

Pancreatobiliary Pathology Society Journal Watch

April - August 2020

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1 PBPath Journal Watch Articles

Welcome 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, molecular pathology, pancreas, gallbladder, bile ducts, and ampulla 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 *Special Section Articles from PBPath Society*

SPECIAL SECTION—CONTRIBUTIONS FROM THE PANCREATOBILIARY PATHOLOGY SOCIETY

Archives of Pathology & Laboratory Medicine - July 2020

- **Challenging Topics in Pancreatic Neoplasia**

Olca Basturk and Alyssa M. Krasinskas

<https://www.archivesofpathology.org/doi/pdf/10.5858/arpa.2020-0142-ED>

- **Pancreatic Neoplasms With Acinar Differentiation: A Review of Pathologic and Molecular Features**

Elizabeth D. Thompson and Laura D. Wood

<https://www.archivesofpathology.org/doi/pdf/10.5858/arpa.2019-0472-RA>

- **Pancreatic Neuroendocrine Neoplasms: Landscape and Horizon**

Laura H. Tang

<https://www.archivesofpathology.org/doi/pdf/10.5858/arpa.2019-0654-RA>

- **Pancreatic Solid Pseudopapillary Neoplasm: Key Pathologic and Genetic Features**

Stefano La Rosa and Massimo Bongiovanni

<https://www.archivesofpathology.org/doi/pdf/10.5858/arpa.2019-0473-RA>

- **Pathology of Treated Pancreatic Ductal Adenocarcinoma and Its Clinical Implications**

Teddy Sutardji Nalaria, Hua Wang, Deyali Chatterjee and Huamin Wang

<https://www.archivesofpathology.org/doi/pdf/10.5858/arpa.2019-0477-RA>

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1.2 Pancreas

- **Carboxypeptidase A1 and regenerating islet-derived 1 as new markers for pancreatic acinar cell carcinoma**

Human pathology 2020 Jul;103():120-126

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=32702400>

Acinar cell carcinoma (ACC) is a rare tumor that differentiates toward pancreatic acinar cells and shows evidence of pancreatic enzyme production. Mixed acinar-neuroendocrine carcinoma (MANC) is defined as having more than 30% of both acinar and neuroendocrine cell types as per immunohistochemistry analysis. Trypsin is currently the most commonly used stain for acinar differentiation. In this study, we investigate the utility of two novel markers, carboxypeptidase A1 (CPA1) and regenerating islet-derived 1 (REG1a), in diagnosing ACC/MANC. Immunohistochemical staining for CPA1 and REG1a was performed on 14 cases of ACC and 5 cases of MANC as well as on 80 other pancreatic tumors including 20 cases each of ductal adenocarcinoma, well-differentiated neuroendocrine tumor, mucinous cystic neoplasm, and solid pseudopapillary tumor. All ACCs and MANCs were positive for CPA1 (all diffuse) and REG1a (12 diffuse, 4 patchy, and 3 focal). A diffuse or patchy staining pattern was significantly more common in ACC/MANC cases (100% diffuse/patchy for CPA1 and 84% for REG1a) than in other pancreatic tumors (5% diffuse/patchy for CPA1 and 7.5% for REG1a), with a P-value of <0.0001 for both CPA1 and REG1a. The sensitivity and specificity of diffuse/patchy staining for CPA1 and REG1a in diagnosing pancreatic ACC/MANC were 100% and 95% for CPA1 and 84% and 93% for REG1a, respectively. In conclusion, CPA1 and REG1a are sensitive markers for ACC that can be used as additional acinar cell differentiation markers to help in the diagnosis of pancreatic ACC and MANC. A negative result for CPA1 virtually excludes ACC/MANC.

doi: <https://doi.org/10.1016/j.humpath.2020.07.019>

- **The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Pancreatic Neuroendocrine Tumors**

