Pancreatobiliary Pathology Society Journal Watch

April May 2019

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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. See the list of journals we search regularly here. Previous months' issues may be found in our *archive* and you may see preparation of upcoming issue here.

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

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Surgical Pathology

Pancreas

Morphology, Diagnostics, IHC

Morphology, Diagnostics, IHC

- Pancreatic Nerve Sheath Tumors: a Single Institutional Series and Systematic Review of the Literature

Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract 2019 Apr;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30941687

INTRODUCTION: Improvement in imaging has resulted in frequent diagnosis of benign and premalignant pancreatic tumors. Pancreatic nerve sheath (PNS) tumors are one of the rarest pancreatic tumors. Literature on PNS is limited and their biology is poorly understood. Here, we report the largest series of PNS tumors to date and review the literature to evaluate the current data available on PNS tumors. METHODS: An institutional database was used to identify patients who underwent resection for PNS tumors. Clinicopathological characteristics and outcomes of these patients were reported. Furthermore, a review of literature was performed. RESULTS: From January 1994 through December 2016, seven patients underwent resection for PNS tumors. The median age was 57.7 years (IQR, 44.9-61.9) and the sex was approximately equally distributed (male = 4; 57.1%). Three (42.9%) patients were diagnosed incidentally and six (85.7%) were misdiagnosed as having other pancreatic tumors. The median tumor size was 2.1 (IQR 1.8-3.0) cm and six (85.7%) had no nodal disease. At a median follow-up of 15.5 (IQR 13.7-49.3) months, six patients were alive without evidence of disease and one patient was lost to follow-up. The literature review identified 49 studies reporting 54 patients with PNS tumors. Forty-six were misdiagnosed as having other pancreatic tumors. The median tumor size was 3.6 (range 1-20) cm, nodal disease was present in six patients (22.2%), and no patient had distant metastatic disease. At the time of last follow-up, all patients were free of disease. CONCLUSION: This is the largest single institution series on PNS tumors reported to date. These tumors are rare and are often misdiagnosed, given their radiological characteristics. PNS tumors have a benign course of disease and surgical resection results in favorable long-term outcomes.

- Primary Extranodal Rosai-Dorfman Disease (Sinus Histiocytosis With Massive Lymphadenopathy) in the Pancreatic Tail: A Case Report With Literature Review

Pancreas 2019 04;48(4):e31-e33

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30973472

- Challenges in Diagnosis and Management of Pancreatic Inflammatory Myofibroblastic Tumors in Children

Pancreas 2019 04;48(4):e27-e29

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30973469

- Incidence and Significance of GATA3 Positivity in Pancreatic Ductal Adenocarcinoma and Cholangiocarcinoma

Applied immunohistochemistry & molecular morphology : AIMM 2019 Apr;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31033498

GATA3 is a transcription factor involved in the development and differentiation of lymphocytes, breast, and hair follicles. The protein is a useful immunohistochemical (IHC) marker for supporting diagnoses of breast or urothelial carcinoma. This can be especially helpful in metastatic neoplasms to help delineate site of origin. GATA3 is also reportedly positive in a percentage of pancreatic ductal adenocarcinomas (PDACs) and cholangiocarcinomas (CCs), but no study has closely evaluated this relationship with respect to clinicopathologic features or patient outcome. Using tissue microarrays, we analyzed 240 PDACs and 60 CCs with GATA3 IHC and compared expression to various clinical and pathologic parameters. Overall, GATA3 positivity was seen in 16% of PDACs and 5% of CCs. GATA3 positivity in PDAC cases was more common in male patients (P=0.013). GATA3-positive PDACs trended toward worse survival on multivariate analysis (P=0.074). The only 3 GATA3-positive CCs were poorly differentiated (P=0.069); low case number precluded multivariate survival analysis for CCs. GATA3 positivity can occur in carcinomas of the pancreatobiliary system, which should be considered during IHC workup of neoplasms of unclear origin. This positivity seems to have minimal relevance to patient outcome.

- Loss of SMAD4 Protein Expression in Gastrointestinal and Extra-Gastrointestinal Carcinomas

Histopathology 2019 May;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31054158

BACKGROUND: SMAD4 (DPC4) is a tumor suppressor gene that is dysregulated in various tumor types, particularly pancreaticobiliary and gastrointestinal carcinomas. Corresponding loss of protein expression has been reported in approximately 50% of pancreatic and 25% of colonic adenocarcinomas. In the evaluation of carcinoma of unknown primary site, immunohistochemical loss of SMAD4 expression is often used to suggest pancreaticobiliary origin, but there is limited data on the spectrum of SMAD4 expression in carcinomas of other sites. This study evaluates the frequency of SMAD4 loss in a large cohort of carcinomas from diverse anatomic sites. DESIGN: Immunohistochemistry for SMAD4 was performed on tissue microarrays or whole tissue sections of 1210 carcinomas from various organs: gastrointestinal tract, liver, pancreas/biliary tract, lung, breast, thyroid, kidney, ovary, and uterus. Expression was considered lost when there was complete absence of staining in tumor cell nuclei, in the presence of intact staining in non-neoplastic cells. RESULTS: SMAD4 loss was seen in 58% of pancreatic adenocarcinomas, 27% of appendiceal adenocarcinomas, 19% of colorectal adenocarcinomas, 16% of cholangiocarcinomas, 10% of lung adenocarcinomas, and <5% of esophageal, breast, gastric and mucinous ovarian adenocarcinomas. All papillary thyroid, hepatocellular, non-mucinous ovarian, endometrial, and renal cell carcinomas showed intact SMAD4 nuclear expression. CONCLUSION: In addition to pancreaticobiliary, appendiceal and colonic tumors, SMAD4 loss is also seen in a small subset of other carcinomas, specifically breast, lung, esophageal and gastric adenocarcinomas, all of which are typically CK7 positive, similar to pancreaticobiliary carcinoma. Awareness of SMAD4 loss in these other carcinoma types is helpful in the evaluation of carcinomas of unknown primary site.

- Expression and prognostic value of NSD1 and SETD2 in pancreatic ductal adenocarcinoma and its precursor lesions

Pathology 2019 Jun;51(4):392-398

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31060750

Epigenetic regulation is emerging as a critical mechanism for pancreatic ductal adenocarcinoma (PDA) development. Histone methylation is an important regulatory mechanism, altering chromatin structure and promoter accessibility and causing aberrant gene expression. NSD1 and SETD2 genes encoding two histone H3K36 methyltransferases, are mutated or altered in 8-10% of PDA cases. However, whether there is altered protein expression of NSD1 or SETD2 in PDA and its precursors, and whether they have diagnostic or prognostic utility is unknown. Tissue microarrays composed of a total of 190 and 192 duplicated cases of PDA (n=74 and 75), metastatic PDA (n=17 and 18), pancreatic intraepithelial neoplasia (PanIN; n=19 and 24), intraductal papillary mucinous neoplasm (IPMN; n=36), mucinous cystic neoplasm (MCN; n=12) and benign pancreatic tissues (n=27 and 32) were analysed for expression of NSD1 and SETD2 by immunohistochemistry. We assessed intensity and percentage of positive cells. NSD1 expression was significantly increased in metastatic PDA compared to benign ducts, primary PDA, and all other lesions combined (p=0.03, 0.02, and 0.03 respectively). Additionally, significantly decreased SETD2 protein expression was found in metastatic PDA and PanIN lesions compared to benign ducts (p=0.04 and 0.007, respectively). High NSD1 expression was associated with clinical stage III/IV disease (p=0.026), tumour grade 2 (p=0.022), use of neoadjuvant therapy (p=0.037), and overall higher clinical stage (p=0.022). There is no significant difference in overall and progression-free survival between NSD1/SETD2 high and low PDA. Expression of NSD1 and SETD2 is specifically altered in metastatic PDA and some of the PDA precursor lesions, supporting their important role in PDA development and metastasis. In addition, increased NSD1 expression is significantly associated with higher clinical stage and neoadjuvant therapy, suggesting that NSD1 may be a useful prognostic marker.

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Staging

Pancreas TNM staging, Margins, Survival

- Tumor location as an indicator of survival in T1 resectable pancreatic ductal adenocarcinoma: a propensity score-matched analysis

BMC gastroenterology 2019 Apr;19(1):59

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31014264

BACKGROUND: The latest 8th edition of the AJCC staging system emphasizes the importance of tumor size however, the clinical significance of the combination of tumor location with tumor size remains unknown. METHODS: We conducted this study to investigate the prognostic role of tumor location in T1 resectable pancreatic ductal adenocarcinoma (PDAC). Resectable PDAC patients from Surveillance, Epidemiology, and End Results (SEER) database (2004-2014) were selected for the propensity score matching analysis. We used matched cohort to analyze the relationship between clinicopathologic features and survival of patients. RESULT: Eight thousand, four hundred nine patients were included in the propensity score matching analysis and 4571 patients were selected for final analysis. In T1 patients, the patients with pancreatic head tumor had worse prognosis compared to the patients with body/tail tumors. Multivariate analysis result showed that pancreatic body/tail location was an independent indicator for better chances of survival in T1 PDAC patients (hazard ratio, 0.69; 95%CI, 0.52-0.93; $P = 0.01$). The modified staging system was more efficient than the AJCC 8th staging system. CONCLUSION: Modified staging system exhibited a good assessment of the survival rate. The tumor location is a good prognostic indicator for T1 resectable PDAC patients. Modification of T1 subgroup according to tumor location exhibited favorable survival prediction effects.

- A Single-Institution Validation Study of Lymph Node Staging By the AJCC 8th Edition for Patients with Pancreatic Head Cancer: A Proposal to Subdivide the N2 Category

Annals of surgical oncology 2019 Jul;26(7):2112-2120

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31037440

BACKGROUND: According to the revised staging of the American Joint Committee on Cancer, 8th edition (AJCC8), the N category in pancreatic ductal adenocarcinoma is classified as N0 (0), N1 (1-3), and N2 (4) based on the number of metastatic lymph nodes (LNs). This study aimed to validate this classification and analyze cutoff values of metastatic LN numbers. METHODS: Patients with pancreatic head ductal adenocarcinoma who underwent pancreaticoduodenectomy at our institution between 2005 and 2016 without preoperative therapy were retrospectively analyzed. The patients were staged by AJCC8, and prognostic analyses were performed. The best cutoff value for the metastatic LN number was determined by the minimum P value approach. RESULTS: In 228 of 309 patients, LN metastases were found (median number of examined LNs, 41). The median survival time (MST) was 56 months in the N0 group, 34 months in the N1 group, and 20 months in the N2 group (N0 vs N1: $P = 0.023$; N1 vs N2: $P < 0.001$). The best cutoff number of metastatic LNs was 4 for patients with LN metastases and 7 for patients with N2 disease. The MST for patients with four to six positive nodes (N2a) was significantly longer than for those with seven or more positive nodes (N2b) (24.0 vs 19.1 months: $P = 0.012$). For N2b patients, conventional adjuvant chemotherapy did not show survival benefits ($P = 0.133$), and overall survival did not differ significantly from that for patients with para-aortic LN metastasis ($P = 0.562$). CONCLUSION: The N staging of AJCC8 was valid. Clinicians should regard N2b as similar to distant LN metastasis, and more intensive adjuvant therapy may be indicated for this group.

