

# Pancreatobiliary Pathology Society Journal Watch

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# ***1 PBPath Journal Watch Articles***

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## **Wellcome to the PBPath Journal Watch!**

This bi-monthly journal watch features exciting recently published pancreas and biliary pathology articles that will provide up to date medical knowledge in our field. These articles will be showcased in several convenient categories, including surgical pathology, cytopathology, and molecular pathology among others. The articles in each category are in no particular order. See the list of journals we search regularly [here](#). Previous months' issues may be found in our *archive* and you may see drafts of the upcoming issue [here](#).

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

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

## 1.1 Surgical Pathology

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### 1.1.1 Pancreas

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#### 1.1.1.1 Morphology, Diagnostics, IHC

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##### - Comparison of pathology sampling protocols for pancreatoduodenectomy specimens

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

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31802231>

Pancreatoduodenectomy is one of the most challenging surgical specimens for pathologists. Recently, two different, standardized protocols have been proposed: the axial slicing Leeds protocol (LP) and the bi-valving Adsay protocol (AP). Comparison between standardized and non-standardized protocols (NSP) was performed with emphasis on margin involvement and lymph node yield. Pancreatoduodenectomy cases were retrospectively recruited: 46 sampled with LP, 52 cases with AP and 46 cases with NSP. Clinico-pathologic data and rates of margin/surface involvement were collected and their prognostic influence on survival was assessed. Statistical differences between NSP and AP and LP were seen for nodal yield ( $p = 0.0001$ ), N+ ( $p = 0.0001$ ) and lymph node ratio - LNR ( $p < 0.0008$ ) but not between AP and LP. Differences in R1/R0 status were statistically significant between NSP group (R1-15%) and both the LP (R1-73.9%) and AP (R1-70%) groups ( $p = 0.0001$ ) but not between LP and AP groups. At univariate survival analysis, grade ( $p = 0.0023$ ) and number of involved margins ( $p = 0.0096$ ) in AP and “N-category” ( $p = 0.0057$ ) “resection margin status” ( $p = 0.0094$ ), “stage” ( $p = 0.0143$ ), and “number of involved margins” ( $p = 0.00398$ ) in LP were statistically significant, while no variable was significant in the NSP group. At multivariate analysis “N category,” “resection margin status,” “stage,” “number of involved margins,” and “LNR” retained significance for the LP group. These results show that both LP and AP perform better than non-standardized sampling making standardization mandatory in pancreatoduodenectomy cut up. Both AP and LP show strengths and weaknesses, and these may impact on the choice of protocol in different institutions.

doi: <https://doi.org/10.1007/s00428-019-02687-6>

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##### - Tumor budding as a prognostic factor in pancreatic ductal adenocarcinoma

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

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31786688>

In this retrospective study, we analyzed the association between tumor budding and perineural invasion as well as their prognostic role in pancreatic ductal adenocarcinoma. A total of N = 119 patients resected for pancreatic ductal carcinoma from 1996 to 2015 were included. Clinical and standard histopathological parameters were retrieved from the patient’s records. One representative hematoxylin and eosin section from the tumor region was examined for perineural invasion and tumor budding using light microscopy. Tumor budding was assessed independently using two different methods: in the first approach, the number of buds was counted over three fields of 0.237 mm<sup>2</sup> at 40-fold magnification; in the second approach, tumor budding was quantified according to the recommendation of the International Tumor Budding Consensus Conference (ITBCC) over a field of 0.785 mm<sup>2</sup> at 20-fold magnification. Linear and logistic regression was applied to delineate association between perineural invasion, tumor budding, and other parameters; Kaplan-Meier and Cox regression were used in the survival analysis. Regardless of the quantification approach, high tumor budding was a significant negative prognostic factor in the univariable Cox regression ( $> 5$  buds/0.237 mm<sup>2</sup>, hazard ratio (HR) 1.66, 95% confidence interval (CI) 1.06-2.61,  $p = 0.027$ ;  $10$  buds/0.785 mm<sup>2</sup>, HR 1.68,

95% CI 1.07-2.64,  $p = 0.024$ ). In the multivariable model adjusting for stage and standard histopathological parameters, lymph vessel invasion (HR = 2.43, 95% CI 1.47-4.03,  $p = 0.001$ ) and tumor budding  $> 5$  buds/0.237 mm<sup>2</sup> (HR = 1.70, 95% CI 1.07-2.7,  $p = 0.026$ ) were independent negative prognostic factors, while adjuvant therapy was a positive prognostic factor (HR = 0.54, 95% CI 0.33-0.86,  $p = 0.009$ ). No significant prognostic value could be delineated for perineural invasion. In conclusion, tumor budding is an independent negative prognostic factor in pancreatic ductal adenocarcinoma associated with lymph node metastasis. The prognostic role of perineural invasion remains uncertain.

doi: <https://doi.org/10.1007/s00428-019-02719-1>

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**- DNAJB1-PRKACA fusions occur in oncocytic pancreatic and biliary neoplasms and are not specific for fibrolamellar hepatocellular carcinoma**

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

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31676785>

Recently discovered DNAJB1-PRKACA oncogenic fusions have been considered diagnostic for fibrolamellar hepatocellular carcinoma. In this study, we describe six pancreatobiliary neoplasms with PRKACA fusions, five of which harbor the DNAJB1-PRKACA fusion. All neoplasms were subjected to a hybridization capture-based next-generation sequencing assay (MSK-IMPACT), which enables the identification of sequence mutations, copy number alterations, and selected structural rearrangements involving 410 genes ( $n = 6$ ) and/or to a custom targeted, RNA-based panel (MSK-Fusion) that utilizes Archer Anchored Multiplex PCR technology and next-generation sequencing to detect gene fusions in 62 genes ( $n = 2$ ). Selected neoplasms also underwent FISH analysis, albumin mRNA in-situ hybridization, and arginase-1 immunohistochemical labeling ( $n = 3$ ). Five neoplasms were pancreatic, and one arose in the intrahepatic bile ducts. All revealed at least focal oncocytic morphology: three cases were diagnosed as intraductal oncocytic papillary neoplasms, and three as intraductal papillary mucinous neoplasms with mixed oncocytic and pancreatobiliary or gastric features. Four cases had an invasive carcinoma component composed of oncocytic cells. Five cases revealed DNAJB1-PRKACA fusions and one revealed an ATP1B1-PRKACA fusion. None of the cases tested were positive for albumin or arginase-1. Our data prove that DNAJB1-PRKACA fusion is neither exclusive nor diagnostic for fibrolamellar hepatocellular carcinoma, and caution should be exercised in diagnosing liver tumors with DNAJB1-PRKACA fusions as fibrolamellar hepatocellular carcinoma, particularly if a pancreatic lesion is present. Moreover, considering DNAJB1-PRKACA fusions lead to upregulated protein kinase activity and that this upregulated protein kinase activity has a significant role in tumorigenesis of fibrolamellar hepatocellular carcinoma, protein kinase inhibition could have therapeutic potential in the treatment of these pancreatobiliary neoplasms as well, once a suitable drug is developed.

doi: <https://doi.org/10.1038/s41379-019-0398-2>

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**- Acinar cell carcinoma of the pancreas with thyroid-like follicular features: first description of a new diagnostic challenging subtype**

*Virchows Archiv : an international journal of pathology* 2019 Dec;475(6):789-794

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31338587>

Acinar cell carcinomas (ACCs) of the pancreas are a heterogeneous group of neoplasms showing a wide spectrum of morphological features including acinar, solid, glandular, and trabecular architecture. In addition, uncommon cytological aspects have recently been described and include oncocytic, spindle, clear, and pleomorphic cell types. This wide histological spectrum represents a challenge in the diagnostic task for pathologists. Molecular mechanisms involved in the onset and progression of ACCs are not completely known, but, in general, they differ from those observed in ductal adenocarcinomas or neuroendocrine neoplasms of the pancreas and frequently include alterations in the APC/ -catenin pathway. In the present

paper, we describe a new variant of ACC showing thyroid-like follicular features and CTNNB1 mutation. This phenotype needs to be included in the spectrum of morphological presentation of ACC.

doi: <https://doi.org/10.1007/s00428-019-02628-3>

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### **- Histomorphology of pancreatic cancer in patients with inherited ATM serine/threonine kinase pathogenic variants**

*Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc* 2019 Dec;32(12):1806-1813

