Pancreatobiliary Pathology Society Journal Watch

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Contents

PANCREATOBILIARY PATHOLOGY SOCIETY

PBPath Journal Watch Articles

Wellcome to the PBPath Journal Watch!

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

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

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

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

Surgical Pathology

Pancreas

Morphology, Diagnostics, IHC

Morphology, Diagnostics, IHC

- Pancreatic cancer arising in the remnant pancreas is not always a relapse of the preceding primary

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30467323

This study aimed to understand the biology of pancreatic ductal adenocarcinoma that arises in the remnant pancreas after surgical resection of a primary pancreatic ductal adenocarcinoma, using integrated histological and molecular analysis. Patients who underwent a completion pancreatectomy for local recurrence following resection of a primary pancreatic ductal adenocarcinoma were studied with histological analysis and next-generation sequencing of the primary and the recurrent cancer. Of six patients that met the inclusion criteria, three cases were classified as “true” recurrences, i.e., the primary and the cancer in the remnant pancreas shared both morphological features and molecular alterations. Two cases were identified as having independent cancers that exhibited different histological and molecular profiles. In the remaining case, the relationship could not be determined. Pancreatic ductal adenocarcinoma that arises in the remnant pancreas can be either a second primary or a “true” relapse of the preceding primary. The differentiation of second primaries from local recurrences may have important implications for patient management.

- Epidermoid cyst in intrapancreatic accessory spleen: A systematic review

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30366677

BACKGROUND/OBJECTIVES: Due to its rarity, epidermoid cyst in intrapancreatic accessory spleen (ECIPAS) is still a diagnostic dilemma during clinical practice. The aim of this review was to summarize the epidemiologic features and management of ECIPAS. METHODS: MEDLINE and EMBASE were searched for English articles reporting on ECIPAS up to April 30th, 2018 following the methodology suggested by the PRISMA guidelines. Categorical variables were reported as frequency and percentage. Continuous variables were reported as median (range). RESULTS: A total of 56 patients from 47 full articles were included for the final data synthesis. More than half of the ECIPASs (59%) were found incidentally. The female/male ratio was 1.33. ECIPAS is typically a single mono-/multi-lobular cystic lesions in the pancreatic tail with thickened cystic wall or various amount of solid component which had identical density/signal to the spleen on imaging examinations. The cyst is filled with serous or non-serous fluid. Recognition of the surrounding ectopic splenic tissue is the key point to diagnose ECIPAS. However, no preoperative examination was able to make a definite diagnosis. Almost all the patients (96%) received surgical treatment, due to the suspicion of pancreatic malignant or potentially malignant cystic tumor, especially mucinous cystic neoplasm (MCN). CONCLUSIONS: Although seldom encountered, ECIPAS should be considered as a differential diagnosis for pancreatic cystic lesions, especially when solid component was detected. As a benign disease, unnecessary surgery should be avoided. Because it is difficult to make a definite diagnosis preoperatively by one single examination, multiple modalities may be required.

- The expression of death receptor systems TRAIL-R1/-R2/-R4, CD95 and TNF-R1 and their cognate ligands in pancreatic ductal adenocarcinoma

Histology and histopathology 2018 Oct;():18054

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30375637

The expression of five members of the TNF receptor superfamily and two of their ligands in human pancreatic ductal adenocarcinoma were investigated in parallel by immunohistochemistry. 41 patients with histologically confirmed ductal carcinoma of the pancreas were enrolled in this study in order (i) to compare the individual TNFR-SF expression and their ligands in PDAC-cells and (ii) to investigate their correlation with survival data. All patients had undergone pancreaticoduodenectomy and were staged as pT3N1M0. Immunostaining was done on FFPE tissue sections of the tumor tissue, using antibodies directed against TRAIL-Receptor-1, -2 and -4, TRAIL, CD95, TNF-Receptor-1 and TNF- . The intensity and quantity of immunostaining were evaluated separately for tumor cell cytoplasm and tumor cell nucleus. Immunostaining results were correlated with each other and with patient survival. All proteins were found to be expressed in the majority of the tumor cells. The expression (i) of the following members of TNFR-SF and their ligands correlated with each other: TNF-Receptor-1 and TNF (cytoplasmatic scores, p=0.001), TNF-Receptor 1 and TRAIL (nuclear antigen expression p=0.005 and the main score p=0.001, which contains the overall intracellular antigen expression), TNF-Receptor 1 and CD95 (main score, p=0.001), TRAIL-Receptor-1 and TRAIL-Receptor-2 (nuclear parameters, p=0.023), TRAIL-Receptor-4 and TRAIL (main score p=0.041). In addition (ii), high cytoplasmatic expression of TNF-Receptor-1 and a strong cytoplasmatic and nuclear expression of CD95 correlated significantly with a better prognosis of the PDAC patients.

- High nuclear Survivin expression as a poor prognostic marker in pancreatic ductal adenocarcinoma

Journal of surgical oncology 2018 Dec;118(7):1115-1121

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30261114

BACKGROUND: Survivin, one of the key regulators of mitosis and apoptosis, has long been well recognized to play important biological roles in many neoplasms, including pancreatic ductal adenocarcinoma (PDAC). However, its prognostic value in PDAC remains controversial. PATIENTS AND METHODS: Nuclear expression of Survivin was detected, using tissue microarray-based immunohistochemistry, in paired-tumor and nontumor samples from 306 patients with radically resected PDAC. The staining H scores were further correlated with clinicopathologic features and disease-specific survival (DSS). RESULTS: Nuclear Survivin expression was much higher in tumor than in nontumor tissues ($P < 0.001$). No significant association between tumoral Survivin expression and clinicopathologic variables was found. For prognosis, high Survivin expression was associated with shortened DSS in all eligible patients and four subgroups, that is, male and nondiabetic patients as well as those with head-located and G1-2 tumors, shown by univariate analyses. In addition, a statistically marginal significance was revealed in eight subgroups. For the entire cohort and two subgroups, nuclear Survivin expression was also multivariate identified as an independent predictor for DSS. For patients with G1-2 tumors, it was the single prognostic marker. CONCLUSION: Our data suggest an association between high nuclear Survivin expression and poor prognosis in PDAC. However, further confirmation might be necessary.

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

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

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

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

- PD-L1 expression in pancreatic adenosquamous carcinoma: PD-L1 expression is limited to the squamous component

Pathology, research and practice 2018 Dec;214(12):2069-2074

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30477643

AIM: We examined the programmed death-ligand 1 (PD-L1) expression in surgically resected pancreatic adenosquamous carcinoma (PASC) samples. Furthermore, the detection rate was also assessed using biopsy cases obtained from endoscopic ultrasound-guided fine needle aspiration (EUS-FNA). METHODS: Fifteen cases of PASC (six resected and nine EUS-FNA biopsied) from the Kurume University Hospital between 2009 and 2016 were used for the evaluation of PD-L1 expression. As a control group, 34 cases of pancreatic ductal adenocarcinomas (PDACs) were selected. To compare the positivity and intensity of PD-L1, two types of clones (SP263, E1L3N) were examined for immunostaining. Only the membrane expression of PD-L1 was regarded as positive. The PD-L1 expressions in the squamous cell carcinoma component (SCc), adenocarcinoma component (ACc), and immune cells were assessed separately. The ratio of PD-L1 expression was calculated by counting the positive tumor cells, and tumor proportion score (TPS) was applied (TPS; Null < 1%, low expression; 1 TPS 49% and high expression; 50%). RESULTS: PD-L1 expression was observed in five surgical PASC samples (83%). This shows that SCc presented a high expression in these cases. However, the overall TPS indicated a low expression. In contrast, only one case (3%) was positive for PD-L1 in PDACs, and the TPS indicated a low expression. No differences in PD-L1 expression were observed between the two clones, SP263 and E1L3N. High PD-L1 expression in the EUS-FNA sample was found in only one case (11%). DISCUSSION: Although assessment using the tumor cells of PASC samples obtained from EUS-FNA was difficult, this study suggests the selective expression of PD-L1 in the SCc of PASC. Furthermore, it was considered that immune checkpoint inhibitors could provide therapeutic effects selectively on the SCc for the entire range of TPSs, though the PD-L1 expression was low.

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

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

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

Invasive pancreatic ductal adenocarcinoma (PDAC) can infiltrate back into and spread along preexisting pancreatic ducts and ductules in a process known as cancerization of ducts (COD). Histologically COD can mimic high-grade pancreatic intraepithelial neoplasia (HG-PanIN). We reviewed pancreatic resections from 100 patients with PDAC for the presence or absence of ducts with histologic features of COD. Features supporting COD included adjacent histologically similar invasive PDAC and an abrupt transition between

markedly atypical intraductal epithelium and normal duct epithelium or circumferential involvement of a duct. As the TP53 and SMAD4 genes are frequently targeted in invasive PDAC but not HG-PanIN, paired PDAC and histologically suspected COD lesions were immunolabeled with antibodies to the p53 and Smad4 proteins. Suspected COD was identified on hematoxylin and eosin sections in 89 (89%) of the cases. Immunolabeling for p53 and Smad4 was performed in 68 (76%) of 89 cases. p53 was interpretable in 55 cases and all 55 (100%) cases showed concordant labeling between COD and invasive PDAC. There was matched aberrant p53 immunolabeling in 37 (67%) cases including overexpression in 30 (55%) cases and lack of expression in 7 (13%) cases. Smad4 immunolabeling was interpretable in 61 cases and 59 (97%) cases showed concordant labeling between COD and invasive PDAC. Matched loss of Smad4 was seen in 28 (46%) cases. The immunolabeling of invasive PDAC and COD for p53 and Smad4 supports the high prevalence of COD observed on hematoxylin and eosin and highlights the utility of p53 and Smad4 immunolabeling in differentiating COD and HG-PanIN.

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

Advances in anatomic pathology 2019 Jan;26(1):31-39

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

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

- Tenascin C, Fibronectin, and Tumor-Stroma Ratio in Pancreatic Ductal Adenocarcinoma

Pancreas 2019 Jan;48(1):43-48

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30451798

OBJECTIVES: Pancreatic ductal adenocarcinoma (PDAC) is characterized by abundant stroma with increased expression of tenascin C and fibronectin. Their role and tumor-stroma ratio in PDAC are not well known. The aim of this study was to evaluate tenascin C and fibronectin expression and tumor-stroma ratio and their prognostic relevance in PDAC. METHODS: Ninety-five resected PDACs were immunohistochemically stained for tenascin C and fibronectin, and the expression was separately assessed in tumor bulk and front. Tumor-stroma ratio was determined with sections stained with hematoxylin-eosin. RESULTS: Tenascin C and fibronectin were abundantly expressed in the stroma of PDAC, but absent in adjacent normal pancreatic tissue. Fibronectin expression of the bulk was associated with high T class ($P = 0.045$). In the main analysis, tenascin C and fibronectin expression and tumor-stroma ratio were not associated with patient survival. In a subgroup analysis of early-stage PDAC (T1-T2 tumors), high tenascin C expression in the tumor bulk was associated with poor prognosis (hazard ratio, 8.23; 95% confidence interval, 2.71-24.96).

CONCLUSIONS: Tenascin C and fibronectin are abundantly expressed in PDAC, but they seem to have no major association with patient survival. However, in early-stage PDAC, tenascin C expression of the tumor bulk may have prognostic impact. Tumor-stroma ratio has no prognostic value in PDAC.

Back to top

Staging

Pancreas TNM staging, Margins, Survival

- International Validation of the Eighth Edition of the American Joint Committee on Cancer (AJCC) TNM Staging System in Patients With Resected Pancreatic Cancer

JAMA surgery 2018 Dec;153(12):e183617

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30285076

Importance: The recently released eighth edition of the American Joint Committee on Cancer TNM staging system for pancreatic cancer seeks to improve prognostic accuracy but lacks international validation. Objective: To validate the eighth edition of the American Joint Committee on Cancer TNM staging system in an international cohort of patients with resected pancreatic ductal adenocarcinoma. Design, Setting, and Participants: This international multicenter cohort study took place in 5 tertiary centers in Europe and the United States from 2000 to 2015. Patients who underwent pancreatoduodenectomy for nonmetastatic pancreatic ductal adenocarcinoma were eligible. Data analysis took place from December 2017 to April 2018. Exposures: Patients were retrospectively staged according to the seventh and eighth editions of the TNM staging system. Main Outcomes and Measures: Prognostic accuracy on survival rates, assessed by Kaplan-Meier and multivariate Cox proportional hazards analyses and concordance statistics. Results: A total of 1525 consecutive patients were included (median [IQR] age, 66 (58-72) years; 802 (52.6%) male). Distribution among stages via the seventh edition was stage IA in 41 patients (2.7%), stage IB in 42 (2.8%), stage IIA in 200 (13.1%), stage IIB in 1229 (80.6%), and stage III in 12 (0.8%); this changed with use of the eighth edition to stage IA in 118 patients (7.7%), stage IB in 144 (9.4%), stage IIA in 22 (1.4%), stage IIB in 643 (42.2%), and stage III in 598 (39.2%). With the eighth edition, 774 patients (50.8%) migrated to a different stage; 183 (12.0%) were reclassified to a lower stage and 591 (38.8%) to a higher stage. Median overall survival for the entire cohort was 24.4 months (95% CI, 23.4-26.2 months). On Kaplan-Meier analysis, 5-year survival rates changed from 38.2% for patients in stage IA, 34.7% in IB, 35.3% in IIA, 16.5% in IIB, and 0% in stage III (log-rank $P < .001$) via classification with the seventh edition to 39.2% for patients in stage IA, 33.9% in IB, 27.6% in IIA, 21.0% in IIB, and 10.8% in stage III (log-rank $P < .001$) with the eighth edition. For patients who were node negative, the T stage was not associated with prognostication of survival in either edition. In the eighth edition, the N stage was associated with 5-year survival rates of 35.6% in N0, 20.8% in N1, and 10.9% in N2 (log-rank $P < .001$). The C statistic improved from 0.55 (95% CI, 0.53-0.57) for the seventh edition to 0.57 (95% CI, 0.55-0.60) for the eighth edition. Conclusions and Relevance: The eighth edition of the TNM staging system demonstrated a more equal distribution among stages and a modestly increased prognostic accuracy in patients with resected pancreatic ductal adenocarcinoma compared with the seventh edition. The revised T stage remains poorly associated with survival, whereas the revised N stage is highly prognostic.

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

Journal of Cancer 2018 09;9(19):3507-3514

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30310507

Background: Nodal status and tumor site are prognostic factors for resectable pancreatic ductal adenocarcinoma (PDAC). Parameters for nodal status are diverse, and the number of examined lymph nodes (eNs) needed for good prognosis are uncertain. We try to modify staging system of resectable PDAC with parameters mentioned above by recursive partitioning analysis. Methods: Patients from the Surveillance, Epidemiology, and End Results (SEER) database were divided into training cohort and internal validation cohort, randomly. PDAC patients from Sun Yat-sen University Cancer Center were regarded as external validation cohort. The training cohort was used to refine staging model by recursive partitioning analysis, while the internal validation cohort and the external validation cohort were applied to assess discriminatory

capacity of staging model. For parameters included in the modified model, their effects were studied. Results: The number of eNs, tumor site and tumor size were risk factors for positive nodal status. Lymph nodes ratio (LNR), tumor site, eNs and T stages of 8th the American Joint Committee on Cancer (AJCC) were selected to develop a refined model, dividing patients into 5 groups of different outcomes, preceding 8th AJCC classification. Besides, we found that (1) for small PDAC (diameter < 1cm), lymph node metastasis was rarely found; (2) enough eNs were needed to ensure better prognosis of node-negative patients; (3) tumors in the head of pancreas were prone to lymph nodes metastasis; (4) for node-positive patients, LNR was a better nodal parameter compared to positive lymph nodes (pNs). Conclusion: Our improved staging system helps to illuminate the interactions among tumor site, size and eNs.

- Evaluation of the prognostic value of the new AJCC 8th edition staging system for patients with pancreatic adenocarcinoma; a need to subclassify stage III?

European journal of cancer (Oxford, England : 1990) 2018 Nov;104():62-69

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30326370

BACKGROUND: There have been several proposed changes for the 8th edition of the American Joint Commission on Cancer (AJCC) for pancreatic adenocarcinoma. The aim of this study was to evaluate the prognostic value of the new staging system for patients with pancreatic adenocarcinoma, especially in stage III patients. METHODS: We analysed the data of patients newly diagnosed with pancreatic adenocarcinoma between 2008 and 2016 at our hospital. Patients were staged according to 7th edition AJCC criteria, as well as the new 8th edition staging system. The pathologic stage was used in the surgical cases, and the clinical stage, determined by radiographic findings, was used in the unresectable cases. RESULTS: Five hundred two patients were identified who met the inclusion criteria. In node-negative patients, there were no significant differences in survival among T 1, 2 and 3 groups according to the 8th edition. The survival rates of patients with N1 (1-3 positive nodes) and N2 (4 positive nodes) disease, according to 8th edition, were significantly different ($p < 0.001$). Although N2 and T4 patients are both stage III according to the new staging system, N2 patients had a better survival rate than T4 patients ($p = 0.038$). The new staging system stratifies patients more evenly across stages without sacrificing the prognostic accuracy. CONCLUSIONS: The AJCC 8th edition has some advantages over the previous version. However, patients with N2 and T4, who have been integrated into stage III, showed different treatment modalities and prognoses, and we proposed dividing stage III into IIIA (T1-3N2M0) and IIIB (T4NanyM0).

- Intra-Operative Frozen Section Histology of the Pancreatic Resection Margins and Clinical Outcome of Patients with Adenocarcinoma of the Head of the Pancreas Undergoing Pancreaticoduodenectomy

Medical science monitor : international medical journal of experimental and clinical research 2018 Jul;24():4905-4913

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30007990

BACKGROUND The aim of this study was to compare the clinical outcome in patients with pancreatic ductal adenocarcinoma who underwent frozen section and paraffin section histology of the surgical resection margins during pancreaticoduodenectomy. MATERIAL AND METHODS Frozen section and routine paraffin section histopathology were performed using the following categories: R0 (no tumor cells at the surgical resection margin), R1 (tumor cells at, or within 1 mm, of the surgical resection margin), and R2 (tumor seen macroscopically at the surgical resection margin). R1 and R2 patients underwent additional resection to achieve R0. RESULTS Of 346 patients who underwent pancreaticoduodenectomy, frozen section histology showed positive resection margins in 22 patients (9.2%) and paraffin section histology was positive in 20 patients (8.4%). The OS was nine months in frozen section-positive patients and 20 months in frozen section-negative patients (p=0.001). The OS rates were significantly different between the paraffin section-positive and paraffin section-negative patients (11 months vs. 21 months) (p=0.001). Univariate and multivariate analysis showed that increased tumor size, high tumor grade, lymph node metastases, a

positive superior mesenteric artery and retroperitoneal margin, and a positive resection margin on frozen section were significantly correlated with reduced OS ($p<0.05$). Twenty-two patients with positive resection margins on frozen section histology underwent further resection; R0 was achieved in 14 patients, with no significant difference in OS. CONCLUSIONS For patients who underwent pancreaticoduodenectomy for pancreatic carcinoma with positive resection margins on frozen section, further surgical resection to achieve R0 had no significant positive impact on OS.

- Nomogram to Predict Cancer-Specific Survival in Patients with Pancreatic Acinar Cell Carcinoma: A Competing Risk Analysis

Journal of Cancer 2018 10;9(22):4117-4127

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30519311

Background: The objective of this study was to evaluate the probability of cancer-specific death of patients with acinar cell carcinoma (ACC) and build nomograms to predict overall survival (OS) and cancer-specific survival (CSS) of these patients. Methods: Data were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Patients diagnosed with ACC between 2004 and 2014 were retrospectively collected. Cancer-specific mortality and competing risk mortality were evaluated. Nomograms for estimating 1-, 2- and 3-year OS and CSS were established based on Cox regression model and Fine and Grey's model. The precision of the 1-, 2- and 3-year survival of the nomograms was evaluated and compared using the area under receiver operating characteristic (ROC) curve (AUC). Results: The study cohort included 227 patients with ACC. The established nomograms were well calibrated, and had good discriminative ability, with a concordance index (C-index) of 0.742 for OS prediction and 0.766 for CSS prediction. The nomograms displayed better discrimination power than 7th or 8th edition Tumor-Node-Metastasis (TNM) stage systems in training set and validation set for predicting both OS and CSS. The AUC values of the nomogram predicting 1-, 2-, and 3-year OS rates were 0.784, 0.797 and 0.805, respectively, which were higher than those of 7th or 8th edition TNM stage systems. Regard to the prediction of CSS rates, the AUC values of the nomogram were also higher than those of 7th or 8th edition TNM stage systems. Conclusion: We evaluated the 1-, 2- and 3-year OS and CSS in patients with ACC for the first time. Our nomograms showed relatively good performance and could be considered as convenient individualized predictive tools for prognosis.

- Pancreatic cancer and autoimmune diseases: An association sustained by computational and epidemiological case-control approaches

International journal of cancer 2018 Sep;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30229903

Deciphering the underlying genetic basis behind pancreatic cancer (PC) and its associated multimorbidities will enhance our knowledge toward PC control. The study investigated the common genetic background of PC and different morbidities through a computational approach and further evaluated the less explored association between PC and autoimmune diseases (AIDs) through an epidemiological analysis. Gene-disease associations (GDAs) of 26 morbidities of interest and PC were obtained using the DisGeNET public discovery platform. The association between AIDs and PC pointed by the computational analysis was confirmed through multivariable logistic regression models in the PanGen European case-control study population of 1,705 PC cases and 1,084 controls. Fifteen morbidities shared at least one gene with PC in the DisGeNET database. Based on common genes, several AIDs were genetically associated with PC pointing to a potential link between them. An epidemiologic analysis confirmed that having any of the nine AIDs studied was significantly associated with a reduced risk of PC (Odds Ratio (OR) = 0.74, 95% confidence interval (CI) 0.58-0.93) which decreased in subjects having 2 AIDs (OR = 0.39, 95%CI 0.21-0.73). In independent analyses, polymyalgia rheumatica, and rheumatoid arthritis were significantly associated with low PC risk (OR = 0.40, 95%CI 0.19-0.89, and OR = 0.73, 95%CI 0.53-1.00, respectively). Several inflammatory-related morbidities shared a common genetic component with PC based on public databases. These molecular links could shed light into the molecular mechanisms underlying PC development and simultaneously generate

novel hypotheses. In our study, we report sound findings pointing to an association between AIDs and a reduced risk of PC.

- Impact of tumor size on survival of patients with resected pancreatic ductal adenocarcinoma: a systematic review and meta-analysis

BMC cancer 2018 Oct;18(1):985

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30326871

BACKGROUND: The impact of tumor size on prognosis for surgically treated patients with pancreatic ductal adenocarcinoma (PDAC) remains controversial. A systematic review and meta-analysis was performed to evaluate this issue. METHODS: Relevant studies published from January 2000 to June 2017 were identified through EMBASE and PUBMED. Data were pooled for meta-analysis using Review Manager 5.3. RESULTS: Twenty eight observational studies involving a total of 23,945 patients were included. Tumors >2 cm was associated with poor prognosis: the pooled hazard ratio (HR) estimate for overall survival was 1.52 (95% confidence interval [CI]: 1.41-1.64; $P < 0.0001$) by univariate analysis and 1.61 (95% CI: 1.35-1.91; $P < 0.0001$) by multivariate analysis; the pooled HR estimate for disease-free survival was 1.74 (95% CI: 1.46-2.07; $P < 0.0001$) by univariate analysis and 1.38 (95% CI: 1.12-1.68; $P = 0.002$) by multivariate analysis. When compared with patients with tumors 2 cm, those with the tumors >2 cm had higher incidences of lymph node metastasis, poor tumor differentiation, lymph vessel invasion, vascular invasion, perineural invasion, and positive intraoperative peritoneal cytology. CONCLUSION: These data demonstrate that PDAC size >2 cm is an independent predictive factor for poor prognosis after surgical resection and associated with more aggressive tumor biology.

- The New American Joint Committee on Cancer TNM Staging System for Pancreatic Cancer-Balancing Usefulness With Prognostication

JAMA surgery 2018 Dec;153(12):e183629

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30285059

- Role of adjuvant therapy in resected stage IA subcentimeter (T1a/T1b) pancreatic cancer

Cancer 2019 Jan;125(1):57-67

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30457666

BACKGROUND: The standard of care for patients with resected stage I to stage III pancreatic ductal adenocarcinoma (PDAC) is adjuvant gemcitabine-based chemotherapy. The role of adjuvant treatment in patients with subcentimeter, stage IA PDAC is unknown. The current study evaluated the effect of adjuvant treatment on survival outcomes among patients with American Joint Committee on Cancer/International Union Against Cancer stage IA (T1N0) resected PDAC using the National Cancer Data Base (NCDB). METHODS: A retrospective review of the NCDB was conducted for patients diagnosed with T1 (tumor limited to the pancreas and measuring 2 cm in greatest dimension), lymph node-negative (N0), resected PDAC between 2004 and 2013. Patient demographics, histology, adjuvant treatment, and survival trends were examined. Kaplan-Meier analysis and log-rank tests were performed to determine the unadjusted association between overall survival (OS), tumor size, and treatment. RESULTS: A total of 876 patients met the inclusion criteria. The patients had a mean age of 66.2 years (range, 32-90 years); approximately 83.3% were white (730 patients) and 53.1% were female (465 patients). Approximately 45.9% of the patients had moderately differentiated tumor histology (402 patients); 70.0% (613 patients) had tumors measuring 1 to 2 cm (T1c) and 30.0% (263 patients) had tumors measuring <1 cm (T1a/T1b). Approximately 94.2% of patients had negative surgical margins (815 patients) and 46.9% (410 patients) received adjuvant therapy. The median OS was significantly different for patients who received adjuvant therapy compared with patients who did not (70.7 months vs 46.9 months; $P = .0001$). For patients with tumors measuring <1 cm, survival

was not found to be significantly different between patients who received adjuvant treatment compared with those who did not (not reached vs 85.3 months; P = .54). In the multivariable analysis, none of the covariates (treatment group, Charlson-Deyo Score, age, insurance, and facility status) demonstrated significant differences for patients with tumors measuring <1 cm. CONCLUSIONS: The current study is the first to demonstrate no survival benefit for adjuvant therapy in patients with resected subcentimeter PDAC.