- Outcome of head compared to body and tail pancreatic cancer: a systematic review and meta-analysis of 93 studies

Journal of gastrointestinal oncology 2019 Apr;10(2):259-269

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31032093

Background: Even when resectable pancreatic cancer (PC) is associated with a dismal prognosis. Initial presentation varies according with primary tumor location. Aim of this systematic review and meta-analysis was to evaluate the prognosis associated with site (head versus body/tail) in patients with PC. Methods: We searched PubMed, Cochrane Library, SCOPUS, Web of Science, EMBASE, Google Scholar, LILACS, and CINAHL databases from inception to March 2018. Studies reporting information on the independent prognostic role of site in PC and comparing overall survival (OS) in head versus body/tail tumors were selected. Data were aggregated using hazard ratios (HRs) for OS of head versus body/tail PC according to fixed- or random-effect model. Results: A total of 93 studies including 254,429 patients were identified. Long-term prognosis of head was better than body/tail cancers (HR =0.96, 95% CI: 0.92-0.99; P=0.02). A pooled HR of 0.95 (95% CI: 0.92-0.99, P=0.02) from multivariate analysis only (n=77 publications) showed that head site was an independent prognostic factor for survival. Conclusions: Primary tumor location in the head of the pancreas at the time of diagnosis is a predictor of better survival. Such indicator should be acknowledged when designing future studies, in particular in the operable and neoadjuvant setting.

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Preneoplastic and Preinvasive Lesions

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

- A Consensus Study of the Grading and Typing of Intraductal Papillary Mucinous Neoplasms of the Pancreas

Pancreas 2019 04;48(4):480-487

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30946243

OBJECTIVE: The grading and typing of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are challenging for pathologists. We aimed to clarify the points of consistency and disagreement in assessing the grades and types of IPMNs. METHODS: Digital slide images of 20 IPMNs were independently assessed by 10 Japanese pathologists, who then held a consensus meeting to discuss the points of disagreement and develop a consensus and recommendations. RESULTS: The average agreement rates for grade and type were 83.5% (range, 100%-40%) and 82.5% (range, 100%-50%) and the Fleiss' values were 0.567 and 0.636, respectively. CONCLUSIONS: The disagreement points and recommendations were as follows: destructed ductal walls with desquamated neoplastic epithelia or mucin lakes partially lined with neoplastic cells could be invasion; intraductal stromal invasion could be dismissed unless vascular or lymphatic invasion existed; elastica staining may help visualize ducts in colloidal nodules; high-grade can be distinguished from low/intermediate grade by marked nuclear disarrangements and complex architecture in the intestinal papillae; oncocytic papillae are characterized by eosinophilic cells with round disoriented nuclei; high-grade gastric papillae can be distinguished from pancreatobiliary papillae by relatively low but complex architecture; and the most dysplastic papillae should be used to assess type in mixed papillae types.

- Clinical assessment of the GNAS mutation status in patients with intraductal papillary mucinous neoplasm of the pancreas

Surgery today 2019 Mar;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30879148

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is characterized by cystic dilation of the pancreatic duct, caused by mucin hypersecretion, with slow progression via the adenoma-carcinoma sequence mechanism. Mutation of GNAS at codon 201 is found exclusively in IPMNs, occurring at a rate of 41-75%. Recent advances in molecular biological techniques have demonstrated that GNAS mutation might play a role in the transformation of IPMNs after the appearance of neoplastic cells, rather than in the tumorigenesis of IPMNs. GNAS mutation is observed frequently in the intestinal subtype of IPMNs with MUC2 expression, and less frequently in IPMNs with concomitant pancreatic ductal adenocarcinoma (PDAC). Research has focused on assessing GNAS mutation status in clinical practice using various samples. In this review, we discuss the clinical application of GNAS mutation assessment to differentiate invasive IPMNs from concomitant PDAC, examine the clonality of recurrent IPMNs in the remnant pancreas using resected specimens, and differentiate pancreatic cystic lesions using cystic fluid collected by endoscopic ultrasound-guided fine needle aspiration (EUS-FNA), duodenal fluid, and serum liquid biopsy samples.

- Intraductal Oncocytic Papillary Neoplasms: Clinical-Pathologic Characterization of 24 Cases, With An Emphasis on Associated Invasive Carcinomas

The American journal of surgical pathology 2019 May;43(5):656-661

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30986801

BACKGROUND: Intraductal oncocytic papillary neoplasm (IOPN) of the pancreas is a rare tumor. Recent molecular data indicate that it is distinct from other intraductal neoplasms; however, its clinicopathologic

characteristics, especially the frequency/significance of an invasive carcinoma component, and biologic behavior remain to be fully defined. DESIGN: Clinicopathologic characteristics and survival of 24 IOPNs were analyzed. By definition, all tumors exhibited intraductal growth and oncocytic morphology. RESULTS: The female:male ratio was 1.7, and mean age was 59. In 44% of the patients, the IOPN was discovered incidentally; however, the working diagnosis was "ductal adenocarcinoma" in 42%. Fourteen IOPNs occurred in the head of the pancreas. The median tumor size was 4.5 cm. The tumors often grew along adjacent benign ducts, mimicking invasion, but only 29% exhibited unequivocal invasive carcinoma, mostly in the form of microscopic foci (pT1a=4, pT1b=1, pT2=2), and only 6% had lymph node metastasis. Invasive carcinoma was predominantly composed of small tubular units lined by oncocytic cells, or individual oncocytic cells infiltrating the periductal stroma. Follow-up information was available for 18 patients (median=6.8 y). No patients died from the disease, and the overall 10-year survival was 94%. Patients with invasive carcinoma trended toward a lower 5-year recurrence-free survival than those with noninvasive IOPNs (66% vs. 93%, P=0.066), but overall survival was not impacted by the presence of invasion (P=0.38). CONCLUSIONS: IOPN is a distinct tumor type in the pancreas. Despite its morphologic complexity and often extensive pagetoid spread to adjacent ducts, conventional invasive carcinoma is seen in only 29% and usually as microscopic foci. Thus, it is not surprising that IOPN exhibits indolent behavior even when invasion is present.

- Cyclooxygenase-2 and Cytosolic Phospholipase A2 Are Overexpressed in Mucinous Pancreatic Cysts

Clinical and translational gastroenterology 2019 Apr;10(4):e00028

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31009406

OBJECTIVES: Expression of prostaglandin biosynthetic pathway enzymes in mucinous pancreatic cysts is unknown. Cyclooxygenase-2 (COX-2) inhibition is a potential cancer chemoprevention strategy for these lesions. We evaluated the expression of COX-2, cytosolic phospholipase A2 (cPLA2), and protein kinase B (AKT) in the epithelium of pancreatic cysts and correlated enzyme expression with aspirin (ASA) use and cyst fluid prostaglandin E2 (PGE2) concentration. METHODS: Pathology of 80 resected pancreatic cysts was reviewed. Expression of COX-2, cPLA2, and AKT was quantified by tissue immunohistochemistry immunoreactivity scores (IRSs). IRS values were compared between cyst types and (in 30 cases) with matched cyst fluid PGE2 concentrations. RESULTS: The mean IRS was higher in the epithelium of mucinous vs nonmucinous cysts for COX-2 (6.1 ± 4.7 vs 3.2 ± 2.8, $P = 0.01$) and cPLA2 (6.9 ± 3.0 vs 2.9 ± 2.9, $P < 0.001$). Cyst epithelial COX-2 expression was higher in mucinous cysts with low-grade dysplasia vs those with high-grade dysplasia or invasive carcinoma (IRS 8.0 ± 3.9 vs 1.5 ± 2.9, $P < 0.001$), whereas the opposite was found for cPLA2 (6.2 ± 3.0 vs 8.6 ± 2.3, $P = 0.005$). Cyst fluid PGE2 concentrations did not correlate with either the IRS or a history of low- to moderate-dose ASA use. CONCLUSIONS: COX-2 and cPLA2 are overexpressed in the epithelium of mucinous pancreatic cysts. COX-2 and/or cPLA2 inhibition might prevent the emergence or progression of mucinous pancreatic cysts, but higher doses of ASA or nonsteroidal anti-inflammatory drugs may be necessary to substantially inhibit cyst epithelial COX-2 activity.

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SPN

Solid Pseudopapillary Neoplasm

- Solid Pseudopapillary Neoplasms of the Pancreas: A Large American Cohort

Pancreas 2019 04;48(4):e21-e22

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30973464

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Bile Ducts

Morphology, Diagnostics, IHC

Morphology, Diagnostics, IHC

- Impact of tumour budding grade in 310 patients who underwent surgical resection for extrahepatic cholangiocarcinoma

Histopathology 2019 May;74(6):861-872

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.