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31285527>

Germline pathogenic variants in the ATM serine/threonine kinase (ATM) gene are associated with an increased risk of pancreatic ductal adenocarcinoma. It is important to identify germline ATM pathogenic variants in pancreatic cancer patients because these alterations are potentially targetable with chemotherapeutic drugs and/or radiation and have implications for other family members. As germline pathogenic variants in other genes have been associated with distinct histologic subtypes of pancreatic cancer, we studied the histomorphology of pancreatic cancer in 23 patients with germline ATM pathogenic variants. The histologic subtype was ductal adenocarcinoma in 19/23 (83%) of the patients, adenosquamous carcinoma in 1/23 (4%), and colloid (mucinous non-cystic) carcinoma in 3/23 (13%). The percentage of colloid (mucinous non-cystic) carcinomas is higher than we have previously observed in patients with familial and sporadic pancreatic cancer (1 and 2% in prior reports,  $p < 0.01$  and  $p < 0.01$ , respectively). Three carcinomas (2 colloid carcinomas, 1 ductal adenocarcinoma) arose in association with intraductal papillary mucinous neoplasms. Among the resected pancreata, non-invasive precursor lesions, including pancreatic intraepithelial neoplasia and incipient intraductal papillary mucinous neoplasms, were identified in 83%. We conclude that pancreatic cancers in patients with germline ATM pathogenic variants are more frequently of colloid (mucinous non-cystic) morphology but are overall morphologically diverse supporting the utility of universal germline genetic testing for patients with pancreatic cancer.

doi: <https://doi.org/10.1038/s41379-019-0317-6>

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### **- Immunohistochemical profiling of liver metastases and matched-pair analysis in patients with metastatic pancreatic ductal adenocarcinoma**

*Pancreatology : official journal of the International Association of Pancreatology (IAP) ... [et al.]* 2019 Oct;19(7):963-970

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31542399>

**BACKGROUND:** The purpose of the current study was to investigate the immunohistochemical (IHC) profile of liver metastases (LM) in patients with pancreatic ductal adenocarcinoma (PDAC). **METHODS:** Expression of 15 IHC markers in liver biopsies from 77 patients with PDAC, who were diagnosed between 2010 and 2014, were evaluated. In a separate subgroup analysis ( $n = 12$ ), paired samples (LM and primary tumor) from the same patient were investigated for IHC profile differences. **RESULTS:** LM samples were classified as pancreatobiliary-type (PB-type) in 72 patients (93.5%), intestinal-type (INT-type) in four patients (5.2%), and squamous in one patient (1.3%). There was no significant difference in overall survival (OS) between LM of the PB-type or INT-type ( $p = 0.097$ ). In a multivariate analysis, age  $< 70$  years ( $p = 0.047$ ), absence of SMAD4 mutation ( $p = 0.026$ ), absence of CDX2 expression ( $p = 0.003$ ), and well to moderate differentiation were significant prognostic factors for better OS in patients with LM ( $p = 0.031$ ). Analysis of paired tissue samples from LM and the primary tumor revealed a difference in CDX2 (50% increase,  $p = 0.125$ ) and SMAD4 (33% loss of SMAD4,  $p = 0.375$ ). **CONCLUSIONS:** CDX2 expression and SMAD4 mutation indicate a poor outcome in patients with LM of PDAC. Matched-pair analysis revealed differences in distinct IHC marker expression.

doi: <https://doi.org/10.1016/j.pan.2019.09.005>

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## - Sclerosing epithelioid mesenchymal neoplasm of the pancreas - a proposed new entity

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

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31383964>

We have encountered pancreatic tumors with unique histologic features, which do not conform to any of the known tumors of the pancreas or other anatomical sites. We aimed to define their clinicopathologic features and whether they are characterized by recurrent molecular signatures. Eight cases were identified; studied histologically and by immunohistochemistry. Selected cases were also subjected to whole-exome sequencing (WES; n = 4), RNA-sequencing (n = 6), Archer FusionPlex assay (n = 5), methylation profiling using the Illumina MethylationEPIC (850k) array platform (n = 6), and TERT promoter sequencing (n = 5). Six neoplasms occurred in females. The mean age was 43 years (range: 26-75). Five occurred in the head/neck of the pancreas. All patients were treated surgically; none received neoadjuvant/adjuvant therapy. All patients are free of disease after 53 months of median follow-up (range: 8-94). The tumors were well-circumscribed, and the median size was 1.8 cm (range: 1.3-5.8). Microscopically, the unencapsulated tumors had a geographic pattern of epithelioid cell nests alternating with spindle cell fascicles. Some areas showed dense fibrosis, in which enmeshed tumor cells imparted a slit-like pattern. The predominant epithelioid cells had scant cytoplasm and round-oval nuclei with open chromatin. The spindle cells displayed irregular, hyperchromatic nuclei. Mitoses were rare. No lymph node metastases were identified. All tumors were positive for vimentin, CD99 and cytokeratin (patchy), while negative for markers of solid pseudopapillary neoplasm, neuroendocrine, acinar, myogenic/rhabdoid, vascular, melanocytic, or lymphoid differentiation, gastrointestinal stromal tumor as well as MUC4. Whole-exome sequencing revealed no recurrent somatic mutations or amplifications/homozygous deletions in any known oncogenes or tumor suppressor genes. RNA-sequencing and the Archer FusionPlex assay did not detect any recurrent likely pathogenic gene fusions. Single sample gene set enrichment analysis revealed that these tumors display a likely mesenchymal transcriptomic program. Unsupervised analysis (t-SNE) of their methylation profiles against a set of different mesenchymal neoplasms demonstrated a distinct methylation pattern. Here, we describe pancreatic neoplasms with unique morphologic/immunophenotypic features and a distinct methylation pattern, along with a lack of abnormalities in any of key genetic drivers, supporting that these neoplasms represent a novel entity with an indolent clinical course. Given their mesenchymal transcriptomic features, we propose the designation of “sclerosing epithelioid mesenchymal neoplasm” of the pancreas.

doi: <https://doi.org/10.1038/s41379-019-0334-5>

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### 1.1.1.2 Pancreas TNM staging, Margins, Survival

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#### - Number of Examined Lymph Nodes and Nodal Status Assessment in Distal Pancreatectomy for Body/Tail Ductal Adenocarcinoma

*Annals of surgery* 2019 Dec;270(6):1138-1146

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=29672406>

**OBJECTIVE:** First, to assess the impact of the number of examined lymph nodes (ELNs) on staging and survival after distal pancreatectomy (DP) for pancreatic adenocarcinoma (PDAC). Second, to identify the minimum number of ELNs (MNELNs) ensuring an accurate detection of nodal involvement. Third, to reappraise the role of lymph node (LN) parameters, including N-status and lymph node ratio (LNR). **BACKGROUND:** In contrast with pancreatoduodenectomy, information on LN staging and the MNELN required in DP is lacking. **METHODS:** Patients undergoing DP for PDAC at 2 academic hospitals from 2000 through 2013 were retrospectively analyzed. The eighth edition of the American Joint Committee on Cancer staging system was used. The MNELN was estimated using the binomial probability law. Survival analyses were performed separately for node-negative and node-positive patients using univariable and multivariable models. **RESULTS:** The study population consisted of 240 patients. The median number of ELN was 21, significantly lower in node-negative patients as compared with node-positive patients (18.5 vs 24.0;  $P = 0.001$ ). The proportion of node-positive patients increased with increasing numbers of ELNs, whereas LNR showed an inverse trend. The estimated MNELN was 20. The number of ELN ( $\geq$  or  $<20$ ) was an independent prognostic factor only in node-negative patients [odds ratio (OR) 3.23 for ELN  $<20$ ], suggesting a stage migration effect. In node-positive patients, N2-class, but not LNR, was a significant predictor of survival at multivariable analysis (OR 1.68). **CONCLUSION:** The number of ELN affects nodal staging in body/tail PDAC. At least 20 LNs are required for correct staging. N-status is superior to LNR in predicting survival of node-positive patients.

doi: <https://doi.org/10.1097/SLA.0000000000002781>

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#### - Impact of Changes in the American Joint Committee on Cancer Staging Manual, Eighth Edition, for Pancreatic Ductal Adenocarcinoma

