatitis and Etiological Risk Factors: A Continental Divide?

- Benchmark, Textbook or Optimal Pancreatic Surgery?

- Comparisons of Outcomes of Real-World Patients With Advanced Pancreatic Cancer Treated With FOLFIRINOX Versus Gemcitabine and Nab-Paclitaxel: A Population-Based Cohort Study

OBJECTIVES: The aim of this study was to compare the efficacy and safety of FOLFIRINOX (5-FU/leucovorin, irinotecan, and oxaliplatin) and gemcitabine/nab-paclitaxel (GnP) in patients with advanced pancreatic cancer. METHODS: Patients with newly diagnosed advanced pancreatic cancer in Saskatchewan, Canada, from 2011 to 2016, who received FOLFIRINOX or GnP were assessed. A Cox proportional multivariate analysis was performed to evaluate prognostic variables. RESULTS: One hundred nineteen eligible patients with median age of 61 years and male/female ratio of 70:49 were identified. Seventy-seven percent had metastatic disease. Of 119 patients, 86 (72%) received FOLFIRINOX and 33 (28%) were treated with GnP. Median progression-free survival of the FOLFIRINOX group was 6.0 months [95% confidence interval (CI), 4.5-7.5] versus 4.0 months (95% CI, 2.9-5.1) with GnP (P = 0.39). The median overall survival of the FOLFIRINOX group was 9.0 months (95% CI, 7-11) compared with 9.0 months (95% CI, 4.2-13.8) with GnP (P = 0.88). On multivariate analysis, albumin [hazard ratio (HR), 0.63; 95% CI, 0.41-0.97], male sex (HR, 0.65; 95% CI, 0.43-0.97), and second-line therapy (HR, 0.50; 95% CI, 0.28-0.86) were correlated with survival. CONCLUSIONS: Our results showed that real-world patients with advanced pancreatic cancer treated with FOLFIIRNOX or GnP had comparable survival with different safety profile.

- Differences in Pancreatic Cancer Incidence Rates and Temporal Trends Across Asian Sub-populations in California (1988-2015)

OBJECTIVE: Ethnic disparities in pancreatic cancer (PanCan) incidence exist, but little is known about incidence trends in heterogeneous Asian Americans. We examined PanCan incidence and temporal patterns among detailed ethnic populations, including Asian American subgroups. METHODS: A total of 71,099 invasive exocrine PanCan cases were identified using the California Cancer Registry between 1988 and 2015. Cases were grouped into mutually exclusive groups of non-Hispanic (NH) white, NH black, Hispanic, NH

Asian/Pacific Islander (API), and NH American Indian/Alaska Native (AIAN). Asians were further identified by specific ethnicity. RESULTS: The age-adjusted incidence rates (AAIRs, per 100,000) of PanCan varied significantly across racial/ethnic groups, ranging from the highest of 10.4 in NH blacks to 7.6 in NH whites, 7.1 in Hispanics, 6.2 in NH APIs, and to the lowest of 5.2 in NH AIAN. Despite the relatively low rate in the NH APIs, the rates across Asian subgroups varied significantly, with rates similar to NH whites in Japanese (8.1) and Koreans (7.5) to the low rate in South Asians (4.4). CONCLUSIONS: Significant heterogeneity of PanCan incidence in disaggregated Asian Americans is a novel finding. These results fill a gap regarding PanCan burden in Asian Americans and underscore the importance of disaggregating ethnic populations in cancer research.

doi: https://doi.org/10.1097/MPA.0000000000001337

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

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

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

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

doi: https://doi.org/10.1158/1078-0432.CCR-19-1280

- **Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer**

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

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

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

and metastatic pancreatic cancer, progression-free survival was longer with maintenance olaparib than with placebo. (Funded by AstraZeneca and others; POLO ClinicalTrials.gov number, NCT02184195.).

- Proton Radiotherapy for Isolated Local Recurrence of Primary Resected Pancreatic Ductal Adenocarcinoma

BACKGROUND: The optimal treatment for isolated local recurrence (ILR) of pancreatic adenocarcinoma (PDAC) after surgical resection remains unclear. This study aimed to evaluate the safety and efficacy of proton radiotherapy (PRT) for ILR of PDAC after surgery. METHODS: The medical records of patients with ILR of PDAC after surgery who underwent proton beam therapy between 2011 and 2015 at Hyogo Ion Beam Medical Center were retrospectively studied. RESULTS: The study analyzed 30 patients (14 women and 16 men) with a median age of 65 years (range 38-81 years) who had initially undergone pancreatoduodenectomy (n = 23) or distal pancreatectomy (n = 7) for their primary tumors. Upon ILR, PRT was administered with a median total cumulative dose of 67.5 gray equivalent (GyE) (range 50-67.5 GyE) using 19 to 25 fractions. For 25 patients, concurrent chemotherapy was administered using gemcitabine (n = 18) or S-1 (n = 7). Four patients (13.3%) experienced acute grade 3 gastrointestinal toxicities. After a median follow-up period of 17.6 months (range 2.1-50.4 months), 23 patients had experienced tumor progression and 10 had died. Nine patients (30%) experienced local tumor progression. The median overall, progression-free, and local progression-free survival rates were 26.1, 12.3, and 41.2 months, respectively. Pre-PRT serum levels of cancer antigen 19-9 higher than 100 U/mL and duke pancreatic monoclonal antigen type 2 higher than 150 U/mL were significantly associated with shorter progression-free survival rates. CONCLUSIONS: Proton radiotherapy for ILR of PDAC after surgery is well tolerated and produces good locoregional control and should be considered for eligible patients.

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

PURPOSE: In research settings, circulating tumor DNA (ctDNA) shows promise as a tumor-specific biomarker for pancreatic ductal adenocarcinoma (PDAC). This study aims to perform analytical and clinical validation of a KRAS ctDNA assay in a Clinical Laboratory Improvement Amendments (CLIA) and College of American Pathology-certified clinical laboratory. EXPERIMENTAL DESIGN: Digital-droplet PCR was used to detect the major PDAC-associated somatic KRAS mutations (G12D, G12V, G12R, and Q61H) in liquid biopsies. For clinical validation, 290 preoperative and longitudinal postoperative plasma samples were collected from 59 patients with PDAC. The utility of ctDNA status to predict PDAC recurrence during follow-up was assessed. RESULTS: ctDNA was detected preoperatively in 29 (49%) patients and was an independent predictor of decreased recurrence-free survival (RFS) and overall survival (OS). Patients who had neoadjuvant chemotherapy were less likely to have preoperative ctDNA than were chemo-naïve patients (21% vs. 69%; P < 0.001). ctDNA levels dropped significantly after tumor resection. Persistence of ctDNA in the immediate postoperative period was associated with a high rate of recurrence and poor median RFS (5 months). ctDNA detected during follow-up predicted clinical recurrence [sensitivity 90% (95% confidence interval (CI), 74%-98%), specificity 88% (95% CI, 62%-98%)] with a median lead time

of 84 days (interquartile range, 25-146). Detection of ctDNA during postpancreatectomy follow-up was associated with a median OS of 17 months, while median OS was not yet reached at 30 months for patients without ctDNA (P = 0.011). CONCLUSIONS: Measurement of KRAS ctDNA in a CLIA laboratory setting can be used to predict recurrence and survival in patients with PDAC.

doi: https://doi.org/10.1158/1078-0432.CCR-19-0197

- **Controversies on the endoscopic and surgical management of pain in patients with chronic pancreatitis: pros and cons!**

Gut 2019 08;68(8):1343-1351

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31129569

doi: https://doi.org/10.1136/gutjnl-2019-318742

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

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

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

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

doi: https://doi.org/10.1016/j.humpath.2019.05.004

- **Arginine Starvation and Docetaxel Induce c-Myc-Driven hENT1 Surface Expression to Overcome Gemcitabine Resistance in ASS1-Negative Tumors**

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PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31113844

PURPOSE: The response to acute and long-term arginine starvation results in a conditional adaptive metabolic reprogramming that can be harnessed for therapeutic opportunities in ASS1-negative tumors. Here, we investigate the underlying biology of priming ASS1- tumors with arginine deiminase (ADI-PEG20) before treatment with gemcitabine (GEM) and docetaxel (DTX) in sarcoma, pancreatic cancer, and melanoma cell lines. EXPERIMENTAL DESIGN: ASS1- tumor cell lines were treated to create LTAT (long-term ADI treated) cell lines (ASS1+) and used for drug combination studies. Protein expression of ASS1, dCK, RRM2, E2F1, c-MYC, and hENT1 was measured. c-MYC activity was determined, live-cell

immunofluorescent studies for hENT1, uptake assays of FITC-cytosine probe, and rescue studies with a c-MYC inhibitor were all determined in the presence or absence of the ADI-PEG20:GEM:DTX. RESULTS: In examining modulations within the pyrimidine pathway, we identified that the addition of DTX to cells treated with ADI-PEG20 resulted in translocation of stabilized c-Myc to the nucleus. This resulted in an increase of hENT1 cell-surface expression and rendered the cells susceptible to GEM. In vivo studies demonstrate that the combination of ADI-PEG20:GEM:DTX was optimal for tumor growth inhibition, providing the preclinical mechanism and justification for the ongoing clinical trial of ADI-PEG20, GEM, and DTX in sarcoma. CONCLUSIONS: The priming of tumors with ADI-PEG20 and DTX results in the stabilization of c-MYC potentiating the effect of GEM treatment via an increase in hENT1 expression. This finding is applicable to ASS1-deficient cancers that are currently treated with GEM.

doi: https://doi.org/10.1158/1078-0432.CCR-19-0206

- **RAS Mutation Decreases Overall Survival After Optimal Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy of Colorectal Peritoneal Metastasis: A Modification Proposal of the Peritoneal Surface Disease Severity Score**

Annals of surgical oncology 2019 Aug;26(8):2595-2604

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31111351

BACKGROUND: Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are currently the most accepted treatment for peritoneal metastases from colorectal cancer. Restrictive selection criteria are essential to obtain the best survival benefits for this complex procedure. The most widespread score for patient selection, the peritoneal surface disease severity score (PSDSS), does not include current biological factors that are known to influence on prognosis. We investigated the impact of including RAS mutational status in the selection criteria for these patients. METHODS: We studied the risk factors for survival by multivariate analysis using a prospective database of consecutive patients with carcinomatosis from colorectal origin treated by CRS and HIPEC in our unit from 2009 to 2017. The risk factors obtained were validated in a multicentre, international cohort, including a total of 520 patients from 15 different reference units. RESULTS: A total of 77 patients were selected for local análisis. Only RAS mutational status (HR: 2.024; p = 0.045) and PSDSS stage (HR: 2.90; p = 0.009) were shown to be independent factors for overall survival. Early PSDSS stages I and II associated to RAS mutations impaired their overall survival with no significant differences with PSDSS stage III overall survival (p > 0.05). These results were supported by the international multicentre validation. CONCLUSIONS: By including RAS mutational status, we propose an updated RAS-PSDSS score that outperforms PSDSS alone providing a quick and feasible preoperative assessment of the expected overall survival for patients with carcinomatosis from colorectal origin undergone to CRS + HIPEC.

