Pancreatobiliary Pathology Society Journal Watch

December 2018 - January 2019

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Contents

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

- Malformations, choristomas, and hamartomas of the gastrointestinal tract and pancreas

Seminars in diagnostic pathology 2019 Jan;36(1):24-38

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30482417

Congenital and hamartomatous lesions of the gastrointestinal tract cause diagnostic challenges for surgical pathologists. Many of these are merely histologic curiosities, whereas others have substantial clinical implications because they herald cancer syndromes or associated anomalies. Although a comprehensive discussion of all developmental abnormalities that can occur in the gastrointestinal tract is beyond the scope of a single manuscript, some entities are more likely to be encountered by surgical pathologists, have important clinical consequences, or pose diagnostic difficulties. The purpose of this review is to discuss the more common malformations and choristomas, as well as hamartomatous lesions that may be clinically important due to their risk for cancer development, frequent associations with heritable cancer syndromes and other anomalies, or potential to simulate other entities.

- AQP1 and AQP3 Expression are Associated With Severe Symptoms and Poor-prognosis of the Pancreatic Ductal Adenocarcinoma

Applied immunohistochemistry & molecular morphology : AIMM 2019 Jan;27(1):40-47

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30531392

BACKGROUND: Approximately 80% of patients with pancreatic ductal adenocarcinoma (PDAC) have metastatic disease with poor prognosis, but clinically available biomarkers for the diagnosis, prediction of prognosis, and target therapy have not yet been identified. OBJECTIVE: To investigate the expression of aquaporin-1 (AQP1) and AQP3 protein and their clinicopathological significances in PDACs. MATERIALS AND METHOD: AQP1 and AQP3 protein expression in 106 PDAC, 35 peritumoral tissues, 55 benign pancreatic lesions, and 13 normal pancreatic tissues was measured by immunohistochemistry. RESULTS: Western blot showed that AQP1 and AQP3 protein expression was significantly higher in PDAC tissues than that in benign pancreatic tissues ($P<0.01$). Immunohistochemistry showed that the percentages of positive AQP1 and AQP3 expressions were significantly higher in PDAC tumors than that in peritumoral tissues, benign, and normal pancreatic tissues ($P<0.01$). Benign pancreatic lesions with positive AQP1 and AQP3 expression exhibited a dysplasia or intraepithelial neoplasia. The percentage of cases with positive AQP1 and AQP3 expression was significantly lower in PDAC patients without lymph node metastasis and invasion, and having low Tumor, Node and Metastasis (TNM) stage disease than in patients with lymph node metastasis, invasion, and high TNM stage disease ($P<0.05$ or <0.01). Kaplan-Meier survival analysis showed that positive AQP1 and AQP3 expression were significantly associated with survival in PDAC patients ($P<0.001$). Cox multivariate analysis revealed that positive AQP1 and AQP3 expression was independent poor prognosis factors in PDAC patients. The area under the curve of receiver operating characteristic curve was 0.669 for AQP1 and 0.707 for AQP3, respectively. CONCLUSIONS: Positive AQP1 and AQP3

expressions are associated with the tumorigenesis and progression of PDAC. Both AQP1 and AQP3 are a diagnostic marker of PDAC and a predictive marker of poor prognosis in PDAC patients.

- Clinicopathologic and prognostic significance of MKK4 and MKK7 in resectable pancreatic ductal adenocarcinoma

Human pathology 2018 Dec;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30537492

Mitogen-activated protein kinase kinase 4 (MKK4) and mitogen-activated protein kinase kinase 7 (MKK7) were shown to regulate biological behavior in many malignancies. In pancreatic ductal adenocarcinoma (PDAC), it remains controversial whether MKK4 and MKK7 have pro-oncogenic or tumor-suppressive activities. Furthermore, their clinicopathologic and prognostic implications are unknown. In the present study, we detected MKK4 and MKK7 expressions in the nucleus and cytoplasm of resected PDAC tissues from 321 patients by tissue microarray-based immunohistochemistry. Cytoplasmic MKK4 and MKK7 expressions were significantly down-regulated, while nuclear MKK4 expression was significantly up-regulated in tumor tissues compared with non-tumor tissues. Tumor cytoplasmic MKK4 and MKK7 expressions were significantly negatively associated with histological grade. Cytoplasmic MKK4 expression was also negatively correlated with CA19-9 level. By univariate analysis, high cytoplasmic MKK4 expression was significantly associated with longer cancer-specific survival (hazard ratio [HR]: 0.705; 95% confidence interval [95%CI]: 0.510-0.974), with a similar trend observed for MKK7 expression. High MKK4 and MKK7 mRNA expressions were significantly associated with longer overall survival in the TCGA database. Although MKK4 expression was not significant in a multivariate Cox regression analysis, combination of MKK4/MKK7 and pN stage was identified as an independent prognostic indicator and had the lowest HR (HR: 0.308; 95%CI: 0.126-0.752). Furthermore, combined analysis of MKK4 and MKK7 greatly increased the prognostic predictive power. In addition, down-regulation of MKK4 or MKK7 increased proliferation of pancreatic cancer cells in vitro. In conclusion, high MKK4 expression and its combination with high MKK7 expression both predicted favorable prognosis in resectable 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.

- Pancreatic Ductal Adenocarcinoma: Recent Updates

The American journal of pathology 2019 Jan;189(1):6-8

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30558724

This Guest Editorial introduces this month's special Pancreatic Cancer Theme Issue, a series of reviews intended to highlight the pathologic to molecular profiles and diagnoses of benign and neoplastic pancreatic lesions.

- Pancreatic Ductal Adenocarcinoma and Its Precursor Lesions: Histopathology, Cytopathology, and Molecular Pathology

The American journal of pathology 2019 Jan;189(1):9-21

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30558727

Pancreatic ductal adenocarcinoma is one of the most aggressive malignant neoplasms with poor outcomes. At the time of diagnosis, the disease is usually at an advanced stage and only a minority is eligible for surgical resection. To improve the prognosis, it is essential to diagnose and treat the disease in an early stage before its progression into an invasive disease. This article reviews clinical features, histopathology, cytopathology, and molecular alterations of pancreatic ductal adenocarcinoma and its precursors. Moreover, we review a recently updated two-tier classification system for precursor lesions, new findings in premalignant cystic neoplasms, and recently updated staging criteria for invasive carcinoma based on the Cancer Staging Manual, eighth edition, from the American Joint Committee on Cancer. Finally, we discuss the potential clinical applications of the rapidly growing molecular and genetic information of pancreatic cancer and its precursors.

- Overexpression of folate receptor alpha is an independent prognostic factor for outcomes of pancreatic cancer patients

Medical molecular morphology 2018 Jun;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29926190

Pancreatic cancer has a poor prognosis; hence, novel prognostic markers and effective therapeutic targets should be identified. We aimed to evaluate folate receptor alpha (FR-) expression in pancreatic cancer and examine its association with clinicopathological features. We utilized tissue samples from 100 primary pancreatic cancer patients who underwent surgery. FR- was expressed in 37 of 100 cases (37%). The FR- -positive group (median, 18.8 months) had a significantly poorer prognosis than the FR- -negative group [median 21.3 months; HR 1.89 (1.12-3.12); P = 0.017]. These groups were not significantly different regarding progression-free survival (P = 0.196). Furthermore, other serum tumor markers including CA19-9 (mean, 186 vs. 822 U/ml; P = 0.001), Dupan-2 (286 vs. 1133 U/ml; P = 0.000), and Span-1 (69.7 vs. 171.9 U/ml; P = 0.006) were significantly downregulated in the FR- -positive group. CA19-9 was another prognostic factor, in addition to FR- , and patient prognosis showed clear stratification curves with the expression of these two molecules. Along with CA19-9, FR- expression was an independent prognostic factor for the overall survival. FR- and CA19-9 helped predict patient prognosis based on stratification curves.

Back to top

Staging

Pancreas TNM staging, Margins, Survival

- Application of the Eighth Edition of the American Joint Committee on Cancer Staging for Pancreatic Adenocarcinoma

Pancreas 2018 07;47(6):742-747

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29851752

OBJECTIVES: Notable modifications have been made in the American Joint Committee on Cancer (AJCC) Staging eighth edition staging for pancreatic cancer for the consideration of the irreproducible and inapplicable of the AJCC seventh edition staging. However, the new staging classification has not been systemically verified. METHODS: A comparison was performed to evaluate the application of the AJCC seventh and eighth staging classifications using the Surveillance, Epidemiology, and End Results registry (18,450 patients) and an institutional series (2040 patients). RESULTS: For the eighth staging classification, patients with tumor diameter of greater than 4 cm (T3N0M0, IIA) had similar prognosis to patients with 1 to 3 positive nodes (T1-3N1M0, IIB). For patients who underwent tumor resection and without lymph node involvement, survival curves of T1 (2 cm), T2 (2-4 cm), and T3 (>4 cm) were well separated. Statistical difference in survival analyses was demonstrated in N0 (0 positive node), N1 (1-3 positive nodes), and N2 (4 positive nodes) patients underwent tumor resection. The AJCC eighth edition had better stage distribution than the AJCC seventh edition for pancreatic cancer. CONCLUSIONS: The eighth edition of AJCC staging is more applicable and accurate than the seventh edition for pancreatic adenocarcinoma.

- Prognostic significance of the degree of lymphatic vessel invasion in locally advanced, surgically resectable pancreatic head cancer: A single center experience

Medicine 2018 Dec;97(49):e13466

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30544433

Little is known concerning the prognostic significance of the degree of lymphatic vessel invasion in pancreatic head cancer. To address this gap in knowledge, we retrospectively examined 60 patients with locally advanced, surgically resectable pancreatic head cancer who underwent pancreaticoduodenectomy and lymph node (LN) dissection.All cases were histopathologically diagnosed as ductal adenocarcinoma, stage II (25 pT3N0 cases, 35 pT3N1 cases). The following variables were investigated: age; sex; neoadjuvant therapy; adjuvant therapy; tumor size; tumor grade; invasion into the serosa, retropancreatic tissue, duodenum, bile duct, portal venous system and perineural area; cut margins; LN metastasis; and the number of invaded lymphatic vessels (LVI-score).Univariate analysis demonstrated that LN metastasis and an LVI-score 5 were significantly associated with poor disease-free survival. Multivariate Cox regression analysis confirmed that LN metastasis and an LVI-score 7 were significantly associated with poor disease-free survival. Additionally, LVI-scores 9 and 10 were comparable to or surpassed the significance of LN metastasis based on the hazard ratio. Univariate analysis demonstrated that tumor size >30mm, duodenal invasion, LN metastasis and an LVI-score 2 were significantly associated with poor overall survival. Multivariate Cox regression analysis confirmed that LN metastasis and LVI-scores 9 and 10 were significantly associated with poor overall survival, and an LVI-score 10 was comparable to or surpassed the significance of LN metastasis based on the hazard ratio.Our study strongly suggests that a high degree of lymphatic vessel invasion is associated with a poor prognosis in patients with locally advanced, surgically resectable pancreatic head cancer.

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

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

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

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

- Pancreatic Cancer Lymph Node Resection Revisited: A Novel Calculation of the Number of Lymph Nodes Required

Journal of the American College of Surgeons 2019 Jan;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30677528

BACKGROUND: Pancreatic cancer is the third leading cause of cancer related deaths in the U.S. Though lymph node metastasis is a prognostic indicator, the extent of lymph node (LN) resection is still debated. Our goal was to use the distribution of the ratio of positive to negative lymph nodes to derive a more adequate number of necessary examined lymph nodes based on the target lymph node threshold (TLNT). STUDY DESIGN: Using the National Cancer Database (NCDB), we performed a retrospective study of surgically resected pancreatic adenocarcinoma (2010-2015). We evaluated the number of positive LN (PNL) and total lymph nodes (LNE) examined, and the log of the ratio of PLNs to negative LNs (LODDS). The distribution of LODDS was examined in order to determine a target LN examined threshold (TLNT) sufficient to detect N1 disease. Using the LODDS distribution of N1 cases, TLNT were calculated to encompass 90 of the N1 group distribution. RESULTS: Of the total 24,038 resected patients included in this study, 26% underwent surgery only, 18% received neoadjuvant therapy and 56% underwent adjuvant therapy. 8,144 (34%) of patients had N0 disease while 15,894(66%) had N1 disease. In order to capture 90-95% of the N1 group, the minimum number of LN examined would be 18 (LODDS -2.74) to 24 (LODDS -3.04) respectively. CONCLUSIONS: Though previous studies have suggested 11-17 LNs required for adequate LN sampling in pancreatic cancer, our findings suggest that in order to capture 90% of cases with N1 disease, 18 LN is more appropriate.

- Determining the optimal number of examined lymph nodes for accurate staging of pancreatic cancer: An analysis using the nodal staging score model

European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 2019 Jan;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30685327

INTRODUCTION: The aim of this study was to determine the optimal number of examined lymph nodes (ELNs) for accurate staging of pancreatic cancer using the nodal staging score model. MATERIALS AND METHODS: Clinicopathological data for patients with resected pancreatic cancer were collected from SEER database (development cohort [DC]) and Fudan University Shanghai Cancer Center database (validation cohort [VC]). Multivariable models were constructed to assess how the number of ELNs was associated with stage migration and overall survival (OS). Using the -binomial distribution, we developed a nodal staging

score model from the DC and tested it with the VC. RESULTS: Both cohorts exhibited significant proportional increases from node-negative to node-positive disease (DC: odds ratio [OR], 1.047; $P < 0.001$; VC: OR, 1.035; $P < 0.001$) and improved OS (DC: hazard ratio [HR], 0.982; $P < 0.001$; VC: HR, 0.979; $P < 0.001$) as ELNs increased. Nodal staging scores escalated separately as ELNs increased for different tumor (T) stages, with plateaus at 16, 21, and 23 LNs (cut-offs) for T1, T2, and T3 tumors, respectively. Multivariable analysis indicated that examining more LNs than the corresponding cut-off value was a significant survival predictor (DC: HR, 0.813; $P < 0.001$; VC: HR, 0.696; $P = 0.028$). CONCLUSION: The optimal number of ELNs for adequate staging of pancreatic cancer was related to T stage. We recommend examining at least 16, 21, and 23 LNs for T1, T2, and T3 tumors, respectively, as a nodal staging quality measure for both surgery and pathological analysis.