- Reappraising the Concept of Conditional Survival After Pancreatectomy for Ductal Adenocarcinoma: A Bi-institutional Analysis

Annals of surgery 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30339622

OBJECTIVE: To reappraise the concept of conditional survival (CS) following pancreatectomy for pancreatic ductal adenocarcinoma (PDAC), accounting for the patient's present disease status relative to recurrence. BACKGROUND: CS, defined as the probability of surviving an additional time frame based on accrued lifespan, offers dynamic survival projections as compared with baseline overall survival. METHODS: Patients undergoing pancreatectomy for PDAC at 2 institutions from 2000 to 2013 were retrospectively analyzed. The 12-month CS was estimated separately for patients who were disease-free or with recurrence at the given time points. Next, the conditional probability of reaching 60-months of survival was examined in each conditioning set across strata of prognostic covariates, including American Joint Committee on Cancer stage, tumor grade, R-status, and adjuvant treatment. RESULTS: The study population consisted of 1005 patients. In disease-free patients, the 12-month CS increased as a function of time already survived, showing an opposite trend compared with overall survival. In patients who recurred, the 12-month CS was lower than the disease-free counterpart, especially within 24 months postoperatively. When stratifying by the levels of prognostic covariates, the 60-months CS estimates for disease-free patients tended to level off progressively, indicating that factors independently associated with survival at the time of pancreatectomy lost power over time. This concept did not apply to the conditioning set of patients with recurrence, where CS estimates across variables strata diverged with accrued lifespan. CONCLUSION: This paper provides new information on how prognosis following pancreatectomy for PDAC evolves over time, adjusting for the time the patient already survived, and for the patient's present disease status relative to recurrence.

- Association Between Very Small Tumor Size and Decreased Overall Survival in Node-Positive Pancreatic Cancer

Annals of surgical oncology 2018 Dec;25(13):4027-4034

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30298331

BACKGROUND: In pancreatic adenocarcinoma (PDAC), increasing tumor size usually correlates with a worse prognosis. However, patients with a very small primary tumor who experience lymph node involvement may have a different disease biology. This study sought to determine the interaction between tumor size and lymph node involvement in terms of overall survival (OS). METHODS: The study identified 17,073 patients with a diagnosis of M0 resected PDAC between 1983 and 2013 using the Surveillance, Epidemiology, and End Results database. The patients were stratified by lymph node involvement (N0 vs N+) and T stage (T1a-T1b vs T1c vs T2 vs T3 vs T4). The Kaplan-Meier method was used to estimate OS, and Cox regression analysis was used to compare survival between subgroups after adjustment for patient-specific factors. RESULTS: Lymph node involvement and T stage significantly interacted ($p < 0.001$). Among the patients with node-negative disease, 5-year OS decreased monotonically with increasing T stage (59.1%, 30.6%, 22.9%, 16.6%, and 8.0%, respectively; $p < 0.001$). In contrast, among the patients with node-positive disease, those with T1a-T1b tumors (< 10 mm) had worse 5-year OS than those with T1c tumors (7.4% vs 17.6%; adjusted hazard ratio, 0.70; 95% confidence interval, 0.50-0.97; $p = 0.034$) and similar survival compared with those who had T2, T3, or T4 tumors (9.7%, 8.2%, and 4.8%, respectively; $p > 0.2$ in all cases). CONCLUSIONS: Among patients with lymph node-positive PDAC, very small primary tumors are associated with decreased

OS. This finding raises the possibility that small tumors capable of lymph node metastasis might represent more biologically aggressive cancers.

- Stratified survival of resected and overall pancreatic cancer patients in Europe and the USA in the early twenty-first century: a large, international population-based study

BMC medicine 2018 08;16(1):125

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30126408

BACKGROUND: The prognosis of pancreatic cancer (PaC) strongly varies across different stages and age groups, which has unfortunately not been well recorded in the literature. This international population-based study aimed to provide tumor-node-metastasis (TNM) stage- and age-specific survival estimates and trends in resected and overall (resected and unresected) PaC in the early twenty-first century. METHODS: Using data from the US Surveillance, Epidemiology, and End Results-18 Program and the national cancer registries of the Netherlands, Belgium, Norway, and Slovenia, short-term and long-term overall survival results stratified by TNM stage and age in resected and overall primary PaC, irrespective of being microscopically confirmed or not, in 2003-2014 were computed using the Kaplan-Meier method. The temporal survival trends over three predefined periods (2003-2005, 2006-2008, and 2009-2011) were further examined using the log-rank test. RESULTS: In total, data for 125,183 patients were analyzed. Overall, age-stratified 3-year survival was 20-34% (< 60 years), 14-25% (60-69 years), and 9-13% (70 years) in stages I-II PaC; and 2-5% (< 60 years), 1-2% (60-69 years), and < 1-1% (70 years) in stages III-IV cancer. Patients who underwent operation had higher 3-year survival in each stage and age group (stages I-II: 23-39% (< 60 years), 16-31% (60-69 years), and 17-30% (70 years); stages III-IV: 5-19% (< 70 years) and 2-14% (70 years)). Perioperative survival also decreased with advancing stage and older age (stages I-II: 98-100% (< 60 years), 97-99% (60-69 years), and 94-99% (70 years); stages III-IV: 94-99% (< 70 years) and 81-96% (70 years)). Between 2003 and 2005 and 2009-2011, for overall PaC, both short-term and long-term survival improvements were observed in all countries except Belgium; for resected disease, short-term improvements were present only in the USA and Slovenia, but long-term improvements were observed in all countries except Slovenia, with stage-specific variations. CONCLUSIONS: Our large international study provides TNM stage- and age-specific population-based survival in overall and resected PaC that will facilitate clinical counseling. While the survival expectations for patients with resected PaC are substantially higher than the widely available and known dismal survival predictions for overall patients, conclusions on the benefits of resection cannot be made from this observational study. Patients with advanced-stage disease and/or older age should undergo careful risk assessment before treatment. Limited but inspiring improvement in survival is observed.

Back to top

Preneoplastic and Preinvasive Lesions

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

- Toll-like receptors 2, 4 and 9 and hypoxia markers HIF-1alpha and CAIX in pancreatic intraepithelial neoplasia

APMIS : acta pathologica, microbiologica, et immunologica Scandinavica 2018 Nov;126(11):852-863

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30357962

Pancreatic cancer arises from precursor lesions called pancreatic intraepithelial neoplasia (PanIN) characterized by inflammatory microenvironment. In pancreatic cancer, strong innate immunity and hypoxia responses are typical. Occurrence and relationship of these responses in human PanINs is unknown. We have studied the expression of toll-like receptors (TLR) TLR2, TLR4 and TLR9, and hypoxia markers HIF-1alpha and Carbonic anhydrase IX (CAIX) in normal and inflamed pancreatic ducts, in PanINs and in cancers. The samples of 69 surgically resected pancreatic ductal adenocarcinoma patients were stained using immunohistochemistry. We found TLR2, TLR9, HIF-1alpha and CAIX to be prominently expressed in pancreatic intraepithelial neoplasia. Expression of TLR2 showed a linear increase from PanIN1 to PanIN3, while the highest TLR4 expression was detected in inflamed ducts, and TLR9 expression in PanIN1 lesions. Within the PanIN1-group, nuclear HIF-1alpha correlated with membranous and cytoplasmic TLR2 expression (= 0.982 and 0.815; $p < 0.001$ and $p = 0.025$, respectively), and in the PanIN2-group nuclear HIF-1alpha correlated with nuclear TLR9 expression 0.636, $p = 0.026$). Our findings show that the expression of TLRs 2, 4 and 9, and hypoxia markers HIF-1alpha and CAIX is abnormal in pancreatic intraepithelial neoplasia suggesting that both the innate immunity activation and hypoxia response are involved in early pancreatic carcinogenesis. However, these processes might be independent.

- Pathways of Progression From Intraductal Papillary Mucinous Neoplasm to Pancreatic Ductal Adenocarcinoma Based on Molecular Features

Gastroenterology 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30342036

BACKGROUND & AIMS: Intraductal papillary mucinous neoplasms (IPMNs) are regarded as precursors of pancreatic ductal adenocarcinomas (PDAs), but little is known about mechanism of progression. This makes it a challenge to assess cancer risk in patients with IPMNs. We investigated associations of IPMNs with concurrent PDAs by genetic and histologic analyses. METHODS: We obtained 30 pancreatic tissues with concurrent PDAs and IPMNs; 168 lesions, including incipient foci, were mapped, microdissected, and analyzed for mutations in 18 pancreatic cancer-associated genes and expression of tumor suppressors. RESULTS: We determined the clonal relatedness of lesions, based on driver mutations shared by PDAs and concurrent IPMNs, and classified the lesions into 3 subtypes. Twelve PDAs contained driver mutations shared by all concurrent IPMNs, which we called the sequential subtype. This subset was characterized by less diversity in incipient foci with frequent GNAS mutations. Eleven PDAs contained some driver mutations that were shared with concurrent IPMNs, which we called the branch-off subtype. In this subtype, PDAs and IPMNs had identical KRAS mutations but different GNAS mutations, although the lesions were adjacent. Whole-exome sequencing and methylation analysis of these lesions indicated clonal origin with later divergence. Ten PDAs had driver mutations not found in concurrent IPMNs, called the de novo subtype. Expression profiles of TP53 and SMAD4 increased our ability to differentiate these subtypes compared with sequencing data alone. The branch-off and de novo subtypes had substantial heterogeneity among early clones, such as differences in KRAS mutations. Patients with PDAs of the branch-off subtype had a longer times of disease-free survival than patients with PDAs of the de novo or the sequential subtypes. CONCLUSIONS: Detailed histologic and genetic analysis of PDAs and concurrent IPMNs identified 3 different pathways by which IPMNs progress to PDAs-we call these the sequential, branch-off, and de novo subtypes. Subtypes

might associate with clinical and pathology features and be used to select surveillance programs for patients with IPMNs.

- Increased SOX9 Expression in Premalignant and Malignant Pancreatic Neoplasms

Annals of surgical oncology 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30357576

BACKGROUND: SOX9, a progenitor cell marker, is important for pancreatic ductal development. Our goal was to examine SOX9 expression differences in intraductal papillary mucinous neoplasms (IPMNs) and ductal adenocarcinoma (PDAC) compared with benign pancreatic duct (BP). METHODS: SOX9 expression was evaluated by immunohistochemistry performed on 93 specimens: 37 BP, 24 low grade (LG) IPMN, 12 high grade (HG) IPMN, and 20 PDAC. A linear mixed-effects model was used to compare the percentage of cells expressing SOX9 by specimen type. A separate linear mixed-effects model evaluated differences in SOX9 expression by staining intensity in pancreatic epithelial cells. RESULTS: Nuclear SOX9 expression was detected in the epithelial cells of 98% HG IPMN, 93% LG IPMN, 83% PDAC, and 60% BP. Compared with BP, SOX9 was expressed from a significantly greater percentage of cells in LG IMPN, HG IMPN, and PDAC ($p < 0.001$ for each). BP and PDAC showed greater variability in SOX9 expression in epithelial cells compared with IPMNs which showed strong, homogenous SOX9 expression in almost all cells. Compared with BP, both LG and HG IPMN showed significantly greater SOX9 expression ($p < 0.001$ for each), but there was no significant difference in SOX9 expression between LG and HG IPMN ($p > 0.05$). PDAC had significantly higher expression of SOX9 compared with BP but significantly lower SOX9 expression compared with LG or HG IPMN ($p < 0.001$ for each). CONCLUSIONS: IPMNs demonstrated the highest expression levels of SOX9. SOX9 expression in BP and PDAC demonstrated much more heterogeneity compared with the strong, uniform expression in IPMN.

- Adjuvant chemotherapy is associated with improved postoperative survival in specific subtypes of invasive intraductal papillary mucinous neoplasms (IPMN) of the pancreas: it is time for randomized controlled data

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30366881

BACKGROUND: Very little is known about adjuvant chemotherapy for invasive Intraductal Papillary Mucinous Neoplasms (IPMNs) of the pancreas. The aim was to assess whether adjuvant chemotherapy affects survival. METHODS: Retrospective evaluation of invasive IPMNs. Patients treated with surgery alone or followed by adjuvant chemotherapy were compared in terms of survival. RESULTS: A total of 102 invasive IPMNs were analyzed. Median follow-up was 72 (5-318) months and 18.6% received adjuvant chemotherapy. Overall, recurrence rate was 40.2%, while 5-year overall survival and disease specific survival (DSS) were 65.3% and 69.4%, respectively. N1 disease (HR5.58, CI95% 2.49-12.51, $p < 0.01$), tubular type (HR2.35, CI95% 1.71-4.82, $p = 0.05$) and G3 tumors (HR4.54, CI95% 2.12-15.49, <0.01) were predictors of reduced DSS. Overall, there was no difference in the 5-year DSS comparing patients treated with adjuvant chemotherapy to surgery alone (61.8 vs. 69.4%, $p = 0.8$). Adjuvant chemotherapy significantly improved DSS only in N1 (5-years-DSS 76 vs. 35.8%, $p = 0.01$) and tubular carcinomas (5-years-DSS 88.9 vs. 53%, $p = 0.03$). CONCLUSIONS: Adjuvant therapy improves survival only in invasive IPMNs with nodal disease or tubular differentiation. Future trials are needed to improve the level of evidence about adjuvant chemotherapy.

- High-grade Dysplasia in Resected Main-duct Intraductal Papillary Mucinous Neoplasm (MD-IPMN) is Associated with an Increased Risk of Subsequent Pancreatic Cancer

The American journal of gastroenterology 2018 Nov;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30413822

BACKGROUND: There is lack of consensus on post-operative surveillance for resected non-invasive intraductal papillary neoplasms (IPMNs). In this study we explored risk factors for subsequent PC in patients with MD-IPMN undergoing partial pancreatectomy. METHODS: We searched the Mayo Clinic surgical pathology database for all cases of resected MD-IPMN between 1997 and 2014. Cases with histologically confirmed main pancreatic duct involvement either isolated or in a mixed pattern with branch-duct involvement were included. Outcomes of PC in the remnant pancreas, and death related to MD-IPMN were assessed with survival analyses (Kaplan-Meier and Cox regression). RESULTS: Among the 179 patients with resected MD-IPMN the incidence of concomitant PC and high-grade dysplasia (HGD) in the resected specimen was 23 and 14%, respectively. The mean duration of follow-up was 4.31 years (range 0.12-13.5 years). Excluding 28 subjects who either underwent initial total pancreatectomy or partial pancreatectomy with surgical margins positive for PC/HGD, the 5-year incidence of subsequent PC was 12%, including 60.6% and15.6% in those with initial PC and HGD, respectively. The 10-year incidence of PC was 21.2% overall, 60.6% for PC, 38.3% for HGD, and 3.0% for LGD. Risk of subsequent PC was significantly higher for those with initial PC compared with HGD (HR = 4.95, 95% CI: 1.63-15.03, p = 0.005 and for HGD compared with LGD (HR = 11.30, 95% CI: 1.55-82.26, p = 0.017). CONCLUSION: Patients with MD-IPMN with PC or HGD undergoing segmental pancreatectomy are at higher risk of subsequent PC and may benefit from post-operative surveillance. The post-operative surveillance intervals in resected MD- IPMNs need to be tailored based on dysplasia grade.

- Cyst location and presence of high grade dysplasia or invasive cancer in intraductal papillary mucinous neoplasms of the pancreas: a seven institution study from the central pancreas consortium

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30361110

BACKGROUND: Traditionally, intraductal papillary mucinous neoplasms (IPMNs) of the pancreas with "high risk stigmata" (HRS) or "worrisome features" (WF) are referred for resection. We aim to assess if IPMN location is predictive of harboring either high grade dysplasia (HGD) or invasive cancer (IC). METHODS: Patients undergoing resection for IPMN from seven institutions between 2000 and 2015 (n = 275) were analyzed. HRS and WF were defined by the 2012 Fukuoka international consensus guidelines. RESULTS: 168 (61%) patients had head/uncinate cysts, while 107 (39%) had neck/body/tail cysts. No differences were noted between groups with regard to age, duct type, cyst size, or presence of at least one WF. Patients with cysts in the head/uncinate were more often male (55% vs. 40%), had at least one HRS (24% vs. 11%), and more often harbored HGD or IC(49% vs. 27%)[all $p < 0.05$]. On multivariate analysis, only cyst location in the head/uncinate remained associated with presence of HGD or IC(odds ratio 4.76, p = 0.02). DISCUSSION: Cyst location is predictive of HGD or IC in patients with IPMNs. Head/uncinated cysts are more likely to harbor malignancy compared to those of the neck/body/tail. Additional studies are needed to confirm these findings, however, cyst location should be considered part of the decision making process for surveillance vs. resection for IPMNs.

- Concomitant Intraductal Papillary Mucinous Neoplasm in Pancreatic Ductal Adenocarcinoma Is an Independent Predictive Factor for the Occurrence of New Cancer in the Remnant Pancreas

Annals of surgery 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30308608

OBJECTIVE: To determine the factors predicting the subsequent development of pancreatic ductal adenocarcinoma in remnant pancreas (PDAC-RP) after partial pancreatectomy for PDAC. SUMMARY BACKGROUND DATA: PDAC-RP after partial pancreatectomy for PDAC is currently not so rare because of improved prognosis of PDAC patients due to recent advances in surgical techniques and adjuvant therapy. However, the predictive factors related to PDAC-RP remain unknown. METHODS: We retrospectively

reviewed the clinicopathological data of a consecutive series of 379 patients with PDAC treated by partial pancreatectomy between 1992 and 2015; 14 patients (3.69%) had PDAC-RP. Clinicopathological variables were compared between PDAC-RP and non-PDAC-RP. RESULTS: In univariate analysis, concomitant intraductal papillary mucinous neoplasm (IPMN) (P = 0.0005), cancer location (body/tail) (P = 0.0060), and lower T factor in UICC (P = 0.0039) were correlated with PDAC-RP development. Multivariate analysis revealed concomitant IPMN (P = 0.0135) to be an independent predictive factor for PDAC-RP. PDAC concomitant with IPMN had higher cumulative incidence of PDAC-RP (47.5%/10 yrs) than PDAC without IPMN (9.96%/10 yrs) (P = 0.0071). Moreover, the density of pancreatic intraepithelial neoplasia lesions in the background pancreas of cases of PDAC concomitant with IPMN (1.86/cm) was higher than that of cases of PDAC without IPMN (0.91/cm) (P = 0.0007). CONCLUSIONS: Concomitant IPMN in PDAC is an independent predictive factor for the development of new PDAC in remnant pancreas. Cancer susceptibility of remnant pancreas after resection for PDAC concomitant with IPMN is probably due to an increased density of pancreatic intraepithelial neoplasia lesions.

Back to top

Pancreatitis & Other Diseases

- Prior History of Pancreatitis Accelerates the Development of Pancreatic Adenocarcinoma

Pancreas 2019 11;47(10):1262-1266

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30286010

OBJECTIVES: Presentation of pancreatic adenocarcinoma (PC) as acute pancreatitis (AP), association of chronic pancreatitis (CP) with PC, and role of inflammation in PC carcinogenesis are well recognized. We hypothesized that inflammatory changes associated with remote history of AP (2 years before PC diagnosis) would result in earlier age of PC diagnosis. METHODS: We evaluated PC patients prospectively enrolled in the Pancreatic Adenocarcinoma Gene Environment Risk (PAGER) study at the University of Pittsburgh for history of pancreatitis and reviewed relevant medical records and imaging studies. Univariate and multivariable linear regression analyses evaluated the relationship between PC and remote history of AP. RESULTS: Among 790 patients with histologically confirmed PC, 114 (14.4%) had a history of pancreatitis (AP within 2 years of PC diagnosis in 69 [8.7%], remote history of AP in 28 [3.5%], CP in 4 [0.5%], and unknown duration of pancreatitis in 13 [1.6%]). After controlling for age, sex, body mass index, smoking, alcohol history, and diabetic status at diagnosis, patients with a remote history of AP were diagnosed on average 4.7 years earlier with PC when compared with PC patients without history of AP ($P < 0.035$). CONCLUSIONS: Remote history of AP may accelerate carcinogenesis in PC.

- Pancreatic Cancer Following Acute Pancreatitis: A Population-based Matched Cohort Study

The American journal of gastroenterology 2018 Nov;113(11):1711-1719

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30315287

BACKGROUND: Acute pancreatitis is linked to pancreatic cancer, but the direction of this association is not fully elaborated. METHODS: This was a population-based cohort study including all Swedish residents diagnosed with a first-time episode of acute pancreatitis between 1997 and 2013 and corresponding matched pancreatitis-free individuals from the general population. Hazard ratios for the association between acute pancreatitis and pancreatic cancer were estimated using multivariable Cox regression models. RESULTS: Overall, 49,749 individuals with acute pancreatitis and 138,750 matched individuals without acute pancreatitis were followed up for 1,192,134 person-years (median 5.3 years). A total of 769 individuals developed pancreatic cancer, of whom 536 (69.7%) had a history of acute pancreatitis. The risk of pancreatic cancer was substantially increased during the first few years after a diagnosis of acute pancreatitis but declined gradually over time, reaching a level comparable to the pancreatitis-free population after >10 years of follow-up. In those with non-gallstone-related acute pancreatitis, the risk of pancreatic cancer declined to a level comparable to the pancreatitis-free population only when follow-up time was censored for a second episode of acute pancreatitis or a diagnosis of chronic pancreatitis. Increasing number of recurrent episodes of acute pancreatitis was associated with increased risk of pancreatic cancer. CONCLUSION: These findings imply a delay in the diagnosis of pre-existing pancreatic cancer, if clinically presented as acute pancreatitis. Any association between non-gallstone-related acute pancreatitis and pancreatic cancer in the long-term (>10 years) could be mediated through recurrent acute pancreatitis or chronic pancreatitis.

- Neonatal Diabetes: Two Cases with Isolated Pancreas Agenesis due to Homozygous PTF1A Enhancer Mutations and One with Developmental Delay, Epilepsy, and Neonatal Diabetes Syndrome due to KCNJ11 Mutation

Journal of clinical research in pediatric endocrinology 2018 06;10(2):168-174

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=28943513

Neonatal diabetes mellitus is a rare form of monogenic diabetes which is diagnosed in the first six months of life. Here we report three patients with neonatal diabetes; two with isolated pancreas agenesis due to mutations in the pancreas-specific transcription factor 1A (PTF1A) enhancer and one with developmental delay, epilepsy, and neonatal diabetes (DEND) syndrome, due to a KCNJ11 mutation. The two cases with mutations in the distal enhancer of PTF1A had a homozygous g.23508363A>G and a homozygous g.23508437A>G mutation respectively. Previous functional analyses showed that these mutations can decrease expression of PTF1A which is involved in pancreas development. Both patients were born small for gestational age to consanguineous parents. Both were treated with insulin and pancreatic enzymes. One of these patients' fathers was also homozygous for the PTF1A mutation, whilst his partner and the parents of the other patient were heterozygous carriers. In the case with DEND sydrome, a previosly reported heterozygous KCNJ11 mutation, p.Cys166Tyr (c.497G>A), was identified. This patient was born to nonconsanguineous parents with normal birth weight. The majority of neonatal diabetes patients with KCNJ11 mutations will respond to sulphonylurea treatment. Therefore Glibenclamide, an oral antidiabetic of the sulphonylurea group, was started. This treatment regimen relatively improved blood glucose levels and neurological symptoms in the short term. Because we could not follow the patient in the long term, we are not able to draw conclusions about the efficacy of the treatment. Although neonatal diabetes mellitus can be diagnosed clinically, genetic analysis is important since it is a guide for the treatment and for prognosis.

- Serum and histological IgG4-negative type 1 autoimmune pancreatitis

Clinical journal of gastroenterology 2018 Nov;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30414073

A 66-year-old man who was on oral medication for type 2 diabetes experienced a rapid decline in glycemic control (increase in glycosylated hemoglobin level from 7.7 to 10.2% over 3 months). Abdominal ultrasonography revealed a 20-mm hypoechoic mass in the pancreatic tail. Serum tumor marker carbohydrate antigen 19-9 and DUPAN2 levels were within the respective normal ranges; serum IgG4 level was also normal at 21.8 mg/dL. Abdominal contrast computed tomography revealed a 26-mm tumor in the pancreatic tail. Magnetic resonance cholangiopancreatography revealed disruption of the main pancreatic duct and dilation of the caudal pancreatic duct. Endoscopic ultrasonography revealed a near-round-shaped hypoechoic mass with interspersed hyperechoic areas. Endoscopic ultrasonography-guided fine needle aspiration was performed using a 22-G needle, but no malignant findings were observed. There were no signs of sialadenitis, retroperitoneal fibrosis, nephropathy, or other conditions associated with IgG4-related diseases. Distal pancreatectomy was performed; a 23-mm white mass was resected from the pancreatic tail. A histopathological examination showed advanced inflammatory cell infiltration mainly involving lymphocytes/plasma cells along with storiform fibrosis and obliterative phlebitis. No more than five IgG4-positive cells were observed per high-power field. These were level 1 pathological findings, and a definitive diagnosis of type 1 autoimmune pancreatitis (AIP) was made according to the International Consensus Diagnostic Criteria. Type 1 AIP associated with normal serum IgG4 levels and absence of IgG4-positive cells on histological examination is a rare clinical entity, which is very difficult to distinguish from pancreatic cancer. Here we report such a case and present a review of the relevant literature.

- The histologic diagnosis of IgG4-related disease on small biopsies: Challenges and pitfalls

Histopathology 2018 Nov;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30408214

INTRODUCTION: The pathologic diagnosis of IgG4-related disease (IgG4-RD) relies on histology, IgG4 positive cells and increased IgG4:IgG. Small biopsies from patients with a presumptive diagnosis of IgG4-RD often fail to meet consensus histologic guidelines. We evaluate consecutive small biopsies from patients with a presumptive diagnosis of IgG4-RD and assess the significance of the pathologic findings. METHODS: We evaluated 55 small biopsies from patients with a presumptive diagnosis of IgG4-RD. The retrospective cohort comprised of 71 patients with IgG4-RD and 57 mimics. We performed immunohistochemistry (IHC) and in

situ hybridization (ISH) for IgG4 and IgG. RESULTS: 26 patients from the prospective cohort met histologic criteria for IgG4-RD (definite); twenty-nine patients lacked one or more pathologic features (borderline). Twenty biopsies (36%) lacked both storiform fibrosis and obliterative phlebitis, nine (16%) lacked increase in IgG4 positive plasma cells. 93% of patients showed IgG4: total IgG of >40% (>30% by ISH). There was no difference in the incidence of multi-organ disease (p=0.9), serum IgG4 (p=0.6) and response to therapy between the definite and borderline groups. A strong correlation (Pearson 0.77) between the IHC and ISH platforms was noted with regard to IgG4:total IgG. CONCLUSION: Patients with a presumptive diagnosis of IgG4-RD but lacking characteristic pathologic features of this disease appear clinically similar to those that meet current pathologic guidelines. An elevated IgG4:total IgG is the most sensitive pathologic feature and ISH provides a robust quantitation platform. We recommend evaluating tumefactive lymphoplasmacytic infiltrates with increased IgG4:IgG, regardless of histological features, for IgG4-RD.

