# Pancreatobiliary Pathology Society Journal Watch

February March 2019

*Last Update on 2019-04-30*

## Contents



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## PBPath Journal Watch Articles

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**Wellcome to the PBPath Journal Watch!**

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Back to top

---

## Surgical Pathology

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**Pancreas**

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**Morphology, Diagnostics, IHC**

Morphology, Diagnostics, IHC

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**- Prognostic evaluation of pancreatic ductal adenocarcinoma: Associations between molecular biomarkers and CT imaging findings**

*Pancreatology : official journal of the International Association of Pancreatology (IAP) ... [et al.] 2019 Mar;19(2):331-339*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30718187

OBJECTIVES: To investigate association between molecular biomarkers and computed tomography (CT) imaging findings in patients with pancreatic ductal adenocarcinoma (PDAC). METHODS: Fifty-three consecutive patients with PDAC (34 men and 19 women; mean age, $70.6 \pm 8.1$ years; range, 56-86 years) who underwent dynamic contrast-enhanced CT prior to pancreatectomy were included. The Ki-67 index and expressions of E-cadherin, Vimentin, and TWIST were immunohistochemically evaluated. Qualitative image analysis and histogram analysis of CT numbers were conducted. Clinical and molecular biomarkers were tested as possible prognostic factors for overall survival (OS) using Kaplan-Meier method and Cox proportional hazards regression. In addition, associations between CT imaging findings and significant molecular biomarkers were investigated. RESULTS: The TNM stage ($P = 0.018$) and E-cadherin expression status ($P = 0.018$) were independently associated with OS. E-cadherin-negative PDACs had a worse prognosis than E-cadherin-positive PDACs (hazard ratio: 2.21). Irregular tumor margin was observed more frequently in E-cadherin-negative PDACs (54.7%) than in E-cadherin-positive PDACs (45.3%) ($P = 0.00054$). The kurtosis of CT number during the pancreatic parenchymal phase was significantly higher in E-cadherin-negative PDACs than in E-cadherin-positive PDACs ($P = 0.035$). CONCLUSIONS: E-cadherin suppression was found to be a prognostic factor for OS in patients with PDAC, and irregular tumor margin and kurtosis of CT numbers during the pancreatic parenchymal phase could be indicators for E-cadherin suppression.

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**- Microvessel Density and Impact of Angiogenesis on Survival of Resected Pancreatic Cancer Patients: A Systematic Review and Meta-analysis**

*Pancreas 2019 02;48(2):233-241*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30629030

OBJECTIVES: Angiogenesis plays a major role in tumor progression and metastasis; however, its role in pancreatic cancer (PC) remains unclear. The aim of the study was to explore the cumulative evidence concerning the impact of microvessel density (MVD), an estimator of angiogenesis, on resected PC patients. METHODS: A systematic review of literature and a meta-analysis of relevant reports were performed. Overall survival and disease-free survival were scrutinized. RESULTS: One thousand five hundred patients were analyzed. Overall survival (hazard ratio, 2.0; 95% confidence interval, 1.57-2.54; $P < 0.001$) and disease-free survival (hazard ratio, 1.99; 95% confidence interval, 1.24-3.2; $P = 0.004$) were in favor of the low-MVD group. Use of CD105 antibody and of a computerized image analysis system was found to significantly reduce the heterogeneity. Disease staging, tumor location, and grading showed significant effect on survival. CONCLUSIONS: High-MVD expression was strongly associated with poorer survival and recurrence among resected PC patients, demonstrating a negative prognostic value. Use of CD105 antibody and of a computerized image analysis system is recommended in future studies because they

reduce heterogeneity of results. The potential role of MVD as a marker to select PC patients who would benefit from antiangiogenetic treatment should be further explored in clinical trials.

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Back to top

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**Staging**

Pancreas TNM staging, Margins, Survival

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

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

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

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

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**- Validation of the eighth edition of the American Joint Committee on Cancer staging system and proposal of an improved staging system for pancreatic ductal adenocarcinoma**

*Annals of hepato-biliary-pancreatic surgery 2019 Feb;23(1):46-55*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30863807

Backgrounds/Aims: This study aimed to validate the eighth edition of the American Joint Committee on Cancer (AJCC) staging system for pancreatic adenocarcinoma and to propose an improved staging system for this disease. Methods: Between 2000 and 2014, 1656 patients underwent surgical resection for pancreatic ductal adenocarcinoma at Asan Medical Center, Seoul, South Korea. The 1169 patients included in this study were recategorized according to the eighth edition of the AJCC staging system. Patients were also categorized according to a new staging system, based on tumor size and number of metastatic lymph nodes. Results: The seventh edition of the AJCC staging system categorized 93.7% of patients as having stage T3 tumors. Stages were distributed more evenly with the eighth edition. In the N0 group, classification according to the seventh edition showed no statistically significant differences in survival rate between patients with T1 and T2 (p=0.717) and with IA and IB (p=0.717) tumors. Survival rates classified according to the eighth edition differed significantly for all pairs of T stages (p<0.05). With both editions, N stages showed statistically significant differences (p<0.05). Reanalysis showed that a staging system using a tumor size 3 cm and 1 metastatic lymph nodes was more predictive of survival rates. Conclusions: Compared with the seventh edition, the eighth edition of the AJCC staging system for pancreatic adenocarcinoma showed a more even distribution in T stage but marginal differences in other stages. The proposed system, using tumor size and number of metastatic lymph nodes, was better at predicting survival.

