

# PBPath Journal Watch

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PANCREATOBILIARY PATHOLOGY SOCIETY

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## Pancreas

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- **S100A10, a Novel Biomarker in Pancreatic Ductal Adenocarcinoma**

*Molecular oncology 2018 Jul;():*

Pancreatic cancer is arguably the deadliest cancer type. The efficacy of current therapies is often hindered by the inability to predict patient outcome. As such, the development of tools for early detection and risk prediction is key for improving outcome and quality of life. Here, we introduce the plasminogen receptor S100A10 as a novel predictive biomarker and a driver of pancreatic tumor growth and invasion. We demonstrated that S100A10 mRNA

and protein are overexpressed in human pancreatic tumors compared to normal ducts and non-ductal stroma. S100A10 mRNA and methylation status were predictive of overall survival and recurrence-free survival across multiple patient cohorts. S100A10 expression was driven by promoter methylation and the oncogene KRAS. S100A10 knockdown reduced surface plasminogen activation, invasiveness and in vivo growth of pancreatic cancer cell lines. These findings delineate the clinical and functional contribution of S100A10 as a biomarker in pancreatic cancer.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=30009399>

doi: <https://doi.org/10.1002/1878-0261.12356>

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- **Integrative landscape of dysregulated signaling pathways of clinically distinct pancreatic cancer subtypes**

*Oncotarget* 2018 Jun;9(49):29123-29139

Despite modern therapeutic advances, the survival prospects of pancreatic cancer patients have remained poor. Besides being highly metastatic, pancreatic cancer is challenging to treat because it is caused by a heterogeneous array of somatic mutations that impact a variety of signaling pathways and cellular regulatory systems. Here we use publicly available transcriptomic, copy number alteration and mutation profiling datasets from pancreatic cancer patients together with data on disease outcomes to show that the three major pancreatic cancer subtypes each display distinctive aberrations in cell signaling and metabolic pathways. Importantly, patients afflicted with these different pancreatic cancer subtypes also exhibit distinctive survival profiles. Within these patients, we find that dysregulation of the phosphoinositide 3-kinase and mitogen-activated protein kinase pathways, and p53 mediated disruptions of cell cycle processes are apparently drivers of disease. Further, we identify for the first time the molecular perturbations of signalling networks that are likely the primary causes of oncogenesis in each of the three pancreatic cancer subtypes.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=30018740>

doi: <https://doi.org/10.18632/oncotarget.25632>

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- **Genomic testing for pancreatic cancer in clinical practice as real-world evidence**

[https://www.pancreatology.net/article/S1424-3903\(18\)30633-1/abstract](https://www.pancreatology.net/article/S1424-3903(18)30633-1/abstract)

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- **Pitfalls of Frozen Section Diagnosis for Paraganglioma: A Clinicopathologic Analysis and Review of the Literature**

*International journal of surgical pathology* 2018 May;26(3):213-220

Few paraganglioma (PG) cases include frozen section diagnoses, and therefore, the accuracy of frozen section diagnosis for PG remains unknown. To better understand the histologic characteristics and pitfalls of frozen section findings for PG, 15 PG cases with frozen section diagnoses were selected from 12 articles through PubMed (1984-2015). In addition, we included 3 cases of PG for which intraoperative consultations were requested during a 5-year period (2012-2016) in 2 hospitals. Seven PGs were from the thyroid; 2 from the pancreas; 4 from the mediastinum, retroperitoneum, or mesentery; 1 from the middle ear; and 4 from the urinary bladder (UB). Out of 18 PGs, correct diagnoses were rendered in only 2 cases, and no thyroid or UB PGs were correctly diagnosed on intraoperative consultation. Thyroid PGs were frequently misdiagnosed as medullary thyroid carcinomas (4/7, 57%) and UB PGs were frequently misdiagnosed as malignancies.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29169281>

doi: <https://doi.org/10.1177/1066896917742199>

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- **Expression of liver X receptors in normal and refractory carcinoma tissues of the human lung and pancreas**

*Histology and histopathology* 2018 May;33(5):497-505

Liver X receptors (LXRs) participate not only in maintaining cholesterol homeostasis but also in controlling cellular growth in many types of normal and tumor cells. We previously reported that LXR $\alpha$  was aberrantly expressed in human oral squamous cell carcinoma (HOSCC) tissues and cell lines, and that LXR stimulation led to significant reduction of proliferation of HOSCC cells via accelerating cholesterol efflux. Since LXRs and downstream proteins involved in cholesterol metabolism could be also applied as therapeutic targets in small cell lung carcinoma (SCLC) and pancreatic ductal adenocarcinoma (PDAC), we herein analyzed the distribution of LXR proteins in these refractory cancers as well as in normal human lung and pancreatic tissues. LXR $\beta$  was observed in ciliated epithelial cells, bronchial gland epithelia, type II alveolar epithelia and alveolar macrophages of the lung, and was less expressed in bronchial basal cells and type I alveolar epithelia. In addition, LXR $\beta$  was detected in epithelium of the pancreatic duct and acinar cells of the pancreas, and was weakly expressed in pancreatic islet cells. By contrast, LXR $\alpha$  expression was restricted to alveolar macrophages, and was not evident in any types of epithelial cells in the lung and pancreas. We also demonstrated that LXR $\beta$  but not LXR $\alpha$  was abundantly expressed in nine

cases of SCLC and twenty cases of PDAC tissues. These findings provide basic information for evaluating the efficacy of LXR-targeted treatment in SCLC and PDAC.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29181837>

doi: <https://doi.org/10.14670/HH-11-949>

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- **Significance of T1a and T1b Carcinoma Arising in Mucinous Cystic Neoplasm of Pancreas**

*The American journal of surgical pathology* 2018 May;42(5):578-586

Mucinous cystic neoplasm (MCN) of pancreas is one of the precursor lesions of pancreatic ductal adenocarcinoma. The 5-year disease-specific survival for noninvasive MCNs was 100% and 20% to 60% for those with pancreatic ductal adenocarcinoma arising in a MCN. However, the significance of T1a ( $\leq 0.5$  cm) and T1b ( $> 0.5$  and  $< 1.0$  cm) carcinoma arising in MCN as defined by the upcoming American Joint Committee on Cancer, eighth edition is unclear. In this study, we examined 3 cases of MCN with T1a or T1b carcinoma and compared their clinicopathologic characteristics and survival to 46 cases of MCN with low-grade dysplasia (MCN-LGD), 7 cases of MCN with high-grade dysplasia (MCN-HGD), and 7 cases of MCN with advanced invasive carcinoma (T2 or higher T stage). The tumors from all 3 cases were submitted in their entirety in 123, 296, and 200 blocks, respectively. All 3 patients were alive with no recurrence during the follow-up of 20.0, 113.8, and 137.2 months, respectively. Similarly, none of the patients who had MCN with either LGD or HGD had recurrence or died of disease. In contrast, 5 of 7 patients who had MCN with advanced invasive carcinoma had recurrence and later died of disease with a median survival of 22.9 months ( $P < 0.001$ ). Our study showed that MCN with T1a and T1b carcinoma had an excellent prognosis similar to MCNs with LGD or HGD after complete tumor sampling for histologic examination. Our results along with the previous studies suggest that close follow-up, rather than aggressive systemic therapy, may be a better approach for these patients.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29462092>

doi: <https://doi.org/10.1097/PAS.0000000000001040>

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- **Interaction of amyloidogenic proteins in pancreatic  $\beta$  cells from subjects with synucleinopathies**

Parkinson's disease patients experience a wide range of non-motor symptoms that may be provoked by deposits of phosphorylated  $\alpha$ -synuclein in the peripheral nervous system. Pre-existing diabetes mellitus might be a risk factor for developing Parkinson's disease, and indeed, nearly 60% of Parkinson's disease patients are insulin resistant. Thus, we have investigated whether phosphorylated  $\alpha$ -synuclein is deposited in pancreatic tissue of subjects with synucleinopathies. We studied pancreatic tissue from 39 subjects diagnosed with Parkinson's disease, Lewy body Dementia or incidental Lewy bodies disease, as well as that from 34 subjects with diabetes mellitus and a normal neuropathological examination, and 52 subjects with a normal neuropathological examination. We examined the pancreatic accumulation of phosphorylated  $\alpha$ -synuclein and of the islet amyloid polypeptide precursor (IAPP), an amyloidogenic protein that plays an unknown role in diabetes mellitus, but that can promote  $\alpha$ -synuclein amyloid deposition in vitro. Moreover, we performed proximity ligation assays to assess whether these two proteins interact in the pancreas of these subjects. Cytoplasmic phosphorylated  $\alpha$ -synuclein deposits were found in the pancreatic  $\beta$  cells of 14 subjects with Parkinson's disease (93%), in 11 subjects with Lewy body Dementia (85%) and in 8 subjects with incidental Lewy body disease (73%). Furthermore, we found similar phosphorylated  $\alpha$ -synuclein inclusions in 23 subjects with a normal neuropathological examination but with diabetes mellitus (68%) and in 9 control subjects (17%). In addition, IAPP/ $\alpha$ -synuclein interactions appear to occur in patients with pancreatic inclusions of phosphorylated  $\alpha$ -synuclein. The presence of phosphorylated  $\alpha$ -synuclein inclusions in pancreatic  $\beta$  cells provides a new evidence of a mechanism that is potentially common to the pathogenesis of diabetes mellitus, PD and DLB. Moreover, the interaction of IAPP and  $\alpha$ -synuclein in the pancreatic  $\beta$  cells of patients may represent a novel target for the development of strategies to treat these diseases.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29536165>

doi: <https://doi.org/10.1007/s00401-018-1832-0>

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- **c-MYC amplification and c-myc protein expression in pancreatic acinar cell carcinomas. New insights into the molecular signature of these rare cancers**

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

The molecular alterations of pancreatic acinar cell carcinomas (ACCs) and mixed acinar-neuroendocrine carcinomas (MANECs) are not completely understood, and the possible role of c-MYC amplification in tumor development, progression, and prognosis is not known. We have investigated c-MYC gene amplification in a series of 35 ACCs and 4 MANECs to evaluate its frequency and a possible prognostic role. Gene amplification was investigated using interphasic fluorescence in situ hybridization analysis simultaneously hybridizing c-MYC and the centromere of chromosome 8 probes. Protein expression was

immunohistochemically investigated using a specific monoclonal anti-c-myc antibody. Twenty cases had clones with different polysomies of chromosome 8 in absence of c-MYC amplification, and 5 cases had one amplified clone and other clones with chromosome 8 polysomy, while the remaining 14 cases were diploid for chromosome 8 and lacked c-MYC amplification. All MANECs showed c-MYC amplification and/or polysomy which were observed in 54% pure ACCs. Six cases (15.3%) showed nuclear immunoreactivity for c-myc, but only 4/39 cases showed simultaneous c-MYC amplification/polysomy and nuclear protein expression. c-myc immunoreactivity as well as c-MYC amplification and/or chromosome 8 polysomy was not statistically associated with prognosis. Our study demonstrates that a subset of ACCs shows c-MYC alterations including gene amplification and chromosome 8 polysomy. Although they are not associated with a different prognostic signature, the fact that these alterations are present in all MANECs suggests a role in the acinar-neuroendocrine differentiation possibly involved in the pathogenesis of MANECs.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29721608>

doi: <https://doi.org/10.1007/s00428-018-2366-5>

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- **Pancreatic Lipomatous Hamartoma: A Hitherto Unrecognized Variant**

*The American journal of surgical pathology* 2018 Jul;42(7):891-897

Pancreatic masses consisting of lipomatous components clinically include lipoma, liposarcoma, lipomatous pseudohypertrophy of the pancreas, fat-containing neoplasms such as perivascular epithelioid cell tumor, and malignant neoplasm with lipoid degeneration. We present pancreatic lipomatous hamartoma, which has not been reported hitherto. A solid pancreatic mass was detected from a computed tomographic scan check-up in each of 3 cases of Japanese men. Macroscopically, well-demarcated solid lipomatous masses were detected at the uncus, body, and tail of the pancreas, respectively. Microscopically, the masses predominantly consisted of mature adipocytes with no atypia, but contained characteristics components of pancreatic hamartoma, such as small ducts, a well-preserved acinar structure, and/or fibrous stroma. On the basis of the unique features, lack of islets and absence of periductal elastic fibers, these tumors are a distinct variant of pancreatic hamartoma. Furthermore, high-mobility group AT-hook 2 expression in the fibro-adipocytes of this tumor indicated that these cells are an integral component of the pancreatic lipomatous hamartoma. Consequently, the unique tumors described herein are pancreatic lipomatous hamartoma, which must be discriminated from other lipomatous lesions of the pancreas.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29738363>

doi: <https://doi.org/10.1097/PAS.0000000000001075>

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- **Primary Hepatoid Carcinoma of the Pancreas: A Clinicopathological Study of 3 Cases With Review of Additional 31 Cases in the Literature**

*International journal of surgical pathology* 2018 Jun;():1066896918783468

Primary pancreatic hepatoid carcinoma (PHC) is very rare. Here, we reported 3 such cases with review of additional 31 cases in the literature. Our 3 patients were male (83, 72, and 54 years old, respectively). Serum  $\alpha$ -fetoprotein (AFP) was elevated in 1 patient (case 3, 8338 ng/mL) and not measured in the other two. The PHC in patient 1 (pathological stage pT2N0M0) and patient 2 (pT3N0M0) showed pure hepatocellular carcinoma (HCC)-like morphology, whereas in case 3 it was a PHC with true glandular differentiation (pT4N0M0). The diagnosis of PHC was confirmed with positive immunohistochemical staining in the tumor cells for AFP (2/3), Hep Par 1 (3/3), glypican-3 (2/3), arginase-1 (2/3), and Sal-like protein 4 (1/3). CD10 and polyclonal carcinoembryonic antigen stains show focal canalicular pattern in 2/3 tumors. Patient 1 did not receive further treatment after resection and was alive with no evidence of disease at 107 months. Patient 2 died of postoperative complications, whereas patient 3 received postsurgical chemoradiation and died of disease at 29 months. Our findings and literature review indicate that PHCs can be divided into 4 histological subtypes: with pure HCC-like morphology (n = 22), with neuroendocrine differentiation (n = 8), with true glandular differentiation (n = 3), and with acinar cell differentiation (n = 1). On univariate analysis, pure HCC-like morphology was associated with better disease-specific survival (DSS; P = .04), whereas lymph node and distant metastases were associated with worse DSS (P = .002 for both). Age, gender, presenting symptoms, serum AFP level, and T stage were not associated with DSS. On multivariate analysis, none of these parameters was significantly associated with DSS.