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- **Nivolumab alone or in combination with cisplatin plus gemcitabine in Japanese patients with unresectable or recurrent biliary tract cancer: a non-randomised, multicentre, open-label, phase 1 study**

The lancet. Gastroenterology & hepatology 2019 Aug;4(8):611-621

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31109808

BACKGROUND: This study aimed to assess the safety and tolerability of the immune checkpoint inhibitor nivolumab, as monotherapy or combined with chemotherapy, in Japanese patients with biliary tract cancer. METHODS: This multicentre, open-label, phase 1 trial was done at four cancer centres in Japan. Eligible patients were aged 20-79 years, had biliary tract adenocarcinoma (intrahepatic bile duct cancer, extrahepatic

bile duct cancer, gallbladder cancer, or ampullary cancer), Eastern Cooperative Oncology Group performance status 0 or 1, adequate hepatic, renal, and haematological function, and tumour tissue samples for PD-L1 expression analysis. Patients with unresectable or recurrent biliary tract cancer that was refractory or intolerant to gemcitabine-based treatment regimens received nivolumab monotherapy (240 mg every 2 weeks [monotherapy cohort]). Chemotherapy-naive patients with unresectable or recurrent biliary tract cancer received nivolumab (240 mg every 2 weeks) and cisplatin (25 mg/m2) plus gemcitabine (1000 mg/m2) chemotherapy (combined therapy cohort). The primary objective was to assess tolerability and safety. The primary objective was assessed in the safety population of all patients who had received at least one dose of nivolumab. This study is registered with www.clinicaltrials.jp, number JapicCTI-153098, and follow-up is ongoing. FINDINGS: 30 patients were enrolled into each cohort between Jan 13, 2016, and April 19, 2017. Data cutoff was Aug 31, 2017. In the monotherapy cohort, the most frequently reported treatment-related adverse events were decreased appetite (five [17%]), malaise (four [13%]), and pruritus (four [13%]). Grade 3-4 treatment-related adverse events were reported by three (10%) patients (rash, maculopapular rash, and amylase increase) and treatment-related serious adverse events were reported by one (3%) patient (pleurisy). In the combined therapy cohort, the most frequently reported treatment-related adverse events were neutrophil count decrease (any grade 25 [83%]; grade 3-4 in 23 [77%] patients) and platelet count decrease (any grade 25 [83%] of 30; grade 3-4 in 15 [50%] patients). Six (20%) patients reported 11 treatment-related serious adverse events (platelet count decrease [three patients], febrile neutropenia [two patients], neutrophil count decrease, anaemia, anaphylactic reaction, decreased appetite, pyrexia, and myocarditis [one patient each]). In the monotherapy cohort, median overall survival was 5·2 months (90% CI 4·5-8·7), median progression-free survival was 1·4 months (90% CI 1·4-1·4), and one of 30 patients had an objective response. In the combined therapy cohort, median overall survival was 15·4 months (90% CI 11·8-not estimable), median progression-free survival was 4·2 months (90% CI 2·8-5·6), and 11 of 30 patients had an objective response. INTERPRETATION: Nivolumab had a manageable safety profile and signs of clinical activity in patients with unresectable or recurrent biliary tract cancer. This initial assessment of nivolumab for the treatment of advanced biliary tract cancer provides supportive evidence for future larger randomised studies of nivolumab in this difficult to treat cancer. FUNDING: Ono Pharmaceutical Co Ltd and Bristol-Myers Squibb Inc.

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

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

PURPOSE: Gene fusions involving neuregulin 1 (NRG1) have been noted in multiple cancer types and have potential therapeutic implications. Although varying results have been reported in other cancer types, the efficacy of the HER-family kinase inhibitor afatinib in the treatment of NRG1 fusion-positive pancreatic ductal adenocarcinoma is not fully understood. EXPERIMENTAL DESIGN: Forty-seven patients with pancreatic ductal adenocarcinoma received comprehensive whole-genome and transcriptome sequencing and analysis. Two patients with gene fusions involving NRG1 received afatinib treatment, with response measured by pretreatment and posttreatment PET/CT imaging. RESULTS: Three of 47 (6%) patients with advanced pancreatic ductal adenocarcinoma were identified as KRAS wild type by whole-genome sequencing. All KRAS wild-type tumors were positive for gene fusions involving the ERBB3 ligand NRG1. Two of 3 patients with NRG1 fusion-positive tumors were treated with afatinib and demonstrated a significant and rapid response while on therapy. CONCLUSIONS: This work adds to a growing body of evidence that NRG1 gene fusions are recurrent, therapeutically actionable genomic events in pancreatic cancers. Based on the clinical outcomes described here, patients with KRAS wild-type tumors harboring NRG1 gene fusions may benefit from treatment with afatinib.See related commentary by Aguirre, p. 4589.

- **Contemporary Improvements in Postoperative Mortality After Major Cancer Surgery are Associated with Weakening of the Volume-Outcome Association**

BACKGROUND: Regionalization of complex visceral surgery across the United States has followed identification of a volume-outcome association. However, improvements in postoperative mortality overall during the last decade may have weakened the strength of this association. METHODS: The National Cancer Database was used to identify patients undergoing colon, esophageal, liver, and pancreatic surgery from 2003 to 2011. Hospitals were divided into low-volume (< 33rd %tile), medium-volume (34-66th %tile), and high-volume (> 67th %tile) groups. Annual cancer-specific adjusted observed versus expected (O/E) ratios for 30- and 90-day mortality for each volume strata were calculated and plotted over time. RESULTS: In the year 2003, the O/E ratios decreased from low- to medium- to high-volume hospitals for all cancer surgeries for both 30- and 90-day mortality, indicating a strong volume-outcome relationship. For all volume strata, the O/E ratios trended downward from 2003 to 2011 for both 30- and 90-day mortality for all cancer surgeries. This trend was more pronounced for low- and medium-volume than for high-volume hospitals. Consequently, by 2011 the confidence intervals of the O/E ratios for the low-volume groups, and particularly for the medium-volume groups, overlapped those for the high-volume groups for most of the cancer surgeries studied. CONCLUSIONS: The volume-outcome association for major cancer surgery is dynamic and has attenuated over time primarily due to improvements in postoperative mortality at low- and medium-volume hospitals.
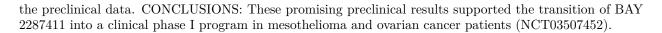
- **Mesothelin-Targeted Thorium-227 Conjugate (MSLN-TTC): Preclinical Evaluation of a New Targeted Alpha Therapy for Mesothelin-Positive Cancers**

PURPOSE: Targeted thorium-227 conjugates (TTC) represent a new class of molecules for targeted alpha therapy (TAT). Covalent attachment of a 3,2-HOPO chelator to an antibody enables specific complexation and delivery of the alpha particle emitter thorium-227 to tumor cells. Because of the high energy and short penetration range, TAT efficiently induces double-strand DNA breaks (DSB) preferentially in the tumor cell with limited damage to the surrounding tissue. We present herein the preclinical evaluation of a mesothelin (MSLN)-targeted thorium-227 conjugate, BAY 2287411. MSLN is a GPI-anchored membrane glycoprotein overexpressed in mesothelioma, ovarian, pancreatic, lung, and breast cancers with limited expression in healthy tissue. EXPERIMENTAL DESIGN: The binding activity and radiostability of BAY 2287411 were confirmed bioanalytically. The mode-of-action and antitumor potency of BAY 2287411 were investigated in vitro and in vivo in cell line and patient-derived xenograft models of breast, colorectal, lung, ovarian, and pancreatic cancer. RESULTS: BAY 2287411 induced DSBs, apoptotic markers, and oxidative stress, leading to reduced cellular viability. Furthermore, upregulation of immunogenic cell death markers was observed. BAY 2287411 was well-tolerated and demonstrated significant antitumor efficacy when administered via single or multiple dosing regimens in vivo. In addition, significant survival benefit was observed in a disseminated lung cancer model. Biodistribution studies showed specific uptake and retention of BAY 2287411 in tumors and enabled the development of a mechanistic pharmacokinetic/pharmacodynamic model to describe

the preclinical data. CONCLUSIONS: These promising preclinical results supported the transition of BAY 2287411 into a clinical phase I program in mesothelioma and ovarian cancer patients (NCT03507452).

doi: https://doi.org/10.1158/1078-0432.CCR-18-3476

- **Advanced stage at diagnosis and elevated mortality among US patients with cancer infected with HIV in the National Cancer Data Base**

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PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31050361

BACKGROUND: People living with HIV (PLWH) are at an increased risk of developing several cancers, but to the authors' knowledge less is known regarding how HIV impacts the rate of progression to advanced cancer or death. METHODS: The authors compared stage of disease at the time of presentation and mortality after diagnosis between 14,453 PLWH and 6,368,126 HIV-uninfected patients diagnosed with cancers of the oral cavity, stomach, colorectum, anus, liver, pancreas, lung, female breast, cervix, prostate, bladder, kidney, and thyroid and melanoma using data from the National Cancer Data Base (2004-2014). Polytomous logistic regression and Cox proportional hazards regression were used to evaluate the association between HIV, cancer stage, and stage-adjusted mortality after diagnosis, respectively. Regression models accounted for the type of health facility at which cancer treatment was administered and the type of individual health insurance. RESULTS: HIV-infected patients with cancer were found to be more likely to be uninsured (HIV-infected: 5.0% vs HIV-uninfected: 3.3%; P < .0001) and were less likely to have private health insurance (25.4% vs 44.7%; P < .0001). Compared with those not infected with HIV, the odds of being diagnosed at an advanced stage of disease were significantly elevated in PLWH for melanoma and cancers of the oral cavity, liver, female breast, prostate, and thyroid (odds ratio for stage IV vs stage I range, 1.24-2.06). PLWH who were diagnosed with stage I to stage III disease experienced elevated mortality after diagnosis across 13 of the 14 cancer sites evaluated, with hazard ratios ranging from 1.20 (95% CI, 1.14-1.26) for lung cancer to 1.85 (95% CI, 1.68-2.04), 1.85 (95% CI, 1.51-2.27), and 2.93 (95% CI, 2.08-4.13), respectively, for cancers of the female breast, cervix, and thyroid. CONCLUSIONS: PLWH were more likely to be diagnosed with advanced-stage cancers and to experience elevated mortality after a cancer diagnosis, even after accounting for health care-related factors.

doi: https://doi.org/10.1002/cncr.32158

- **GNAS but Not Extended RAS Mutations Spectrum are Associated with a Better Prognosis in Intraductal Pancreatic Mucinous Neoplasms**