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**- Should a standard lymphadenectomy include the No. 9 lymph nodes for body and tail pancreatic ductal adenocarcinoma?**

*Pancreatology : official journal of the International Association of Pancreatology (IAP) … [et al.] 2019 Apr;19(3):414-418*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30902419

OBJECTIVES: This study aimed to use a retrospective data base to investigate whether a standard lymphadenectomy during distal pancreatectomy should include the No. 9 lymph nodes (LNs) for resectable pancreatic ductal adenocarcinoma (PDAC) located in the body and tail of the pancreas. METHODS: Data from 169 patients undergoing curative distal pancreatectomy for PDAC between Jan 1, 2013 and Dec 31, 2016 were collected. According to the tumor location, patients were divided into three groups: pancreatic neck tumor, pancreatic body and tail tumor with margin-to-bifurcation-distance (MTBD) 2.5 cm and pancreatic body and tail tumor with MTBD > 2.5 cm. The metastatic rate of the No. 9 LNs was compared among the 3 groups. The survival outcomes were analyzed. RESULTS: The involvement rate for No. 9 LNs was 20.7% (6/29) for pancreatic neck tumors, 17.6% (15/85) for body and tail tumors with MTBD 2.5 cm and 1.8% (1/55) for MTBD > 2.5 cm. The No. 9 LNs were significantly more frequently involved in neck or body and tail tumors with MTBD 2.5 cm than with the cases with MTBD >2.5 cm (OR 0.082, P = 0.016). No. 9 LN involvement was not associated with worse survival compared with survival associated with involvement of other LNs (P = 0.780). CONCLUSIONS: For PDAC located in the neck or in the body and tail of the pancreas with MTBD 2.5 cm, the involvement rate for No. 9 LNs is high. Standard lymphadenectomy should include the No. 9 LNs.

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Back to top

---

**Microenvironment**

Tumor Stroma Interactions, Microenvironment, Inflammatory Response

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**- Immune cell score in pancreatic cancer-comparison of hotspot and whole-section techniques**

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30843106

An immune cell score (ICS) was introduced for predicting survival in pancreatic ductal adenocarcinoma (PDAC). Few studies have compared different methods of evaluating immune infiltrate. This study compared ICSs determined in whole sections or tissue microarray-like hotspots for predicting survival after PDAC surgery. We included in 79 consecutive patients from a single geographical area that underwent surgery for PDAC (R0/R1, stages I-III). We performed digital image analyses to evaluate CD3 and CD8 staining. ICSs were classified as low, moderate, or high, based on the numbers of immune cells in the tumour core and invasive margin. We compared ICS groups determined with the hotspot and whole-section techniques. Associations between ICS and survival were analysed with Cox regression models, adjusted for sex, age, tumour stage, differentiation grade, perineural invasion, and resection radicality. In hotspot ICS analysis, 5-year overall survival rates for low, moderate, and high groups were 12.1%, 26.3%, and 26.8%, respectively ($p = 0.193$). In whole-section analyses, overall survival rates were 5.3%, 26.4%, and 43.8%, respectively ($p = 0.030$). In the adjusted Cox model, whole-section ICS groups were inversely associated with the overall mortality hazard ratio (HR): low, moderate, and high ICS groups had HRs of 1.00, 0.42 (95% CI 0.20-0.88), and 0.27 (95% CI 0.11-0.67), respectively. The number of immune cells per square millimetre in the tumour core and the invasive margin were significantly higher and had a wider range in hotspots than in whole-tissue sections. Accordingly, ICS could predict survival in patients with PDAC after surgery. Whole tissue section ICSs exhibited better prognostic value than hotspot ICSs.

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**- Fibroblasts in Pancreatic Ductal Adenocarcinoma: Biological Mechanisms and Therapeutic Targets**

*Gastroenterology 2019 May;156(7):2085-2096*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30721663

The desmoplastic reaction of pancreas cancer may begin as a wound healing response to the nascent neoplasm, but it soon creates an insidious shelter that can sustain the growing tumor and rebuff therapy. Among the many cell types subverted by transformed epithelial cells, fibroblasts are recruited and activated to lay a foundation of extracellular matrix proteins and glycosaminoglycans that alter tumor biophysics and signaling. Their near-universal presence in pancreas cancer and ostensible support of disease progression make fibroblasts attractive therapeutic targets. More recently, however, it has also become apparent that diverse subpopulations of fibroblasts with distinct phenotypes and secretomes inhabit the stroma, and that targeted depletion of particular fibroblast subsets could either provide substantial therapeutic benefit or accelerate disease progression. An improved characterization of these fibroblast subtypes, along with their potential relationships to tumor subtypes and mutational repertoires, is needed in order to make anti-fibroblast therapies clinically viable.

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Back to top

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**Bile Ducts**

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**Morphology, Diagnostics, IHC**

Morphology, Diagnostics, IHC

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**- Overexpression of matriptase in tumor stroma is a poor prognostic indicator of extrahepatic bile duct cancer**

*Pathology international 2019 Feb;69(2):86-93*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30729623

Bile duct cancer is known to contain numerous fibroblasts, and reported to recruit cancer- associated fibroblasts by secreting platelet-derived growth factor-D (PDGF-D) which needs serine proteases, such as matriptase, to behave as a ligand. However, their expression pattern, and prognostic value have not been clarified. In this study, we investigated the clinicopathological significance of PDGF-D and matriptase expression in patients with extrahepatic bile duct cancer. The samples were obtained from 256 patients who underwent the surgical resection between 1991 and 2015, and the expression levels of PDGF-D and matriptase were evaluated immunohistochemically. Staining intensities and distribution were scored, and finally classified into low and high expression groups in cancer cells and stroma respectively. High expression of matriptase in the cancer stroma was detected in 91 tumors (40%). The high stromal matriptase expression was significantly associated with shorter recurrence-free survival (RFS) and overall survival (OS) ($P = 0.0027$ and 0.0023, respectively). Multivariate analyses also demonstrated that the stromal matriptase expression level was an independent influential factor in RFS ($P = 0.0050$) and OS ($P = 0.0093$). Our findings suggest that the high stromal matriptase expression was strongly associated with tumor progression, recurrence and poor outcomes in patients with extrahepatic bile duct cancer.