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doi: <https://doi.org/10.1177/1066896918783468>

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- **Hereditary Pancreatitis in the United States: Survival and Rates of Pancreatic Cancer**

*The American journal of gastroenterology* 2018 Jul;():

**OBJECTIVES:** Hereditary pancreatitis (HP), an autosomal dominant disease typically caused by mutations in PRSS1, has a broad range of clinical characteristics and high cumulative risk of pancreatic cancer. We describe survival and pancreatic cancer risk in the largest HP cohort in the US. **METHODS:** HP probands and family members prospectively recruited from 1995 to 2013 completed medical and family history questionnaires, and provided



blood for DNA testing. Overall survival (until 12/31/2015) was determined from the Social Security Death Index (SSDI), National Death Index (NDI), and family members. Cause of death was obtained from the NDI. RESULTS: 217 PRSS1 carriers (181 symptomatic) formed the study cohort. The most frequently detected mutations were p.R122H (83.9%) and p.N29I (11.5%). Thirty-seven PRSS1 carriers (30 symptomatic, 7 asymptomatic) were deceased at conclusion of the study (5 from pancreatic cancer). Median overall survival was 79.3 years (IQR 72.2-85.2). Risk of pancreatic cancer was significantly greater than age- and sex- matched SEER data (SIR 59, 95% CI 19-138), and cumulative risk was 7.2% (95% CI 0-15.4) at 70 years. DISCUSSION: We confirm prior observations on survival and pancreatic cancer SIR in PRSS1 subjects. Although risk of pancreatic cancer was significantly high in these patients, its cumulative risk was much lower than previous reports.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=30018304>

doi: <https://doi.org/10.1038/s41395-018-0194-5>

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- **Loss of SATB2 Expression in Colorectal Carcinoma is Associated With DNA Mismatch Repair Protein Deficiency and BRAF Mutation**

*The American journal of surgical pathology 2018 Jul;():*

The special AT-rich sequence binding protein (SATB2) has been reported to be a specific immunohistochemical marker for colorectal carcinoma; however, correlation of SATB2 expression with molecular alterations commonly assessed in colorectal carcinoma has not been performed. We examined the immunohistochemical expression of SATB2 in 586 adenocarcinomas of the gastrointestinal (GI) tract and pancreas to assess its utility in diagnosis and analyze the clinicopathologic and molecular characteristics of colorectal carcinoma stratified by SATB2 expression. SATB2 and CDX2 expression were evaluated in 266 adenocarcinomas of lower GI tract origin (246 colorectal and 20 appendiceal mucinous), 208 adenocarcinomas of upper GI tract and small intestinal origin (74 esophagus/esophagogastric junction, 103 stomach, 20 duodenal, and 11 jejunoileal), and 112 pancreatic ductal adenocarcinomas. SATB2 expression was more frequently identified in adenocarcinomas of lower GI tract origin (222/266, 83%) compared with upper GI tract, small intestinal, or pancreatic origin (26/320, 8%) ( $P<0.001$ ). Compared with CDX2 alone, dual positive expression for SATB2 and CDX2 (SATB2/CDX2) has a significantly higher specificity for adenocarcinoma of lower GI tract origin (94% vs. 57%,  $P<0.001$ ). In colorectal carcinoma, loss of SATB2 expression was more frequently observed in DNA mismatch repair (MMR) protein deficient tumors (31%) compared with MMR protein proficient tumors (13%) ( $P<0.01$ ). A BRAF V600E mutation was more frequently identified in colorectal carcinomas with loss of SATB2 expression compared with those with positive SATB2 expression (29% vs. 3%) ( $P<0.001$ ). In summary, SATB2 expression is a relatively specific marker of lower GI tract origin; however, loss of SATB2 expression is more commonly seen in colorectal carcinoma with MMR protein deficiency and BRAF mutation.



PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=30001238>

doi: <https://doi.org/10.1097/PAS.0000000000001116>

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- **Mutations in BRCA1, BRCA2, and PALB2, and a panel of 50 cancer-associated genes in pancreatic ductal adenocarcinoma**

*Scientific reports* 2018 May;8(1):8105

<https://www.nature.com/articles/s41598-018-26526-x>

Mutations in genes of the breast cancer susceptibility gene (BRCA) pathway, namely, BRCA1, BRCA2, and PALB2, can provide useful information for the efficacy of platinum-based or poly ADP-ribose polymerase inhibitors chemotherapeutic regimens. Pancreatic ductal adenocarcinoma (PDAC) is an important target for such precision chemotherapies because of its dismal prognosis. We analyzed mutations in the entire coding regions of the BRCA pathway genes, expression of breast cancer 2 (BRCA2), and mutations in hotspots of 50 cancer-associated genes in 42 surgically resected PDACs, and evaluated their associations with clinicopathological features. We identified 13 rare germline mutations in the BRCA pathway genes; 68 somatic mutations in KRAS, TP53, SMAD4, CDKN2A, GNAS, SMARCB1, and RB1; and 2 germline variations in MLH1. Among them, BRCA2S2148fs was known to be pathogenic. BRCA2R18H and BRCA2G2044V were enriched in tumor tissues. BRCA2K799R and BRCA2R2964T were novel germline variations. Patients harboring potentially deleterious mutations in the BRCA pathway genes showed significantly better prognosis than those with benign mutations or no mutation. These results indicate that rare germline variations in BRCA pathway genes could be found more frequently than previously anticipated and, more importantly, potentially deleterious mutations of them could be a favorable prognostic factor in patients with resectable PDACs.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29802286>

doi: <https://doi.org/10.1038/s41598-018-26526-x>

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- **The BRG1/SOX9 axis is critical for acinar cell-derived pancreatic tumorigenesis**

*The Journal of clinical investigation* 2018 Jul;():

Chromatin remodeler Brahma related gene 1 (BRG1) is silenced in approximately 10% of human pancreatic ductal adenocarcinomas (PDAs). We previously showed that BRG1

inhibits the formation of intraductal pancreatic mucinous neoplasm (IPMN) and that IPMN-derived PDA originated from ductal cells. However, the role of BRG1 in pancreatic intraepithelial neoplasia-derived (PanIN-derived) PDA that originated from acinar cells remains elusive. Here, we found that exclusive elimination of Brg1 in acinar cells of Ptf1a-CreER; KrasG12D; Brg1<sup>fl/fl</sup> mice impaired the formation of acinar-to-ductal metaplasia (ADM) and PanIN independently of p53 mutation, while PDA formation was inhibited in the presence of p53 mutation. BRG1 bound to regions of the Sox9 promoter to regulate its expression and was critical for recruitment of upstream regulators, including PDX1, to the Sox9 promoter and enhancer in acinar cells. SOX9 expression was downregulated in BRG1-depleted ADMs/PanINs. Notably, Sox9 overexpression canceled this PanIN-attenuated phenotype in KBC mice. Furthermore, Brg1 deletion in established PanIN by using a dual recombinase system resulted in regression of the lesions in mice. Finally, BRG1 expression correlated with SOX9 expression in human PDAs. In summary, BRG1 is critical for PanIN initiation and progression through positive regulation of SOX9. Thus, the BRG1/SOX9 axis is a potential target for PanIN-derived PDA.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=30010625>

doi: <https://doi.org/10.1172/JCI94287>

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- **Immunoprevention of Pancreatic Cancer**

*Current medicinal chemistry* 2018 ;25(22):2576-2584

**BACKGROUND:** Pancreatic cancer (PC) is considered an incurable disease due to late diagnosis, rapid spread and negligible response treatment methods, with a 5-year survival rate of only 7%. Hence, there is an urgency in developing novel strategies for PC prevention. This review is focused on discussing the challenges in understanding complex immune functions in tumor microenvironment and host-induced immune responses against tumors, selection of antigens for development of preventive vaccines, lessons from immunoprevention clinical trials and challenges in developing future vaccines. **METHODS:** 65 original articles were referenced from various sources, based on immunoprevention or criteria pertaining to tumor antigens and immune responses in PC. All these articles were analyzed for the method details and results obtained, and the existing challenges were derived for successful development of clinical immunoprevention strategies. **RESULTS:** The analysis of these articles and our experience with preclinical efficacy evaluations of various preventive approaches against PC helped in identifying specific tumor antigens as targets which can overcome tumor cell immune suppression. This review discussed the status of primary, secondary and tertiary preventive vaccines and reasons for failure of therapeutic vaccines. The key parameters for effective vaccination were identified, including stage of the disease for vaccination efficacy, use of appropriate animal models for development of preventive vaccines. Potential of chemopreventive agents as adjuvants in immunoprevention was discussed. This review identified new challenges for development

of immunopreventive vaccines. CONCLUSION: This review analyzed various aspects of vaccine development for immunoprevention of PC and emphasized the challenges for development of immunoprevention strategies.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=28240168>

doi: <https://doi.org/10.2174/0929867324666170223153509>

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## Biliary Tract

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### Gallbladder

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- **Epithelial Inclusions in Gallbladder Specimens Mimic Parasite Infection: Histologic and Molecular Examination of Reported *Cystoisopora belli* Infection in Gallbladders of Immunocompetent Patients**

*The American journal of surgical pathology* 2018 Jul;():

Recent publications have described epithelial cytoplasmic vacuoles and inclusions incidentally noted within gallbladder epithelium and concluded that they represent coccidian parasite infection, in particular, *Cystoisopora belli*. We identified 8 gallbladder specimens from our institution in the past 3 years in which this diagnosis was suggested or in which similar epithelial alterations were prominent. Molecular analysis was performed on the 8 gallbladder specimens and on 3 positive control specimens: small bowel biopsies from acquired immunodeficiency syndrome patients with diarrhea. Polymerase chain reaction using primers designed to amplify an internal transcribed spacer (ITS2) in the *C. belli* ribosomal gene cluster was performed on the DNA samples. All 8 gallbladder specimens were negative for amplification, while a product consistent with *C. belli* was amplified from all 3 positive controls. Histologically, the gallbladder cytoplasmic inclusions stained diffusely positive for Grocott-Gomori's methenamine silver and Periodic acid-Schiff with diastase. In contrast, sections from a positive control small bowel biopsy demonstrated organisms that were negative for Grocott-Gomori's methenamine silver and showed a distinct capsular and punctate internal staining on Periodic acid-Schiff with diastase in various parasite forms. Together, the lack of molecular evidence of *C. belli* and the distinct morphologic and special staining patterns in these gallbladders compared with positive control small bowel suggest that these epithelial changes do not represent true *C. belli* infection. Our results suggest that gallbladders of immunocompetent patients may occasionally show epithelial changes that can morphologically mimic *C. belli* infection. Pathologists should be aware of this histologic variant to minimize unnecessary treatment, testing, and patient anxiety.