Annals of surgical oncology 2019 Aug;26(8):2640-2650

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31025231

BACKGROUND: The management of intraductal papillary mucinous neoplasms (IPMNs) is mainly based on imaging features and clinical symptoms, and remains challenging. OBJECTIVE: The aim of this study was to assess GNAS, RAS family (KRAS, NRAS and HRAS), BRAF, and PIK3CA mutation status in resected IPMNs and correlate it with clinicopathological characteristics and patient survival. METHODS: Overall, 149 consecutive unselected patients who underwent pancreatectomy for IPMNs were included. After dissection from formalin-fixed and paraffin-embedded tumors, GNAS mutational screening was assessed by allelic discrimination using Taqman® probes and confirmed by SNaPshot analysis. RAS family, BRAF, and PIK3CA mutational screening was assessed by high resolution melt and Sanger sequencing. RESULTS: Gastric- and intestinal-type IPMNs were the most frequent lesions (52% and 41%, respectively). Intestinal-type IPMNs were more frequently associated high-grade dysplasia (49%) and were the only IPMNs associated

with colloid-type carcinoma. All pancreatobiliary IPMNs were invasive lesions, located in the main pancreatic duct. GNAS-activating mutations were strongly associated with the intestinal phenotype ($p < 10$-4), while RAS pathway mutations were not associated with any particular phenotype. Mutations within other members of the epidermal growth factor receptor (EGFR) pathway were very rare (2%). GNAS-mutated IPMNs were rarely invasive (11%) and almost exclusively (83%) of the colloid type. For invasive lesions, multivariate analyses determined that only node negativity was associated with improved cancer-specific survival, but, in univariate analysis, GNAS mutation was associated with prolonged survival. CONCLUSION: In patients selected for surgery, GNAS mutation analysis and tumor phenotype can help to better predict patient prognosis. In the near future, a more precise mutational analysis of IPMNs might help to better tailor their management.

doi: https://doi.org/10.1245/s10434-019-07389-6

- **The Pancreas as a Site of Metastasis or Second Primary in Patients with Small Bowel Neuroendocrine Tumors**

BACKGROUND: The small bowel and pancreas are the most common primary sites of neuroendocrine tumors (NETs) giving rise to metastatic disease. Some patients with small bowel NETs (SBNETs) present with synchronous or metachronous pancreatic NETs (PNETs), and it is unclear whether these are separate primaries or metastases from one site to the other. METHODS: A surgical NET database including patients undergoing operations for SBNETs or PNETs was reviewed. Patients with synchronous or metachronous tumors in both the small bowel and pancreas were identified, and available tissues from primary tumors and metastases were examined using a 4-gene quantitative polymerase chain reaction (qPCR) and immunohistochemistry (IHC) panel developed for evaluating NETs of unknown primary. RESULTS: Of 338 patients undergoing exploration, 11 had NETs in both the small bowel and pancreas. Tissues from 11 small bowel tumors, 9 pancreatic tumors, and 10 metastases were analyzed. qPCR and IHC data revealed that three patients had separate SBNET and PNET primaries, and five patients had SBNETs that metastasized to the pancreas. Pancreatic tissue was unavailable in two patients, and qPCR and IHC gave discrepant results in one patient. CONCLUSIONS: NETs in both the small bowel and pancreas were found in 3% of our patients. In nearly two-thirds of evaluable patients, the pancreatic tumor was a metastasis from the SBNET primary, while in the remaining one-third of patients it represented a separate primary. Determining the origin of these tumors can help guide the choice of systemic therapy and surgical management.

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- **ASO Author Reflections: Tending Towards a Personalized Medicine for Colorectal Carcinomatosis by Adding the RAS Mutation Status in the Workup for CRS and HIPEC**

- **Defining the Role of Lymphadenectomy for Pancreatic Neuroendocrine Tumors: An Eight-Institution Study of 695 Patients from the US Neuroendocrine Tumor Study Group**

BACKGROUND: Preoperative factors that reliably predict lymph node (LN) metastases in pancreatic neuroendocrine tumors (PanNETs) are unclear. The number of LNs needed to accurately stage PanNETs has not been defined. METHODS: Patients who underwent curative-intent resection of non-functional PanNETs at eight institutions from 2000 to 2016 were analyzed. Preoperative factors associated with LN metastases were identified. A procedure-specific target for LN retrieval to accurately stage patients was determined. RESULTS: Of 695 patients who underwent resection, 33% of tumors were proximal (head/uncinate) and 67% were distal (neck/body/tail). Twenty-six percent of patients (n = 158) had LN-positive disease, which was associated with a worse 5-year recurrence-free survival (RFS; 60% vs. 86%; p < 0.001). The increasing number of positive LNs was not associated with worse RFS. Preoperative factors associated with positive LNs included tumor size 2 cm (odds ratio [OR] 6.6; p < 0.001), proximal location (OR 2.5; p < 0.001), moderate versus well-differentiation (OR 2.1; p = 0.006), and Ki-67 3% (OR 3.1; p < 0.001). LN metastases were also present in tumors without these risk factors: < 2 cm (9%), distal location (19%), well-differentiated (23%), and Ki-67 < 3% (16%). Median LN retrieval was 13 for pancreatoduodenectomy (PD), but only 9 for distal pancreatectomy (DP). Given that PD routinely includes a complete regional lymphadenectomy, a minimum number of LNs to accurately stage patients was not identified. However, for DP, removal of less than seven LNs failed to discriminate 5-year RFS between LN-positive and LN-negative patients (less than seven LNs: 72% vs. 83%, p = 0.198; seven or more LNs: 67% vs. 86%; p = 0.002). CONCLUSIONS: Tumor size 2 cm, proximal location, moderate differentiation, and Ki-67 3% are preoperative factors that predict LN positivity in resected non-functional PanNETs. Given the 9-23% incidence of LN metastases in patients without such risk factors, routine regional lymphadenectomy should be considered. PD inherently includes sufficient LN retrieval, while DP should aim to remove seven or more LNs for accurate staging.

- Detection of NRG1 Gene Fusions in Solid Tumors

PURPOSE: NRG1 gene fusions are rare but potentially actionable oncogenic drivers that are present in some solid tumors. Details regarding the incidence of these gene rearrangements are lacking. Here, we assessed the incidence of NRG1 fusions across multiple tumor types and described fusion partners. EXPERIMENTAL DESIGN: Tumor specimens submitted for molecular profiling at a Clinical Laboratory Improvement Amendments (CLIA)-certified genomics laboratory and that underwent fusion testing by anchored multiplex PCR for targeted RNA sequencing were retrospectively identified. The overall and tumor-specific incidence was noted, as was the specific fusion partner. RESULTS: Out of 21,858 tumor specimens profiled from September 2015 to December 2018, 41 cases (0.2%) harbored an NRG1 fusion. Multiple fusion partners were identified. Fusion events were seen across tumor types. The greatest incidence was in non-small cell lung cancer (NSCLC, 25), though this represented only 0.3% of NSCLC cases tested. Other tumor types harboring an NRG1 fusion included gallbladder cancer, renal cell carcinoma, bladder cancer, ovarian cancer, pancreatic cancer, breast cancer, neuroendocrine tumor, sarcoma, and colorectal cancer. CONCLUSIONS: NRG1 fusions can be detected at a low incidence across multiple tumor types with significant heterogeneity in fusion partner.See related commentary by Dimou and Camidge, p. 4865.

- Tspan8 is expressed in breast cancer and regulates E-cadherin/catenin signalling and metastasis accompanied by increased circulating extracellular vesicles

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PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30982971

Tspan8 exhibits a functional role in many cancer types including pancreatic, colorectal, oesophagus carcinoma, and melanoma. We present a first study on the expression and function of Tspan8 in breast cancer. Tspan8 protein was present in the majority of human primary breast cancer lesions and metastases in the brain, bone, lung, and liver. In a syngeneic rat breast cancer model, Tspan8+ tumours formed multiple liver and spleen metastases, while Tspan8- tumours exhibited a significantly diminished ability to metastasise, indicating a role of Tspan8 in metastases. Addressing the underlying molecular mechanisms, we discovered that Tspan8 can mediate up-regulation of E-cadherin and down-regulation of Twist, p120-catenin, and -catenin target genes accompanied by the change of cell phenotype, resembling the mesenchymal-epithelial transition. Furthermore, Tspan8+ cells exhibited enhanced cell-cell adhesion, diminished motility, and decreased sensitivity to irradiation. As a regulator of the content and function of extracellular vesicles (EVs), Tspan8 mediated a several-fold increase in EV number in cell culture and the circulation of tumour-bearing animals. We observed increased protein levels of E-cadherin and p120-catenin in these EVs; furthermore, Tspan8 and p120-catenin were co-immunoprecipitated, indicating that they may interact with each other. Altogether, our findings show the presence of Tspan8 in breast cancer primary lesion and metastases and indicate its role as a regulator of cell behaviour and EV release in breast cancer. © 2019 The Authors. The Journal of Pathology published by John Wiley & Sons Ltd on behalf of Pathological Society of Great Britain and Ireland.

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- Laparoscopic Complete Mesocolic Excision for Double Flexural Colon Cancers

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BACKGROUND: Laparoscopic complete mesocolic excision (CME) for hepatic or splenic flexural colon cancer is considered technically demanding. The double (hepatic and splenic) flexural colon cancers are rare, and the laparoscopic CME procedure for such disease is not standardized. METHODS: This video presents laparoscopic CME for double (hepatic and splenic) flexural colon cancers using a medial and cranial approach. RESULTS: The patient was a 60-year-old woman with the diagnosis of splenic flexure cancer (cT4N1M0) and hepatic flexure cancer (cT3N0M0). Laparoscopic subtotal colectomy was performed. First, the left colic artery was divided at its origin, and the inferior mesenteric vein also was divided at the same level. The descending mesocolon was widely separated from the retroperitoneal tissues using a medial approach. Then, lymph node dissection along the surgical trunk was performed using a cranial approach. Finally, the transverse mesocolon was divided at the inferior border of the pancreas, and CME was achieved. The specimen was extracted through a small incision at the umbilicus, and side-to-side ileo-sigmoid anastomosis was performed extracorporeally. CONCLUSIONS: The approach presented in the video might be useful for standardization of laparoscopic CME for double flexural colon cancers.