- Autoimmune pancreatitis in children: A single centre experience in diagnosis, management and long term follow up

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30455055

OBJECTIVES: Autoimmune pancreatitis (AIP) is a rare form of chronic pancreatitis and data is limited in the paediatric population. We aim to describe in detail a cohort of paediatric patients with AIP including their presentation, investigations that led to their diagnosis, management and long-term follow up. METHODS: We retrospectively reviewed the data of 6 patients diagnosed with AIP over an 10-year period. Data including demographics, clinical information, laboratory parameters, serological markers, radiological and histological findings as well as longitudinal follow up were collected. RESULTS: Out of the six patients, one was diagnosed with definitive Type 1 AIP, two with definitive Type 2 AIP, two with probable Type 2 AIP and one with suspected Type 2 AIP. Median time of follow up was 3.9 years (range 2.6-10.1). 4 patients had pancreatic biopsies with 2 of these patients showing granulocytic epithelial lesions (GELs). 4 patients received steroids and two of them developed ulcerative colitis. Azathioprine was commenced on the patient with Type 1 AIP to help her wean off steroids that caused significant side effects on her. Only two patients developed exocrine insufficiency. CONCLUSIONS: The long term follow up of our cohort of paediatric AIP shows good prognosis. More follow up data on patients with AIP is needed to help further characterize and define the disease.

Back to top

Epidemiology, Screening, Cancer Risk Factors

- Prevalence of Asymptomatic Intraductal Papillary Mucinous Neoplasms in Healthy and Ill Populations Detected by Ultrasonography: A Single-Center Study of 6353 Outpatients

Pancreas 2019 Jan;48(1):113-120

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30451793

OBJECTIVES: The aim of this study was to establish the prevalence of intraductal papillary mucinous neoplasms (IPMNs) without and with high-risk stigmata (HRS)/worrisome features (WF) and the epidemiologic association between IPMNs and other diseases. METHODS: Ultrasound examinations of outpatients were evaluated. The IPMN was confirmed by magnetic resonance imaging. The prevalence of IPMNs and HRS/WF IPMNs was calculated. The association between IPMNs and other diseases was studied. RESULTS: The prevalence rate of IPMNs was 3.4%. A total of 1,531,264 IPMNs were expected in Italian population (2.5%), whereas 2257 per 100,000 citizens (2.3%) were expected in the European standard population (ESP2013). The prevalence rates of HRS/WF IPMNs were 0.5%, 0.7%, and 0.6%, in our, the Italian, and the ESP2013 populations, respectively. A total of 432,881 and 620 HRS/WF IPMNs per 100,000 residents were expected in the Italian and the ESP2013 populations, respectively. The IPMN prevalence increased over 50 years of age (odds ratio [OR], 3.2; $P < 0.001$) and over 70 years of age (OR, 1.9; $P < 0.001$). Female sex was related to the presence of IPMNs (OR, 1.9; $P < 0.001$). CONCLUSIONS: Intraductal papillary mucinous neoplasms had a high prevalence in asymptomatic nonhospitalized populations. Age older than 50 years identified a possible risk category.

Back to top

Bile Ducts

- Prognostic role of BAP-1 and PBRM-1 expression in intrahepatic cholangiocarcinoma

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30377796

Intrahepatic cholangiocarcinoma (ICC) has universally poor outcome, mainly due to its late clinical presentation. Identification of specific biomarkers and development of effective treatment are still urgently required. Mutations in PBRM-1 and BAP-1 genes, and the expression of S100P have been related to survival in ICC. miR-31 seems also to play important regulatory functions in ICC and it directly regulates BAP-1 expression in lung cancer. In this study, tissue expression of BAP-1, PBRM-1, S100P, and miR-31 was investigated in ICC and correlated with clinical-pathological features. Sixty-one consecutive patients who underwent curative hepatic resection for ICC were enrolled. None received any therapy prior to surgery. Immunostaining for BAP-1, PBRM-1, and S100P, and in situ hybridization for miR-31 were performed, using tissue microarray slides. A strong retained expression of BAP-1 and PBRM-1 was associated with a reduced overall ($p = 0.04$ and $p = 0.002$, respectively) and disease-free survival ($p = 0.05$ and $p = 0.02$, respectively). An overexpression of S100P was related to a reduced overall survival ($p = 0.005$). The multivariate analyses identified the presence of perineural invasion and the retained PBRM-1 expression as independent predictors of worse overall [$p = 0.02$, hazard ratio (HR) $= 2.25$ (1.16-4.39) and $p = 0.001$, HR $= 3.13$ (1.56-6.28), respectively] and disease-free survivals [$p = 0.03$, HR $= 2.43$ (1.09-5.4) and $p = 0.03$, HR $= 2.51$ (1.11-5.67), respectively]. An overexpression of S100P was predictive of a worse overall survival [$p = 0.02$, HR $= 1.66$ (1.08-2.55)]. High levels of miR-31 were significantly associated to a low expression of BAP-1 protein ($p = 0.03$). In ICC, a retained expression of BAP-1 and PBRM-1, and an overexpression of S100P are related to a poor prognosis.

- Mismatch repair deficiency is a rare but putative therapeutically relevant finding in non-liver fluke associated cholangiocarcinoma

British journal of cancer 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30377340

BACKGROUND: A major molecular pathway of genetic instability in cancer is DNA mismatch repair deficiency. High-level microsatellite instability (MSI-H) is currently the best predictor of responsiveness towards immune checkpoint blockade. Data about the prevalence of high-level microsatellite instability in cholangiocarcinoma (CCA) has been conflicting. METHODS: We employed a cohort comprising 308 Western-world, non-liver fluke-associated CCAs (159 intrahepatic, 106 perihilar, and 43 distal). We analysed the mononucleotide microsatellite instability marker panel consisting of BAT25, BAT26, and CAT25 and detected MSI-H in 4/308 CCAs (1.3%). RESULTS: Patients affected by MSI-H CCA had mostly an atypical histomorphology ($p = 0.004$), showed a longer overall survival, although having a high tumour stage, and were of younger age. Correlation analysis of microsatellite instability status with tumour-infiltrating immune cells, MHC I, and PD-L1 expression in the same cholangiocarcinoma cohort showed higher numbers of CD8 + T cells, FOXP3 + regulatory T cells, CD20 + B cells and high or at least moderate MHC I expression levels in MSI-H CCAs. CONCLUSIONS: Even though the overall number of MSI-H CCAs is low, the dismal prognosis of the disease and the therapeutic option of immune checkpoint blockade in the respective patients justify MSI testing of cholangiocarcinoma, particularly in younger patients showing an atypical histomorphology.

- Outcomes of surgery for 2010 WHO classification-based intraductal papillary neoplasm of the bile duct: Case-control study of a single Japanese institution's experience with special attention to mucin expression patterns

European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30389302

INTRODUCTION: The World Health Organization (WHO) proposed an integrated classification for intraductal papillary neoplasm of the bile duct (IPNB) in 2010. However, IPNB reportedly shows considerable geographic variation. This Japanese single-institution study examined outcomes of surgery for IPNB and the prognostic impact of immunohistochemical mucin expression patterns. MATERIALS AND METHODS: Patients with IPNB were identified from 413 patients who underwent curative-intent surgery for biliary tract (excluding gallbladder) neoplasms from 1992 to 2016 by retrospective macro- and microscopic reevaluation of resected specimens. Their clinicopathological variables were analyzed. RESULTS: Twenty-two (5%) 2010 WHO classification-based patients with IPNB were identified. The other 391 patients had common-type cholangiocarcinoma. The histopathological grade was low/intermediate in 2 patients (9%), high in 8 (36%), and invasive carcinoma (ICa) in 12 (55%). The 10-year overall survival rate was 100% in 10 patients with low-high grade IPNB and 69% in 12 patients with ICa. These rates were significantly ($p = 0.018$) or marginally ($p = 0.089$) better than that (38%) of 391 other-cholangiocarcinoma patients. In the 12 patients with ICa, R0 or R1 resection, MUC5AC, and MUC6 expression significantly affected survival. Notably, all seven patients with ICa exhibiting MUC5AC expression survived throughout the study period, while four of five patients with ICa who did not exhibit MUC5AC expression died of recurrence (with vs. without MUC5AC: 10-year overall survival, 100% vs. 60%, respectively; $p = 0.018$). CONCLUSION: Our 24-year, single institution's experience suggests that Japanese patients with IPNB favorably respond to surgery, even with ICa. MUC5AC and MUC6 expression may be predictive of favorable outcomes.

- Comparison of the Clinicopathologic Characteristics of Intraductal Papillary Neoplasm of the Bile Duct according to Morphological and Anatomical Classifications

Journal of Korean medical science 2018 Oct;33(42):e266

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30310366

Background: Intraductal papillary neoplasm of the bile duct (IPNB) is a recently defined entity and its clinical characteristics and classifications have yet to be established. We aimed to clarify the clinical features of IPNB and determine the optimal morphological classification criteria. Methods: From 2003 to 2016, 112 patients with IPNB who underwent surgery were included in the analysis. After pathologic reexamination by a specialized biliary-pancreas pathologist, previously suggested morphological and anatomical classifications were compared using the clinicopathologic characteristics of IPNB. Results: In terms of histologic subtypes, most patients had the intestinal type (n = 53; 48.6%) or pancreatobiliary type (n = 33; 30.3%). The simple "modified anatomical classification" showed that extrahepatic IPNB comprised more of the intestinal type and tended to be removed by bile duct resection or pancreatoduodenectomy. Intrahepatic IPNB had an equally high proportion of intestinal and pancreatobiliary types and tended to be removed by hepatobiliary resection. Morphologic classifications and histologic subtypes had no effect on survival, whereas a positive resection margin (75.9% vs. 25.7%; P = 0.004) and lymph node metastasis (75.3% vs. 30.0%; P = 0.091) were associated with a poor five-year overall survival rate. In the multivariate analysis, a positive resection margin and perineural invasion were important risk factors for survival. Conclusion: IPNB showed better long-term outcomes after optimal surgical resection. The "modified anatomical classification" is simple and intuitive and can help to select a treatment strategy and establish the proper scope of the operation.

- Cholangiocarcinoma: Classification, Histopathology and Molecular Carcinogenesis

Pathology oncology research : POR 2018 Nov;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30448973

Cholangiocarcinoma (CC) is the second most common tumor of the liver, originating from the biliary system with increasing incidence and mortality worldwide. Several new classifications review the significance of tumor localization, site of origin, proliferation and biomarkers in the intrahepatic, perihilar and distal forms of the lesion. Based on growth pattern mass-forming, periductal-infiltrating, intraductal, undefined

and mixed types are differentiated. There are further subclassifications which are applied for the histological features, in particular for intrahepatic CC. Recognition of the precursors and early lesions of CC including biliary intraepithelial neoplasia (BilIN), intraductal papillary neoplasm of the bile ducts (IPNB), biliary mucinous cystic neoplasm (MCNB) and the candidate precursors, such as bile duct adenoma and von Meyenburg complex is of increasing significance. In addition to the previously used biliary markers detected by immunohistochemistry, several new markers have been added to the differentiation of both the benign and malignant lesions, which can be used to aid in the subclassification in association with the outcome of CC. Major aspects of biliary carcinogenesis have been revealed, yet, the exact way of this diverse process is still unclear. The factors contributing to molecular cholangiocarcinogenesis include various risk factors, different anatomical localizations, multiple cellular origins, genetic and epigenetic alterations, tumor microenvironment, heterogeneity and clonal evolution. Driver mutations have been identified, implying that they are optimal candidates for targeted therapy. The most promising therapeutic candidates have entered clinical trials.

- Frequency of bile duct confluence variations in subjects with pancreas divisum: an analysis of MRCP findings

Diagnostic and interventional radiology (Ankara, Turkey) 2018 5;24(2):72-76

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29757145

PURPOSE: We aimed to evaluate the frequency of bile duct branching pattern variations at the hepatic confluence in patients with pancreas divisum (PD). METHODS: A search was performed through the hospital database using the keyword "pancreas divisum" to identify patients. The magnetic resonance cholangiopancreatography (MRCP) images of 137 patients who were diagnosed with PD between August 2011 and November 2016 were retrospectively analyzed for the presence of bile duct variations. A control group of 137 patients without PD was established among patients investigated during the same period. Variations of the biliary tract were grouped into seven types according to the McSweeney et al. classification. RESULTS: Biliary tract variations were detected in 103 of a total of 274 patients. Fifty-eight PD patients (42.3%) and 45 control patients (32.8%) had bile duct variation at the hepatic confluence level. The patients with PD were more likely to have biliary tract variation compared with the control group; however, it was not statistically significant (P = 0.105). The most common variation in PD patients was type 3a variation (16.8%). CONCLUSION: MRCP studies showed atypical bile duct confluence pattern in nearly half of both PD patients and controls. There was no statistically significant difference in the frequency of anatomic variations at bile duct confluence in patients with PD versus those without PD. Derivation of these structures from different outpouchings in early embryological life may explain this insignificant difference.

- EVI1 expression is associated with aggressive behavior in intrahepatic cholangiocarcinoma

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30349952

Ecotropic virus integration site 1 protein homolog (EVI1), a well-known oncogenic transcriptional factor of hematopoietic cells, contributes to pancreatic cancer oncogenicity through increased expression of KRAS. Because EVI1 was upregulated in cholangiocarcinoma by referring The Cancer Genome Atlas, we investigated the importance of EVI1 in intrahepatic cholangiocarcinoma (ICC) which has been regarded as a heterogeneous group of cancers. Immunohistochemical analysis results demonstrated that EVI1 was overexpressed in about half of ICC (53/101, 52.5%). Moreover, all intraductal papillary neoplasms of the bile duct cases expressed EVI1 regardless of histological grading and subtypes such as gastric, intestinal, pancreatobiliary, or oncocytic (20/20, 100%). EVI1-positive ICC showed higher frequencies of aggressive pathological indicators such as periductal infiltrative growth ($p = 0.022$), hilar invasion ($p = 0.041$), advanced UICC stage ($p = 0.026$), major vascular invasion ($p = 0.026$), and perineural invasion ($p = 0.007$) than EVI1-negative ICC. Patients with EVI1-positive ICC showed worse overall survival and recurrence-free survival in all resected cases and in curative resected cases. Recently, we proposed type 1/2 (large/small duct types) classification

of ICC based on mucin productivity and immunophenotypes (S100P, N-cadherin, and NCAM). Type 1 predominantly consisted of EVI1-positive ICC (33/42 cases, 79%), and the frequency was significantly higher than type 2 (18/55 cases, 32.7%) ($p < 0.0001$). EVI1-positive ICC was likely to express stomach-specific claudin CLDN18 (correlation coefficient $r = 0.55373$) and mucin MUC5AC ($r = 0.42718$). EVI1-positive ICC is an aggressive ICC showing both large-duct and/or gastric phenotypes. Consequently, a transcriptional factor EVI1 is associated with aggressive behavior in ICC and can be a therapeutic target molecule, while EVI1 might be a key molecule for the development of intraductal papillary neoplasms of the bile duct.

Back to top

Staging

Bile Duct TNM staging, Margins, Survival

- Prognostic comparison of the 7th and 8th editions of the American Joint Committee on Cancer staging system for intrahepatic cholangiocarcinoma

Journal of hepato-biliary-pancreatic sciences 2018 Apr;25(4):240-248

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29450978

BACKGROUND: Several important changes were made to the 8th edition of the American Joint Committee on Cancer (AJCC) tumor staging system for intrahepatic cholangiocarcinoma (ICC). We assessed the prognostic impact of this new tumor staging system compared to the 7th edition. METHODS: A retrospective single-institution study was performed with 626 patients who underwent R0 resection for ICC over 20-year period. RESULTS: Anatomical resection and concurrent bile duct resection were performed in 571 (91.2%) and 62 (9.9%) patients, respectively. Cumulative tumor recurrence and patient survival rates were 40.6% and 73.3% at 1 year; 66.7% and 43.8% at 3 years; 73.6% and 30.4% at 5 years; and 74.4% and 20.3% at 10 years, respectively. Independent prognostic factors for tumor recurrence and patient survival were multiple tumors, carbohydrate antigen 19-9 >200 U/ml, tumor size >5 cm, direct invasion to extrahepatic structure, and lymph node metastasis. For tumor-node-metastasis stages in the 7th versus the 8th editions, concordance index was 0.615 and 0.625 for tumor recurrence and 0.626 and 0.628 for patient survival, respectively. CONCLUSIONS: The 8th edition of the AJCC staging system appears to provide high prognostic contrast for T stage categories, except for T3. However, overall prognostic performance of the 8th edition was not markedly improved over the 7th edition.

Back to top

Epidemiology, Screening, Cancer Risk Factors

- Pattern of distant metastases in primary extrahepatic bile-duct cancer: A SEER-based study

Cancer medicine 2018 Oct;7(10):5006-5014

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30277653

Extrahepatic bile duct cancer (EBDC) is a combined type of malignancy mainly consisting of extrahepatic cholangiocarcinoma and gallbladder cancer. Clinically, it is featured with latent symptoms and early metastasis, leading to a poor prognosis. Therefore, this cohort study aimed to depict the possible metastatic patterns of EBDC of diverse sub-types and evaluate the prognostic significance of diverse metastatic destinations with data from the clinical database. Relevant data of total 4061 confirmed EBDC patients diagnosed between 2010 and 2013 from the Surveillance, Epidemiology and End Results (SEER) database was obtained. We applied t test to describe the baseline data of patients included and used chi-square test to compare the distribution of distant metastatic sites. We further adopted odds ratio assess the combined metastatic patterns and compared survival difference of patients with different distal metastasis organ by Kaplan-Meier analysis. We identified totally 4061 patients over 18 years old diagnosed with extrahepatic bile tract malignancies between 2010 and 2013, with clear metastatic status and follow-up data, without primary malignancies. Liver and distant lymph (DL) are the two most common sites as a single metastasis organ. In combined metastasis patterns, bi-organ is more frequent than the other types. Lung is the organ preferentially for bi-organ metastasis, while bone and distant lymph similarly intend to co-metastasize with brain. Distal metastasis in EBDC patients indicates an extremely poor prognosis. According to the final analysis results, malignancies in extrahepatic bile duct exhibit similar metastatic patterns, suggesting that we can regard them as a unity to assess its development. Profound differences exist in distribution of distant extrahepatic metastatic sites and their combinations. Results from our studies would provide some information for follow-up strategies and future studies.

Back to top

Gallbladder

Morphology, Diagnostics, IHC

Morphology, Diagnostics, IHC

- Intracholecystic papillary-tubular neoplasm of gallbladder: A 5-year retrospective pathological study

Indian journal of pathology & microbiology 2018 10;61(4):516-519

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30303140

Background: Intracholecystic papillary-tubular neoplasm (ICPN) is a relatively new entity which includes neoplastic polyps, adenomas, and papillary neoplasms that are 1.0 cm. This study is done to evaluate the pathological features of ICPN and to find out the factors associated with invasion. Materials and Methods: This is a 5-year retrospective study in a referral pathology center. A total of 19 cases of ICPN are found. The cases are analyzed for age and sex distribution, clinical suspicion, stages, histological architecture, differentiation, and grade of dysplasia. Descriptive statistics and test of significance by Chi-square and t-test are used in the study. Results: ICPN comprises 23.5% of all gallbladder neoplasms. Two-thirds of the cases were suspected radiologically. Age range is 26-65 years with mean age of 50 years. They are 2.8 times more common in female. Approximately one-third of the cases show invasion. The most common histological pattern is papillary, followed by papillary-tubular and finally by tubular pattern. Pyloric and biliary are the most common differentiation pattern followed by oncocytic and intestinal pattern. About three-fourths of the cases are associated with high-grade dysplasia mostly diffuse high-grade dysplasia. Conclusion: We have found the younger age of presentation, less proportion of invasive tumors, fewer tumors with biliary phenotypes, and fewer tumors with high-grade dysplasia as compared to previous studies. Factors significantly associated with invasion are grade and extent of dysplasia particularly diffuse high-grade dysplasia.

Back to top

Staging

Gallbladder TNM staging, Margins, Survival

- Gallbladder polypoid lesions >15mm as indicators of T1b gallbladder cancer risk

Arab journal of gastroenterology : the official publication of the Pan-Arab Association of Gastroenterology 2017 Sep;18(3):156-158

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=28958638

BACKGROUND AND STUDY AIMS: Gallbladder polyps (GBPs) are found in 5-7% of the adult population. However, it is very important to differentiate between benign and malignant polyps to establish an appropriate treatment. The present study aimed to determine the relevance of the 10-mm size criterion and attempted to determine the cut-off diameter of T1b tumours, which requires additional surgical intervention. PATIENTS AND METHODS: Cases with GBPs were collected between January 2005 and January 2015. A total of 109 patients were enroled retrospectively. Information on age, sex, ultrasound findings, and blood laboratory tests was reviewed. The 10-mm criterion and T1b tumours were examined. RESULTS: Sixty-nine females and 40 males were included in the study. Patient age was 45±10.7years (range 27-70years). The 10-mm cut-off sensitivity and specificity for predicting malignant polyps was 93.6% and 85.2%, respectively. Fifteen patients had malignant pathologic results, and one patient had GBP <10mm (intraepithelial, 8mm). Two patients had intraepithelial tumours of 12 and 13mm. Twelve malignant patients had T1b tumours with polyp sizes >15mm. CONCLUSION: Gallbladder cancer may occur in polyps of <10mm. Larger size and older age were predictors of neoplastic GBPs. We suggest 15mm as the optimal cut-off point to predict T1b cancer.

- Impact of the number of examined lymph nodes on outcomes in patients with lymph node-negative gallbladder carcinoma

World journal of gastroenterology 2018 Jul;24(26):2886-2892

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30018483

AIM: To determine whether the number of examined lymph nodes (LNs) is correlated with the overall survival of gallbladder carcinoma (GBC) patients. METHODS: Patients were collected from the Surveillance Epidemiology and End Results database (2004-2013) and categorized by the number of LNs into six groups: 1 LN, 2 LNs, 3 LNs, 4 LNs, 5 LNs, and 6 LNs. Survival curves for overall survival were plotted with a Kaplan-Meier analysis. The log-rank test was used for univariate comparisons. RESULTS: In a cohort of 893 patients, the median number of examined LNs was two for the entire cohort. The survival for the 1 LN group was significantly poorer than those of the stageI and II disease groups and for the entire cohort. By dichotomizing the number of LNs from 1 to 6, we found that the minimum number of LNs that should be examined was four for stageI, four or five for stage II, and six for stage IIIA disease. Therefore, for the entire cohort, the number of examined LNs should be at least six, which is exactly consistent with the American Joint Committee on Cancer criteria. CONCLUSION: The examination of higher numbers of LNs is associated with improved survival after resection surgery for N0 GBC. The guidelines for GBC surgery, which recommend that six LNs be examined at least, are statistically valid and should be applied in clinical practice widely.

Back to top

Ampulla of Vater

Morphology, Diagnostics, IHC

Morphology, Diagnostics, IHC

- Duodenal Epithelial Polyps: A Clinicopathologic Review

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30354274

CONTEXT.—: Duodenal epithelial polyps are reported in 1.5% to 3% of individuals referred for upper endoscopy. Most duodenal epithelial polyps are asymptomatic and nonneoplastic; however, a small subset is neoplastic and may progress to adenocarcinoma. Recent advances in immunohistochemical and molecular techniques have helped further characterize these polyps, shedding light on their origin, classification, and risk of progression to adenocarcinoma. OBJECTIVE.—: To provide a comprehensive clinicopathologic review of nonneoplastic and neoplastic duodenal epithelial polyps, with particular emphasis on recent developments in classification schemes and risk stratification based upon immunohistochemical and molecular profiles. DATA SOURCES.—: This review is based on peer-reviewed literature and the authors' experiences. CONCLUSIONS.—: In this review we provide an update on the clinicopathologic, immunohistochemical, and molecular features of duodenal epithelial polyps; and discuss the surveillance recommendations and treatment options available. Particular attention should be placed in recognizing duodenal adenomas with intestinal, gastric, and serrated phenotype, as they have an increased risk of malignant transformation if not completely excised.

- Microanatomical profiles on the lymphatic system in the human ampulla of Vater (immunohistochemistry and scanning electron microscopy)

Journal of hepato-biliary-pancreatic sciences 2017 Oct;24(10):570-575

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=28846834

BACKGROUND: Little information is available regarding microanatomy of lymphatic system in the ampulla of Vater, though it is of critical importance for an understanding of tumor progression via the lymphatics and determination of surgical strategy. The present study, therefore, aimed to demonstrate the distribution and microanatomical profiles on the lymphatic system in the ampulla. METHODS: The fine distribution and structure of the lymphatic vessels were investigated in the ampulla and the stomach by immunohistochemistry for lymphatic- (D2-40) and blood vascular- (CD31) specific markers and scanning electron microscopy. The densities of lymphatic and blood vessels were also compared. RESULTS: The duodenal papilla densely developed the lymphatics with distinct aspects of lymphatic capillaries, together with blood vessels. The density of lymphatic capillaries in the extramuscular layer in the ampulla was higher than those of both the other ampullary layers and the gastric extramuscular (subserosal) layer. CONCLUSIONS: The ampulla of Vater showed widespread lymphatic capillaries throughout the entire wall. The specific vascular system is suited to produce lymph everywhere and drain without via such a large vessel as lymphatic collector. This suggests that tumor cells invade the lymphatics and metastasize more easily in the ampulla than in the other gastrointestinal regions.