Back to top

Preneoplastic and Preinvasive Lesions

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

- New Model for Predicting Malignancy in Patients With Intraductal Papillary Mucinous Neoplasm

Annals of surgery 2018 Nov;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30499803

OBJECTIVE: To create a simple, objective model to predict the presence of malignancy in patients with intraductal papillary mucinous neoplasm (IPMN), which can be easily applied in daily practice and, importantly, adopted for any lesion types. BACKGROUND: No predictive model for malignant IPMN has been widely applied in clinical practice. METHODS: The clinical details of 466 patients with IPMN who underwent pancreatic resection at 3 hospitals were retrospectively analyzed for model development. Then, the model was validated in 664 surgically resected patients at 8 hospitals in Japan.In the preoperative examination, endoscopic ultrasonography (EUS) was considered to be essential to observe mural nodules in both the model development and external validation sets. Malignant IPMNs were defined as those with high-grade dysplasia and associated invasive carcinoma. RESULTS: Of the 466 patients, 258 (55%) had malignant IPMNs (158 high-grade dysplasia, 100 invasive carcinoma), and 208 (45%) had benign IPMNs. Logistic regression analysis resulted in 3 variables (mural nodule size, main pancreatic duct diameter, and cyst size) being selected to construct the model. The area under the receiver operating characteristic curve (AUC) for the model was 0.763. In external validation sets, the pathological diagnosis was malignant and benign IPMN in 351 (53%) and 313 (47%) cases, respectively. For the external validation, the malignancy prediction ability of the model corresponded to an AUC of 0.725. CONCLUSION: This predictive model provides important information for physicians and patients in assessing an individual's risk for malignancy and may help to identify patients who need surgery.

- Subtyping of intraductal papillary mucinous neoplasms - pitfalls of MUC1 immunohistochemistry

APMIS : acta pathologica, microbiologica, et immunologica Scandinavica 2019 Jan;127(1):27-32

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30549137

Intraductal papillary mucinous neoplasms (IPMNs) are precursor lesions of pancreatic ductal adenocarcinoma (PDAC). Current edition of WHO Classification of Tumors of the Digestive System recognizes four different subtypes (gastric, intestinal, pancreatobiliary, and oncocytic) and recommends analysis of mucin expression (MUC1, MUC2, MUC5AC, MUC6) as well as evaluation of architectural and cell differentiation patterns for correct classification. However, there is no consensus on MUC1 expression of IPMN-lesions in the literature. Current recommendations are based on studies where antibodies against the core MUC1 protein or sialylated MUC1 (tumor associated MUC1), not the fully glycosylated MUC1 were used. We have recently reported that MUC1 is strongly expressed in both gastric and intestinal types IPMN specimens from the cystic wall, obtained by endoscopic ultrasound guided microbiopsy procedure. We have used a commercial MUC1 antibody, validated and recommended for diagnostic use, which recognizes fully glycosylated MUC1. Based on the above, we propose a revision of the WHO Classification, specifying that antibodies against tumor associated MUC1 should be used for IPMN subtyping.

- Should we regard all main duct type intraductal papillary mucinous neoplasms of the pancreas (MD-IPMN) as an indication of surgery? -A retrospective study in 29 patients with MD-IPMN showing mural nodules

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30679137

PURPOSE: To elucidate predictive factors for malignant main duct type IPMN (MD-IPMN). METHODS: All 29 subjects had mural nodules (MNs) in the main pancreatic duct (MPD) on preoperative endoscopic ultrasonography and underwent surgery (19, malignant; 10, benign). Possible predictive factors for malignancy such as background, imaging, and histological factors including histological subtype (HS), were evaluated. RESULTS: Multivariate analysis revealed an MPD diameter of 12 mm ($p = 0.042$) and non-gastric type ($p = 0.001$) to be the statistically significant predictive factors for malignancy. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy to detect malignancy by using "an MPD diameter of 12 mm and/or non-gastric type" were 95%, 70%, 86%, 88%, and 86%, respectively. In 7 subjects in whom HS was preoperatively evaluated using pancreatic specimens obtained before surgery, the agreement rate of the preoperative HS with definitive HS evaluated using resected specimens was 86%. CONCLUSIONS: For MD-IPMNs with MNs, "an MPD diameter of 12 mm and/or non-gastric type" are indicated for surgery. On the other hand, careful surveillance without immediate pancreatic surgery may be an option for MD-IPMNs showing both an MPD diameter of <12 mm and gastric type.

Back to top

Microenvironment

Tumor Stroma Interactions, Microenvironment, Inflammatory Response

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- Quasimesenchymal phenotype predicts systemic metastasis in pancreatic ductal adenocarcinoma

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30683911

Metastasis following surgical resection is a leading cause of mortality in pancreatic ductal adenocarcinoma. Epithelial-mesenchymal transition is thought to play an important role in metastasis, although its clinical relevance in metastasis remains uncertain. We evaluated a panel of RNA in-situ hybridization probes for epithelial-mesenchymal transition-related genes expressed in circulating tumor cells. We assessed the predictive value of this panel for metastasis in pancreatic ductal adenocarcinoma and, to determine if the phenotype is generalizable between cancers, in colonic adenocarcinoma. One hundred fifty-eight pancreatic ductal adenocarcinomas and 205 colonic adenocarcinomas were classified as epithelial or quasimesenchymal phenotype using dual colorimetric RNA-in-situ hybridization. SMAD4 expression on pancreatic ductal adenocarcinomas was assessed by immunohistochemistry. Pancreatic ductal adenocarcinomas with quasimesenchymal phenotype had a significantly shorter disease-specific survival ($P = 0.031$) and metastasis-free survival ($P = 0.0001$) than those with an epithelial phenotype. Pancreatic ductal adenocarcinomas with SMAD4 loss also had lower disease-specific survival ($P = 0.041$) and metastasis-free survival ($P = 0.001$) than those with intact SMAD4. However, the quasimesenchymal phenotype proved a more robust predictor of metastases-area under the curve for quasimesenchymal $= 0.8$; SMAD4 $= 0.6$. The quasimesenchymal phenotype also predicted metastasis-free survival ($P = 0.004$) in colonic adenocarcinoma. Epithelial-mesenchymal transition defined two phenotypes with distinct metastatic capabilities-epithelial phenotype tumors with predominantly organ-confined disease and quasimesenchymal phenotype with high risk of metastatic disease in two epithelial malignancies. Collectively, this work validates the relevance of epithelial-mesenchymal transition in human gastrointestinal tumors.

- The Paradoxical Web of Pancreatic Cancer Tumor Microenvironment

The American journal of pathology 2019 Jan;189(1):44-57

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30558722

Pancreatic ductal adenocarcinoma (PDAC) is increasing in incidence and is projected to become the second leading cause of cancer death in the United States. Despite significant advances in understanding the disease, there has been minimal increase in PDAC patient survival. PDAC tumors are unique in the fact that there is significant desmoplasia. This generates a large stromal compartment composed of immune cells, inflammatory cells, growth factors, extracellular matrix, and fibroblasts, comprising the tumor microenvironment (TME), which may represent anywhere from 15% to 85% of the tumor. It has become evident that the TME, including both the stroma and extracellular component, plays an important role in tumor progression and chemoresistance of PDAC. This review will discuss the multiple components of the TME, their specific impact on tumorigenesis, and the multiple therapeutic targets.

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

Gastroenterology 2018 11;155(5):1625-1639.e2

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

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

- Inter- and intra-tumoral heterogeneity in cancer-associated fibroblasts of human pancreatic ductal adenocarcinoma

The Journal of pathology 2018 Dec;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30575030

Cancer-associated fibroblasts (CAF) are orchestrators of the pancreatic ductal adenocarcinoma (PDAC) microenvironment. Stromal heterogeneity may explain differential pathophysiological roles of the stroma (pro- vs. anti-tumoral) in PDAC. We hypothesized that multiple CAF functional subtypes exist in PDAC, that contribute to stromal heterogeneity through interactions with cancer cells. Using molecular and functional analysis of patient-derived CAF primary cultures, we demonstrated that human PDAC-derived CAFs display a high level of inter- and intra-tumour heterogeneity. We identified at least four subtypes of CAFs based on transcriptomic analysis, and propose a classification for human PDAC-derived CAFs (pCAFassigner). Multiple CAF subtypes co-existed in individual patient samples. The presence of these CAF subtypes in bulk tumours was confirmed using publicly available gene expression profiles, and immunostainings of CAF subtype markers. Each subtype displayed specific phenotypic features (matrix- and immune-related signatures, vimentin and -smooth muscle actin expression, proliferation rate), and was associated with an assessable prognostic impact. A prolonged exposure of non-tumoral pancreatic stellate cells to conditioned media from cancer cell lines (cancer education experiment) induced a CAF-like phenotype, including loss of capacity to revert to quiescence and an increase in the expression of genes related to CAF subtypes B and C. This classification demonstrates molecular and functional inter- and intra-tumoral heterogeneity of CAFs in human PDAC. Our subtypes overlap with those identified from single-cell analyses in other cancers, and pave the way for the development of therapies targeting specific CAF sub-populations in PDAC. This article is protected by copyright. All rights reserved.

- Epithelial-Stromal Interactions in Pancreatic Cancer

Annual review of physiology 2018 Nov;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30418798

Pancreatic cancer is characterized by an extensive fibroinflammatory reaction that includes immune cells, fibroblasts, extracellular matrix, vascular and lymphatic vessels, and nerves. Overwhelming evidence indicates that the pancreatic cancer microenvironment regulates cancer initiation, progression, and maintenance. Pancreatic cancer treatment has progressed little over the past several decades, and the prognosis remains one of the worst for any cancer. The contribution of the microenvironment to carcinogenesis is a key area of research, offering new potential targets for treating the disease. Here, we explore the composition of the pancreatic cancer stroma, discuss the network of interactions between different components, and describe recent attempts to target the stroma therapeutically. We also discuss current areas of active research related to the tumor microenvironment. Expected final online publication date for the Annual Review of Physiology Volume 81 is February 10, 2019. Please see http://www.annualreviews.org/page/journal/pubdates for revised estimates.

Back to top

SPN

Solid Pseudopapillary Neoplasm

- Prognostic value of progesterone receptor in solid pseudopapillary neoplasm of the pancreas: evaluation of a pooled case series

BMC gastroenterology 2018 Dec;18(1):187

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30547767

BACKGROUND: The role of progesterone receptor (PR) has been reported in a series of pancreatic cysts. However, the relationship between PR and prognosis of solid pseudopapillary neoplasm of the pancreas (SPNP) has not been elucidated so far. The aim of our study was to evaluate the prognostic value of PR in SPNP. METHODS: A total of 76 patients with SPNP treated in our institution from January 2012 to December 2017 were included. Demographic parameters, laboratory data, pathologic information and clinical outcomes were analyzed by the use of survival analysis. In addition, a pooled case series was performed to evaluate the results. RESULTS: The institutional data included 76 patients (17 male and 59 female) ranging from 8 to 90 years (median, 30 years) in age. Kaplan-Meier survival analysis confirmed negative PR result was significantly associated with poorer disease-free survival (DFS) and disease-specific survival (DSS) (both $P < 0.001$). In the pooled analysis, a total of 62 studies comprising 214 patients with SPNP were included. After multivariable cox analysis, negative PR result remained an independent prognostic factor for SPNP (DFS HR: 14.50, 95% CI: 1.98-106.05, $P = 0.008$; DSS HR: 9.15, 95% CI: 1.89-44.17, $P = 0.006$). CONCLUSION: Our results indicated the role of PR in predicting adverse outcome of patients with SPNP and negative PR result may serve as a potential prognostic factor.

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

Virchows Archiv : an international journal of pathology 2019 Jan;474(1):105-109

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

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

Back to top

Analogue Tumors & Lesions

- Pancreatic Acinar Metaplasia in Distal Esophageal Biopsies Is Associated With Chronic Nonsteroidal Anti-inflammatory Drug Use

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30525934

CONTEXT.—: The cause of pancreatic acinar metaplasia (PAM) at the distal esophagus/esophagogastric junction is still controversial. Whereas some authors believe it is congenital, others believe it is acquired because of inflammation of the gastric cardia, and more recently it was proposed to be due to chronic proton pump inhibitor use based on a study in rats. OBJECTIVE.—: To determine whether there is correlation between chronic proton pump inhibitor use and PAM in humans. We also investigated the correlation between several clinical and pathologic factors and PAM. DESIGN.—: Four hundred forty-four consecutive biopsies from the distal esophagus/esophagogastric junction were reviewed for the presence of PAM, which was then correlated with several clinical and pathologic findings. RESULTS.—: Pancreatic acinar metaplasia was found in 71 patients (16%). Pancreatic acinar metaplasia was significantly associated with patient age younger than 51 years ($P < .001$), chronic carditis ($P = .01$), and chronic proton pump inhibitor use ($P = .008$). Surprisingly, we also found significant association between PAM and chronic nonsteroidal anti-inflammatory drug use ($P < .001$). These associations, including that with chronic nonsteroidal anti-inflammatory drug use, remained significant in multivariate analysis. CONCLUSIONS.—: Our findings confirm the previous reports of significant association between PAM and chronic carditis and the findings from animal studies of association with chronic proton pump inhibitor use. The strong association with chronic nonsteroidal anti-inflammatory drug use has not been previously reported and warrants further studies.

Back to top

- Tumefactive Inflammatory Diseases of the Pancreas

The American journal of pathology 2019 Jan;189(1):82-93

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30558726

Advances in the past two decades have resulted in the recognition of several tumefactive pancreatic lesions that, on histologic evaluation, show a varying combination of inflammation and fibrosis. Autoimmune pancreatitis, the prototypic tumefactive pancreatic fibroinflammatory lesion, is composed of two distinct diseases, type 1 autoimmune pancreatitis and the less common type 2 autoimmune pancreatitis. Although designated as autoimmune pancreatitis, the two diseases show little morphologic or pathogenic overlap. In type 1 disease, subsets of T lymphocytes (type 2 helper T cells, regulatory T cells, and T follicular helper 2 cells) are hypothesized to drive the inflammatory reaction. The B-cell response is characterized by an oligoclonal expansion of plasmablasts, with dominant clones that vary among patients and distinct clones that emerge at the time of relapse. Although the precise role of IgG4 in this condition remains uncertain, recent studies suggest that other IgG subclasses (eg, IgG1) may mediate the immune reactions, whereas IgG4 represents a response to dampen excessive inflammation. A recent study of type 2 autoimmune pancreatitis highlights the role of CXCL8 (alias IL-8), with duct epithelium and infiltrating T lymphocytes expressing this chemokine; the latter may contribute to the distinct form of neutrophilic inflammation in this disease. The review also highlights other forms of mass-forming chronic pancreatitis: follicular pancreatitis, groove pancreatitis, and those associated with rheumatologic diseases.