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- Response to Comment on "Letter to Editor Re Manuscript by Bannone et al." Ann Surg. 2018 Dec 20

Annals of surgery 2019 Aug;270(2):e60-e61

- Clear Cell Variant of Solid Pseudopapillary Neoplasm of the Pancreas: A Report of a Rare Variant and Review of the Literature

The clear cell variant of solid pseudopapillary neoplasm (ccSPN) of the pancreas was first described in 2006. In this article, we report a case of this rare variant and review the few published reports. Both the current and previous reports show that ccSPN has several morphologic differences from conventional SPN, including clear vacuoles, fewer pseudopapillary formations, more solid/diffuse architecture, less hemorrhage, and fewer cholesterol clefts. Some of these features peculiar to ccSPN, such as solid/diffuse architecture, have been proposed to suggest aggressive behavior, though reports of ccSPN are rare and often have limited clinical follow-up. ccSPN also appears to occur more frequently in males than conventional SPNs. These clinical and pathologic features lead to unique set of differential diagnostic considerations for ccSPN, including metastatic renal cell carcinoma, perivascular epithelial cell tumor, and clear cell variants of other carcinomas. These unique features, atypical differential, and uncertain prognostic ramifications all make ccSPN an important variant to be aware of and report.

- Benchmarks in Pancreatic Surgery: A Novel Tool for Unbiased Outcome Comparisons

OBJECTIVE: To use the concept of benchmarking to establish robust and standardized outcome references after pancreatico-duodenectomy (PD). BACKGROUND: Best achievable results after PD are unknown. Consequently, outcome comparisons among different cohorts, centers or with novel surgical techniques remain speculative. METHODS: This multicenter study analyzes consecutive patients (2012-2015) undergoing PD in 23 international expert centers in pancreas surgery. Outcomes in patients without significant comorbidities and major vascular resection (benchmark cases) were analyzed to establish 20 outcome benchmarks for PD. These benchmarks were tested in a cohort with a poorer preoperative physical status (ASA class 3) and a cohort treated by minimally invasive approaches. RESULTS: Two thousand three hundred seventy-five (38%) low-risk cases out of a total of 6186 PDs were analyzed, disclosing low in-hospital mortality (1.6%) but high morbidity, with a 73% benchmark morbidity rate cumulated within 6 months following surgery. Benchmark cutoffs for pancreatic fistulas (B-C), severe complications (grade 3), and failure-to-rescue rate were 19%, 30%, and 9%, respectively. The ASA 3 cohort showed comparable morbidity but a higher in hospital-mortality (3% vs 1.6%) and failure-to-rescue rate (16% vs 9%) than the benchmarks. The proportion of benchmark cases performed varied greatly across centers and continents for both open (9%-93%) and minimally invasive (11%-62%) PD. Centers operating mostly on complex PD cases disclosed better results than those with a majority of low-risk cases. CONCLUSION: The proposed outcome benchmarks for PD, established in a large-scale international patient cohort and tested in 2 different cohorts, may allow for meaningful comparisons between different patient cohorts, centers, countries, and surgical techniques.

- The Impact of Preoperative Immune Modulating Nutrition on Outcomes in Patients Undergoing Surgery for Gastrointestinal Cancer: A Systematic Review and Meta-analysis

OBJECTIVE: To define the influence of preoperative immune modulating nutrition (IMN) on postoperative outcomes in patients undergoing surgery for gastrointestinal cancer. BACKGROUND: Although studies have shown that perioperative IMN may reduce postoperative infectious complications, many of these have included patients with benign and malignant disease, and the optimal timing of such an intervention is not clear. METHODS: The Embase, Medline, and Cochrane databases were searched from 2000 to 2018, for prospective randomized controlled trials evaluating preoperative oral or enteral IMN in patients undergoing surgery for gastrointestinal cancer. The primary endpoint was the development of postoperative infectious complications. Secondary endpoints included postoperative noninfectious complications, length of stay, and up to 30-day mortality. The analysis was performed using RevMan v5.3 software. RESULTS: Sixteen studies reporting on 1387 patients (715 IMN group, 672 control group) were included. Six of the included studies reported on a mixed population of patients undergoing all gastrointestinal cancer surgery. Of the remaining, 4 investigated IMN in colorectal cancer surgery, 2 in pancreatic surgery, and another 2 in patients undergoing surgery for gastric cancer. There was 1 study each on liver and esophageal cancer. The formulation of nutrition used in all studies in the treated patients was Impact (Novartis/Nestlé), which contains -3 fatty acids, arginine, and nucleotides. Preoperative IMN in patients undergoing surgery for gastrointestinal cancer reduced infectious complications [odds ratio (OR) 0.52, 95% confidence interval (CI) 0.38-0.71, $P < 0.0001$, I = 16%, n = 1387] and length of hospital stay (weighted mean difference -1.57 days, 95% CI -2.48 to -0.66, $P = 0.0007$, I = 34%, n = 995) when compared with control (isocaloric isonitrogeneous feed or normal diet). It, however, did not affect noninfectious complications (OR 0.98, 95% CI 0.73-1.33, $P = 0.91$, I = 0%, n = 1303) or mortality (OR 0.55, 95% CI 0.18-1.68, $P = 0.29$, I = 0%, n = 955). CONCLUSION: Given the significant impact on infectious complications and a tendency to shorten length of stay, preoperative IMN should be encouraged in routine practice in patients undergoing surgery for gastrointestinal cancer.

- [Microcystic serous cystadenoma: An uncommon neoplasm of pancreas. Report of two cases]

Microcystic variant of serous cystadenoma of the pancreas is a rare neoplasm; essentially located in the body or tail of the pancreas and associated with the von Hippel-Lindau. Often, patients are asymptomatic and the neoplasm is incidentally discovered. Usually radiographic manifestations are characteristic. Histopathological examination revealed uniform clear cuboidal cells; they can be confused with other clear cell neoplasms like renal cell carcinomas, well-differentiated neuroendocrine tumors and solid pseudopapillary tumors of the pancreas. Immunohistochemistry can be help to establish the diagnosis and to remove differential diagnosis. Serous cystadenoma is a benign neoplasm whose prognosis is excellent. We herein report two cases of microcystic serous cystadenomas of the pancreas diagnosed in two asymptomatic women and review analysis in the literature to remind the main features of this lesion and the main differential diagnosis.

- Response to Comment on "Characterization and Optimal Management of High-risk Pancreatic Anastomoses During Pancreatoduodenectomy: Response to Goussous and Cunningham"

Annals of surgery 2019 Aug;270(2):e58-e59

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30499813

doi: https://doi.org/10.1097/SLA.0000000000003121

- Comment on "Interpreting Clinical Benefits of Neoadjuvant Chemoradiation With Gemcitabine Versus Upfront Surgery in Patients With Borderline Resectable Pancreatic Cancer (BRPC)"

Annals of surgery 2019 Aug;270(2):e48-e50

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- DYRK1A modulates c-MET in pancreatic ductal adenocarcinoma to drive tumour growth

Gut 2019 08;68(8):1465-1476

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30343272

BACKGROUND AND AIMS: Pancreatic ductal adenocarcinoma (PDAC) is a very aggressive tumour with a poor prognosis using current treatments. Targeted therapies may offer a new avenue for more effective strategies. Dual-specificity tyrosine regulated kinase 1A (DYRK1A) is a pleiotropic kinase with contradictory roles in different tumours that is uncharacterised in PDAC. Here, we aimed to investigate the role of DYRK1A in pancreatic tumorigenesis. DESIGN: We analysed DYRK1A expression in PDAC genetic mouse models and in patient samples. DYRK1A function was assessed with knockdown experiments in pancreatic tumour cell lines and in PDAC mouse models with genetic reduction of Dyrk1a dosage. Furthermore, we explored a mechanistic model for DYRK1A activity. RESULTS: We showed that DYRK1A was highly expressed in PDAC, and that its protein level positively correlated with that of c-MET. Inhibition of DYRK1A reduced tumour progression by limiting tumour cell proliferation. DYRK1A stabilised the c-MET receptor through SPRY2, leading to prolonged activation of extracellular signal-regulated kinase signalling. CONCLUSIONS: These findings reveal that DYRK1A contributes to tumour growth in PDAC, at least through regulation of c-MET accumulation, suggesting that inhibition of DYRK1A could represent a novel therapeutic target for PDAC.

doi: https://doi.org/10.1136/gutjnl-2018-316128

- A Prospective, Randomized Phase II Study of Adjuvant Gemcitabine Versus S-1 After Major Hepatectomy for Biliary Tract Cancer (KHBO 1208): Kansai Hepato-Biliary Oncology Group

Annals of surgery 2019 Aug;270(2):230-237

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30339627

OBJECTIVE: To evaluate each arm independently and compare adjuvant gemcitabine (GEM) and S-1 chemotherapy after major hepatectomy (hemihepatectomy or trisectionectomy) for biliary tract cancer (BTC). BACKGROUND: Standardized adjuvant therapy is not performed after major hepatectomy for

BTC, and we determined the recommended dose in the former study (KHBO1003). METHODS: We performed a multicenter, randomized phase II study. The primary measure was 1-year recurrence-free survival (RFS); the secondary measures were other RFS, overall survival (OS), and others. The following 6-month adjuvant chemotherapy was administered within 12 weeks of R0/1: GEM (1000mg/m) every 2 weeks; or S-1 (80mg/m/d) for 28 days every 6 weeks. Thirty-five patients were assigned to each arm (alpha error, 10%; beta error, 20%). RESULTS: No patients were excluded for the per-protocol analysis. There were no statistically significant differences in the patient characteristics of the 2 arms. The 1-year RFS and 1-year OS rates of the GEM arm were 51.4% and 80.0%, respectively, whereas those of the S-1 group were 62.9% and 97.1%. The comparison of the 2 arms revealed that 2-year RFS rate, 1 and 2-year OS rates, and OS curve of the S-1 arm were superior to GEM. With regard to OS, the hazard ratio of the S-1 group was 0.477 (90% confidence interval 0.245-0.927). CONCLUSION: The comparison of the survival of the 2 groups revealed that adjuvant S-1 therapy may be superior to adjuvant GEM therapy after major hepatectomy for BTC.

- Response to Comment on "The Virtual Hepatectomy Changed the Practice of Liver Surgery: More Details, More Significance"

- Determinants of Severity in Acute Pancreatitis: A Nation-wide Multicenter Prospective Cohort Study

OBJECTIVE: The aim of this study was to compare and validate the different classifications of severity in acute pancreatitis (AP) and to investigate which characteristics of the disease are associated with worse outcomes. SUMMARY OF BACKGROUND DATA: AP is a heterogeneous disease, ranging from uneventful cases to patients with considerable morbidity and high mortality rates. Severity classifications based on legitimate determinants of severity are important to correctly describe the course of disease. METHODS: A prospective multicenter cohort study involving patients with AP from 23 hospitals in Spain. The Atlanta Classification (AC), Revised Atlanta Classification (RAC), and Determinant-based Classification (DBC) were compared. Binary logistic multivariate analysis was performed to investigate independent determinants of severity. RESULTS: A total of 1655 patients were included; 70 patients (4.2%) died. RAC and DBC were equally superior to AC for describing the clinical course of AP. Although any kind of organ failure was associated with increased morbidity and mortality, persistent organ failure (POF) was the most significant determinant of severity. All local complications were associated with worse outcomes. Infected pancreatic necrosis correlated with high morbidity, but in the presence of POF, it was not associated to higher mortality when compared with sterile necrotizing pancreatitis. Exacerbation of previous comorbidity was associated with increased morbidity and mortality. CONCLUSION: The RAC and DBC both signify an advance in the description and differentiation of AP patients. Herein, we describe the complications of the disease independently associated to morbidity and mortality. Our findings are valuable not only when designing future studies on AP but also for the improvement of current classifications.