Pancreas 2020 Aug;49(7):863-881

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=32675783>

This article is the result of the North American Neuroendocrine Tumor Society consensus conference on the medical management of pancreatic neuroendocrine tumors from July 19 to 20, 2018. The guidelines panel consisted of medical oncologists, pathologists, gastroenterologists, endocrinologists, and radiologists. The panel reviewed a series of questions regarding the medical management of patients with pancreatic neuroendocrine tumors as well as questions regarding surveillance after resection. The available literature was reviewed for each of the question and panel members voted on controversial topics, and the recommendations were included in a document circulated to all panel members for a final approval.

doi: <https://doi.org/10.1097/MPA.0000000000001597>

- **Epithelial-mesenchymal transition in undifferentiated carcinoma of the pancreas with and without osteoclast-like giant cells**

Virchows Archiv : an international journal of pathology 2020 Jul;():

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=32661742>

Undifferentiated carcinoma (UC) and undifferentiated carcinoma with osteoclast-like giant cells (UCOGC) are peculiar variants of pancreatic ductal adenocarcinoma (PDAC), characterized by hypercellularity and absence of glandular patterns. The inflammatory microenvironment is peculiar in UCOGC, since it is dominated by macrophages and osteoclast-like giant cells. However, from a molecular point of view, both UC and UCOGC are very similar to conventional PDAC, sharing alterations of the most common genetic drivers. Clinically, UC usually show a worse prognosis, whereas UCOGC may show a better prognosis if it is not associated with a PDAC component. To highlight potential biological differences between these entities, we investigated the role of the epithelial to mesenchymal transition (EMT) in UC and UCOGC. Specifically, we analyzed the immunohistochemical expression of three well-known EMT markers, namely Twist1, Snai2, and E-cadherin, in 16 cases of UCOGC and 10 cases of UC. We found that EMT is more frequently activated in UC (10/10 cases) than in UCOGC (8/16 cases; $p = 0.05$). Furthermore, in UCOGC, EMT was activated with a higher frequency in cases with an associated PDAC component. Snai2 was the most frequently and strongly expressed marker in both tumor types (10/10 UC, 8/16 UCOGC), and its expression was higher in UC than in UCOGC (mean immunohistochemical score: 4.8 in UC vs. 2.1 in UCOGC, $p < 0.01$). Our results shed new light on the biology of UC and UCOGC: EMT appeared as a more important process in UC, and Snai2 emerged as a central EMT effector in this setting.

doi: <https://doi.org/10.1007/s00428-020-02889-3>

- **Evaluation of Pathologic Response on Overall Survival After Neoadjuvant Therapy in Pancreatic Ductal Adenocarcinoma**

Pancreas 2020 Aug;49(7):897-903

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=32658070>

OBJECTIVES: Single-institution studies have shown improved outcomes among patients with a pathologic complete response (pCR) following neoadjuvant therapy. We sought to evaluate the impact of pCR and near-complete response (nCR) on overall survival (OS) using a large national database. **METHODS:** The National Cancer Database was queried for patients given a diagnosis of pancreatic cancer from 2004 to 2014. A pCR was defined as no tumor identified in the pancreas after surgical resection. An nCR was defined as a primary tumor less than 1 cm without lymph node metastases. The primary outcome was OS. **RESULTS:** A total of 5364 patients underwent neoadjuvant chemotherapy and/or radiation followed by pancreatectomy. Forty-one patients (0.8%) had a pCR, 54 (1%) had an nCR, and the remaining 5266 (98.2%) had an otherwise incomplete response. Patients with pCR had a median OS of 43 months compared with 24 months for nCR and 23 months for incomplete response ($P < 0.0001$). Only pCR was associated with improved OS on adjusted Cox regression. **CONCLUSIONS:** For patients given a diagnosis of pancreatic cancer who underwent neoadjuvant treatment and surgical resection, achieving a pCR was associated with improved OS compared with those with residual tumor. An association between nCR and improved survival was not observed.

doi: <https://doi.org/10.1097/MPA.0000000000001590>

- **Comparison of Different Anti-Ki67 Antibody Clones and Hotspot Sizes for Assessing Proliferative Index and Grading in Pancreatic Neuroendocrine Tumours using Manual and Image Analysis**

Histopathology 2020 Jul;():