- Clinicopathological and immunological features of follicular pancreatitis-a distinct disease entity characterized by Th17 activation

Histopathology 2018 Dec;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30515871

AIM: Follicular pancreatitis is a recently recognized, distinct clinicopathological entity characterized by the presence of many intrapancreatic lymphoid follicles with reactive germinal centres. However, the clinicopathological and immunological features and causes have not yet been established. We assessed the clinicopathological and immunological profiles of patients with follicular pancreatitis who underwent surgery. METHODS AND RESULTS: This study included three patients with pancreatic masses (age range: 62-75 years; women:men: 1:2). A histopathological study of the resected pancreatic masses revealed abundant lymphoid follicles with reactive germinal centres in both periductal regions and diffusely within the parenchyma. No storiform fibrosis, obliterative phlebitis, or granulocytic epithelial lesions were observed. The immunohistochemical examination revealed an IgG4/IgG-positive plasma cell ratio <30% in all patients. Podoplanin (Th17 marker)-expressing lymphocytes were present in the lymphoid follicles of those with follicular pancreatitis, whereas these were absent in normal lymph nodes and in lymphoid follicles of those with IgG4-related autoimmune pancreatitis (AIP). An RNA digital counting assay clearly demonstrated that the expression counts of 20 genes, including dendritic cells and lymphoid follicles markers, and related cytokines were significantly higher in follicular pancreatitis than in IgG4-related AIP ($p<0.01$). The expressions of CCR6 and IL23A, which are genes related to Th17, were high. CONCLUSIONS: This study shows that follicular pancreatitis is a histopathologically and immunologically distinct disease entity of pancreatitis and is characterized by upregulated Th17 expression. This article is protected by copyright. All rights reserved.

Back to top

Bile Ducts

Morphology, Diagnostics, IHC

Morphology, Diagnostics, IHC

- Cholangiolocellular Carcinoma With "Ductal Plate Malformation" Pattern may be Characterized by ARID1A Genetic Alterations

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30520820

Cholangiolocellular carcinoma (CLC) is a unique subtype of primary liver carcinoma, which sometimes coexists with hepatocellular carcinoma (HCC), cholangiocarcinoma and combined hepatocellular-cholangiocarcinoma (cHCC-CCA). "Ductal plate malformation" (DPM)-pattern of primary liver carcinoma, which resembles biliary lesions in Caroli disease and von Meyenburg complex, is sometimes associated with CLC. We examined genetic alterations of hTERT promoter (hTERT), IDH1 or 2 (IDH1/2), KRAS, ARID1A, PBRM1, ARID2, BAP1, p53 and their association with histologic features such as proportion of CLC and DPM-pattern in 77 patients with primary liver carcinoma diagnosed as cHCC-CCA or CLC. Primary liver carcinomas were histologically subdivided into 29 CLC-predominant (CLC component >80%), 31 with CLC (5% to 80%) and 17 without CLC (<5%). CLC-predominant group was characterized by older age, male-predominant and smaller tumor size. Genetic alterations were detected in hTERT (25%), ARID1A (21%), PBRM1 (20%), ARID2 (3%), BAP1 (1%), p53 (46%), KRAS (5%), and IDH1/2 (8%). ARID1A alteration was more frequent in CLC-predominant group, compared with other groups ($P<0.05$) and was correlated with the degree of DPM-pattern ($P<0.01$). Alterations of hTERT and p53 were less frequent in CLC-predominant group compared with "with CLC group" ($P<0.05$). hTERT mutation was less frequent in carcinomas with DPM-pattern ($P<0.01$). PBRM1 alteration was more frequent in CLC with focal HCC subgroup and without CLC group compared with other groups ($P<0.05$). CLC may be a distinct subgroup of primary liver carcinoma, which is different from cHCC-CCA, based on clinicopathologic and genetic alterations. ARID1A alterations may characterize CLC with DPM-pattern and could be a diagnostic immunohistochemical marker for small CLCs with DPM-pattern.

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

Histopathology 2018 Sep;73(3):369-385

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29573451

Optimal patient management benefits from comprehensive and accurate pathology reports that contribute to cancer staging and prognostication. Proforma reports are used in many countries, but these vary in their structure and implementation. The International Collaboration on Cancer Reporting (ICCR) is an alliance formed by the Royal College of Pathologists of Australasia, the Royal College of Pathologists of the United Kingdom, the College of American Pathologists, the Canadian Partnership Against Cancer the European Society of Pathology and the American Society of Clinical Pathology (ASCP), with the aim of developing an evidence-based reporting data set for each cancer site. It is argued that this should reduce the global burden of cancer data set development and reduplication of effort by different international institutions that commission, publish and maintain standardised cancer reporting data sets. The resultant standardisation of cancer reporting will benefit not only those countries directly involved in the collaboration but also others not in a position to develop their own data sets. We describe the development of a cancer data set by the ICCR expert panel for the reporting of the main malignant liver tumours: intrahepatic cholangiocarcinoma, perihilar cholangiocarcinoma and hepatocellular carcinoma and present the 'required'

and 'recommended' elements to be included in the report with an explanatory commentary. This data set incorporates definitions and classifications in the most recent World Health Organisation (WHO) publication on hepatic malignancies (4th edition) and the recently published tumour-node-metastasis (TNM)8 staging system. Widespread adoption and implementation of this data set will enable consistent and accurate data collection, comparison of epidemiological and pathological parameters between different populations, facilitate research and ultimately result in better patient outcomes.

- Clinical features of isolated proximal-type IgG4-related sclerosing cholangitis

Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society 2018 Dec;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30570170

BACKGROUND AND AIMS: IgG4-related sclerosing cholangitis (IgG4-SC) presents as isolated proximal-type sclerosing cholangitis (i-SC). This study sought to clarify the imaging differences between i-SC and Klatskin tumor. The differences between i-SC and IgG4-SC associated with autoimmune pancreatitis (AIP-SC) were also studied. METHODS: Differentiating factors between i-SC and Klatskin tumor were studied. The serum IgG4 level, CA19-9 level, CT findings, cholangiography findings (symmetrical smooth long stricture extending into upper bile duct [SSLS]), endosonographic features (continuous symmetric mucosal lesion to the hilar part [CSML]), endoscopic biopsy results, treatment, relapse, and survival were also compared between patients with i-SC and those with AIP-SC. RESULTS: For a differential diagnosis between i-SC (N = 9) and Klatskin tumor (N = 47), the cutoff value of serum IgG4 level was 150mg/dL (sensitivity=0.857, specificity=0.966). Logistic regression analysis indicated that serum IgG4 level, the presence of SSLS, presence of CSML and the presence of ampulla swollen are independent factor for identifying i-SC. The relapse rate was significantly higher in the IgG4-SC with AIP group than in the i-SC group (log rank, p = 0.046). CONCLUSION: i-SC presents as a nodular lesion with SSLS and/or CSML mimicking a Klatskin tumor. Those endoscopic features might provide a diagnostic clue for i-SC. i-SC is likely to have a more favorable prognosis than IgG4-SC with AIP. This article is protected by copyright. All rights reserved.

- Impact of Tumour Budding Grade in 310 Patients Who Underwent Surgical Resection for Extrahepatic Cholangiocarcinoma

Histopathology 2019 Jan;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30667537

AIMS: Tumour budding is a risk factor for poor prognosis in various cancers. Tumour buds may present an epithelial-mesenchymal transition (EMT) morphological phenotype. This study aimed to elucidate the prognostic impact of tumour budding grade and its association with clinicopathological and EMT-related features in perihilar cholangiocarcinoma (PHCC) or distal cholangiocarcinoma (DCC). METHODS AND RESULTS: Subjects included 195 PHCC and 115 DCC patients. The numbers of tumour buds in different patients were stratified for postoperative survival using the recursive partitioning technique. Consequently, the numbers of tumour buds in PHCC patients were classified into three grades, namely, low (0-4 buds); intermediate (5-11 buds); and high (12 buds); those of DCC patients were classified into two grades, namely, low (0-4 buds) and high (5 buds). In both PHCC and DCC patients, high tumour budding grade was associated with poor histological differentiation, higher pT factor, presence of lymphatic, venous, perineural invasion, and regional lymph node metastasis. In PHCC patients, residual invasive tumour in the resected margin was also associated with high tumour budding grade. For both PHCC and DCC patients, high tumour budding grade was an independent adverse prognostic factor in multivariate analysis ($p<0001$ and $p=0.046$, respectively). Immunohistochemical examination revealed that the number of tumour buds increased in patients with tumours showing a mesenchymal profile (negative for E-cadherin and positive for vimentin). CONCLUSIONS: Higher tumour budding grade is associated with invasive clinicopathological features, adverse postoperative prognosis, and EMT status in extrahepatic cholangiocarcinoma. This article is protected by copyright. All rights reserved.

Back to top

Staging

Bile Ducts TNM staging, Margins, Survival

- Proposal for a new classification for perihilar cholangiocarcinoma based on tumour depth

The British journal of surgery 2019 Jan;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30675908

BACKGROUND: The T system for distal cholangiocarcinoma has been revised from a layer-based to a depth-based approach in the current American Joint Committee on Cancer (AJCC) classification. In perihilar cholangiocarcinoma, tumour depth in the staging scheme has not yet been addressed. The aim of this study was to propose a new T system using measured tumour depth in perihilar cholangiocarcinoma. METHODS: Patients who underwent hepatectomy for perihilar cholangiocarcinoma between 2001 and 2014 were reviewed retrospectively. The vertical distance between the top of the tumour and deepest invasive cells was measured as invasive tumour thickness (ITT) by two independent pathologists. Log rank statistics were used to determine cut-off points, and the concordance (C) index was used to assess survival discrimination of each T system. RESULTS: ITT was measurable in all 440 patients, with a median value of $6 \cdot 0$ (range 0-45) mm. The median difference in ITT between observers was $0 \cdot 6$ (range 0-20) mm. Cut-off points for prognosis were 1, 5 and 8 mm. Five-year survival decreased with increasing ITT ($P < 0 \cdot 001$): 67 per cent for ITT less than 1 mm (25 patients), $54 \cdot 9$ per cent for ITT 1 mm and over to less than 5 mm (138 patients), $43 \cdot 4$ per cent for ITT 5 mm and over to less than 8 mm (118 patients), and $32 \cdot 2$ per cent for ITT 8 mm and over (159 patients). The C-index of this classification was comparable to that of the current AJCC T classification ($0 \cdot 598$ versus $0 \cdot 589$). CONCLUSION: ITT is a reliable approach for making a depth assessment in perihilar cholangiocarcinoma. A four-tier ITT classification with cut-off points of 1, 5 and 8 mm is an adequate alternative to the current layer-based T classification.

- Validation of the Eighth American Joint Committee on Cancer Staging System for Distal Bile Duct Carcinoma

Cancer research and treatment : official journal of Korean Cancer Association 2019 Jan;51(1):98-111

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=29510611

PURPOSE: T category of the eighth edition of the American Joint Committee on Cancer (AJCC) staging system for distal bile duct carcinoma (DBDC) was changed to include tumor invasion depth measurement, while the N category adopted a 3-tier classification system based on the number of metastatic nodes. Materials and Methods: To validate cancer staging, a total of 200 surgically resected DBDCs were staged and compared according to the seventh and eighth editions. RESULTS: T categories included T1 (n=37, 18.5%), T2 (n=114, 57.0%), and T3 (n=49, 24.5%). N categories included N0 (n=133, 66.5%), N1 (n=50, 25.0%), and N2 (n=17, 8.5%). Stage groupings included I (n=33, 16.5%), II (n=150, 75.0%), and III (n=17, 8.5%). The overall 5-year survival rates (5-YSRs) of T1, T2, and T3 were 59.3%, 42.4%, and 12.2%, respectively. T category could discriminate patient survival by both pairwise (T1 and T2, p=0.011; T2 and T3, $p < 0.001$) and overall ($p < 0.001$) comparisons. The overall 5-YSRs of N0, N1, and N2 were 47.3%, 17.0%, and 14.7%, respectively. N category could partly discriminate patient survival by both pairwise (N0 and N1, $p < 0.001$; N1 and N2, p=0.579) and overall ($p < 0.001$) comparisons. The overall 5-YSRs of stages I, II, and III were 59.0%, 35.4%, and 14.7%, respectively. Stages could distinguish patient survival by both pairwise (I and II, p=0.002; II and III, p=0.015) and overall ($p < 0.001$) comparisons. On multivariate analyses, T and N categories (p=0.014 and p=0.029) and pancreatic invasion (p=0.006) remained significant prognostic factors. CONCLUSION: The T andNcategories of the eighth edition AJCC staging system for DBDC accurately predict patient prognosis.

Back to top

Gallbladder

Morphology, Diagnostics, IHC

Morphology, Diagnostics, IHC

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

- Systematic review of management of incidental gallbladder cancer after cholecystectomy

The British journal of surgery 2019 Jan;106(1):32-45

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30582640

BACKGROUND: Gallbladder cancer is rare, but cancers detected incidentally after cholecystectomy are increasing. The aim of this study was to review the available data for current best practice for optimal management of incidental gallbladder cancer. METHODS: A systematic PubMed search of the English literature to May 2018 was conducted. RESULTS: The search identified 12 systematic reviews and meta-analyses, in addition to several consensus reports, multi-institutional series and national audits. Some $0 \cdot 25$-$0 \cdot 89$ per cent of all cholecystectomy specimens had incidental gallbladder cancer on pathological examination. Most patients were staged with pT2 (about half) or pT1 (about one-third) cancers. Patients with cancers confined to the mucosa (T1a or less) had 5-year survival rates of up to 100 per cent after cholecystectomy alone. For cancers invading the muscle layer of the gallbladder wall (T1b or above), reresection is recommended. The type, extent and timing of reresection remain controversial. Observation time may be used for new cross-sectional imaging with CT and MRI. Perforation at initial surgery had a higher risk of disease dissemination. Gallbladder cancers are PET-avid, and PET may detect residual disease and thus prevent unnecessary surgery. Routine laparoscopic staging before reresection is not warranted for all stages. Risk of peritoneal carcinomatosis increases with each T category. The incidence of port-site metastases is about 10 per cent. Routine resection of port sites has no effect on survival. Adjuvant chemotherapy is poorly documented and probably underused. CONCLUSION: Management of incidental gallbladder cancer continues to evolve, with more refined suggestions for subgroups at risk and a selective approach to reresection.