- Survival in Locally Advanced Pancreatic Cancer After Neoadjuvant Therapy and Surgical Resection

OBJECTIVE: The aim of the study was to identify the survival of patients with locally advanced pancreatic cancer (LAPC) and assess the effect of surgical resection after neoadjuvant therapy on patient outcomes. BACKGROUND: An increasing number of LAPC patients who respond favorably to neoadjuvant therapy undergo surgical resection. The impact of surgery on patient survival is largely unknown. MATERIALS AND METHODS: All LAPC patients who presented to the institutional pancreatic multidisciplinary clinic (PMDC) from January 2013 to September 2017 were included in the study. Demographics and clinical data on neoadjuvant treatment and surgical resection were documented. Primary tumor resection rates after neoadjuvant therapy and overall survival (OS) were the primary study endpoints. RESULTS: A total of 415 LAPC patients were included in the study. Stratification of neoadjuvant therapy in FOLFIRINOX-based, gemcitabine-based, and combination of the two, and subsequent outcome comparison did not demonstrate significant differences in OS of 331 non-resected LAPC patients (P = 0.134). Eighty-four patients underwent resection of the primary tumor (20%), after a median duration of 5 months of neoadjuvant therapy. FOLFIRINOX-based therapy and stereotactic body radiation therapy correlated with increased probability of resection (P = 0.006). Resected patients had better performance status, smaller median tumor size (P = 0.029), and lower median CA19-9 values (P < 0.001) at PMDC. Patients who underwent surgical resection had significant higher median OS compared with those who did not (35.3 vs 16.3 mo, P < 0.001). The difference remained significant when non-resected patients were matched for time of neoadjuvant therapy (19.9 mo, P < 0.001). CONCLUSIONS: Surgical resection of LAPC after neoadjuvant therapy is feasible in a highly selected cohort of patients (20%) and is associated with significantly longer median overall survival.

- Metastatic low-grade endometrial stromal sarcoma of uterus presenting as a primary pancreatic tumor: case presentation and literature review

BACKGROUND: Metastatic tumors to the pancreas are uncommon, accounting for approximately 2% of pancreatic malignancies. The most common primary tumors to give rise to pancreatic metastases are carcinomas. CASE PRESENTATION: A 50-year old female patient was investigated for a cause of abdominal discomfort. She had a 2-year history of menorrhagia and dysmenorrhea which was ascribed to a fibroid uterus. On imaging, she was found to have a large solid and cystic mass in the tail of the pancreas. Imaging also confirmed a fibroid uterus. A distal pancreatectomy and splenectomy showed a 9 cm circumscribed mass within, and grossly confined to, the parenchyma of the pancreatic tail. Microscopically, the pancreatic lesion was lobulated, and well-circumscribed, but focally infiltrative. It comprised sheets of uniform spindled to epithelioid cells with round to oval nuclei, coarse to vesicular chromatin, visible nucleoli, nuclear grooves and clear to eosinophilic cytoplasm. Prominent arterioles were identified. The stroma was collagenized in areas. Occasional hemosiderin-laden macrophages were seen, and focal cystic change was present. There was no evidence of nuclear pleomorphism, mitotic activity or necrosis, and there was no evidence of endometriosis despite multiple sections being taken. Immunohistochemistry showed that the tumor cells were positive for CD10, estrogen receptor (ER), progesterone receptor (PR), Wilms tumor-1 (WT-1) and smooth muscle actin (SMA). RNA sequencing detected a PHF1 rearrangement. The morphological, immunohistochemical and molecular features were of a low-grade endometrial stromal sarcoma (LG-ESS). Subsequent total hysterectomy and bilateral salpingo-oophorectomy 3 months later, showed uterine fibroids and a 5 cm

low-grade endometrial stromal sarcoma confined to the uterus, with lymphatic invasion. CONCLUSIONS: To the best of our knowledge, this is the first documented case of metastatic endometrial stromal sarcoma of uterus presenting as a primary pancreatic neoplasm. An unexpected extra-uterine location and unusual presentation of ESS may make the diagnosis challenging, despite classic histological features. Morphological, immunohistochemical and molecular findings must be combined to render the correct diagnosis.

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- [**Heterotopic tissue in the gastrointestinal tract**]

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Heterotopia of the gastrointestinal tract is a common finding. This is due to the complex embryogenesis and the relative ease to detect heterotopic tissue during endoscopy. The reason for biopsy is mostly to rule out neoplasms or to define specific causes of inflammation. Heterotopic tissue can occur in any location of the gastrointestinal tract. The most frequent are gastric heterotopia, pancreatic heterotopia, and heterotopia of Brunner's gland. On rare occasions, heterotopic tissue of salivary gland type as well as heterotopias of apocrine glands, thyroid, and prostatic tissue have been described. The most frequently involved organs are the small intestine, in particular the duodenum, the esophagus, and the stomach. Heterotopia of the large bowel occurs exclusively in the rectum. Most heterotopias do not cause symptoms and are easily diagnosed by biopsy and histology. However, depending on location, size, and the kind of underlying heterotopic tissue, they may cause significant complications, such as inflammation, ulceration and perforation, obstruction, intussusception, and severe life-threatening bleeding. Another rare but significant complication is neoplasia. Gastric heterotopias may give rise to pyloric gland adenomas within the bowel or rarely adenocarcinomas of the esophagus. Pancreatic heterotopia can be complicated by ductal type pancreatic adenocarcinomas, by acinus cell carcinomas, by intraductal papillary mucinous neoplasias, and also by endocrine tumors. The present paper summarizes our current knowledge about heterotopias in a topographic clinico-pathological manner.

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Gallbladder

- Transpapillary Endoscopic Removal of Gallbladder Stones Through a Fully Covered Metallic Stent

The American journal of gastroenterology 2019 Aug;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31403962

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- A 12-year trend analysis of the incidence of gastrointestinal cancers in East Azerbaijan: last updated results of an ongoing population-based cancer registry

BMC cancer 2019 Aug;19(1):782

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31391032

BACKGROUND: The most recent results of Global Cancer Statistics indicated that gastrointestinal cancers, including gastric, colorectal, esophageal, and liver cancers, are among the most commonly diagnosed cancers worldwide. Previous reports from cancer registries in East Azerbaijan have shown that there is a high incidence of gastrointestinal cancer in this region, so we performed a trend analysis to determine the pattern of change over the last decade. METHODS: In total, 12 years of cancer registry data were collected from different sources in East Azerbaijan, and a data quality check was performed to ensure clean data. Using the 2000 World Health Organization standard population, we then generated age-standardized incidence rates (ASRs) for different cancers, and for each year from 1383 to 1394 of the Persian calendar (i.e., 19 March 2004 to 20 March 2015). Annual percent changes (APCs) and Average annual percent changes (AAPCs) in the ASRs for esophageal, gastric, small intestine, colorectal, anal, liver, gallbladder, and pancreatic cancers were calculated using Joinpoint Software (Version 4.5.0.1, June 2017). RESULTS: An increase in most types of cancer was observed during the study period. The ASR for colorectal cancer increased from 2.9 to 13.6 per 100,000 women (APC, 9.7%) and from 2.2 to 17.8 per 100,000 men (APC, 10.2%). The ASR for gastric cancer showed a slight increasing trend from 10.5 to 13.5 per 100,000 women (APC, 1.3%) and from 3.1 to 29.9 per 100,000 men (APC, 3.2%). However, trend analysis showed a decreasing pattern for the ASR of esophageal cancer in both genders (APC,- 3%), with APCs of - 1.1% in females and - 0.4% in males. CONCLUSIONS: The latest results of the East Azerbaijan Population-Based Cancer Registry indicate that gastrointestinal cancers remain common, with significant increasing trends in their ASRs. Improved screening and early detection are needed in this region.

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- Classification of the cystic duct patterns and endoscopic transpapillary cannulation of the gallbladder to prevent post-ERCP cholecystitis

BMC gastroenterology 2019 Aug;19(1):139

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31382888

BACKGROUND: Endoscopic transpapillary cannulation of the gallbladder is useful but challenging. This study aimed to investigate cystic duct anatomy patterns, which may guide cystic duct cannulation. METHODS: A total of 226 patients who underwent endoscopic transpapillary cannulation of the gallbladder were analyzed retrospectively. RESULTS: According to the cystic duct take-off, 226 cystic duct patterns were divided into 3 patterns: Type I (193, 85.4%), located on the right and angled up; Type II (7, 3.1%), located on the right and angled down; and Type III (26, 11.5%), located on the left and angled up. Type I was

further divided into three subtypes: Line type, S type (S1, not surrounding the common bile duct; S2, surrounding the common bile duct), and   type (1, forward ; 2, reverse). Types I and III cystic ducts were easier to be cannulated with a higher success rate (85.1 and 86.4%, respectively) compared with Type II cystic duct (75%) despite no statistically significant difference. The reasons for the failure of gallbladder cannulation included invisible cyst duct take-off, severe cyst duct stenosis, impacted stones in cyst duct or neck of the gallbladder, sharply angled cyst duct, and markedly dilated cyst duct with the tortuous valves of Heister. CONCLUSION: Classification of cystic duct patterns was helpful in guiding endoscopic transpapillary gallbladder cannulation.

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- Efficacy and Safety of Eluxadoline in Patients With Irritable Bowel Syndrome With Diarrhea Who Report Inadequate Symptom Control With Loperamide: RELIEF Phase 4 Study

The American journal of gastroenterology 2019 Jul;():

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OBJECTIVES: Irritable bowel syndrome with diarrhea (IBS-D) is a functional gastrointestinal disorder with limited effective treatment options. We evaluated the efficacy and safety of eluxadoline in patients with IBS-D who reported inadequate symptom control with prior loperamide. METHODS: Three hundred forty-six adults with IBS-D (Rome III criteria) were randomly assigned to placebo or eluxadoline 100 mg twice daily for 12 weeks. Patients recorded daily IBS-D symptoms, including worst abdominal pain (WAP) and stool consistency (through Bristol Stool Scale). The primary endpoint was proportion of composite responders, defined as patients who met daily composite response criteria (40% WAP improvement and <5 Bristol Stool Scale score) for at least 50% of treatment days, and recorded 60 days of diary entries over the 12-week period. RESULTS: Over 12 weeks, a significantly greater proportion of eluxadoline patients achieved the primary composite responder endpoint compared to placebo (22.7% vs 10.3%, P = 0.002), and component endpoints of improvements in stool consistency (27.9% vs 16.7%, P = 0.01) and WAP (43.6% vs 31.0%, P = 0.02). Additionally, a greater proportion of eluxadoline patients met the composite responder endpoint assessed at monthly intervals compared to placebo (weeks 1-4: 14.0% vs 6.9%, P = 0.03; weeks 5-8: 26.7% vs 14.9%, P = 0.006; weeks 9-12: 30.8% vs 16.7%, P = 0.002). Rates of adverse events were comparable in both groups (37.4% vs 35.3%); no treatment-related serious adverse event, cases of sphincter of Oddi spasm, or pancreatitis were reported. DISCUSSION: Eluxadoline appears safe and effective for treating IBS-D symptoms in patients with an intact gallbladder reporting inadequate relief with prior loperamide use.