<https://journals.lww.com/ajsp/Pages/articleviewer.aspx?year=9000&issue=00000&article=97799&type=Abstract>

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=30020094>

doi: <https://doi.org/10.1097/PAS.0000000000001094>

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- **Pyloric Gland Adenoma (PGA) of the Gallbladder: A Unique and Distinct Tumor from PGAs of the Stomach, Duodenum, and Pancreas**

*The American journal of surgical pathology 2018 Jul;():*

Twenty-four surgically resected, gallbladder pyloric gland adenomas (GB-PGAs) were examined and their features were compared with the reported features of stomach, duodenum, and pancreatic PGAs to better understand GB-PGAs. Clinical information on background gallbladder lesions and histologic data, including tumor grade, existence of squamoid morules, intratumoral cholesterosis, and intracytoplasmic mucins were collected. Immunohistochemical staining for MUC2, MUC5AC, MUC6, CDX2, pepsinogen I, p53, and MIB-1/nuclear  $\beta$ -catenin were evaluated. Targeted mutational analyses of KRAS exon2, GNAS exon 7, and CTNNB1 exon 3 were conducted. We found that 29.2% of the GB-PGAs were histologically high-grade dysplasias/carcinomas; 70.8% were low grade; and 20.8% and 33.3% contained squamoid morules and intratumoral cholesterosis, respectively. In addition, 45.8% and 54.2% of GB-PGAs were mucin-rich and mucin-poor types, respectively. Immunohistochemically, MUC6 was diffusely positive in all GB-PGAs; MUC2, MUC5AC, and CDX2 were only focally positive, and no pepsinogen-I positive cells were observed. Nuclear  $\beta$ -catenin accumulation was observed in all cases; however, the ratio varied among cases. Mucin-poor types were significantly associated with high histologic grade dysplasias/carcinomas and high nuclear  $\beta$ -catenin labeling indices. Mutational analyses identified CTNNB1 mutations in 100% of GB-PGAs (21/21), KRAS in 4.2% (1/23), and GNAS in 0% (0/22). The present study clarified the unique histologic features, phenotypic differentiation, and molecular statuses frequently associated with GB-PGAs. Altogether, our data suggest that tumorigenesis of GB-PGA is distinct from that of stomach, duodenum, and pancreatic PGAs.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29975247>

doi: <https://doi.org/10.1097/PAS.0000000000001117>

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- **Clinical relevance of PD-L1 expression in gallbladder cancer: a potential target for therapy**

*Histopathology* 2018 Jun;():

AIMS: Programmed death-ligand 1 (PD-L1), a potential target for immune checkpoint inhibitors in various solid neoplasms, has been studied in very few cases of Gall Bladder Carcinoma (GBC). The current study aimed to evaluate PD-L1 expression at primary and metastatic sites of GBC, and its associations with standard prognostic clinicopathological parameters, as well as with overall survival. METHODS AND RESULTS: One hundred and seventy-four cases of GBC were evaluated for PD-L1 expression by the use of the SP263 clone in tissue microarrays. Clinicopathological characteristics and survival data were correlated with PD-L1 expression analysed at different cut-offs of  $\geq 1\%$ ,  $\geq 10\%$  and  $\geq 50\%$  in tumour cells and tumour-infiltrating lymphocytes (TILs). The mean age of patients was 49.9 years, and the male/female ratio was 1:2.9. Of the cases, 73.6% presented with stage 3/4 disease. Tumour cells expressed PD-L1 in 23.0% of cases, and TILs expressed PD-L1 in 24.1% of cases. At a cut-off of 10%, 14.9% of cases expressed PD-L1, and at a cut-off of 50%, 7.5% of cases expressed PD-L1. Significant associations were seen between tumour proportion score and histological type ( $P = 0.004$ ), histological grade ( $P = 0.004$ ), nuclear grade ( $P = 0.008$ ), nodal metastasis ( $P = 0.051$ ), higher stage ( $P = 0.058$ ), and TILs ( $P < 0.001$ ). Tumour size, growth pattern, the presence of necrosis and lymphovascular emboli showed no significant associations with PD-L1 in tumour cells or TILs. In synchronous paired samples from primary and metastatic lymph nodes, discordantly higher PD-L1 expression was evident in lymph nodes. Overall survival was not associated with PD-L1 expression ( $P = 0.546$ ). CONCLUSION: PD-L1 does not appear to be a prognostic marker or influence survival in GBC patients. However, PD-L1 expression occurs in one of four GBCs, supporting the future possibility of immune-modulation therapy to improve the dismal overall survival.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29882997>

doi: <https://doi.org/10.1111/his.13669>

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- **Intramural capillary hemangioma of gallbladder artery: age-related or treatment-induced change?**

*Cardiovascular pathology : the official journal of the Society for Cardiovascular Pathology* 2018 Jun;36():22-24

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=30005393>

doi: <https://doi.org/10.1016/j.carpath.2018.05.006>

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- **Research gaps and unanswered questions in gallbladder cancer**

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

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29784604>

doi: <https://doi.org/10.1016/j.hpb.2018.03.006>

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- **Contrast-enhanced ultrasound findings of gallbladder adenocarcinoma with sarcomatoid carcinoma accompanied by intrahepatic metastasis: A case report and literature review**

*Medicine* 2018 May;97(21):e10773

**RATIONALE:** Gallbladder adenocarcinoma is the most common subtype of malignant tumor in gallbladder carcinoma; its incidence is quite low. Preoperative diagnosis of gallbladder adenocarcinoma appears to be very difficult because they are normally asymptomatic and are often found incidentally. Adenocarcinoma with sarcomatoid carcinoma of gallbladder is exceedingly rare with no case reported in the literature to date. **PATIENT CONCERNS:** A 69-year-old male was referred to our hospital due to right upper quadrant pain. To further diagnosis, he received laboratory tests, gray-scale US, and contrast-enhanced ultrasound (CEUS). In this present study, ethical approval was not necessary, as this article is a case report, which is based on the clinical information of the patient. The patient gave his permission for publication of the case. **DIAGNOSES:** Gray-scale abdominal ultrasound image demonstrated a hypoechoic intraluminal mass of gallbladder and a heterogeneous mass at the inferior segment of the right anterior liver lobe. In CEUS, the lesion of gallbladder was hyper-enhanced in the arterial phase, and hypo-enhanced in the later arterial phase. On liver, the hepatic lesion appeared heterogeneous mild enhancement in the arterial phase. In portal and parenchymal phase, the hepatic lesion displayed hypo-enhancement, which conformed to the hepatic metastasis. **INTERVENTIONS:** The patient received cholecystectomy, right hepatectomy, and lymphadenectomy. **OUTCOMES:** He had an uneventful recovery from the procedure. **LESSONS:** We presented a case report with gallbladder adenocarcinoma with sarcomatoid carcinoma accompanied by intrahepatic metastasis, focusing on the ultrasound imaging features of this tumor, especially its enhancement pattern on CEUS. CEUS provided helpful information for diagnosis. Herein, we report the case; and the associated literature is further reviewed.

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doi: <https://doi.org/10.1097/MD.00000000000010773>

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## Bile Duct

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- **Coexistence of double gallbladder with cholangiocarcinoma: A case report**

*Medicine 2018 Jun;97(25):e11015*

**RATIONALE:** Gallbladder duplication is a rare congenital disorder, which could cause an increasing risk of complications during surgery. The coexistence of cholangiocarcinoma with double gallbladder is extremely rare, which might lead to an even higher possibility of misdiagnosis and postsurgery complications. **PATIENT CONCERNS:** A 58-year-old female was presented with abdominal pain and jaundice. Abdominal ultrasonography showed duplication of gallbladder, one of which with a thickened wall and a rough surface. This was also confirmed by an abdominal computed tomography (CT), magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) scan. During the surgery, we found a tumor inside one bile duct. The postsurgery pathology showed adenosquamous carcinoma. **DIAGNOSES:** Gallbladder duplication, cholangiocarcinoma. **INTERVENTIONS:** The tumor was removed by surgery. **OUTCOMES:** The patient died of tumor relapse six months after surgery. **LESSONS:** This is the first reported case with coexistence of gallbladder duplication and cholangiocarcinoma, which was diagnosed by abdominal ultrasound, CT and MRCP, as well as further confirmed in surgery and pathology. This case emphasized the importance of a thorough examination of gallbladder before surgery, especially in those cases with suspected double gallbladder, since each gallbladder could have the possibility of an independent cholangiocarcinoma.

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- **Pyloric metaplasia, pseudopyloric metaplasia, ulcer-associated cell lineage and spasmolytic polypeptide-expressing metaplasia: reparative lineages in the gastrointestinal mucosa**

*The Journal of pathology 2018 Jun;245(2):132-137*

The gastrointestinal mucosae provide a critical barrier between the external and internal milieu. Thus, damage to the mucosa requires an immediate response to provide appropriate



wound closure and healing. Metaplastic lineages with phenotypes similar to the mucous glands of the distal stomach or Brunner's glands have been associated with various injurious scenarios in the stomach, small bowel, and colon. These lineages have been assigned various names including pyloric metaplasia, pseudopyloric metaplasia, ulcer-associated cell lineage (UACL), and spasmolytic polypeptide-expressing metaplasia (SPEM). A re-examination of the literature on these various forms of mucous cell metaplasia suggests that pyloric-type mucosal gland lineages may provide a ubiquitous response to mucosal injury throughout the gastrointestinal tract as well as in the pancreas, esophagus, and other mucosal surfaces. While the cellular origin of these putative reparative lineages likely varies in different regions of the gut, their final phenotypes may converge on a pyloric-type gland dedicated to mucous secretion. In addition to their healing properties in the setting of acute injury, these pyloric-type lineages may also represent precursors to neoplastic transitions in the face of chronic inflammatory influences. Further investigations are needed to determine how discrete molecular profiles relate to the origin and function of pyloric-type metaplasias previously described by histological characteristics in multiple epithelial mucosal systems in the setting of acute and chronic damage. Copyright © 2018 Pathological Society of Great Britain and Ireland. Published by John Wiley & Sons, Ltd.

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- **Interleukin-33 overexpression reflects less aggressive tumour features in large-duct type cholangiocarcinomas**

*Histopathology* 2018 Aug;73(2):259-272

AIMS: The aim of the present study was to elucidate the clinicopathological significance of interleukin (IL)-6 and IL-33 expression in intrahepatic cholangiocarcinomas (iCCAs) and perihilar cholangiocarcinomas (pCCAs). METHODS AND RESULTS: IL-6 and IL-33 mRNA expression levels were examined in iCCAs (n = 55) and pCCAs (n = 32) by the use of quantitative real-time polymerase chain reaction and a highly sensitive in-situ hybridisation protocol (RNAscope), and expression levels were correlated with clinicopathological features. According to a recently proposed classification scheme, iCCAs were separated into small-duct (n = 33) and large-duct (n = 22) types. IL-6 and IL-33 expression levels were higher in large-duct iCCAs and pCCAs than in small-duct iCCAs, and there was a positive correlation between the expression levels of these cytokines. Double in-situ hybridisation/immunostaining showed that IL-6 mRNA was expressed in actin-positive (myo)fibroblasts, whereas IL-33 mRNA was mainly produced by CD31-positive endothelial cells. With the average expression level as a cut-off point, cases were classified as IL-6high and IL-6low or IL-33high and IL-33low. In the combined cohort of large-duct iCCAs and pCCAs, IL-6high and IL-6low cholangiocarcinomas shared many features, whereas IL-33high cases had less aggressive characteristics than IL-33low cases, as shown

by lower tumour marker concentrations, smaller tumour sizes, less common vascular invasion, lower pT stages, and higher lymphocyte/monocyte ratios in blood. KRAS mutations were slightly less common in IL-33<sup>high</sup> cases than in IL-33<sup>low</sup> cases (9% versus 29%; P = 0.061). The strong expression of IL-33 in tissue appeared to be an independent favourable prognostic factor. CONCLUSIONS: IL-33<sup>high</sup> cholangiocarcinomas may represent a unique, less aggressive carcinogenetic process of the large bile ducts.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29675965>

doi: <https://doi.org/10.1111/his.13633>

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- **B7-H3 expression and its correlation with clinicopathologic features, angiogenesis, and prognosis in intrahepatic cholangiocarcinoma**

*APMIS : acta pathologica, microbiologica, et immunologica Scandinavica* 2018 May;126(5):396-402

This study was designed to explore the expression of B7-H3 in human intrahepatic cholangiocarcinoma (ICC) and its association with the clinicopathologic factors. In the current study, the expression of B7-H3 in 45 patients with intrahepatic cholangiocarcinoma and 8 patients with hepatolithiasis was analyzed by immunohistochemistry, which revealed that B7-H3 was not expressed in hepatolithiatic tissues, but positively expressed in 57.8% (26/45) of the ICC cases. The expression of B7-H3 was significantly associated with lymph node metastases and venous invasion. A positive correlation was also observed between the expression of B7-H3 and MVD, an index for tumor angiogenesis. Further survival analysis indicated that patients with B7-H3 negative expression had higher overall survival (OS) and cancer-specific survival (CSS) rates than those with B7-H3 positive expression. Multivariate analysis revealed that B7-H3 expression was an independent prognostic indicator for poor OS and CSS of ICC patients. Our results suggest that B7-H3 may be a valuable biomarker in determining tumor progression and prognosis of intrahepatic cholangiocarcinoma. It is also a potential target for antivasular therapy of ICC.

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doi: <https://doi.org/10.1111/apm.12837>

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- **SurePath® LBC improves the diagnostic accuracy of intrahepatic and hilar cholangiocarcinoma**

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

**INTRODUCTION:** The current study aimed to compare cytology using SurePath® (SP)-LBC and biliary tissue histology (BTH) for the diagnosis of biliary disease. **METHODS:** Between January 2014 and December 2016, 57 patients underwent endoscopic retrograde cholangiopancreatography for the diagnosis of biliary disease. Biliary cytological samples were processed using SP-LBC and subsequently BTH was performed. A final diagnosis was confirmed by surgery (23 malignant cases) and clinical follow-up (34 benign and malignant cases): 18 extrahepatic cholangiocarcinoma; 17 intrahepatic/hilar cholangiocarcinoma (intra/H-CC); eight other malignant disease; and 14 benign biliary disease. The diagnoses made using SP-LBC and BTH were classified into four categories: (1) benign; (2) indeterminate; (3) suspicious for malignancy/malignant; and (4) inadequate. In addition, diagnostic accuracy was compared between SP-LBC and BTH. **RESULTS:** Although 23% (13/57) of BTH samples were classified as inadequate, all SP-LBC cases were classified as adequate. Among 43 malignant cases, 11 normal, four indeterminate and 28 suspicious for malignancy/malignant were found using SP-LBC (26%, 9% and 65%, respectively), in contrast to 10 inadequate, nine normal, 10 indeterminate and 14 suspicious for malignancy/malignant observed using BTH (23%, 21%, 23%, and 33%, respectively). The identification of malignant cells was strikingly different between SP-LBC and BTH. Furthermore, limited to intra/H-CC, accuracy was significantly higher using SP-LBC than using BTH ( $P < .001$ ). **CONCLUSIONS:** SP-LBC of the biliary tract is a useful and reliable method for diagnosing biliary malignant disease and has an advantage over BTH for detecting malignant cells and accurately diagnosing intra/H-CC.