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Back to top

---

**Gallbladder**

**Staging**

Gallbladder TNM staging, Margins, Survival

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**- The optimal number of lymph nodes to evaluate among patients undergoing surgery for gallbladder cancer: Correlating the number of nodes removed with survival in 6531 patients**

*Journal of surgical oncology 2019 Mar;():*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30864246

BACKGROUND: The aim of the current study was to identify the minimum number and the optimal range of lymph nodes (LNs) to be examined among patients with gallbladder cancer (GBC). METHODS: Between January 1, 2004, and December 31, 2015, patients with a diagnosis of GBC were identified in the National Cancer Database. A machine-based learning approach was used to identify the minimum number and range of LNs to evaluate relative to long-term outcomes. RESULTS: Among 6531 patients with GBC, median number of LNs evaluated was 2 (IQR:1-5); only 21.1% (n = 1376) of patients had 6 or more LNs evaluated. The median number of metastatic LNs was 0 (IQR: 0-1). On multivariable analysis, evaluation of $< 4$ LNs was associated with a higher hazard of death (referent 4-7 LNs: $< 4$ LNs, HR = 1.27, 95% CI, 1.16-1.40; $P < 0.001$), whereas, patients who had 4 to 7 LNs and $> 7$ LNs evaluated had comparable long-term mortality risk (HR = 1.10, 95%CI, 0.98-1.24; P = 0.11). There was no difference in the proportion of patients who had at least one metastatic LN identified per T category based on total number of nodes resected (all $P > 0.05$). CONCLUSION: The overwhelming majority of patients did not have the American Joint Committee on Cancer (AJCC) recommended 6 total LN count . A machine-based learning approach identified evaluation of 4 to 7 LNs as the LN number associated with optimal staging and survival. While obtaining 6 LNs may be challenging, evaluation of at least 4 LNs may be a more appropriate threshold as this cut-off value was associated with optimal patient outcomes and staging.

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Back to top

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**Ampulla of Vater**

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**Morphology, Diagnostics, IHC**

Morphology, Diagnostics, IHC

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**- 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.

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**- Clinical relevance of pancreatobiliary and intestinal subtypes of ampullary and duodenal adenocarcinoma: Pattern of recurrence, chemotherapy, and survival after pancreatoduodenectomy**

*Pancreatology : official journal of the International Association of Pancreatology (IAP) … [et al.] 2019 Mar;19(2):316-324*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30713128

BACKGROUND: The clinical relevance of the classification of ampullary adenocarcinoma (AC) into pancreatobiliary (PB) or intestinal (Int) subtypes has not been resolved. METHODS: Clinicopathological factors, survival, and localization and treatment of recurrence were investigated for patients with AC and duodenal adenocarcinoma (DC) treated by pancreatoduodenectomy from 2000 to 2015. RESULTS: A total of 109 AC (45 PB, 64 Int) and 71 DC (all Int) were identified. Median overall survival (OS) for ACPB vs DC vs ACInt was 43.6 vs 51 vs 75 months, respectively. ACPB had significantly shorter OS than ACInt ($p = 0.036$). However, for AC stage (HR = 2.39; 95 %CI 1.23-4.64, $p = 0.010$) was the only factor associated with mortality risk in multivariate analysis. Localization of recurrence ($n = 88$) was predominantly distant (ACPB 81.5%; ACInt 92%; DC 91.7%, $p = 0.371$). Post-recurrence survival (PRS) for ACPB, ACInt and DC did not differ (6.9 vs 9.2 vs 7.5 months, $p = 0.755$). Best supportive care or palliative chemotherapy were offered for recurrent disease to 44.5%/48.1% for ACPB, 40%/56% for ACInt, and 41.7%/52.8% for DC ($p = 0.947$). The choice of chemotherapy regimen varied considerably. Five patients underwent surgical resection or ablation with curative intent. All deaths among ACPB were caused by recurrent disease, whereas 29.4% of ACInt and 23.1% of DC deaths was non-cancer related or caused by other specific cancer. CONCLUSION: ACPB, ACInt and DC have similar recurrence patterns and PRS. The difference in survival between ACPB and ACInt was not statistically significant when stratified by stage. The optimal chemotherapy in patients with recurrent AC remains undefined.

Back to top

**Staging**

Ampulla of Vater TNM staging, Margins, Survival

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**- The Prognostic Relevance of the New 8th Edition of the Union for International Cancer Control Classification of TNM Staging for Ampulla of Vater Carcinoma**

*Annals of surgical oncology 2019 Feb;():*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30790111

OBJECTIVE: The aim of this study was to investigate the clinical relevance of the 8th edition of the Union for International Cancer Control classification of TNM staging for ampulla of Vater carcinoma (AC). METHODS: A total of 104 consecutive patients who underwent macroscopic curative resection for AC between January 2002 and September 2017 were investigated. RESULTS: Significant differences in recurrence-free survival (RFS) were found between T1a and T1b ($p = 0.0030$), but not between T1b and T2 ($p = 0.9319$), T2 and T3a ($p = 0.0732$), or T3a and T3b ($p = 0.2118$). The prognostic impact of the depth of duodenal invasion and pancreatic invasion, which define the T category, were evaluated. With regard to duodenal invasion, significant differences in RFS were found between the negative and submucosa classifications ($p = 0.0012$) and the muscularis propria and serosa classifications ($p = 0.0131$), but not between the submucosa and muscularis propria classifications ($p = 0.6390$). With regard to pancreatic invasion, significant differences in RFS were found between the negative and  0.5 cm classifications ($p = 0.0001$), and  0.5 cm and $> 0.5$ cm classifications ($p = 0.0062$). A Cox proportional hazard analysis for RFS revealed that duodenal invasion (submucosa or muscularis propria/negative, hazard ratio [HR] 5.08; serosa/negative, HR 7.42), and pancreatic invasion (  0.5 cm/negative, HR 8.23; $> 0.5$ cm/negative, HR 9.81) were independent prognostic factors. An alternative new T category was proposed, based on the HRs, as follows: T1, tumor limited to the ampulla of Vater or sphincter of Oddi; T2, duodenal invasion (submucosa or muscularis propria); T3, pancreatic invasion (  0.5 cm) or duodenal invasion (serosa); and T4, pancreatic invasion ($> 0.5$ cm). This alternative T category can well classify each subgroup with prognostic differences. CONCLUSIONS: Reconsideration of the T category based on the prognostic impact of TNM factors, including the depth of duodenal and pancreatic invasion, are required in the 8th edition T category.