Back to top

Staging

Gallbladder TNM staging, Margins, Survival

- Optimal surgical treatment in patients with T1b gallbladder cancer: An international multicenter study

Journal of hepato-biliary-pancreatic sciences 2018 Dec;25(12):533-543

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30562839

BACKGROUND: There is no consensus on the optimal treatment of T1b gallbladder cancer (GBC) due to the lack of evidence and the difficulty of anatomy and pathological standardization. METHODS: A total of 272 patients with T1b GBC who underwent surgical resection at 14 centers with specialized hepatobiliary-pancreatic surgeons and pathologists in Korea, Japan, Chile, and the United States were studied. Clinical outcomes including disease-specific survival (DSS) rates according to the types of surgery were analyzed. RESULTS: After excluding patients, the 237 qualifying patients consisted of 90 men and 147 women. Simple cholecystectomy (SC) was performed in 116 patients (48.9%) and extended cholecystectomy (EC) in 121 patients (51.1%). The overall 5-year DSS was 94.6%, and it was similar between SC and EC patients (93.7% vs. 95.5%, P = 0.496). The 5-year DSS was similar between SC and EC patients in America (82.3% vs. 100.0%, P = 0.249) as well as in Asia (98.6% vs. 95.2%, P = 0.690). The 5-year DSS also did not differ according to lymph node metastasis (P = 0.688) or tumor location (P = 0.474). CONCLUSIONS: SC showed similar clinical outcomes (including recurrence) and survival outcomes as EC; therefore, EC is not needed for the treatment of T1b GBC.

- Positive relationship between number of negative lymph nodes and duration of gallbladder cancer cause-specific survival after surgery

Cancer management and research 2018 ;10():6961-6969

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30588101

Background: Although the prognostic implications of negative lymph nodes (NLNs) has been reported for a variety of tumors, little information has been published about the NLNs in gallbladder cancer (GBC). Patients and methods: In this study, clinicopathological characteristics and survival times of patients who had undergone surgery for GBC were collected from the Surveillance, Epidemiology, and End Results Program-registered TNM stage database and analyzed. Univariate and multivariate Cox proportional hazards models were used to identify the predictors of survival. Results: It was found that a cutoff of one to two NLNs is optimal when assessing the association with survival, survival rates being consistently better with two or more NLNs than with fewer than two. This optimal cutoff value of 2 was identified as an independent prognostic factor by univariate and multivariate analyses (all P<0.001). Specifically, patients with two or more NLNs had better 5-year gallbladder cancer cause-specific survival than those with fewer than NLNs examined for stage I/II, stage III/IV, and all TNM stages (all P<0.001). Conclusion: Our findings indicate that the number of NLNs is an independent prognostic factor after GBC surgery, and, together with the number of positive lymph nodes, this will provide better prognostic information than the number of positive lymph nodes alone.

- External validation of the 8th American Joint Committee on Cancer staging system for gall bladder carcinoma

Journal of gastrointestinal oncology 2018 Dec;9(6):1084-1090

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30603127

Background: To validate the changes within the American Joint Committee on Cancer (AJCC) 8th staging system for gall bladder carcinoma compared to AJCC 7th staging system. Methods: Surveillance,

Epidemiology and End Results (SEER) database [2004-2014] was queried. Kaplan-Meier survival analyses and Log-rank testing were assessed according to both AJCC 7th and 8th staging systems. Likewise, Cox cancer-specific hazard ratio was evaluated according to both staging systems. Results: Overall survival was assessed according to the two staging systems; and P values for overall trend (log/rank test) were significant ($P<0.001$) for both scenarios. Cox regression cancer-specific hazard adjusted for age, gender, histology, gender and surgery was evaluated according to the two staging systems. According to AJCC 7th staging system, the following pair wise hazard ratio comparisons were significant (II vs. IIIA; IIIB vs. IVA; IVA vs. IVB). According to AJCC 8th staging system, the following pair wise hazard ratio comparisons were significant (II vs. IIIA; IVA vs. IVB). C-statistic was assessed using death from gall bladder carcinoma as the dependent variable; and the findings for the two staging systems were as follows: AJCC 7th staging system: 0.684 (SE: 0.008; 95% CI: 0.667-0.701); AJCC 8th staging system: 0.682 (SE: 0.009; 95% CI: 0.665-0.698). Conclusions: There is a comparable discriminatory performance for AJCC 8th staging system compared to AJCC 7th staging system. Change form location-based to number-based N category assessment does not improve the overall prognostic performance of the staging system.

Back to top

Ampulla of Vater

Morphology, Diagnostics, IHC

Morphology, Diagnostics, IHC

- Identification of ampullary carcinoma mixed subtype using a panel of six antibodies and its clinical significance

Journal of surgical oncology 2019 Mar;119(3):295-302

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30548547

OBJECTIVES: To investigate the function of immunomarkers CK7, CK20, CK17, CDX2, MUC1, and MUC2 in the identification of primary ampullary carcinoma mixed subtype. METHODS: Forty-two cases of primary ampullary carcinoma were performed by immunohistochemical studies. The correlation between the mixed subtype and the other two subtypes and patient survival data was analyzed using the SPSS 16.0 statistical software. RESULTS: Among 42 cases, 12 (28.6%) cases were classified as mixed subtype, which showed variable expression patterns: 91.7% (11/12) for CK7, 83.3% (10/12) for CK20; 66.7% (8/12) for CK17, CDX2, and MUC1; and 50% (6/12) for MUC2. Ten (83.3%) mixed types coexpressed four or more immunomarkers. Eight (19%) intestinal subtypes mainly showed a positive expression of CK20, CDX2, and MUC2. Twenty-two (52.4%) pancreaticobiliary subtypes showed a positive expression of CK7, MUC1, and CK17. Stages III and IV diseases in mixed subtype (25%) and intestinal subtype (25%) were less than pancreaticobiliary subtype(63.6%) ($p = 0.039$). Follow-up data appeared to show a better survival rate for patients with mixed subtype than those with pancreaticobiliary subtypes. CONCLUSION: Immunohistochemical staining provided a more reliable means of diagnosing mixed ampulla carcinoma. Accurate subtyping of ampullary carcinoma is clinically important to select effective chemotherapy regimens and to assess disease prognosis.

- Distinct immunological properties of the two histological subtypes of adenocarcinoma of the ampulla of Vater

Cancer immunology, immunotherapy : CII 2019 Jan;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30604042

Adenocarcinoma of the ampulla of Vater (AOV) is classified into intestinal type (IT) and pancreatobiliary type (PB); however, the immunological properties of these subtypes remain to be characterized. Here, we evaluated the clinical implications of PD-L1 expression and CD8+ T lymphocyte density in adenocarcinomas of the AOV and their potential association with Yes-associated protein (YAP). We analyzed 123 adenocarcinoma-of-the-AOV patients who underwent surgical resection, and tumors were classified into IT or PB type. Tumor or inflammatory cell PD-L1 expression, CD8+ T lymphocyte density in the cancer cell nest (intratumoral) or in the adjacent stroma, and YAP localization and intensity were analyzed using immunohistochemical staining. PB-type tumors showed higher tumoral PD-L1 expression than IT-type tumors, and tumoral PD-L1 expression was associated with a shorter disease-free survival (DFS) [hazard ratio (HR), 1.77; $p = 0.045$] and overall survival (OS) (HR 1.99; $p = 0.030$). Intratumoral CD8+ T lymphocyte density was higher in IT type than in PB type and was associated with a favorable DFS (HR 0.47; $p = 0.022$). The nuclear staining pattern of YAP in tumor cells, compared to non-nuclear staining patterns, was more frequently associated with PB type and increased tumoral PD-L1 expression. Nuclear YAP staining was a significant prognostic factor for OS (HR 2.21; $p = 0.022$). These results show that the two subtypes of adenocarcinoma of the AOV exhibit significant differences in tumoral PD-L1 expression and intratumoral CD8+ T lymphocyte density, which might contribute to their distinct clinical features.

Back to top

Staging

Ampulla of Vater TNM staging, Margins, Survival

- Histopathologic Predictors of Survival and Recurrence in Resected Ampullary Adenocarcinoma: International Multicenter Cohort Study

Annals of surgery 2019 Jan;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30628913

OBJECTIVE: The aim of the study was to define histopathologic characteristics that independently predict overall survival (OS) and disease-free survival (DFS), in patients who underwent resection of an ampullary adenocarcinoma with curative intent. SUMMARY BACKGROUND DATA: A broad range of survival rates have been described for adenocarcinoma of the ampulla of Vater, presumably due to morphological heterogeneity which is a result of the different epitheliums ampullary adenocarcinoma can arise from (intestinal or pancreaticobiliary). Large series with homogenous patient selection are scarce. METHODS: A retrospective multicenter cohort analysis of patients who underwent pancreatoduodenectomy for ampullary adenocarcinoma in 9 European tertiary referral centers between February 2006 and December 2017 was performed. Collected data included demographics, histopathologic details, survival, and recurrence. OS and DFS analyses were performed using Kaplan-Meier curves and Cox proportional hazard models. RESULTS: Overall, 887 patients were included, with a mean age of 66±10 years. The median OS was 64 months with 1-, 3-, 5-, and 10-year OS rates of 89%, 63%, 52%, and 37%, respectively. Histopathologic subtype, differentiation grade, lymphovascular invasion, perineural invasion, T-stage, N-stage, resection margin, and adjuvant chemotherapy were correlated with OS and DFS. N-stage (HR = 3.30 [2.09-5.21]), perineural invasion (HR = 1.50 [1.01-2.23]), and adjuvant chemotherapy (HR = 0.69 [0.48-0.97]) were independent predictors of OS in multivariable analysis, whereas DFS was only adversely predicted by N-stage (HR = 2.65 [1.65-4.27]). CONCLUSIONS: Independent predictors of OS in resected ampullary cancer were N-stage, perineural invasion, and adjuvant chemotherapy. N-stage was the only predictor of DFS. These findings improve predicting survival and recurrence after resection of ampullary adenocarcinoma.

- Prognostic importance of lymph node ratio after resection of ampullary carcinomas

Journal of gastrointestinal oncology 2018 Dec;9(6):1144-1149

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30603134

Background: The prognosis of the lymph node ratio (LNR) in Vater's ampulla carcinomas (VACs) is recently studied. However, there are not enough data in several populations like Latin American people. Our aim is to demonstrate the prognosis significance of the LNR in this setting. Methods: Pancreaticoduodenectomies for VACs were identified (n=128) from 1980 through 2015. Based on a ROC curve, a cut-off point of 0.1 was assigned for the LNR and the population was divided into two groups for comparison. Results: The LNR 0.1 group was statistically significant associated with recurrence (38.5% vs. 19.5%), pT3-T4 tumors (69.2% vs. 29.3%), poorly differentiated tumors (46.2% vs. 17.5%), lymphovascular invasion (61.5 vs. 17.1%), perineural invasion (38.5% vs. 19.5%), and positive margins (15.4% vs. 2.4%). In the multivariate analysis, LNR (HR 2.891; CI: 1.987-3.458, P=0.02), LNM (HR 2.945; CI: 2.478-3.245, P=0.002), perineural invasion (HR 3.327; CI: 3.172-4.156, P=0.003), and recurrence (HR 3.490; CI: 2.896-4.122, P=0.001) were associated with lower survival. Conclusions: The LNR is a good predictor of survival and worse oncological outcomes for VACs after resection.

- Prognostic Nomogram for Disease-Specific Survival in Patients with Non-metastatic Ampullary Carcinoma After Surgery

Annals of surgical oncology 2019 Jan;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30659390

OBJECTIVE: The aim of this study was to establish and validate an individualized nomogram for predicting disease-specific survival (DSS) in patients with non-metastatic ampullary carcinoma after surgery. METHODS: The nomogram was prepared using retrospective data from the Surveillance, Epidemiology, and End Results database, and included 2022 patients (training dataset: 1276; validation dataset: 746 patients) with non-metastatic ampullary carcinoma who were surgically treated between 2004 and 2014. Cox multivariate regression was performed to identify independent risk factors. The predictive accuracy was determined using the concordance index (C-index) and calibration curves. Results were validated internally using bootstrap resampling, and externally against the validation dataset. RESULTS: The median follow-up for the training dataset was 25.5 months (range 1-143), the median survival time was 52 months [95% confidence interval (CI) 41.67-62.33], and the postoperative 1-, 3-, and 5-year DSS rates were 86.7%, 57.3%, and 47.2%, respectively. Univariate and multivariate regression analysis demonstrated that age, grade, tumor size, lymph node ratio, extension range, and histology were independent risk factors for DSS. The C-index of the internal validation dataset for predicting DSS was 0.70 (95% CI 0.68-0.72), which was superior to that of the American Joint Committee on Cancer staging, i.e. 0.64 (95% CI 0.62-0.66; $p < 0.001$). The 5-year DSS and median DSS time for the low-risk group were significantly greater than those for the high-risk group ($p < 0.001$). CONCLUSION: Our nomogram reliably and accurately predicted DSS in patients with non-metastatic ampullary carcinoma after surgery. This model may help clinicians in their decision making.