- Intrahepatic Cholangiocarcinomas Have Histologically and Immunophenotypically Distinct Small and Large Duct Patterns

The American journal of surgical pathology 2018 Oct;42(10):1334-1345

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30001234

Intrahepatic cholangiocarcinomas are histologically heterogenous. Using a cohort of 184 clinically defined, resected intrahepatic cholangiocarcinomas, we retrospectively classified the histology into 4 subtypes: large duct (LD), small duct (SD) (predominantly tubular [SD1] or predominantly anastomosing/cholangiolar, [SD2]), or indeterminate. Then, we tested the 4 subtypes for associations with risk factors, patient outcomes, histology, and immunophenotypic characteristics. SD was the most common (84%; 24% SD1 and 60% SD2) with lower proportions of LD (8%), and indeterminate (8%). Primary sclerosing cholangitis was rare (2%), but correlated with LD (P=0.005). Chronic hepatitis, frequent alcohol use, smoking, and steatosis had no histologic association. LD was associated with mucin production (P<0.001), perineural invasion (P=0.002), CA19-9 staining (P<0.001), CK7, CK19, CD56 immunophenotype (P=0.005), and negative albumin RNA in situ hybridization (P<0.001). SD was histologically nodular (P=0.019), sclerotic (P<0.001), hepatoid (P=0.042), and infiltrative at the interface with hepatocytes (P<0.001). Albumin was positive in 71% of SD and 18% of LD (P=0.0021). Most albumin positive tumors (85%) lacked extracellular mucin (P<0.001). S100P expression did not associate with subtype (P>0.05). There was no difference in disease-specific or recurrence-free survival among the subtypes. Periductal infiltration and American Joint Committee on

Cancer eighth edition pT stage predicted survival by multivariable analysis accounting for gross configuration, pT stage, and histologic type. pT2 had worse outcome relative to other pT stages. Significant differences in histology and albumin expression distinguish LD from SD, but there is insufficient evidence to support further subclassification of SD.

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Staging

Bile Ducts TNM staging, Margins, Survival

- The Evaluation of the Eighth Edition of the AJCC/UICC Staging System for Intrahepatic Cholangiocarcinoma: a Proposal of a Modified New Staging System

Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract 2019 Apr;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31012045

BACKGROUND: The objective was to clarify the prognostic impact of the 8th edition of American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) of intrahepatic cholangiocarcinoma (ICC). METHODS: A total of 103 ICC patients who underwent hepatectomy between 2002 and 2016 were enrolled. The survival impact of AJCC/UICC 8th edition was examined. RESULTS: The 5-year disease-specific survival (DSS) rate was 75.9% in T1a (n = 23), 88.9% in T1b (n = 10), 14.9% in T2 (n = 24), 52.5% in T3 (n = 11), and 15.2% in T4 (n = 35). The DSS was comparable among T2, T3, and T4 (T2 vs. T3; p = 0.345, T3 vs. T4; 0.295). A multivariate analysis identified multiple tumors (hazard ratio [HR] 2.821), periductal infiltrating (HR 2.439), perforation of the visceral peritoneum (HR 1.850), and vascular invasion (HR 1.872) as independent prognostic factors that were associated with the DSS. The optimum tumor size with the greatest difference in the DSS was 2 cm (p = 0.014). The new T classification was developed as follows: T1, size 2 cm without other factors; T2, size > 2 cm without other factors; T3, vascular invasion or perforation of the visceral peritoneum; and T4, multiple tumors or periductal infiltrating. The 5-year DSS was 100% in T1 (n = 7), 76.6% in T2 (n = 28), 45.1% in T3 (n = 28), and 3.4% in T4 (n = 40). There were differences in the DSS between T2 and T3 (p = 0.035) and between T3 and T4 (p = 0.003). CONCLUSIONS: T2, T3, and T4 of AJCC/UICC overlapped with regard to the DSS. The new staging can classify ICC patients with sufficient prognostic differences.

- Validation Study of Tumor Invasive Thickness for Postoperative Prognosis in 110 Patients Who Underwent Pancreatoduodenectomy for Distal Cholangiocarcinoma at a Single Institution

The American journal of surgical pathology 2019 May;43(5):717-723

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30986803

The pT classification of the 8th American Joint Committee on Cancer (AJCC) for distal cholangiocarcinoma (DCC) is classified according to depth of invasion (DOI), which is the distance from the basal lamina to the most deeply advanced tumor cells. The Nagoya group proposed a new T classification for DCC based on invasive tumor thickness (ITT), which is the maximal vertical distance of the invasive cancer component (the ITT grade). In this study, we aimed to validate the ITT grade for the next pT classification of DCC in 110 patients. ITT could be measured in all patients, but DOI could only be measured in 62 (56%) patients. According to ITT grade, patients were classified into grades A to D, as follows: grade A, ITT <1 mm (n=9); grade B, ITT 1 mm or more but <5 mm (n=35); grade C, ITT 5 mm or more but <10 mm (n=40); and grade D, ITT 10 mm or greater (n=26). The median overall survival times in patients with ITT grades A, B, C, and D were 12.8, 5.7, 3.7, and 2.0 years, respectively. ITT grade could discriminate postoperative survivals between grades. On multivariate analysis, ITT grade, regional lymph node metastasis, and distant metastasis were selected as independent prognostic factors. In summary, our results showed that ITT grade was a suitable alternative to DOI for pT classification in the next edition of the AJCC for DCC.

- Should Utilization of Lymphadenectomy Vary According to Morphologic Subtype of Intrahepatic Cholangiocarcinoma?

Annals of surgical oncology 2019 Jul;26(7):2242-2250

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30927194

OBJECTIVE: We sought to evaluate the utilization of lymphadenectomy (LND) and the incidence of lymph node metastasis (LNM) among different morphologic types of intrahepatic cholangiocarcinoma (ICC). METHODS: Clinical data of patients undergoing curative-intent resection for ICC between 1990 and 2017 were collected and analyzed. The preoperative nodal status was evaluated by imaging studies, and the morphologic and lymph node (LN) status was collected on final pathology report. RESULTS: Overall, 1032 patients had a mass-forming (MF) or intraductal growth (IG) ICC subtype, whereas 150 patients had a periductal infiltrating (PI) or MF + PI subtype. Among the 924 patients with MF/IG ICC subtype who had nodal assessment on preoperative imaging, 747 (80.8%) were node-negative, whereas 177 (19.2%) patients were suspicious for metastatic nodal disease. On final pathological analysis, 71 of 282 (25.2%) patients who had preoperative node-negative disease ultimately had LNM. In contrast, 79 of 135 (58.5%) patients with preoperative suspicious/metastatic LNs had pathologically confirmed LNM (odds ratio [OR] 4.2, $p < 0.001$). Among the 129 patients with PI/MF + PI ICC subtype and preoperative nodal information, 72 (55.8%) were node-negative on preoperative imaging. In contrast, 57 (44.2%) patients had suspicious/metastatic LNs. On final pathologic examination, 45.3% ($n = 24$) of patients believed to be node-negative on preoperative imaging had LNM; 68.0% ($n = 34$) of patients who had suspicious/positive nodal disease on imaging ultimately had LNM (OR 2.6, $p = 0.009$). CONCLUSION: Given the low accuracy of preoperative imaging evaluation of nodal status, routine LND should be performed at the time of resection for both MF/IG and PI/MF + PI ICC subtypes.

- Assessment of the Lymph Node Status in Patients Undergoing Liver Resection for Intrahepatic Cholangiocarcinoma: the New Eighth Edition AJCC Staging System

Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract 2018 01;22(1):52-59

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=28424987

INTRODUCTION: The role of routine lymphadenectomy for intrahepatic cholangiocarcinoma (ICC) is still controversial. The AJCC eighth edition recommends a minimum of six harvested lymph nodes (HLNs) for adequate nodal staging. We sought to define outcome and risk of death among patients who were staged with 6 HLNs versus <6 HLNs. MATERIALS AND METHODS: Patients undergoing hepatectomy for ICC between 1990 and 2015 at 1 of the 14 major hepatobiliary centers were identified. RESULTS: Among 1154 patients undergoing hepatectomy for ICC, 515 (44.6%) had lymphadenectomy. On final pathology, 200 (17.3%) patients had metastatic lymph node (MLN), while 315 (27.3%) had negative lymph node (NLN). Among NLN patients, HLN was associated with 5-year OS ($p = 0.098$). While HLN did not impact 5-year OS among MLN patients ($p = 0.71$), the number of MLN was associated with 5-year OS ($p = 0.02$). Among the 317 (27.5%) patients staged according the AJCC eighth edition staging system, N1 patients had a 3-fold increased risk of death compared with N0 patients (hazard ratio 3.03; $p < 0.001$). CONCLUSION: Only one fourth of patients undergoing hepatectomy for ICC had adequate nodal staging according to the AJCC eighth edition. While the six HLN cutoff value impacted prognosis of N0 patients, the number of MLN rather than HLN was associated with long-term survival of N1 patients.

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Gallbladder

Morphology, Diagnostics, IHC

Morphology, Diagnostics, IHC

- **Follicular cholecystitis: clinicopathologic associations**

Human pathology 2019 Jun;88():1-6

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30946935

Follicular cholecystitis (FC) is a relatively rare entity with uncertain causal associations. In this study, we aimed to explore different clinicopathologic associations of FC, and to better characterize the entity. A retrospective review of archival hematoxylin and eosin slides and pertinent clinical information was undertaken for all cholecystectomy cases with a rendered diagnosis of "follicular cholecystitis," from 1991 to 2017. Concurrent conventional chronic cholecystitis (CC) and lymphocytic cholecystitis (LC) were documented. Forty-three consecutive patients were confirmed to have FC. The majority of the patients (88.4%) had at least one other histologic association in the gallbladder (LC, CC, or both). Remarkably, functional distal biliary obstruction (from choledocholithiasis, sclerosing cholangitis, distal biliary strictures, or malignancies of the pancreatic head or ampulla) was found in 76.7% of the patients, irrespective of the presence of other concurrent histologic findings. FC associated with CC was relatively more common in females (61%) and strongly associated with cholelithiasis (70%). However, those without CC were predominantly males (70%) and had a significant association with LC (75%). All four cases of FC without any other histologic associations who had clinical information available showed some form of distal biliary obstruction. FC cases without concurrent LC were often associated with CC (74%). FC is strongly associated with extrahepatic biliary obstruction distal to the gallbladder. Therefore, this finding at routine cholecystectomy may warrant further evaluation to rule out a cause for distal biliary tract obstruction. Additionally, it is commonly associated with other concomitant histologic abnormalities in the gallbladder such as CC and/or LC.