- A Rare Case of Ampullary Goblet Cell Carcinoid

Internal medicine (Tokyo, Japan) 2018 Sep;57(17):2489-2496

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29607953

An asymptomatic 70-year-old woman was referred to our hospital because of liver enzyme elevation. Enhanced abdominal computed tomography demonstrated a small, round-shaped tumor with dilation of the

common bile duct and main pancreatic duct. A biopsy specimen from the papilla showed mucin-containing cells that were positive for endocrine markers on immunohistochemical staining. Endoscopic snare resection was done, and there was a positive vertical margin on pathology. Pancreaticoduodenectomy was then performed later. The final diagnosis was goblet cell carcinoid, pT2N0M0, pStage IIA [Union for International Cancer Control (UICC) 7th edition]. Ampullary goblet cell carcinoid is an extremely rare disease of which there have been no recent reports.

- Duodenal tumor risk in Lynch syndrome

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30448460

BACKGROUND AND AIMS: Lynch syndrome (LS) is associated with an increased risk of small bowel tumors but routine screening is not recommended in international guidelines. The aim of our study was to determinate the prevalence of duodenal tumors in a French cohort of LS patients. METHODS: Patients carrying a germline pathogenic variant in a MMR gene, supported by our local network, in which at least one upper endoscopy had been performed, were included. We registered the occurrence of duodenal lesions in those patients. RESULTS: 154 LS patients were identified including respectively 85 MSH2 and 41 MLH1 mutated patients respectively. Seven out of 154 (4.5%) had at least one duodenal lesion. Median age at diagnosis was 58 years (range: 49-73). The twelve lesions locations were: descending duodenum (n = 7), genu inferius (n = 2), duodenal bulb (n = 1), ampulla (n = 1), fourth duodenum (n = 1). Three lesions were invasive adenocarcinomas. The incidence rate of duodenal lesions in patients with MSH2 or MLH1 pathogenic variants was respectively 7.1% (6 out of 85) and 2.4% (1 out of 41) emphasizing a trend toward increased risk of developing duodenal lesion in MSH2 mutated patients: OR: 5.17, IC95% (0.8-60.07), p = 0.1307. CONCLUSION: Regarding this high prevalence rate, especially in MSH2 patients, regular duodenal screening during upper endoscopy should be considered in routine in LS patients.

Back to top

Staging

Ampulla of Vater TNM staging, Margins, Survival

- Perineural Invasion is a Strong Prognostic Moderator in Ampulla of Vater Carcinoma: A Meta-analysis

Pancreas 2019 Jan;48(1):70-76

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30451797

OBJECTIVE: Ampulla of Vater carcinoma (AVC) has a broad spectrum of different prognoses. As such, new moderators of survival are urgently needed. We aimed at clarifying the prognostic role of perineural invasion in AVC. METHODS: Using PubMed and SCOPUS databases, we conducted the first systematic review and meta-analysis on this topic. RESULTS: Analyzing 29 articles for a total of 2379 patients, we found that the presence of perineural invasion increased the risk of all-cause mortality more than 2 times (relative risk [RR], 2.07; 95% confidence interval [CI], 1.78-2.42 [P < 0.0001]; hazard ratio [HR], 2.72; 95% CI, 1.86-3.97 [P < 0.0001]), of cancer-specific mortality more than 6 times (RR, 6.12; 95% CI, 3.25-11.54 [P < 0.0001]; HR, 6.59; 95% CI, 2.29-3.49 [P < 0.0001]), and of recurrence more than 2 times (RR, 2.63; 95% CI, 1.89-3.67 [P < 0.0001]; HR, 2.54; 95% CI, 1.24-5.21 [P = 0.01]). CONCLUSIONS: Perineural invasion is strongly associated with a poorer prognosis in AVC, influencing both survival and risk of recurrence. It should be reported in the final pathology report and should be taken into account by future oncologic staging systems, identifying a group of AVC with a more malignant biological behavior.

- Validation of the eighth edition of the American Joint Committee on Cancer staging system for ampulla of Vater cancer

Surgery 2018 05;163(5):1071-1079

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29452703

BACKGROUND: The American Joint Committee on Cancer recently proposed the eighth edition of cancer staging system. Validation studies are required to evaluate the prognostic stratification of ampulla of Vater cancer patients. METHODS: In the study, 369 operatively resected patients with ampullary cancers were grouped based on the eighth T (T1a, limited to sphincter of Oddi; T1b, invasion to duodenal submucosa; T2, invasion to duodenal proper muscle; T3a, invasion to pancreas 0.5 cm; T3b, invasion to pancreas >0.5 cm; and T4, involvement of celiac axis or superior mesenteric artery) and N (N0, no nodal metastasis; N1, 1-3 nodal metastasis; and N2, 4 nodal metastasis) category of ampullary cancer staging. RESULTS: Overall 5-year survival rates for T and N categories were as followed: T1a, 83%; T1b, 71%; T2, 46%; T3a, 48%; T3b, 28.5%, T4, 7% (P< .001); N0, 44.8%; N1, 20%; N2, 4% (P < .001). Pair-wise comparisons demonstrated significant differences between T1a-b (P = .005), T3a-T3b (P = .03), N0-N1 (P < .001), and N1-N2 (P = .007) tumors, but not between T1b-T2 (P = .20), T2-T3a (P = .84), and T3b-T4 (P = .17) lesions. CONCLUSION: The eighth edition T category for ampullary cancer does not stratify patients accurately with regard to prognosis. Modification of the current T category with eliminating subcategories (T1, invasion to duodenal submucosa; T2, invasion to duodenal proper muscle; T3, invasion to pancreas or duodenal subserosa) is a better way for determining prognosis of ampullary cancer. The current N category segregates patient survival well.

- Pancreaticoduodenectomy for periampullary tumours: a review article based on Surveillance, End Results and Epidemiology (SEER) database

Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico 2018 Sep;20(9):1153-1160

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29335829

INTRODUCTION: This study set to examine relative survival of patients with periampullary cancers undergoing pancreaticoduodenectomy (PD). METHODS: Using the Surveillance, End Results and Epidemiology (SEER) database, this study identified 9877 patients with non-metastatic pancreatic adenocarcinoma who underwent PD between 2004 and 2013. RESULTS: Ampullary carcinomas have the best survival among periampullary malignancies. Lymph node ratio is a significant prognostic factor, even when stratified by tumour types. Patients receiving adjuvant radiotherapy following PD have superior survival than patients without radiotherapy (median 25 vs 20 months, $p < 0.001$), particularly ductal adenocarcinoma (HR: 0.74, CI95% 0.69-0.78; $p < 0.001$), cholangiocarcinoma (HR: 0.75, CI95% 0.59-0.97; $p = 0.027$), and ampullary carcinoma (HR: 0.79, CI95% 0.64-0.98; $p = 0.029$) with greatest survival benefit at 1-year postresection. CONCLUSION: Future studies aiming to further define genetic signatures of individual periampullary cancers would allow a personalised therapeutic approach in improving survival.

- Definition of an extended minimum level of lymphadenectomy in non-pancreatic periampullary cancer resections

HPB : the official journal of the International Hepato Pancreato Biliary Association 2018 Nov;20(11):1028-1033

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29929786

BACKGROUND: The number of lymph nodes to be resected in surgery for non-pancreatic periampullary cancer remains unclear. METHODS: The Surveillance, Epidemiology, and End Results (SEER) database was used to gather information from a large retrospective cohort. To define a novel, reasonable cut-off associated with survival, we stratified patients into subgroups depending on the number of resected lymph nodes. RESULTS: 1481 nodal-negative patients resected for periampullary cancer (excluding pancreatic ductal adenocarcinoma) were included. The median number of resected lymph nodes was ten. Median overall survival in the subgroup with less than 10 removed lymph nodes was 40 months, while median survival for patients with 10 lymph nodes was 97 months ($p < 0.001$). A significant survival benefit was seen if 16 lymph nodes were harvested (median survival, 117 months), while no further benefit was observed if more than 21 nodes were removed (median survival, >120 months). CONCLUSION: Sixteen or more resected lymph nodes are associated with improved survival in node-negative periampullary carcinoma. We propose to aim at harvesting and analyzing at least 16 lymph nodes.

Back to top

Neuroendocrine

PanNet

PanNET, Pancreatic Neuroendocrine Tumors and related neuroendocrine neoplasms

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- Comparison of Monitor-Image and Printout-Image Methods in Ki-67 Scoring of Gastroenteropancreatic Neuroendocrine Tumors

Endocrine pathology 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30367334

Gastroenteropancreatic neuroendocrine tumors (GEP-NET) are classified according to tumor grade. Ki-67 and mitotic count are the two determinants of this classification. Therefore, Ki-67 scoring becomes very important in classifying the patients accurately. Eye-balling, counting of cells through the microscope, automated image analysis systems, and manual counting of printed image are the four major scoring methods in use. The aim of this study is to show the agreement between monitor-image method (MIM) and printout-image method (PIM) of Ki-67 scoring. In our study, 120 GEP-NETs from 85 patients diagnosed between January 2005 and July 2017 were evaluated. Thirty-seven cases with either polypectomy or resection material were selected. Seven different scoring methods using either a monitor-image or a printout-image were applied for Ki-67 scoring. They are as follows: whole-PIM, 1/9-PIM, whole-MIM, 1/4-MIM, 1/6-MIM, 1/9-MIM, and 1/12-MIM. In the comparison of Ki-67 scoring methods, intraclass correlation coefficients ranging from 0.951 to 0.999 were found. The Bland-Altman analysis showed near-perfect agreement between whole-MIM and whole-PIM as well as 1/9-MIM and 1/9-PIM. The level of agreements among the other methods were sufficient too, but there was a relative decrease in the level of agreement as the area of counting becomes smaller. The average application time decreased from 373.7 to 41.7 s gradually as the scoring area becomes smaller. Our study shows that there is a remarkable agreement between the MIM and PIM used in Ki-67 scoring.

- Natural History of Small Pancreatic Lesions Suspected to Be Nonfunctioning Pancreatic Neuroendocrine Tumors

Pancreas 2018 10;47(10):1357-1363

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30308537

OBJECTIVES: Nonfunctioning pancreatic neuroendocrine tumors (NF-PNETs) are a rare disease but have been diagnosed more frequently than before. The aim of this study was to evaluate the natural course of small NF-PNETs. METHODS: We performed a retrospective analysis of patients with incidentally found small NF-PNETs (<20 mm) from 1999 to 2015. The patients who were recommended surveillance were included. RESULTS: There were 69 patients with small NF-PNETs with a mean size of 10.9 (standard deviation [SD], 3.1) mm. The average follow-up period was 52.2 (SD, 38.7) months. The changes in tumor size were as follows: increased (13.0%), sustained (84.1%), and decreased (2.9%). Eighteen were evaluated with grade 1 NF-PNETs and 1 with grade 2 among the obtained tissues. Thirteen patients underwent surgery after an average 32.9 (SD, 42.6) months later. There were 7 patients of Ia, 1 of Ib, 2 of IIa, and 1 of IIb according to the pathologic stages. Two patients received reoperation for recurrent tumors, and 2 patients showed distant metastasis after surgery, but no disease-related death occurred. CONCLUSIONS: Most of the small NF-PNETs did not increase in size and seldom showed metastasis. The wait-and-see strategy can be used for NF-PNETs less than 2 cm.

- Immunohistochemical Biomarkers of Gastrointestinal, Pancreatic, Pulmonary, and Thymic Neuroendocrine Neoplasms

Endocrine pathology 2018 Jun;29(2):150-168

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29520563

Neuroendocrine neoplasms (NENs) are a heterogeneous group of epithelial neoplastic proliferations that irrespective of their primary site share features of neural and endocrine differentiation including the presence of secretory granules, synaptic-like vesicles, and the ability to produce amine and/or peptide hormones. NENs encompass a wide spectrum of neoplasms ranging from well-differentiated indolent tumors to highly aggressive poorly differentiated neuroendocrine carcinomas. Most cases arise in the digestive system and in thoracic organs, i.e., the lung and thymus. A correct diagnostic approach is crucial for the management of patients with both digestive and thoracic NENs, because their high clinical and biological heterogeneity is related to their prognosis and response to therapy. In this context, immunohistochemistry represents an indispensable diagnostic tool that pathologists need to use for the correct diagnosis and classification of such neoplasms. In addition, immunohistochemistry is also useful in identifying prognostic and theranostic markers. In the present article, the authors will review the role of immunohistochemistry in the routine workup of digestive and thoracic NENs.

- COMPETITIVE TESTING THE WHO 2010 VS THE WHO 2017 GRADING OF PANCREAS NEUROENDOCRINE NEOPLASIA: DATA FROM A LARGE INTERNATIONAL COHORT STUDY

Neuroendocrinology 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30300897

Background: the World Health Organization (WHO) and the American Joint Cancer Committee (AJCC) modified the grading of pancreatic neuroendocrine neoplasms from a three-tiers (WHO-AJCC 2010) to a four-tiers system by introducing the novel category of NET G3 (WHO-AJCC 2017). This study aims at validating the WHO-AJCC 2017 and identifying the most effective grading system. 2102 patients were enrolled; entry criteria were i) performed surgery; ii) at least two years of follow-up; iii) observation time up to 2015. Data from 34 variables were collected; grading was assessed and compared for efficacy by statistical means including Kaplan Meier method, Cox regression analysis, Harrell's C statistics and Royston's explained variation in univariable and multivariable analyses. At descriptive analysis, the two grading systems demonstrated statistically significant differences for the major category sex but not for age groups. At Cox regression analysis, both grading systems showed statistically significant differences between grades for OS and EFS, however no statistically significant difference was observed between the two G3 classes of WHO-AJCC 2017. At multivariable analysis for the two models fitted to compare efficacy, the two grading systems performed equally well with substantially similar optimal discrimination and well-explained variation for both OS and EFS. The WHO-AJCC 2017 grading system retained statistically significant difference between the two G3 classes for OS but not for EFS. the WHO-AJCC 2017 grading is at least equally performing as the WHO-AJCC 2010 but allows the successful identification of the most aggressive PanNET subgroup. Grading is confirmed as probably the most powerful tool for patient survival prediction. .

- Ki-67 and presence of liver metastases identify different progression-risk classes in pancreatic neuroendocrine neoplasms (pNEN) undergoing resection

European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30366875

In pancreatic neuroendocrine neoplasms (pNEN), size 2 cm and Ki-67 < 3% suggest indolent behavior, but no factor alone predicts prognosis. We investigated factors predictive of tumor progression in 80 pNENs surgically resected in a single Institution from 1995 to 2015. At multivariable analysis the only two independent variables related to PFS were Ki-67 (HR 2.97; 95%CI 1.26-7.02) and presence of synchronous liver metastases (HR 3.60; 95%CI 1.70-7.61). Using Ki-67 < 3% and M0 as reference, the HR for tumor progression was 3.21 (95%CI 1.18-8.74) for M0 patients with Ki-67 3-20%, 5.06 (2.29-11.2) for M1 patients with

Ki-67 20% and 24.3 (6.64-89.2) for those with Ki-67 > 20%. Tumor size (2 vs. >2 cm) was not a predictive factor at any analysis. Intra-class correlation of Ki-67 values on pre-surgical biopsies vs. surgical specimens was 0.99 and Ki-67 classes were correctly identified in 97% of biopsies. Ki-67 and presence of liver metastases are the major prognostic factors in pNEN and identify different progression risks regardless of tumor size. Pre-surgical pNEN biopsy for Ki-67 assessment should be included in the evaluation of patients with 1-2 cm tumors to help in the decision on whether to perform surgical resection.

- Limited role of Chromogranin A as clinical biomarker for pancreatic neuroendocrine tumors

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30366884

BACKGROUND: Serum Chromogranin A (CgA) is widely used as a biomarker for pancreatic neuroendocrine tumors (PanNETs). The aim of this study was to investigate the value of CgA as a diagnostic and prognostic marker for well-differentiated PanNETs. METHODS: Patients with well-differentiated PanNET and a baseline CgA measurement, between 2011 and 2016 were reviewed. The diagnostic value was determined by comparing CgA values from patients with PanNETs to those with other pancreatic neoplasms and healthy controls. The Kaplan-Meier method was used to investigate the CgA prognostic significance. RESULTS: Ninety-nine patients met inclusion criteria. As a diagnostic marker, CgA had a sensitivity of 66%, specificity of 95%, and overall accuracy of 71%. The use of PPIs was associated with a higher CgA level ($p = 0.015$). When excluding patients on PPIs, CgA accuracy in distinguishing PanNETs from other pancreatic neoplasms was 66%, the sensitivity and specificity were 60% and 75% respectively. Elevated CgA ($p = 0.004$), Ki67% ($p < 0.001$), tumor grade ($p < 0.001$) and stage of disease ($p = 0.036$) were associated with disease-specific survival. CONCLUSION: CgA has a limited role as a diagnostic biomarker for well-differentiated PanNETs. An elevated CgA level may have prognostic value but its role should be further investigated with respect to other known pathological factors.

- High Minichromosome maintenance protein 7 proliferation indices: a powerful predictor of progression in pancreatic neuroendocrine neoplasms without distant metastasis at the time of surgery

Human pathology 2018 Nov;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30447299

Pancreatic neuroendocrine neoplasms (PanNENs) have an unpredictable clinical course that varies from indolent to highly malignant. No immunohistochemical markers are available for reliable prediction of the biological behavior of early-stage PanNENs. Minichromosome maintenance protein 7 (MCM7) is a putative powerful marker of cell proliferation. Whether the expression of MCM7 is related to the risk of PanNENs progression remains unclear. We assessed the clinical behavior of 156 PanNENs with respect to stage, grade, Ki-67 index, MCM7 index, and other pathologic features. A high MCM7 index was significantly associated with larger tumor size (P<.001), nonfunctioning tumor (P<.001), increased grade (P<.0001), and later TNM stage (P<.001). In multivariate analysis, G2/G3 (hazard ratio (HR), 2.21; 95% confidence interval (CI), 1.35-3.62; P<.001), stage III/IV (HR, 2.11; 95% CI, 1.31-3.41; P<.001), and MCM7 labeling index (LI)>5% (HR, 3.81; 95% CI, 1.30-11.17; P=.02) were independent negative prognostic factors related to the risk of tumor progression in stage I-IV disease. MCM7 LI>5% was associated with an increased risk of progression in stages I-V, I-III, and I-II. Our study confirms that MCM7 is a valuable marker for assessing the progression of PanNENs, especially in patients with early-stage disease and without distant metastasis.

- Endoscopic Resection of Duodenal Carcinoid Tumors: A Single-Center Comparison Between Simple Polypectomy and Endoscopic Mucosal Resection

Pancreas 2019 Jan;48(1):60-65

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30451799

OBJECTIVES: Endoscopic resection is preferred for duodenal carcinoids less than 20 mm; however, the efficacy of simple polypectomy has not been compared with advanced endoscopic resection techniques. METHODS: We performed a retrospective review of 33 patients who underwent endoscopic duodenal carcinoid resection (10 simple, 23 endoscopic mucosal resection) at the Hospital of the University of Pennsylvania between January 1, 2006, and June 15, 2017. The primary outcomes were resection margin positivity and local tumor recurrence. RESULTS: There were no significant differences in demographics or tumor functionality. Lesions managed with simple polypectomy had smaller median gross specimen size (6.0 mm vs 8.0 mm, P = 0.043). There was no significant difference in pathology resection margins between simple polypectomy and endoscopic mucosal resection (86% vs 68% positive, P = 0.64). Local recurrence on surveillance endoscopy was also similar (14.3% vs 17.7%, respectively; P = 1.000), with median time to recurrence 2.3 months (interquartile range, 1.2-5.4 months). The median follow-up time in patients without local recurrence was 21.4 months (interquartile range, 7.1-39.6 months). CONCLUSIONS: Simple polypectomy may be adequate treatment of small duodenal carcinoids, although further studies are needed for validation and to define the upper limits of tumor size that can be managed with this technique.

- Proinsulin Expressing Neuroendocrine Tumors of the Pancreas: An Underrecognized Entity

Pancreas 2019 Jan;48(1):55-59

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30451800

OBJECTIVES: Rare cases of pancreatic neuroendocrine tumors (PNETs) that produce only proinsulin (PI) and manifest with hypoglycemia have been reported. Proinsulin expression in PNET has not been systematically studied, and the clinicopathologic features of such tumors remain unknown. METHODS: We studied expression of PI by immunohistochemistry (IHC) in 136 PNETs from 2 high-volume surgical oncology centers and assessed all available clinicopathologic data. RESULTS: Thirty-six (26%) of PNETs were positive for PI by IHC, most (89%) of which coexpressed insulin IHC. Nine PI-positive tumors represented functional insulinomas. Patients with PI IHC-positive tumors demonstrated significantly lower mean preoperative serum glucose compared with PI-negative PNET patients, even when insulinomas were excluded. No differences in survival between PI IHC-positive and PI IHC-negative tumors were observed. We identified 2 PI-positive PNETs from hypoglycemic patients, which were not insulinomas or other functional variants and in which serum PI was never tested. These may have been undetected proinsulinomas. CONCLUSIONS: Proinsulin-expressing PNETs (functional or non) are not uncommon. Patients who present with hypoglycemia and normal insulin levels should be screened for proinsulinoma. Proinsulin IHC could also be used to screen for proinsulinoma. To further elucidate the clinical significance of PI expressing PNETs, prospective studies are required.

- Neuroendocrine Liver Metastasis-a Specific Set of Markers to Detect Primary Tumor Sites

Endocrine pathology 2018 Nov;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30456697

The diagnosis of neuroendocrine neoplasia (NEN) is often made at an advanced stage of disease, including hepatic metastasis. At this point, the primary may still be unknown and sometimes cannot even be detected by functional imaging, especially in very small tumors of the pancreas (pan) and small intestinal (si) entities. The site of the primary may be based on biopsy specimens of the liver applying a specific set of markers. Specimens of liver metastases from 87 patients with NENs were studied. In retrospect, 50 patients had si and 37 pan NENs. Tissue samples were evaluated by immunohistochemistry. The markers applied were insulin gene enhancer protein Islet-1 (ISL-1), homeobox protein CDX-2 (CDX2), thyroid transcription factor 1 (TTF-1), and serotonin. Positive stains for CDX2 were documented in 43 (86%) and for serotonin in 45 (90%) of 50 siNENs. Three panNENs were positive for CDX2 and one for serotonin, respectively. ISL-1 was negative throughout in siNENs and also negative in 8 of 50 panNENs (21.6%). TTF-1 was negative in more

than 90% of the specimens of either entity. Immunohistochemical markers in liver metastasis can lead the way to the site of the primary NEN. They should always be used in combined clusters.

- Association between preoperative Vasostatin-1 and pathological features of aggressiveness in localized nonfunctioning pancreatic neuroendocrine tumors (NF-PanNET)

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30470614

BACKGROUND: A reliable and accessible biomarker for nonfunctioning pancreatic neuroendocrine tumors (NF-PanNET) is currently unavailable. Chromogranin A (CgA) represents the best-described neuroendocrine biomarker, but its accuracy is low. Vasostatin-1 (VS-1), a fragment derived from the cleavage of CgA, was recently investigated and found to be more accurate as tumor biomarker in a cohort of patients affected by mainly metastatic small intestinal NET. METHODS: Patients submitted to surgery for sporadic localized NF-PanNET at San Raffaele Hospital were included. Preoperative plasma samples were prospectively collected. Circulating levels of total-CgA and VS-1 were retrospectively investigated by sandwich Enzyme-Linked ImmunoSorbent Assays. RESULTS: Overall, 50 patients were included. VS-1 value (P=0.0001) was the only preoperatively retrievable factor independently associated with NF-PanNET size. No significant correlation between CgA and tumor diameter was found ($P = 0.057$). A VS-1 value of 0.39 nM was identified as the optimal VS-1 cut-off accurately associated with NF-PanNET larger than 4 cm. Patients with VS-1 $>$ 0.39 nM had a significantly higher frequency of microvascular invasion ($P = 0.005$) and nodal metastasis ($P = 0.027$). Median VS-1 plasma level was significantly higher in the presence of microvascular invasion ($P = 0.001$) and nodal metastasis ($P = 0.012$). PPI assumption significantly increased total-CgA levels, but not those of VS-1 ($P = 0.111$). CONCLUSIONS: In localized, non-metastatic NF-PanNET, VS-1 is strongly associated to tumor dimension and its plasma levels are significantly higher in the presence of microvascular invasion and nodal metastases; moreover, VS-1 value is not affected by the PPI use.

- Unmet Needs in Functional and Nonfunctional pancreatic neuroendocrine neoplasms(PanNENs)

Neuroendocrinology 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30282083

Recently, European Neuroendocrine Tumor Society (ENETS)held working sessions composed of members of the advisory board and other Neuroendocrine neoplasms (NEN) experts to attempt to identify unmet needs in NENs in different locations or with advanced/poorly differentiated NENs. This section briefly summarizes the main proposed areas of unmet needs in patients with functional and non-functional pancreatic neuroendocrine neoplasms (PanNENs).

Back to top

Cytopathology

Pancreas

- Imaging and Cytopathological Criteria Indicating Malignancy in Mucin-Producing Pancreatic Neoplasms: A Series of 68 Histopathologically Confirmed Cases

Pancreas 2018 10;47(10):1283-1289

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30308535

OBJECTIVES: This study aims to evaluate the performance of clinical, imaging, and cytopathological criteria in the identification of high-grade dysplasia/carcinoma (HGD/Ca) in pancreatic mucin-producing cystic neoplasms. METHODS: Sixty-eight consecutive, histopathologically confirmed mucin-producing cystic neoplasms, evaluated by endoscopic ultrasound-guided fine-needle aspiration, were enrolled; specifically, 39 branch duct intraductal papillary mucinous neoplasms (BD-IPMNs), 21 main duct IPMNs, and 8 mucinous cystic neoplasms. The associations between HGD/Ca in histopathology and findings of endoscopic ultrasound and cytology, demographic, lifestyle, and clinical parameters were evaluated, separately in IPMNs and mucinous cystic neoplasms. RESULTS: Age 65 years or more was associated with HGD/Ca in IPMNs. In BD-IPMNs, cyst diameter 3 cm or greater (sensitivity, 68.8%; specificity, 65.2%), a mural nodule (sensitivity, 56.3%; specificity, 78.3%), main pancreatic duct diameter 5 to 9 mm (sensitivity, 50.0%; specificity, 87.0%), and suspicious cytology (sensitivity, 81.3%; specificity, 100%) signaled the presence of HGD/Ca. Similarly, in main duct IPMNs, suspicious cytology predicted HGD/Ca with high sensitivity (88.9%) and excellent specificity (100%). Regarding cytopathological criteria, in BD-IPMNs, HGD/Ca was associated with a high nuclear/cytoplasmic ratio, background necrosis, presence of papillary structures, hypochromatic nuclei, hyperchromatic nuclei, and major nuclear membrane irregularities (thickening and/or indentations). CONCLUSIONS: Clinical, imaging, and cytopathological criteria are useful in the identification of HGD/Ca in IPMNs.