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**- Staging for Ampullary Carcinoma: Is Less Actually More?**

*Annals of surgical oncology 2019 Feb;():*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30788628

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Back to top

---

**Neuroendocrine**

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**PanNET**

PanNET, Pancreatic Neuroendocrine Tumors and related neuroendocrine neoplasms

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**- Cystic pancreatic neuroendocrine tumors: A more favorable lesion?**

*Pancreatology : official journal of the International Association of Pancreatology (IAP) … [et al.] 2019 Mar;19(2):372-376*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30704851

BACKGROUND: Pancreatic neuroendocrine tumors (PNETs) are predominantly solid lesions with malignant potential. Cystic PNETs are a small subset in which data are scarce. The aim of this study was to compare clinical and biologic differences between cystic and solid PNETs. METHODS: Patients with PNETs undergoing pancreatectomy between 1988 and 2016 at a high-volume center were reviewed retrospectively. Demographic, clinical, and histopathologic data were collected and analyzed. RESULTS: 347 patients with PNETs were identified; 27% (n = 91) were cystic. Patients with cystic PNETs were generally older (59 vs. 55 years, p = 0.05). Cystic PNETs were more commonly non-functional (95% vs. 82%, p = 0.004), asymptomatic (44% vs. 28%, p = 0.009), and located in the pancreatic body/tail (81% vs. 60%, p < 0.001) than solid PNETs. Although cystic and solid PNETs had similar sizes and pathologic stage at the time of resection, Ki-67 proliferation index (Ki-67 9%: 98% vs. 85%; p = 0.007), and histologic grade (grade I: 84% vs. 59%; p = 0.009) had less aggressive features in cystic PNETs. CONCLUSION: In addition to reporting a higher than previously published incidence of cystic PNET (27%), this study found significant differences in multiple clinicopathologic variables between cystic and solid PNETs. Cystic PNET may be a distinct and possibly less aggressive subtype of PNET yet have similar pathologic stage, recurrence, and survival to solid PNETs. Cystic PNETs require further attention to better understand the true natural history.

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**- Distinct clinicopathological and prognostic features of insulinoma with synchronous distant metastasis**

*Pancreatology : official journal of the International Association of Pancreatology (IAP) … [et al.] 2019 Apr;19(3):472-477*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30850220

BACKGROUND: The clinicopathological and prognostic features of insulinoma with synchronous metastases are unclear. This study aimed to verify the distinct clinicopathological and prognostic features of insulinoma with synchronous distant metastasis. METHODS: Patients with pancreatic neuroendocrine tumor (PanNET) were retrospectively enrolled and divided into cohort 1 (Fudan University Shanghai Cancer Center) and cohort 2 (Surveillance, Epidemiology, and End Results Program database). Both cohorts were further divided into three subgroups: insulinoma, nonfunctioning pancreatic neuroendocrine tumor (NF-PanNET), and non-insulinoma functioning pancreatic neuroendocrine tumor (NiF-PanNET). RESULTS: Cohorts 1 and 2 comprised 505 and 2761 patients (1566 M0 patients and 1195 M1 patients), respectively. In cohort 1 and cohort 2 M0 subgroup, insulinoma showed longer disease-free survival, overall survival (OS), and disease-specific survival (DSS) than NiF-PanNET and NF-PanNET (not reached vs. 48 and 60months, p < 0.001; 183months vs. 87 and 109months, p < 0.001; 247months vs. 121 and 140months, p = 0.002). However, in cohort 2 M1, the mDSS for metastatic insulinoma was shorter than that for NiF-PanNET (31months vs. 61months, p = 0.045), while the mDSS and mOS were similar to those for NF-PanNET. The percentage of T1 and N0 patients was similar between the metastatic insulinoma subgroup and NiF-PanNET and NF-PanNET subgroups. The Ki-67 index and recurrence had a positive linear relationship only for NiF-PanNET and NF-PanNET (p = 0.009). CONCLUSIONS: Insulinoma with synchronous metastasis showed

clinicopathological and prognostic characteristics similar to those of NF-PanNET. Metastatic insulinoma had worse prognosis than non-insulinoma F-PanNET. These findings may help in the clinical management of metastatic insulinoma.

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**- Neuroendocrine Tumors (NETs) of the Minor Papilla/Ampulla: Analysis of 16 Cases Underlines Homology With Major Ampulla NETs and Differences From Extra-Ampullary Duodenal NETs**

*The American journal of surgical pathology 2019 Mar;():*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30913089

Neuroendocrine tumors (NETs) of the minor papilla/ampulla (MIPA) are rare and poorly studied. Only individual case reports and no comprehensive analysis are available from the literature. We collected 16 MIPA NETs and investigated their clinicopathologic and immunohistochemical features, including markers such as somatostatin, pancreatic polypeptide, gastrin, serotonin, MUC1, cytokeratin 7, and somatostatin receptors type 2A and 5. The median age at diagnosis was 57.5 years, and the female-to-male ratio was 2.2:1. The median NET size was 1.45 cm, and most (94%) were low-grade (G1) tumors. Similarly to what was observed in the major ampulla, 3 histotypes were found: (i) ampullary-type somatostatin-producing tumors (ASTs, 10 cases), characterized by somatostatin expression in most tumor cells, focal-to-extensive tubuloacinar structures, often with psammoma bodies, MUC1 reactivity, and no or rare membranous reactivity for somatostatin receptor type 2A; (ii) gangliocytic paragangliomas (3 cases), characterized by the coexistence of 3 tumor cell types: epithelioid, often reactive for pancreatic polypeptide, ganglion-like cells, and S100 reactive sustentacular/stromal cells; and (iii) ordinary nonfunctioning NETs (3 cases), resembling those more commonly observed in the extra-ampullary duodenum. Comparable histotypes could also be recognized among the 30 MIPA NETs from the literature. No NET-related patient death among MIPA cases was observed during a median follow-up of 38 months; however, MIPA ASTs showed lymph node metastases and invasion of the duodenal muscularis propria or beyond in 44% and 40% of cases, respectively. In conclusion, MIPA NETs closely resemble tumors arising in the major ampulla, with predominance of ASTs.