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=32617996>

AIMS: Ki67 proliferative index (PI) is essential for grading gastroenteric and pancreatic neuroendocrine tumours (GEP NETs). Analytical and preanalytical variables can affect Ki67 PI. In contrast to counting

methodology, until now little attention has focussed on the question of clone equivalence and effect of hotspot size on Ki67 PI in GEP NETs. Using manual counting and image analysis, this study compared the Ki67 PI achieved using MM1, K2 and 30-9 to MIB1, a clone which has been validated for, and is referenced in guidelines relating to, assessment of Ki67 PI in GEP NETs. METHODS AND RESULTS: 42 pancreatic NETs were each immunohistochemically stained for the anti-Ki67 clones MIB1, MM1, K2 and 30-9. Ki67 PI was calculated manually and by image analysis, the latter using 3 different hotspot sizes. In manual comparisons using single hotspot high power fields, non-MIB1 clones overestimated Ki67 PI compared to MIB1, resulting in grading discordances. Image analysis shows good agreement with manual Ki67 PI but a tendency to overestimate absolute Ki67 PI. Increasing the size of tumour hotspot from 500 to 2000 cells resulted in a decrease in Ki67 PI. CONCLUSION: Different anti-Ki67 clones do not produce equivalent PIs in GEP NETs and clone selection may therefore affect patient care. Increasing the hotspot size decreases the Ki67 PI. Greater standardisation in terms of antibody clone selection and hotspot size is required for grading GEP NETs. Image analysis is an effective tool for assisting Ki67 assessment and allows easier standardisation of the size of the tumour hotspot.

doi: <https://doi.org/10.1111/his.14200>

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- **Prevalence of histological features resembling autoimmune pancreatitis in neoplastic pancreas resections**

Histopathology 2020 Jul;():

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=32608526>

INTRODUCTION: Type 1 and type 2 autoimmune pancreatitis (AIP) can mimic pancreatic neoplasia. Due to the small quantity of tissue in mass-targeted pancreas biopsies, inflammatory features may raise the differential of AIP. However, the frequency of AIP-like histology in neoplastic pancreas is not well characterized. Therefore, the specificity of inflammatory lesions on biopsy with respect to the diagnosis of AIP is uncertain. MATERIALS AND METHODS: Neoplastic pancreas resections performed at our institution between 2008 to 2019 were retrospectively reviewed. Features of AIP type 1 and 2 were assessed in the non-neoplastic areas. If features of IgG4-associated AIP were seen, IgG4 immunohistochemistry was performed. RESULTS: We identified 163 neoplastic pancreas resections. Of these, 34 had one or more types of inflammatory lesions in non-neoplastic pancreatic tissue. Dense lymphoplasmacytic inflammation mimicking type 1 AIP was found in 6 cases with mild to moderately increased IgG4 positive plasma cells. Neutrophilic infiltrates in small intralobular ducts were found in 20 cases. Mild extra-lobular ductitis or duct microabscess was found in 10 specimens. Marked neutrophilic duct destruction that resembled granulocytic epithelial lesions was found in 12 cases. Some cases showed multiple features. CONCLUSION: Approximately 20% of neoplastic pancreas resections showed focal areas that could raise the differential of AIP. More cases showed neutrophilic predominant inflammation, as seen in type 2 autoimmune pancreatitis, compared to dense lymphoplasmacytic infiltrates seen in type 1 AIP. Pathologists must be cautious when making a diagnosis of AIP on biopsy tissue based on histological findings alone.

doi: <https://doi.org/10.1111/his.14197>

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- **Next-generation sequencing of residual cytologic fixative preserved DNA from pancreatic lesions: A pilot study**

Cancer cytopathology 2020 Jun;():

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=32598087>

BACKGROUND: Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is a sensitive and specific tool in the risk stratification of pancreatic lesions, including cysts. The sensitivity and specificity of EUS-