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- Acute Recurrent and Chronic Pancreatitis as Initial Manifestations of Cystic Fibrosis and Cystic Fibrosis Transmembrane Conductance Regulator-Related Disorders

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OBJECTIVES: Recurrent pancreatitis is considered a rare manifestation of cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction; this case series highlights that pancreatitis can be a presenting symptoms of cystic fibrosis (CF) or a CFTR-related disorder (CFTR-RD). METHODS: Retrospective review of patients younger than 30 years diagnosed as having acute recurrent pancreatitis (ARP) or chronic pancreatitis (CP) and subsequently diagnosed as having CF or CFTR-RD. RESULTS: Among 18 patients, median time from diagnosis of ARP/CP to diagnosis of CF was 0.4 years (range, 0-33 years). Eight were classified as having CF by elevated sweat chloride testing (SCT). Five had intermediate SCT (30-59 mmol/L) with 2

pathogenic mutations. Five had CFTR-RD with intermediate SCT and 0 to 1 pathogenic mutations. Eight patients (44%) had exocrine pancreatic insufficiency, and pancreatic fluid collections were more common in this group. Based on the CFTR mutation, 6 patients were eligible for CFTR potentiator therapy, although none received it during the study period. Nine of the 18 had 1 other likely CF manifestations, including sinusitis (33%), nasal polyps (11%), pneumonia (22%), and gallbladder disease (22%). CONCLUSIONS: Cystic fibrosis or CFTR-RD can present as ARP/CP. Complete diagnostic testing for CFTR-RD in patients with ARP/CP will broaden treatment options and help to identify comorbid illness.

- Epithelial Inclusions in Gallbladder May Mimic Parasite Infection

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- Nivolumab alone or in combination with cisplatin plus gemcitabine in Japanese patients with unresectable or recurrent biliary tract cancer: a non-randomised, multicentre, open-label, phase 1 study

BACKGROUND: This study aimed to assess the safety and tolerability of the immune checkpoint inhibitor nivolumab, as monotherapy or combined with chemotherapy, in Japanese patients with biliary tract cancer. METHODS: This multicentre, open-label, phase 1 trial was done at four cancer centres in Japan. Eligible patients were aged 20-79 years, had biliary tract adenocarcinoma (intrahepatic bile duct cancer, extrahepatic bile duct cancer, gallbladder cancer, or ampullary cancer), Eastern Cooperative Oncology Group performance status 0 or 1, adequate hepatic, renal, and haematological function, and tumour tissue samples for PD-L1 expression analysis. Patients with unresectable or recurrent biliary tract cancer that was refractory or intolerant to gemcitabine-based treatment regimens received nivolumab monotherapy (240 mg every 2 weeks [monotherapy cohort]). Chemotherapy-naive patients with unresectable or recurrent biliary tract cancer received nivolumab (240 mg every 2 weeks) and cisplatin (25 mg/m2) plus gemcitabine (1000 mg/m2) chemotherapy (combined therapy cohort). The primary objective was to assess tolerability and safety. The primary objective was assessed in the safety population of all patients who had received at least one dose of nivolumab. This study is registered with www.clinicaltrials.jp, number JapicCTI-153098, and follow-up is ongoing. FINDINGS: 30 patients were enrolled into each cohort between Jan 13, 2016, and April 19, 2017. Data cutoff was Aug 31, 2017. In the monotherapy cohort, the most frequently reported treatment-related adverse events were decreased appetite (five [17%]), malaise (four [13%]), and pruritus (four [13%]). Grade 3-4 treatment-related adverse events were reported by three (10%) patients (rash, maculopapular rash, and amylase increase) and treatment-related serious adverse events were reported by one (3%) patient (pleurisy). In the combined therapy cohort, the most frequently reported treatment-related adverse events were neutrophil count decrease (any grade 25 [83%]; grade 3-4 in 23 [77%] patients) and platelet count decrease (any grade 25 [83%] of 30; grade 3-4 in 15 [50%] patients). Six (20%) patients reported 11 treatment-related serious adverse events (platelet count decrease [three patients], febrile neutropenia [two patients], neutrophil count decrease, anaemia, anaphylactic reaction, decreased appetite, pyrexia, and myocarditis [one patient each]). In the monotherapy cohort, median overall survival was $5 \cdot 2$ months (90% CI $4 \cdot 5$-$8 \cdot 7$), median progression-free survival was $1 \cdot 4$ months (90% CI $1 \cdot 4$-$1 \cdot 4$), and one of 30 patients had an objective response. In the combined therapy cohort, median overall survival was $15 \cdot 4$ months (90% CI

11 · 8-not estimable), median progression-free survival was 4 · 2 months (90% CI 2 · 8-5 · 6), and 11 of 30 patients had an objective response. INTERPRETATION: Nivolumab had a manageable safety profile and signs of clinical activity in patients with unresectable or recurrent biliary tract cancer. This initial assessment of nivolumab for the treatment of advanced biliary tract cancer provides supportive evidence for future larger randomised studies of nivolumab in this difficult to treat cancer. FUNDING: Ono Pharmaceutical Co Ltd and Bristol-Myers Squibb Inc.

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- Detection of NRG1 Gene Fusions in Solid Tumors

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PURPOSE: NRG1 gene fusions are rare but potentially actionable oncogenic drivers that are present in some solid tumors. Details regarding the incidence of these gene rearrangements are lacking. Here, we assessed the incidence of NRG1 fusions across multiple tumor types and described fusion partners. EXPERIMEN-TAL DESIGN: Tumor specimens submitted for molecular profiling at a Clinical Laboratory Improvement Amendments (CLIA)-certified genomics laboratory and that underwent fusion testing by anchored multiplex PCR for targeted RNA sequencing were retrospectively identified. The overall and tumor-specific incidence was noted, as was the specific fusion partner. RESULTS: Out of 21,858 tumor specimens profiled from September 2015 to December 2018, 41 cases (0.2%) harbored an NRG1 fusion. Multiple fusion partners were identified. Fusion events were seen across tumor types. The greatest incidence was in non-small cell lung cancer (NSCLC, 25), though this represented only 0.3% of NSCLC cases tested. Other tumor types harboring an NRG1 fusion included gallbladder cancer, renal cell carcinoma, bladder cancer, ovarian cancer, pancreatic cancer, breast cancer, neuroendocrine tumor, sarcoma, and colorectal cancer. CONCLUSIONS: NRG1 fusions can be detected at a low incidence across multiple tumor types with significant heterogeneity in fusion partner.See related commentary by Dimou and Camidge, p. 4865.

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- Gallbladder Papilloma in a Child Unmasking Metachromatic Leukodystrophy: A Case Report With Review of Literature

Fetal and pediatric pathology 2019 Aug;38(4):345-351

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Background: Metachromatic leukodystrophy (MLD) is a lipid storage disease characterized the accumulation of sulfatides in different viscera including the gallbladder. Case report: A 2-year-old girl had upper right quadrant lesion that was preoperatively thought to be a biliary cystadenoma. Histologically, the gallbladder lesion was a tubulo-villous papilloma with multiple foci of papillary mucosal hyperplasia. Many storage histiocytes containing metachromatic granules, characteristic of MLD, were present in the tips of the papillae. MLD was later confirmed by enzyme studies. Conclusion: Gallbladder papilloma can be the presenting feature of MLD.

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- Incidental Hepatic Tissue Obtained via Routine Cholecystectomy

Background. The hepatic tissue that may occupy specimens from routine cholecystectomies has yet to be studied. Our objectives were to determine the prevalence of hepatic tissue obtained at routine cholecystectomy, to determine whether such hepatic tissue can histologically withstand technical artifacts commonly associated with cholecystectomy, and to determine whether examining such hepatic tissue has diagnostic utility. Materials and Methods. We retrospectively reviewed 50 specimens from routine cholecystectomies that were performed by surgeons who lacked knowledge of our study. All 50 specimens were grossed according to standard protocol, with only limited, nontargeted sampling of the rough nonperitonealized margin, and were received without fixative. Results. Twelve specimens (24.0%) contained hepatic tissue. The hepatic tissue measured up to 44.5-mm long and 1.8-mm wide and contained up to 11 complete portal tracts. Hepatic tissue in 3 specimens satisfied criteria for adequacy established for core biopsies based on number of portal tracts or size. Despite cautery and delayed fixation, all hepatic tissue had surprisingly well-preserved histology. Pathologic findings included nonalcoholic fatty liver disease, von Meyenburg complex, chronic cholestasis, and senescence. Conclusions. The hepatic tissue that accompanies specimens from routine cholecystectomies may be relatively common, can be large, is well preserved, and can harbor diagnostically useful information.

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Bile Ducts

- Fragile X mental retardation protein protects against tumour necrosis factor-mediated cell death and liver injury

Gut 2019 Aug;():

OBJECTIVE: The Fragile X mental retardation (FMR) syndrome is a frequently inherited intellectual disability caused by decreased or absent expression of the FMR protein (FMRP). Lack of FMRP is associated with neuronal degradation and cognitive dysfunction but its role outside the central nervous system is insufficiently studied. Here, we identify a role of FMRP in liver disease. DESIGN: Mice lacking Fmr1 gene expression were used to study the role of FMRP during tumour necrosis factor (TNF)-induced liver damage in disease model systems. Liver damage and mechanistic studies were performed using real-time PCR, Western Blot, staining of tissue sections and clinical chemistry. RESULTS: Fmr1null mice exhibited increased liver damage during virus-mediated hepatitis following infection with the lymphocytic choriomeningitis virus. Exposure to TNF resulted in severe liver damage due to increased hepatocyte cell death. Consistently, we found increased caspase-8 and caspase-3 activation following TNF stimulation. Furthermore, we demonstrate FMRP to be critically important for regulating key molecules in TNF receptor 1 (TNFR1)-dependent apoptosis and necroptosis including CYLD, c-FLIPS and JNK, which contribute to prolonged RIPK1 expression. Accordingly, the RIPK1 inhibitor Necrostatin-1s could reduce liver cell death and alleviate liver damage in Fmr1null mice following TNF exposure. Consistently, FMRP-deficient mice developed increased pathology during acute cholestasis following bile duct ligation, which coincided with increased hepatic expression of RIPK1, RIPK3 and phosphorylation of MLKL. CONCLUSIONS: We show that FMRP plays a central role in the inhibition of TNF-mediated cell death during infection and liver disease.