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Back to top

---

**Microenvironment**

Tumor Stroma Interactions, Microenvironment, Inflammatory Response

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**- Characterization of the Neuroendocrine Tumor Immune Microenvironment**

*Pancreas 2018 10;47(9):1123-1129*

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

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

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Back to top

---

**Staging**

PanNET TNM staging, Margins, Survival

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**- A modified M-stage classification based on the metastatic patterns of pancreatic neuroendocrine neoplasms: a population-based study**

*BMC endocrine disorders 2018 Oct;18(1):73*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30340569

BACKGROUND: The present study aims to improve the M-stage classification of pancreatic neuroendocrine neoplasms (pNENs). METHODS: Two thousand six hundred sixty six pNENs were extracted from the Surveillance, Epidemiology, and End Results database to explore the metastatic patterns of pNENs. Metastatic patterns were categorized as single, two, or multiple (three or more) distant organ metastasis. The mean overall survival and hazard rate of different metastatic patterns were calculated by Kaplan-Meier and Cox proportional hazards models, respectively. The discriminatory capability of the modified M-stage classification was evaluated by Harrell's concordance index. RESULTS: The overall survival time significantly decreased with an increasing number of metastatic organs. In addition, pNENs with only liver metastasis had better prognosis when compared to other metastatic patterns. Thus, we modified the M-stage classification (mM-stage) as follows: mM0-stage, tumor without metastasis; mM1-stage, tumor only metastasized to liver; mM2-stage, tumor metastasized to other single distant organ (lung, bone, or brain) or two distant organs; mM3-stage, tumor metastasized to three or more distant organs. Harrell's concordance index showed that the modified M-stage classification had superior discriminatory capability than both the American Joint Committee on Cancer (AJCC) and the European Neuroendocrine Tumor Society (ENETS) M-stage classifications. CONCLUSIONS: The modified M-stage classification is superior to both AJCC and ENETS M-stage classifications in the prognosis of pNENs. In the future, individualized treatment and follow-up programs should be explored for patients with distinct metastatic patterns.

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**- Pancreatic neuroendocrine tumours: Grade is superior to T, N, or M status in predicting outcome and selecting patients for chemotherapy:A retrospective cohort study in the SEER database**

*International journal of surgery (London, England) 2019 Mar;():*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30872175

BACKGROUND: Pancreatic neuroendocrine tumours (pNETs) are a rare and heterogeneous group of tumours with an increasing incidence. Current staging criteria for pNETs remain limited and controversial. Meanwhile, the impact of chemotherapy on overall survival has not been fully defined. OBJECTIVES: The current study aimed to explore epidemiologic trends of pancreatic neuroendocrine tumours (pNETs). To determine feasible improvements to staging criteria and investigate the relationship between chemotherapy and survival. METHODS: A retrospective cohort study design was used to analyse annual cancer incidence rates, patient demographics, tumour site and stage, and treatment of pNETs. Data were obtained from the National Cancer Institute's SEER registry for all patients diagnosed with pNETs between January 1973 and December 2015. RESULTS: Patients diagnosed after 2010 were more likely to present with age greater than 45 years, T0, T1 status, N0 status, M0 status, and well differentiation. Current AJCC staging criteria was applicable to patients with well differentiation, but not other differentiation. The revised system, defined by Grade, T, N, and M status, could robustly discriminate between survival curves. Chemotherapy was associated with significantly improved survival for patients with poorly differentiated and undifferentiated tumour grading. CONCLUSIONS: Grade is superior to 'T', 'N', or 'M' status in predicting outcomes and selecting patients for chemotherapy. It is necessary and feasible to combine grade into current staging criteria.

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Back to top

## Cytopathology

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### Bile Ducts

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**- Bile cytology: A new scoring system for improving diagnostic accuracy**

*Diagnostic cytopathology 2019 Feb;():*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30730608

BACKGROUND: Benign and malignant cells need to be distinguished in any cytological examination of bile. Here, we report an original scoring system to improve the diagnostic accuracy of bile cytology. METHODS: The study used 158 bile aspiration samples obtained for cytological examination. Fourteen cytological findings were used to differentiate benign and malignant samples. Statistical significance tests and multivariate analysis were used to determine and quantify significant findings and develop a scoring system. RESULTS: Four cytological findings were significant in discriminating between benign and malignant cells: abnormal chromatin, irregularly arranged nuclei, irregularly overlapped nuclei, and irregular cluster margins. Our newly developed scoring system based on these four cytological findings yielded excellent results with a sensitivity of 87%, specificity of 98%, and an odds ratio of 329. CONCLUSIONS: The use of our new scoring system is expected to contribute to the diagnostic accuracy of cytological evaluations of bile samples.

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Back to top

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## Molecular Pathology

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**Pancreas**

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**Pancreas**

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**- Knockdown of KDM1B inhibits cell proliferation and induces apoptosis of pancreatic cancer cells**

*Pathology, research and practice 2019 May;215(5):1054-1060*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30846414

Pancreatic cancer (PC) is one of the common malignant tumors in digestive tract with a high fatality rate. The oncogenic role of lysine-specific demethylase1 (LSD1/KDM1 A) has been well recognized in PC. While, the role of its homolog LSD2 (KDM1B) in regulating PC progression is poorly understood. In this study, we attempted to evaluate the functional role of KDM1B in PC cells. The expression of KDM1B was detected by immunohistochemistry and immunoblotting in PC tissues and cells. Lentivirus-mediated shRNA was applied to silence KDM1B in PANC-1 and SW1990 cells. Cell proliferation was measured by MTT and Celigo assay. Cell apoptosis was determined by both Caspase-Glo®3/7 assay and Flow cytometry. Intracellular signaling molecules were detected using a PathScan intracellular signaling array kit. In this study, we found KDM1B was highly expressed in PC tissues compared to paracancerous tissues. Moreover, elevated expression of KDM1B was detected in PC cell lines (BxPC-3, CFPAC-1, PANC-1 and SW1990) as compared with a normal human pancreatic duct epithelial cell line (HPDE6-C7). Further investigations revealed that KDM1B knockdown significantly inhibited PC cell proliferation. Furthermore, the apoptosis of PANC-1 and SW1990 cells was significantly increased after KDM1B knockdown. Notably, the activations of p-ERK1/2, p-Smad2, p-p53, cleaved PARP, cleaved Caspase-3, cleaved Caspase-7, p-eIF2a and Survivin were promoted by KDM1B knockdown, while IkBa was suppressed. Taken together, our findings provided new insights into the critical and multifaceted roles of KDM1B in the regulation of cell proliferation and apoptosis, and offered a potentially novel target in preventing the progression of PC.