FNA has been shown to improve when cytology is combined with next-generation sequencing (NGS). Ideally, fresh cyst fluid is used for NGS. In this pilot study, we explore the possibility of sequencing DNA derived from residual alcohol-fixed pancreatic aspirates. METHODS: Residual cytologic fixatives (n = 42) from 39 patients who underwent EUS-FNA for pancreatic lesions were collected along with demographics, imaging, and laboratory studies. Samples were designated as nonneoplastic/nonmucinous benign (NB), mucinous cyst (MC), pancreatic ductal adenocarcinoma (PDAC), or well-differentiated neuroendocrine tumor (NET) on the basis of cytopathologic evaluation and sequenced on the OncoPrint platform (ThermoFisher Scientific, Waltham, Massachusetts). RESULTS: Ten of 14 (71.4%) MCs exhibited clinically significant variants, including KRAS, GNAS, and TP53. Ten of 15 (66.7%) PDACs had KRAS alterations, and 9 of 15 (60%) showed variants in TP53. No variants were detected in any NETs. Only 1 of 9 (11.1%) NB aspirates showed variants in KRAS and MAP2K. Sequencing of formalin-fixed, paraffin-embedded tissue revealed variants identical to those detected in fixative-derived DNA in 4 of 5 cases (80%). CONCLUSION: Residual DNA from alcohol-fixed aspirates are an underutilized source for NGS. Sequencing residual fixative-derived DNA has the potential to be integrated into the workup of pancreatic aspirates, possibly impacting management.

doi: <https://doi.org/10.1002/cncy.22315>

- **Alterations in driver genes are predictive of survival in patients with resected pancreatic ductal adenocarcinoma**

Cancer 2020 Sep;126(17):3939-3949

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=32573775>

BACKGROUND: KRAS, TP53, CDKN2A, and SMAD4 are established driver genes in pancreatic ductal adenocarcinoma (PDAC). This study was aimed at determining whether the mutational status of driver genes and those involved in DNA repair pathways are associated with clinical outcomes for individuals who undergo resection. METHODS: Eligible individuals were those who underwent resection of PDAC and consented to targeted sequencing of their primary tumor via Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT). Genomic alterations were determined on the basis of MSK-IMPACT results from formalin-fixed, paraffin-embedded samples. Associations between genomic alterations and clinical outcomes were assessed. RESULTS: Targeted sequencing was performed on 283 primary tumors resected between 2004 and 2017. The median follow-up was 23 months among survivors. Alterations in KRAS and TP53 were associated with worse overall survival (OS) in comparison to wild type (median for KRAS, 38.8 months [95% CI, 33.0-45.5 months] vs 91.0 months [95% CI, 34.8 months to not available (NA)]; P = .043; median for TP53, 37.4 months [95% CI, 32.1-42.8 months] vs 65.0 months [95% CI, 33.0 months to NA]; P = .035). KRAS G12D mutations were associated with worse OS (median, 31.6 months [95% CI, 25.3-45.5 months] vs 39.2 months [95% CI, 37.4-75.2 months]; P = .012). TP53 truncating mutations (median, 39.6 months [95% CI, 32.4-75.2 months] vs 33.9 months [95% CI, 24.0-39.0 months]; P = .020) and those associated with loss of heterozygosity (median, 26.6 months [95% CI, 21.6-44.2 months] vs 39.2 months [95% CI, 34.5-49.1 months]; P = .048) had decreased OS. TP53 alterations were independently associated with OS in a multivariate analysis (hazard ratio, 1.54; 95% CI, 1.01-2.33; P = .042). Individuals with germline alterations in homologous recombination deficiency (HRD) genes had improved OS in comparison with those without them (median, not reached vs 37.0 months; 95% CI, 33.0-49.8 months; P = .035). CONCLUSIONS: In patients with resected PDAC, genomic alterations in KRAS and TP53 are associated with worse outcomes, whereas alterations in HRD genes are associated with a favorable prognosis. Further studies are needed to better define these alterations as biomarkers in resected PDAC.

doi: <https://doi.org/10.1002/cncr.33038>

- **Morphologic Variants of Pancreatic Neuroendocrine Tumors: Clinicopathologic Analysis and Prognostic Stratification**