Back to top

Neuroendocrine

PanNET

PanNET, Pancreatic Neuroendocrine Tumors and related neuroendocrine neoplasms

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- Clinicopathological characteristics of non-functioning cystic pancreatic neuroendocrine tumors

Pancreatology : official journal of the International Association of Pancreatology (IAP) ... [et al.] 2019 Jan;19(1):50-56

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30497875

BACKGROUND/OBJECTIVES: The biological features of cystic pancreatic neuroendocrine tumors (PNETs) remain unclear. The aim of this study was to clarify the clinicopathological characteristics of non-functioning PNETs (NF-PNETs) with a cystic component. METHODS: The medical records of 75 patients with NF-PNETs who had undergone resection in our institution were retrospectively reviewed. Clinicopathological factors were compared between PNETs with and without a cystic component. Expression of somatostatin 2 receptor (SSTR-2) was also analyzed. RESULTS: Cystic PNETs were diagnosed in 14 patients (19%). The proportion of men was significantly higher for cystic than solid PNETs (79% vs. 44%, $P < 0.05$) and cystic PNETs were significantly larger than solid PNETs (25 mm vs. 17 mm, $P < 0.01$). However, there were no significant differences in the prevalence of lymph node metastases (14% vs. 10%, $P = 0.64$), hepatic metastasis (7% vs. 3%, $P = 0.54$), or disease-free survival rate (both 86%, $P = 0.29$) between PNETs with and without a cystic component. SSTR-2 expression was more frequently observed in PNETs with a cystic component than in those without (100% vs. 70%, $P < 0.01$). CONCLUSIONS: Although cystic PNETs were larger upon diagnosis than solid PNETs in this study, prognosis after surgical resection did not differ significantly between these types of PNET. Somatostatin receptor scintigraphy and somatostatin analogues may be more useful for diagnosing and treating cystic PNETs, respectively.

- In Situ Hybridization Analysis of Long Non-coding RNAs MALAT1 and HOTAIR in Gastroenteropancreatic Neuroendocrine Neoplasms

Endocrine pathology 2019 Jan;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30600442

Recent studies suggest onco-regulatory roles for two long non-coding RNAs (lncRNAs), MALAT1 and HOTAIR, in various malignancies; however, these lncRNAs have not been previously examined in neuroendocrine neoplasms (NENs) of gastroenteropancreatic origins (GEP-NENs). In this study, we evaluated the expressions and prognostic significance of MALAT1 and HOTAIR in 83 cases of GEP-NENs (60 grade 1, 17 grade 2, and 6 grade 3 tumors) diagnosed during the years 2005-2017. Expression levels of MALAT1 and HOTAIR were digitally quantitated in assembled tissue microarray slides labeled by chromogenic in situ hybridization (ISH) using InForm 1.4.0 software. We found diffuse nuclear expression of both HOTAIR and MALAT1 in all primary tumors of GEP-NENs with variable intensities. By multivariate model which adjusted for age and histologic grade, high expression of HOTAIR was associated with lower presenting T and M stages and subsequent development of metastases ($P < 0.05$). MALAT1 expression was associated with presenting T stage and development of metastases ($P < 0.05$). In summary, MALAT1 and HOTAIR are commonly expressed in GEP-NENs. High expression of either lncRNA showed grade-independent associations with clinically less aggressive disease.

- Can we predict recurrence in WHO G1-G2 pancreatic neuroendocrine neoplasms? Results from a multi-institutional Spanish study

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30683515

INTRODUCTION: Pancreatic neuroendocrine neoplasms (PNEN) are rare tumours and well differentiated PNEN are associated with relatively indolent physiological behaviour. For this reason, only few studies have investigated those factors associated with recurrence in this group of patients. The aim of this study is to analyse whether it is possible to predict tumour recurrence in World Health Organization (WHO) 2017 G1-G2 PNEN patients. METHODS: This is a retrospective multi-institutional study. Patients submitted to pancreatic resection from 7 Spanish centres were reviewed. Only patients with WHO G1-G2 PNEN were included. Demographic and clinicopathological variables were analysed. RESULTS: Data from 137 patients were reviewed. Median age was 59.2 (25-84) years. Recurrence of disease occurred in 19 (13.9%) patients. Median DFS was 55 months. At multivariate analysis, tumour size >20 mm, lymphnode metastasis and a new tumour grade 2 incorporating Ki-67 labelling index (LI) > 5% and mitotic index (MI) > 2 were independently associated with recurrence. We developed a risk score model with these three factors. High-risk patients had a significantly lower 5-year disease-specific survival compared to low-risk patients (70% vs 100%). CONCLUSION: We propose a novel risk score for recurrence based on lymphnode metastasis, tumour size > 20 mm and a new grade 2 based on Ki-67 LI >5% and MI > 2. If 2 factors are present, patients have a higher risk for recurrence and a significantly poorer DSS, and therefore they should be closely monitored during follow-up. The role of adjuvant chemotherapy in these patients needs to be evaluated in clinical trials.

Back to top

Cytopathology

Pancreas

- Touch imprint cytology on endoscopic ultrasound fine-needle biopsy provides comparable sample quality and diagnostic yield to standard endoscopic ultrasound fine-needle aspiration specimens in the evaluation of solid pancreatic lesions

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30484917

OBJECTIVES: Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is the gold standard for the diagnosis of solid pancreatic lesions (SPLs). Cytological samples can also be obtained using touch imprint cytology (TIC) on EUS fine-needle biopsy (FNB) specimens. We aimed to compare sample quality and diagnostic yield of EUS-FNA-standard cytology (EUS-FNA-SC) to that of EUS-FNB-TIC in a series of patients with SPLs. METHODS: Thirty-two consecutive patients referred for EUS-tissue acquisition of SPLs who underwent rapid on-site evaluation of both EUS-FNA-SC and paired EUS-FNB-TIC during the same endoscopic session were retrospectively identified. Sample quality (evaluated in terms of blood contamination, presence of clots, tissue casts, cellularity, and necrosis) and diagnostic yield were compared between the techniques. RESULTS: The mean number of passes to reach diagnosis at rapid on-site evaluation was similar between EUS-FNA-SC and EUS-FNB-TIC (1.09 ± 0.3 vs 1.13 ± 0.34, P = .711). EUS-FNA-SC scores of sample quality were comparable to those of EUS-FNB-TIC (blood contamination, 2.47 ± 1.11 vs 2.25 ± 1.14, P = .109; clots, 1.25 ± 0.76 vs 1.19 ± 0.69, P = .624; tissue casts, 3.56 ± 0.88 vs 3.59 ± 1.09, P = .872; cellularity, 2.84 ± 1.11 vs 3.09 ± 1.09, P = .244; necrosis, 2.25 ± 1.08 vs 2.53 ± 1.02 P = .059; total score, 12.38 ± 2.88 vs 17.66 ± 2.38, P = .536). Adequacy, sensitivity and diagnostic accuracy of the two sampling techniques were equal (93.7%, 90.6% and 90.6%, respectively). CONCLUSIONS: EUS-FNB-TIC provides comparable samples to those of EUS-FNA-SC and combines the benefits of cytology and histology for the evaluation of SPLs by employing a single needle during the same endoscopic procedure.

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

- Pleomorphic and atypical multinucleated giant cells in solid pseudopapillary neoplasm of pancreas: A diagnostic pitfall in cytology and a review of the literature

Diagnostic cytopathology 2018 Dec;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30552752

Solid pseudopapillary neoplasm of the pancreas (SPN) is a rare low-grade malignancy typically occurring in young women. Occasionally, these neoplasms present with pleomorphic to atypical multinucleated giant tumor cells which may mimic high-grade malignancy. Our patient is a 25-year-old male who presented with one year of intermittent epigastric pain. Magnetic resonance imaging showed a 3.1×2.5 cm mass in the pancreas body. Endoscopic ultrasound-guided fine needle aspiration of the mass showed large pleomorphic cells and atypical multinucleated giant cells in a background of singly scattered polygonal cells. Focally, these cells surrounded delicate hyalinized to fibrovascular cores forming pseudopapillae. Immunohistochemical stains show tumor cells are positive for beta-catenin, CD10, vimentin, and CD56. Although rare surgical pathology publications have described the presence of pleomorphic to atypical multinucleated giant cells

occurring in SPN, to our knowledge, this is the first case reported example focused on cytomorphologic illustration and description.

- Cytopathological results of initial endoscopic ultrasound-guided fine needle aspiration for primary mass and prognosis in pancreatic cancer patients

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30570774

OBJECTIVES: Clinical outcomes remain unclear in patients suspected of having pancreatic cancer with indeterminate endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) results. This work aimed to investigate the prognosis of pancreatic cancer patients with indeterminate findings at initial EUS-FNA. METHODS: Findings in all patients who underwent EUS-FNA for suspected pancreatic cancer between 2008 and 2015 at the National Cancer Center, Korea, were retrospectively reviewed. A final diagnosis of pancreatic ductal adenocarcinoma was based on pathology reports. RESULTS: Of the 144 patients evaluated, 113 (78%) were diagnosed as being positive/suspicious for malignancy on cytological evaluation and 31 (22%) as having atypia/negative/non-diagnostic findings at initial EUS-FNA but subsequently diagnosed with pancreatic ductal adenocarcinoma. Tumour size, clinical stage and treatment modalities did not differ significantly between these two groups. Median overall survival was significantly shorter in patients diagnosed (11.3 ± 0.74 months; 95% confidence interval [CI], 9.4-12.8 months) than non-diagnosed (16.9 ± 2.34 months; 95% CI, 12.0-17.4 months) on initial EUS-FNA (P = .024). Multivariate Cox regression analysis showed that a non-diagnosis on initial EUS-FNA was independently associated with better overall survival (hazard ratio, 0.58; 95% CI, 0.38-0.88; P = .011). CONCLUSIONS: Non-diagnostic results on initial EUS-FNA of a primary mass may be associated with better prognosis in patients with pancreatic cancer.

- Utility of cytomorphology in distinguishing solid pseudopapillary neoplasm of pancreas from pancreatic neuroendocrine tumor with emphasis on nuclear folds and nuclear grooves

Diagnostic cytopathology 2019 Jan;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30677247

BACKGROUND: Pancreatic solid pseudopapillary tumor (SPN) and pancreatic neuroendocrine tumors (Pan-NET) have close resemblance on imaging and cytomorphology, though they differ in their prognosis and treatment strategy. SPNs are low-grade indolent tumors while Pan-NETs harbor malignant potential with propensity to metastasize. We aim to differentiate SPN from Pan-NET based on cyto-morphology; to classify nuclear membrane (NM) irregularities or nuclear folds into four grades and see whether they bear any difference with respect to the two entities. METHODS: Eighteen and ten confirmed cases of SPN and Pan-NET were included in the study. Smears were assessed for architecture, background changes, cellular, and nuclear features, which were compared between the two study groups. Nuclear folds were classified into four grades. Nuclear folds and nuclear grooves were also compared between the two groups. RESULTS: All SPN patients were females; mean age of 28 years. Pan-NET patients had equal male to female ratio; mean age of 46 years. Both SPN (78%) and Pan-NET (71%) showed predilection for pancreatic head. Mean size of lesion was 4.8 cm and 3.1 cm in SPN and Pan-NET groups. Papillary pattern, branching capillaries, degenerative background were significantly more prominent in SPN; sudden anisonucleosis and cytoplasmic granularity in Pan-NET. Metachromatic matrix, hyaline globules, and nuclear grooves were noted exclusively in SPNs. Nuclear fold grades 2 and 3 were more characteristic of SPN than Pan-NET (P = 0.041 and 0.002, respectively). CONCLUSIONS: Cytomorphology is vital in differentiating SPN from Pan-NET with nuclear folds being an important nuclear feature.

Back to top

Bile Ducts

- Factors Associated with Malignant Biliary Strictures in Patients with Atypical or Suspicious Cells on Brush Cytology

Clinical endoscopy 2019 Jan;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30625267

Background/Aims: Pathological diagnosis of biliary strictures with atypical or suspicious cells on endoscopic retrograde brush cytology and indeterminate strictures on imaging is challenging. The aim of this study was to identify markers for malignant strictures in such cases. Methods: We retrospectively analyzed data collected from 146 consecutive patients with indeterminate biliary strictures on imaging who underwent endoscopic retrograde brush cytology from 2007 to 2013. Factors associated with malignant strictures in patients with atypical or suspicious cells on brush cytology were identified. Results: Among the 67 patients with a malignant disease (48 cholangiocarcinoma, 6 gallbladder cancer, 5 pancreatic cancer, 5 ampulla of Vater cancer, and 3 other types), 36 (53.7%) had atypical or suspicious cells on brush cytology. Among these, the factors that independently correlated with malignant strictures were stricture length (odds ratio [OR], 5.259; 95% confidence interval [CI], 1.802- 15.294) and elevated carbohydrate antigen 19-9 (CA19-9) (OR, 3.492; 95% CI, 1.242-9.815), carcinoembryonic antigen (CEA) (OR, 4.909; 95% CI, 1.694-14.224), alkaline phosphatase (ALP) (OR, 3.362; 95% CI, 1.207-9.361), and gamma-glutamyl transpeptidase (rGT) (OR, 4.318; 95% CI, 1.512-12.262). Conclusions: Elevated levels of CA19-9, CEA, ALP, and rGT and stricture length are associated with malignant strictures in patients with indeterminate biliary strictures on imaging and atypical or suspicious cells on brush cytology.

Back to top

Neuroendocrine

- 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.

Back to top

Molecular Pathology

Pancreas

- miRNA and Gene Expression in Pancreatic Ductal Adenocarcinoma

The American journal of pathology 2019 Jan;189(1):58-70

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30558723

Pancreatic ductal adenocarcinoma (PDAC) remains a challenging disease that is mostly diagnosed late in the course of the illness. Unlike other cancers in which measurable successes have been achieved with traditional chemotherapy, targeted therapy, and, recently, immunotherapy, PDAC has proved to be poorly responsive to these treatments, with only marginal to modest incremental benefits using conventional cytotoxic therapy. There is, therefore, a great unmet need to develop better therapies based on improved understanding of biology and identification of predictive and prognostic biomarkers that would guide therapy. miRNAs are small noncoding RNAs that regulate the expression of some key genes by targeting their 3'-untranslated mRNA region. Aberrant expression of miRNAs has been linked to the development of various malignancies, including PDAC. A series of miRNAs have been identified as potential tools for early diagnosis, prediction of treatment response, and prognosis of patients with PDAC. In this review, we present a summary of the miRNAs that have been studied in PDAC in the context of disease biology.