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**- Real-Time Targeted Genome Profile Analysis of Pancreatic Ductal Adenocarcinomas Identifies Genetic Alterations That Might Be Targeted With Existing Drugs or Used as Biomarkers**

*Gastroenterology 2019 Mar;():*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30836094

BACKGROUND & AIMS: It has been a challenge to select treatment for patients with pancreatic ductal adenocarcinomas (PDACs) based on genome alterations. We performed targeted genomic profile analyses of a large number of PDACs to assess the full spectrum of actionable genomic alterations. METHODS: We performed targeted genomic profile analyses of 3594 PDAC samples from an international cohort, including capture-based targeted genomic profiling of as many as 315 cancer-associated genes and intron regions of 28 genes that are rearranged in cancer cells. Tumor mutation burden (TMB) and microsatellite instability (MSI) status were also assessed. TMB was calculated across a 1.14-megabase region; TMB-high was defined as  20 mutations/megabase. MSI-high status was assigned based on analysis of 114 intron homopolymer loci. RESULTS: KRAS, TP53, CDKN2A, and SMAD4 were the most frequently altered genes in the PDAC tissues. We found KRAS mutations in 88% of samples. Among PDACs without mutations in KRAS, we found alterations in genes whose products are in the mitogen-activated protein kinase signaling pathway and are candidate drug targets (actionable targets, n = 132; 4%), as well as gene fusions (n = 51), gene amplifications (n = 35), genes with missense mutations (n = 30), and genes that contain deletions (n = 16). Many of these encode proteins in receptor tyrosine kinase, RAS, or mitogen-activated protein kinase

signaling pathways. Aside from TP53, alterations in genes encoding DNA damage repair proteins (BRCA and FANC) were detected in in 14% of PDACs. Among PDACs evaluated for MSI (n = 2563) and TMB (n = 1021), MSI-high and/or TMB-high phenotypes were detected in 0.5% of samples. Alterations in FGF23, CCND2, PIK3CA, and FGF6 were more commonly detected in intraductal papillary mucinous neoplasm-associated PDACs. CONCLUSIONS: In targeted genomic profile analyses of 3594 PDACs, we found 17% to contain genomic alterations that might make the tumor cells susceptible to currently used anticancer agents. We identified mutations in genes that could contribute to progression of intraductal papillary mucinous neoplasms into malignancies. These alterations might be used as biomarkers for early detection.

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**- Transcriptomic analysis of the Aquaporin (AQP) gene family interactome identifies a molecular panel of four prognostic markers in patients with pancreatic ductal adenocarcinoma**

*Pancreatology : official journal of the International Association of Pancreatology (IAP) ... [et al.] 2019 Apr;19(3):436-442*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30826259

BACKGROUND: This study aimed to assess the differential gene expression of aquaporin (AQP) gene family interactome in pancreatic ductal adenocarcinoma (PDAC) using data mining techniques to identify novel candidate genes intervening in the pathogenicity of PDAC. METHOD: Transcriptome data mining techniques were used in order to construct the interactome of the AQP gene family and to determine which genes members are differentially expressed in PDAC as compared to controls. The same techniques were used in order to evaluate the potential prognostic role of the differentially expressed genes. RESULTS: Transcriptome microarray data of four GEO datasets were incorporated, including 142 primary tumor samples and 104 normal pancreatic tissue samples. Twenty differentially expressed genes were identified, of which nineteen were downregulated and one up-regulated. A molecular panel of four genes (Aquaporin 7 - AQP7; Archain 1 - ARCN1; Exocyst Complex Component 3 - EXOC3; Coatomer Protein Complex Subunit Epsilon - COPE) were identified as potential prognostic markers associated with overall survival. CONCLUSION: These outcomes should be further assessed in vitro in order to fully understand the role of these genes in the pathophysiological mechanism of PDAC.

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**- A pipeline for rapidly generating genetically engineered mouse models of pancreatic cancer using in vivo CRISPR-Cas9-mediated somatic recombination**

*Laboratory investigation; a journal of technical methods and pathology 2019 Feb;():*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30728464

Genetically engineered mouse models (GEMMs) that recapitulate the major genetic drivers in pancreatic ductal adenocarcinoma (PDAC) have provided unprecedented insights into the pathogenesis of this lethal neoplasm. Nonetheless, generating an autochthonous model is an expensive, time consuming and labor intensive process, particularly when tissue specific expression or deletion of compound alleles are involved. In addition, many of the current PDAC GEMMs cause embryonic, pancreas-wide activation or loss of driver alleles, neither of which reflects the cognate human disease scenario. The advent of CRISPR/Cas9 based gene editing can potentially circumvent many of the aforementioned shortcomings of conventional breeding schema, but ensuring the efficiency of gene editing in vivo remains a challenge. Here we have developed a pipeline for generating PDAC GEMMs of complex genotypes with high efficiency using a single "workhorse" mouse strain expressing Cas9 in the adult pancreas under a p48 promoter. Using adeno-associated virus (AAV) mediated delivery of multiplexed guide RNAs (sgRNAs) to the adult murine pancreas of p48-Cre; LSL-Cas9 mice, we confirm our ability to express an oncogenic Kras G12D allele through homology-directed repair (HDR), in conjunction with CRISPR-induced disruption of cooperating alleles (Trp53, Lkb1 and Arid1A). The resulting GEMMs demonstrate a spectrum of precursor lesions (pancreatic intraepithelial neoplasia [PanIN] or Intraductal papillary mucinous neoplasm [IPMN] with eventual progression to PDAC. Next generation sequencing of the resulting murine PDAC confirms HDR of oncogenic KrasG12D allele at the endogenous locus, and insertion deletion ("indel") and frameshift mutations of targeted tumor suppressor

alleles. By using a single "workhorse" mouse strain and optimal AAV serotype for in vivo gene editing with combination of driver alleles, we present a facile autochthonous platform for interrogation of the PDAC genome.