Endocrine pathology 2020 Sep;31(3):239-253

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=32488621>

Better prognostication/stratification of pancreatic neuroendocrine tumors (PanNETs) is needed. In this detailed morphologic study of 163 resected PanNETs, 11 unusual variants, some of which were not previously recognized, and others scarcely documented in the literature, were identified, and their pathologic characteristics were further analyzed. By behavior and clinicopathologic associations, these variants could be grouped into three prognostically different categories. I. More aggressive (20%). Included in this group were the variants that in average showed higher grade and stage and adverse outcome including oncocytic, plasmacytoid, lipid-rich and previously unrecognized hepatoid variants, which often had a more diffuse/broad-band growth pattern, with some also displaying discohesiveness. They were characterized by abundant cytoplasm and often had prominent nucleoli (as seen in metabolically active cells), thus the provisional name “metabolic cell phenotype.” Because of their diversion from classical neuroendocrine cytomorphology, these variants created challenges on original diagnostic workup, particularly hepatoid examples, which revealed Arginase 1/Hep Par-1 expression in 50%. II. Less aggressive (10%). These cases either showed signs of maturation, including nested growth, paraganglioid pattern (which was previously unrecognized), and organoid PanNETs such as “ductulo-insular” growth, or showed symplastic/degenerative changes, and despite their paradoxically disconcerting histology, were more benevolent in behavior. III. Undetermined. There were other variants including mammary tubulolobular-like, pseudoglandular, peliotic, and sclerotic PanNETs, which although diagnostically challenging, their biologic significance could not be determined because of rarity or heterogeneous characteristics. Prognostic associations: Features that were significantly different in the more aggressive group than the less aggressive group were median size (5.0 vs 1.6 cm, $p < 0.001$), percentage of pT3+T4 cases (72% vs 12%, $p < 0.001$), Ki67 index (5.3% vs 2.3%, $p = 0.001$), % G2 and G3 cases (77% vs 27%, $p < 0.001$), and rate of lymph node and distant metastasis (96% vs 27%, $p < 0.001$). In stepwise logistic regression model using the 3 established prognosticators of T stage, size, and grade along with morphology, only aggressive-morphology (metabolic cell phenotype) was found to be associated with metastatic behavior with an odds ratio of 5.9 with 95% confidence interval (C.I.) 1.688 to 22.945 and p value 0.007. In conclusion, PanNETs display various morphologic patterns that are not only challenging and important diagnostically but appear to have biologic significance. Tumors with more diffuse growth of cells with nucleoli and abundant cytoplasm and/or discohesion (oncocytic, hepatoid, lipid-rich, plasmacytoid PanNETs), provisionally termed “metabolic cell phenotype,” show aggressive characteristics and are an independent determinant of adverse outcome and thus may require closer post-surgical follow-up, whereas variants with more degenerative or mature features (ductuloinsular, pleomorphic, paraganglioma-like) appear to be more benevolent despite their more atypical and worrisome morphology.

doi: <https://doi.org/10.1007/s12022-020-09628-z>

- **Ki-67 proliferation index in neuroendocrine tumors: Can augmented reality microscopy with image analysis improve scoring?**

Cancer cytopathology 2020 Aug;128(8):535-544

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=32401429>

BACKGROUND: The Ki-67 index is important for grading neuroendocrine tumors (NETs) in cytology. However, different counting methods exist. Recently, augmented reality microscopy (ARM) has enabled real-time image analysis using glass slides. The objective of the current study was to compare different traditional Ki-67 scoring methods in cell block material with newer methods such as ARM. **METHODS:** Ki-67 immunostained slides from 50 NETs of varying grades were retrieved (39 from the pancreas and 11 metastases). Methods with which to quantify the Ki-67 index in up to 3 hot spots included: 1) “eyeball” estimation (EE); 2) printed image manual counting (PIMC); 3) ARM with live image analysis; and 4) image

analysis using whole-slide images (WSI) (field of view [FOV] and the entire slide). RESULTS: The Ki-67 index obtained using the different methods varied. The pairwise kappa results varied from no agreement for image analysis using digital image analysis WSI (FOV) and histology to near-perfect agreement for ARM and PIMC. Using surgical pathology as the gold standard, the EE method was found to have the highest concordance rate (84.2%), followed by WSI analysis of the entire slide (73.7%) and then both the ARM and PIMC methods (63.2% for both). The PIMC method was the most time-consuming whereas image analysis using WSI (FOV) was the fastest method followed by ARM. CONCLUSIONS: The Ki-67 index for NETs in cell block material varied by the method used for scoring, which may affect grade. PIMC was the most time-consuming method, and EE had the highest concordance rate. Although real-time automated counting using image analysis demonstrated inaccuracies, ARM streamlined and hastened the task of Ki-67 quantification in NETs.