- Mechanosignalling via integrins directs fate decisions of pancreatic progenitors

Nature 2018 12;564(7734):114-118

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30487608

The pancreas originates from two epithelial evaginations of the foregut, which consist of multipotent epithelial progenitors that organize into a complex tubular epithelial network. The trunk domain of each epithelial branch consists of bipotent pancreatic progenitors (bi-PPs) that give rise to both duct and endocrine lineages, whereas the tips give rise to acinar cells1. Here we identify the extrinsic and intrinsic signalling mechanisms that coordinate the fate-determining transcriptional events underlying these lineage decisions1,2. Single-cell analysis of pancreatic bipotent pancreatic progenitors derived from human embryonic stem cells reveal that cell confinement is a prerequisite for endocrine specification, whereas spreading drives the progenitors towards a ductal fate. Mechanistic studies identify the interaction of extracellular matrix (ECM) with integrin 5 as the extracellular cue that cell-autonomously, via the F-actin-YAP1-Notch mechanosignalling axis, controls the fate of bipotent pancreatic progenitors. Whereas ECM-integrin 5 signalling promotes differentiation towards the duct lineage, endocrinogenesis is stimulated when this signalling cascade is disrupted. This cascade can be disrupted pharmacologically or genetically to convert bipotent pancreatic progenitors derived from human embryonic stem cells to hormone-producing islet cells. Our findings identify the cell-extrinsic and intrinsic mechanotransduction pathway that acts as gatekeeper in the fate decisions of bipotent pancreatic progenitors in the developing pancreas.

- Identification of Key Potential Targets and Pathway for Arsenic Trioxide by Systemic Bioinformatics Analysis in Pancreatic Cancer

Pathology oncology research : POR 2018 Nov;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30506130

Arsenic trioxide is an approved chemotheraputic agent for the treatment of acute promyelocytic leukemia (APL). Recently, numerous studies suggested that arsenic trioxide acts as anti-cancer roles in various human malignancies. However, the molecular mechanisms are not fully elucidated. In this study, we ex-

plored the critical targets of arsenic trioxide and their interaction network systematically by searching the publicly available published database like DrugBank (DB) and STRING. Seven direct protein targets (DPTs) and 111 DPT-associated genes were identified. The enrichment analysis of arsenic trioxide associated genes/proteins revealed 10 Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. Among these pathways, phosphatidylinositol-4,5-bisphosphate-3-kinase -Akt (PI3K-Akt) single pathway and pancreatic cancer pathway are highly correlated with arsenic trioxide and have 5 overlapped targets. Then we investigated the gene alternation of selected critical genes in pancreatic cancer studies using cBio portal. These results indicated that arsenic trioxide could act anti-tumor function through PI3K-Akt single pathway and identified critical genes might be therapeutic targets for pancreatic cancer.

- Is mitochondrial DNA copy number a good prognostic marker in resectable pancreatic cancer?

Pancreatology : official journal of the International Association of Pancreatology (IAP) ... [et al.] 2019 Jan;19(1):73-79

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30528645

BACKGROUND: The aim of this prospective study was to investigate mitochondrial DNA (mtDNA) copy number in a group of resectable pancreatic cancer (PC) tumor tissues and adjacent normal pancreatic tissues, and to explore the correlation between the mtDNA content in tissues and the clinicopathological parameters and the overall survival. METHODS: Relative mtDNA copy number was measured by the quantitative PCR-based assay. The tumors specimens ($n = 43$) originated from the patients with pathologically confirmed pancreatic ductal adenocarcinoma who did not receive any neoadjuvant systemic therapy. The adjacent normal pancreatic tissue samples ($n = 31$) were obtained from surgical margins. RESULTS: mtDNA copy number was significantly lower in PC tissue ($P < 0.001$) compared to adjacent normal pancreatic tissue. Jonckheere-Terpstra trend testing indicated a statistically significant decrease in median mtDNA copy number across the differentiation (adjacent normal pancreatic tissue, low-grade, intermediate-grade, high-grade cancer), $P < 0.001$. However, the survival analyses failed to show a significant difference in survival between patients with high and low mtDNA copy number. CONCLUSIONS: To the best of our knowledge, we provided the first evidence that mitochondrial DNA copy number was significantly lower in pancreatic cancer tissue ($P < 0.001$) compared to adjacent normal pancreatic tissue. Also, we demonstrated that mitochondrial copy number was not a significant marker for predicting prognosis in resectable pancreatic cancer.

- Sonic Hedgehog Protein is Frequently Up-Regulated in Pancreatic Cancer Compared to Colorectal Cancer

Pathology oncology research : POR 2018 Dec;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30539521

Sonic hedgehog (SHH) is a secreted protein which functions in autocrine or paracrine fashion on target cells to activate hedgehog (HH) signalling cascade responsible for growth and proliferation. This study is an attempt to understand the expression dynamics of SHH protein in colon, rectal and pancreatic cancers. Protein expression of SHH was studied by Western Blotting in the histologically confirmed colon, rectum and pancreatic cancer tissue samples along with their adjacent normal tissues. Only 31.4% (11 of 35) and 26.9% (7 of 26) of colon and rectal cancer cases respectively showed an increase in SHH expression in tumours compared to 72.7% (24 of 33) of the pancreatic cancer cases when compared with their adjacent normal tissues. Our results suggest that SHH may have a strong role in the predisposition of Pancreatic cancer and could possibly be used as a diagnostic or prognostic biomarker.

- 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.

- ALKBH5 gene is a novel biomarker that predicts the prognosis of pancreatic cancer: A retrospective multicohort study

Annals of hepato-biliary-pancreatic surgery 2018 Nov;22(4):305-309

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30588520

Backgrounds/Aims: Discovery of new prognostic factors for cases in which the pancreatic cancer scoring and staging system does not result in a clear definition is imperative. We examined the role of Human AlkB homolog H5 (ALKBH5) as a prognostic marker for pancreatic cancer. Methods: Patient data were extracted from the International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA). The prognostic value of ALKBH5 was confirmed via analysis of ALKBH5 and other clinical factors, such as age, sex, and stage, using the time-dependent area under the curve (AUC) of Uno's C-index, the AUC value of the receiver operating characteristics (ROC) at three years, the Kaplan-Meier survival curve, and multivariate analysis. Results: ALKBH5 showed excellent prognosis prediction in comparison with existing markers in the two independent cohorts (n=262). Kaplan-Meier survival analysis showed that ALKBH5 expression was positively associated with overall survival (log-rank test, ICGC, p=0.001; TCGA, p=0.01). Notably, comparison of C-index and AUC values in ROC analysis showed that ALKBH5 was associated with high C-index and AUC values compared with other clinical variables (C-index: ICGC, 0.621; TCGA, 0.614 and AUC at three years: ICGC, 0.609; TCGA, 0.558). Multivariate analysis demonstrated thatALKBH5 is an independent prognostic factor (ICGC, p=0.0123; TCGA, p<0.001). Conclusions: These findings contribute to the study of RNA methylation in pancreatic cancer. We believe that ALKBH5 is a new prognostic marker for pancreatic cancer.

- Agnostic Pathway/Gene Set Analysis of Genome-Wide Association Data Identifies Associations for Pancreatic Cancer

Journal of the National Cancer Institute 2018 Dec;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30541042

Background: Genome-wide association studies (GWAS) identify associations of individual single-nucleotide polymorphisms (SNPs) with cancer risk but usually only explain a fraction of the inherited variability. Pathway analysis of genetic variants is a powerful tool to identify networks of susceptibility genes. Methods: We conducted a large agnostic pathway-based meta-analysis of GWAS data using the summary-based adaptive rank truncated product method to identify gene sets and pathways associated with pancreatic ductal adenocarcinoma (PDAC) in 9040 cases and 12 496 controls. We performed expression quantitative trait loci (eQTL) analysis and functional annotation of the top SNPs in genes contributing to the top associated pathways and gene sets. All statistical tests were two-sided. Results: We identified 14 pathways and gene sets associated with PDAC at a false discovery rate of less than 0.05. After Bonferroni correction (P 1.3 × 10-5), the strongest associations were detected in five pathways and gene sets, including maturity-onset diabetes of the young, regulation of beta-cell development, role of epidermal growth factor (EGF) receptor transactivation by G protein-coupled receptors in cardiac hypertrophy pathways, and the Nikolsky breast cancer chr17q11-q21 amplicon and Pujana ATM Pearson correlation coefficient (PCC) network gene sets. We identified and validated rs876493 and three correlating SNPs (PGAP3) and rs3124737 (CASP7) from the Pujana ATM PCC gene set as eQTLs in two normal derived pancreas tissue datasets. Conclusion: Our agnostic pathway and gene set analysis integrated with functional annotation and eQTL analysis provides insight into genes and pathways that may be biologically relevant for risk of PDAC, including those not previously identified.

- High Expression of Long Noncoding RNA HOTAIRM1 is Associated with the Proliferation and Migration in Pancreatic Ductal Adenocarcinoma

Pathology oncology research : POR 2019 Jan;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30613920

Pancreatic ductal adenocarcinoma (PDAC) is an incurable malignancy. Long noncoding RNA (LncRNA) HOTAIRM1 (HOX antisense intergenic RNA myeloid 1) has been shown to play important roles in the progression of several type cancers. However, the exact role of HOTAIRM1 in PDAC development remains largely unknown. This study aims to evaluate the potential function of HOTAIRM1 in the development and progress of PDAC. HOTAIRM1 expression was measured by RT-qPCR in forty seven paired human PDAC tissues and five PDAC cell lines. SW1990 and PANC-1 cells were transfected with siHOTAIRM1 to achieve HOTAIRM1 silence. MTT assay and colony formation assay were used to detect the effect of HOTAIRM1 knockdown on cell proliferation. The impact of HOTAIRM1 silence on cell cycle and apoptosis was assessed by flow cytometry assay. Transwell migration assay was performed to explore the influence of HOTAIRM1 downregulation on the migratory potential of PDAC cells. Western blot assay was applied to determine the expression changes of cell cycle, apoptosis, and migration-related genes before and after downregulating HOTAIRM1. HOTAIRM1 expression was abnormally upregulated in PDAC tissues and cells when compared with the control samples, and was positively associated with the expression of KRAS gene mutation. In vitro functional experiments, HOTAIRM1 expression was significantly downregulated by transfection with siHOTAIRM1 in SW1990 and PANC cell lines. HOTAIRM1 knockdown attenuated cell proliferation by inducing cell cycle arrest at G0/G1 phase, promoted cell apoptosis, and inhibited cell migration in PDAC cells by regulating related-genes expression. In conclusion, HOTAIRM1 plays a critical role in PDAC progression, which may be a novel diagnostic and rational therapeutic target for the treatment of pancreatic ductal adenocarcinoma.

- Genomic Landscape of Pancreatic Adenocarcinoma in Younger vs Older Patients: Does Age Matter?

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30617137

PURPOSE: State-of the art genomic analyses of pancreatic adenocarcinoma (PDAC) have yielded insight into signaling pathways underlying carcinogenesis. PDAC is characterized by substantial genomic heterogeneity.

We aimed to determine if early-onset PDAC (EOPC; 55 years) displays a distinctive molecular landscape from average-age onset PDAC (AOPC; 70 years). EXPERIMENTAL DESIGN: Three distinct datasets for PDAC were analyzed. In the first, patients undergoing treatment at Memorial Sloan Kettering (MSK) were consented for MSK-IMPACT next generation sequencing. The second cohort analyzed was The Cancer Genome Atlas (TCGA) dataset for differences in somatic mutations, gene expression and protein expression. The third dataset was an Australian cohort of PDAC. Clinical data were correlated with genomic analyses. RESULTS: Two hundred and ninety-three samples were analyzed, yielding 90 patients (pts) aged 55 years and 203 pts aged 70 years. Among the genes known to be associated with carcinogenesis SMAD4 displayed higher mutation rates in younger patients. Comprehensive transcriptomic analysis of cellular pathways indicated that the TGFb pathway has increased activation and the expression levels of phospo-GSK3 were higher in EOPC. Survival outcomes revealed no differences between age groups. CONCLUSIONS: These exploratory analyses suggest that there may be somatic gene alterations within the population of early onset PDAC patients that involve unique cellular pathways compared with average onset PDAC. Former studies imply these cellular pathways may play a role in smoking-related PDAC carcinogenesis. Larger genomic datasets are warranted for future evaluation to extend these observations.

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

Virchows Archiv : an international journal of pathology 2019 Jan;474(1):59-69

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.

- Identification of candidate diagnostic and prognostic biomarkers for pancreatic carcinoma

EBioMedicine 2019 Jan;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30639415

BACKGROUND: Pancreatic carcinoma (PC) is one of the most aggressive cancers affecting human health. It is essential to identify candidate biomarkers for the diagnosis and prognosis of PC. The present study aimed to investigate the diagnosis and prognosis biomarkers of PC. METHODS: Differentially expressed genes (DEGs) were identified from the mRNA expression profiles of GSE62452, GSE28735 and GSE16515. Functional analysis and the protein-protein interaction network analysis was performed to explore the biological function of the identified DEGs. Diagnosis markers for PC were identified using ROC curve analysis. Prognosis markers were identified via survival analysis of TCGA data. The protein expression pattern of

the identified genes was verified in clinical tissue samples. A retrospective clinical study was performed to evaluate the correlation between the expression of candidate proteins and survival time of patients. Moreover, comprehensive analysis of the combination of multiple genes/proteins for the prognosis prediction of PC was performed using both TCGA data and clinical data. In vitro studies were undertaken to elaborate the potential roles of these biomarkers in clonability and invasion of PC cells. FINDINGS: In total, 389 DEGs were identified. These genes were mainly associated with pancreatic secretion, protein digestion and absorption, cytochrome P450 drug metabolism, and energy metabolism pathway. The top 10 genes were filtered out following Fisher's exact test. ROC curve analysis demonstrated that TMPRSS4, SERPINB5, SLC6A14, SCEL, and TNS4 could be used as biomarkers for the diagnosis of PC. Survival analysis of TCGA data and clinical data suggested that TMC7, TMPRSS4, SCEL, SLC2A1, CENPF, SERPINB5 and SLC6A14 can be potential biomarkers for the prognosis of PC. Comprehensive analysis show that a combination of identified genes/proteins can predict the prognosis of PC. Mechanistically, the identified genes attributes to clonability and invasiveness of PC cells. INTERPRETATION: We synthesized several sets of public data and preliminarily clarified pathways and functions of PC. Candidate molecular markers were identified for diagnosis and prognosis prediction of PC including a novel gene, TMC7. Moreover, we found that the combination of TMC7, TMPRSS4, SCEL, SLC2A1, CENPF, SERPINB5 and SLC6A14 can serve as a promising indicator of the prognosis of PC patients. The candidate proteins may attribute to clonability and invasiveness of PC cells. This research provides a novel insight into molecular mechanisms as well as diagnostic and prognostic markers of PC. FUND: National Natural Science Foundation of China [No. 81602646 &81802339], Natural Science Foundation of Guangdong Province [No. 2016A030310254] and China Postdoctoral Science Foundation [No. 2016M600648].