- Reclassification of lesions in biopsies by fine-needle aspiration of pancreas and biliary tree using Papanicolaou classification

Journal of gastrointestinal oncology 2018 Oct;9(5):847-852

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30505584

Background: Our aim was to evaluate the application of the classification of the Papanicolaou Cytopathology Society for the report of biopsies by fine-needle aspiration (FNA) of pancreas and bile duct. Methods: The FNAs obtained consecutively during 1 year were analyzed. Descriptive statistics were performed and sensitivity, specificity, positive predictive value, negative predictive value, and cytohistological correlation were determined. The reference standard test was the histopathological study. Results: A total of 134 cases of FNA were reclassified with ultrasound guidance according to the classification of the Papanicolaou Society, the median age was 59 years (range, 25-80 years). A case interpreted as non-diagnostic was reclassified to category 4 and 3 cases with atypical cells were reclassified to category 5. All malignant cases remained unchanged. Surgical follow-up was performed in 35 patients (26.1%), with a cytohistological concordance in 21 cases (91.3%) and 2 discordant cases (8.7%), the reasons for the discrepancy were due to sampling error, one of them with scarce material to make a diagnosis of higher category, the other case with partial agreement, because cytology was observed atypical cylindrical epithelium, with histology of grade 2 neuroendocrine neoplasia and low grade mucinous intraepithelial neoplasia. In general, the sensitivity and specificity were 100% and 75% respectively, the positive predictive value 88% and the negative predictive value 100%. Conclusions: The FNA guided with endoscopic ultrasound (EUS) and interpreted according to the Papanicolaou Cytopathology Society Classification is an accurate method to evaluate pancreatic and biliary tract lesions with a high positive predictive value of 88%.

- Abnormal immunolabelling of SMAD4 in cell block specimens to distinguish malignant and benign pancreatic cells

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30421464

BACKGROUND: Accurate diagnosis of malignant and benign pancreatic lesions can be challenging, especially with endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) samples that are small and/or degraded. In the present study, we determined how to best evaluate abnormal SMAD4 expression by immunohistochemical staining on cell block specimens from EUS-FNA samples. RESULTS: In surgically resected pancreas, when abnormal SMAD4 immunolabelling was evaluated as negative SMAD4 expression, the sensitivity was low (33%), but when it was evaluated as decreased SMAD4 expression, the sensitivity improved (53%). Specificity and positive predictive value were high for both evaluations. There were no false-positive cases. In cell block specimens, decreased SMAD4 expression showed 47% sensitivity and 72% specificity, while negative SMAD4 expression showed lower sensitivity (20%) and higher specificity (100%). Both evaluations in cell block specimens showed lower sensitivity and specificity compared to resected specimens. False-positive and -negative rates were higher for cell blocks than for resected specimens. CONCLUSIONS: Decreased SMAD4 immunolabelling provided improved sensitivity as compared to negative SMAD4 immunolabelling; therefore, it is important to compare SMAD4 expression in a sample to its expression in normal cells. Abnormal SMAD4 labelling showed low sensitivity and high specificity; therefore, SMAD4 staining using EUS-FNA samples might be helpful to detect malignancies that possess SMAD4 gene abnormalities.

- Cytomorphology of ciliated foregut cyst of the pancreas

Diagnostic cytopathology 2018 Nov;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30478999

Ciliated foregut cysts are benign congenital lesions that are commonly found in the mediastinum but are rare in the retroperitoneum. So far only very few cases of ciliated foregut cyst found in the pancreas have been reported, and less with cytologic findings described. We report a case of ciliated foregut cyst in pancreas in an asymptomatic patient diagnosed on fine needle aspiration cytology. We also discuss the cytology features that would help with the diagnosis, and the differential diagnosis that should be considered.

- Rationale and feasibility of mucin expression profiling by qRT-PCR as diagnostic biomarkers in cytology specimens of pancreatic cancer

Pancreatology : official journal of the International Association of Pancreatology (IAP) ... [et al.] 2018 Dec;18(8):977-982

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30268674

BACKGROUND: Aberrantly expressed mucin glycoproteins (MUC) play important roles in pancreatic ductal adenocarcinoma (PDAC), yet their use as a diagnostic aid in fine-needle aspiration biopsy (FNAB) is poorly documented. The aim of this study was to investigate the rationale and feasibility of mucin (MUC1, MUC2, MUC3, MUC4, MUC5AC, and MUC6) expression profiling by RT-PCR for diagnostic applications in cytology. METHODS: Mucin expression was examined by RT-PCR and immunohistochemistry in specimens resected from patients with pancreatic (n = 101), ampullary (n = 23), and common bile duct (n = 10) cancers and 33 with chronic pancreatitis. Furthermore, mucin profiling by RT-PCR was prospectively compared in surgical and biopsy specimens of 40 patients with pancreatic solid tumours qualified for FNAB prior to surgery. RESULTS: A logistic regression model to distinguish PDAC from chronic pancreatitis using RT-PCR profiling included MUC3, MUC5AC, and MUC6. The same set of mucins differentiated ampullary and bile duct cancers from chronic pancreatitis. AUCs for the ROC curves derived from the two

models were 0.95 (95%CI 0.87-0.99) and 0.92 (95%CI 0.81-0.98), respectively. The corresponding positive likelihood ratios were 6.02 and 5.97, while the negative likelihood ratios were 0.10 and 0.12. AUCs of ROC curves obtained by RT-PCR and immunohistochemistry demonstrated that both analytical methods were comparable. Surgical and cytological samples showed significantly correlated values of ΔCt for individual mucins with the overall Pearson's correlation coefficient $r = 0.841$ ($P = 0.001$). CONCLUSIONS: Mucin expression profiling of pancreatic cancer with RT-PCR is feasible and may be a valuable help in discriminating malignant lesions from chronic pancreatitis in FNAB cytology.

- Insulinoma-associated protein 1 expression in pancreatic neuroendocrine tumours in endoscopic ultrasound-guided fine-needle aspiration cytology: An analysis of 14 patients

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30290028

BACKGROUND: Insulinoma-associated protein 1 (INSM1) has been reported to be a useful marker for diagnosing pancreatic neuroendocrine tumours (PNETs). However, INSM1 expression in endoscopic ultrasound-guided fine needle aspiration cytology has not been examined. We evaluated INSM1 expression in the cytology of cases diagnosed with PNETs. METHODS: We immunocytochemically stained INSM1 and Ki-67 in 14 PNET cases, and according to the 2017 World Health Organisation criteria, seven PNET Grade 1 cases, four Grade 2 cases and three Grade 3/neuroendocrine carcinoma cases were identified. As a control for INSM1 and Ki-67 expression, we used cytological specimens from 15 cases of pancreatic ductal adenocarcinoma. RESULTS: In PNET cases, INSM1-expressing tumour cells were identified in all cytological specimens of PNET. The median INSM1 expression rate in Grade 1 cases was 49.8% (mean ± standard deviation: 55.1 ± 12.5%, min: 39.3%, max: 74.1%), and in Grade 2 and Grade 3/neuroendocrine carcinoma cases was 81.1% (mean ± standard deviation: 77.6 ± 18.6%, min: 50.3%, max: 100%). However, there was no correlation between INSM1 and Ki-67 expression (r = -0.15). The median expression rate in PNET cases was 64.3%, which was significantly higher than that in pancreatic ductal adenocarcinoma cases ($P < 0.0001$). CONCLUSION: INSM1 immunocytochemistry of cytological specimens obtained from endoscopic ultrasound-guided fine needle aspiration cytology can accurately diagnose PNETs; therefore, INSM1 could be an important diagnostic tool in assessing therapeutic strategies, including molecular-targeted therapy.

- Endoscopic ultrasound-guided fine needle aspiration with liquid-based cytology preparation in the diagnosis of metastatic small-cell carcinoma in the pancreas

Diagnostic cytopathology 2018 Nov;46(11):977-980

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30353700

Pancreatic metastasis is extremely rare, particularly from small-cell lung cancer (SCLC). Studies on the role of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) with liquid-based cytology (LBC) in the diagnosis of metastatic small-cell carcinoma in the pancreas have been rarely conducted. We report herein a case of pancreatic metastasis from SCLC diagnosed using EUS-FNA with LBC (ThinPrep). A 71-year-old man presented with chief complaints of hemoptysis and jaundice over the past 1 month. Lung & pancreas tumors with multiple liver nodules were detected on computed tomography. The aspirated material from the pancreas using EUS-FNA was prepared as a cytologic specimen with ThinPrep method, which revealed scattered and clustered "small blue cells" with scant cytoplasm and stippled chromatin with frequent apoptotic bodies. Immunocytochemical staining of the cellblock material revealed strong positivity for CD56 and thyroid transcription factor-1. Endobronchial biopsy for lung mass revealed nests of small, round, blue tumor cells with hyperchromatic nuclei showing salt and pepper chromatin, scant cytoplasm, and brisk mitotic activity. Therefore, a diagnosis of metastatic small-cell carcinoma to the pancreas with an extensive stage was finally made.

- Comparison of Native Aspirates and Cytological Smears Obtained by EUS-Guided Biopsies for Effective DNA/RNA Marker Testing in Pancreatic Cancer

Pathology oncology research : POR 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30361898

We compare two types of pancreatic carcinoma samples obtained by EUS-guided fine needle biopsy (EUS-FNB) in terms of the success rates and clinical validity of analysis of two most commonly investigated DNA/RNA pancreatic cancer markers, KRAS mutations and miR-21 expression. 118 patients with pancreatic ductal adenocarcinoma underwent EUS-FNB. The collected sample was divided, one part was stored in a stabilizing solution as native aspirate (EUS-FNA) and second part was processed into the cytological smear (EUS-FNC). DNA/RNA extraction was followed by analysis of KRAS mutations and miR-21 expression. For both sample types, the yields of DNA/RNA extraction and success rates of KRAS mutation and miRNA expression were evaluated. Finally, the resulting KRAS mutation frequency and miR-21 prognostic role were compared to literature data from tissue resections. The overall amount of isolated DNA/RNA from EUS-FNC was lower compared to the EUS-FNA, average yield 10 ng vs 147 ng for DNA and average yield 164 vs. 642 ng for RNA, but the success rates for KRAS and miR-21 analysis was 100% for both sample types. The KRAS-mutant detection frequency in EUS-FNC was 12% higher than in EUS-FNA (90 vs 78%). The prognostic role of miR-21 was confirmed in EUS-FNC ($p = 0.02$), but did not reach statistical significance in EUS-FNA ($p = 0.06$). Although both types of EUS-FNB samples are suitable for DNA/RNA extraction and subsequent DNA mutation and miRNA expression analysis, reliable results with clinical validity were only obtained for EUS-FNC.

- Needle-based confocal laser endomicroscopy of pancreatic cystic lesions: a prospective multicenter validation study in patients with definite diagnosis

Endoscopy 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30347425

BACKGROUND: Needle-based confocal laser endomicroscopy (nCLE) enables observation of the inner wall of pancreatic cystic lesions (PCLs) during an endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). This study prospectively evaluated the diagnostic performance of nCLE for large, single, noncommunicating PCLs using surgical histopathology or EUS-FNA cytohistopathology as a reference diagnosis. METHODS: From April 2013 to March 2016, consecutive patients referred for EUS-FNA of indeterminate PCLs without evidence of malignancy or chronic pancreatitis were prospectively enrolled at five centers. EUS-FNA and nCLE were performed and cystic fluid was aspirated for cytohistopathological and carcinoembryonic antigen (CEA) analysis. The diagnostic performance of nCLE was assessed against the reference standard and compared with that of EUS and CEA. This study was registered on ClinicalTrials.gov (NCT01563133). RESULTS: 206 patients underwent nCLE and 78 PCLs (mean size 40mm, range 20-110mm) had reference diagnoses (53 premalignant and 25 benign PCLs). Post-procedure pancreatitis occurred in 1.3% of the patients. nCLE was conclusive in 71 of the 78 cases (91%). The sensitivies and specifities of nCLE for the diagnosis of serous cystadenoma, mucinous PCL, and premalignant PCL were all 0.95 (with 95% confidence interval from 0.85 to 1.0). The AUROC was significantly larger for nCLE than for CEA or EUS. CONCLUSIONS: nCLE had excellent diagnostic performance that surpassed that of CEA and EUS for the diagnosis of large, single, noncommunicating PCLs. The nCLE procedure should be considered in patients with indeterminate PCLs to ensure a more specific diagnosis.

Back to top

Gallbladder

- Mucinous adenocarcinoma of gallbladder: Subcategorisation on fine-needle aspiration cytology

Diagnostic cytopathology 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30375181

BACKGROUND: Mucinous adenocarcinoma (MC) of gallbladder is a rare histological subtype of gallbladder carcinoma (CaGB) which presents at an advanced stage and is associated with a poor prognosis compared to the conventional CaGB. This variant has been described mostly as reports or series, except for a single detailed histological and immunohistochemical analysis. Till date, there are no studies describing the cytomorphology of MC in detail. Hence, we undertook this study to analyse the cytomorphological features of MC. METHODS: A retrospective cytomorphological analysis was performed on MC identified out of all CaGB diagnosed on cytology over a period of last 4 years. The architectural and cellular features were recorded in a structured proforma. RESULTS: Thirty-three cases (33/987, 3.3%) were identified as MC. Extracellular mucin >90% was seen only in 3 cases whereas the remaining 30 had 50%-90% mucin. The predominant architectural pattern was tight epithelial fragments (14/33). The tumour cells were mostly of intermediate size (31/33) and had moderate amount of cytoplasm (31/33). Majority of the cases showed moderate nuclear pleomorphism (28/33) and nuclear chromatin was fine granular (17/33) or vesicular (14/33). Most of the cases had single and small nucleoli (26/33). Presence of inflammation composed predominantly of polymorphs was noted in 25 cases. Majority of the cases showed no (15/33) or scant necrosis (13/33). CONCLUSION: The morphological features of MC can very well be demonstrated on cytology. As they are associated with poor prognosis compared to conventional CaGB, cytopathologists should try to document the subtype.

Back to top

Neuroendocrine

- Immunohistochemical analysis of OTP and NKX6.1 in neuroendocrine tumors of the lung and pancreas

Diagnostic cytopathology 2018 Dec;46(12):1010-1014

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30284410

BACKGROUND: Homeobox transcription factors have demonstrated utility in diagnosing neuroendocrine tumors. Orthopedia homeobox protein (OTP) has a well-defined role in embryonic neurodevelopment and has also been described as a prognostic marker in lung neuroendocrine tumors (NET). Additionally, NK6 homeobox-1 (NKX6.1) has been described to be necessary for the development of neuroendocrine cells in the pancreas. We evaluated immunohistochemical (IHC) expression of OTP and NKX6.1 to determine their utility in the diagnosis of NETs from lung and pancreas fine-needle aspirations (FNA). METHODS: Our study examined 50 FNA specimens, including 30 primary pulmonary NETs (8 carcinoid tumors (CT), 6 atypical carcinoids (AC), 11 small-cell neuroendocrine carcinomas (SCNEC), 5 large-cell neuroendocrine carcinomas (LCNEC)) and 20 primary pancreatic NETs (17 well-differentiated pancreatic neuroendocrine tumors (PanNET) and 3 poorly differentiated pancreatic neuroendocrine carcinomas (PanNEC)). IHC expression of OTP, NKX6.1, and Ki-67 was evaluated on FNA cell blocks. RESULTS: Half of the pulmonary TC tumors expressed OTP, while only 17% of AC and 20% of LCNEC expressed OTP. Neither SCNECs nor any pancreatic NET expressed OTP. In contrast, intermediate and high-grade tumors expressed NKX6.1 (LCNEC-80%, SCNEC-82%, and AC-83%) more often than low-grade tumors (TC-63%, PanNET-71%). All three PanNECs expressed NKX6.1. CONCLUSIONS: OTP may be useful in diagnosing well-differentiated NETs of pulmonary origin. NKX6.1 may have utility in segregating high from low-grade NETs of both pulmonary and pancreatic origin, although other methods will be required to determine site of origin.

- Advances in the cytologic diagnosis of gastroenteropancreatic neuroendocrine neoplasms

Cancer cytopathology 2018 Dec;126(12):980-991

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30485690

Two-thirds of neuroendocrine neoplasms arising in the human body originate from the gastrointestinal system or pancreas. Gastroenteropancreatic neuroendocrine neoplasms are heterogeneous, comprising both well differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). The clinical presentation, molecular characteristics, and behavior are distinct for NETs and NECs. Fine-needle aspiration is an important modality for the primary diagnosis and staging of these neoplasms and can provide information of prognostic and therapeutic significance. Our evolving understanding of neuroendocrine neoplasm biology has led to several iterations of classification. In this review, new concepts and issues most relevant to cytology diagnosis of gastroenteropancreatic neuroendocrine neoplasms are discussed, such as newer detection methods that aid in diagnosis and staging, recent changes in World Health Organization classification, practical issues related to grading these neoplasms on cytology, guidelines for diagnostic reporting, and panels of immunohistochemical stains for the diagnosis of metastasis. The current understanding of genetic and epigenetic events related to tumor development and potential applications for cytology also are presented as they relate to prognostication and recent therapeutic advances.

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

Pancreas 2018 9;47(10):1296-1303

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

OBJECTIVES: There is an increasing need for grading with small endoscopic ultrasound-guided fine needle aspiration biopsy (EUS-FNAB) specimens for the proper diagnosis and therapy selection of patients with unresectable pancreatic neuroendocrine tumors (PanNET). However, our understanding of EUS-FNAB specimen grading is limited compared with surgically resected specimens. METHODS: We retrospectively determined Ki-67 labeling index (LI) of 33 matched EUS-FNAB and surgically resected PanNETs with digital image analyzer. Pairwise grades between the matched biopsy and surgically resected PanNET specimens were compared. RESULTS: The mean Ki-67 LI was higher in surgically resected PanNET specimens (5.5%) than in biopsy specimens (3.2%; P = 0.022). There was moderate agreement between the Ki-67 LI grades when individually evaluated matched biopsy and resected specimen pairs were compared (value = 0.62; P < 0.0001). However, discordance was noted in 6 cases (18%), and all of them were either grade 2 or 3 in resected PanNETs. CONCLUSIONS: Although Ki-67 LI grading of EUS-FNAB specimens may be concordant with that of matched surgically resected specimens in a large proportion of the PanNET cases, Ki-67 LI grading of EUS-FNAB specimens should be carefully applied in clinical practice because of the possibility of grading underestimation with grade 2 to 3 PanNET cases.

- Accuracy of grading pancreatic neuroendocrine neoplasms with Ki-67 index in fine-needle aspiration cellblock material

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30303569

OBJECTIVE: The aim of this study was to assess the preoperative tumour grade of pancreatic neuroendocrine neoplasms (panNENs) by determining the Ki-67 index in endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) material and to correlate the preoperative tumour grade with the postoperative tumour grade in surgical specimens. METHODS: We performed a retrospective review of the institutional pathology database over a 10-year period (2007-2017) to identify all cases of panNENs with corresponding preoperative EUS-FNA cytological material and surgical specimens. Fifteen cases with adequate EUS-FNA material (more than 400 tumour cells on cellblock) were identified. The cytological and histological samples were graded based on the mitotic rate and the Ki-67 index in accordance with the 2017 World Health Organisation grading system for panNENs. The tumour grades determined on EUS-FNA cellblock material were compared with the histological tumour grades. RESULTS: Mean age at diagnosis was 64.8 ± 12.7 years (range, 38-85 years). The grading scores assigned to the cytological and histological samples were concordant in all 15 (100%) cases. Of those, two (13%) cases were scored as grade 1, nine (60%) cases as grade 2 and four (27%) cases as grade 3 tumours. CONCLUSION: Our study shows that tumour grade in patients with PanNENs can be reliably determined by assessing the Ki-67 index in EUS-FNA specimens based on the 2017 World Health Organisation classification and grading system.

Back to top

Molecular Pathology

Pancreas

- Integrated whole genome microarray analysis and immunohistochemical assay identifies COL11A1, GJB2 and CTRL as predictive biomarkers for pancreatic cancer

Cancer cell international 2018 11;18():174

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30410422

Background: Pancreatic cancer is characterized by its unsatisfying early detection rate, rapid disease progression and poor prognosis. Further studies on molecular mechanism and novel predictive biomarkers for pancreatic cancer based on a large sample volume are required. Methods: Multiple bioinformatic analysis tools were utilized for identification and characterization of differentially expressed genes (DEGs) from a merged microarray data (100 pancreatic cancer samples and 62 normal samples). Data from the GEO and TCGA database was utilized to validate the diagnostic and prognostic value of the top 5 upregulated/downregulated DEGs. Immunohistochemical assay (46 paired pancreatic and para- cancerous samples) was utilized to validate the expression and prognostic value of COL11A1, GJB2 and CTRL from the identified DEGs. Results: A total number of 300 DEGs were identified from the merged microarray data of 100 pancreatic cancer samples and 62 normal samples. These DEGs were closely correlated with the biological characteristics of pancreatic cancer. The top 5 upregulated/downregulated DEGs showed good individual diagnostic/prognostic value and better combined diagnostic/prognostic value. Validation of COL11A1, GJB2 and CTRL with immunohistochemical assay showed consistent expression level with bioinformatics analysis and promising prognostic value. Conclusions: Merged microarray data with bigger sample volume could reflect the biological characteristics of pancreatic cancer more effectively and accurately. COL11A1, GJB2 and CTRL are novel predictive biomarkers for pancreatic cancer.

- Identification of a 5-microRNA signature and hub miRNA-mRNA interactions associated with pancreatic cancer

Oncology reports 2019 Jan;41(1):292-300

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30365134

miRNA-gene axes have been reported to serve an important role in the carcinogenesis of pancreatic cancer (PC). The aim of the present study was to systematically identity the microRNA signature and hub molecules, as well as hub miRNA-gene axes, and to explore the potential biomarkers and mechanisms associated with the carcinogenesis of PC. Eleven microRNA profile datasets were obtained from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO) and ArrayExpress databases, and a meta-analysis was performed to identify the differentially expressed miRNAs (DEMs) between tumor tissue and normal tissue. Subsequently, a diagnostic regression model was constructed to identify PC based on The Cancer Genome Atlas (TCGA) miRNA sequence data by using the least absolute shrinkage and selection operator (LASSO) method. In addition, GSE41368 was downloaded, and a weighted gene co-expression network analysis (WGCNA) was performed to obtain the gene module associated with carcinogenesis by using the TCGAbiolinks and WGCNA packages, respectively. Finally, miRNA-gene networks were constructed and visualized using Cytoscape software, followed by Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses based on the Database for Annotation, Visualization, and Integrated Discovery (DAVID). A total of 14 DEMs were identified, and a 5-microRNA-based score generated by the LASSO regression model provided a high accuracy for identifying PC [area under the curve (AUC)=0.918]. In addition, 44 miRNA-mRNA interactions were constructed, and 4 hub genes were screened on the basis of the above bioinformatic tools and databases. Furthermore, 14 biological process (BP) functions and 6 KEGG pathways were identified according to gene set enrichment analysis (GSEA). In summary, the present

study applied integrated bioinformatics approaches to generate a holistic view of PC, thereby providing a basis for further clinical application of the 5-miRNA signature and the identified hub molecules, as well as the miRNA-gene axes, which could serve as diagnostic markers and potential treatment targets.

- Prospective Evaluation of Germline Alterations in Patients With Exocrine Pancreatic Neoplasms

Journal of the National Cancer Institute 2018 Oct;110(10):1067-1074

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29506128

Background: Identification of pathogenic germline alterations (PGAs) has important clinical and therapeutic implications in pancreas cancer. We performed comprehensive germline testing (GT) in an unselected prospective cohort of patients with exocrine pancreatic neoplasms with genotype and phenotype association to facilitate identification of prognostic and/or predictive biomarkers and examine potential therapeutic implications. Methods: Six hundred fifteen unselected patients with exocrine pancreatic neoplasms were prospectively consented for somatic tumor and matched sample profiling for 410-468 genes. GT for PGAs in 76 genes associated with cancer susceptibility was performed in an "identified" manner in 356 (57.9%) patients and in an "anonymized" manner in 259 (42.1%) patients, using an institutional review board-approved protocol. Detailed clinical and pathological features, response to platinum, and overall survival (OS) were collected for the identified cohort. OS was analyzed with Kaplan-Meier curves. Results: PGAs were present in 122 (19.8%) of 615 patients involving 24 different genes, including BRCA1/2, ATM, PALB2, and multiple additional genes associated with the DNA damage response pathway. Of 122 patients with germline alterations, 41.8% did not meet current guidelines for GT. The difference in median OS was not statistically significant between patients with and without PGA (50.8 months, 95% confidence interval = 34.5 to not reached, two-sided P = .94). Loss of heterozygosity was found in 60.0% of BRCA1/2. Conclusions: PGAs frequently occur in pancreas exocrine neoplasms and involve multiple genes beyond those previously associated with hereditary pancreatic cancer. These PGAs are therapeutically actionable in about 5% to 10% of patients. These data support routinely offering GT in all pancreatic ductal adenocarcimona patients with a broad panel of known hereditary cancer predisposition genes.

- Identification of hub genes with diagnostic values in pancreatic cancer by bioinformatics analyses and supervised learning methods

World journal of surgical oncology 2018 Nov;16(1):223

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30428899

BACKGROUND: Pancreatic cancer is one of the most lethal tumors with poor prognosis, and lacks of effective biomarkers in diagnosis and treatment. The aim of this investigation was to identify hub genes in pancreatic cancer, which would serve as potential biomarkers for cancer diagnosis and therapy in the future. METHODS: Combination of two expression profiles of GSE16515 and GSE22780 from Gene Expression Omnibus (GEO) database was served as training set. Differentially expressed genes (DEGs) with top 25% variance followed by protein-protein interaction (PPI) network were performed to find candidate genes. Then, hub genes were further screened by survival and cox analyses in The Cancer Genome Atlas (TCGA) database. Finally, hub genes were validated in GSE15471 dataset from GEO by supervised learning methods k-nearest neighbor (kNN) and random forest algorithms. RESULTS: After quality control and batch effect elimination of training set, 181 DEGs bearing top 25% variance were identified as candidate genes. Then, two hub genes, MMP7 and ITGA2, correlating with diagnosis and prognosis of pancreatic cancer were screened as hub genes according to above-mentioned bioinformatics methods. Finally, hub genes were demonstrated to successfully differ tumor samples from normal tissues with predictive accuracies reached to 93.59 and 81.31% by using kNN and random forest algorithms, respectively. CONCLUSIONS: All the hub genes were associated with the regulation of tumor microenvironment, which implicated in tumor proliferation, progression, migration, and metastasis. Our results provide a novel prospect for diagnosis and treatment of pancreatic cancer, which may have a further application in clinical.