*Pancreas* 2019 08;48(7):876-882

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31268985>

**OBJECTIVE:** Consistent and reliable tumor staging is a critical factor in determining treatment strategy, selection of patients for adjuvant therapy, and for therapeutic clinical trials. The aim of this study was to evaluate the number and extent of pancreatic ductal adenocarcinoma (PDAC) cases that would have a different pT, pN, and overall stages based on the new eighth edition American Joint Committee on Cancer staging system when compared with the seventh edition. **METHODS:** Patients diagnosed with PDAC who underwent pancreaticoduodenectomy, total pancreatectomy, or distal pancreatectomy from 2007 to 2017 were retrospectively reviewed. A total of 340 cases were included. **RESULTS:** According to the seventh edition, the vast majority of tumors in our cohort were staged as pT3 tumors (88.2%). Restaging these cases with the new size-based pT system resulted in a more equal distribution among the 3 pT categories, with higher percentage of pT2 cases (55%). **CONCLUSIONS:** The newly adopted pT stage protocol for PDAC is clinically relevant, ensures a more equal distribution among different stages, and allows for a significant prognostic stratification. In contrast, the new pN classification (pN1 and pN2) based on the number of positive lymph nodes failed to show survival differences and remains controversial.

doi: <https://doi.org/10.1097/MPA.0000000000001349>

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### 1.1.1.3 Preneoplastic and Preinvasive Lesions

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#### - Intraductal Papillary Mucinous Neoplasms: Have IAP Consensus Guidelines Changed our Approach?: Results from a Multi-institutional Study

*Annals of surgery* 2019 Dec;():

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31804389>

**OBJECTIVE:** To evaluate the influence of consensus guidelines on the management of intraductal papillary mucinous neoplasms (IPMN) and the subsequent changes in pathologic outcomes. **BACKGROUND:** Over time, multiple guidelines have been developed to identify high-risk IPMN. We hypothesized that the development and implementation of guidelines should have increased the percentage of resected IPMN with high-risk disease. **METHODS:** Memorial Sloan-Kettering (MSK), Johns Hopkins (JH), and Massachusetts General Hospital (MGH) databases were queried for resected IPMN (2000-2015). Patients were categorized into main-duct (MD-IPMN) versus branch-duct (BD-IPMN). Guideline-specific radiographic/endoscopic features were recorded. High-risk disease was defined as high-grade dysplasia/carcinoma. Fisher's exact test was used to detect differences between institutions. Logistic regression evaluated differences between time-points [preguidelines (pre-GL, before 2006), Sendai (SCG, 2006-2012), Fukuoka (FCG, after 2012)]. **RESULTS:** The study included 1210 patients. The percentage of BD-IPMN with 1 high-risk radiographic feature differed between centers (MSK 69%, JH 60%, MGH 45%;  $P < 0.001$ ). In MD-IPMN cohort, the presence of radiographic features such as solid component and main pancreatic duct diameter 10mm also differed (solid component: MSK 38%, JH 30%, MGH 18%;  $P < 0.001$ ; duct 10mm: MSK 49%, JH 32%, MGH 44%;  $P < 0.001$ ). The percentage of high-risk disease on pathology, however, was similar between institutions (BD-IPMN:  $P = 0.36$ , MD-IPMN:  $P = 0.48$ ). During the study period, the percentage of BD-IPMN resected with 1 high-risk feature increased (52% pre-GL vs 67% FCG;  $P = 0.005$ ), whereas the percentage of high-risk disease decreased (pre-GL vs FCG: 30% vs 20%). For MD-IPMN, there was not a clear trend towards guideline adherence, and the rate of high-risk disease was similar over the time (pre-GL vs FCG: 69% vs 67%;  $P = 0.63$ ). **CONCLUSION:** Surgical management of IPMN based on radiographic criteria is variable between institutions, with similar percentages of high-risk disease. Over the 15-year study period, the rate of BD-IPMN resected with high-risk radiographic features increased; however, the rate of high-risk disease decreased. Better predictors are needed.

doi: <https://doi.org/10.1097/SLA.00000000000003703>

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### 1.1.2 Bile Ducts

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#### 1.1.2.1 Morphology, Diagnostics, IHC

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##### - Utility and limitations of Albumin RNA in situ hybridization in the diagnosis of hepatobiliary lesions and metastatic carcinomas to the liver

*Histopathology* 2019 Dec;():

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31834956>

**BACKGROUND:** Albumin messenger RNA in situ hybridization (RISH) is a sensitive and specific marker for hepatocellular carcinoma (HCCs). Intrahepatic cholangiocarcinoma (ICC) shows variable sensitivity, whereas extrahepatic cholangiocarcinomas (ECCs) and metastatic carcinomas are usually negative. We studied the clinical utility and limitations of albumin RISH in a cohort of HCCs, ICCs, ECCs, bile duct adenomas (BDAs), bile duct hamartomas (BDHs) and metastatic carcinomas to the liver; and investigated the variability in sensitivity observed for this marker in ICCs. **DESIGN:** We identified 122 cases (40 resections and 82 biopsies) of hepatobiliary lesions and metastatic carcinomas. Albumin RISH was performed using the RNAscope (Leica Biosystems, Buffalo Grove, IL), the Bond III autostainer and probe Hs-ALB-01 (ACD, Newark, CA) with negative (DapB) and positive probes (PPIB) for RNA. ICCs were categorized according to the classification proposed by Hayashi et al. in small duct (SD), large duct (LD) and indeterminate (IND) subtypes. **RESULTS:** Albumin RISH was positive in all 17 HCCs, and focally in 75% of BDAs. All 28 non-hepatic carcinomas, 13 BDHs and 9 ECCs were negative. 35/47 (74.4%) ICCs expressed albumin with 35/37 (94.6%) being of SD subtype, 2/3 (66.6%) of the IND subtype and 1/7 (14.2%) of the LD subtype,  $P < 0.003$ . **CONCLUSION:** Albumin RISH performed on resection specimens or on small core biopsies is a sensitive and specific marker for HCCs. It is highly sensitive and moderately specific in the diagnosis of ICC with small gland morphology, but not in ICCs with large duct morphology and in metastatic carcinoma. The variability in sensitivity of albumin RISH in ICCs may depend on the subtypes of ICCs.

doi: <https://doi.org/10.1111/his.14046>

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##### - Tumor Budding in Intrahepatic Cholangiocarcinoma: A Predictor of Postsurgery Outcomes

*The American journal of surgical pathology* 2019 Sep;43(9):1180-1190

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31335353>

Intrahepatic cholangiocarcinoma (ICC) is an extremely aggressive carcinoma. Useful predictors for the patients' prognosis after surgery have not been fully established. From the University of Tokyo Hospital pathology archives, we reviewed 107 cases of ICC, 54 cases of perihilar cholangiocarcinoma, and 40 cases of extrahepatic cholangiocarcinoma (ECC); we also investigated the significance of tumor budding in ICC, in comparison with perihilar cholangiocarcinoma and ECC. The tumor-budding frequencies were different by tumor location: 40.2% (43/107) in ICC, 70.4% (38/54) in perihilar cholangiocarcinoma, and 60.0% (24/40) in ECC. Tumor budding in ICC was associated with many pathologic indicators associated with invasion, such as major vascular invasion ( $P = 0.012$ ) and Union for International Cancer Control stage ( $P = 0.007$ ). Univariate and multivariate Cox regression analyses revealed tumor budding as a powerful prognostic factor for both recurrence-free survival (RFS) and overall survival (OS) in ICC by univariate (RFS: hazard ratio [HR]: 2.666; 95% confidence interval [CI]: 1.517-4.683, OS: HR: 4.206; 95% CI: 2.447-7.230) and by multivariate analyses (RFS: HR: 3.038; 95% CI: 1.591-5.973, OS: HR: 4.547, 95% CI: 2.348-8.805). Tumor budding was also a significant prognostic factor of perihilar cholangiocarcinoma, but not of ECC. When ICC was divided into 2 subtypes, type 1 (hilar) and type 2 (peripheral), tumor budding was the strong prognostic factor in type 2 ICC, but not in type 1 ICC, suggesting that some differences in biological behavior exist between type 1 ICC and perihilar cholangiocarcinoma. Tumor budding is prognostically important in ICC, and its pathogenetic role in biliary tract carcinomas might be different by anatomic location.

doi: <https://doi.org/10.1097/PAS.0000000000001332>

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### **- The Pathologic and Genetic Characteristics of the Intestinal Subtype of Intraductal Papillary Neoplasms of the Bile Duct**