- **Primary Gallbladder Neuroendocrine Tumors: Insights into a Rare Histology Using a Large National Database**

Annals of surgical oncology 2019 May;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31102094

BACKGROUND: Primary gallbladder neuroendocrine tumors (NETs) are rare, poorly understood cancers infrequently encountered at even the largest of tertiary referral centers. We therefore sought to identify a large cohort of patients with gallbladder NETs using a national database, with the aim of defining treatment modalities employed and survival associated with these uncommon malignancies. METHODS: Patients with primary gallbladder NETs were identified in the National Cancer Database, and clinicopathologic characteristics were recorded. A univariate log-rank survival analysis was completed for patients who underwent resection. Parameters found to be significant were entered into a multivariate accelerated failure time analysis. For context, survival comparisons were included for patients who underwent resections for NETs at any gastrointestinal site and for gallbladder adenocarcinoma. RESULTS: Overall, 754 patients with gallbladder NETs were identified. Patients were predominantly female ($n = 518$, 69%), White ($n = 503$, 67%), presented with stage IV disease ($n = 295$, 39%) and had high-grade lesions ($n = 312$, 41%). The majority underwent resection ($n = 480$, 64%), primarily simple cholecystectomy ($n = 431$, 90%), whereas a minority received multimodal therapy ($n = 145$, 21%). Among patients who underwent resection, older age ($p = 0.001$), large cell histology ($p = 0.012$), and positive margins ($p = 0.030$) were independently associated with worse overall survival. Patients with gallbladder NETs had improved survival relative to those with gallbladder adenocarcinoma ($p = 0.001$), but significantly worse survival than patients with NETs from other gastrointestinal sites ($p < 0.001$). CONCLUSIONS: Primary gallbladder NETs are aggressive lesions that carry a worse prognosis

than NETs of other gastrointestinal sites. Older age, positive margins, and large cell histology are associated with abbreviated survival after resection.

- Low frequency of mismatch repair deficiency in gallbladder cancer

Diagnostic pathology 2019 May;14(1):36

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31068195

BACKGROUND: DNA mismatch repair (MMR) deficiency is a major pathway of genomic instability in cancer. It leads to the accumulation of numerous mutations predominantly at microsatellite sequences, a phenotype known as microsatellite instability (MSI). MSI tumors have a distinct clinical behavior and commonly respond well to immune checkpoint blockade, irrespective of their origin. Data about the prevalence of MSI among gallbladder cancer (GBC) have been conflicting. We here analyzed a well-characterized cohort of 69 Western-world GBCs. METHODS: We analyzed the mononucleotide MSI marker panel consisting of BAT25, BAT26, and CAT25 to determine the prevalence of MMR deficiency-induced MSI. RESULTS: MSI was detected in 1/69 (1.4%) of analyzed GBCs. The detected MSI GBC had a classical histomorphology, i.e. of acinar/tubular/glandular pancreatobiliary phenotype, and showed nuclear expression of all four MMR proteins MLH1, MSH2, MSH6, and PMS2. The MSI GBC patient showed a prolonged overall survival, despite having a high tumor stage at diagnosis. The patient had no known background or family history indicative of Lynch syndrome. CONCLUSIONS: Even though the overall number of MSI tumors is low in GBC, the potentially therapeutic benefit of checkpoint blockade in the respective patients may justify MSI analysis of GBC.

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Staging

Gallbladder TNM staging, Margins, Survival

- Systematic review of management of incidental gallbladder cancer after cholecystectomy

The British journal of surgery 2019 01;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.

- Staging gallbladder cancer with lymphadenectomy: the practical application of new AHPBA and AJCC guidelines

HPB : the official journal of the International Hepato Pancreato Biliary Association 2019 Apr;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31010632

BACKGROUND: Current guidelines recommend harvesting a total lymph node count (TLNC) 6 from portal lymphadenectomy in pT1b gallbladder cancers (GBC) for accurate staging and prognostication. This study aimed to determine nodal yields from portal lymphadenectomy and identify measures to maximize TLNC. METHODS: We retrospectively reviewed all pT1b GBC which underwent resection with curative intent including portal lymphadenectomy at our specialized HPB center from 2007 to 2017. We compared outcomes of TLNC $<$ 6 and TLNC 6 cohorts and determined factors predictive of TLNC. RESULTS: Of 92 patients, 20% had a TLNC 6 (IQR 7-11) and 9% had no nodes found on pathology. Malignant lymphadenopathy was twice as common in TLNC 6 as TLNC $<$ 6 ($p = 0.003$) most frequently from portal, cystic and pericholedochal stations. On logistic regression analysis, concomitant liver resection was an independent predictor of higher TLNC [4b/5 wedge resection (OR 0.166, CI 0.057-0.486, $p = 0.001$) extended hepatectomy (OR 0.065, CI 0.012-0.340, $p = 0.001$)]; biliary resection and en bloc adjacent organ resection were not. CONCLUSION: At our center, prior to current guidelines, a TLNC 6 was not met in 80% undergoing portal lymphadenectomy for pT1b GBC. To increase nodal yield, future guidelines should consider including additional lymph node stations and incorporation of frozen section analysis.

- The incidence rates and survival of gallbladder cancer in the USA

European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP) 2019 01;28(1):1-9

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=28683010

Gallbladder cancer is a rare malignancy in most countries. The racial and sociodemographic factors associated with its incidence and survival are poorly defined. We aimed to investigate population-based gallbladder cancer incidence and survival trends on the basis of clinical characteristics and sociodemographic factors in the USA. Gallbladder cancer incidence and survival data from 2001 to 2012 were obtained from 18 registries of the Surveillance, Epidemiology, and End Results database. Incidence rates and Joinpoint trends were calculated by demographic subgroup. Survival trends were assessed using Cox proportional hazard models. A total of 7769 patients were identified. The overall gallbladder cancer incidence rates did not significantly change during the 2001-2012 period. Incidence rates were three times higher in Hispanics and 1.6 times higher in Blacks compared with Whites. Over the time period, incidence rates significantly increased among Blacks and decreased among Hispanics. Male sex [hazard ratio (HR): 1.10, 95% confidence interval (CI): 1.03-1.17], older age (HR: 1.73, 95% CI: 1.53-1.96), and single and divorced statuses (HR: 1.19, 95% CI: 1.09-1.30 and 1.12, 95% CI: 1.01-1.24) were independently associated with shorter overall survival, whereas higher education (HR: 0.89, 95% CI: 0.82-0.97) and higher income (HR: 0.89, 95% CI: 0.82-0.96) were associated with longer survival. Furthermore, overall survival has improved in all races/ethnicities except for Hispanics and Blacks. The overall incidence rates for gallbladder cancer were stable during 2001-2012. Hispanics have the highest incidence rates, but the incidence rates in Blacks are on the rise.

- 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.

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Ampulla of Vater

Morphology, Diagnostics, IHC

Morphology, Diagnostics, IHC

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

Cancer immunology, immunotherapy : CII 2019 Mar;68(3):443-454

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.

- Role of Immunohistochemistry in the Subtyping of Periampullary Adenocarcinoma

International journal of surgical pathology 2019 Apr;():1066896919837606

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30942099

CONTEXT: Subtyping of periampullary adenocarcinoma into intestinal and pancreatobiliary subtypes has emerged as an important prognostic factor with potential therapeutic implications. This distinction on morphology alone is often difficult with significant interobserver variability. OBJECTIVE: To analyze the usefulness of a panel of immunohistochemistry (IHC) markers as an aid to morphologic subtyping of periampullary adenocarcinoma. DESIGN: A total of 172 periampullary adenocarcinomas were classified morphologically by 3 study pathologists. Interobserver agreement was assessed in each case. Cases were then typed using a predetermined IHC panel (comprising CK7, CK20, MUC1, and CDX2). RESULTS: Morphologically, 66 (38.4%) cases were intestinal, 56 (32.6%) pancreatobiliary, 25 (14.5%) mixed, 16 (9.3%) poorly differentiated, 6 (3.5%) mucinous, and 3 (1.7%) signet ring cell adenocarcinoma. Concordant diagnosis was reached in 138 cases (80.2%) with moderate overall interobserver agreement (= 0.47). Concordance was higher in morphologically distinct mucinous (100%; = 0.94) and signet ring cell subtypes (100%; = 1.0) than in intestinal (84.6%; = 0.47) and pancreatobiliary (82.1%; = 0.43) types. Concordance was poor for mixed (64%; = 0.27) and poorly differentiated (68.8%; = 0.76) tumors. IHC subtyped 79 cases (46%) as pancreatobiliary, 73 (42.4%) as intestinal, and was inconclusive in 20 cases (11.6%). IHC helped classify 21 out of 25 (84%) mixed and 10 out of 16 poorly differentiated (62.5%) adenocarcinomas. Combination of histology and IHC classified 161 of the total 172 cases (93.6%). CONCLUSION: Use of an IHC panel aids in subtyping of periampullary adenocarcinomas, especially in tumors with mixed morphology and poor differentiation.

- Can we classify ampullary tumours better? Clinical, pathological and molecular features. Results of an AGEO study

British journal of cancer 2019 Apr;120(7):697-702

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30837681

BACKGROUND: Ampullary adenocarcinoma (AA) originates from either intestinal (INT) or pancreaticobiliary (PB) epithelium. Different prognostic factors of recurrence have been identified in previous studies. METHODS: In 91 AA patients of the AGEO retrospective multicentre cohort, we evaluated the centrally reviewed morphological classification, panel markers of Ang et al. including CK7, CK20, MUC1, MUC2 and CDX2, the 50-gene panel mutational analysis, and the clinicopathological AGEO prognostic score. RESULTS: Forty-three (47%) of the 91 tumours were Ang-INT, 29 (32%) were Ang-PB, 18 (20%) were ambiguous (Ang-AMB) and one could not be classified. Among these 90 tumours, 68.7% of INT tumours were Ang-INT and 78.2% of PB tumours were Ang-PB. MUC5AC expression was detected in 32.5% of the 86 evaluable cases. Among 71 tumours, KRAS, TP53, APC and PIK3CA were the most frequently mutated genes. The KRAS mutation was significantly more frequent in the PB subtype. In multivariate analysis, only AGEO prognostic score and tumour subtype were associated with relapse-free survival. Only AGEO prognostic score was associated with overall survival. CONCLUSIONS: Mutational analysis and MUC5AC expression provide no additional value in the prognostic evaluation of AA patients. Ang et al. classification and the AGEO prognostic score were confirmed as a strong prognosticator for disease recurrence.