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- **DJ-1 is a useful biomarker for invasive extrahepatic cholangiocarcinoma**

*Human pathology 2018 Jun;76():28-36*

We have previously reported that DJ-1 protein is up-regulated in cholangiocarcinoma compared with non-neoplastic epithelium of the bile duct in a study using liquid-chromatography mass spectrometry-based proteomics. The aim of this study was to clarify whether DJ-1 expression offers a biomarker for patients with invasive extrahepatic cholangiocarcinoma (EHCC) who undergo surgical resection with curative intent. Positive immunohistochemical (IHC) staining of DJ-1 was significantly more frequent in the cytoplasm of 96 invasive EHCCs ( $n = 28$ , 29.2%) than in that of 66 non-neoplastic epithelial lesions adjacent to invasive EHCC ( $n = 7$ , 10.6%;  $P = .006$ ). No significant difference in clinicopathological features was evident between invasive EHCC patients with negative ( $n = 68$ ) and positive ( $n = 28$ ) IHC staining. However, negative IHC staining for DJ-1 in cytoplasm was selected as an independent risk factor for adverse prognosis on multivariate

analysis ( $P = .004$ , hazard ratio 2.13, 95% confidence interval 1.28-3.57). Serum levels of DJ-1 in 16 invasive EHCC patients with metastasis were compared with 12 invasive EHCC patients without metastasis. Serum levels of DJ-1 tended to be higher in 16 patients with metastasis (median, 40.9 ng/ml) than in 12 patients without (27.6 ng/ml,  $P = .137$ ). In addition, patients with high serum levels ( $\geq 40$  ng/ml) of DJ-1 tended to have metastasis more frequently than those without ( $P = .054$ , Fisher's exact test). We concluded that IHC staining pattern and serum level of DJ-1 in patients with invasive EHCC might be predictive of prognosis and metastasis, respectively.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29447925>

doi: <https://doi.org/10.1016/j.humpath.2018.02.010>

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

*The American journal of surgical pathology* 2018 Jul;():

Intrahepatic cholangiocarcinomas are histologically heterogeneous. 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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- **The prognostic impact of differentiation at the invasive front of biliary tract cancer**

*Journal of surgical oncology* 2018 May;117(6):1278-1287

BACKGROUND: The invasive front of tumor can provide prognostic information in many cancers. We investigated the prognostic morphological factors at the invasive front including tumor differentiation (Difinv ) and tumor budding (Bud) in biliary tract cancer (BTC). METHODS: The resected specimen from the 299 BTC patients were examined. Intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer, and ampulla of Vater cancer were found in 16%, 48%, 17%, and 19%, respectively. Difinv grade (G) 3 and Bud foci  $\geq 5$  were found in 47% and 10%. Tumor with Difinv G3 showed the high frequencies of Bud, vascular invasion (Ve) and nodal metastasis (LN) compared to tumor with Difinv G1/2 (Bud: 21% vs 0%, Ve: 71% vs 50%, LN: 52% vs 36%). Multivariate analysis revealed that the independent predictors were Difinv G3 (HR: 1.71), Bud foci  $\geq 5$  (HR: 2.14), Ve (HR: 1.56) and LN (HR: 2.59) in overall survival and were positive resection margin (HR: 1.71), Difinv G3 (HR: 1.75), Ve (HR: 1.50), and LN (HR: 2.19) in relapse free survival. CONCLUSION: Poor differentiation at the invasive front of tumor was associated with poor prognosis and early relapse in BTC patients.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29572828>

doi: <https://doi.org/10.1002/jso.24946>

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- **Postradiation Synovial Sarcoma of the Common Bile Duct: A Previously Unreported Anatomic Site**

*International journal of surgical pathology* 2018 Aug;26(5):469-474

Synovial sarcoma is a ubiquitous neoplasm predominantly affecting soft tissues of young adults of any gender; few cases have been described in the digestive system, mostly in the stomach. The (X;18)(p11.2; q11.2) translocation yields unique SS18-SSX fusion genes. Synovial sarcoma has been related to radiotherapy, but no synovial sarcoma has been associated with the digestive system. This article describes the case of a synovial sarcoma arising along the extrahepatic biliary tree, 10 years after the application of an abdominal radiotherapy schedule due to a retroperitoneal metastatic seminoma in a male who developed progressive obstructive jaundice. Ninety percent of the analyzed cells carried the SS18 gene with separation of sequences, thus denoting a translocation. There are only 8

post-radiotherapy synovial sarcomas that have been reported previously, and this is the first report of a radiotherapy-related synovial sarcoma arising from the extrahepatic biliary tree, and the second case described in this anatomic region.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29336183>

doi: <https://doi.org/10.1177/1066896917752863>

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## Ampulla of Vater

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- **Intraobserver and Interobserver Variability in the Assessment of Dysplasia in Ampullary Mucosal Biopsies**

*The American journal of surgical pathology* 2018 Aug;42(8):1095-1100

Endoscopic mucosal biopsies of the ampulla of Vater (AmpBx) are obtained to histologically assess for dysplasia or carcinoma. However, biopsy material is often scant and a host of factors can induce histologic changes that pose diagnostic challenges. We sought to investigate observer variability in interpretation of AmpBx and the impact clinical data may have on diagnostic interpretation. Thirty-one cases from institutional archives were selected, including 12 cases of reactive atypia (RA), 8 indefinite for dysplasia (ID), and 11 showing low-grade dysplasia (LGD). Slides were independently reviewed at 3 time points with and without clinical information by 6 pathologists who categorized the biopsies RA, ID, or LGD. Following the reviews, intraobserver and interobserver agreement was assessed. Review of AmpBx without clinical data showed fair ( $\kappa$ , 0.27), poor ( $\kappa$ , 0.07), and good ( $\kappa$ , 0.42) interobserver agreement for diagnoses of RA, ID, and LGD, respectively. Interobserver agreement improved for LGD ( $\kappa$ , 0.66 and 0.73) when clinical information was provided; however, agreement remained fair for RA ( $\kappa$ , 0.4 and 0.42) and poor-to-fair for ID ( $\kappa$ , 0.17 and 0.25). When follow-up data were reviewed, all cases that reached unanimous agreement had that diagnosis substantiated by subsequent endoscopic or histologic findings. The same was true of 13 of 19 cases that reached majority consensus. Given the potential clinical consequences of these diagnoses combined with the significant intraobserver and interobserver variability found in this study, we conclude that better-defined diagnostic criteria and consensus reads on difficult cases would assist in the histologic assessment of these challenging cases.

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doi: <https://doi.org/10.1097/PAS.0000000000001079>



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- **Ampullary adenocarcinoma: Defining predictors of survival and the impact of adjuvant therapy following surgical resection for stage I disease**

*Journal of surgical oncology* 2018 Jun;117(7):1500-1508

BACKGROUND AND OBJECTIVES: Outcomes and recommendations regarding adjuvant therapy (AT) for stage I ampullary adenocarcinoma (AAC) are inadequately described. We sought to determine factors associated with survival and better define the impact of AT. METHODS: The NCDB was queried for stage I AAC patients undergoing resection. We evaluated variables influencing the administration of AT and affecting survival, including the receipt of AT. RESULTS: Five hundred thirty-seven patients were identified. 1, 3, and 5-year OS were 91.3%, 78.8%, and 67.4%, respectively. 103 received AT: 101 chemotherapy, 31 radiation, and 29 a combination of both. AT was more commonly utilized in patients with poorly differentiated and T2 tumors. Comorbid disease was inversely associated with use of AT. Age  $\geq 65$  was associated with decreased survival for stage IA and IB, while positive resection margins and sampling of  $<12$  LNs were associated with decreased OS for stage IA and IB, respectively. After propensity matching key covariates, no significant difference in OS was observed between those receiving and not receiving AT ( $P = 0.449$ ). CONCLUSION: This analysis revealed a modest 5-year OS for stage I AAC. Age, positive resection margins, and evaluation of  $<12$  LNs negatively influenced OS and AT did not convey a survival benefit.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29518820>

doi: <https://doi.org/10.1002/jso.25021>

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

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

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



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

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

doi: <https://doi.org/10.1016/j.prp.2018.04.018>

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- **Primary small bowel adenomas and adenocarcinomas-recent advances**

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

The small intestine represents 75% of the length and 90% of the absorptive surface area of the gastrointestinal tract (GIT), yet only 2% of digestive system cancers occur at this site. Adenocarcinoma accounts for half of small bowel malignancies. There have been a number of important recent advances in our understanding, classification and treatment of small bowel tumours. Over recent years, ampullary tumours have become recognised as a form of small bowel carcinoma, distinct from head of pancreas and lower biliary tract tumours. This is reflected in separate TNM systems and increasing interest in separating intestinal from pancreatobiliary subtypes. The recognition of the importance of microsatellite (MSI) status and the advent of molecular pathology has also changed our approach to these neoplasms.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29998424>

doi: <https://doi.org/10.1007/s00428-018-2400-7>

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- **Prognostic factors and benefits of adjuvant therapy after pancreatoduodenectomy for ampullary adenocarcinoma: Mayo Clinic experience**

**INTRODUCTION:** Ampullary adenocarcinoma is a rare entity with limited data on prognostic factors. The aim of this study is to identify prognostic factors and assess the benefit of adjuvant therapy in patients with ampullary adenocarcinoma who underwent pancreatoduodenectomy. **METHODS:** A cohort of 121 consecutive patients underwent pancreatoduodenectomy for ampullary adenocarcinoma from 2006 to 2016 at Mayo Clinic in Rochester, MN. All patients were confirmed by independent pathologic review to have ampullary carcinoma. Patient survival and its correlation with patient and tumor variables were evaluated by univariate and multivariate analysis. **RESULTS:** Fifty three patients (45%) received adjuvant therapy (34 patients had chemotherapy alone, while 19 patients received both chemotherapy and radiation therapy). Fifty seven percent of the patients were diagnosed with advanced stage disease (Stage IIB or higher). Nearly all patients (98.3%) had negative surgical margins. Median overall survival (OS) was 91.8 months (95% CI:52.6 months-not reached). In multivariate analysis, excellent performance status (ECOG: 0), adjuvant therapy, and advanced stage remained statistically significant. Adjuvant therapy was independently associated with improved disease free survival (Hazard ratio [HR]:0.52, P = 0.04) and overall survival (HR:0.45, P = 0.03) in patients with advanced disease. **CONCLUSIONS:** Adjuvant therapy was associated with improved survival in patients with resected ampullary cancer, especially with advanced stage disease. A multi-institutional randomized trial is needed to further assess the role of adjuvant therapy in ampullary adenocarcinoma.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29506768>

doi: <https://doi.org/10.1016/j.ejso.2018.02.008>

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- **Retrospective cohort of pancreatic and Vater ampullary adenocarcinoma from a reference center in Mexico**

*Annals of medicine and surgery (2012) 2018 Jun;30():7-12*

**Introduction:** Pancreatic ductal adenocarcinoma (PDAC) and ampulla of Vater adenocarcinomas (AVAC) are periampullary tumors. These tumors have overlapping symptoms and a common treatment, but present differences in their survival and biology. No recent studies in Mexico have been published that describe the clinicopathological characteristics of these tumors. Therefore, the aim of this study was to describe the clinicopathological characteristics of PDAC and AVAC in patients at a reference center in Mexico. **Methods:** A retrospective cohort of patients with PDAC or AVAC was analyzed at our institution (July 2007 to June 2016). Inferential analysis of the clinical data was performed with Student's t-test or a  $\chi^2$  test with odds ratios (OR) and confidence intervals (CI), depending on the variables. Overall survival was compared using Kaplan-Meier curves

with log-rank p values. Results: Forty patients with PDAC and 76 with AVAC were analyzed, including 77 females and 39 males with a mean age of 60.6 years and a mean evolution time of 5.7 months. PDAC patients had more abdominal pain, a larger tumor size and more advanced stages than AVAC patients. In contrast, AVAC patients had more jaundice, a higher percentage of complete resections and higher overall survival. Up to 70% of patients were overweight. PDAC cohort included a higher proportion of smokers. Conclusions: Our cohort was slightly younger, had a larger percentage of females, and a greater percentage of obese patients than those in many international reports. A high proportion of PDAC patients are diagnosed in advanced stages and have a low likelihood of resectability.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29707208>

doi: <https://doi.org/10.1016/j.amsu.2018.04.002>

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- **Myoepithelial Hamartoma in the Ampulla of Vater**

*Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association* 2018 May;():

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29857148>

doi: <https://doi.org/10.1016/j.cgh.2018.05.032>

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- **Adenosquamous Carcinoma of the Ampulla of Vater: A Rare Cause of Obstructive Jaundice**

*GE Portuguese journal of gastroenterology* 2018 Jun;25(4):195-197

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29998166>

doi: <https://doi.org/10.1159/000481457>

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- **Long-term complete remission of a patient with high grade neuroendocrine carcinoma of ampulla of Vater**