*The American journal of surgical pathology* 2019 Sep;43(9):1212-1220

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31166202>

The present study aimed to identify the pathologic and genetic characteristics of intestinal subtype of intra-ductal papillary neoplasm of the bile duct (iIPNB) showing columnar cells with pseudostratified, cigar-shaped nuclei, and basophilic or amphophilic cytoplasm with the diffuse immunohistochemical expression of CK20 and/or CDX2. A total of 34 cases of iIPNB were pathologically examined according to their anatomic location (the bile duct) and were then compared with the intestinal subtype of intraductal papillary mucinous neoplasm (iIPMN) of the pancreas (n=22). Mutations of 26 somatic genes were examined in formalin-fixed paraffin-embedded tissue specimens from 21 cases of iIPNB using the TruSight Tumor 26 gene panel and next-generation sequencing. iIPNB cases were divided into intrahepatic (n=6) and extrahepatic (n=28) categories. Intrahepatic IPNBs showed a less-complicated villous-papillary pattern, while extrahepatic IPNBs showed a papillary pattern with tubular and/or villous components and predominant high-grade dysplasia with complicated architectures. MUC5AC was frequently and extensively expressed in intrahepatic iIPNBs and iIPMNs but not in extrahepatic iIPNBs. CD10 was frequently expressed in extrahepatic IPNBs but not in intrahepatic iIPNBs or iIPMN. Genetic mutations of TP53 and PIK3CA, which were infrequent or absent in iIPMNs, were frequently detected in extrahepatic iIPNBs, while KRAS and GNAS, which were commonly observed in iIPMNs, were frequently detected in intrahepatic iIPNBs. Intrahepatic iIPNBs showed villous-papillary growth with features reminiscent of iIPMNs, while extrahepatic iIPNBs showed papillary growth with tubular and/or villous components, complicated histology and variable differences from iIPMNs, suggesting differences in the tumorigenesis of iIPNBs along the biliary tree.

doi: <https://doi.org/10.1097/PAS.0000000000001295>

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### **- Programmed cell death ligand-1 (PD-L1) expression in extrahepatic biliary tract cancers: a comparative study using 22C3, SP263 and E1L3N anti-PD-L1 antibodies**

*Histopathology* 2019 Oct;75(4):526-536

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31081949>

AIMS: Pembrolizumab has shown promising results for patients with programmed cell death ligand-1 (PD-L1)-positive advanced biliary tract cancer in an ongoing clinical trial. However, data on PD-L1 expression in bile duct cancers is limited, and the frequency of PD-L1 positivity varies, which may be partly due to the assay used. The aim of this study was to evaluate PD-L1 expression status in bile duct cancers by using 22C3, SP263 and E1L3N antibodies. METHODS AND RESULTS: We evaluated PD-L1 expression in tissue microarrays of 183 extrahepatic bile duct cancers, including 89 perihilar and 94 distal bile duct cancers, by using 22C3, SP263 and E1L3N. When the 22C3 assay was used, tumoral PD-L1 was shown to be expressed in 16.9% of cases at a 1% threshold. When the SP263 and E1L3N assays were used, tumoral PD-L1 was shown to be expressed in 26% and 7.1% of cases, respectively. When whole tissue sections were examined, 59.6% of PD-L1-positive cases showed a low percentage (<10%) of positive tumour cells. Tumoral PD-L1 positivity was associated with poor histological differentiation (P = 0.017) and the biliary epithelial phenotype (P = 0.041). High tumoral PD-L1 expression (10%) was associated with worse overall survival (OS) and disease-free survival (DFS) (OS, P = 0.012; DFS, P = 0.042). CONCLUSIONS: PD-L1 was expressed in a small subset of patients with bile duct cancer, and the percentage of positive tumour cells was low in PD-L1-positive cases. The SP263 assay showed the highest PD-L1 positivity in both tumour cells and immune cells, followed by the 22C3 and E1L3N assays. High PD-L1 expression was associated with a poor prognosis in extrahepatic bile duct cancer patients.

doi: <https://doi.org/10.1111/his.13901>

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### 1.1.2.2 Bile Ducts TNM staging, Margins, Survival

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#### - Clinicopathologic and Prognostic Significance of Gallbladder and Cystic Duct Invasion in Distal Bile Duct Carcinoma

*Archives of pathology & laboratory medicine* 2019 Nov;():

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31755778>

CONTEXT.—: The roles of the gallbladder and cystic duct (CD) invasions in distal bile duct carcinoma (DBDC) have not been well elucidated. OBJECTIVE.—: To define the characteristics and prognostic significance of gallbladder or CD invasions in patients with DBDC. DESIGN.—: Organ invasion patterns with clinicopathologic features were assessed in 258 resected DBDCs. RESULTS.—: CD invasions (N = 31) were associated with frequent concomitant pancreatic and/or duodenal invasions (23 of 31, 74%) and showed stromal infiltration (16 of 31, 52%) and intraductal cancerization (15 of 31, 48%) patterns. In only 2 cases, invasions with intraductal cancerization were observed in the gallbladder neck. Conversely, all pancreatic (N = 175) and duodenal (83) invasions developed through stromal infiltration. CD invasions were associated with larger tumor size (P = .001), bile duct margin positivity (P = .001), perineural invasions (P = .04), and higher N categories (P = .007). Patients with pancreatic or duodenal invasions had significantly lower survival rates than those without pancreatic (median, 31.0 versus 93.9 months) or duodenal (27.5 versus 56.8 months, P < .001, both) invasions. However, those with gallbladder or CD invasions did not have different survival times (P = .13). Patients with concomitant gallbladder/CD and pancreatic/duodenal invasions demonstrated significantly lower survival rates than those without organ invasions (P < .001). CONCLUSIONS.—: Gallbladder invasions were rare in DBDCs as neck invasions with intraductal cancerization. CD invasions occurred by stromal infiltrations and intraductal cancerization, whereas all pancreatic and duodenal invasions had stromal infiltration patterns. Gallbladder and/or CD invasions did not affect survival rates of patients with DBDC, while pancreatic and duodenal invasions affected survival rates. Therefore, these differences in survival rates may originate from the different invasive patterns of DBDCs.

doi: <https://doi.org/10.5858/arpa.2019-0218-OA>

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### 1.1.3 Gallbladder

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#### 1.1.3.1 Morphology, Diagnostics, IHC

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##### - Non-neoplastic Polyps of the Gallbladder: A Clinicopathologic Analysis of 447 Cases

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

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31725469>

There is no systematic histopathologic analysis of non-neoplastic polyps in the gallbladder. In this study, in addition to a computer search for cases designated as “polyp,” a systematic review of 2533 consecutive routinely sampled archival and 203 totally submitted prospective cholecystectomies were analyzed for >2 mm polyps (cut-off was based on radiologic sensitivity). A total of 447 non-neoplastic polyps were identified. The frequency was 3% in archival cases and 5% in totally submitted cases. Only 21 (5%) were 1 cm. The average age was 52 years, and the female to male ratio was 3.1. Two distinct categories were delineated: (1) injury-related polyps (n=273): (a) Fibro(myo)glandular polyps (n=214) were small (mean=0.4 cm), broad-based, often multiple (45%), almost always (98%) gallstone-associated, and were composed of a mixture of (myo)fibroblastic tissue/lobular glandular units with chronic cholecystitis. Dysplasia seen in 9% seemed to be secondary involvement. (b) Metaplastic pyloric glands forming polypoid collections (n=42). (c) Inflammatory-type polyps associated with acute/subacute injury (11 granulation tissue, 3 xanthogranulomatous, 3 lymphoid). (2) Cholesterol polyps (n=174) occurred in uninjured gallbladders, revealing a very thin stalk, edematous cores devoid of glands but with cholesterol-laden macrophages in 85%, and cholesterolosis in the uninvolved mucosa in 60%. Focal low-grade dysplasia was seen in 3%, always confined to the polyp, unaccompanied by carcinoma. In conclusion, non-neoplastic polyps are seen in 3% of cholecystectomies and are often small. Injury-related fibromyoglandular polyps are the most common. Cholesterol polyps have distinctive cauliflower architecture, often in a background of uninjured gallbladders with cholesterolosis and may lack the cholesterol-laden macrophages in the polyp itself. Although dysplastic changes can involve non-neoplastic polyps, they do not seem to be the cause of invasive carcinoma by themselves.

doi: <https://doi.org/10.1097/PAS.0000000000001405>

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##### - HER2 gene (ERBB2) amplification is a low-frequency driver with potential predictive value in gallbladder carcinoma