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Neuroendocrine

PanNET

PanNET, Pancreatic Neuroendocrine Tumors and related neuroendocrine neoplasms

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- Loss of Menin Expression by Immunohistochemistry in Pancreatic Neuroendocrine Tumors: Comparison Between Primary and Metastatic Tumors

Pancreas 2019 04;48(4):510-513

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30946241

OBJECTIVES: Molecular characterization of sporadic pancreatic neuroendocrine tumors (PanNETs) demonstrates frequent alterations in MEN1. As the role of menin immunohistochemistry as a potential biomarker is being developed, knowledge of whether the pattern of menin expression is the same in primary tumors and distant metastases may help in patient care. Therefore, we compared patterns of menin expression in matched primary tumors and metastases. METHODS: We evaluated loss of menin nuclear expression by immunohistochemistry in 44 matched samples of primary and metastatic PanNETs and concordance in staining pattern between primary and metastatic tumors. RESULTS: Menin nuclear expression was lost in 18 (41%) of 44 primary tumors and 17 (39%) of 44 metastases. Concordant loss of menin expression was observed in 41 cases (93%); discordance was observed in 3 cases (7%; 95% confidence interval, 1.4%-18.7%), including 2 with loss in the primary tumor but not the metastasis. CONCLUSIONS: The concordance of menin staining between primary tumor and metastasis in most cases suggests that menin loss is an early event in PanNET tumorigenesis. The discordant expression observed in a small subset may be a source of menin-directed therapy failure; thus, repeat assessment of metastases may be helpful for treatment selection.

- Predicting Survival of Small Intestine Neuroendocrine Tumors: Experience From a Major Referral Center

Pancreas 2019 04;48(4):514-518

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30946234

OBJECTIVE: Neuroendocrine tumors (NETs) comprise 41.8% of small intestine malignancies. The NET nomogram is a 15-item prognostic tool that includes relevant factors for guiding management decisions. This is the first external validation of this tool among American patients at a tertiary treatment center. METHODS: Patients who underwent surgical intervention from 2005 to 2017 were screened by retrospective chart review. Nomogram scores were calculated following the methods outlined by Modlin et al (Neuroendocrinology. 2010;92:143-157). Validation assessed the association between nomogram scores and survival using Wilcoxon test and Cox regression. RESULTS: Among the 121 patients selected, the NET nomogram significantly predicted survival as a continuous variable ($P < 0.01$) and when dichotomized using 83 points to distinguish low-risk versus high-risk groups ($P < 0.01$). However, the nomogram was not universally applicable as even at our specialty center, variables such as chromogranin A and urinary 5-hydroxyindoleacetic acid are not routinely collected, whereas others, like tumor grade, do not reflect the most recently updated classifications. CONCLUSION: The NET nomogram accurately identified patients at low and high risk of death. However, revision to update prognosticators could improve its usefulness for predicting survival of small intestine NETs.

- Clinicopathological characteristics and risk factors for recurrence of well-differentiated pancreatic neuroendocrine tumors after radical surgery: a case-control study

World journal of surgical oncology 2019 Apr;17(1):66

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30975157

BACKGROUND: Well-differentiated pancreatic neuroendocrine tumors (PanNETs) usually have a good prognosis; however, there are patients that experience recurrence after curative resection. AIM: To explore recurrence-related risk factors by analyzing clinicopathological data of PanNETs after radical surgery. METHODS: Clinical and pathological data from 47 patients with well-differentiated PanNETs at China-Japan Friendship Hospital from January 2012 to March 2016 were analyzed retrospectively. Univariate and multivariate analyses of the risk factors of PanNETs for postoperative recurrence were conducted. RESULTS: Among the 47 patients with well-differentiated PanNETs, there were 38 cases with non-functioning tumors, 9 cases with functional tumors (6 insulinomas, 1 gastrinoma, 1 glucagonoma, and 1 VIPomas). There are 17 cases (36.2%) in the pancreatic head, 17 (36.2%) in the body and tail, 9 (19.1%) in the tail, and 4 (8.5%) in the body. The median tumor size was 3.65 (IQR 2-5.5) cm. Fourteen cases (29.8%) were NET G1, and 33 cases (70.2%) were NET G2. In regard to the clinical stage, 9 (19.1%) cases were IA, 14 (29.8%) cases were IB, 7 (14.9%) cases were IIA, 14 (29.8%) cases were IIB, and 3 cases unknown. There were 17 patients who presented with postoperative recurrence. Univariate analysis showed that AJCC TNM staging, Ki67 index, vascular invasion, margin status, and the regional stage of the tumors are related to the recurrence of patients with PanNETs ($p < 0.05$). The results of multivariate analysis showed that Ki67 index 10% is an independent risk factor for the postoperative recurrence of PanNETs ($p < 0.05$). CONCLUSION: The Ki67 index 10% is an independent risk factor for recurrence in well-differentiated PanNETs after radical surgery, and close surveillance for these patients may be needed.

- Pancreatic islet (of Langerhans) revisited

Histology and histopathology 2019 Apr;():18118

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31020988

One hundred and fifty years ago, Paul Langerhans described what would come to be known as pancreatic 'islet of Langerhans'. Since then, we have accumulated knowledge about the pancreatic islet, the cells that exist there and the hormones secreted by these cells. The increasing prevalence of obesity, diabetes and Alzheimer's disease in the population (three conditions that are linked to pancreatic islet function), the islet has been playing a significant role in endocrinological and metabolic studies searching how we can protect the pancreatic islet and its cell content, or how we can regenerate it. This review will be interested in the most recent and relevant aspects of knowledge regarding the pancreatic islet, always mentioning the evolution of knowledge and future perspectives for the treatment of diabetes and Alzheimer's disease. The most recent research with microRNAs and islet culture and pseudoislet culture (organoids) allows predicting advances in knowledge with new drugs to act on the islet/cells (such as the hormone glucagon-like peptide (GLP) -1) as well as induction of other islet cells like alpha-cells and delta-cells to transform into beta-cells.

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Staging

PanNET TNM staging, Margins, Survival

- Validation of the 8th AJCC Cancer Staging System for Pancreas Neuroendocrine Tumors Using Korean Nationwide Surgery Database

Cancer research and treatment : official journal of Korean Cancer Association 2019 Apr;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30999719

Purpose: The 8th edition of the American Joint Committee on Cancer (AJCC) staging system for pancreatic neuroendocrine tumor (PNET) included several significant changes. We aim to evaluate this staging system compared to the 7th edition AJCC staging system and European Neuroendocrine Tumors Society (ENETS) system. Materials and Methods: We used Korean nationwide surgery database (2000-2014). Of 972 patients who had undergone surgery for PNET, excluding patients diagnosed with ENETS/World Health Organization 2010 grade 3 (G3), only 472 patients with accurate stage were included. Results: Poor discrimination in overall survival rate (OSR) was noted between AJCC 8th stage III and IV (p=0.180). The disease-free survival (DFS) curves of 8th AJCC classification were well separated between all stages. Compared with stage I, the hazard ratio of II, III, and IV was 3.808, 13.928, and 30.618, respectively (p=0.007, p < 0.001, and p < 0.001). The curves of OSR and DFS of certain prognostic group in AJCC 7th and ENETS overlapped. In ENETS staging system, no significant difference in DFS between stage IIB versus IIIA (p=0.909) and IIIA versus IIIB (p=0.291). In multivariable analysis, lymphovascular invasion (p=0.002), perineural invasion (p=0.003), and grade (p < 0.001) were identified as independent prognostic factors for DFS. Conclusion: This is the first large-scale validation of the AJCC 8th edition staging system for pancreatic neuroendocrine tumor. The revised 8th system provides better discrimination compared to that of the 7th edition and ENETS TNM system. This supports the clinical use of the system.

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

Annals of surgical oncology 2019 Aug;26(8):2517-2524

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31004295

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

without such risk factors, routine regional lymphadenectomy should be considered. PD inherently includes sufficient LN retrieval, while DP should aim to remove seven or more LNs for accurate staging.

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Cytopathology

Pancreas

- Glycosylation of ascites-derived exosomal CD133: a potential prognostic biomarker in patients with advanced pancreatic cancer

Medical molecular morphology 2019 Feb;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30805710

Cancer cells surviving in ascites exhibit cancer stem cell (CSC)-like features. This study analyzed the expression of the CSC marker CD133 in the ascites-derived exosomes obtained from patients with unresectable pancreatic cancer. In addition, inverse correlation of CD133 expression with prognosis was examined. Of the 133 consecutive patients, 19 patients were enrolled in the study. Exosomes derived from the malignant ascites demonstrated higher density and wider variation in size than those from non-malignant ascites. Western blot revealed enhanced expression of CD133 in exosomes obtained from patients with pancreatic cancer compared to those obtained from patients with gastric cancer or liver cirrhosis. A xenograft mouse model with malignant ascites was established by intraperitoneal inoculation of human pancreatic cancer cells in nude mice. Results obtained from the human study were reproduced in the mouse model. Statistically significant equilateral correlation was identified between the band intensity of CD133 in western blot and overall survival of patients. Lectin microarray analyses revealed glycosylation of CD133 by sialic acids as the major glycosylation among diverse others responsible for the glycosylation of exosomal CD133. These findings suggest that highly glycosylated CD133 in ascites-derived exosomes as a potential biomarker for better prognosis of patients with advanced pancreatic cancer.

- Assessment of CD133-positive extracellular membrane vesicles in pancreatic cancer ascites and beyond

Medical molecular morphology 2019 Apr;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30953194

- Intraoperative Peritoneal Washing Cytology on Survival in Pancreatic Ductal Adenocarcinoma With Resectable, Locally Advanced, and Metastatic Disease

Pancreas 2019 04;48(4):519-525

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30946232

OBJECTIVES: The prognostic implications of intraoperative peritoneal washing cytology (IPWC) in patients with pancreatic ductal adenocarcinoma (PDAC) remains incompletely understood. METHODS: A meta-analysis was conducted to investigate the impact of IPWC status on the clinicopathologic features and survival outcomes in potentially resectable, locally advanced, and metastatic PDAC. Hazard ratio (HR) and 95% confidence interval (CI) were used as the pooled estimates. RESULTS: A total of 12 studies qualified for inclusion with 3751 PDAC patients. In resectable PDAC, the postoperative 5-year overall survival was significantly better in negative IPWC than in positive IPWC patients, with a pooled HR of 2.47 (95% CI, 1.90-3.21; $P < 0.001$; $I = 69\%$) in a random-effects model. Likely, combined outcome showed a significantly longer survival benefit in the negative IPWC group (HR, 2.80; 95% CI, 1.94-4.04; $P < 0.001$) in terms of recurrence-free survival. The presence of positive IPWC did not significantly alter survival outcomes in those PDAC patients with locally advanced or metastatic disease. CONCLUSIONS: This systematic review and meta-analysis demonstrated that a positive IPWC status in patients with clinically resectable PDAC

predicts a poor prognosis. Patients with positive IPWC should be regarded as a specific subgroup, with intensive adjuvant chemotherapy that seems to be warranted for further evaluation.