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Back to top

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**SPN**

Solid Pseudopapillary Neoplasm

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**- Targeted next generation sequencing of pancreatic solid pseudopapillary neoplasms show mutations in Wnt signaling pathway genes**

*Pathology international 2019 Feb;():*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30811747

Solid pseudopapillary neoplasms of the pancreas are rare neoplasms that have been shown to harbor recurrent somatic pathogenic variants in the beta-catenin gene, CTNNB1. Here, we used targeted next generation sequencing to analyze these tumors for other associated mutations. Six cases of solid pseudopapillary neoplasms were studied. DNA extracted from formalin-fixed paraffin embedded tissue blocks was analyzed using the Ion Torrent platform, with the 50-gene Ampliseq Cancer Hotspot Panel v2 (CHPv2), with further variant validation performed by Sanger sequencing. Four tumors (67%) were confirmed to harbor mutations within CTNNB1, two with c.109T > G p.(Ser37Ala) and two with c.94G > A p.(Asp32Asn). One case showed a frameshift deletion in the Adenomatous Polyposis Coli gene, APC c.3964delG p.(Glu1322Lysfs*93) with a variant allele frequency of 42.6%. Sanger sequencing on non-tumoral tissue confirmed the variant was somatic. The patient with the APC mutation developed metastasis and died. In addition to the four cases harboring CTNNB1 variants, we found a case characterized by poor outcome, showing a rare frameshift deletion in the APC gene. Since the APC product interacts with beta-catenin, APC variants may, in addition to CTNNB1, contribute to the pathogenesis of solid pseudopapillary neoplasms via the Wnt signaling pathway.

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Back to top

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**Pancreatitis & Other Diseases**

Molecular Studies on Pancreatitis & Other Diseases

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**- STING signalling protects against chronic pancreatitis by modulating Th17 response**

*Gut 2019 Jan;():*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30705050

OBJECTIVE: Chronic pancreatitis (CP) is an inflammatory disease with progressive fibrosis leading to exocrine and endocrine dysfunction. Currently, there are no approved effective therapies for CP. Stimulator of interferon genes (STING) signalling is a key innate immune sensor of DNA. In this study, we evaluated the role of STING signalling in CP. DESIGN: We used an experimental model of CP to test the effect of STING signalling in STING wild-type and knockout mice as well as bone marrow chimaeras (BMCs). STING was activated using a pharmacological agent. Since we found changes in Th17 cells, we used neutralising and control antibodies to determine the role of IL-17A. The effect of STING signalling was further explored in IL-17A generation and we examined the effect of IL-17A on pancreatic stellate cells (PSCs). Human pancreas from patients with CP and without CP were also stained for IL-17A. RESULTS: STING activation decreased CP-associated pancreatic inflammation and fibrosis, whereas absence of STING led to worsening of the disease. BMCs showed that leucocytes play an important role in STING signalling-mediated amelioration of experimental CP. STING deletion was associated with increased Th17 cell infiltration in the pancreas, whereas STING agonist limited this Th17 response. Importantly, anti-IL-17A antibody treatment mitigated the severity of CP in the absence of STING signalling. STING deficiency promoted Th17 polarisation and PSCs express functional IL-17 receptor by upregulating fibrosis genes. Compared with tumour margins, pancreas from patients with CP had significant increase in IL-17A+ cells. CONCLUSION: Unlike acute pancreatitis, STING activation is protective in CP. STING signalling is important in regulating adaptive immune responses by diminishing generation of IL-17A during CP and presents a novel therapeutic target for CP.

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Back to top

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**Molecular Research on Microenvironment**

Tumor Stroma Interactions, Microenvironment, Inflammatory Response, Microbiome

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**- Reliable evaluation of tumor-infiltrating lymphocytes in pancreatic cancer tissue biopsies**

*Oncotarget 2019 Feb;10(10):1149-1159*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30800224

Tumor-infiltrating lymphocytes (TILs) represent cancer microenvironment. We previously reported TILs was prognosticators in pancreatic ductal adenocarcinoma (PDAC) patients by immunohistochemically measuring them in surgically-resected tissues. The aim of this study was to assess how best to evaluate TILs in PDAC tissue biopsies. First, we showed expression of CD3, CD4, or CD8 genes in PDAC tissue measured by quantitative RT-PCR (RT-qPCR) was prognostic using 241 surgically-resected specimens. We assessed whether the TILs in biopsied tissues can be effectively evaluated by comparing between immunohistochemistry and RT-qPCR. As a study model, we sampled twenty biopsies from surgically-resected PDAC specimen (n = 17). We investigated the variation levels of TILs in the different biopsies from the same specimen and evaluated using the intraclass correlation coefficient (ICC). The ICC value was 0.58 for CD3, 0.61 for CD4, and 0.46 for CD8, respectively; these ICC values meant correlations of "moderate" to "substantial" levels. To reach "near perfect", 3, 3, and 5 times biopsies were necessary for CD3, CD4, and CD8, respectively. When ICC values of immunolabeled TILs were of "low", 6 times biopsies were necessary to reach "moderate" levels. We found that TILs measured by RT-qPCR and repeated sampling increased reliability in TILs detected from biopsied PDAC tissues.