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

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31838585>

Gallbladder carcinoma (GBC) is an aggressive type of cancer with a dismal prognosis. Recent case reports have highlighted the human epidermal growth factor receptor 2 (HER2) as a promising target for individualized therapy in biliary tract cancer; however, current data on HER2 positivity in GBC is contradictory. This study aimed to assess the proportion of HER2 positivity and its clinical implications in a large and well-characterized European GBC cohort. HER2 status was determined in 186 cases of surgically resected gallbladder adenocarcinoma and a subset of coexistent high-grade biliary intraepithelial neoplasia (BilIN, n = 74) in accordance with the up-to-date consensus for HER2 testing in gastric cancer by immunohistochemistry and dual-color chromogenic in situ hybridization. Positivity for HER2 was observed in 5.4% of all cases (n = 10). In those patients with concomitant high-grade BilIN, two of four positive samples also showed amplification in the precursor lesion, while in the two remaining cases, positivity was either confined to invasive tumor or high-grade BilIN, exclusively. Equivocal staining found in eleven cases was not accompanied by gene amplification. Staging of the HER2-positive group was significantly different from the HER2-negative group with most cases presenting at stage IV, paralleled by a trend towards decreased survival. One patient who received dual HER2 inhibition almost went into full clinical remission despite treatment initiation in a

metastasized state. Our results reveal a low prevalence of HER2 positivity and highlight HER2 gene amplification as an early, potentially driving event in gallbladder carcinogenesis. Prospective standardized HER2 testing and randomized control studies are needed to prove clinical efficacy of targeted HER2 inhibition in GBC.

doi: <https://doi.org/10.1007/s00428-019-02706-6>

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### **- Ultrastructural Characteristics of Gallbladder Epithelial Inclusions Mimicking Cystoisospora**

*American journal of clinical pathology 2020 Jan;153(1):88-93*

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31600399>

**OBJECTIVES:** There is recently reported increased prevalence of Isospora organisms in cholecystectomy specimens from immunocompetent patients, especially in acalculous cholecystectomies. We performed an ultrastructural and molecular evaluation of these specimens. **METHODS:** From 28 gallbladders with intraepithelial inclusions, two specimens with diffuse involvement of the gallbladder epithelium were analyzed by electron microscopy. Polymerase chain reaction was performed on five samples for the ITS2 region of *C. belli* and eukaryotic 18S region. The 18S products were sequenced by next-generation sequencing. **RESULTS:** Electron microscopic analysis showed cytoplasmic condensations leading to vacuole formation. In contrast with true *C. belli*, there were no identifiable organelles or organization. None of these cases showed amplified products other than human on molecular analysis. **CONCLUSIONS:** Electron microscopic analysis demonstrates that the inclusions are condensed cytoplasmic material and not true organisms.

doi: <https://doi.org/10.1093/ajcp/aqz137>

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

*Annals of surgical oncology 2019 Oct;26(11):3577-3585*

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

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

doi: <https://doi.org/10.1245/s10434-019-07440-6>

### **- Cytoplasmic Fibrillar Aggregates in Gallbladder Epithelium Are a Frequent Mimic of Cystoisospora in Pediatric Cholecystectomy Specimens**

*Archives of pathology & laboratory medicine* 2019 Oct;143(10):1259-1264

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=30969156>

CONTEXT.—: *Cystoisospora belli* is an intracellular parasite associated with gastrointestinal disease in immunocompromised hosts. Although infection has been classically associated with intestinal disease, studies have identified *Cystoisospora* in the gallbladder of immunocompetent patients based on hematoxylin-eosin morphology. Recently, the identity of this histologic finding as *Cystoisospora* has been questioned based on negative results of nucleic acid studies. OBJECTIVE.—: To determine the prevalence of this histologic feature in pediatric patients, we retrospectively reviewed all cholecystectomy specimens from a pediatric hospital during a 24-month period. DESIGN.—: In 180 cholecystectomy specimens, we identified 11 cases (6.1%) with classical histologic features previously described to represent *Cystoisospora* organisms. To further investigate these structures, we retrieved tissue from paraffin-embedded blocks and performed electron microscopy. RESULTS.—: Ultrastructural examination identified ovoid perinuclear cytoplasmic structures composed of dense fibrillar aggregates rather than organisms. Patients with positive cases were similar in age to controls (positive cases: mean patient age 13.4 years [range, 2-23 years]; negative cases: mean patient age 14.7 years [range, 12 weeks-31 years];  $P = .35$ ). There was no significant association of this finding with cholelithiasis (54.5% versus 65.1%,  $P = .52$ ), cholesterosis (0% versus 22.5%,  $P = .12$ ), acute cholecystitis (9.1% versus 10.1%,  $P > .99$ ), or chronic cholecystitis (45.5% versus 66.3%,  $P = .20$ ). CONCLUSIONS.—: To our knowledge, this is the first positive identification of these structures as cytoplasmic fibrillar aggregates rather than parasitic inclusions by ultrastructural examination, and the first study of this histologic finding in pediatric cholecystectomies.

doi: <https://doi.org/10.5858/arpa.2018-0335-OA>

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### **- IL-33 overexpression in gallbladder cancers associated with pancreatobiliary maljunction**

*Histopathology* 2019 Sep;75(3):365-375

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=30882917>

AIMS: To investigate whether genetic or inflammatory pro-oncogenic factors are relevant to the increased risk of gallbladder cancers in patients with pancreatobiliary maljunction (PBM). METHODS AND RESULTS: Mutations in KRAS exon 2 were examined by a highly sensitive, droplet digital PCR platform using surgically resected specimens of PBM-associated ( $n = 31$ ) and non-associated gallbladder cancers ( $n = 49$ ). The tissue expression of IL-6 and IL-33, which are suspected to promote biliary carcinogenesis, was analysed by quantitative real-time PCR and in-situ hybridisation. The incidence of KRAS mutations was similarly low in PBM-associated (five of 32 cases; 16%) and non-associated cancers (four of 49 cases; 8%) ( $P = 0.272$ ). The tissue expression of IL-33 mRNA, but not IL-6 mRNA, was significantly higher in PBM-associated gallbladder cancers than in gallbladder cancers without PBM ( $P = 0.004$ ). A similar degree of IL-33 overexpression was also observed in the background non-cancerous mucosa in cases of PBM-associated gallbladder cancers, and was significantly greater than that in PBM cases with cholecystitis alone ( $P < 0.001$ ). The results of in-situ hybridisation indicated that the source of IL-33 production in PBM-associated carcinomas was the endothelium, cancer cells and non-neoplastic biliary epithelium. In a combined PBM-associated and non-associated cohort, IL-33 overexpression in gallbladder cancers correlated with less aggressive features (e.g. a lower pT stage and longer overall survival), similar to recently reported findings on large-duct cholangiocarcinomas. CONCLUSIONS: KRAS mutations do not appear to be associated with a high risk of malignancy in PBM, while IL-33 overexpression may provide a pro-oncogenic microenvironment in the gallbladder mucosa of patients with PBM.

doi: <https://doi.org/10.1111/his.13863>

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### 1.1.4 Ampulla of Vater

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#### 1.1.4.1 Morphology, Diagnostics, IHC

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##### - Mutational profiling and immunohistochemical analysis of a surgical series of ampullary carcinomas

*Journal of clinical pathology* 2019 Nov;72(11):762-770

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31256008>

AIMS: Knowledge regarding the genetic features of ampullary carcinoma (AC) in European patients is limited. The utility of tumour markers for the establishment of a malignant diagnosis in biopsies from the ampullary region has not been fully elucidated. We aimed to describe the clinical, pathological, immunohistochemical (IHC) and genetic features of a Danish series of surgically resected ACs. METHODS: Surgically resected ACs (n=59) were examined regarding (1) clinicopathological features, (2) histological subtypes, (3) expression of IMP3, maspin, MUC5AC and S100P and (4) next-generation sequencing using a hybrid capture-based platform (Illumina HiSeq2500), including 315 cancer-related genes plus introns from 28 genes often rearranged or altered in cancer. Tumour mutational burden (TMB) and microsatellite instability (MSI) were also evaluated. RESULTS: Pancreatobiliary adenocarcinomas (PB-AC), intestinal adenocarcinomas (INT-AC), other ampullary tumours and mixed adenocarcinomas represented 45.8%, 23.7%, 16.9% and 13.6%. The proportion of IHC-positive ACs (score 2) was: Maspin (94.9%), IMP3 (67.8%), S100P (39.0%) and MUC5AC (18.6%). Most frequently altered genes were TP53 (59.3%), KRAS (40.7%), APC (27.8%), SMAD4 (20.4%), CDKN2A (16.7%) and ARID2/PIK3CA (each 11.1%). MUC5AC and S100P were frequently expressed in PB-AC, APC alterations frequent in INT-AC, SOX9 alterations were exclusive in INT-AC and MDM2 and FRS2 alterations in PB-AC. Four of 49 ACs (8.2%) were TMB-high/MSI-high and showed loss of MLH1 and PMS2. CONCLUSIONS: PB-AC was the most frequent histological subtype of AC. Maspin and IMP3 were the IHC tumour markers with the highest sensitivity. Adenocarcinoma subtypes differed regarding several genetic alterations, whose predictive value remains to be evaluated.