- Higher notch expression implies poor survival in pancreatic ductal adenocarcinoma: A systematic review and meta-analysis

Pancreatology : official journal of the International Association of Pancreatology (IAP) ... [et al.] 2018 Dec;18(8):954-961

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30297095

BACKGROUND: At present, pancreatic ductal adenocarcinoma (PDAC) is a fetal disease lack of effective prognostic and therapeutic methods resulting in high mortality. The Notch signaling has been demonstrated being up- or down-regulated in many cancers, but the effects in pancreatic ductal adenocarcinoma are still controversial. Moreover, the available cases in an individual study are of small samples. Therefore, it is essential to define the effect of Notch signaling in pancreatic ductal adenocarcinoma with larger samples. METHODS: Conducted from 6 eligible studies and 463 pancreatic ductal adenocarcinoma patients, this was the first meta-analysis to analyze the correlation between the Notch signal pathway and pancreatic ductal adenocarcinoma. All data were sourced from The National Center for Biotechnology Information, Web of Science and Cochrane. The articles which matched the inclusion criteria were included. All included data were analyzed and performed by Review Manager 5.3. RESULTS: The results indicated that high expression of Notch signaling proteins was associated with poor overall survival of pancreatic ductal adenocarcinoma patients (pooled hazard ratio>2.00; $P < 0.001$). Moreover, poor survival was related to high expression of Notch3 (pooled hazard ratio: 2.05; confidence interval: 1.49-2.82; $P < 0.001$) and DLL4 (pooled hazard ratio: 2.13; confidence interval: 1.37-3.32; $P < 0.001$). CONCLUSIONS: This meta-analysis supports that Notch signaling proteins may be available as prognostic factors for pancreatic ductal adenocarcinoma progression and patient survival. Higher expression of Notch signaling proteins indicated poor survival of pancreatic ductal adenocarcinoma patients. Targeting Notch signaling components, especially Notch3 protein, would be beneficial for therapies.

- SNX6 predicts poor prognosis and contributes to the metastasis of pancreatic cancer cells via activating epithelial-mesenchymal transition

Acta biochimica et biophysica Sinica 2018 Nov;50(11):1075-1084

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30307473

Pancreatic cancer remains a challenging disease with an overall cumulative 5-year survival rate around 6%. Though significant progress has been made in the availability of diagnostic techniques and treatment strategies, pancreatic cancer remains a disease of high mortality rate. Therefore, there is an urgent need for a better understanding of the molecular mechanisms that governs the oncogenesis and metastasis process of pancreatic cancer. In the present study, by using the Cancer Genome Atlas (TCGA) dataset analysis, we demonstrated that sorting nexin 6 (SNX6) serves as a biomarker for predicting prognosis of pancreatic cancer. In vitro studies demonstrated that silencing of SNX6 expression reduced cell proliferation, colony formation, invasion, and metastasis. Higher level of SNX6 helps maintain the mesenchymal properties, which renders migration and invasive capacities to pancreatic cancer cells. Moreover, in the process of TGF- -induced epithelial to mesenchymal transition (EMT), the expression level of SNX6 was increased, and silencing of SNX6 expression could inhibit the TGF- -induced EMT program. These results collectively uncovered a novel predictive marker for pancreatic cancer and provided the possible underlying molecular mechanism.

- Identification of key microRNAs and their targets in exosomes of pancreatic cancer using bioinformatics analysis

Medicine 2018 Sep;97(39):e12632

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30278585

Pancreatic cancer (PC) is one of the most lethal tumors, due to late diagnosis and limited surgical strategies. It has been reported that serum exosomal microRNAs (S-Exo-miRNAs) play a pivotal role as signaling molecules and serve as noninvasive diagnosis methods for PC. The combination of S-Exo-miRNAs with the corresponding target also plays an important role in the tumor microenvironment.Here we investigated S-Exo-miRNAs involved in PC. The gene expression profile was downloaded from the Gene Expression Omnibus (GEO) database. The analysis was carried out using GEO2R. The targets of differentially expressed serum exosomal miRNAs (DE-S-Exo-miRNAs) were predicted by 4 bioinformatic algorithms (miRanda, miRDB, miRWalk, and Targetscan). Further analysis with gene ontology (GO) and Kyoto Encyclopedia of Genomes pathway (KEGG) enrichment analyses were performed with Cytoscape software version 3.4.0. Subsequently, the interaction regulatory network of target genes was performed with the Search Tool for the Retrieval of Interacting Genes (STRING) database (http://www.string-db.org/) and visualized using Cytoscape software.We downloaded the gene expression profile GSE50632, which was based on an Agilent microarray GPL17660 platform containing 4 eligible samples. In total 467 DE-S-Exo-miRNAs were obtained, including 7 overexpressed miRNAs (1.50%), and 460 remaining underexpressed miRNAs (98.50%). The databases miRWalk, miRDB, miRanda, and TargetScan were used to predict their potential targets, which were subsequently submitted to Cytoscape software version 3.4.0 (www.cytoscape.org). Next the functional and pathway enrichment analysis were used for the KEGG pathway and GO categories analysis. The enrichment analysis identified the genes involved in such processes as developmental and negative regulation of multicellular organismal processes, regulation of anatomical structure morphogenesis, regulation of cell death, apoptotic processes and mitogen-activated protein kinase (MAPK) signaling pathway, transforming growth factor - beta (TGF -) signaling pathway, cyclic adenosine monophosphate (cAMP) signaling pathway, and the phosphatidylinositol-3kinases/Akt (PI3K-Akt) signaling pathway. Subsequently according to the protein-protein interaction (PPI) network, the top 10 genes were obtained. The enrichment analyses of the genes involved in a significant module revealed that these genes were related to the TGF- signaling pathway. After reviewing the literature, we identified the apoptosis genes, and their corresponding miRNAs that have a relationship with apoptosis of the tumor.This analysis provides a comprehensive understanding of the roles of S-Exo-miRNAs and the related targets in the development of PC. Additionally, the present study provides promising candidate targets for early diagnosis and therapeutic intervention. However, these predictions require further experimental validation in future studies.

- Transcriptome-wide association study identifies multiple genes and pathways associated with pancreatic cancer

Cancer medicine 2018 Nov;7(11):5727-5732

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30334361

AIM: To identify novel candidate genes for pancreatic cancer. METHODS: We performed a transcriptome-wide association study (TWAS) analysis of pancreatic cancer (PC). GWAS summary data were driven from the published studies of PC, totally involving 558 542 SNPs in 1896 individuals with pancreatic cancer and 1939 healthy controls. FUSION software was applied to the PC GWAS summary data for tissue-related TWAS analysis, including whole blood, peripheral blood, adipose, and pancreas. The functional relevance of identified genes with PC was further validated by Oncomine, STRING, and CluePedia tool. RESULTS: Transcriptome-wide association study analysis identified 19 genes significantly associated with PC, such as LRP5L (P value = 5.21 × 10-5), SOX4 (P value = 3.2 × 10-4), and EGLN3 (P value = 6.2 × 10-3). KEGG pathway enrichment analysis detected several PC-associated pathways, such as One carbon pool by folate (P value = 1.60 × 10-16), Cell cycle (P value = 1.27 × 10-7), TGF-beta signaling pathway (P value = 4.64 × 10-6). Further comparing the 19 genes with previously identified overexpressed genes in PC patients found one overlapped gene SOX4. CONCLUSION: We identified some novel candidate genes and pathways associated with PC. Our results provide novel clues for the genetic mechanism studies of pancreatic cancer.

- Gene expression analysis of embryonic pancreas development master regulators and terminal

cell fate markers in resected pancreatic cancer: A correlation with clinical outcome

Pancreatology : official journal of the International Association of Pancreatology (IAP) … [et al.] 2018 Dec;18(8):945-953

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30293872

BACKGROUND: Despite the recent introduction of new drugs and the development of innovative multi-target treatments, the prognosis of pancreatic ductal adenocarcinoma (PDAC) remains very poor. Even when PDAC is resectable, the rate of local or widespread disease recurrence remains particularly high. Currently, reliable prognostic biomarkers of recurrence are lacking. We decided to explore the potential usefulness of pancreatic developmental regulators as biomarkers of PDAC relapse. METHODS: We analyzed by quantitative real-time PCR the mRNA of selected factors involved either in pancreatic organogenesis (ISL1, NEUROD1, NGN3, NKX2.2, NKX6.1, PAX4, PAX6, PDX1 and PTF1) or associated with terminally committed pancreatic cells (CHGA, CHGB, GAD2, GCG, HNF6 , INS, KRT19, SYP) in 17 PDAC cell lines and in frozen tumor samples from 41 PDAC patients. RESULTS: High baseline levels of the ISL1, KRT19, PAX6 and PDX1 mRNAs in PDAC cell lines, were risk factors for time-dependent xenograft appearance after subcutaneous injection in CD1-Nude mice. Consistently, in human PDAC samples, high levels of KRT19 mRNA were associated with reduced overall survival and earlier recurrence. Higher levels of PDX1 or PAX6 mRNAs were instead associated with a higher frequency of local recurrence. CONCLUSIONS: Our findings suggest that selected factors associated with pancreas development or its terminal differentiation might be implicated in mechanisms of PDAC progression and/or metastatic spread and that the measurement of their mRNA in tumors might be potentially used to improve patient prognostic stratification and prediction of the relapse site.

- The receptor for advanced glycation end products: A fuel to pancreatic cancer

Seminars in cancer biology 2018 04;49():37-43

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=28811077

The receptor for advanced glycation end products (RAGEs) was first illustrated in the year 1992. RAGE is a single-transmembrane and multi-ligand component of the immunoglobulin protein super family. The engagement of RAGE turns out to an establishment of numerous intracellular signalling mechanisms resulting in the progression and perpetuation of many types of cancer including, the pancreatic cancer. The present review primarily focuses on the multi-ligand activation of RAGEs leading to the downstream signalling cascade activation. The kick start of the RAGEs activation leads to the several anomalies and includes multiple types of cancers. The RAGE expression correlates well with the survival of pancreatic cancer cells leading to the myeloid response. RAGEs assist in the tumourogenesis which enhance and thrive to its fullest in the stressed tumour microenvironment. An improved perceptive of its involvement in pancreatic cancer may offer novel targets for tumour supervision and risk measurement.

Back to top

Molecular Techniques & Research Methods, Liquid Biopsy

Molecular Techniques & Research Methods, Liquid Biopsy

- Plasma miR-181a-5p Downregulation Predicts Response and Improved Survival After FOLFIRINOX in Pancreatic Ductal Adenocarcinoma

Annals of surgery 2018 Nov;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30394883

OBJECTIVE: The aim of the study was to identify plasma microRNA (miRNA) biomarkers for stratifying and monitoring patients with locally advanced or metastatic pancreatic ductal adenocarcinoma (PDAC) treated with FOLFIRINOX, and to investigate their functional roles. SUMMARY BACKGROUND DATA: FOLFIRINOX has become a standard therapy for patients with advanced PDAC and can be used to potentially downstage disease. However, only a subset of patients respond, and biomarkers to guide decision-making are urgently needed. METHODS: We used microarray-based profiling to discover deregulated miRNAs in pre- and postchemotherapy plasma samples from patients based on their progression-free survival (PFS) after FOLFIRINOX. Nine candidate plasma miRNAs were validated in an independent cohort (n = 43). The most discriminative plasma miRNA was correlated with clinicopathological factors and survival, and also investigated in an additional cohort treated with gemcitabine plus nab-paclitaxel. Expression patterns were further evaluated in matched tumor tissues. In vitro studies explored its function, key downstream gene-targets, and interaction with 5-fluorouracil, irinotecan, and oxaliplatin. RESULTS: Plasma miR-181a-5p was significantly downregulated in non-progressive patients after FOLFIRINOX. In multivariate analysis, this decline correlated with improved PFS and overall survival, especially when combined with CA19-9 decline [hazard ratio (HR) = 0.153, 95% confidence interval (CI), 0.067-0.347 and HR = 0.201, 95% CI, 0.070-0.576, respectively]. This combination did not correlate with survival in patients treated with gemcitabine plus nab-paclitaxel. Tissue expression of miR-181a-5p reflected plasma levels. Inhibition of miR-181a-5p coupled with oxaliplatin exposure in pancreatic cell lines decreased cell viability. CONCLUSIONS: Plasma miR-181a-5p is a specific biomarker for monitoring FOLFIRINOX response. Decline in plasma miR-181a-5p and CA19-9 levels is associated with better prognosis after FOLFIRINOX and may be useful for guiding therapeutic choices and surgical exploration.

Back to top

Microenvironment

Tumor Stroma Interactions, Microenvironment, Inflammatory Response, Epithelial Mesenchymal Transition

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- Typing of pancreatic cancer-associated fibroblasts identifies different subpopulations

World journal of gastroenterology 2018 Nov;24(41):4663-4678

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30416314

AIM: To determine whether it is possible to identify different immune phenotypic subpopulations of cancer-associated fibroblasts (CAFs) in pancreatic cancer (PC). METHODS: We defined four different stromal compartments in surgical specimens with PC: The juxtatumoural, peripheral, lobular and septal stroma. Tissue microarrays were produced containing all pre-defined PC compartments, and the expression of 37 fibroblast (FB) and 8 extracellular matrix (ECM) markers was evaluated by immunohistochemistry, immunofluorescence (IF), double-IF, and/or in situ hybridization. The compartment-specific mean labelling score was determined for each marker using a four-tiered scoring system. DOG1 gene expression was examined by quantitative reverse transcription PCR (qPCR). RESULTS: CD10, CD271, cytoglobin, DOG1, miR-21, nestin, and tenascin C exhibited significant differences in expression profiles between the juxtatumoural and peripheral compartments. The expression of CD10, cytoglobin, DOG1, nestin, and miR-21 was moderate/strong in juxtatumoural CAFs (j-CAFs) and barely perceptible/weak in peripheral CAFs (p-CAFs). The upregulation of DOG1 gene expression in PC compared to normal pancreas was verified by qPCR. Tenascin C expression was strong in the juxtatumoural ECM and barely perceptible/weak in the peripheral ECM. CD271 expression was barely perceptible in j-CAFs but moderate in the other compartments. Galectin-1 was stronger expressed in j-CAFs vs septal fibroblasts, PDGF-R , tissue transglutaminase 2, and hyaluronic acid were stronger expressed in lobular fibroblasts vs p-CAFs, and plectin-1 was stronger expressed in j-CAFs vs l-FBs. The expression of the remaining 33 markers did not differ significantly when related to the quantity of CAFs/FBs or the amount of ECM in the respective compartments. CONCLUSION: Different immune phenotypic CAF subpopulations can be identified in PC, using markers such as cytoglobin, CD271, and miR-21. Future studies should determine whether CAF subpopulations have different functional properties.

- Mast cells and angiogenesis in pancreatic ductal adenocarcinoma

Clinical and experimental medicine 2018 Aug;18(3):319-323

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29492715

Mast cells are recognized as critical components of the tumor stromal microenvironment in several solid and hematological malignancies, promoting angiogenesis and tumor growth. A correlation between mast cells infiltration, angiogenesis and tumor progression has been reported for pancreatic ductal adenocarcinoma as well. Mast cells contribute to the aggressiveness of the pancreatic ductal carcinoma enhancing the expression of several pro-angiogenic factors such as vascular endothelial growth factor, fibroblast growth factor-2, platelet-derived growth factor and angiopoietin-1 as well as stimulating the pancreatic cancer cells proliferation by IL-13 and tryptase. The disruption of this pro-angiogenic and proliferative stimulation by inhibiting the mast cells migration and degranulation is under investigation as a potential therapeutic approach in pancreatic ductal adenocarcinoma patients. This review will summarize the literature concerning the mast cells infiltration in the pancreatic ductal adenocarcinoma analyzing its role in angiogenesis and tumor progression.

- Rab14 overexpression regulates gemcitabine sensitivity through regulation of Bcl-2 and mitochondrial function in pancreatic cancer

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30267303

Rab family protein Rab14 has been implicated in the development of human cancers. To date, its expression pattern, biological function, and potential mechanism in pancreatic cancer have not been explored. In this study, we analyzed Rab14 expression in 103 cases of pancreatic cancer tissues using immunohistochemistry (IHC) and found that Rab14 was overexpressed in 41/103 cases (39.8%). Rab14 overexpression correlated with the advanced stage. Moreover, elevated Rab14 levels indicated poor prognosis of patients with pancreatic cancers. We used BxPC-3 and Capan-2 respectively for plasmid and siRNA transfection. MTT and colony formation assays showed that Rab14 transfection increased cell proliferation and colony formation in BxPC-3 cells. Rab14 siRNA knockdown inhibits proliferation and colony formation ability in Capan-2 cell line. Cell cycle analysis showed that Rab14 facilitated cell cycle progression. Matrigel invasion assay showed that Rab14 promoted BxPC-3 cell invasion while its depletion inhibited Capan-2 cell invasion. In addition, MTT and AnnexinV/PI analysis demonstrated that overexpression of Rab14 reduced gemcitabine sensitivity which conversely was increased by Rab14 knockdown. We also demonstrated that Rab14 upregulated mitochondrial membrane potential (MMP) while its depletion downregulated MMP during gemcitabine treatment. In addition, western blotting revealed that Rab14 overexpression upregulated cyclin D1, cyclin A, cyclin E, p-Rb, and Bcl-2 and downregulated p21. Rab14 also downregulated caspase3, PARP cleavage, and cytochrome c release. In conclusion, our data indicated that Rab14 was overexpressed in pancreatic cancer and promotes growth and gemcitabine resistance, possibly through regulation of mitochondrial function and Bcl-2.

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

Annals of surgical oncology 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30374923

BACKGROUND: Tumor-infiltrating neutrophils (TINs) indicate poor prognosis for patients with pancreatic ductal adenocarcinoma (PDAC). Activated neutrophils can generate neutrophil extracellular traps (NETs). Little is known about the presence and prognostic significance of tumor-infiltrating NETs in PDAC. METHODS: This study enrolled 317 patients, in two independent sets (training and validation), who underwent curative pancreatectomy for PDAC in Shanghai Cancer Center. TINs and NETs were identified by immunohistochemical staining for CD15 and citrullinated histone H3, respectively. The relationship between clinicopathological features and outcomes was analyzed. Accuracy of prognostic prediction models was evaluated using concordance index (C-index) and Akaike information criterion (AIC). RESULTS: NETs were associated with OS (both, $P < 0.001$) and RFS (both, $P < 0.001$) in the training and validation sets. Tumor-infiltrating NETs predicted poor postsurgical survival of patients with PDAC. Moreover, multivariate analysis identified NETs and AJCC TNM stage as two independent prognostic factors for OS and RFS. Combination of NETs with the 8th edition TNM staging system (C-index, 0.6994 and 0.6669, respectively; AIC, 1067 and 1126, respectively) generated a novel model that improved the predictive accuracy for survival in both sets (C-index, 0.7254 and 0.7117, respectively; AIC, 1047 and 1102, respectively). The model combining presence of NETs with the 7th edition AJCC TNM staging system also had improved predictive accuracy. CONCLUSIONS: NETs were an independent prognostic factor in PDAC and incorporation of NETs along with the standard TNM stating system refined risk-stratification and predicted survival in PDAC with improved accuracy.

- Mesenchymal-epithelial transition of pancreatic cancer cells at perineural invasion sites is induced by Schwann cells

Pathology international 2018 Apr;68(4):214-223

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29457853

Epithelial-mesenchymal transition (EMT) promotes invasion and metastasis of pancreatic ductal adenocarci-

noma (PDAC). However, the importance of its reverse process, mesenchymal-epithelial transition (MET), for PDAC remains unclear. We aimed to characterize the histological finding "focal differentiation" in PDAC at perineural invasion sites in the context of MET and to investigate the role of Schwann cells in inducing tumor MET. Tumor differentiation and immunohistochemical expressions of E-cadherin, SMAD3, and vimentin at perineural invasion sites were examined in 168 PDAC tissues. Four PDAC cell lines were co-cultured with Schwann cells to investigate cell morphology, motility, or EMT-related markers using immunocytochemistry and quantitative PCR. Of 168 tumors, 124 (74%) showed focal differentiation with enhanced E-cadherin membrane expression ($P < 0.001$) and decreased nuclear accumulation of SMAD3 ($P < 0.001$). Among 115 PDACs harboring grade 1/2 tumor, tumors with focal differentiation showed worse survival compared to those without focal differentiation ($P = 0.019$). PDAC cells co-cultured with Schwann cells demonstrated a sheet-like appearance, increased E-cadherin expression, decreased expressions of SMAD3 and vimentin, and reduced cell motility. In conclusion, MET-like change is induced by Schwann cells, suggesting that Schwann cells contribute to PDAC colonization in pancreatic nerves through activating the MET machinery inside tumor cells in the pancreatic tumor microenvironment.

- Expression of Epithelial-Mesenchymal Transition Proteins in Pancreatic Anaplastic (Undifferentiated) Carcinoma

Pancreas 2019 Jan;48(1):36-42

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30451796

OBJECTIVES: The aim of this study was to identify an association of pancreatic anaplastic carcinoma (APC) with the epithelial-mesenchymal transition (EMT). METHODS: Resected APCs (n = 24) were examined to assess components of APCs, including carcinomatous, transitional, and sarcomatous regions. Analysis was performed based on the immunoreactivity of E-cadherin and 3 EMT-related proteins: Slug (zinc finger protein SNAI2), Twist (Twist-related protein 1), and Zeb1 (zinc finger E-box-binding homeobox 1). Expression score was determined based on staining intensity and stained area of the target cells. Finally, we performed a hierarchical clustering based on the expression pattern of E-cadherin and EMT-related proteins of the sarcomatous component. RESULTS: The expression score of E-cadherin decreased in the order of sarcomatous > transitional > carcinomatous components ($P < 0.01$). Although there were significant differences in the immunohistochemical scores of Slug, Twist, and Zeb1 between carcinomatous and transitional components ($P < 0.01$), the significant difference in immunohistochemical score of Zeb1 between transitional and sarcomatous components was found ($P < 0.05$). Furthermore, APCs were divided into 2 subgroups based on the expression patterns of E-cadherin and EMT-related proteins (hierarchical clustering analysis). Consequently, these subgroups were distinguished by Twist expression. CONCLUSIONS: Epithelial-mesenchymal transition plays an essential role in the pathogenesis of APC.

- Hyperglycemia aggravates microenvironment hypoxia and promotes the metastatic ability of pancreatic cancer

Computational and structural biotechnology journal 2018 10;16():479-487

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30455857

Background: Diabetes mellitus and pancreatic cancer are intimately related. Our previous studies showed that high levels of blood glucose promote epithelial-mesenchymal transition of pancreatic cancer. In this study, we evaluated the relationship between hyperglycemia and hypoxic tumor microenvironments. Methods: HIF-1 expression was evaluated by immunohistochemistry in clinical pancreatic cancer tissues with or without diabetes mellitus. Statistcal analysis was performed to explore the relationship between HIF-1 expression and pathological features of patients with pancreatic cancer. In vivo and in vitro models was established to detect whether a hyperglycemia environment could cause hypoxia in the pancreatic parenchyma and promote pancreatic cancer. In addition, we also tested the effect of HIF-1 siRNA on the high glucose-induced invasive and migratory abilities of BxPC-3 cells in culture. Result: Our data showed that pancreatic cancer patients with diabetes had a higher level of HIF-1 expression as well as biliary duct invasion and

larger tumor volumes than individuals in the euglycemic group. Diabetic nude mice treated with streptozotocin (STZ) exhibited larger tumors and were more likely to develop liver metastasis than control mice. Acinar cells of the pancreas in diabetic mice showed an obvious expansion of the endoplasmic reticulum and increased nuclear gaps as well as chromatin close to the cellular membrane in some acinar cells. The expression area for Hypoxyprobe-1 and HIF-1 in the diabetic orthotopic xenograft group was larger than that in the control group. The expression level of HIF-1 in the BxPC-3 cancer cell line increased in response to high glucose and CoCl2 concentrations. The high glucose-induced invasive ability, migratory capacity and MMP-9 expression were counter-balanced by siRNA specific to HIF-1 . Conclusion: Our results demonstrate that the association between hyperglycemia and poor prognosis can be attributed to microenvironment hypoxia in pancreatic cancer.

- **Elucidating the link between collagen and pancreatic cancer: what's next?**

Expert review of gastroenterology & hepatology 2018 04;12(4):315-317

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29495889

Back to top

Molecular Research on Microenvironment

Tumor Stroma Interactions, Microenvironment, Inflammatory Response, Microbiome

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- The microbiome of pancreatic cancer: from molecular diagnostics to new therapeutic approaches to overcome chemoresistance caused by metabolic inactivation of gemcitabine

Expert review of molecular diagnostics 2018 Nov;():1-5

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30392417

Pancreatic cancer is a complex disease, with an extremely poor response to chemotherapy. Emerging evidence indicates that the tumor microenvironment (TME) might play an important role in mediating chemoresistance. Areas covered: The evaluated study by Geller and collaborators describes several bacterial species within pancreatic tumor tissues and TME and investigated their roles in gemcitabine chemoresistance. Intratumor bacteria express the enzyme cytidine deaminase (CDD), whose long form (CDDL) was shown to metabolize gemcitabine into its inactive metabolite. CDDL is mostly expressed by Gammaproteobacteria and this was among the most common species in pancreatic cancer tissues. Interestingly, mouse models of colorectal cancer injected with bacterial CDDL displayed a reduced response to gemcitabine, but this resistance was neutralized by the antibiotic ciprofloxacin. Expert Commentary: The increased knowledge on the microbiome in pancreatic tissues, as well as its role in chemoresistance, will provide innovative prognostic and therapeutic strategies.