- Decompressive laparotomy for abdominal compartment syndrome resulting from severe acute pancreatitis: a case report

BMC gastroenterology 2019 Aug;19(1):141

BACKGROUND: Abdominal compartment syndrome (ACS) is associated with mortality in patients with critical illness such as severe acute pancreatitis, but it remains unclear whether decompressive laparotomy for ACS can improve the prognosis of patients. CASE PRESENTATION: A woman in her 60s visited our hospital because of upper abdominal pain. On the basis of her laboratory data and abdominal contrast-enhanced computed tomography findings, acute gallstone pancreatitis was diagnosed. She underwent endoscopic sphincterotomy for the removal of the common bile duct stone. Then, a drainage tube was placed in the bile duct. However, on the 5th hospital day, her intra-abdominal pressure increased to 22 mmHg and renal dysfunction was observed, which led to the diagnosis of ACS. As intensive medical treatments did not improve her ACS, she underwent decompressive laparotomy on the 9th hospital day. Postoperatively, her laboratory data and intravesical pressure improved, and she was discharged from the hospital after abdominal closure, continuous drainage, and antibiotic therapy. CONCLUSION: As the effectiveness of decompressive laparotomy for ACS has not been established, this treatment indication remains controversial. Decompressive laparotomy is considered useful for the management of ACS, if it is performed at an appropriate time, as in the present case.

- Classification of the cystic duct patterns and endoscopic transpapillary cannulation of the gallbladder to prevent post-ERCP cholecystitis

BACKGROUND: Endoscopic transpapillary cannulation of the gallbladder is useful but challenging. This study aimed to investigate cystic duct anatomy patterns, which may guide cystic duct cannulation. METH-ODS: A total of 226 patients who underwent endoscopic transpapillary cannulation of the gallbladder were analyzed retrospectively. RESULTS: According to the cystic duct take-off, 226 cystic duct patterns were divided into 3 patterns: Type I (193, 85.4%), located on the right and angled up; Type II (7, 3.1%), located on the right and angled down; and Type III (26, 11.5%), located on the left and angled up. Type I was further divided into three subtypes: Line type, S type (S1, not surrounding the common bile duct; S2, surrounding the common bile duct), and   type (1, forward ; 2, reverse). Types I and III cystic ducts were easier to be cannulated with a higher success rate (85.1 and 86.4%, respectively) compared with Type II cystic duct (75%) despite no statistically significant difference. The reasons for the failure of gallbladder cannulation included invisible cyst duct take-off, severe cyst duct stenosis, impacted stones in cyst duct or neck of the gallbladder, sharply angled cyst duct, and markedly dilated cyst duct with the tortuous valves of Heister. CONCLUSION: Classification of cystic duct patterns was helpful in guiding endoscopic transpapillary gallbladder cannulation.

- Liver biopsy in primary biliary cholangitis: is sinusoidal fibrosis the missing key?

AIMS: The role of liver biopsy in primary biliary cholangitis (PBC) is controversial, as is the optimal method of histological assessment. We compared the Ludwig and Ishak systems and three components of the Japanese (Nakanuma) staging system to evaluate their clinical and biochemical correlations and prognostic value. METHODS: We reviewed biopsies from 106 patients with PBC, derived from a previous trial of colchicine therapy with 24-34 years' follow-up, following which five clinical outcomes were evaluated: hepatic decompensation, cholestatic PBC death/liver transplant, portal hypertensive PBC death, all PBC deaths and overall survival. RESULTS: Ludwig and Ishak stages correlated well with prognostically significant parameters, including serum bilirubin, and both Mayo and Child Scores. Serum aspartate aminotransferase correlated with interface hepatitis (IFH), and alkaline phosphatase with orcein deposition, bile duct (BD) loss and cholestasis. Ludwig correlated with all five clinical outcomes, while Ishak stage was only significantly correlated with two. While sinusoidal fibrosis, orcein deposition, BD loss and cholestasis all predicted hepatic death/transplant, after correction for Mayo Score, the only histological parameters predictive of clinical outcomes were IFH (associated with two) and sinusoidal fibrosis (associated with all five). CONCLUSION: Liver biopsy is required in the diagnosis of around 20% of patients with PBC. The Ludwig system is of more prognostic value than both Ishak and any of the three individual components of the Nakanuma staging system, but the major histological parameter providing independent prognostic value beyond the Mayo Score is sinusoidal fibrosis.

- Immunoglobulin G4-related hepatobiliary disease

Immunoglobuline G4-related disease (IgG4-RD) is a systemic disease that can involve virtually any organs including the biliary tract and liver. The biliary tract involvement of IgG4-RD is known as IgG4-sclerosing cholangitis (IgG4-SC) and may or may not present with an inflammatory pseudotumor. Large bile ducts such as extrahepatic, hilar, and perihilar ducts are typically affected and demonstrate marked bile duct wall thickening and develop strictures. Histologically, the involved ducts show transmural dense lymphoplasmacytic infiltrates with storiform fibrosis extending into peribiliary glands and periductal soft tissue. The luminal epithelium is usually preserved. Tissue eosinophilia and obliterative phlebitis are also frequently noted. Liver biopsy findings of IgG4-SC are heterogeneous and rather nonspecific, but two features specific to IgG4-SC have been described: >10 IgG4-positive plasma cell/HPF and small portal-based fibroinflammatory nodules. Secondary changes, due to downstream bile duct obstruction are often appreciated. When considering the differential diagnosis, primary sclerosing cholangitis and cholangiocarcinoma are great clinical and histologic mimics of IgG4-SC. Liver involvement in IgG4-RD has not been well characterized and includes IgG4-hepatopathy and IgG4-related autoimmune hepatitis (AIH). IgG4-hepatopathy is a generic term covering hepatic lesions related to IgG4-RD and /or IgG4-SC. It includes primary liver parenchymal changes inherent to IgG4-RD, liver parenchymal involvement of IgG4-SC, and secondary changes related to IgG4-SC. IgG4-related AIH is characterized by clinical and histologic features of classical AIH but with prominent (>10/HPF) IgG4-positive plasma cells. It is unclear whether this represents a hepatic manifestation of IgG4-RD or a subset of AIH with increased IgG4-positive plasma cells at the present time. Synchronous or metachronous involvement of other organs, offers a clue to make this distinction. IgG4 immunohistochemistry has an important role in diagnosing IgG4-RD. But the diagnosis cannot be made solely based on the number of IgG4-positive plasma cells, and results need to be interpreted with caution as increased IgG4-positive plasma cells can be seen in other inflammatory conditions or even in malignancy.

- Checkpoint inhibitor-induced liver injury: A novel form of liver disease emerging in the era of cancer immunotherapy

Liver injury triggered by immune checkpoint inhibitors has been increasingly seen in clinical practice, and the incidence is likely to rise further in the next several years because of expanded indications for cancer immunotherapy. Tissue damage driven by disrupted immune tolerance against self-antigens is called an immune-related adverse event (irAE). irAEs in the liver histologically presents panlobular hepatitis (70%), isolated central zonal necrosis (20%), primarily granulomatous hepatitis (5%), and other minor forms of tissue injury (5%). Infiltrating cells are mainly lymphocytes and occasional eosinophils. Unlike classic autoimmune hepatitis (AIH), plasma cell infiltration is not conspicuous. Immunostaining reveals a large number of CD8+ T lymphocytes and a markedly smaller number of CD4+ cells or CD20+ B lymphocytes. The unique CD3+/CD20+ and CD4+/CD8+ ratios shifted in favor of CD8+ cytotoxic T lymphocytes are helpful to discriminate irAEs from other conditions (e.g., AIH, idiosyncratic drug-induced liver injury). Another hepatobiliary manifestation of irAEs is sclerosing cholangitis clinically characterized by elevations of biliary enzymes, diffuse duct wall thickening, and duct dilatation. Lymphocytic infiltration can be observed by endoscopic biopsies from the thick extrahepatic bile ducts, and liver needle biopsies may also show severe lymphocytic cholangitis resembling primary biliary cholangitis. An important differential diagnosis of irAEs is previously asymptomatic or subclinical liver disease unmasked by cancer immunotherapy, which is often challenging and requires close clinicopathological correlations.

- Clinical value of DPOC for detecting and removing residual common bile duct stones (video)

BMC gastroenterology 2019 Jul;19(1):135

BACKGROUND: This study aims to evaluate the efficacy and safety of detecting and removing residual common bile duct stones (CBDS) using direct peroralcholangioscopy (DPOC) after performing endoscopic retrograde cholangiopancreatography (ERCP) for stone retrieval. METHODS: From January 5, 2017 to December 27, 2017, a total of 164 cases of choledocholithiasis were treated by ERCP for stone retrieval. According to the inclusion and exclusion criteria, the remaining 79 cases (39 males; mean age: 63.3 years old, range: 52-79 years old) were enrolled in the present study. The maximum transverse stone diameter was 6-15 mm (12.7 ± 4.2 mm), as determined by ERCP. Furthermore, there were 57 cases of multiple stones (number of stones: two in 41 cases, three in nine cases, and 4 in seven cases), 13 cases of post-mechanical lithotripsy, and nine cases of broken stones. RESULTS: The overall success rate of DPOC was 94.9% (75/79). Furthermore, 18.7%(14/75) of cases were directly inserted, 72%(54/75) of cases required guide wire assistance, and 9.3%(7/75) of cases were successfully inserted with overtube assistance. The average insertion time was 7-17 min (4.9 ± 2.9 min). Residual stones were detected in 19 cases (25.3%), and all of which were < 5 mm in diameter. Moreover, five cases of formed stones were removed by basket and balloon catheter, while the remaining cases were cleaned after irrigation and suction. There were no serious complications. CONCLUSION: DPOC is safe and effective for both the detection and removal of residual CBDS after conventional ERCP.