doi: <https://doi.org/10.1136/jclinpath-2019-205912>

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##### - Poorly Cohesive (Signet Ring Cell) Carcinoma of the Ampulla of Vater

*International journal of surgical pathology* 2019 Oct;():1066896919880968

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31612756>

In the ampulla of Vater, carcinomas with “diffuse-infiltrative”/“signet ring cell” morphology, designated as “poorly cohesive carcinoma” (PCC) in the WHO classification, are very rare and poorly characterized. Nine cases with a classical PCC morphology constituting >50% of the tumor were identified. Mean age was 64.8 years (vs 64.6 in ampullary carcinomas [ACs]) and 6 were males, 3 females. The mean invasive tumor size was 2.5 cm (vs 1.9 in ACs). Other morphologic patterns displayed included cord-like infiltration (n=2), plasmacytoid cells (n=2), and microglandular component (n=4), including goblet cell adenocarcinoma-like foci. None of the cases were associated with dysplasia. By immunohistochemistry, the carcinomas did not show intestinal differentiation (CDX2 0/9, CK20 1/9, MUC2 3/9), MUC1 was positive in 4/9, MUC5AC was positive in 7/8. E-cadherin loss was noted in 4/9. All cases were advanced stage (6/9-pT3, 3/9-pT4) (vs 43% in ACs). Lymph node metastases were identified in 44% (vs 45% in AC). Six patients (67%) died of disease at a median of 25 months, 3 were alive at 13, 15, and 60 months. Overall median survival was significantly worse than that of intestinal-type ACs (26 vs 122 months, P = .006) and trended toward worse than pancreatobiliary type (26 vs 42 months, P = .1). In conclusion, PCCs constitute 2.45% of all ACs. These present as advanced tumors and express upper-gastrointestinal immunoprofile with frequent MUC5AC labeling, which may be helpful in identifying subtle infiltration in the surface mucosa since MUC5AC is not expressed in the ampullary mucosa. Patients have poor prognosis.

doi: <https://doi.org/10.1177/1066896919880968>

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### 1.1.5 Neuroendocrine

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#### 1.1.5.1 PanNET

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#### - Immunohistochemically Detected Expression of ATRX, TSC2, and PTEN Predicts Clinical Outcomes in Patients With Grade 1 and 2 Pancreatic Neuroendocrine Tumors

*Annals of surgery* 2019 Oct;():

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31599805>

**OBJECTIVE:** The goal of this retrospective study was to clarify the clinical implications of immunohistochemically detected protein expression for genes that are frequently mutated in pancreatic neuroendocrine tumors (PNETs). **BACKGROUND:** The clinical management of PNETs is hindered by their heterogeneous biological behavior. Whole-exome sequencing recently showed that 5 genes (DAXX/ATRX, MEN1, TSC2, and PTEN) are frequently mutated in PNETs. However, the clinical implications of the associated alterations in protein expression remain unclear. **METHODS:** We collected Grade 1 and 2 (World Health Organization 2017 Classification) primary PNETs samples from 100 patients who underwent surgical resection. ATRX, DAXX, MEN1, TSC2, and PTEN expression were determined immunohistochemically to clarify their relationships with prognosis and clinicopathological findings. **RESULTS:** Kaplan-Meier analysis indicated that loss of TSC2 (n = 58) or PTEN (n = 37) was associated with significantly shorter overall survival, and that loss of TSC2 or ATRX (n = 41) was associated with significantly shorter recurrence-free survival. Additionally, loss of ATRX or TSC2 was significantly associated with nodal metastasis. In a multivariate analysis, combined loss of TSC2 and ATRX (n = 31) was an independent prognostic factor for shorter recurrence-free survival (hazard ratio 10.1, 95% confidence interval 2.1-66.9, P = 0.003) in G2 PNETs. **CONCLUSIONS:** Loss of ATRX, TSC2, and PTEN expression might be useful as a method of clarifying the behavior and clinical outcomes of Grade 1 and 2 PNETs in routine clinical practice. Combined loss of TSC2 and ATRX had an especially strong, independent association with shorter recurrence-free survival in patients with G2 PNETs. Loss of pairs in ATRX, TSC2, or PTEN would be useful for selecting the candidate for postoperative adjuvant therapy.

doi: <https://doi.org/10.1097/SLA.0000000000003624>

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### 1.1.5.2 Staging

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#### - Trends in the Number of Lymph Nodes Evaluated Among Patients with Pancreatic Neuroendocrine Tumors in the United States: A Multi-Institutional and National Database Analysis

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

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31838609>

**BACKGROUND:** The role of routine lymphadenectomy in the surgical treatment of pancreatic neuroendocrine tumors (pNET) remains poorly defined. The objective of the current study was to investigate trends in the number of lymph nodes (LN) evaluated for pNET treatment at a nationwide level. **METHODS:** Patients undergoing surgery for pNET between 2000 and 2016 were identified in the U.S. Neuroendocrine Tumor Study Group (US-NETSG) database as well as the Surveillance, Epidemiology, and End Results (SEER) database. The number of LNs examined was evaluated over time. **RESULTS:** The median number of evaluated LNs increased roughly fourfold over the study period (US-NETSG, 2000: 3 LNs vs. 2016: 13 LNs; SEER, 2000: 3 LNs vs. 2016: 11 LNs, both  $p < 0.001$ ). While no difference in 5-year OS and RFS was noted among patients who had 1-3 lymph node metastases (LNM) vs. 4 LNM between 2000-2007 (OS 73.5% vs. 69.9%,  $p = 0.12$ ; RFS: 64.9% vs. 40.1%,  $p = 0.39$ ), patients who underwent resection and LN evaluation during the period 2008-2016 had an incrementally worse survival if the patient had node negative disease, 1-3 LNM and 4 LNM (OS 86.8% vs. 82.7% vs. 74.9%,  $p < 0.001$ ; RFS: 86.3% vs. 64.7% vs. 50.4%,  $p < 0.001$ ). On multivariable analysis, a more recent year of diagnosis, pancreatic head tumor location, and tumor size  $> 2$  cm were associated with 12 or more LNs evaluated in both US-NETSG and SEER databases. **CONCLUSION:** The number of LNs examined nearly quadrupled over the last decade. The increased number of LNs examined suggested a growing adoption of the AJCC staging manual recommendations regarding LN evaluation in the treatment of pNET.

doi: <https://doi.org/10.1245/s10434-019-08120-1>

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## 1.2 Cytopathology

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### 1.2.1 Pancreas

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#### - Assessment of preoperative pancreatic biopsy, cytological/histological review of cell-block-specimens obtained by endoscopic ultrasound-guided fine-needle aspiration: Laboratory-based study

*Diagnostic cytopathology 2019 Dec;():*

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31825182>

**BACKGROUND:** Pancreatic cancer is among the most lethal cancers worldwide due to the limited availability of techniques for early detection of signs and symptoms. Reportedly, it is the fourth-leading cause of cancer-related mortality among Japanese adults. With the advent of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) for diagnosing pancreatic cancer, the rate of the cytological and histological diagnoses of cell-block-specimens has significantly increased in Japan. **METHODS:** The cytological specimens of 165 patients with pancreatic lesions obtained using EUS-FNA between January 2010 and July 2016 at the Kyorin University Hospital were investigated. The clinical course of 153 patients was assessed from their clinical records, which included information on their imaging diagnosis, laboratory data, final clinical diagnosis and treatment; moreover, the accuracy of the cytological/histological examination and clinical diagnosis at our hospital were analysed. **RESULTS:** The number of cells in cell-block-specimens was too small to estimate data. However, cytological specimens were sufficient to observe the findings of suspected malignancy such as necrosis. Biopsy was deemed necessary for diagnosis using both histological and cytological specimens. **CONCLUSION:** EUS-FNA can be used not only to diagnose benign or malignant types of pancreatic cancers but also to assess the sensitivity of molecular target drugs and chemotherapy methods. Therefore, both histological and cytological diagnoses are required to enhance diagnostic precision both in our hospital and at other institutions.