- Experimental microdissection enables functional harmonisation of pancreatic cancer subtypes

Gut 2019 Jan;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30658994

OBJECTIVE: Pancreatic ductal adenocarcinoma (PDA) has among the highest stromal fractions of any cancer and this has complicated attempts at expression-based molecular classification. The goal of this work is to profile purified samples of human PDA epithelium and stroma and examine their respective contributions to gene expression in bulk PDA samples. DESIGN: We used laser capture microdissection (LCM) and RNA sequencing to profile the expression of 60 matched pairs of human PDA malignant epithelium and stroma samples. We then used these data to train a computational model that allowed us to infer tissue composition and generate virtual compartment-specific expression profiles from bulk gene expression cohorts. RESULTS: Our analysis found significant variation in the tissue composition of pancreatic tumours from different public cohorts. Computational removal of stromal gene expression resulted in the reclassification of some tumours, reconciling functional differences between different cohorts. Furthermore, we established a novel classification signature from a total of 110 purified human PDA stroma samples, finding two groups that differ in the extracellular matrix-associated and immune-associated processes. Lastly, a systematic evaluation of cross-compartment subtypes spanning four patient cohorts indicated partial dependence between epithelial and stromal molecular subtypes. CONCLUSION: Our findings add clarity to the nature and number of molecular subtypes in PDA, expand our understanding of global transcriptional programmes in the stroma and harmonise the results of molecular subtyping efforts across independent cohorts.

- Genetics of Familial and Sporadic Pancreatic Cancer

Gastroenterology 2019 Jan;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30660730

In the previous decade, comprehensive genomic analyses have yielded important insights about the genetic alterations that underlie pancreatic tumorigenesis. Whole exome and whole genome sequencing of pancreatic ductal adenocarcinomas have confirmed the critical driver genes altered in the majority of pancreatic cancers, as well as identifying numerous less frequently altered driver genes and has delineated cancer subgroups with

unique biological and clinical features. It is now appreciated that pancreatic susceptibility gene alterations are often identified in patients with pancreatic cancer without family histories suggestive of a familial cancer syndrome, prompting recent efforts to expand gene testing to all patients with pancreatic cancer. Studies of pancreatic cancer precursor lesions have begun to elucidate the evolutionary history of pancreatic tumorigenesis and help to understand the utility of biomarkers for early detection as well as targets to develop new therapeutic strategies. In this review, we discuss the results of comprehensive genomic characterization of pancreatic ductal adenocarcinoma and its precursor lesions, and we highlight translational applications in early detection and therapy.

- Importance of gene expression signatures in pancreatic cancer prognosis and the establishment of a prediction model

Cancer management and research 2019 ;11():273-283

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30643453

Background and aim: Pancreatic cancer (PC) is one of the most common tumors with a poor prognosis. The current American Joint Committee on Cancer (AJCC) staging system, based on the anatomical features of tumors, is insufficient to predict PC outcomes. The current study is endeavored to identify important prognosis-related genes and build an effective predictive model. Methods: Multiple public datasets were used to identify differentially expressed genes (DEGs) and survival-related genes (SRGs). Bioinformatics analysis of DEGs was used to identify the main biological processes and pathways involved in PC. A risk score based on SRGs was computed through a univariate Cox regression analysis. The performance of the risk score in predicting PC prognosis was evaluated with survival analysis, Harrell's concordance index (C-index), area under the curve (AUC), and calibration plots. A predictive nomogram was built through integrating the risk score with clinicopathological information. Results: A total of 945 DEGs were identified in five Gene Expression Omnibus datasets, and four SRGs (LYRM1, KNTC1, IGF2BP2, and CDC6) were significantly associated with PC progression and prognosis in four datasets. The risk score showed relatively good performance in predicting prognosis in multiple datasets. The predictive nomogram had greater C-index and AUC values, compared with those of the AJCC stage and risk score. Conclusion: This study identified four new biomarkers that are significantly associated with the carcinogenesis, progression, and prognosis of PC, which may be helpful in studying the underlying mechanism of PC carcinogenesis. The predictive nomogram showed robust performance in predicting PC prognosis. Therefore, the current model may provide an effective and reliable guide for prognosis assessment and treatment decision-making in the clinic.

- LIMS1 Promotes Pancreatic Cancer Cell Survival Under Oxygen-Glucose Deprivation Conditions by Enhancing HIF1A Protein Translation

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30679163

PURPOSE: Oxygen and glucose deprivation is a common feature of the solid tumor. Regulatory network underlying the adaptation of cancer cells to harsh microenvironment remains unclear. We determined the mechanistic role of LIM and senescent cell antigen-like-containing domain protein 1 (LIMS1) in cancer cell survival under oxygen-glucose deprivation conditions. EXPERIMENTAL DESIGN: The expression level of LIMS1 was determined by immunohistochemical staining and analysing the mRNA expression profiles from The Cancer Genome Atlas of three human solid tumors. Roles of LIMS1 in cancer cell metabolism and growth were determined by molecular and cell biology methods. A jetPEI nanocarrier was used as vehicle for anti-LIMS1 siRNAs in mouse models of cancer therapeutics. RESULTS: LIMS1 expression was drastically elevated in PDAC. High LIMS1 level was associated with advanced TNM stage and poor prognosis of tumour patients. Increased LIMS1 expression was pivotal for tumour cells to survive in the oxygen-glucose deprivation conditions. Mechanistically, LIMS1 enhanced GLUT1 expression and membrane translocation, which facilitated tumor cell adaptation to the glucose deprivation stress. Furthermore, LIMS1 promoted

HIF1A protein translation by activating AKT/mTOR signalling, while HIF1 transactivated LIMS1 transcription, thus forming a positive feedback loop in PDAC cell adaptation to oxygen deprivation stress. Inhibition of LIMS1 with jetPEI nanocarrier-delivered anti-LIMS1 siRNAs significantly increased cell death and suppressed tumour growth. CONCLUSIONS: LIMS1 promotes pancreatic cancer cell survival under oxygen-glucose deprivation conditions by activating AKT/mTOR signaling and enhancing HIF1A protein translation. LIMS1 is crucial for tumor adaptation to oxygen-glucose deprivation conditions and is a promising therapeutic target for cancer treatment.

Back to top

Pancreatitis & Other Diseases

Molecular Studies on Pancreatitis & Other Diseases

- Loss of TLR3 and its downstream signaling accelerates acinar cell damage in the acute phase of pancreatitis

Pancreatology : official journal of the International Association of Pancreatology (IAP) ... [et al.] 2019 Jan;19(1):149-157

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30583980

BACKGROUND: Acute pancreatitis is accompanied by acinar cell damage releasing potential toll-like receptor 3 (TLR3) ligands. So far, TLR3 is known as a pattern recognition receptor in the immune signaling cascade triggering a type I interferon response. In addition, TLR3 signaling contributes to programmed cell death through the activation of caspase 8. However, the functional role of TLR3 and its downstream toll-like receptor adaptor molecule 1 (TICAM1) in the inflamed pancreas is unknown. METHODS: To uncover the role of TLR3 signaling in acute pancreatitis, we induced a cerulein-mediated pancreatitis in Tlr3 and Ticam1 knockout (KO) mice and in wildtype animals. The exocrine damage was determined by blood serum analysis and histological examination. Immunohistochemistry, gene expression and immunoblot analysis were conducted to study TLR3 function. RESULTS: After the induction of an acute pancreatitis, wildtype mice showed a high endosomal TLR3 expression in acinar cells. In comparison to wildtype and Ticam1 KO mice, Tlr3 KO mice exhibited the highest severity of pancreatitis with an increased NF- B activation and elevated expression of the pro-inflammatory cytokines Il6 and Tnf, although the amount of infiltrating immune cells was unaffected. Additionally, we detected a strong elevation of acinar cell necrosis and reduced levels of cleaved caspase 8 in Tlr3 and Ticam1 KO mice. CONCLUSIONS: TLR3 and its downstream adaptor TICAM1 are important mediators of acinar cell damage in acute pancreatitis. They possess a critical role in programmed cell death and our data suggest that TLR3 signaling controls the onset and severity of acute pancreatitis.

Back to top

Molecular Research on Microenvironment

Tumor Stroma Interactions, Microenvironment, Inflammatory Response, Microbiome

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

Gastroenterology 2018 12;155(6):1999-2013.e3

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

BACKGROUND & AIMS: Genomic studies have revealed subtypes of pancreatic ductal adenocarcinoma (PDA) based on their molecular features, but different studies have reported different classification systems. It is a challenge to obtain high-quality, freshly frozen tissue for clinical analysis and determination of PDA subtypes. We aimed to redefine subtypes of PDA using a large number of formalin-fixed and paraffin-embedded PDA samples, which are more amenable to routine clinical evaluation. METHODS: We collected PDA samples from 309 consecutive patients who underwent surgery from September 1996 through December 2010 at 4 academic hospitals in Europe; nontumor tissue samples were not included. Samples were formalin fixed and paraffin embedded. DNA and RNA were isolated; gene expression, targeted DNA sequencing, and immunohistochemical analyses were performed. We used independent component analysis to deconvolute normal, tumor, and microenvironment transcriptome patterns in samples. We devised classification systems from an unsupervised analysis using a consensus clustering approach of our data set after removing normal contamination components. We associated subtypes with overall survival and disease-free survival of patients using Cox proportional hazards regression with estimation of hazard ratios and 95% confidence interval. We used The Cancer Genome Consortium and International Cancer Genome Consortium PDA data sets as validation cohorts. RESULTS: We validated the previously reported basal-like and classical tumor-specific subtypes of PDAs. We identified features of the PDA, including microenvironment gene expression patterns, that allowed tumors to be categorized into 5 subtypes, called pure basal like, stroma activated, desmoplastic, pure classical, and immune classical. These PDA subtypes have features of cancer cells and immune cells that could be targeted by pharmacologic agents. Tumor subtypes were associated with patient outcomes, based on analysis of our data set and the International Cancer Genome Consortium and The Cancer Genome Consortium PDA data sets. We also observed an exocrine signal associated with acinar cell contamination (from pancreatic tissue). CONCLUSIONS: We identified a classification system based on gene expression analysis of formalin-fixed PDA samples. We identified 5 PDA subtypes, based on features of cancer cells and the tumor microenvironment. This system might be used to select therapies and predict patient outcomes. We found evidence that the previously reported exocrine-like (called ADEX) tumor subtype resulted from contamination with pancreatic acinar cells. ArrayExpress accession number: E-MTAB-6134.

- Increase of Tumor Infiltrating T-cells in Pancreatic Ductal Adenocarcinoma Through Remodeling of the Extracellular Matrix by a Hyaluronan Synthesis Suppressor, 4-Methylumbelliferone

Pancreas 2019 Feb;48(2):292-298

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30589828

OBJECTIVES: Desmoplastic changes of extracellular matrix (ECM) containing large amounts of hyaluronan (HA) are of interest in chemo- and immunoresistance of pancreatic ductal adenocarcinoma (PDAC). The goal of this study was to evaluate the effects of 4-methylumbelliferone (MU), a selective inhibitor of HA, on ECM and to examine how MU affects adoptive immunotherapy. METHODS: The effect of MU on cell proliferation, HA synthesis and formation of ECM were investigated in four PDAC cell lines. In addition, the cytotoxicity of T-cell-rich peripheral blood mononuclear cells (PBMCs) collected from healthy donors and stimulated with zoledronate and interleukin-2 was examined in the presence of MU. The amount of HA and tumor-infiltrating lymphocytes were also investigated in mice xenograft models. RESULTS: In vitro, 1.0 mM MU inhibited cell proliferation by 45-70% and HA synthesis by 55-80% in all four PDAC cell

lines, and enhanced T-cell-rich PBMC-mediated cytotoxicity against PDAC cells. In vivo, MU reduced intratumoral HA and promoted infiltration of inoculated T-cells into tumor tissue, and consequently suppressed tumor growth. CONCLUSIONS: 4-methylumbelliferone may be an effective immunosensitizer against PDAC through induction of structural changes in the ECM.

- Evaluating the Regulatory Immunomodulation Effect of Irreversible Electroporation (IRE) in Pancreatic Adenocarcinoma

Annals of surgical oncology 2019 Mar;26(3):800-806

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30610562

BACKGROUND: Irreversible electroporation (IRE) has been demonstrated as an effective local method for locally advanced (stage 3) pancreatic adenocarcinoma. Immune regulatory T cells (Tregs) induce immunosuppression of tumors by inhibiting patients' anti-tumor adaptive immune response. This study aimed to evaluate the immunomodulation effect of IRE to identify an ideal time point for potential adjuvant immunotherapy. METHODS: This study prospectively evaluated an institutional review board-approved study of patients undergoing either in situ IRE or pancreatectomy. Patient blood samples were collected at different time points (before surgery [preOP] and on postoperative day [POD] 1, POD3, and POD5). Peripheral blood mononuclear cells (PBMCs) were isolated and evaluated for three different CD4 + Treg subsets (CD25 + CD4 +, CD4 + CD25 + FoxP3 +, CD4 + CD25 + FoxP3 -) by flow cytometry and analyzed for median fold change (MFC) between each two consecutive time points (MFC = log2(T2/T1)). RESULTS: The study analyzed 15 patients with in situ IRE (n = 11) or pancreatectomy (PAN) (n = 4). In both groups, CD25 + CD4 + Tregs decreased on POD1 followed by a steady increase in pancreatectomy, whereas the trend in the IRE group reversed between D3 and D5 (MFC: IRE [- 0.01], PAN [+ 0.39]). For each period, CD4 + CD25 + FoxP3 + Tregs showed the most dramatic inverse effect, with D3 to D5 showing the most change (MFC: IRE [- 0.18], PAN [+ 0.39]). Also, CD4 + CD25 + FoxP3 - Tregs showed an inverse effect between D3 and D5 (MFC: IRE [- 0.25], PAN [+ 0.49]). Altogether, the Treg trend was inversely affected by the in situ IRE procedure, with the greatest cumulative significant change for all three Treg subsets between D3 and D5 (MFC ± SEM: IRE [- 0.24 ± 0.05], PAN [+ 0.37 ± 0.02]; p = 0.016). CONCLUSIONS: The study data suggest that in situ IRE procedure-mediated Treg attenuation between POD3 and POD5 can provide a clinical window of opportunity for potentiating clinical efficacy in combination with immunotherapy.