*BMJ case reports 2018 Jun;2018():*

We describe a case report of a 53-year-old man with a 5-months history of progressive jaundice and upper abdominal pain. The patient was further evaluated and finally diagnosed with a high-grade ampullary neuroendocrine tumour (based on endoscopic-guided biopsy). Thereafter, he underwent pancreatoduodenectomy and adjuvant platinum-based chemotherapy. This extremely rare case presents his long-lasting disease-free survival compared with similar cases; this case report exemplifies a new, potentially efficient method for treating high-grade papillary neuroendocrine tumour and may pave the way for further clinical trials utilising this blueprint in the treatment of related conditions.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29950363>

doi: <https://doi.org/10.1136/bcr-2018-224845>

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

*Surgery 2018 May;163(5):1071-1079*

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

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

doi: <https://doi.org/10.1016/j.surg.2017.12.018>

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- **Immunohistochemical Predictors for Intestinal and Pancreatobiliary Types of Adenocarcinoma of The Ampulla of Vater**

*Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 2018 May;():

**OBJECTIVES:** To investigate immunohistochemical predictors for intestinal and pancreatobiliary types of adenocarcinoma of ampulla of Vater and identify clinicopathological characteristics associated with the histological types and patient survival. **METHODS:** Immunohistochemical markers included MUC1, MUC2, MUC5AC, CDX2, CK7, and CK20. The data were analyzed by univariate and multivariate methods. The two-step cluster method was used to determine the best immunohistochemical markers to discriminate the intestinal from the pancreatobiliary type. **RESULTS:** This study identified 9 (33.3%) intestinal and 21 (66.7%) pancreatobiliary tumors. CK7 and CDX2 achieved the highest value (= 1) as predictor markers, while CK20, MUC1, and MUC2 showed degrees of importance equal to 0.77, 0.71, and 0.68, respectively. MUC5AC did not reach 0.50 of importance. In the univariate analysis, lymph node involvement, staging (TNM), and angiolymphatic and perineural invasions were associated with histological types. The independent clinicopathological variable in the multivariate model to predict the histological type was angiolymphatic invasion ( $p = 0.005$ ), OR = 17 (95% CI 2.33 to 123.83). The final model showed positive nodes (N1) associated with shorter survival (HR = 9.5;  $p = 0.006$ ). Overall survival at 12, 36, and 60 months was 88.5, 67.0, and 47.6%, respectively. **CONCLUSIONS:** CDX2 and CK7 were the immunohistochemical markers that best discriminated the intestinal from the pancreatobiliary type. Lymph node involvement had a high impact on survival and proved to be more frequent in the pancreatobiliary type.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29736668>

doi: <https://doi.org/10.1007/s11605-018-3797-7>

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- **A Case of Gangliocytic Paraganglioma with Carcinoma of the Ampulla of Vater: A Case Report**

*Internal medicine (Tokyo, Japan)* 2018 May;():

The patient was a "73" -year-old woman who visited our hospital with the chief complaint of weight loss. Upper gastrointestinal endoscopy revealed an enlarged ampulla of Vater, and a biopsy led to a diagnosis of Group "4" gastric carcinoma; suspicious of adenocarcinoma.

There were no findings suggesting invasion into the muscle layer of duodenum, despite tumor mass formation being observed in the sphincter of Oddi. We performed endoscopic papillectomy for both diagnostic and therapeutic purposes. Pathologically, a well-differentiated adenocarcinoma existed in the superficial layer of the mucous membrane of the papilla of Vater, and gangliocytic paraganglioma was present in the deep portion. The resected margins of both lesions were negative.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29780117>

doi: <https://doi.org/10.2169/internalmedicine.0464-17>

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- **Signet Ring Cell Carcinoma of the Ampulla of Vater With Focal Neuroendocrine Differentiation of the Amphicrine Type: Report of a Case With Long-Term Survival**

*International journal of surgical pathology* 2018 Jul;():1066896918784666

Carcinoma of the ampulla of Vater is an uncommon neoplasm and represents 0.5% of all gastrointestinal malignancies, being less common than carcinoma of the pancreas and bile ducts. The most common ampullary tumor is the adenocarcinoma with tubular growth pattern. Signet ring cell carcinoma is extremely rare. In this article, we report a case of signet ring cell carcinoma of the ampulla of Vater showing focal neuroendocrine amphicrine differentiation and intestinal phenotype, which occurred in a 49-year-old male who is still alive 7 years after surgery, without evidence of recurrence. This long-term survival might be attributed not only to the early stage of the disease but also to the neuroendocrine differentiation and the absence of genetic alterations.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29996669>

doi: <https://doi.org/10.1177/1066896918784666>

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- **Sarcomatoid Adenocarcinoma of the Ampulla of Vater**

*Indian journal of surgical oncology* 2018 Jun;9(2):274-277

Sarcomatoid adenocarcinoma of ampulla of Vater is an extremely rare malignant neoplasm that displays both carcinomatous and sarcomatous component. A 58-year-old woman was admitted to our hospital under the suspicion of an ampulla of Vater cancer. Abdominal computed tomography and endoscopy demonstrated a bulging of ampulla and the biopsy

specimen revealed an adenocarcinoma, well differentiated in the background of tubulovillous adenoma. So we performed the pylorus preserving pancreaticoduodenectomy. At postoperative biopsy, the tumor was composed of adenocarcinoma component and sarcomatoid component. Thus, a diagnosis of sarcomatoid adenocarcinoma of ampulla of Vater could be made. Here, we present a case of sarcomatoid adenocarcinoma of ampulla of Vater.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29887717>

doi: <https://doi.org/10.1007/s13193-018-0743-9>

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- **Primary small bowel adenomas and adenocarcinomas-recent advances**

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

The small intestine represents 75% of the length and 90% of the absorptive surface area of the gastrointestinal tract (GIT), yet only 2% of digestive system cancers occur at this site. Adenocarcinoma accounts for half of small bowel malignancies. There have been a number of important recent advances in our understanding, classification and treatment of small bowel tumours. Over recent years, ampullary tumours have become recognised as a form of small bowel carcinoma, distinct from head of pancreas and lower biliary tract tumours. This is reflected in separate TNM systems and increasing interest in separating intestinal from pancreatobiliary subtypes. The recognition of the importance of microsatellite (MSI) status and the advent of molecular pathology has also changed our approach to these neoplasms.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29998424>

doi: <https://doi.org/10.1007/s00428-018-2400-7>

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- **Signet Ring Cell Carcinoma of the Ampulla of Vater With Focal Neuroendocrine Differentiation of the Amphicrine Type: Report of a Case With Long-Term Survival**

*International journal of surgical pathology* 2018 Jul;():1066896918784666

Carcinoma of the ampulla of Vater is an uncommon neoplasm and represents 0.5% of all gastrointestinal malignancies, being less common than carcinoma of the pancreas and bile ducts. The most common ampullary tumor is the adenocarcinoma with tubular growth pattern. Signet ring cell carcinoma is extremely rare. In this article, we report a case of



signet ring cell carcinoma of the ampulla of Vater showing focal neuroendocrine amphicrine differentiation and intestinal phenotype, which occurred in a 49-year-old male who is still alive 7 years after surgery, without evidence of recurrence. This long-term survival might be attributed not only to the early stage of the disease but also to the neuroendocrine differentiation and the absence of genetic alterations.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29996669>

doi: <https://doi.org/10.1177/1066896918784666>

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- **Prognostic factors of non-ampullary duodenal adenocarcinoma**

*Japanese journal of clinical oncology* 2018 Jun;():

Background: Non-ampullary duodenal adenocarcinoma, excluding carcinoma in the ampulla of Vater, is a rare disease. Although several prognostic factors have been reported, they remain controversial due to the rarity of non-ampullary duodenal adenocarcinoma. The aims of this study were to investigate prognostic factors in patients with non-ampullary duodenal adenocarcinoma and to assess chemotherapy in patients with recurrence. Patients and methods: Records of 25 patients who underwent surgical treatment for non-ampullary duodenal adenocarcinoma from 2004 to 2016 were retrospectively reviewed. The relationship between the clinicopathological factors and outcomes was investigated. Results: Serum level of CA19-9, gross appearance, tumor size, tumor invasion, lymph node metastases, TNM stage and lymphatic and vascular invasion were significant risk factors of recurrence. Patients with recurrence who received chemotherapy according to regimens used to treat colorectal cancer had a better prognosis than those without chemotherapy ( $P = 0.016$ ). Conclusion: Advanced non-ampullary duodenal adenocarcinoma has a poor prognosis, but chemotherapy possibly improves the prognosis in the patients with recurrent non-ampullary duodenal adenocarcinoma.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29931295>

doi: <https://doi.org/10.1093/jjco/hyy086>

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- **Heterotopic Gastric Mucosa in the Common Bile Duct With Cholangiocarcinoma**

*International journal of surgical pathology* 2018 May;():1066896918775531

Gastric heterotopia within the biliary system is extremely rare. Moreover, the combination of gastric heterotopia in the bile duct with cholangiocarcinoma has not been reported. We describe a case of heterotopic gastric mucosa in the common bile duct with cholangiocarcinoma. An 80-year-old male was admitted with abdominal pain. Abdominal computed tomography revealed wall thickening from the hilar duct to the distal common bile duct. Biopsy from the distal bile duct showed only benign gastric foveolar-type epithelium and fundic glands. Although the diagnosis of the biopsy was benign, malignancy was strongly suspected from the radiologic findings, and excision of the bile ducts was performed. Microscopically, the resected specimen showed poorly formed malignant glands and gastric heterotopia also identified in the common bile duct. Three months later, the patient's state worsened due to recurrence, and he died. To our knowledge, this is the first report of gastric heterotopia in the bile duct accompanying cholangiocarcinoma.

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doi: <https://doi.org/10.1177/1066896918775531>

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## Neuroendocrine

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- **Fine-needle aspiration of a pancreatic neuroendocrine tumor with prominent rhabdoid features**

*Diagnostic cytopathology* 2018 Jul;46(7):600-603

Pancreatic neuroendocrine tumors (PanNETs) are uncommon neoplasms that conventionally possess architectural and cytomorphological features seen in neuroendocrine neoplasms found at other sites. When present, these features often allow rapid identification of neuroendocrine differentiation and an accurate diagnosis. Here, we report the cytologic findings seen on fine-needle aspiration (FNA) of a PanNET with distinct rhabdoid features. This morphology is rare in PanNETs and has been reported in only two case series examining surgical resection specimens and has not been described on FNA. It is important to recognize this morphology as this variant appears to portend an aggressive clinical course. Furthermore, unfamiliarity with this morphologic variant may lead to a larger initial differential and thus delay final diagnosis.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29359517>

doi: <https://doi.org/10.1002/dc.23892>

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- **Well differentiated grade 3 pancreatic neuroendocrine tumors compared with related neoplasms: A morphologic study**

*Cancer cytopathology 2018 May;126(5):326-335*

BACKGROUND: Pancreatic neuroendocrine neoplasms with a Ki-67 labeling index greater than 20% were reclassified in 2017 by the World Health Organization into well differentiated (WD) and poorly differentiated grade 3 neuroendocrine carcinoma (NEC). The authors describe the cytologic features of grade 3 WD pancreatic neuroendocrine neoplasms compared with grade 2 neoplasms and NEC. METHODS: Fine-needle aspirates from 65 pancreatic neuroendocrine neoplasms were reviewed, and their cytomorphologic features were compared across grade 2, WD grade 3, and PD small cell type (PD-S), large cell type (PD-L), and type not otherwise specified (PD-NOS) neoplasms. RESULTS: The 65 aspirates consisted of 19 grade 2 neoplasms, 32 WD grade 3 neoplasms, and 14 NECs (6 PD-S, 5 PD-L, and 3 PD-NOS). The medians Ki-67 proliferation index was 11% (range, 3.2%-17%) in grade 2 neoplasms, 40% (range, 21%-89%) in WD grade 3 neoplasms, 80% (range, 63%-95%) in PD-S neoplasms, 39% (range, 25%-61%) in PD-L neoplasms, and 70% (range, 30%-80%) in PD-NOS neoplasms. Both grade 2 and WD grade 3 neoplasms were associated with plasmacytoid morphology and smooth nuclear contours, but WD grade 3 neoplasms had significant increases in abundant cytoplasm (72% vs 17%;  $P = .007$ ), nuclear tangles (75% vs 42%;  $P = .006$ ), and apoptosis (86% vs 58%;  $P = .005$ ). Compared with NECs, WD grade 3 neoplasms had increased plasmacytoid morphology (75% vs 7%;  $P < .001$ ), smooth nuclear contours (94% vs 64%;  $P = .02$ ), round nuclei (59% vs 21%;  $P = .01$ ), and less pleomorphism (13% vs 50%;  $P = .004$ ), molding (9% vs 79%;  $P < .001$ ), and necrosis (13% vs 43%;  $P = .003$ ). WD grade 3 neoplasms had less pleomorphism (13% vs 50%;  $P = .04$ ), less necrosis (13% vs 60%;  $P = .04$ ), and more plasmacytoid morphology (75% vs 20%;  $P = .03$ ) than PD-L. CONCLUSIONS: The prevalence of cytologic features differs in WD grade 3 pancreatic neuroendocrine neoplasms compared with grade 2 neoplasms and NECs, and these differences assist in the recognition of this newly classified entity. *Cancer Cytopathol* 2018;126:326-35. © 2018 American Cancer Society.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29451738>

doi: <https://doi.org/10.1002/cncy.21982>

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- **Pancreatic neuroendocrine carcinomas reveal a closer relationship to ductal adenocarcinomas than to neuroendocrine tumors G3**