- Addition of analysis of KRAS mutation or immunohistochemistry with MUC1 and carcinoembryonic antigen improves the diagnostic performance of fine needle aspiration cytology for the diagnosis of pancreatic carcinoma

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30929285

BACKGROUND: Pancreatic adenocarcinoma (PAC) is a health problem because of high lethality, increasing incidence and the absence of an early diagnosis. Biopsy by fine needle aspiration guided by endoscopic ultrasound has allowed obtaining tissue for cytopathological analysis, but there are several problems with their interpretation. We aimed to compare the diagnostic performance of the cytopathological analysis with the addition of either an immunohistochemical (IHC) panel or the KRAS mutation for the diagnosis of PAC. METHODS: We evaluated 62 pancreatic lesions by fine needle aspiration guided by endoscopic ultrasound, applying an IHC panel with mucin (MUC)-1, MUC4, carcinoembryonic antigen (CEA) and p53. All cases also had a KRAS mutation determination. Three cytopathologists blinded to clinical data and the KRAS status reviewed the cytology independently. We calculated diagnostic performances for the cytology alone, cytology+IHC and cytology+KRAS to show the best method to diagnose PAC. RESULTS: From 62 samples, 50 (80.6%) were PAC and 12 benign lesions. The cytopathological analysis correctly interpreted 26 malignant and 12 non-neoplastic cases (sensitivity 52%, specificity 100% and diagnostic accuracy 61.3%). The KRAS mutation was present in 88% of PAC. The cytology+ KRAS mutation increased the sensitivity by 10% and the diagnostic accuracy by 8%. The sensitivity increased by 2% adding either MUC1 or CEA to the cytology, and the diagnostic accuracy by 10 or 18%, respectively. CONCLUSION: The addition of IHC either with CEA or MUC1 improved the diagnostic performance of the cytology alone to diagnose PAC. The cytology + IHC evaluation was superior to the cytology + KRAS mutation to diagnose PAC.

- Ancillary Techniques in Cytologic Specimens Obtained from Solid Lesions of the Pancreas: A Review

Acta cytologica 2019 Apr;():1-21

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30970350

Advanced methods of molecular characterization have elucidated the genetic, epigenetic, and proteomic alterations associated with the broad spectrum of pancreatic disease, particularly neoplasia. Next-generation sequencing, in particular, has revealed the genomic diversity among pancreatic ductal adenocarcinoma, neuroendocrine and acinar tumors, solid pseudopapillary neoplasm, and other pancreatico-biliary neoplasms. Differentiating these entities from one another by morphologic analysis alone may be challenging, especially when examining the small quantities of diagnostic material inherent to cytologic specimens. In order to enhance the sensitivity and specificity of pancreatic cytomorphology, multiple diagnostic, prognostic, and predictive ancillary tests have been and continue to be developed. Although a great number of such tests have been developed for evaluation of specimens collected from cystic lesions and strictures, ancillary techniques also play a significant role in the evaluation of cytologic specimens obtained from solid lesions of the pancreas. Furthermore, while some tests have been developed to differentiate diagnostic entities from one another, others have been developed to simply identify dysplasia and malignancy. Ancillary studies are particularly important in the subset of cases for which cytomorphologic analysis provides a result that is equivocal or insufficient to guide clinical management. Selection of appropriate ancillary testing modalities requires familiarity with both their methodology and the molecular basis of the pancreatic diseases for which testing is being performed.

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Bile Ducts

- Improving the diagnostic accuracy of biliary cytology

Diagnostic cytopathology 2019 Jul;47(7):639-640

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31041845

- Washing cytology of removed self-expandable metal stent for biliary stricture: A novel cytology technique

Diagnostic cytopathology 2019 Jul;47(7):743-745

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31059182

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Neuroendocrine

- 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 Jun;43(6):725-736

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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Molecular Pathology

Pancreas

- A Multiscale Map of the Stem Cell State in Pancreatic Adenocarcinoma

Cell 2019 Apr;177(3):572-586.e22

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30955884

Drug resistance and relapse remain key challenges in pancreatic cancer. Here, we have used RNA sequencing (RNA-seq), chromatin immunoprecipitation (ChIP)-seq, and genome-wide CRISPR analysis to map the molecular dependencies of pancreatic cancer stem cells, highly therapy-resistant cells that preferentially drive tumorigenesis and progression. This integrated genomic approach revealed an unexpected utilization of immuno-regulatory signals by pancreatic cancer epithelial cells. In particular, the nuclear hormone receptor retinoic-acid-receptor-related orphan receptor gamma (ROR), known to drive inflammation and T cell differentiation, was upregulated during pancreatic cancer progression, and its genetic or pharmacologic inhibition led to a striking defect in pancreatic cancer growth and a marked improvement in survival. Further, a large-scale retrospective analysis in patients revealed that ROR expression may predict pancreatic cancer aggressiveness, as it positively correlated with advanced disease and metastasis. Collectively, these data identify an orthogonal co-option of immuno-regulatory signals by pancreatic cancer stem cells, suggesting that autoimmune drugs should be evaluated as novel treatment strategies for pancreatic cancer patients.

- Syndecan 1 is a critical mediator of macropinocytosis in pancreatic cancer

Nature 2019 Apr;568(7752):410-414

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30918400

Pancreatic ductal adenocarcinoma (PDAC) remains recalcitrant to all forms of cancer treatment and carries a five-year survival rate of only 8%1. Inhibition of oncogenic KRAS (hereafter KRAS*), the earliest lesion in disease development that is present in more than 90% of PDACs, and its signalling surrogates has yielded encouraging preclinical results with experimental agents2-4. However, KRAS*-independent disease recurrence following genetic extinction of Kras* in mouse models anticipates the need for co-extinction strategies5,6. Multiple oncogenic processes are initiated at the cell surface, where KRAS* physically and functionally interacts to direct signalling that is essential for malignant transformation and tumour maintenance. Insights into the complexity of the functional cell-surface-protein repertoire (surfaceome) have been technologically limited until recently and-in the case of PDAC-the genetic control of the function and composition of the PDAC surfaceome in the context of KRAS* signalling remains largely unknown. Here we develop an unbiased, functional target-discovery platform to query KRAS-*dependent changes of the PDAC surfaceome, which reveals syndecan 1 (SDC1, also known as CD138) as a protein that is upregulated at the cell surface by KRAS*. Localization of SDC1 at the cell surface-where it regulates macropinocytosis, an essential metabolic pathway that fuels PDAC cell growth-is essential for disease maintenance and progression. Thus, our study forges a mechanistic link between KRAS* signalling and a targetable molecule driving nutrient salvage pathways in PDAC and validates oncogene-driven surfaceome annotation as a strategy to identify cancer-specific vulnerabilities.

- Ring1b-dependent epigenetic remodelling is an essential prerequisite for pancreatic carcinogenesis

Gut 2019 Apr;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30954952

BACKGROUND AND AIMS: Besides well-defined genetic alterations, the dedifferentiation of mature acinar cells is an important prerequisite for pancreatic carcinogenesis. Acinar-specific genes controlling cell homeostasis are extensively downregulated during cancer development; however, the underlying mechanisms are poorly understood. Now, we devised a novel in vitro strategy to determine genome-wide dynamics in the epigenetic landscape in pancreatic carcinogenesis. DESIGN: With our in vitro carcinogenic sequence, we performed global gene expression analysis and ChIP sequencing for the histone modifications H3K4me3, H3K27me3 and H2AK119ub. Followed by a comprehensive bioinformatic approach, we captured gene clusters with extensive epigenetic and transcriptional remodelling. Relevance of Ring1b-catalysed H2AK119ub in acinar cell reprogramming was studied in an inducible Ring1b knockout mouse model. CRISPR/Cas9-mediated Ring1b ablation as well as drug-induced Ring1b inhibition were functionally characterised in pancreatic cancer cells. RESULTS: The epigenome is vigorously modified during pancreatic carcinogenesis, defining cellular identity. Particularly, regulatory acinar cell transcription factors are epigenetically silenced by the Ring1b-catalysed histone modification H2AK119ub in acinar-to-ductal metaplasia and pancreatic cancer cells. Ring1b knockout mice showed greatly impaired acinar cell dedifferentiation and pancreatic tumour formation due to a retained expression of acinar differentiation genes. Depletion or drug-induced inhibition of Ring1b promoted tumour cell reprogramming towards a less aggressive phenotype. CONCLUSIONS: Our data provide substantial evidence that the epigenetic silencing of acinar cell fate genes is a mandatory event in the development and progression of pancreatic cancer. Targeting the epigenetic repressor Ring1b could offer new therapeutic options.

- Evaluation of the prognostic significances of -secretase genes in pancreatic cancer

Oncology letters 2019 May;17(5):4614-4620

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30944650

With the growing requirement for novel prognostic biomarkers for pancreatic cancer, many studies have focused on clinical and/or genomic variables. Although many studies have been performed, carbohydrate antigen 19-9 is the only biomarker in clinical use. Therefore, the present study examined whether -secretase genes, including presenilin (PSEN), nicastrin (NCSTN), presenilin enhancer protein 2 (PSENEN), and anterior pharynx-defective 1 (APH1-), could serve as prognostic factors for pancreatic cancer. The cohorts selected included >100 pancreatic cancer patients. Patient data were downloaded from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GSE21501). The prognostic roles of the -secretase genes were analyzed by several survival analysis methods. Among the -secretase genes, the prognosis tended to be worse in the 2 cohorts with increasing expression of PSEN1, APH1A, and PSENEN, while the remaining genes were the opposite in the 2 cohorts. Notably, although the patient characteristics were quite different, APH1A was statistically significantly associated with prognosis in the 2 cohorts. The hazard ratio of APH1A for overall survival was 1.598 (TCGA) and 2.724 (GSE21501). These results contribute to the study of -secretase in pancreatic cancer. We believe that -secretase, particularly APH1A, will be a new prognostic biomarker for pancreatic cancer.

- Hear Pancreatic Cancer Stem Cells ROR

Cell 2019 Apr;177(3):516-518

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31002791

In this issue of Cell, Lytle et al. (2019) integrate functional genomic approaches to identify molecular dependencies of pancreatic cancer stem cells that may be exploited therapeutically. The comprehensive analysis reveals an unexpected role for retinoic acid receptor-related orphan receptor gamma (ROR), a T-cell-associated transcription factor, in defining the stemness and the aggressive behavior of pancreatic cancer.