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

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

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

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

- Comparison of immune infiltrates in melanoma and pancreatic cancer highlights VISTA as a potential target in pancreatic cancer

Proceedings of the National Academy of Sciences of the United States of America 2019 Jan;116(5):1692-1697

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30635425

Immune checkpoint therapy (ICT) has transformed cancer treatment in recent years; however, treatment response is not uniform across tumor types. The tumor immune microenvironment plays a critical role in determining response to ICT; therefore, understanding the differential immune infiltration between ICT-sensitive and ICT-resistant tumor types will help to develop effective treatment strategies. We performed a comprehensive analysis of the immune tumor microenvironment of an ICT-sensitive tumor (melanoma, n = 44) and an ICT-resistant tumor (pancreatic cancer, n = 67). We found that a pancreatic tumor has minimal to moderate infiltration of CD3, CD4, and CD8 T cells; however, the immune infiltrates are predominantly present in the stromal area of the tumor and are excluded from tumoral area compared with melanoma, where the immune infiltrates are primarily present in the tumoral area. Metastatic pancreatic ductal adenocarcinomas (PDACs) had a lower infiltration of total T cells compared with resectable primary PDACs, suggesting that metastatic PDACs have poor immunogenicity. Further, a significantly higher number of CD68+ macrophages and VISTA+ cells (also known as V-domain immunoglobulin suppressor of T cell activation) were found in the pancreatic stromal area compared with melanoma. We identified VISTA as a potent inhibitory checkpoint that is predominantly expressed on CD68+ macrophages on PDACs. These data suggest that VISTA may be a relevant immunotherapy target for effective treatment of patients with pancreatic cancer.

Back to top

Preneoplastic and Preinvasive Lesions

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

- Cancer-associated acinar-to-ductal metaplasia within the invasive front of pancreatic cancer contributes to local invasion

Cancer letters 2019 Mar;444():70-81

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30590101

The pancreas is an organ prone to inflammation, fibrosis, and atrophy because of an abundance of acinar cells that produce digestive enzymes. A characteristic of pancreatic cancer is the presence of desmoplasia, inflammatory cell infiltration, and cancer-associated acinar atrophy (CAA) within the invasive front. CAA is characterized by a high frequency of small ducts and resembles acinar-to-ductal metaplasia (ADM). However, the clinical significance of changes in acinar morphology, such as ADM with acinar atrophy, within the tumor microenvironment remains unclear. Here, we find that ADM within the invasive front of tumors is associated with cell invasion and desmoplasia in an orthotopic mouse model of pancreatic cancer. An analysis of resected human tumors revealed that regions of cancer-associated ADM were positive for TGF , and that this TGF expression was associated with primary tumor size and shorter survival times. Gene expression analysis identified distinct phenotypic profiles for cancer-associated ADM, sporadic ADM and chronic pancreatitis ADM. These findings suggest that the mechanisms driving ADM differ according to the specific tissue microenvironment and that cancer-associated ADM and acinar atrophy contribute to tumor cell invasion of the local pancreatic parenchyma.

- No Cell Left Unturned: Intraductal Papillary Mucinous Neoplasm Heterogeneity

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30642914

Intraductal papillary mucinous neoplasm (IPMN) is a pancreatic cancer precursor lesion with established genetic features, but the cellular ecosystem of these tumors remains to be fully characterized. This study utilizes single cell RNA-seq to describe the dynamic landscape of epithelial, immune, and stromal cells during IPMN progression to invasive cancer.

Back to top

Bile Ducts

- DLEC1 methylation is associated with a better clinical outcome in patients with intrahepatic cholangiocarcinoma of the small duct subtype

Virchows Archiv : an international journal of pathology 2019 Jan;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30610381

Intrahepatic cholangiocarcinoma is a complex disease with three different histologic subtypes, the large duct, small duct, and bile ductular types. In the present study, we elucidated whether the three histological subtypes have differences in their methylation profiles and developed a DNA methylation marker that might help identify a subset of ICC with a different prognosis. We screened 113 promoter CpG island loci against 10 cases of intrahepatic cholangiocarcinoma and normal cystic ducts using the MethyLight assay and selected 30 CpG island loci with cancer-associated hypermethylation. Then, we analyzed 172 intrahepatic cholangiocarcinomas for the methylation state at these 30 loci. Six loci, including DLEC1, were more frequently methylated in the bile ductular type and small duct type, whereas six loci were more frequently methylated in the large duct type. Of these 30 loci, DLEC1 methylation was found mainly in the bile ductular type and small duct type but rarely in the large duct type. DLEC1 methylation was significantly associated with a better clinical outcome in intrahepatic cholangiocarcinomas of the small duct type but not of the bile ductular type. DLEC1 methylation was an independent prognostic variable in both cancer-specific survival and recurrence-free survival. For patients with intrahepatic cholangiocarcinoma of the small duct type ($n = 68$), DLEC1 methylation was found in 26 (38.2%) and was associated with a better clinical outcome for both cancer-specific survival and recurrence-free survival. Our findings suggest that DLEC1 methylation can be utilized to identify a subset with a better prognosis in intrahepatic cholangiocarcinomas of the small duct type.

- EVI1 expression is associated with aggressive behavior in intrahepatic cholangiocarcinoma

Virchows Archiv : an international journal of pathology 2019 Jan;474(1):39-46

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.

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

Virchows Archiv : an international journal of pathology 2019 Jan;474(1):29-37

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.

Back to top

Gallbladder

- MiR-1-5p is down-regulated in gallbladder carcinoma and suppresses cell proliferation, migration and invasion by targeting Notch2

Pathology, research and practice 2019 Jan;215(1):200-208

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30497876

BACKGROUND: Numerous studies have demonstrated that aberrant microRNAs (miRNAs) are involved in tumorigenesis and tumor progression. Nevertheless, the precise role of miR-1-5p in gallbladder carcinoma cell growth and metastasis remains not fully revealed. MATERIAL AND METHODS: The levels of miR-1-5p were detected in gallbladder carcinoma tissues and cell lines using qRT-PCR method. A series of functional assays, including cell proliferation, colony formation, wound healing and Transwell invasion were conducted using miR-1-5p or miR-1-5p inhibitor transfected cells. RESULTS: MiR-1-5p was remarkably down-regulated in gallbladder carcinoma tissues and cell lines compared to normal. In addition, over-expression of miR-1-5p markedly suppressed the growth, migration and invasion of gallbladder carcinoma cell. Conversely, down-expression of miR-1-5p facilitated gallbladder carcinoma cell proliferation and aggressiveness. Mechanistic investigations demonstrated that neurogenic locus notch homolog protein 2 (Notch2) was the directly target of miR-1-5p and Notch2 mediated the inhibitory effect of miR-1-5p in gallbladder carcinoma cell growth and aggressiveness. CONCLUSION: Our findings demonstrated that miR-1-5p acted as a suppressive miRNA and played vital roles in the growth, migration and invasion of gallbladder carcinoma cell through targeting Notch2.

- Roles of Pin1 as a Key Molecule for EMT Induction by Activation of STAT3 and NF- B in Human Gallbladder Cancer

Annals of surgical oncology 2019 Mar;26(3):907-917

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30610554

BACKGROUND: Despite developments in multidisciplinary treatment, the prognosis for advanced gallbladder cancer (GBC) still is poor because of its rapid progression. Epithelial-mesenchymal transition (EMT) plays a central role in promoting tumor invasion and metastasis in malignancies thorough signal transducer and activator of transcription-3 (STAT3) and nuclear factor B (NF- B) activation. Whereas Pin1 mediates STAT3 and NF- B activation, the involvement of Pin1 in GBC progression is unclear. METHODS: Factors regulating Pin1-related STAT3 and NF- B activation were evaluated using surgical specimens collected from 76 GBC patients, GBC cells, and orthotopic GBC xenograft mice. RESULTS: In the patients with GBC, high Pin1 expression in GBC was associated with aggressive tumor invasion and increased tumor metastasis, and was an independent factor for a poor prognosis. Pin1 expression was correlated with phosphorylation of STAT3(Ser727) and NF- B-p65(Ser276), thereby activating STAT3 and NF- B in GBC. Pin1-mediated STAT3 and NF- B activation induced EMT in GBC. When Pin1 knockdown was performed in GBC cells, the phosphorylation of STAT3(Ser727) and NF- B-p65(Ser276) was inhibited, and STAT3 and NF- B activation was suppressed. Inactivation of STAT3 and NF- B in Pin1-depleted cells decreased snail and zeb-2 expression, thereby reducing the rate of mesenchymal-like cells, suggesting that EMT was inhibited in GBC cells. PiB, a Pin1-specific inhibitor, inhibited EMT and reduced tumor cell invasion by inactivating STAT3 and NF- B in vitro. Moreover, PiB treatment inhibited lymph node metastasis and intrahepatic metastasis in orthotopic GBC xenograft tumor in vivo. CONCLUSIONS: Pin1 accelerates GBC invasion and metastasis by activating STAT3 and NF- B. Therefore, Pin1 inhibition by PiB is an excellent therapy for GBC by safely inhibiting its metastasis.

Back to top

Ampulla of Vater

- Ampullary cancer: Evaluation of somatic and germline genetic alterations and association with clinical outcomes

Cancer 2019 Jan;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30620386

BACKGROUND: Ampullary carcinoma (AC) is a rare gastrointestinal cancer. Pathogenic germline alterations (PGAs) in BRCA2 and potentially targetable somatic alterations (SAs) in ERBB2 and ELF3 have been previously described in AC. Memorial Sloan Kettering Cancer Center has implemented an opt-in strategy for germline testing (GT) and somatic testing (ST) for patients with AC to further evaluate the spectrum of PGAs and SAs. METHODS: Forty-five patients with pathologically confirmed AC prospectively consented with the Memorial Sloan Kettering Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) test (410-468 genes). A subset of the cohort (23 of the 45 patients) also consented to GT with MSK-IMPACT (76-88 genes). Germline data for 21 of the remaining 22 patients who had not consented to GT were obtained in a de-identified fashion without clinical correlation. Clinicopathologic features, treatment histories, and survival data for consenting patients were collected and analyzed. RESULTS: Pancreaticobiliary, intestinal, and mixed features of the 2 types were the primary pathologic subtypes of AC identified in this cohort. No difference in median overall survival was found between pathologic subtypes. Eight of 44 patients (18%) were identified as harboring pathogenic mutations in BRCA2, ATM, RAD50, and MUTYH. In addition, this study found a wide spectrum of SAs in genes such as KRAS, MDM2, ERBB2, ELF3, and PIK3CA. Two patients in the cohort underwent SA-targeted therapy, and 1 had a partial radiographic response. CONCLUSIONS: Mutations in multiple somatic and germline genes were identified in this cohort. Significantly, actionable targets were identified in the tumors, and broader testing for PGAs and SAs should be considered for all patients with AC.

Back to top

Neuroendocrine

- The Molecular and Clinical Landscape of Pancreatic Neuroendocrine Tumors

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Pancreatic neuroendocrine tumors are rare tumors of the pancreas originating from the islets of the Langerhans. These tumors comprise 1% to 3% of all newly diagnosed pancreatic cancers every year and have a unique heterogeneity in clinical presentation. Whole-genome sequencing has led to an increased understanding of the molecular biology of these tumors. In this review, we will summarize the current knowledge of the signaling pathways involved in the tumorigenesis of pancreatic neuroendocrine tumors as well as the major studies targeting these pathways at preclinical and clinical levels.

- Distinct genome-wide methylation patterns in sporadic and hereditary nonfunctioning pancreatic neuroendocrine tumors

Cancer 2019 Jan;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30620390

BACKGROUND: Aberrant methylation is a known cause of cancer initiation and/or progression. There are scant data on the genome-wide methylation pattern of nonfunctioning pancreatic neuroendocrine tumors (NFPanNETs) and sporadic and hereditary NFPanNETs. METHODS: Thirty-three tissue samples were analyzed: they included samples from sporadic (n = 9), von Hippel-Lindau (VHL)-related (n = 10), and multiple endocrine neoplasia type 1 (MEN1)-related NFPanNETs (n = 10) as well as normal islet cells (n = 4) for comparison. Genome-wide CpG methylation profiling was performed with the Infinium MethylationEPIC BeadChip assay and was analyzed with R-based tools. RESULTS: In unsupervised hierarchical clustering, sporadic and MEN1-related NFPanNETs clustered together, and the VHL group was in a separate cluster. MEN1-related NFPanNETs had a higher rate of hypermethylated CpG sites in comparison with sporadic and VHL-related tumor groups. Differentially methylated region analysis confirmed the higher rate of hypermethylation in MEN1-related tumors. Moreover, in an integrated analysis of gene expression data for the same tumor samples, downregulated gene expression was found in most genes that were hypermethylated. In a CpG island methylator phenotype analysis, 3 genes were identified and confirmed to have downregulated gene expression: secreted frizzle-related protein 5 (SFRP5) in sporadic NFPanNETs and cell division cycle-associated 7-like (CDCA7L) and RNA binding motif 47 (RBM47) in MEN1-related NFPanNETs. CONCLUSIONS: MEN1 NFPanNETs have a higher rate of geno me-wide hypermethylation than other NFPanNET subtypes. The similarity between the pathways enriched in a methylation analysis of known genes involved in NFPanNET tumorigenesis suggests a key role for aberrant methylation in the pathogenesis of NFPanNETs.

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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Back to top