*Human pathology 2018 Jul;77():70-79*

Pancreatic neuroendocrine carcinoma is a rare aggressive tumor commonly harboring TP53 and RB1 alterations and lacking neuroendocrine-related genetic changes such as

mutations in MEN1 and ATRX/DAXX. Little is known about its genetic profile with regard to that of pancreatic ductal adenocarcinoma. We therefore conducted a detailed genetic study in 12 pancreatic neuroendocrine carcinomas of large cell (n = 9) and small cell type (n = 3) using massive parallel sequencing applying a 409-gene panel on an Ion Torrent system. The genetic data were compared with known data of pancreatic ductal adenocarcinoma and correlated with exocrine lineage marker expression. A similar analysis was performed in 11 pancreatic neuroendocrine tumors G3. Neuroendocrine carcinomas harbored 63 somatic mutations in 45 different genes, affecting most commonly TP53 (8/12 cases), KRAS (5/12 cases), and RB1 (loss of expression with or without deletion in 4/12 cases). Five carcinomas had both TP53 and KRAS mutations. Neuroendocrine tumors G3 only shared singular mutations in 5 different genes with neuroendocrine carcinomas, including TP53, CDKN2A, ARID1A, LRP1B, and APC, affecting 5 different cases. Most KRAS-positive neuroendocrine carcinomas also expressed MUC1 (4/5) and carcinoembryonic antigen (3/5) as markers of ductal differentiation. Our data indicate that almost half of the pancreatic neuroendocrine carcinomas are genetically and phenotypically related to pancreatic ductal adenocarcinoma, and might therefore respond to chemotherapies targeting the latter carcinomas.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29596894>

doi: <https://doi.org/10.1016/j.humpath.2018.03.018>

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- **Carbonic anhydrase 9 expression in well-differentiated pancreatic neuroendocrine neoplasms might be associated with aggressive behavior and poor survival**

*Virchows Archiv : an international journal of pathology* 2018 May;472(5):739-748

Well-differentiated pancreatic neuroendocrine neoplasms/tumors (PanNETs) are rare neoplasms with diverse clinical behavior. Biomarker discovery is important for predicting clinical course and prognosis of PanNET patients. Carbonic anhydrase 9 (CA9) and vimentin are hypoxia and epithelial-mesenchymal transition-related proteins of which expression in many carcinomas has been associated with poor prognosis, but their significance in PanNET has yet to be determined. We assessed CA9 and vimentin expression in 164 PanNETs and compared this with clinicopathologic characteristics. CA9 expression was observed in normal islets, while neuroendocrine microadenomas and small (< 1 cm) PanNETs showed loss of CA9 expression. CA9 and vimentin expression was observed in 38 (23%) and 36 (22%) of PanNETs, respectively. CA9 expression was associated with larger size (p = 0.001), higher grade (p < 0.001), higher pT category (p < 0.001), lymph node (p = 0.003) and distant (p = 0.047) metastases, higher AJCC stage (p < 0.001), and lymphovascular (p < 0.001) and perineural (p = 0.002) invasion. PanNET patients with CA9 expression had a shorter recurrence-free survival (5-year survival rate 47%) than those without CA9 expression (76%) by univariate (p = 0.001) but not multivariate analysis. Vimentin expression correlated with CA9 expression (p < 0.001) but not with other clinicopathologic factors. In

conclusion, CA9 expression was observed in normal islets, while neuroendocrine microadenomas and small (< 1 cm) PanNETs showed CA9 expression loss. CA9 expression gradually reappeared in larger PanNETs, and this was associated with clinical progression and decreased patient survival by univariate but not multivariate analysis.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29666945>

doi: <https://doi.org/10.1007/s00428-018-2353-x>

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- **Pancreatic islets communicate with lymphoid tissues via exocytosis of insulin peptides**

<https://www.nature.com/articles/s41586-018-0341-6>

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- **Hepatic micrometastases are associated with poor prognosis in patients with liver metastases from neuroendocrine tumors of the digestive tract**

*Human pathology 2018 May;():*

Pathologic examination of hepatic metastasectomies from patients with metastatic small intestinal or pancreatic neuroendocrine tumor frequently reveals micrometastases undetectable by radiologic or macroscopic gross examination. This finding raises the possibility that undetectable micrometastases remain in these patients after metastasectomy. Here we examined liver resections for micrometastases and assessed their impact on prognosis. Hepatic metastasectomies from 65 patients with neuroendocrine tumor of the small intestine (N=43) or pancreas (N=22) were reviewed for the presence of micrometastases, which were defined as microscopic tumor foci  $\leq 1\text{mm}$  in greatest dimension. Medical records were also reviewed for patient demographics, clinical history, and follow-up data. Micrometastasis was identified in 36 (55%) of 65 hepatic resection specimens. More hepatic micrometastases were seen in small intestinal cases than in pancreatic cases (29/43, 67% versus 7/22, 32%;  $P<.01$ ). They were typically present within portal tracts, sometimes with extension into the periportal region or sinusoidal spaces away from the portal tracts. Patients without hepatic micrometastases had fewer macrometastases or more R0 hepatic resections than those with micrometastases. The presence of hepatic micrometastases was associated with poor overall survival both before (hazard ratio [HR] 3.43; 95% CI 1.1410.30;  $P=.03$ ) and after accounting for confounding variables in stratified Cox regression (HR 4.82; 95% CI 1.0621.79;  $P=.04$ ). In conclusion, hepatic micrometastases are common in patients with metastatic small intestinal or pancreatic neuroendocrine tumor and are independently associated with poor prognosis. These data suggest that surgical resection of hepatic metastases is likely not curative in these patients.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29763717>

doi: <https://doi.org/10.1016/j.humpath.2018.05.006>

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- **Neoplasms of the Neuroendocrine Pancreas: An Update in the Classification, Definition, and Molecular Genetic Advances**

*Advances in anatomic pathology 2018 Jun;():*

This review focuses on discussing the main modifications of the recently published 2017 WHO Classification of Neoplasms of the Neuroendocrine Pancreas (panNEN). Recent updates separate pancreatic neuroendocrine tumors into 2 broad categories: well-differentiated pancreatic neuroendocrine tumors (panNET) and poorly differentiated pancreatic neuroendocrine carcinoma (panNEC), and incorporates a new subcategory of “well-differentiated high-grade NET (G3)” to the well-differentiated NET category. This new classification algorithm aims to improve the prediction of clinical outcomes and survival and help clinicians select better therapeutic strategies for patient care and management. In addition, these neuroendocrine neoplasms are capable of producing large quantity of hormones leading to clinical hormone hypersecretion syndromes. These functioning tumors include, insulinomas, glucagonomas, somatostatinomas, gastrinomas, VIPomas, serotonin-producing tumors, and ACTH-producing tumors. Although most panNENs arise as sporadic diseases, a subset of these heterogeneous tumors present as parts on inherited genetic syndromes, such as multiple endocrine neoplasia type 1, von Hippel-Lindau, neurofibromatosis type 1, tuberous sclerosis, and glucagon cell hyperplasia and neoplasia syndromes. Characteristic clinical and morphologic findings for certain functioning and syndromic panNENs should alert both pathologists and clinicians as appropriate patient management and possible genetic counseling may be necessary.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29912000>

doi: <https://doi.org/10.1097/PAP.0000000000000201>

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- **Neuroendocrine tumor of the pancreas with rhabdoid feature**

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

Imaging of a 53-year-old Japanese man revealed two tumors in the liver and a tumor in the head of the pancreas with a swelling lymph node. A needle biopsy for the liver tumors was performed, revealing a neuroendocrine tumor. Enucleation, lymphadenectomy, and partial

hepatectomy were performed. The microscopic examination identified many tumor cells with intracytoplasmic inclusions arranged in a nested, cord, or tubular fashion. The intracytoplasmic inclusions displayed densely eosinophilic globules and displaced the nuclei toward the periphery, which constitutes “rhabdoid” features. The tumor cells were positive for synaptophysin and weakly positive for NCAM, but negative for chromogranin A. Epithelial markers (AE1/AE3 and CAM5.2) accentuated intracytoplasmic globules. Pancreatic neuroendocrine tumors with rhabdoid features are very rare. Generally, rhabdoid features are aggressive and dedifferentiated characteristics of various types of tumor. Pancreatic neuroendocrine tumors containing rhabdoid cells tend to display extrapancreatic spread at the time of presentation, although some of these tumors with rhabdoid features are not always associated with aggressive behavior.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29938394>

doi: <https://doi.org/10.1007/s00428-018-2398-x>

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- **Incidentally detected pancreatic neuroendocrine microadenoma with lymph node metastasis**

<https://link.springer.com/article/10.1007/s00428-018-2407-0>

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

Pancreatic neuroendocrine microadenomas (NEMAs) are non-functioning neuroendocrine tumors < 0.5 cm with a low proliferation rate and are considered benign. We report on a pancreatic NEMA with lymph node metastasis. A male in his 70s had pylorus-preserving pancreaticoduodenectomy for a distal bile duct carcinoma, which was a 2.1 cm well-differentiated-infiltrating adenocarcinoma with invasion limited to the bile duct wall. An incidental separate 0.4 cm well-differentiated NEMA was found in the pancreatic head with metastatic well-differentiated neuroendocrine tumor in one peripancreatic lymph node. Both neuroendocrine tumors in the pancreatic head and in the lymph node were composed of nests of uniform neoplastic cells with a fine chromatin pattern. The Ki-67 labeling index of NEMA was 0.85%. The neoplastic neuroendocrine cells in both the pancreas and node were diffusely positive for synaptophysin, chromogranin, and insulin. Therefore, this unusual case provides an exception to the current classification system which regards NEMAs as benign lesions.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=30003325>

doi: <https://doi.org/10.1007/s00428-018-2407-0>



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- **Reduced RNA-binding protein HuD in pancreatic neuroendocrine tumors lowers p27Kip1 levels linked to poor prognosis**

*The Journal of pathology 2018 Jul;():*

For the majority of patients diagnosed with pancreatic neuroendocrine tumors (pancreatic NETs) there is a significant malignant potential with a poor prognosis, however the molecular abnormalities and pathogenesis of pancreatic NETs have not been firmly established. Here, we report that loss of RNA-binding protein HuD expression correlates with low p27Kip1 (p27) levels and poor prognosis in pancreatic NETs. HuD expression was frequently lost in many human pancreatic NETs and these pancreatic NETs showed aggressive clinico-pathological phenotypes with low p27 levels, increased tumor size, higher WHO grade and pathological T stage of the tumor, and presence of angioinvasion. Furthermore, loss of HuD was an independent, progress-free prognostic factor in multivariate survival analysis. However, level of HuR, the same Hu protein family member with HuD, was not significantly correlated with pancreatic NET size and progression. Mechanistically, HuD enhanced p27 mRNA translation by interacting with both 5'- and 3'-untranslated regions (UTRs) of p27 mRNA and consequently suppressed cell cycle progression and tumor growth. In addition, HuD competed with miR-30a-3p for binding to 3'UTR of p27 mRNA, suggesting interplay between HuD and miR-30a-3p in controlling p27 translation. Our results identify HuD as a pivotal suppressor of pancreatic NET growth, and propose that HuD has potential value as a prognostic factor of pancreatic NETs. This article is protected by copyright. All rights reserved.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=30014466>

doi: <https://doi.org/10.1002/path.5135>

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## Cytopathology

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- **Factors Impacting the Performance Characteristics of Bile Duct Brushings: A Clinico-Cytopathologic Analysis of 253 Patients**

*Archives of pathology & laboratory medicine 2018 Jul;142(7):863-870*

CONTEXT: - Literature on factors impacting bile duct brushings (BDBs) performance characteristics remain limited. OBJECTIVE: - To capture the current state of daily practice with BDB sign-out. DESIGN: - Two hundred fifty-three of 444 BDBs signed out by more than 7 cytopathologists, with histopathologic and/or clinical follow-up of at least 18 months, were examined. RESULTS: - One hundred thirty-five of 253 BDBs (53%) had histologically

confirmed malignancies, 22 (9%) had cancer-related deaths, and 96 (38%) were benign. Cytologic diagnoses in the 444 BDBs were nondiagnostic (11 [2.5%]), negative (284 [64%]), atypical (62 [13.9%]), suspicious (34 [7.7%]), and malignant (53 [11.9%]). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of malignancy detection were 35%, 100%, 100%, 58%, and 66%, respectively. When atypical, suspicious, and malignant (ASM) categories were combined, sensitivity increased (58%), specificity and PPV dropped (97%), and accuracy increased (73%). Carcinoma type (bile-duct versus pancreatic-ductal) had no effect on accuracy (  $P = .60$ ) or diagnostic class (  $P = .84$ ), nor did time of performance (first 7.5 versus latter 7.5 years,  $P = .13$ ). Interestingly, ThinPrep + cell block (  $n = 41$ ) had higher sensitivity (61%) and lower specificity (80%) than ThinPrep only (versus 51% and 100%, respectively). Sensitivity and specificity were higher (47% and 100%) in nonstented than stented specimens (59% and 97%). Relative risk of malignancy for “suspicious” (2.30) and “atypical” (2.28) categories was lower but not very different from that of “malignant” category (2.41). CONCLUSIONS: - Bile duct brushings had fairly low sensitivity but high specificity and PPV with no false positives. Sensitivity almost doubled and specificity dipped minimally when ASM categories were combined, highlighting the need for better classification criteria for atypical/suspicious cases. Higher specificity, PPV, NPV, and accuracy but lower sensitivity in stented BDBs suggest that they be called malignant only when evidence is overwhelmingly convincing.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29582676>

doi: <https://doi.org/10.5858/arpa.2017-0150-OA>

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- **UroVysion Multi-Target Fluorescence in situ Hybridization Assay for the Detection of Malignant Bile Duct Brushing Specimens: A Comparison with Routine Cytology**