- MiR-539 functions as a tumor suppressor in pancreatic cancer by targeting TWIST1

Experimental and molecular pathology 2019 Jun;108():143-149

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31022384

The dysregulation of microRNA (miRNA) expression has been highlighted in a variety of human malignant conditions with reports implicating a critical role in the process of tumor growth. The role of miR-539 in pancreatic cancer (PC) is yet to be fully elucidated, hence the aim of the current study was to investigate the effect of miR-539 expression in relation to a cohort of 52 PC specimens. The application of a real-time quantitative polymerase chain reaction (qRT-PCR) revealed a significantly down-regulated miR-539 level, which was accompanied by an increased TWIST1 expression in PC when compared with the controls. The in vitro experiment results demonstrated that the endogenic mimic of miR-539 significantly suppressed the growth of the xenograft tumors in PANC-1 cells, when compared to the delivery of the control miRNA and blank control. Meanwhile, the key epithelial-mesenchymal transition (EMT) inducer, TWIST1 was verified as a direct target gene of miR-539 through the application of a luciferase reporter assay. In conclusion, the results of the current study present evidence emphasizing the significance of the interactions between miR-539 and TWIST1 in the development of and progression of PC, highlighting its potential as a therapeutic target in the treatment of PC patients.

- The ERBB receptor inhibitor dacomitinib suppresses proliferation and invasion of pancreatic ductal adenocarcinoma cells

Cellular oncology (Dordrecht) 2019 Aug;42(4):491-504

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31025257

PURPOSE: Pancreatic ductal adenocarcinoma (PDAC), the most common malignancy of the pancreas, is the fourth most common cause of cancer-related death in the USA. Local progression, early tumor dissemination and low efficacy of current treatments are the major reasons for its high mortality rate. The ERBB family is over-expressed in PDAC and plays essential roles in its tumorigenesis; however, single-targeted ERBB inhibitors have shown limited activity in this disease. Here, we examined the anti-tumor activity of dacomitinib, a pan-ERBB receptor inhibitor, on PDAC cells. METHODS: Anti-proliferative effects of dacomitinib were determined using a cell proliferation assay and crystal violet staining. Annexin V/PI staining, radiation therapy and cell migration and invasion assays were carried out to examine the effects of dacomitinib on apoptosis, radio-sensitivity and cell motility, respectively. Quantitative reverse transcription-PCR (qRT-PCR) and Western blot analyses were applied to elucidate the molecular mechanisms underlying the anti-tumor activity of dacomitinib. RESULTS: We found that dacomitinib diminished PDAC cell proliferation via inhibition of FOXM1 and its targets Aurora kinase B and cyclin B1. Moreover, we found that dacomitinib induced apoptosis and potentiated radio-sensitivity via inhibition of the anti-apoptotic proteins survivin and MCL1. Treatment with dacomitinib attenuated cell migration and invasion through inhibition of the epithelial-to-mesenchymal transition (EMT) markers ZEB1, Snail and N-cadherin. In contrast, we found that the anti-tumor activity of single-targeted ERBB agents including cetuximab (anti-EGFR mAb), trastuzumab (anti-HER2 mAb), H3.105.5 (anti-HER3 mAb) and erlotinib (EGFR small molecule inhibitor) were marginal. CONCLUSIONS: Our findings indicate that dacomitinib-mediated blockade of the ERBB receptors yields advantages over single-targeted ERBB inhibition and provide a rationale for further investigation of the therapeutic potential of dacomitinib in the treatment of ERBB-driven PDAC.

- Regulation of pH by Carbonic Anhydrase 9 Mediates Survival of Pancreatic Cancer Cells With Activated KRAS in Response to Hypoxia

Gastroenterology 2019 May;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31078621

BACKGROUND & AIMS: Most pancreatic ductal adenocarcinomas (PDACs) express an activated form of KRAS, become hypoxic and dysplastic, and are refractory to chemo and radiation therapies. To survive in the hypoxic environment, PDAC cells upregulate enzymes and transporters involved in pH regulation, including

the extracellular facing carbonic anhydrase 9 (CA9). We evaluated the effect of blocking CA9, in combination with administration of gemcitabine, in mouse models of pancreatic cancer. METHODS: We knocked down expression of KRAS in human (PK-8 and PK-1) PDAC cells with small hairpin RNAs. Human and mouse (KrasG12D/Pdx1-Cre/Tp53/RosaYFP) PDAC cells were incubated with inhibitors of MEK (trametinib) or extracellular signal-regulated kinase (ERK), and some cells were cultured under hypoxic conditions. We measured levels and stability of the hypoxia-inducible factor 1 subunit alpha (HIF1A), endothelial PAS domain 1 protein (EPAS1, also called HIF2A), CA9, solute carrier family 16 member 4 (SLC16A4, also called MCT4), and SLC2A1 (also called GLUT1) by immunoblot analyses. We analyzed intracellular pH (pHi) and extracellular metabolic flux. We knocked down expression of CA9 in PDAC cells, or inhibited CA9 with SLC-0111, incubated them with gemcitabine, and assessed pHi, metabolic flux, and cytotoxicity under normoxic and hypoxic conditions. Cells were also injected into either immune-compromised or immune-competent mice and growth of xenograft tumors was assessed. Tumor fragments derived from patients with PDAC were surgically ligated to the pancreas of mice and the growth of tumors was assessed. We performed tissue microarray analyses of 205 human PDAC samples to measure levels of CA9 and associated expression of genes that regulate hypoxia with outcomes of patients using the Cancer Genome Atlas database. RESULTS: Under hypoxic conditions, PDAC cells had increased levels of HIF1A and endothelial PAS domain 1 protein (EPAS1, also called HIF2A), upregulated expression of CA9, and activated glycolysis. Knockdown of KRAS in PDAC cells, or incubation with trametinib, reduced the posttranscriptional stabilization of HIF1A and HIF2A, upregulation of CA9, pHi, and glycolysis in response to hypoxia. CA9 was expressed by 66% of PDAC samples analyzed; high expression of genes associated with metabolic adaptation to hypoxia, including CA9, correlated with significantly reduced survival times of patients. Knockdown or pharmacologic inhibition of CA9 in PDAC cells significantly reduced pHi in cells under hypoxic conditions, decreased gemcitabine-induced glycolysis, and increased their sensitivity to gemcitabine. PDAC cells with knockdown of CA9 formed smaller xenograft tumors in mice, and injection of gemcitabine inhibited tumor growth and significantly increased survival times of mice. In mice with xenograft tumors grown from human PDAC cells, oral administration of SLC-0111 and injection of gemcitabine increased intratumor acidosis and increased cell death. These tumors, and tumors grown from PDAC patient-derived tumor fragments, grew more slowly than xenograft tumors in mice given control agents, resulting in longer survival times. In KrasG12D/Pdx1-Cre/Tp53/RosaYFP genetically modified mice, oral administration of SLC-0111 and injection of gemcitabine reduced numbers of B cells in tumors. CONCLUSIONS: In response to hypoxia, PDAC cells that express activated KRAS increase expression of CA9, via stabilization of HIF1A and HIF2A, to regulate pH and glycolysis. Disruption of this pathway slows growth of PDAC xenograft tumors in mice and might be developed for treatment of pancreatic cancer.

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Pancreatitis & Other Diseases

Molecular Studies on Pancreatitis & Other Diseases

- Novel p.K374E variant of CPA1 causes misfolding-induced hereditary pancreatitis with autosomal dominant inheritance

Gut 2019 Apr;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31005883

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Molecular Research on Microenvironment

Tumor Stroma Interactions, Microenvironment, Inflammatory Response, Microbiome

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- Mobilization of CD8+ T Cells via CXCR4 Blockade Facilitates PD-1 Checkpoint Therapy in Human Pancreatic Cancer

Clinical cancer research : an official journal of the American Association for Cancer Research 2019 Jul;25(13):3934-3945

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30940657

PURPOSE: Pancreatic ductal adenocarcinoma (PDA) is rarely cured, and single-agent immune checkpoint inhibition has not demonstrated clinical benefit despite the presence of large numbers of CD8+ T cells. We hypothesized that tumor-infiltrating CD8+ T cells harbor latent antitumor activity that can be reactivated using combination immunotherapy. EXPERIMENTAL DESIGN: Preserved human PDA specimens were analyzed using multiplex IHC (mIHC) and T-cell receptor (TCR) sequencing. Fresh tumor was treated in organotypic slice culture to test the effects of combination PD-1 and CXCR4 blockade. Slices were analyzed using IHC, flow cytometry, and live fluorescent microscopy to assess tumor kill, in addition to T-cell expansion and mobilization. RESULTS: mIHC demonstrated fewer CD8+ T cells in juxtatumoral stroma containing carcinoma cells than in stroma devoid of them. Using TCR sequencing, we found clonal expansion in each tumor; high-frequency clones had multiple DNA rearrangements coding for the same amino acid binding sequence, which suggests response to common tumor antigens. Treatment of fresh human PDA slices with combination PD-1 and CXCR4 blockade led to increased tumor cell death concomitant with lymphocyte expansion. Live microscopy after combination therapy demonstrated CD8+ T-cell migration into the juxtatumoral compartment and rapid increase in tumor cell apoptosis. CONCLUSIONS: Endogenous tumor-reactive T cells are present within the human PDA tumor microenvironment and can be reactivated by combined blockade of PD-1 and CXCR4. This provides a new basis for the rational selection of combination immunotherapy for PDA.See related commentary by Medina and Miller, p. 3747.

- L1CAM induces perineural invasion of pancreas cancer cells by upregulation of metalloproteinase expression

Oncogene 2019 01;38(4):596-608

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30171263

Pancreas cancer cells have a tendency to invade along nerves. Such cancerous nerve invasion (CNI) is associated with poor outcome; however, the exact mechanism that drives cancer cells to disseminate along nerves is unknown. Immunohistochemical analysis of human pancreatic ductal adenocarcinoma (PDAC) specimens showed overexpression of the L1 cell adhesion molecule (L1CAM) in cancer cells and in adjacent Schwann cells (SC) in invaded nerves. By modeling the neural microenvironment, we found that L1CAM secreted from SCs acts as a strong chemoattractant to cancer cells, through activation of MAP kinase signaling. L1CAM also upregulated expression of metalloproteinase-2 (MMP-2) and MMP-9 by PDAC cells, through STAT3 activation. Using a transgenic Pdx-1-Cre/KrasG12D /p53R172H (KPC) mouse model, we show that treatment with anti-L1CAM Ab significantly reduces CNI in vivo. We provide evidence of a paracrine response between SCs and cancer cells in the neural niche, which promotes cancer invasion via L1CAM secretion.