- GPR68, a proton-sensing GPCR, mediates interaction of cancer-associated fibroblasts and cancer cells

FASEB journal : official publication of the Federation of American Societies for Experimental Biology 2018 03;32(3):1170-1183

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29092903

The microenvironment of pancreatic ductal adenocarcinoma (PDAC) is characterized by a dense fibrotic stroma (desmoplasia) generated by pancreatic cancer-associated fibroblasts (CAFs) derived from pancreatic stellate cells (PSCs) and pancreatic fibroblasts (PFs). Using an unbiased GPCRomic array approach, we identified 82 G-protein-coupled receptors (GPCRs) commonly expressed by CAFs derived from 5 primary PDAC tumors. Compared with PSCs and PFs, CAFs have increased expression of GPR68 (a proton-sensing GPCR), with the results confirmed by immunoblotting, The Cancer Genome Atlas data, and immunohistochemistry of PDAC tumors. Co-culture of PSCs with PDAC cells, or incubation with TNF- , induced GPR68 expression. GPR68 activation (by decreasing the extracellular pH) enhanced IL-6 expression via a cAMP/PKA/cAMP response element binding protein signaling pathway. Knockdown of GPR68 by short interfering RNA diminished low pH-induced production of IL-6 and enhancement of PDAC cell proliferation by CAF conditioned media. CAFs from other gastrointestinal cancers also express GPR68. PDAC cells thus induce expression by CAFs of GPR68, which senses the acidic microenvironment, thereby increasing production of fibrotic markers and IL-6 and promoting PDAC cell proliferation. CAF-expressed GPR68 is a mediator of low-pH-promoted regulation of the tumor microenvironments, in particular to PDAC cell-CAF interaction and may be a novel therapeutic target for pancreatic and perhaps other types of cancers.-Wiley, S. Z., Sriram, K., Liang, W., Chang, S. E., French, R., McCann, T., Sicklick, J., Nishihara, H., Lowy, A. M., Insel, P. A. GPR68, a proton-sensing GPCR, mediates interaction of cancer-associated fibroblasts and cancer cells.

- E-cadherin is downregulated by microenvironmental changes in pancreatic cancer and induces EMT

Oncology reports 2018 Sep;40(3):1641-1649

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29956814

The aim of the present study was to research the effect of microenvironmental change on epithelial-mesenchymal transition (EMT) in pancreatic cancer cells and to determine the correlation between E-cadherin expression and the prognosis of pancreatic cancer patients. We established hypoxic, serum-deficient and TGF- -induced microenvironment models of pancreatic cancer cells and studied the changes in the mRNA and protein expression of EMT-related molecules, E-cadherin and vimentin, using western blot analysis and real-time PCR. Furthermore, immunohistochemistry was used to investigate E-cadherin expression in pancreatic cancer tissues, and survival analysis and COX regression analysis were conducted. In pancreatic cancer cells under hypoxic, serum-starved and TGF- -induced microenvironments, E-cadherin protein and mRNA levels were significantly decreased ($P<0.05$), while vimentin protein and mRNA expression levels were significantly increased ($P<0.05$). The results of immunohistochemistry showed that the protein level of E-cadherin in pancreatic cancer tissues was positively correlated with overall survival ($P<0.01$). The results of Cox regression analysis showed that E-cadherin was an independent prognostic factor in pancreatic cancer. In conclusion, E-cadherin expression was significantly decreased by microenvironment changes, and this decrease induced EMT in pancreatic cancer cells. E-cadherin is an independent prognostic marker in pancreatic cancer patients.

- From Friend to Enemy: Dissecting the Functional Alteration of Immunoregulatory Components during Pancreatic Tumorigenesis

International journal of molecular sciences 2018 Nov;19(11):

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30428588

Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease with a 5-year survival rate of approximately 8%. More than 80% of patients are diagnosed at an unresectable stage due to metastases or local extension. Immune system reactivation in patients by immunotherapy may eliminate tumor cells and is a new strategy for cancer treatment. The anti-CTLA-4 antibody ipilimumab and anti-PD-1 antibodies pembrolizumab and nivolumab have been approved for cancer therapy in different countries. However, the results of immunotherapy on PDAC are unsatisfactory. The low response rate may be due to poor immunogenicity with low tumor mutational burden in pancreatic cancer cells and desmoplasia that prevents the accumulation of immune cells in tumors. The immunosuppressive tumor microenvironment in PDAC is important in tumor progression and treatment resistance. Switching from an immune tolerance to immune activation status is crucial to overcome the inability of self-defense in cancer. Therefore, thoroughly elucidation of the roles of various immune-related factors, tumor microenvironment, and tumor cells in the development of PDAC may provide appropriate direction to target inflammatory pathway activation as a new therapeutic strategy for preventing and treating this cancer.

Back to top

Preneoplastic and Preinvasive Lesions

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

- Single-cell sequencing defines genetic heterogeneity in pancreatic cancer precursor lesions

The Journal of pathology 2018 Nov;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30430578

Intraductal papillary mucinous neoplasms (IPMNs) are precursors to pancreatic cancer; however, little is known about genetic heterogeneity in these lesions. The objective of this study was to characterize genetic heterogeneity in IPMNs at the single-cell level. We isolated single cells from fresh tissue from ten IPMNs, followed by whole genome amplification and targeted next generation sequencing of pancreatic driver genes. We then determined single-cell genotypes using a novel multi-sample mutation calling algorithm. Our analyses revealed that different mutations in the same driver gene frequently occur in the same IPMN. Two IPMNs had multiple mutations in the initiating driver gene KRAS that occurred in unique tumor clones, suggesting the possibility of polyclonal origin or an unidentified initiating event preceding this critical mutation. Multiple mutations in later-occurring driver genes were also common and were frequently localized to unique tumor clones, raising the possibility of convergent evolution of these genetic events in pancreatic tumorigenesis. Single-cell sequencing of IPMNs demonstrated genetic heterogeneity with respect to early and late occurring driver gene mutations, suggesting a more complex pattern of tumor evolution than previously appreciated in these lesions.

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

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

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

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

Back to top

SPN

Solid Pseudopapillary Neoplasm

- Molecular alterations associated with metastases of solid pseudopapillary neoplasms of the pancreas

The Journal of pathology 2019 Jan;247(1):123-134

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30306561

Solid pseudopapillary neoplasms (SPN) of the pancreas are rare, low-grade malignant neoplasms that metastasise to the liver or peritoneum in 10-15% of cases. They almost invariably present somatic activating mutations of CTNNB1. No comprehensive molecular characterisation of metastatic disease has been conducted to date. We performed whole-exome sequencing and copy-number variation (CNV) analysis of 10 primary SPN and comparative sequencing of five matched primary/metastatic tumour specimens by high-coverage targeted sequencing of 409 genes. In addition to CTNNB1-activating mutations, we found inactivating mutations of epigenetic regulators (KDM6A, TET1, BAP1) associated with metastatic disease. Most of these alterations were shared between primary and metastatic lesions, suggesting that they occurred before dissemination. Differently from mutations, the majority of CNVs were not shared among lesions from the same patients and affected genes involved in metabolic and pro-proliferative pathways. Immunostaining of 27 SPNs showed that loss or reduction of KDM6A and BAP1 expression was significantly enriched in metastatic SPNs. Consistent with an increased transcriptional response to hypoxia in pancreatic adenocarcinomas bearing KDM6A inactivation, we showed that mutation or reduced KDM6A expression in SPNs is associated with increased expression of the HIF1 -regulated protein GLUT1 at both primary and metastatic sites. Our results suggest that BAP1 and KDM6A function is a barrier to the development of metastasis in a subset of SPNs, which might open novel avenues for the treatment of this disease. © 2018 The Authors. The Journal of Pathology published by John Wiley & Sons Ltd on behalf of Pathological Society of Great Britain and Ireland.

Back to top

Bile Ducts

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

The American journal of surgical pathology 2018 Dec;42(12):1674-1685

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

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

- Comprehensive analysis of long noncoding RNA-associated competing endogenous RNA network in cholangiocarcinoma

Biochemical and biophysical research communications 2018 Dec;506(4):1004-1012

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30404735

BACKGROUND: Long non-coding RNAs (lncRNAs) can interact with microRNAs (miRNAs) as a competing endogenous RNA (ceRNA) to regulate the expression of target genes, which can largely influence on tumorigenesis and tumor progression. However, the role of lncRNA-mediated ceRNAs in cholangiocarcinoma (CCA) remains unknown. This study aimed to develop novel lncRNAs as well as their action mechanisms in CCA. METHODS: The expression profiles of lncRNAs, miRNAs, and mRNAs of 36 CCA tissues and 9 non-tumor bile duct tissues were obtained from The Cancer Genome Atlas (TCGA) database. The differentially expressed RNAs werre identified using the DESeq package in R. The ceRNA network was constructed in CCA based on bioinformatics generated from miRcode, miRTarBase, miRDB, and TargetScan. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were performed using "DAVID 6.8" and R packages "Clusterprofile". Survival analysis was performed based on Kaplan-Meier curve analysis. RESULTS: We identified a total of 1411 differentially expressed lncRNAs, 3494 mRNAs, and 64 miRNAs between CCA and matched normal tissues. By combining the data predicted by databases with intersection RNAs, a lncRNA-miRNA-mRNA ceRNA network consisting of 116 lncRNAs, 14 miRNAs and 59 mRNAs was established. According to the survival analysis, we detected 11 DElncRNA to have a significant impact on the overall survival in patients with CCA ($P < 0.05$). CONCLUSIONS: Our study identified novel lncRNAs associated with CCA progression and prognosis and provided data to further understand lncRNA-mediated ceRNA regulatory mechanisms in the pathogenesis of CCA.

- Over-expression of TNNI3K is associated with early-stage carcinogenesis of cholangiocarcinoma

Molecular carcinogenesis 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30334579

Cholangiocarcinoma (CCA) is a devastating disease with very poor prognosis due to late diagnosis and resistance to traditional chemotherapies and radiotherapies. Herein, thioacetamide (TAA)-induced rat CCA model and CGCCA cell line were used; we aim to study the cytogenetic features during tumoral development of CCA and uncover the mystery regarding carcinogenesis of CCA. The Array comparative genomic hybridization analysis, in silico method, gene knockdown, Western blot, cell count proliferation assay, clonogenecity assay, and IHC staining were applied in this study. Array comparative genomic hybridization analysis was performed on all different TAA-induced phases of rat tissues to reveal the certain pattern, +2q45, +Xq22, -12p12, have been identified for the tumor early stage, where involve the gene TNNI3K. In addition, 16 genes and 3 loci were associated with rapid tumor progression; JAK-STAT signaling pathway was highly correlated to late stage of CCA. In silico database was used to observe TNNI3K was highly express at tumor part compared with normal adjacent tissue in CCA patients from TCGA dataset. Furthermore, the growth of TNNI3K-knockdown SNU308 and HuCCT1 cells decreased when compared with cells transfected with an empty vector cell demonstrated by proliferation and colonogenecity assay. Besides, over expression of TNNI3K was especially confirmed on human CCA tumors and compared with the intrahepatic duct stone bile duct tissues and normal bile duct tissues ($P < 0.001$). Our findings might uncover the mystery regarding carcinogenesis of CCA, and provide the potential genetic mechanism to the clinicians some ideas for the patients' treatment.

Back to top

Gallbladder

- Regional differences in gallbladder cancer pathogenesis: Insights from a multi-institutional comparison of tumor mutations

Cancer 2018 Nov;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30427539

BACKGROUND: Although rare in the United States, gallbladder cancer (GBCA) is a common cause of cancer death in some parts of the world. To investigate regional differences in pathogenesis and outcomes for GBCA, tumor mutations were analyzed from a sampling of specimens. METHODS: Primary tumors from patients with GBCA who were treated in Chile, Japan, and the United States between 1999 and 2016 underwent targeted sequencing of known cancer-associated genes. Fisher exact and Kruskal-Wallis tests assessed differences in clinicopathologic and genetic factors. Kaplan-Meier methods evaluated differences in overall survival from the time of surgery between mutations. RESULTS: A total of 81 patients were included. Japanese patients (11 patients) were older (median age, 72 years [range, 54-81 years]) compared with patients from Chile (21 patients; median age, 59 years [range, 32-73 years]) and the United States (49 patients; median age, 66 years [range, 46-87 years]) (P = .002) and had more well-differentiated tumors (46% vs 0% for Chile/United States; P < .001) and fewer gallstone-associated cancers (36% vs 67% for Chile and 69% for the United States; P = .13). Japanese patients had a median mutation burden of 6 (range, 1-23) compared with Chile (median mutation burden, 7 [range, 3-20]) and the United States (median mutation burden, 4 [range, 0-27]) (P = .006). Tumors from Japanese patients lacked AT-rich interaction domain 1A (ARID1A) and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutations, whereas Chilean tumors lacked Erb-B2 receptor tyrosine kinase 3 (ERBB3) and AT-rich interaction domain 2 (ARID2) mutations. SMAD family member 4 (SMAD4) was found to be mutated similarly across centers (38% in Chile, 36% in Japan, and 27% in the United States; P = .68) and was univariately associated with worse overall survival (median, 10 months vs 25 months; P = .039). At least one potentially actionable gene was found to be altered in 80% of tumors. CONCLUSIONS: Differences in clinicopathologic variables suggest the possibility of distinct GBCA pathogenesis in Japanese patients, which may be supported by differences in mutation pattern. Among all centers, SMAD4 mutations were detected in approximately one-third of patients and may represent a converging factor associated with worse survival. The majority of patients carried mutations in actionable gene targets, which may inform the design of future trials.

Back to top

Ampulla of Vater

- Ampullary carcinoma-A genetic perspective

Mutation research 2018 03;776():10-22

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29807574

Ampulla of vater carcinoma (AVC) is a rare gastrointestinal tumour that is associated with a high mortality rate and it's often diagnosed at later stages due to lack of clinical symptoms. Early diagnosis of this condition is essential to effectively treat patients for better prognosis. A significant amount of advancement has been made in understanding the molecular nature of cancer in the past decade. A substantial number of mutations and alterations have been detected in various tumors. Despite the occurrence of AVC across the globe, the number of studies conducted on this tumor type remains low; this is largely due to its rare occurrence. Moreover, AVC tissues are complex and contain mutations in oncogenes, tumour suppressors, apoptotic proteins, cell proliferation proteins, cell signaling proteins, transcription factors, chromosomal abnormalities and cellular adhesion proteins. The frequently mutated genes included KRAS, TP53 and SMAD4 and are associated with prognosis. Several molecules of the PI3K, Wnt signaling, TGF-beta pathway and cell cycle have also been altered in AVCs. This review comprises of all the genetic mutations, associated pathways and related prognosis that are involved in AVCs from the year 1989 to 2017. This report can be used as a stepping-stone to establish biomarkers for early diagnosis of AVC and to discover molecular targets for drug therapy.

- Ampulla of Vater carcinoma: Molecular landscape and clinical implications

World journal of gastrointestinal oncology 2018 Nov;10(11):370-380

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30487949

Ampulla of Vater is a peculiar anatomical structure, characterized by the crossroad of three distinct epithelia: Intestinal, ductal pancreatic and biliary. Adenocarcinomas arising in this area represent an opportunity to understand the comparative biology of all periampullary malignancies. These neoplasms can exhibit intestinal, pancreaticobiliary or mixed features, whereas the subclassification based on morphology and immunohistochemical features failed in demonstrating a robust prognostic reliability. In the last few years, the molecular landscape of this tumor entity has been uncovered, identifying alterations that may serve as prognostic and predictive biomarkers. In this review, the histological and genetic characteristics of ampullary carcinomas are discussed, taking into account the main clinical and therapeutic implications related to this tumor type as well.

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

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

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

Poor information is available on the molecular landscape characterizing the carcinogenetic process leading to ampullary carcinoma. MiR-21 is one of the most frequently up-regulated miRNAs in pancreatic adenocarcinoma, a tumor sharing similar molecular features with ampullary adenocarcinomas (AVCs), above all with the pancreatic-biliary type. We profiled, by in situ hybridization (ISH), miR-21 expression in a series of 26 AVCs, 50 ampullary dysplastic lesions (35 low-grade [LG-IEN] and 15 high-grade [HG-IEN]) and 10 normal duodenal mucosa samples. The same series was investigated by immunohistochemistry for -catenin, p53 and HER2 expression. HER2 gene amplification was evaluated by chromogenic in situ hybridization. To validate miR-21 ISH results we performed miR-21 qRT-PCR analysis in a series of 10 AVCs and their matched normal samples. All the normal control samples showed a negative or faint miR-21 expression, whereas a significant miR-21 up-regulation was observed during the carcinogenetic cascade ($p < 0.001$), with 21/26

(80.8%) of cancer samples showing a miR-21 overexpression. In comparison to control samples, a significant overexpression was found in samples of LG-IEN ($p = .0003$), HG-IEN ($p = .0001$), and AVCs ($p < 0.0001$). No significant difference in miR-21 overexpression was observed between LG-IEN, HG-IEN and AVCs. By qRT-PCR analysis, AVCs showed a 1.7-fold increase over the controls ($p = .003$). P53 was frequently dysregulated in both dysplastic and carcinoma samples (44 out of 76; 57.9%). A 20% (10/50) of dysplastic lesions and 11% (3/26) of carcinomas were characterized by a nuclear localization of -catenin. Only 2 AVCs (7.7%; both intestinal-type) showed a HER2 overexpression (both 2+), which corresponded to a HER2 gene amplification at CISH analysis. This is the first study demonstrating a miRNA dysregulation in the whole spectrum of ampullary carcinogenesis. MiR-21 overexpression is an early molecular event during ampullary carcinogenesis and its levels increase with the neoplastic progression.

- Adenosquamous carcinoma of the papilla of Vater: A phenotypic heterogeneity characterized by a common molecular landscape

Pathology international 2018 Dec;68(12):715-716

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30417956

Back to top

Neuroendocrine

- Clinical and in vitro studies of the correlation between MGMT and the effect of streptozocin in pancreatic NET

Cancer chemotherapy and pharmacology 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30310970

PURPOSE: This study aimed to determine the correlation between DNA repair enzyme O6-methylguanine DNA methyltransferase (MGMT) status and the response to streptozocin in advanced well-differentiated pancreatic neuroendocrine tumors (WD panNETs). METHODS: To test the hypothesis that MGMT deficiency was required for an alkylating drug response, we retrospectively reviewed the response of 13 patients with WD panNETs to alkylating agents in relation to MGMT status. We also studied MGMT expression in streptozocin resistance using panNET cell lines. RESULTS: The cohort included 54% of patients with and 46% without MGMT expression. Among these, 83.3% (5/6) of MGMT-negative cases showed a partial response to streptozocin. In contrast, only 14.2% (1/7) of MGMT-positive cases showed a partial response ($P = 0.013$). Induced expression of MGMT in BON1 cells (a panNET cell line with undetectable endogenous MGMT) produced streptozocin resistance. Knockdown of MGMT in QGP1 cells, which express MGMT endogenously, did not alter the response to streptozocin. CONCLUSIONS: We observed a relationship between MGMT status and streptozocin response in both patients and cell culture. Despite limited cases examined, high concordance of negative expression of MGMT and response to streptozocin treatment suggest that MGMT expression can be a potential biomarker for this treatment.

- Evaluating gastroenteropancreatic neuroendocrine tumors through microRNA sequencing

Endocrine-related cancer 2019 Jan;26(1):47-57

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30021866

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) can be challenging to evaluate histologically. MicroRNAs (miRNAs) are small RNA molecules that often are excellent biomarkers due to their abundance, cell-type and disease stage specificity and stability. To evaluate miRNAs as adjunct tissue markers for classifying and grading well-differentiated GEP-NETs, we generated and compared miRNA expression profiles from four pathological types of GEP-NETs. Using quantitative barcoded small RNA sequencing and state-of-the-art sequence annotation, we generated comprehensive miRNA expression profiles from archived pancreatic, ileal, appendiceal and rectal NETs. Following data preprocessing, we randomly assigned sample profiles to discovery (80%) and validation (20%) sets prior to data mining using machine-learning techniques. High expression analyses indicated that miR-375 was the most abundant individual miRNA and miRNA cistron in all samples. Leveraging prior knowledge that GEP-NET behavior is influenced by embryonic derivation, we developed a dual-layer hierarchical classifier for differentiating GEP-NET types. In the first layer, our classifier discriminated midgut (ileum, appendix) from non-midgut (rectum, pancreas) NETs based on miR-615 and -92b expression. In the second layer, our classifier discriminated ileal from appendiceal NETs based on miR-125b, -192 and -149 expression, and rectal from pancreatic NETs based on miR-429 and -487b expression. Our classifier achieved overall accuracies of 98.5% and 94.4% in discovery and validation sets, respectively. We also found provisional evidence that low- and intermediate-grade pancreatic NETs can be discriminated based on miR-328 expression. GEP-NETs can be reliably classified and potentially graded using a limited panel of miRNA markers, complementing morphological and immunohistochemistry-based approaches to histologic evaluation.

- Neuroendocrine neoplasia goes molecular - time for a change

Nature reviews. Clinical oncology 2018 Nov;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30390038

- **Blood mRNA Measurement (NETest) for Neuroendocrine Tumors diagnosis of Image-negative liver metastatic disease**

The Journal of clinical endocrinology and metabolism 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30358858

Context: Early cancer detection is critical to optimize treatment. This is particularly problematic in neuroendocrine tumors (NETs) which exhibit a 5-year diagnostic delay due to covert symptomatology, limitations in imaging and circulating biomarkers. Despite development of continuous monitoring strategies utilizing advanced modalities (CT/MRI or 68Gallium-PET/CT), or a repertoire of monoanalyte biomarkers (e.g. chromogranin A [CgA], pancreastatin, serotonin), detection of minimal residual disease or micro-recurrence, remains elusive. Emerging molecular liquid biopsies (e.g. NETest) provide a significant improved threshold for disease detection. Case Description: We describe the utility of a blood-based multigene PCR neuroendocrine measurement (NETest), representative of core molecular drivers of neuroendocrine tumorigenesis, to detect hepatic micrometastases in a patient with negative blood biomarkers, and negative anatomical/functional imaging. A 52-year old female who had undergone margin-negative resection for a NET of the ileocecal valve, 8 months later developed persistently elevated NETest levels. CT/MRI/68Gallium-PET and biomarkers remained negative. Blood multi-gene analysis identified disease and peptide receptor radionuclide therapy (PRRT) was undertaken. Over 9 months, NETest levels increased (conventional biomarkers/imaging remained normal). Liver biopsy was undertaken, and foci of 3mm NET in segment VI were histologically documented. 3.3 years after PRRT, the disease remains as a microscopic burden and stable, biomarker/68Gallium PET/MRI occult despite elevated blood levels of NET genes. Conclusions: Blood measurement of neuroendocrine tumor transcripts can identify image- and CgA-negative disease. A NET liquid biopsy strategy has clinical utility for the early identification of residual or metastatic disease and optimizes the consideration of adjuvant therapeutic intervention.

- **Neuropilin-1 (NRP-1) upregulated by IL-6/STAT3 signaling contributes to invasion in pancreatic neuroendocrine neoplasms**

Human pathology 2018 Nov;81():192-200

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30420046

Although the upregulation of Neuropilin-1 (NRP-1) is associated with many solid tumors, its role in pancreatic neuroendocrine neoplasms (pNEN) has not been well elucidated. The aim of this study was to investigate the role of NRP-1 in improving treatment and determining the prognosis of pNEN. In this study, the expression of NRP-1 in pNEN tissue samples and pNEN cell line BON1 was analyzed by Western blot, polymerase chain reaction (PCR) and immunocytochemistry upon exposure to interleukin-6 (IL-6). Additionally, pNEN cell line BON1 was transfected with small interfering RNAs against NRP-1 or signal transducer and activator of transcription 3 (STAT3) and assessed by in vitro invasion assays. The expression of NRP-1 in pNEN tissues was markedly increased compared with adjacent normal pancreatic tissues. High NRP-1 expression was strongly correlated with tumor grades (P = .026), lymph node metastasis (P = .025), and tumor-node-metastasis stages (P = .012). Furthermore, NRP-1 downregulation notably inhibited the metastatic capacity of pNEN cells, and STAT3 knockdown was found to downregulate the expression of NRP-1. BON1 cells upregulated NRP-1 expression upon stimulation with IL-6. This was accompanied by activation/phosphorylation of the AKT and STAT3 signaling pathways. Western blot of extracts of human pNENs confirmed increased NRP-1 expression, as well as AKT/STAT3 phosphorylation in tissue of pNENs with elevated expression levels of IL-6. In conclusion, our findings suggest that NRP-1 is upregulated in pNEN and is correlated with the metastatic capacity of pNEN cells, potentially via interaction with the IL-6/STAT3 signaling pathway.

- Cell-Free DNA From Metastatic Pancreatic Neuroendocrine Tumor Patients Contains Tumor-Specific Mutations and Copy Number Variations

Frontiers in oncology 2018 11;8():467

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30443491

Background: Detection of tumor-specific alterations in cell-free DNA (cfDNA) has proven valuable as a liquid biopsy for several types of cancer. So far, use of cfDNA remains unexplored for pancreatic neuroendocrine tumor (PNET) patients. Methods: From 10 PNET patients, fresh frozen tumor tissue, buffy coat and plasma samples were collected. Whole-exome sequencing of primary tumor and germline DNA was performed to identify tumor-specific variants and copy number variations (CNVs). Subsequently, tumor-specific variants were quantified in plasma cfDNA with droplet digital PCR. In addition, CNV analysis of cfDNA was performed using shallow whole-genome sequencing. Results: Tumor-specific variants were detected in perioperative plasma samples of two PNET patients, at variant allele fractions (VAFs) of respectively 19 and 21%. Both patients had metastatic disease at time of surgery, while the other patients presented with localized disease. In the metastatic patients, CNV profiles of tumor tissue and cfDNA were significantly correlated. A follow-up plasma sample of a metastatic patient demonstrated an increased VAF (57%) and an increased chromosomal instability, in parallel with an increase in tumor burden. Conclusions: We are the first to report the presence of tumor-specific genetic alterations in cfDNA of metastatic PNET patients and their evolution during disease progression. Additionally, CNV analysis in cfDNA shows potential as a liquid biopsy.