*Acta cytologica* 2018 May;():1-7

OBJECTIVE: Routine bile duct brushing cytology is an important diagnostic tool in the evaluation of bile duct stricture. The purpose of this study was to evaluate the performance of the UroVysion fluorescence in situ hybridization (FISH) assay for the detection of malignant bile duct brushing specimens. STUDY DESIGN: Thirty-five bile duct brushing specimens were included in the study. The FISH assay utilized the commercially available UroVysion probes. The indeterminate cytology results were considered as negative for statistical analysis. RESULTS: Twenty-two of 35 patients were diagnosed as having malignancy based on tissue diagnosis or clinical progression of disease by image assessment. The sensitivity of routine cytology and FISH for the detection of malignancy was 14% (3/22) and 55% (12/22), respectively ( $p = 0.003$ ). The specificity of routine cytology and FISH was 100% (13/13) and 62% (8/13), respectively ( $p = 0.025$ ). The false-positive rate for routine cytology and FISH was 0% (0/13) and 38% (5/13), respectively. CONCLUSIONS: Our study shows that FISH is significantly more sensitive than routine

cytology for the detection of malignancy in bile duct brushing specimens. However, in our study, the specificity of FISH was poor compared to the excellent specificity of routine cytology. The compromised specificity of FISH may limit its utility in the detection of malignant bile duct brushing specimens.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29734171>

doi: <https://doi.org/10.1159/000488636>

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- **Cytological features of mixed adenoneuroendocrine carcinoma of the ampulla of Vater: A case report with immunocytochemical analyses**

*Diagnostic cytopathology 2018 Jun;46(6):540-546*

Mixed adenoneuroendocrine carcinoma (MANEC) is defined as a tumor that has morphologically recognizable both adenocarcinoma and neuroendocrine carcinoma components comprising at least 30% of either components. MANEC occurring in the ampulla of Vater is extremely rare, and only 16 cases have been reported in the English language literature. In the present report, we describe the first case of MANEC of the ampulla of Vater with immunocytochemical analyses. An 82-year-old Japanese male was incidentally found to have a tumorous lesion in the ampulla of Vater. Endoscopic ultrasound-fine needle aspiration (EUS-FNA) of the tumor was performed. The Papanicolaou smear demonstrated the presence of different three components. The most dominant component was cohesive clusters of small round cells with round to oval nuclei with powdery chromatin and scant cytoplasm, which corresponded to small cell carcinoma. The second component was an adenocarcinoma, which was composed of irregularly overlapping clusters of tall columnar cells with large round to oval nuclei containing conspicuous nucleoli. The third component was an adenoma, which was comprised of flat cohesive clusters of columnar cells without atypia. Immunocytochemical analyses demonstrated that synaptophysin was expressed in the small round cells, and cdx-2 was expressed in all three components. Accordingly, a cytodiagnosis of MANEC with adenoma component was made. Preoperative diagnosis of ampullary MANEC is difficult. However, this report clearly demonstrates three different components in the EUS-FNA cytological specimen. Therefore, we suggest that cytological examination is a useful method for diagnosis of MANEC of the ampulla of Vater.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29341470>

doi: <https://doi.org/10.1002/dc.23891>

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- **The Diagnostic Accuracy of Cytology for the Diagnosis of Hepatobiliary and Pancreatic Cancers**

*Acta cytologica* 2018 Jun;():1-6

**OBJECTIVE:** Although cytology testing is considered a valuable method to diagnose tumors that are difficult to access such as hepato-biliary-pancreatic (HBP) malignancies, its diagnostic accuracy remains unclear. We therefore aimed to investigate the diagnostic accuracy of cytology testing for HBP tumors. **STUDY DESIGN:** We performed a retrospective study of all cytology samples that were used to confirm radiologically detected HBP tumors between 2002 and 2016. The cytology techniques used in our center included fine needle aspiration (FNA), brush cytology, and aspiration of bile. Sensitivity, specificity, positive and negative predictive values, and likelihood ratios were calculated in comparison to histological confirmation. **RESULTS:** From a total of 133 medical records, we calculated an overall sensitivity of 76%, specificity of 74%, a negative likelihood ratio of 0.30, and a positive likelihood ratio of 2.9. Cytology was more accurate in diagnosing lesions of the liver (sensitivity 79%, specificity 57%) and biliary tree (sensitivity 100%, specificity 50%) compared to pancreatic (sensitivity 60%, specificity 83%) and gallbladder lesions (sensitivity 50%, specificity 85%). Cytology was more accurate in detecting primary cancers (sensitivity 77%, specificity 73%) when compared to metastatic cancers (sensitivity 73%, specificity 100%). FNA was the most frequently used cytological technique to diagnose HBP lesions (sensitivity 78.8%). **CONCLUSION:** Cytological testing is efficient in diagnosing HBP cancers, especially for hepatobiliary tumors. Given its relative simplicity, cost-effectiveness, and paucity of alternative diagnostic methods, cytology should still be considered as a first-line tool for diagnosing HBP malignancies.

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- **Fine-needle aspiration of a pancreatic neuroendocrine tumor with prominent rhabdoid features**

*Diagnostic cytopathology* 2018 Jul;46(7):600-603

Pancreatic neuroendocrine tumors (PanNETs) are uncommon neoplasms that conventionally possess architectural and cytomorphological features seen in neuroendocrine neoplasms found at other sites. When present, these features often allow rapid identification of neuroendocrine differentiation and an accurate diagnosis. Here, we report the cytologic findings seen on fine-needle aspiration (FNA) of a PanNET with distinct rhabdoid features. This morphology is rare in PanNETs and has been reported in only two case series examining surgical resection specimens and has not been described on FNA. It is

important to recognize this morphology as this variant appears to portend an aggressive clinical course. Furthermore, unfamiliarity with this morphologic variant may lead to a larger initial differential and thus delay final diagnosis.

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- **Well differentiated grade 3 pancreatic neuroendocrine tumors compared with related neoplasms: A morphologic study**

*Cancer cytopathology 2018 May;126(5):326-335*

**BACKGROUND:** Pancreatic neuroendocrine neoplasms with a Ki-67 labeling index greater than 20% were reclassified in 2017 by the World Health Organization into well differentiated (WD) and poorly differentiated grade 3 neuroendocrine carcinoma (NEC). The authors describe the cytologic features of grade 3 WD pancreatic neuroendocrine neoplasms compared with grade 2 neoplasms and NEC. **METHODS:** Fine-needle aspirates from 65 pancreatic neuroendocrine neoplasms were reviewed, and their cytomorphologic features were compared across grade 2, WD grade 3, and PD small cell type (PD-S), large cell type (PD-L), and type not otherwise specified (PD-NOS) neoplasms. **RESULTS:** The 65 aspirates consisted of 19 grade 2 neoplasms, 32 WD grade 3 neoplasms, and 14 NECs (6 PD-S, 5 PD-L, and 3 PD-NOS). The medians Ki-67 proliferation index was 11% (range, 3.2%-17%) in grade 2 neoplasms, 40% (range, 21%-89%) in WD grade 3 neoplasms, 80% (range, 63%-95%) in PD-S neoplasms, 39% (range, 25%-61%) in PD-L neoplasms, and 70% (range, 30%-80%) in PD-NOS neoplasms. Both grade 2 and WD grade 3 neoplasms were associated with plasmacytoid morphology and smooth nuclear contours, but WD grade 3 neoplasms had significant increases in abundant cytoplasm (72% vs 17%;  $P = .007$ ), nuclear tangles (75% vs 42%;  $P = .006$ ), and apoptosis (86% vs 58%;  $P = .005$ ). Compared with NECs, WD grade 3 neoplasms had increased plasmacytoid morphology (75% vs 7%;  $P < .001$ ), smooth nuclear contours (94% vs 64%;  $P = .02$ ), round nuclei (59% vs 21%;  $P = .01$ ), and less pleomorphism (13% vs 50%;  $P = .004$ ), molding (9% vs 79%;  $P < .001$ ), and necrosis (13% vs 43%;  $P = .003$ ). WD grade 3 neoplasms had less pleomorphism (13% vs 50%;  $P = .04$ ), less necrosis (13% vs 60%;  $P = .04$ ), and more plasmacytoid morphology (75% vs 20%;  $P = .03$ ) than PD-L. **CONCLUSIONS:** The prevalence of cytologic features differs in WD grade 3 pancreatic neuroendocrine neoplasms compared with grade 2 neoplasms and NECs, and these differences assist in the recognition of this newly classified entity. *Cancer Cytopathol* 2018;126:326-35. © 2018 American Cancer Society.

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- **Inspissated cyst fluid in endoscopic ultrasound-guided fine needle aspiration of pancreatic cysts**

*Diagnostic cytopathology* 2018 May;46(5):395-399

**BACKGROUND:** Inspissated cyst fluid may be identified on pancreatic cyst aspiration cytology. We report on the cytomorphologic characteristics of inspissated cyst fluid on EUS-FNA of pancreatic cysts and correlate this finding with histopathology or multimodal (cytology, cyst fluid analysis, molecular pathology, imaging) classification of cyst type. **METHODS:** The department archives were searched for pancreatic cyst fine-needle aspiration biopsies that contained dessicated, crystalline or inspissated material on cytologic preparations. **RESULTS:** Twenty-eight cases of pancreatic cysts containing inspissated material were identified. The cytomorphology of the inspissated material ranged from fibrillary fan-like structure (54%), ball-like structures (57%), and granular material (43%). When present, the fibrillary inspissated material was associated with neoplastic mucinous cysts in 11/15 (73%) cases, but was also seen in 2 pseudocysts, 1 serous cystadenoma, and 1 cyst of uncertain type (suggestive of mucinous cyst on EUS). The presence of fibrillary inspissated cyst material on cytology had a positive predictive value of 79% and a specificity of 63% for a neoplastic mucinous cyst. **CONCLUSION:** Although not highly specific, the presence of inspissated cyst fluid with fibrillary architecture should be recognized by cytopathologists and interpreted as at least “atypical” given the potential association with neoplastic mucinous cysts of the pancreas.

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- **Telomere length determined by the fluorescence in situ hybridisation distinguishes malignant and benign cells in cytological specimens**

*Cytopathology : official journal of the British Society for Clinical Cytology* 2018 Jun;29(3):262-266

**BACKGROUND:** Telomeres are tandem repeats of TTAGGG at the end of eukaryotic chromosomes that play a key role in preventing chromosomal instability. The aim of the present study is to determine telomere length using fluorescence in situ hybridisation (FISH) on cytological specimens. **METHODS:** Aspiration samples (n = 41) were smeared on glass slides and used for FISH. **RESULTS:** Telomere signal intensity was significantly lower in positive cases (cases with malignancy, n = 25) as compared to negative cases (cases without malignancy, n = 16), and the same was observed for centromere intensity. The



difference in DAPI intensity was not statistically significant. The ratio of telomere to centromere intensity did not show a significant difference between positive and negative cases. There was no statistical difference in the signal intensities of aspiration samples from ascites or pleural effusion (n = 23) and endoscopic ultrasound-guided FNA samples from the pancreas (n = 18). CONCLUSIONS: The present study revealed that telomere length can be used as an indicator to distinguish malignant and benign cells in cytological specimens. This novel approach may help improve diagnosis for cancer patients.

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- **Diagnosis of paraganglioma as a pancreatic mass: A case report**

*Diagnostic cytopathology 2018 Jun;():*

Paragangliomas are rare neoplasms that arise from the chromaffin cells of the autonomic nervous system. Although paragangliomas can occur anywhere paraganglia are present, they tend to occur in the head, neck, and retroperitoneum. Rarely, paragangliomas can occur in the peripancreatic area and present as a pancreatic mass, creating a diagnostic challenge for the clinician, radiologist, and pathologist. Here, we present a case of a 70-year-old woman with history of breast carcinoma who presented with chronic constipation, early satiety, and an abdominal mass. Her first abdominal CT described a 3.6 cm × 5 cm × 4.5 cm cystic and solid mass involving the pancreatic tail that was suspicious for a pancreatic neoplasm. A subsequent abdominal CT described a 5.9 cm multilobulated solid and cystic lesion close to the pancreatic tail. Endoscopic ultrasound-guided fine-needle aspirate of the mass demonstrated scant to moderate cellularity of a heterogeneous population of atypical cells, some with epithelioid morphology and others appearing neuroendocrine-like. By morphology and immunohistochemical stains, an extra-adrenal paraganglioma or pheochromocytoma was considered as a possible diagnosis. The surgical resection specimen confirmed the diagnosis of paraganglioma. This case demonstrates the importance of awareness of paragangliomas in the differential diagnosis of a fine-needle aspiration of a pancreatic mass to avoid erroneous diagnosis.