- Development of a Theranostic Convergence Bioradiopharmaceutical for Immuno-PET based Radioimmunotherapy of L1CAM in Cholangiocarcinoma Model

Clinical cancer research : an official journal of the American Association for Cancer Research 2019 Jul;():

PURPOSE: Cholangiocarcinoma (CCA) is a malignancy of bile duct with a poor prognosis. Conventional chemotherapy and radiation therapy are generally ineffective and surgical resection is the only curative treatment for CCA. L1-cell adhesion molecule (L1CAM) has been known as a novel prognostic marker and therapeutic target for CCA. This study aimed to evaluate the feasibility of immuno-positron emission tomography (PET) imaging-based radioimmunotherapy using radiolabeled anti-L1CAM antibody in CCA xenograft model. EXPERIMENTAL DESIGN: We prepared a theranostic convergence bioradiopharmaceutical using chimeric anti-L1CAM antibody (cA10-A3) conjugated with 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA) chelator and labeled with 64Cu or 177Lu and evaluated the immuno-PET or SPECT/CT imaging and biodistribution with 64Cu-/177Lu-cA10-A3 in various CCA xenograft models. Therapeutic efficacy and response monitoring were performed by 177Lu-cA10-A3 and 18F-FDG-PET, respectively, and immuno-histochemistry was done by TUNEL and Ki-67. RESULTS: Radiolabeled cA10-A3 antibodies specifically recognized L1CAM in vitro, clearly visualized CCA tumors in immuno-PET and SPECT/CT imaging, and differentiated the L1CAM expression level in CCA xenograft models. 177Lu-cA10-A3 (12.95 MBq/100 g) showed statistically significant reduction in tumor volumes (P < 0.05) and decreased glucose metabolism (P < 0.01). IHC analysis revealed 177Lu-cA10-A3 treatment increased TUNEL-positive and decreased Ki-67-positive cells, compared with saline, cA10-A3, or 177Lu-isotype. CONCLUSIONS: Anti-L1CAM immuno-PET imaging using 64Cu-cA10-A3 could be translated into the clinic for characterizing the pharmacokinetics and selecting pertinent patient for radioimmunotherapy. Radioimmunotherapy using 177Lu-cA10-A3 may provide survival benefit in L1CAM expressing CCA tumor. Theranostic convergence bioradiopharmaceutical

strategy would be applied as an imaging biomarker based personalized medicine in L1CAM expressing CCA patients.

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- Nivolumab alone or in combination with cisplatin plus gemcitabine in Japanese patients with unresectable or recurrent biliary tract cancer: a non-randomised, multicentre, open-label, phase 1 study

The lancet. Gastroenterology & hepatology 2019 Aug;4(8):611-621

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31109808

BACKGROUND: This study aimed to assess the safety and tolerability of the immune checkpoint inhibitor nivolumab, as monotherapy or combined with chemotherapy, in Japanese patients with biliary tract cancer. METHODS: This multicentre, open-label, phase 1 trial was done at four cancer centres in Japan. Eligible patients were aged 20-79 years, had biliary tract adenocarcinoma (intrahepatic bile duct cancer, extrahepatic bile duct cancer, gallbladder cancer, or ampullary cancer), Eastern Cooperative Oncology Group performance status 0 or 1, adequate hepatic, renal, and haematological function, and tumour tissue samples for PD-L1 expression analysis. Patients with unresectable or recurrent biliary tract cancer that was refractory or intolerant to gemcitabine-based treatment regimens received nivolumab monotherapy (240 mg every 2 weeks [monotherapy cohort]). Chemotherapy-naive patients with unresectable or recurrent biliary tract cancer received nivolumab (240 mg every 2 weeks) and cisplatin (25 mg/m2) plus gemcitabine (1000 mg/m2) chemotherapy (combined therapy cohort). The primary objective was to assess tolerability and safety. The primary objective was assessed in the safety population of all patients who had received at least one dose of nivolumab. This study is registered with www.clinicaltrials.jp, number JapicCTI-153098, and follow-up is ongoing. FINDINGS: 30 patients were enrolled into each cohort between Jan 13, 2016, and April 19, 2017. Data cutoff was Aug 31, 2017. In the monotherapy cohort, the most frequently reported treatment-related adverse events were decreased appetite (five [17%]), malaise (four [13%]), and pruritus (four [13%]). Grade 3-4 treatment-related adverse events were reported by three (10%) patients (rash, maculopapular rash, and amylase increase) and treatment-related serious adverse events were reported by one (3%) patient (pleurisy). In the combined therapy cohort, the most frequently reported treatment-related adverse events were neutrophil count decrease (any grade 25 [83%]; grade 3-4 in 23 [77%] patients) and platelet count decrease (any grade 25 [83%] of 30; grade 3-4 in 15 [50%] patients). Six (20%) patients reported 11 treatment-related serious adverse events (platelet count decrease [three patients], febrile neutropenia [two patients], neutrophil count decrease, anaemia, anaphylactic reaction, decreased appetite, pyrexia, and myocarditis [one patient each]). In the monotherapy cohort, median overall survival was $5 \cdot 2$ months (90% CI $4 \cdot 5$-$8 \cdot 7$), median progression-free survival was $1 \cdot 4$ months (90% CI $1 \cdot 4$-$1 \cdot 4$), and one of 30 patients had an objective response. In the combined therapy cohort, median overall survival was $15 \cdot 4$ months (90% CI $11 \cdot 8$-not estimable), median progression-free survival was $4 \cdot 2$ months (90% CI $2 \cdot 8$-$5 \cdot 6$), and 11 of 30 patients had an objective response. INTERPRETATION: Nivolumab had a manageable safety profile and signs of clinical activity in patients with unresectable or recurrent biliary tract cancer. This initial assessment of nivolumab for the treatment of advanced biliary tract cancer provides supportive evidence for future larger randomised studies of nivolumab in this difficult to treat cancer. FUNDING: Ono Pharmaceutical Co Ltd and Bristol-Myers Squibb Inc.

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- Evaluation of histologic changes in the livers of patients with early and late hepatic artery thrombosis

Human pathology 2019 Aug;90():8-13

Hepatic artery thrombosis (HAT) following orthotopic liver transplantation (OLT) can cause hepatic parenchymal necrosis and ischemic cholangiopathy. This study investigates additional histologic features that may suggest HAT in post-OLT liver specimens. For 94 liver specimens (explanted allografts and biopsies) from patients with a clinical or pathologic diagnosis of HAT, we recorded length of time between OLT and procedure, categorizing cases into early HAT (; 30 days since OLT) and late HAT (>30 days since OLT). Common histologic findings in HAT included lobular necrosis (60 cases, 64%), portal inflammation (68 cases, 72%), ductular reaction (73 cases, 78%), lobular cholestasis (70 cases, 74%), and bile-tinged macrophages (40 cases, 43%). Ductular cholestasis was seen in 30 cases (32%); 10 of those patients were clinically septic. Bile in veins was seen in 16 (17%) cases and arteritis in 6 (6%) cases. Findings more common in resection than biopsy specimens included lobular necrosis ($P < .0001$), hemorrhage ($P = .0044$), ductular cholestasis ($P = .0003$), and bile-tinged macrophages ($P < .0001$). Lobular necrosis was more common in early HAT ($P = .0002$), and ductular reaction ($P = .006$) and bile in veins ($P = .03$) were more common in late HAT. Histologic changes in HAT vary based on specimen type and whether HAT is early or late. In late HAT, biliary injury might occur after a prolonged period of ischemia, with subsequent bile duct necrosis, bile in veins, and remodeling (eg, ductular reaction). Bile in veins is an unusual finding that may occur in HAT, although it can be seen in bile infarcts from other causes.

- **Intraoperative Air Leak Test to Prevent Bile Leak After Right Posterior Sectionectomy with En Bloc Diaphragm Resection for Metastatic Teratoma**

BACKGROUND: The intraoperative air cholangiogram, or "air leak test" (ALT), at the time of hepatectomy can significantly reduce the rates of bile leak and symptomatic fluid collection after high-risk procedures.[1,2] Because a bile leak in the setting of an en bloc diaphragm resection and mesh reconstruction would be a particularly dreaded complication, this video shows the technique for resection, reconstruction, and ALT. PRESENTATION: The video presents the case of a 29-year-old woman who had metastatic teratoma with an 8×7-cm liver metastasis in segment 7 and diaphragm invasion to the level of the right hepatic vein. OPERATION: The authors performed a formal right posterior sectionectomy with en bloc diaphragm resection. The 12×8-cm diaphragmatic defect was reconstructed using biologic mesh (Surgimend, Integra LifeSciences, Plainsboro, NJ). An intraoperative ALT (air injection into the cystic duct with finger compression of the distal bile duct) identified several areas of bubbles from biliary radicles on the cut surface of the liver, which were ligated with 4-0 polypropylene. The ALT was repeated until no bubbles remained. Because no evidence of bubbles was observed, no surgical drain was needed. The patient did well postoperatively with no complications. CONCLUSION: In cases of combined liver and diaphragmatic resection, prevention of bile leak, with subsequent contamination of the diaphragm repair and even the thoracic cavity, is particularly vital. An easily replicated intraoperative air leak test can mitigate the risk of bile leak and organ-space infection, as well as associated sequelae on quality of life, return to intended oncologic therapy, and oncologic outcomes.

- **Microbiota as a cornerstone in the development of primary sclerosing cholangitis: paving the path for translational diagnostic and therapeutic approaches**

- Statin use and reduced risk of biliary tract cancers in the UK Clinical Practice Research Datalink

OBJECTIVE: To evaluate the association between statin use and risk of biliary tract cancers (BTC). DE-SIGN: This is a nested case-control study conducted in the UK Clinical Practice Research Datalink. We included cases diagnosed with incident primary BTCs, including cancers of the gall bladder, bile duct (ie, both intrahepatic and extrahepatic cholangiocarcinoma), ampulla of Vater and mixed type, between 1990 and 2017. For each case, we selected five controls who did not develop BTCs at the time of case diagnosis, matched by sex, year of birth, calendar time and years of enrolment in the general practice using incidence density sampling. Exposures were defined as two or more prescription records of statins 1 year prior to BTC diagnosis or control selection. ORs and 95% CIs for associations between statins and BTC overall and by sub-types were estimated using conditional logistic regression, adjusted for relevant confounders. RESULTS: We included 3118 BTC cases and 15 519 cancer-free controls. Current statin use versus non-use was associated with a reduced risk of all BTCs combined (adjusted OR=0.88, 95% CI 0.79 to 0.98). The reduced risks were most pronounced among long-term users, as indicated by increasing number of prescriptions (ptrend=0.016) and cumulative dose of statins (ptrend=0.008). The magnitude of association was similar for statin use and risk of individual types of BTCs. The reduced risk of BTCs associated with a record of current statin use versus non-use was more pronounced among persons with diabetes (adjusted OR=0.72, 95% CI 0.57 to 0.91). Among non-diabetics, the adjusted OR for current statin use versus non-use was 0.91 (95% CI 0.81 to 1.03, pheterogeneity=0.007). CONCLUSION: Compared with non-use of statins, current statin use is associated with 12% lower risk of BTCs; no association found with former statin use. If replicated, particularly in countries with a high incidence of BTCs, our findings could pave the way for evaluating the value of statins for BTC chemoprevention.

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Ampulla

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