doi: <https://doi.org/10.1002/dc.24358>

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#### - EUS-FNA diagnosis of pancreatic serous cystadenoma with the aid of cell blocks and -inhibin immunochemistry: A case series

*Diagnostic cytopathology 2019 Nov;():*

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31785091>

Serous cystadenoma (SCA) is an uncommon benign pancreatic neoplasm that is most often managed conservatively with follow-up rather than surgical excision. Therefore, to avoid the serious complications of pancreatic surgery, SCA should be diagnosed accurately at the preoperative level. Preoperative SCA diagnosis requires a multimodal diagnostic approach that includes imaging, cystic fluid biochemical analysis and/or endoscopic ultrasound fine-needle aspiration (EUS-FNA). In this brief report, we describe six EUS-FNA cases from five patients that were reported as “benign, consistent with serous cystadenoma”. Samples were hypocellular, composed of loose clusters and single cuboidal, bland-looking cells among epithelial sheets representing gastrointestinal contamination. Cell blocks were prepared and all six FNA cases revealed cuboidal cells with a positive -inhibin immunophenotype, consistent with a diagnosis of SCA. As EUS-FNAs of SCA commonly result in non-diagnostic interpretations, cell block preparations with subsequent immunochemistry can increase their diagnostic accuracy and guide patient management.

doi: <https://doi.org/10.1002/dc.24348>

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**- Dissecting the presence of malignant squamous cells in pancreatic cytopathology: A case series**

*Diagnostic cytopathology* 2019 Dec;47(12):1287-1292

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31407529>

The presence of malignant squamous cells in pancreatic cytopathology is a rare phenomenon that results either from a primary or a metastatic process. Pancreatic adenosquamous carcinoma (PASC) represents the most common variant of pancreatic ductal adenocarcinoma and is associated with a dismal prognosis. Within the period of 2013-2018, the archives of “Hygeia and Mitera Hospital” were searched for pancreatic cytopathology-related diagnoses that included the interpretation of “malignant squamous cells present.” All fine needle aspirations (FNAs) of pancreatic lesions, including liver metastases in patients with known pancreatic primaries, were retrieved along with their relevant clinical information. Five pancreatic and two liver FNAs acquired from a total of six patients were reexamined. None of these patients had any documented history of primary squamous malignancy elsewhere. All pancreatic and one of the two liver FNAs showed malignant squamous cells, identified based on either morphology or immunochemistry. The other liver FNA represented a metastatic deposit which comprised of only a glandular component, whereas the associated pancreatic FNA exhibited both squamous and glandular counterparts. Most cases characteristically showed necrosis and keratinization. Of interest, two cases revealed the presence of tumor-associated giant cells. In conclusion, the presence of malignant squamous cells in pancreatic FNAs could mean the presence of PASC, especially when there is no documented history of a primary malignancy and a complete clinical and imaging workup has been performed. Immunochemistry on cell block material could help to confirm squamous differentiation in the absence of overt keratinization.

doi: <https://doi.org/10.1002/dc.24302>

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**- Pancreatoblastoma: Cytologic and histologic analysis of 12 adult cases reveals helpful criteria in their diagnosis and distinction from common mimics**

*Cancer cytopathology* 2019 Nov;127(11):708-719

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31581358>

**BACKGROUND:** Pancreatoblastoma (PBL) is a rare malignant pancreatic tumor seen predominantly in childhood, and its cytologic diagnosis remains challenging. **METHODS:** Twelve fine-needle-aspirations from 11 adults were analyzed. **RESULTS:** In total, 6 men and 5 women (median age, 45 years; age range, 32-60 years) had tumors measuring a median 5.6 cm (range, 2.5-12 cm) located in the pancreatic head (n = 7) or tail (n = 4), including 3 with familial adenomatous polyposis (FAP)/FAP-related syndromes and 4 with metastasis at diagnosis. The median follow-up was 39.8 months (range, 0.8-348 months), and 5 patients died of disease. The original cytology diagnoses were: PBL (n = 2), neuroendocrine neoplasm (n = 2), poorly differentiated neuroendocrine carcinoma (n = 2), well differentiated neuroendocrine tumor (n = 1), poorly differentiated carcinoma (n = 2), “positive for malignancy” (n = 1), acinar cell carcinoma (n = 1), and epithelioid neoplasm with endocrine and acinar differentiation versus PBL (n = 1). Universal cytopathologic findings included hypercellularity; 3-dimensional clusters; and single, monotonous, blast-like cells that were from 1.5 to 2.0 times the size of red blood cells with high nuclear-to-cytoplasmic ratio, fine chromatin, small, distinct nucleoli, and a resemblance to well differentiated neuroendocrine tumor and poorly differentiated neuroendocrine carcinoma. Branching pseudopapillae (n = 7) and grooved nuclei (n = 3) raised the differential diagnosis of solid-pseudopapillary neoplasm, but with more atypia. Uncommon features included pleomorphism (n = 4) and numerous mitoses (n = 1). Squamoid morules were seen on smears (n = 5) or cell blocks (n = 6) in 70% of patients and were characterized by epithelioid cells with elongated, streaming nuclei, fine chromatin, absent nucleoli, and positive nuclear  $\beta$ -catenin (n = 6 of 8). The median Ki-67 index was 21% (range, 2%-70%), and neuroendocrine marker expression was common (100%), but acinar markers were variable (63%). **CONCLUSIONS:** A combination of cytologic findings in PBL, including a predominant population of primitive blast-like cells, subtle squamoid morules, frequent neuroendocrine and variable acinar phenotype, should facilitate accurate cytologic diagnosis and distinction from common mimics.

doi: <https://doi.org/10.1002/cncy.22187>

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## 1.3 Molecular Pathology

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### 1.3.1 Pancreas

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#### - The Proteomic Landscape of Pancreatic Ductal Adenocarcinoma Liver Metastases Identifies Molecular Subtypes and Associations with Clinical Response

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

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31848187>

**PURPOSE:** Pancreatic ductal adenocarcinoma (PDAC) is a highly metastatic disease that can be separated into distinct subtypes based on molecular signatures. Identifying PDAC subtype-specific therapeutic vulnerabilities is necessary to develop precision medicine approaches to treat PDAC. **EXPERIMENTAL DESIGN:** 56 PDAC liver metastases were obtained from the UNMC Rapid Autopsy Program and analyzed with quantitative proteomics. PDAC subtypes were identified by Principal Component Analysis based on protein expression profiling. Proteomic subtypes were further characterized by the associated clinical information, including but not limited to survival analysis, drug treatment response, smoking and drinking status. **RESULTS:** Over 3960 proteins were identified and used to delineated 4 distinct PDAC microenvironment subtypes: (1) Metabolic; (2) Progenitor-like; (3) Proliferative; and (4) Inflammatory. PDAC risk factors of alcohol and tobacco consumption correlate with subtype classifications. Enhanced survival is observed in FOLFIRINOX treated Metabolic and Progenitor-like subtypes compared to the Proliferative and Inflammatory subtypes. In addition, TYMP, PDCD6IP, ERAP1, and STMN showed significant association with patient survival in a subtype-specific manner. Gemcitabine-induced alterations in the proteome identify proteins, such as SHMT1, associated with drug resistance. **CONCLUSIONS:** These data demonstrate that proteomic analysis of clinical PDAC liver metastases can identify molecular signatures unique to disease subtypes and point to opportunities for therapeutic development to improve the treatment of PDAC.

doi: <https://doi.org/10.1158/1078-0432.CCR-19-1496>

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#### - Germline DNA Sequencing Reveals Novel Mutations Predictive of Overall Survival in a Cohort of Pancreatic Cancer Patients

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

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31871297>

**Background and Aims** Family history of BRCA-related tumors may correlate with response to chemotherapy and overall survival (OS) in pancreatic cancer. The frequency of germline mutations has been reported in patients predominantly under the age of 60 or with strong family history. We examine the incidence of deleterious germline mutations and compare the chemotherapy responses and OS in an unselected group of metastatic pancreatic cancer patients. **Methods** Metastatic pancreatic cancer patients, who were seen at a single cancer center between 2010 and 2016, were included. Germline DNA was sequenced using a 263-gene panel to identify novel mutations (N = 133 MD Anderson cohort, N = 127 TCGA cohort). Chemotherapy response and OS were determined by review of medical records. **Results** Deleterious germline mutations were identified in 26 of 133 patients (19.5%). Patients with DNA damage repair (DDR) gene mutations (ATM, BRCA1/2, CDKN2A, CHEK2, ERCC4, PALB2, n = 15) had an improved OS as compared to patients without (16.8 versus 9.1 months, P = 0.03). Conversely, patients with other deleterious mutations had a trend towards worse OS. Although, survival in the later group was longer (P= NS) in those mutants initially treated with gemcitabine/nab-paclitaxel. A family history of multiple breast, ovarian, and pancreatic cancers was associated with DDR gene mutations and better survival. **Conclusion** We have identified novel germline mutations that are prognostic for survival in pancreatic cancer patients. We observe improved survival in patients with DDR gene mutations and worsened survival in patients with deleterious mutations in non-DDR genes.