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- **Endoscopic ultrasound guided brush/fine-needle aspiration cytology: A 15-month study**

*Diagnostic cytopathology 2018 Jun;46(6):461-472*

BACKGROUND: Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) has become increasingly popular for the diagnosis and staging of gastrointestinal diseases and peri-gastrointestinal lesions. The application of FNA/Brush has dramatically expanded the clinical utility of EUS. AIMS AND OBJECTIVE: To evaluate the diagnostic accuracy, study the spectrum of lesions encountered in EUS-FNAC/brush cytology of gastrointestinal and peri-gastrointestinal lesions. MATERIALS AND METHODS: Total of 124 patients during the period from August 2015 to November 2016 was included in the study. Routine staining was done. RESULTS: A total of 124 cases were studied with 86% (107 cases) being satisfactory for evaluation. M:F ratio was 1:1.03, mean age of 50.5 years. The most common site was common bile duct (CBD) (37%) followed by lymph node (21%), pancreas (17.7%), esophagus (17%), stomach (3.5%), liver (1.8%), gallbladder (1%), and spleen (1%). In total, 53.4% lesions were benign, in 6.5% atypical cells were seen, 12.1% were suspicious for malignancy, and 28% cases were positive for malignancy. Follow-up was available in 102 cases with cyto-histopathological concordance rate of 90%. CONCLUSION: EUS-FNA/Brush is a reliable, sensitive, specific and minimally invasive way to establish a diagnosis. It can be utilized as a pre-operative procedure for the management of many intra-abdominal lesions and prevent unnecessary invasive procedures.

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- **Immunohistochemical Staining for S100P, SMAD4, and IMP3 on Cell Block Preparations is Sensitive and Highly Specific for Pancreatic Ductal Adenocarcinoma**

<https://www.sciencedirect.com/science/article/pii/S2213294518301042>

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## Others

### Techniques

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- **The diagnostic and cellularity yield of reverse bevel versus fork-tip fine needle biopsy**

*Diagnostic cytopathology 2018 May;():*

**INTRODUCTION:** Two new systems with a novel tip (Procore™ and SharkCore™) have been introduced for ultrasound-guided fine needle biopsy (US-FNB). Direct comparison of the diagnostic yield of these needles in the evaluation of pancreatic lesions is currently under investigation. This study aims to compare the diagnostic and cellular yields of the two needle systems. **METHODS:** Consecutive patients with upper gastrointestinal lesions undergoing EUS-FNB using 22 gauge Procore™ (reverse bevel) or SharkCore™ (fork-tip) needles were included in the study. Cytological rapid on-site evaluation (ROSE) slides were scored on a numerical scale of diagnostic yield relative to the number of passes. Similarly, histology of biopsy material was assessed on diagnostic quality using a numeric score. The final diagnosis was based on resection specimens and/or follow-up of clinical and imaging data of the subject. **RESULTS:** The diagnostic yield was similar between the fork-tip and reverse bevel needles (125/163; 77% vs 103/139; 74% with  $P = .60$ ). Sub-analysis for solid pancreatic masses demonstrated similar results (69/88; 78% vs. 83/107; 78% with  $P = .88$ ). The fork-tip needle had a lower mean number of passes (2.5 vs 3.1;  $P = .04$ ) and ROSE was utilized in significantly less cases than in the reverse bevel needle group (77% versus 98.3%). **CONCLUSIONS:** Although we observed no difference in the diagnostic yield using either the fork-tip or the reverse bevel needle, the fork-tip needle had significantly better performance with regards to achieving more adequate cytologic specimen in fewer number of passes while at the same time requiring fewer episodes of ROSE.

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- **Comparison of 3 Ways of Dissecting the Pancreatoduodenectomy Specimen and Their Impact in the Lymph Node Count and the Lymph Node Metastatic Ratio**

*International journal of surgical pathology 2018 Jun;():1066896918780343*

**BACKGROUND:** Lymph node metastasis (LNM) is a strong prognostic factor in the cancer of the pancreatobiliary tree, but it is influenced by the number of lymph nodes (LNs). The lymph node ratio (LNR) is considered a more reliable factor than the number of LNM. The aim was to examine the LN retrieval and the LNR of 3 pathologic work-up strategies. **METHODS:** Pancreaticoduodenectomies ( $n = 165$ ) were analyzed comparing 3 pathological dissection techniques, classified as “control,” “Verbeke method,” and “Adsay method” groups. **RESULTS:** The mean of the dissected LNs and the number of cases with  $>20$  LNs were superior in the Adsay method group, compared with the other groups ( $P < .001$ ). The LNR was different between the Adsay and Verbeke groups (0.144 vs 0.069,  $P = .032$ ). The median of the 3 positive LNs was associated with decreased survival compared with an absence of LNM (3-year specific survival of 48% vs 22%,  $P = .011$ ). In the multivariate analysis, LNM (hazard ratio = 6.148, 95% confidence interval = 2.02-8.1,  $P = .042$ ) and the evaluation of  $>15$  LNs (hazard ratio = 12.52, 95% confidence interval = 5.51-21.01,  $P =$

.001) were independent predictors of survival. CONCLUSION: The Adsay technique for LN retrieval was associated with a better LN count, more cases with LNM, and an LNR >0.1.

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doi: <https://doi.org/10.1177/1066896918780343>

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- **Immunolabeling of Cleared Human Pancreata Provides Insights into Three-Dimensional Pancreatic Anatomy and Pathology**

*The American journal of pathology* 2018 Jul;188(7):1530-1535

Visualizing pathologies in three dimensions can provide unique insights into the biology of human diseases. A rapid and easy-to-implement dibenzyl ether-based technique was used to clear thick sections of surgically resected human pancreatic parenchyma. Protocols were applicable to both fresh and formalin-fixed, paraffin-embedded tissue. The penetration of antibodies into dense pancreatic parenchyma was optimized using both gradually increasing antibody concentrations and centrifugal flow. Immunolabeling with antibodies against cytokeratin 19 was visualized using both light sheet and confocal laser scanning microscopy. The technique was applied successfully to 26 sections of pancreas, providing three-dimensional (3D) images of normal pancreatic tissue, pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasms, and infiltrating pancreatic ductal adenocarcinomas. 3D visualization highlighted processes that are hard to conceptualize in two dimensions, such as invasive carcinoma growing into what appeared to be pre-existing pancreatic ducts and within venules, and the tracking of long cords of neoplastic cells parallel to blood vessels. Expanding this technique to formalin-fixed, paraffin-embedded tissue opens pathology archives to 3D visualization of unique biosamples and rare diseases. The application of immunolabeling and clearing to human pancreatic parenchyma provides detailed visualization of normal pancreatic anatomy, and can be used to characterize the 3D architecture of diseases including pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasm, and pancreatic ductal adenocarcinomas.

<https://www.sciencedirect.com/science/article/pii/S0002944018300014>

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29684363>

doi: <https://doi.org/10.1016/j.ajpath.2018.04.002>

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## Animal Studies

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- **Distribution of bile acid receptor TGR5 in the gastrointestinal tract of dogs**

*Histology and histopathology* 2018 Jul;():18025

Takeda-G-protein-receptor-5 (TGR5) is a receptor for bile acids and its expression has been described in a variety of tissues and species. Characterization of TGR5 distribution and function has been investigated in drug discovery for the treatment of metabolic diseases in humans. Because dogs are one of the species used in biomedical research and share some similarities with human gastrointestinal diseases, the objective of this study was to characterize the distribution of TGR5 receptor in the canine species. This study characterizes the distribution of TGR5 receptor in the gastrointestinal tract, liver, gallbladder, and pancreas of 8 dogs. The distribution of TGR5 antigen and mRNA expression was investigated using immunohistochemistry and RNA in situ hybridization, respectively. TGR5 immunolabeling was located in the cell membrane or in the cell membrane and cytoplasm. TGR5 immunolabeling was broadly distributed in macrophages, endothelial cells, ganglion cells, and leiomyocytes throughout all the examined tissues. Epithelial cells from tongue, stomach to rectum, as well as from gallbladder, biliary and pancreatic ducts demonstrated TGR5 immunolabeling. In endocrine cells, TGR5 immunolabeling was observed in intestinal enteroendocrine cells and islets of Langerhans in the pancreas. The hepatocytes had a unique pattern of immunolabeling located on the canalicular surface of the cell membrane. TGR5 mRNA expression was located mainly in the nucleus and the only negative cells throughout all examined tissues were striated muscle from tongue and esophagus, muscularis mucosae, esophageal glands, and hepatic sinusoids. These findings indicate that the bile acid receptor TGR5 is ubiquitously distributed in the canine gastrointestinal tract.

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doi: <https://doi.org/10.14670/HH-18-025>

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- **Pancreatic Effects of a Bruton's Tyrosine Kinase Small-molecule Inhibitor in Rats Are Strain-dependent**

*Toxicologic pathology* 2018 Jun;46(4):460-472

Inhibitors of Bruton's tyrosine kinase (BTK) are under development as potential therapies for various autoimmune diseases. In repeat-dose toxicity studies, small-molecule BTK inhibitors (BTKi) have been reported to cause a constellation of histologic effects at the pancreatic endocrine-exocrine interface in male rats; however, similar findings were not reported in other species. Since the BTKi-induced pancreatic effect is morphologically

similar to well-documented spontaneous changes (predominantly characterized by insular/peri-insular hemorrhage, pigment deposition, chronic inflammation, and fibrosis) that are known to vary by rat strain, we investigated potential strain-dependent differences in the pancreatic effects of a small-molecule BTKi, LY3337641. Following 13 weeks of LY3337641 treatment, Crl:CD(SD) rats were most sensitive, Crl:WI(Han) rats were of intermediate sensitivity, and Hsd:SD rats were least sensitive. These strain differences appear to be related to differences in rate of weight gain across strains and sexes; however, a definitive mechanism was not determined. This study demonstrated that BTKi-induced pancreatic effects were highly dependent on rat strain and correlated with differences in the incidence and severity of the spontaneous background change. When considered with the lack of pancreas effects in nonrat species, these changes in rats are unlikely predictive of similar changes in humans administered a BTK inhibitor.

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doi: <https://doi.org/10.1177/0192623318770163>

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- **Histopathological alterations in mice under sub-acute treatment with *Hintonia latiflora* methanolic stem bark extract**

*Histology and histopathology* 2018 Jun;():18016

The indiscriminate use of herbal products is increasingly growing worldwide; nonetheless consumers are not warned about the potential health risks that these products may cause. *Hintonia latiflora* (Hl) is a tree native to the American continent belonging to the Rubiaceae family and its stem bark is empirically used mainly to treat diabetes and malaria; supplements containing Hl are sold in America and Europe without medical prescription, thus scientific information regarding its toxicity as a consequence of a regular consumption is needed. In the present study, the histopathological effect of 200 and 1000 mg/kg of *Hintonia latiflora* methanolic stem bark extract (HlMeOHe) was evaluated in the small bowel, liver, pancreas, kidneys and brain of CD-1 male mice after oral sub-acute treatment for 28 days. No histopathological alterations were observed in the brain and small bowel of the treated animals; however, mice presented diarrhea from day 2 of treatment with both doses. No histological changes were observed in the tissues collected from the animals treated with 200 mg/kg, except for the liver that depicted periportal hepatitis. Animals treated with the higher dose showed in the liver sections hydropic degeneration, hepatitis and necrosis, kidney sections depicted tubular necrosis and in pancreas sections, hydropic degeneration of the pancreatic islets was observed. In conclusion, HlMeOHe damaged the liver with an oral dose of 200 mg/kg, and at 1000 mg/kg injured the kidneys and pancreas of the CD-1 male mice.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29923593>

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- **Orthotopic and heterotopic murine models of pancreatic cancer and their different responses to FOLFIRINOX chemotherapy**

*Disease models & mechanisms* 2018 Jun;():

**INTRODUCTION:** Syngeneic, immunocompetent allograft tumor models recapitulate important aspects of the tumor microenvironment and have short tumor latency with predictable growth kinetics, making them useful for trialing novel therapeutics. We describe surgical techniques for orthotopic and heterotopic PDAC tumor implantation and characterize phenotypes based on implantation site. **METHODS:** Mice (n=8 per group) were implanted with 104 cells in the pancreas or flank. Hy15549 and Han4.13 cell lines were derived from primary murine PDAC (Ptf1-Cre; LSL-KRAS-G12D; p53 Lox/+) on C57BL/6 and FVB strains, respectively. Single cell suspension and solid tumor implants were compared. Tumors were treated with two intravenous doses of FOLFIRINOX and responses evaluated. **RESULTS:** All mice developed pancreatic tumors within 7 days. Orthotopic tumors grew faster and larger than heterotopic tumors. By 3 weeks, orthotopic mice began losing weight, and showed declines in body condition requiring euthanasia starting at 4 weeks. Single cell injection into the pancreas had near 100% engraftment, but solid tumor implant engraftment was approximately 50% and was associated with growth restriction. Orthotopic tumors were significantly more responsive to IV FOLFIRINOX compared to heterotopic tumors, with greater reductions in size and increased apoptosis. Heterotopic tumors were more desmoplastic and hypovascular. However, drug uptake into tumor tissue was equivalent regardless of tumor location or degree of fibrosis, indicating that microenvironment differences between heterotopic and orthotopic tumors influenced response to therapy. **CONCLUSION:** Orthotopic and heterotopic allograft locations confer unique microenvironments that influence growth kinetics, desmoplastic response, and angiogenesis. Tumor location influences chemosensitivity to FOLFIRINOX and should inform future preclinical trials.

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29903803>

doi: <https://doi.org/10.1242/dmm.034793>

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