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**- Activation of IGF/IGF-IR signaling pathway fails to induce epithelial-mesenchymal transition in pancreatic cancer cells**

*Pancreatology : official journal of the International Association of Pancreatology (IAP) … [et al.] 2019 Mar;19(2):390-396*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30799278

BACKGROUND: Pancreatic cancer stromal cells produce various protein factors, which presumably provide cancer cells with drug resistance and may influence their ability to form metastasis via induction of epithelial-mesenchymal transition ( ). The goal of our project was to study the effects of IGF-I on expression of protein markers of epithelial and mesenchymal differentiation, and on expression of transcriptional regulators of EMT in pancreatic cancer cell lines. METHODS: We used Western blot analysis to study the expression patterns of epithelial and mesenchymal protein markers in pancreatic cancer cell lines, which have been stimulated with IGF-I for various periods of time. The ELISA technique was employed to determine the concentration of IGF-I in conditioned media. Additionally, the effect of IGF-I on proliferation of pancreatic cancer cells was measured via MTS technique. RESULTS: We investigated the effect of IGF/IGF-IR signaling pathway activation on expression levels of cell differentiation markers in five pancreatic cancer cell lines (AsPC-1, BxPC-3, Capan-2, MiaPaCa-2 and Panc1). The IGF-I stimulation led to phosphorylation of IGF-IR and activation of PI-3K/Akt signaling cascade. At the same time our results reveal that the activation of IGF/IGF-IR signaling pathway in pancreatic cancer cells does not induce a significant shift in cell phenotype towards mesenchymal differentiation and does not induce a decrease in expression levels of epithelial protein markers. CONCLUSIONS: Our results demonstrate that IGF-I does not function as an effective inductor of EMT in pancreatic cancer cell lines and that stimulation of IGF-I/IGF-IR signaling pathway does not lead to EMT associated changes in cell differentiation.

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**- Signaling Networks That Control Cellular Plasticity in Pancreatic Tumorigenesis, Progression, and Metastasis**

*Gastroenterology 2019 May;156(7):2073-2084*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30716326

Pancreatic ductal adenocarcinoma is one of the deadliest cancers, and its incidence on the rise. The major challenges in overcoming the poor prognosis with this disease include late detection and the aggressive biology of the disease. Intratumoral heterogeneity; presence of a robust, reactive, and desmoplastic stroma; and the crosstalk between the different tumor components require complete understanding of the pancreatic tumor biology to better understand the therapeutic challenges posed by this disease. In this review, we discuss the processes involved during tumorigenesis encompassing the inherent plasticity of the transformed cells, development of tumor stroma crosstalk, and enrichment of cancer stem cell population during tumorigenesis.

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**- Semaphorin-5A maintains epithelial phenotype of malignant pancreatic cancer cells**

*BMC cancer 2018 Dec;18(1):1283*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30577767

BACKGROUND: Pancreatic cancer (PC) is a highly aggressive disease, and the lethality of this disease stems from early metastatic dissemination where surgical removal cannot provide a cure. Improvement of the therapeutic outcome and overall survival of PC patients requires to understand the fundamental processes that lead to metastasis such as the gain of cellular migration ability. One such family of proteins, which are essential players of cellular migration, is Semaphorin. Previously, we have identified one of the Semaphorin family member, Semaphorin-5A (SEMA5A) to be involved in organ-specific homing during PC metastasis. We have also demonstrated that SEMA5A has a constitutive expression in PC cell lines derived from metastatic sites in comparison with low endogenous expression in the primary tumor-derived cell line. In this study, we examined whether constitutive SEMA5A expression in metastatic PC cells regulates tumor growth and metastatic potential. METHODS: We generated SEMA5A knockdown in T3M-4 and CD18/HPAF cells and assessed their phenotypes on in vitro motility, tumor growth, and metastatic progression. RESULTS: In contrary to our initial expectations, orthotopic injection of SEMA5A knockdown cells into nude mice resulted in a significant increase in both tumor burden and liver metastases in comparison with the Control cells. Similarly, we observed higher in vitro migratory potential with pronounced morphological changes associated with epithelial-mesenchymal transition (EMT), a decrease in the expression of epithelial marker E-cadherin (E-Cad), increase in the expression of mesenchymal markers N-cadherin (N-Cad) and Snail and the activation of the Wnt-signaling pathway in SEMA5A knockdown cells. Furthermore, re-establishing SEMA5A expression with a knockdown resistant mouse Sema5A in SEMA5A knockdown cells resulted in a reversion to the epithelial state (mesenchymal-epithelial transition; MET), as indicated by the rescue of E-Cad expression and a decrease in N-Cad and Snail expression. CONCLUSIONS: Collectively, our data suggest that SEMA5A expression maintains epithelial phenotype in the metastatic microenvironment.

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Back to top

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**Preneoplastic and Preinvasive Lesions**

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

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**- Prevalence of Germline Mutations Associated With Cancer Risk in Patients With Intraductal Papillary Mucinous Neoplasms**

*Gastroenterology 2019 May;156(6):1905-1913*

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30716324

BACKGROUND & AIMS: Many patients with pancreatic adenocarcinoma carry germline mutations associated with increased risk of cancer. It is not clear whether patients with intraductal papillary mucinous neoplasms (IPMNs), which are precursors to some pancreatic cancers, also carry these mutations. We assessed the prevalence of germline mutations associated with cancer risk in patients with histologically confirmed IPMN. METHODS: We obtained nontumor tissue samples from 315 patients with surgically resected IPMNs from 1997 through 2017, and we sequenced 94 genes with variants associated with cancer risk. Mutations associated with increased risk of cancer were identified and compared with individuals from the Exome Aggregation Consortium. RESULTS: We identified 23 patients with a germline mutation associated with cancer risk (7.3%; 95% confidence interval, 4.9-10.8). Nine patients had a germline mutation associated with pancreatic cancer susceptibility (2.9%; 95% confidence interval, 1.4-5.4). More patients with IPMNs carried germline mutations in ATM ($P < .0001$), PTCH1 ($P < .0001$), and SUFU ($P < .0001$) compared with controls. Patients with IPMNs and germline mutations associated with pancreatic cancer were more like to have concurrent invasive pancreatic carcinoma compared with patients with IPMNs without these mutations ($P < .0320$). CONCLUSIONS: In sequence analyses of 315 patients with surgically resected IPMNs, we found that almost 3% to carry mutations associated with pancreatic cancer risk. More patients with IPMNs and germline mutations associated with pancreatic cancer had concurrent invasive pancreatic carcinoma compared with patients with IPMNs without these mutations. Genetic analysis of patients with IPMNs might identify those at greatest risk for cancer.

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Back to top

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