- Genetic Analysis of Small Well-differentiated Pancreatic Neuroendocrine Tumors Identifies Subgroups With Differing Risks of Liver Metastases

Annals of surgery 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30339629

OBJECTIVE:: The aim of this study was to investigate the key molecular alterations in small primary pancreatic neuroendocrine tumors (PanNETs) associated with the development of liver metastases. BACKGROUND: Well-differentiated PanNETs with small size are typically indolent; however, a limited subset metastasize to the liver. METHODS: A total of 87 small primary PanNETs (<3cm), including 32 metastatic cases and 55 nonmetastatic cases after a 5-year follow-up, were immunolabeled for DAXX/ATRX and analyzed for alternative lengthening of telomeres (ALT) by Fluorescence In Situ Hybridization. A subset of these cases, 24 that metastasized and 24 that did not metastasize, were assessed by targeted next-generation sequencing and whole-genome copy number variation. RESULTS: In the entire cohort, high Ki-67 (OR 1.369; 95% CI 1.121-1.673; P = 0.002), N-stage (OR 4.568; 95% CI 1.458-14.312; P = 0.009), and ALT-positivity (OR 3.486; 95% CI 1.093-11.115; P = 0.035) were independently associated with liver metastases. In the subset assessed by next-generation sequencing and copy number variation analysis, 3 molecular subtypes with differing risks of liver metastases were identified. Group 1 (n = 15; 73% metastasized) was characterized by recurrent chromosomal gains, CN-LOH, DAXX mutations, and ALT-positivity. Group 2 (n = 19; 42% metastasized, including 5 G1 tumors) was characterized by limited copy number alterations and mutations. Group 3 (n = 14; 35% metastasized) were defined by chromosome 11 loss. CONCLUSIONS: We identified genomic patterns of small PanNETs associated with a different risk for liver metastases. Molecular alterations, such as DAXX mutations, chromosomal gains, and ALT, are associated with an increased risk of metastasis in small PanNETs. Therefore, targeted sequencing and/or ALT analysis may help in the clinical decisions for these small PanNETs.

- DAXX Mutation Status of Embolization-Treated Neuroendocrine Tumors Predicts Shorter Time to Hepatic Progression

Journal of vascular and interventional radiology : JVIR 2018 Nov;29(11):1519-1526

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30342802

PURPOSE: To identify common gene mutations in patients with neuroendocrine liver metastases (NLM) undergoing transarterial embolization (TAE) and establish relationship between these mutations and response to TAE. MATERIALS AND METHODS: Patients (n = 51; mean age 61 y; 29 men, 22 women) with NLMs who underwent TAE and had available mutation analysis were identified. Mutation status and clinical variables were recorded and evaluated in relation to hepatic progression-free survival (HPFS) (Cox proportional hazards) and time to hepatic progression (TTHP) (competing risk proportional hazards). Subgroup analysis of patients with pancreatic NLM was performed using Fisher exact test to identify correlation between mutation and event (hepatic progression or death) by 6 months. Changes in mutation status over time and across specimens in a subset of patients were recorded. RESULTS: Technical success of TAE was 100%. Common mutations identified were MEN1 (16/51; 31%) and DAXX (13/51; 25%). Median overall survival was 48.7 months. DAXX mutation status (hazard ratio = 6.21; 95% confidence interval [CI], 2.67-14.48; P < .001) and tumor grade (hazard ratio = 3.05; 95% CI, 1.80-5.17; P < .001) were associated with shorter HPFS and TTHP on univariate and multivariate analysis. Median HPFS was 3.6 months (95% CI, 1.7-5.3) for patients with DAXX mutation compared with 8.9 months (95% CI, 6.6-11.4) for patients with DAXX wild-type status. In patients with pancreatic NLMs, DAXX mutation status was associated with hepatic progression or death by 6 months (P = .024). DAXX mutation status was concordant between primary and metastatic sites. CONCLUSIONS: DAXX mutation is common in patients with pancreatic NLMs. DAXX mutation status is associated with shorter HPFS and TTHP after TAE.

Back to top

Experimental / Others

Experimental Studies

- Direct therapeutic targeting of immune checkpoint PD-1 in pancreatic cancer

British journal of cancer 2018 Oct;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30377341

BACKGROUND: Pancreatic cancer (PC) hijacks innate cellular processes to promote cancer growth. We hypothesized that PC exploits PD-1/PD-L1 not only to avoid immune responses, but to directly enhance growth. We also hypothesized that immune checkpoint inhibitors (ICIs) have direct cytotoxicity in PC. We sought to elucidate therapeutic targeting of PD-1/PD-L1. METHODS: PD-1 was assessed in PC cells, patient-derived organoids (PDOs), and clinical tissues. Then, PC cells were exposed to PD-L1 to evaluate proliferation. To test PD-1/PD-L1 signaling, cells were exposed to PD-L1 and MAPK was examined. Radio-immunoconjugates with anti-PD-1 drugs were developed to test uptake in patient-derived tumor xenografts (PDTXs). Next, PD-1 function was assessed by xenografting PD-1-knockdown cells. Finally, PC models were exposed to ICIs. RESULTS: PD-1 expression was demonstrated in PCs. PD-L1 exposure increased proliferation and activated MAPK. Imaging PDTXs revealed uptake of radio-immunoconjugates. PD-1 knockdown in vivo revealed 67% smaller volumes than controls. Finally, ICI treatment of both PDOs/PDTXs demonstrated cytotoxicity and anti-MEK1/2 combined with anti-PD-1 drugs produced highest cytotoxicity in PDOs/PDTXs. CONCLUSIONS: Our data reveal PCs innately express PD-1 and activate druggable oncogenic pathways supporting PDAC growth. Strategies directly targeting PC with novel ICI regimens may work with adaptive immune responses for optimal cytotoxicity.

- Silencing of TRPM8 inhibits aggressive tumor phenotypes and enhances gemcitabine sensitivity in pancreatic cancer

Pancreatology : official journal of the International Association of Pancreatology (IAP) ... [et al.] 2018 Dec;18(8):935-944

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30316690

The transient receptor potential TRPM8 ion channel is required for cellular proliferation in pancreatic epithelia and adenocarcinoma. To elucidate the mechanism that mediates the function of TRPM8, we examined its role in the proliferation and invasion of pancreatic cancer (PC) cells. TRPM8 expression increased in both the PC tissues and cell lines; a high TRPM8 expression was correlated with poorer prognosis in patients with PC. In PC cell lines, PACN-1 and BxPC-3, Ca2+ influxes could be evoked by TRPM8; the sensitivity of PC cells to gemcitabine was increased, while the proliferation and invasion of PC cells were suppressed after RNA interference-mediated silencing of TRPM8. The mechanism of TRPM8 in gemcitabine-based chemotherapy was then investigated. The expression and activity of multidrug resistance-associated proteins, P-gp, MRP-2, LRP, was significantly reduced in response to TRPM8 silence. Moreover, TRPM8 knockdown significantly increased hENT1 protein levels and the ratio of Bax/Bcl-2 while decreased the protein levels of RRM1. Thus, TRPM8 is required for PC cell proliferation and invasion and was closely related to the gemcitabine sensitivity of PC. The modulation of TRPM8 expression may help improve treatment response of PC by combining with traditional chemotherapy.

- Abrogation of glutathione peroxidase-1 drives EMT and chemoresistance in pancreatic cancer by activating ROS-mediated Akt/GSK3 /Snail signaling

Oncogene 2018 Nov;37(44):5843-5857

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29980787

The devastating prognosis of pancreatic ductal adenocarcinoma (PDAC) is partially attributed to chemotherapy resistance. Glutathione peroxidase-1 (GPx1) plays various roles in the development and progression of multiple tumors, with the exception of pancreatic cancer. Here, we tentatively explored the role of GPx1 in the malignant biological behavior and gemcitabine (GEM) resistance of PDAC. GPx1 levels were detected using tissue microarrays and were negatively correlated with the overall survival of patients with PDAC. GPx1 silencing induced a mesenchymal transition phenotype and increased GEM resistance in vitro and in vivo. Additionally, the activation of reactive oxygen species (ROS)-mediated Akt/glycogen synthase kinase 3 (GSK3)/Snail signaling was involved in this process, as determined by RNA sequencing. Moreover, low GPx1 expression correlated with a worse survival rate in patients with PDAC who received GEM adjuvant chemotherapy, whereas this correlation was not detected in patients receiving fluoropyrimidine. Based on our results, GPx1 inhibits the epithelial-mesenchymal transition (EMT) and chemoresistance by regulating the Akt/GSK3 /Snail signaling axis in PDAC. Furthermore, GPx1 may be a potential predictive biomarker in GEM-treated PDAC patients.

- Targeting Purinergic Receptor P2Y2 prevents the growth of pancreatic ductal adenocarcinoma by inhibiting cancer cell glycolysis

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30420446

PURPOSE: Extensive research has reported that the tumor microenvironment components play crucial roles in tumor progression. Thus, blocking the supports of tumor microenvironment is a promising approach to prevent cancer progression. We aimed to determine whether blocking extracellular ATP-P2RY2 axis could be a potential therapeutic approach for PDAC treatment. EXPERIMENTAL DESIGN: Expression of P2RY2 was determined in 264 human PDAC samples, and correlated to patient survival. P2RY2 was inhibited in human PDAC cell lines by antagonist and shRNA, respectively, and cell viability, clonogenicity and glycolysis were determined. RNA sequencing of PDAC cell line was applied to reveal underlying molecular mechanisms. Multiple PDAC mouse models were used to assess the effects of the P2RY2 inhibition on PDAC progression. RESULTS: P2RY2 was upregulated and associated with poor prognosis in PDAC. Activated P2RY2 by increased extracellular ATP in tumor microenvironment promoted PDAC growth and glycolysis. Further studies showed that the agonist-activated P2RY2 triggered PI3K/AKT-mTOR signaling by crosstalk with PDGFR mediated by Yes1, resulting in elevating expression of c-Myc and HIF1a, which subsequently enhanced cancer cell glycolysis. Genetic and pharmacological inhibition of P2RY2 impaired tumor cell growth in subcutaneous and orthotopic xenograft model, as well as delayed tumor progression in inflammation-driven PDAC model. Additionally, synergy was observed when AR-C118925XX, the selective antagonist of P2RY2 receptor, and gemcitabine were combined, resulting in prolonged survival of xenografted PDAC mice. CONCLUSIONS: These findings revealed the roles of the P2RY2 in PDAC metabolic reprogramming, suggesting that P2RY2 might be a potential metabolic therapeutic target for PDAC.

- Suppression of stromal-derived Dickkopf-3 (DKK3) inhibits tumor progression and prolongs survival in pancreatic ductal adenocarcinoma

Science translational medicine 2018 Oct;10(464):

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30355799

Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis, and it is unclear whether its stromal infiltrate contributes to its aggressiveness. Here, we demonstrate that Dickkopf-3 (DKK3) is produced by pancreatic stellate cells and is present in most human PDAC. DKK3 stimulates PDAC growth, metastasis, and resistance to chemotherapy with both paracrine and autocrine mechanisms through NF- B activation. Genetic ablation of DKK3 in an autochthonous model of PDAC inhibited tumor growth, induced a peritumoral infiltration of CD8+ T cells, and more than doubled survival. Treatment with a DKK3-blocking

monoclonal antibody inhibited PDAC progression and chemoresistance and prolonged survival. The combination of DKK3 inhibition with immune checkpoint inhibition was more effective in reducing tumor growth than either treatment alone and resulted in a durable improvement in survival, suggesting that DKK3 neutralization may be effective as a single targeted agent or in combination with chemotherapy or immunotherapy for PDAC.

- TP63-Mediated Enhancer Reprogramming Drives the Squamous Subtype of Pancreatic Ductal Adenocarcinoma

Cell reports 2018 Nov;25(7):1741-1755.e7

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30428345

The aberrant expression of squamous lineage markers in pancreatic ductal adenocarcinoma (PDA) has been correlated with poor clinical outcomes. However, the functional role of this putative transdifferentiation event in PDA pathogenesis remains unclear. Here, we show that expression of the transcription factor TP63 (ΔNp63) is sufficient to install and sustain the enhancer landscape and transcriptional signature of the squamous lineage in human PDA cells. We also demonstrate that TP63-driven enhancer reprogramming promotes aggressive tumor phenotypes, including enhanced cell motility and invasion, and an accelerated growth of primary PDA tumors and metastases in vivo. This process ultimately leads to a powerful addiction of squamous PDA cells to continuous TP63 expression. Our study demonstrates the functional significance of squamous transdifferentiation in PDA and reveals TP63-based reprogramming as an experimental tool for investigating mechanisms and vulnerabilities linked to this aberrant cell fate transition.

- Desumoylating Isopeptidase 2 (DESI2) Inhibits Proliferation and Promotes Apoptosis of Pancreatic Cancer Cells through Regulating PI3K/AKT/mTOR Signaling Pathway

Pathology oncology research : POR 2018 Nov;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30411297

This study aimed to investigate the effects of desumoylating isopeptidase 2 (DESI2) on tumor cell proliferation, apoptosis and invasion of pancreatic cancer, and to assess the signaling pathway involved. Overexpression and silence of DESI2 were designed and the experiments were divided into 5 groups: a normal control group, an interference control group (shRNA-NC); an interference group (sh-DESI2); an overexpression control group (NC), an overexpression group (DESI2). Quantitative real time polymerase chain reaction (qRT-PCR) was used to screen the appropriate interference sequence. The silencing and overexpression of DESI2 were confirmed by qRT-PCR and western blotting. Cell cycling, apoptosis, invasion, and the expression of phosphatidylinositol-3-kinase (PI3K)-protein kinase B (AKT)-mammalian target of rapamycin (mTOR) pathway and caspase 3 were measured. Overexpression and silence of DESI2 were successfully designed in two pancreatic cancer cells, and the interference effect of sh-DESI2-3 showed the best silencing effects. The biological activities of DESI2 were detected in both ASPC-1 and PANCE-1 cells. Our results showed that cell proliferation was significantly increased in the sh-DESI2 group, while decreased in DESI2 group compared with the control group in both cell lines. In ASPC-1 cells, the events in G1 phase decreased and in S phase increased obviously in the sh-DESI2 group, compared with control group. An opposite result was found when DESI2 was overexpressed. In PANCE-1 cells, the events in G2 phase were higher in the sh-DESI2 group, while in the DESI2 group was significantly lower than that in control group. In ASPC-1 and PANCE-1 cells, sh-DESI2 group showed decreased apoptosis, increased cell invasion and increased expression of AKT, p-Akt, PI3K, p-PI3K, p-mTOR and mTOR and decreased caspase 3 expression compared with the control group, while overexpression of DESI2 leaded to increased apoptosis, decreased cell invasion and reduced expression of AKT, p-Akt, PI3K, p-PI3K, p-mTOR and mTOR and increased expression of caspase 3. DESI2 regulates the proliferation and apoptosis of pancreatic cancer cells through PI3K/AKT/mTOR signaling pathway.

- Disruption of stromal hedgehog signaling initiates RNF5-mediated proteasomal degradation of PTEN and accelerates pancreatic tumor growth

Life science alliance 2018 Oct;1(5):e201800190

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30456390

The contribution of the tumor microenvironment to pancreatic ductal adenocarcinoma (PDAC) development is currently unclear. We therefore examined the consequences of disrupting paracrine Hedgehog (HH) signaling in PDAC stroma. Herein, we show that ablation of the key HH signaling gene Smoothened (Smo) in stromal fibroblasts led to increased proliferation of pancreatic tumor cells. Furthermore, Smo deletion resulted in proteasomal degradation of the tumor suppressor PTEN and activation of oncogenic protein kinase B (AKT) in fibroblasts. An unbiased proteomic screen identified RNF5 as a novel E3 ubiquitin ligase responsible for degradation of phosphatase and tensin homolog (PTEN) in Smo-null fibroblasts. Ring Finger Protein 5 (Rnf5) knockdown or pharmacological inhibition of glycogen synthase kinase 3 (GSK), the kinase that marks PTEN for ubiquitination, rescued PTEN levels and reversed the oncogenic phenotype, identifying a new node of PTEN regulation. In PDAC patients, low stromal PTEN correlated with reduced overall survival. Mechanistically, PTEN loss decreased hydraulic permeability of the extracellular matrix, which was reversed by hyaluronidase treatment. These results define non-cell autonomous tumor-promoting mechanisms activated by disruption of the HH/PTEN axis and identifies new targets for restoring stromal tumor-suppressive functions.

- The Long Noncoding RNA HOST2 Promotes Gemcitabine Resistance in Human Pancreatic Cancer Cells

Pathology oncology research : POR 2018 Nov;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30406400

Our study was aimed to identify the fundamental role of lncRNA HOST2 in gemcitabine resistance regulation in human pancreatic cancer cells. The levels of HOST2 in pancreatic cancer cell lines were measured by quantitative real-time PCR (qRT-PCR). Due to high expression and strong gemcitabine resistance, Hs766T and AsPC-1 cell lines were selected to be knockdown the expression of HOST2 by transfection sh-HOST2. After manipulation of HOST2, the cell proliferation induced by gemcitabine was examined by CCK-8 assay. Next, colony formation ability of Hs766T and AsPC-1 cell lines was determined by clone-forming assay. At last, the relationship between HOST2 and cell apoptosis in Hs766T and AsPC-1 cell lines was evaluated by flow cytometry. QRT-PCR revealed that HOST2 was overexpressed in six pancreas neoplasm cell lines compared with normal cell lines HPDE6-C7. HOST2 expression levels in group resistant to gemcitabine were higher than the group sensitive to gemcitabine. Additionally, CCK-8 assay verified that cell proliferation was inhibited by sh-HOST2 with or without gemcitabine treatment. Furthermore, clone-forming assay revealed that colony formation ability was weakened by down-regulated HOST2 with or without gemcitabine treatment. Flow cytometry revealed that cell apoptosis induced by gemcitabine was promoted by sh-HOST2. In conclusion, down-regulated HOST2 inhibited proliferation and promoted apoptosis of pancreas cancer cells with or without gemcitabine treatment. Thus, HOST2 is a potential therapeutic target for gemcitabine chemoresistance in pancreatic neoplasms.

- Preprogramming therapeutic response of PI3K/mTOR dual inhibitor via the regulation of EHMT2 and p27 in pancreatic cancer

American journal of cancer research 2018 09;8(9):1812-1822

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30323973

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive disease, which is characterized by its high invasiveness, rapid progression, and profound resistance to therapy. Gemcitabine is the first-line treatment

option for pancreatic cancer patients, but the overall survival is quite low. Therefore, it is an urgent issue to identify new molecules for improved therapies, with better efficacy and less toxicity. Our previous data indicated that Euchromatic histone-lysine N-methyltransferase 2 (EHMT2) functions as a therapeutic target to override GEM resistance and promote metastasis in the treatment of pancreatic cancer. Here, we screened a small-molecule library of 143 protein kinase inhibitors, to verify cytotoxicity of different inhibitors in EHMT2-depleted cells. We determined that the EHMT2 plays a promising modulating role for targeted PI3K/mTOR inhibition. Our data revealed that EHMT2 down-regulates p27 expression, and this contributes to tumor growth. The depletion of EHMT2, ectopic expression of methyltransferase-dead EHMT2, or treatment with an EHMT2 inhibitor decreases H3K9 methylation of p27 promoter and induces G1 arrest in PANC-1 pancreatic cancer cells. Consistent with these findings, in vivo tumor xenograft models, primary tumors, and the Oncomine database utilizing bioinformatics approaches, also show a negative correlation between EHMT2 and p27. We further demonstrated that low EHMT2 elevated BEZ235 sensitivity through up-regulation of p27 in PDAC cells; high levels of SKP2 decrease BEZ235 responsiveness in PDAC cells. Altogether, our results suggest the EHMT2-p27 axis as a potential marker to modulate cell response to dual PI3K/mTOR inhibition, which might provide a strategy in personalized therapeutics for PDAC patients.

- MicroRNA let-7d targets thrombospondin-1 and inhibits the activation of human pancreatic stellate cells

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30393009

OBJECTIVES: The microRNA (miRNA) let-7d is linked to the formation of pancreatic cancer-related fibrosis. In this study, the mechanism by which let-7d regulates the activation of the human pancreatic stellate cell (hPSC) was evaluated. METHODS: The transient transfection of a let-7d mimic in the hPSCs was performed, and the altered thrombospondin 1 (THBS1) expression was confirmed by western blotting and real-time qPCR. Targeting of the 3'-untranslated region (UTR) of THBS1 by let-7d was investigated by the luciferase assays. After hPSC transfection using THBS1 siRNA, the fibrosis markers (-SMA and collagen 1A1) were evaluated by western blotting and real-time qPCR. The correlation between tumor fibrosis and let-7d or THBS1 was estimated using the data from The Cancer Genome Atlas project. Finally, the effects of genistein on the hPSCs were evaluated. RESULTS: We found that a let-7d mimic inhibits THBS1 expression by targeting its 3'-UTR. THBS1 inhibition by siRNA inhibited hPSC activation. An in silico analysis revealed that let-7d and THBS1 expression are negatively correlated. Additionally, let-7d was negatively correlated with the stromal score, while THBS1 was positively correlated with this score. Genistein substantially induced let-7d and decreased the expression of fibrosis marker along with the inhibition of THBS1. CONCLUSIONS: Let-7d inhibited hPSC activation by targeting THBS1. Genistein induced the expression of let-7d and might modulate pancreatic fibrosis.

- Evaluation of NCAM and c-Kit as hepatic progenitor cell markers for intrahepatic cholangiocarcinomas

Pathology, research and practice 2018 Dec;214(12):2011-2017

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30301635

BACKGROUND: Intrahepatic cholangiocarcinomas (ICCs) are primary liver malignancies and are the second most common type of malignancy after hepatocellular carcinoma. ICCs are heterogeneous in clinical features, genotype, and biological behavior, suggesting that ICCs can initiate in different cell lineages. AIM: We investigated intrahepatic cholangiocarcinoma RBE cell lines for the markers neural cell adhesion molecule (NCAM) and c-Kit, which possess hepatic progenitor cells properties. METHODS: NCAM + c-Kit + cells were tested for hepatic progenitor cell properties including proliferation ability, colony formation, spheroid formation, and invasiveness in NOD/SCID mice. The Agilent Whole Human Genome Microarray Kit was

used to evaluate differences in gene expression related to stem cell signaling pathways between NCAM + c-Kit + and NCAM-c-Kit- subset cells. Microarray results were further confirmed by real-time RT-PCR. RESULTS: NCAM + c-Kit + cells showed hepatic progenitor cell-like traits including the abilities to self-renew and differentiate and tumorigenicity in NOD/SCID mice. Differences were observed in the expression of 421 genes related to stem cell signaling pathways (fc 2 or fc 0.5), among which 231 genes were upregulated and 190 genes were downregulated. CONCLUSION: NCAM + c-Kit + subset cells in RBE may have properties of hepatic progenitor cells. NCAM combined with c-Kit may be a valuable marker for isolating and purifying ICC stem/progenitor cells.

Back to top

Techniques & Research Methods

- Understanding Pancreatic Diseases Using Animated Pancreas Patient: Informing Patients for Better Health Outcomes With Visual Formats of Learning

Pancreas 2018 10;47(10):1256-1261

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30286013

OBJECTIVES: The aim of this study was to evaluate the impact of Animated Pancreas Patient (APP) educational modules (APP website and YouTube) on pancreas education, awareness, and health outcomes. METHODS: This was a retrospective study of APP metrics data from September 2013 to October 2017. We evaluated audience reach (number of visit sessions, unique visitors, page views) and calculated top views by media type (animation, expert video, patient video, and slide show) and top retention videos from the modules. We also assessed the educational impact through learner feedback survey. RESULTS: The APP had 1,475,252 views (547,693 unique visitors, 63.1% in United States) during the study period. Most popular topic viewed among the animations was "Role and Anatomy of the Pancreas" (n = 361,116), and most common expert video viewed was "Chronic Pancreatitis: What Foods and Beverages Should I Avoid?" (n = 31,667). Participants who completed the online feedback survey reported knowledge gains and commitments to change. CONCLUSIONS: Pancreas education in visual formats of learning provided by APP demonstrated wide reach and has substantial potential to inform and impact behaviors of patients and caregivers. Continued efforts should be made to provide patient resources that address health literacy and patient education and respond to patient needs for better quality of life and improved health outcomes in pancreatic diseases.

- Standard Operating Procedures for Biospecimen Collection, Processing, and Storage: From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer

Pancreas 2019 11;47(10):1213-1221

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30325860

High-quality and well-annotated biorepositories are needed to better understand the pathophysiology and biologic mechanisms of chronic pancreatitis (CP) and its consequences. We report a methodology for the development of a robust standard operating procedure (SOP) for a biorepository based on the experience of the clinical centers within the consortium to study Chronic Pancreatitis, Diabetes and Pancreas Cancer Clinical Centers (CPDPC), supported by the National Cancer Institute and the National Institute for Diabetes and Digestive and Kidney Diseases as a unique multidisciplinary model to study CP, diabetes, and pancreatic cancer in both children and adults. Standard operating procedures from the CPDPC centers were evaluated and consolidated. The literature was reviewed for standard biorepository operating procedures that facilitated downstream molecular analysis. The existing literature on biobanking practices was harmonized with the SOPs from the clinical centers to produce a biorepository for pancreatic research. This article reports the methods and basic principles behind the creation of SOPs to develop a biorepository for the CPDPC. These will serve as a guide for investigators developing biorepositories in pancreas research. Rigorous and meticulous adherence to standardized biospecimen collection will facilitate investigations to better understand the pathophysiology and biologic mechanisms of CP, diabetes, and pancreatic cancer.

Back to top

Journals Reviewed

Advances in Anatomic Pathology
American Journal of Clinical Pathology
The American Journal of Gastroenterology
The American Journal of Pathology
American Journal of Surgical Pathology
Annals of Diagnostic Pathology
Annals of Surgery
Annals of Surgical Oncology
Annual Review of Pathology-Mechanisms of Disease
APMIS
Applied Immunohistochemistry & Molecular Morphology
Archives of Pathology & Laboratory Medicine
Cancer
Cancer Cell
Cancer Cytopathology
Cell
Clinical Cancer Research
Cytojournal
Cytopathology
Diagnostic Cytopathology
Diagnostic Pathology
Endocrine Pathology
Experimental and Molecular Pathology
Expert Review of Molecular Diagnostics
Gastroenterology
Gut
Histology and Histopathology
Histopathology
Human Pathology
International Journal of Surgical Pathology
International Journal of Clinical and Experimental Pathology
Journal of Clinical Pathology
Journal of Molecular Diagnostics
Journal of Pathology
Laboratory investigation
Lancet
Medical Molecular Morphology
Modern Pathology
Nature
Nature Reviews Gastroenterology & Hepatology
NEJM
Pancreas
Pancreatology
Pathobiology
Pathologie Biologie
Pathology
Pathology & Oncology Research
Pathology International
Pathology Research and Practice
PNAS
Seminars in Diagnostic Pathology

Seminars in Immunopathology
Surgical pathology clinics
Virchows Archiv

Back to top

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Back to top

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- Older Issues
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Back to top