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**- RET gene rearrangements occur in a subset of pancreatic acinar cell carcinomas**

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

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31558784>

Pancreatic acinar cell carcinoma is relatively rare (1 to 2% of pancreatic malignancies) but may be under-recognized. In contrast to pancreatic ductal adenocarcinoma, most acinar cell carcinomas lack mutations in KRAS, DPC, CDKN2A or TP53, but appear to have a high incidence of gene rearrangements, with up to 20% reported to be driven by BRAF fusions. With the development of a new class of RET-specific tyrosine kinase inhibitors, which appear to have particularly strong activity against RET gene rearranged tumours, there is now considerable interest in identifying RET gene rearrangements across a wide range of cancers. RET rearrangements have been reported to occur at a very low incidence (<1%) in all pancreatic carcinomas. We postulated that given its unique molecular profile, RET gene rearrangements may be common in acinar cell carcinomas. We performed fluorescent in-situ hybridization (FISH) studies on a cohort of 40 acinar cell spectrum tumours comprising 36 pure acinar cell carcinomas, three pancreatoblastomas and one mixed acinar-pancreatic neuroendocrine tumour. RET gene rearrangements were identified in 3 (7.5%) cases and BRAF gene rearrangements in 5 (12.5%). All gene rearranged tumours were pure acinar cell carcinomas. Our findings indicate that amongst all pancreatic carcinomas, acinar carcinomas are highly enriched for potentially actionable gene rearrangements in RET or BRAF. FISH testing is inexpensive and readily available in the routine clinical setting and may have a role in the assessment of all acinar cell carcinomas-at this stage to recruit patients for clinical trials of new targeted therapies, but perhaps in the near future as part of routine care.

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### 1.3.1.1 Preneoplastic and Preinvasive Lesions

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#### - Recurrent Rearrangements in PRKACA and PRKACB in Intraductal Oncocytic Papillary Neoplasms of the Pancreas and Bile Duct

*Gastroenterology* 2019 Oct;():

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31678302>

**BACKGROUND & AIMS:** Intraductal oncocytic papillary neoplasms (IOPNs) of the pancreas and bile duct contain epithelial cells with numerous, large mitochondria and are cystic precursors to pancreatic ductal adenocarcinoma (PDAC) and cholangiocarcinoma (CCA), respectively. However, IOPNs do not have the genomic alterations found in other pancreatobiliary neoplasms. In fact, no recurrent genomic alterations have been described in IOPNs. PDACs without activating mutations in KRAS contain gene rearrangements, so we investigated whether IOPNs have recurrent fusions in genes. **METHODS:** We analyzed 20 resected pancreatic IOPNs and 3 resected biliary IOPNs using a broad RNA-based targeted sequencing panel to detect cancer-related fusion genes. Four invasive PDACs and 2 intrahepatic cholangiocarcinomas from the same patients as the IOPNs, were also available for analysis. Samples of pancreatic cyst fluid (n=5, collected before surgery) and bile duct brushings (n=2) were analyzed for translocations. For comparison, we analyzed pancreatobiliary lesions from 126 patients without IOPN (controls). **RESULTS:** All IOPNs evaluated were found to have recurring fusions of ATP1B1-PRKACB (n = 13), DNAJB1-PRKACA (n = 6), or ATP1B1-PRKACA (n = 4). These fusions were also found in corresponding invasive PDACs and intrahepatic cholangiocarcinomas, as well as in matched pancreatic cyst fluid and bile duct brushings. These gene rearrangements were absent from all 126 control pancreatobiliary lesions. **CONCLUSIONS:** We identified fusions in PRKACA and PRKACB genes in pancreatic and biliary IOPNs, as well as in PDACs and pancreatic cyst fluid and bile duct cells from the same patients. We did not identify these gene fusions in 126 control pancreatobiliary lesions. These fusions might be used to identify patients at risk for IOPNs and their associated invasive carcinomas.

doi: <https://doi.org/10.1053/j.gastro.2019.10.028>

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#### - Multiple KRAS mutations in the non-mucinous epithelial lining in the majority of mucinous cystic neoplasms of the pancreas

*Histopathology* 2019 Oct;75(4):559-567

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31077597>

**AIMS:** Mucinous cystic neoplasms (MCNs) of the pancreas are cystic neoplasms lined by mucinous lining epithelium (MLE) with associated ovarian-type stroma. Although a non-MLE (NMLE) can be observed in some MCNs, whether cystic neoplasms with ovarian-type stroma and NMLE should be classified as MCNs or separately designated is debated. **METHODS AND RESULTS:** To test this, NMLEs were defined as flat or cuboidal epithelial cells without intracytoplasmic mucin. A total of 112 MCNs were reviewed, and the epithelium was classified as NMLE or MLE. A total of 110 females and two males with a mean age of  $46.5 \pm 12.3$  years were included in this study. At least focal NMLE was noted in 76.8% (86/112) of MCNs. The mean percentage of the neoplastic epithelium that was NMLE in these 86 cases was 46%. NMLE was predominant (>50%) in 38.4% (43/112) of cases. MCNs with NMLE were smaller ( $42 \pm 21$  mm) than those with MLE ( $60 \pm 36$  mm,  $P < 0.001$ ), and all NMLEs had low-grade dysplasia. Twelve MCNs with NMLE or MLE were selected for KRAS mutation analysis with droplet digital polymerase chain reaction after laser capture microdissection. All 12 MCNs showed multiple types of KRAS mutation, which were detected in 92% (11/12) of NMLE foci and 89% (8/9) of MLE foci. Predominant NMLE was common in small MCNs with low-grade dysplasia. **CONCLUSIONS:** Clonal KRAS mutations were observed in both NMLE and MLE, supporting the hypothesis that MCNs with NMLE should be classified as MCNs.

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### 1.3.2 Bile Ducts

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#### - Targeted next-generation sequencing identifies distinct clinicopathologic and molecular entities of intraductal papillary neoplasms of the bile duct

*Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc* 2019 Nov;32(11):1637-1645

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31231124>

Intraductal papillary neoplasm of the bile duct (IPNB) is a mass-forming neoplasm in the bile duct considered to be the biliary counterpart of pancreatic intraductal papillary mucinous neoplasm (IPMN). By its cell lineage, IPNB can be classified into gastric, intestinal, pancreatobiliary, and oncocytic types. Recently, a group of Japanese and Korean pathologists proposed that IPNB be classified into two types, with type 1, being the histological counterpart of IPMN and type 2, having a more complex histological architecture. We used targeted next-generation sequencing to study the molecular change of 37 IPNBs and identified frequent mutations of KRAS (49%), GNAS (32%), RNF43 (24%), APC (24%), TP53 (24%), and CTNNB1 (11%) in IPNBs. Intestinal-type IPNB was associated with KRAS, GNAS, and RNF43 mutations. Japan-Korea consensus type 1 was associated with KRAS and GNAS mutations. All four IPNBs with CTNNB1 mutations were of pancreatobiliary type and located in the extrahepatic bile duct. A hierarchical analysis identified three distinct groups within IPNB: group 1 was Japan-Korea consensus type 1 tumors with macroscopic mucin, old age, and frequent KRAS, GNAS, and RNF43 mutations. Group 2 was Japan-Korea consensus type 2 with intestinal differentiation and frequent KRAS mutation but rare GNAS mutation, MUC2 expression, and macroscopic mucin. Group 3 was characterized by CTNNB1 mutation, extrahepatic location, lack of expression of intestinal markers, Japan-Korea consensus type 2, and lack of mutations in KRAS, APC, RNF43, and GNAS. Our results indicated that IPNB is a heterogeneous disease and that the activation of Ras-mitogen-activated protein kinase (MAPK), Wnt/ -catenin, and G-protein-coupled receptor (GPCR)-cAMP signaling is the main oncogenic mechanism of IPNB.

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