- Targeting LIF-mediated paracrine interaction for pancreatic cancer therapy and monitoring

Nature 2019 05;569(7754):131-135

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30996350

Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis largely owing to inefficient diagnosis and tenacious drug resistance. Activation of pancreatic stellate cells (PSCs) and consequent development of dense stroma are prominent features accounting for this aggressive biology1,2. The reciprocal interplay between PSCs and pancreatic cancer cells (PCCs) not only enhances tumour progression and metastasis but also sustains their own activation, facilitating a vicious cycle to exacerbate tumorigenesis and drug resistance3-7. Furthermore, PSC activation occurs very early during PDAC tumorigenesis8-10, and activated PSCs comprise a substantial fraction of the tumour mass, providing a rich source of readily detectable factors. Therefore, we hypothesized that the communication between PSCs and PCCs could be an exploitable target to develop effective strategies for PDAC therapy and diagnosis. Here, starting with a systematic proteomic investigation of secreted disease mediators and underlying molecular mechanisms, we reveal that leukaemia inhibitory factor (LIF) is a key paracrine factor from activated PSCs acting on cancer cells. Both pharmacologic LIF blockade and genetic Lifr deletion markedly slow tumour progression and augment the efficacy of chemotherapy to prolong survival of PDAC mouse models, mainly by modulating cancer cell differentiation and epithelial-mesenchymal transition status. Moreover, in both mouse models and human PDAC, aberrant production of LIF in the pancreas is restricted to pathological conditions and correlates with PDAC pathogenesis, and changes in the levels of circulating LIF correlate well with tumour response to therapy. Collectively, these findings reveal a function of LIF in PDAC tumorigenesis, and suggest its translational potential as an attractive therapeutic target and circulating marker. Our studies underscore how a better understanding of cell-cell communication within the tumour microenvironment can suggest novel strategies for cancer therapy.

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Preneoplastic and Preinvasive Lesions

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

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

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

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

BACKGROUND: The management of intraductal papillary mucinous neoplasms (IPMNs) is mainly based on imaging features and clinical symptoms, and remains challenging. OBJECTIVE: The aim of this study was to assess GNAS, RAS family (KRAS, NRAS and HRAS), BRAF, and PIK3CA mutation status in resected IPMNs and correlate it with clinicopathological characteristics and patient survival. METHODS: Overall, 149 consecutive unselected patients who underwent pancreatectomy for IPMNs were included. After dissection from formalin-fixed and paraffin-embedded tumors, GNAS mutational screening was assessed by allelic discrimination using Taqman® probes and confirmed by SNaPshot analysis. RAS family, BRAF, and PIK3CA mutational screening was assessed by high resolution melt and Sanger sequencing. RESULTS: Gastric- and intestinal-type IPMNs were the most frequent lesions (52% and 41%, respectively). Intestinal-type IPMNs were more frequently associated high-grade dysplasia (49%) and were the only IPMNs associated with colloid-type carcinoma. All pancreatobiliary IPMNs were invasive lesions, located in the main pancreatic duct. GNAS-activating mutations were strongly associated with the intestinal phenotype ($p < 10\text{-}4$), while RAS pathway mutations were not associated with any particular phenotype. Mutations within other members of the epidermal growth factor receptor (EGFR) pathway were very rare (2%). GNAS-mutated IPMNs were rarely invasive (11%) and almost exclusively (83%) of the colloid type. For invasive lesions, multivariate analyses determined that only node negativity was associated with improved cancer-specific survival, but, in univariate analysis, GNAS mutation was associated with prolonged survival. CONCLUSION: In patients selected for surgery, GNAS mutation analysis and tumor phenotype can help to better predict patient prognosis. In the near future, a more precise mutational analysis of IPMNs might help to better tailor their management.

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

Gastroenterology 2019 05;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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Bile Ducts

- Integrating next-generation sequencing to endoscopic retrograde cholangiopancreatography (ERCP)-obtained biliary specimens improves the detection and management of patients with malignant bile duct strictures

Gut 2019 Apr;():

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30971436

OBJECTIVE: Despite improvements in imaging, serum CA19-9 and pathological evaluation, differentiating between benign and malignant bile duct strictures remains a diagnostic conundrum. Recent developments in next-generation sequencing (NGS) have opened new opportunities for early detection and management of cancers but, to date, have not been rigorously applied to biliary specimens. DESIGN: We prospectively evaluated a 28-gene NGS panel (BiliSeq) using endoscopic retrograde cholangiopancreatography-obtained biliary specimens from patients with bile duct strictures. The diagnostic performance of serum CA19-9, pathological evaluation and BiliSeq was assessed on 252 patients (57 trainings and 195 validations) with 346 biliary specimens. RESULTS: The sensitivity and specificity of BiliSeq for malignant strictures was 73% and 100%, respectively. In comparison, an elevated serum CA19-9 and pathological evaluation had sensitivities of 76% and 48%, and specificities of 69% and 99%, respectively. The combination of BiliSeq and pathological evaluation increased the sensitivity to 83% and maintained a specificity of 99%. BiliSeq improved the sensitivity of pathological evaluation for malignancy from 35% to 77% for biliary brushings and from 52% to 83% for biliary biopsies. Among patients with primary sclerosing cholangitis (PSC), BiliSeq had an 83% sensitivity as compared with pathological evaluation with an 8% sensitivity. Therapeutically relevant genomic alterations were identified in 20 (8%) patients. Two patients with ERBB2-amplified cholangiocarcinoma received a trastuzumab-based regimen and had measurable clinicoradiographic response. CONCLUSIONS: The combination of BiliSeq and pathological evaluation of biliary specimens increased the detection of malignant strictures, particularly in patients with PSC. Additionally, BiliSeq identified alterations that may stratify patients for specific anticancer therapies.

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Ampulla of Vater

- Diagnosis, risk stratification, and management of ampullary dysplasia by DNA flow cytometric analysis of paraffin-embedded tissue

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

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=30976103

The limited accuracy of endoscopic biopsy in detecting high-grade dysplasia or adenocarcinoma within ampullary adenoma or dysplasia has been reported. The natural history of ampullary dysplasia is also unclear, and there are no established guidelines to determine which patients with ampullary dysplasia require resection versus surveillance endoscopy. DNA flow cytometry was performed on 47 ampullary biopsies with low-grade dysplasia, 18 high-grade dysplasia, and 23 negative for dysplasia, as well as 11 cases of ampullary adenocarcinoma. Abnormal DNA content (aneuploidy or elevated 4N fraction > 6%) was identified in 9 (82%) of adenocarcinoma, 13 (72%) of high-grade dysplasia, 7 (15%) of low-grade dysplasia, and none (0%) of non-dysplastic mucosa. One-, 2-, and 7-year detection rates of high-grade dysplasia or adenocarcinoma in low-grade dysplasia patients with abnormal DNA content were 57%, 86%, and 88%, respectively, whereas low-grade dysplasia patients in the setting of normal DNA content had 1-, 2-, and 7-year detection rates of 10%, 10%, and 10%, respectively. The univariate and multivariate hazard ratios (HRs) for subsequent detection of high-grade dysplasia or adenocarcinoma in low-grade dysplasia patients with DNA content abnormality were 16.8 (p = <0.01) and 9.8 (p = <0.01), respectively. Among the 13 high-grade dysplasia patients with DNA content abnormality, 5 patients (38%) were subsequently found to have adenocarcinoma within a mean follow-up time of 3 months, whereas only 1 (20%) of the remaining 5 patients in the setting of normal DNA content developed adenocarcinoma in a month (HR = 2.6, p = 0.39). The overall 1- and 2-year detection rates of adenocarcinoma in all high-grade dysplasia patients (regardless of flow cytometric results) were 34% (95% confidence interval = 16-63%) and 47% (95% confidence interval = 23-79%), respectively. In conclusion, the majority of low-grade dysplasia patients (86%) in the setting of abnormal DNA content developed high-grade dysplasia or adenocarcinoma within 2 years and thus may benefit from resection, whereas those with normal DNA content may be followed with surveillance endoscopy. The presence of DNA content abnormality can also confirm a morphologic suspicion of high-grade dysplasia, which should be managed with resection, as nearly 50% of the high-grade dysplasia patients were found to have adenocarcinoma within 2 years.

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Neuroendocrine

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

Annals of surgical oncology 2019 Aug;26(8):2525-2532

PubMed: https://www.ncbi.nlm.nih.gov/pubmed/?term=31011904

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

- PLAC8 is overexpressed and regulates cell proliferation in low-grade human PanNET

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Background/Aims: Many aspects of the biology of pancreatic neuroendocrine tumors (PanNETs), including determinants of proliferative, invasive and metastatic potential, remain poorly understood. Placenta-specific 8 (PLAC8), a gene with unknown molecular function, has been reported to have tumor-promoting roles in different human malignancies, including exocrine pancreatic cancer. Since preliminary data suggested deregulation of PLAC8 expression in PanNET, we have performed detailed analyses of PLAC8 expression and function in human PanNET. Primary tissue from PanNET patients was immunohistochemically stained for PLAC8 and expression was correlated with clinicopathological data. In vitro, PLAC8 expression was inhibited by siRNA transfection in PanNET cell lines and effects were analyzed by qRT-PCR, Western blot and proliferation assays. We report that PLAC8 is expressed in the majority of well-differentiated human PanNETs, predominantly in early stage and low grade tumors. SiRNA-mediated knockdown of PLAC8 in PanNET cells resulted in decreased proliferation and viability, while apoptosis was not induced. Mechanistically, these effects were mediated by attenuation of cell cycle progression, as Western blot analyses demonstrated upregulation of the tumor suppressor p21/CDKN2A and downregulation of the cell cycle regulator Cyclin D1 as well as reduced levels of phosphorylated ribosomal protein s6 (pRPS6) and retinoblastoma protein (pRb). Our findings establish PLAC8 as a central mediator of cell growth in a subset of human PanNET, providing evidence for the existence of distinct molecular subtypes within this class of tumors..

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