doi: <https://doi.org/10.1002/cncy.22272>

- **Simple mucinous cysts of the pancreas have heterogeneous somatic mutations**

Human pathology 2020 Jul;101():1-9

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=32380013>

Simple mucinous cysts of the pancreas have an epithelial lining resembling pancreatic intraepithelial neoplasia but may have a clinical presentation similar to premalignant mucinous neoplasms such as intraductal papillary mucinous neoplasms. Whether the epithelial lining shares genomic alterations with other pancreatic preinvasive neoplasms such as PanIN and intraductal papillary mucinous neoplasm has not been determined. We performed targeted sequencing analysis using a custom-designed MiSeq panel including the full coding regions of 18 pancreatic cancer genes on 13 clinically and pathologically well-characterized simple mucinous cysts. We detected 59 mutations in 15 genes in the cohort, with a median of 4 mutations per cyst (range = 0-16 mutations per cyst). The mutated genes and rate of detected mutations were as follows: KMT2C (MLL3) (62%), KRAS (15%), BRAF (8%), RNF43 (8%), CDKN2a (8%), TP53 (15%), and SMAD4 (8%). No GNAS mutations were detected. Four cases (31%) had no mutations detected. These findings place the majority of simple mucinous cysts of the pancreas in the spectrum of early, low-grade mucinous neoplasia, albeit with a different spectrum of genomic alterations compared with PanIN and intraductal papillary mucinous neoplasm.

doi: <https://doi.org/10.1016/j.humphath.2020.04.006>

- **Detection of Circulating Tumor DNA in Patients with Pancreatic Cancer Using Digital Next-Generation Sequencing**

The Journal of molecular diagnostics : JMD 2020 Jun;22(6):748-756

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=32205290>

Circulating tumor DNA (ctDNA) measurements can be used to estimate tumor burden, but avoiding false-positive results is challenging. Herein, digital next-generation sequencing (NGS) is evaluated as a ctDNA detection method. Plasma KRAS and GNAS hotspot mutation levels were measured in 140 subjects, including 67 with pancreatic ductal adenocarcinoma and 73 healthy and disease controls. To limit chemical modifications of DNA that yield false-positive mutation calls, plasma DNA was enzymatically pretreated, after which DNA was aliquoted for digital detection of mutations (up to 384 aliquots/sample) by PCR and NGS. A digital NGS score of two SDs above the mean in controls was considered positive. Thirty-seven percent of patients with pancreatic cancer, including 31% of patients with stages I/II disease, had positive KRAS codon 12 ctDNA scores; only one patient had a positive GNAS mutation score. Two disease control patients had positive ctDNA scores. Low-normal-range digital NGS scores at mutation hotspots were found

at similar levels in healthy and disease controls, usually at sites of cytosine deamination, and were likely the result of chemical modification of plasma DNA and NGS error rather than true mutations. Digital NGS detects mutated ctDNA in patients with pancreatic cancer with similar yield to other methods. Detection of low-level, true-positive ctDNA is limited by frequent low-level detection of false-positive mutation calls in plasma DNA from controls.

doi: <https://doi.org/10.1016/j.jmoldx.2020.02.010>

- **Tumor-insular Complex in Neoadjuvant Treated Pancreatic Ductal Adenocarcinoma Is Associated With Higher Residual Tumor**

The American journal of surgical pathology 2020 Jun;44(6):817-825

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=32091434>

The tumor microenvironment in pancreatic ductal adenocarcinoma (PDAC) plays a vital role in treatment response, and therefore, patient survival. We and others have observed an intimate association of neoplastic ductal cells with non-neoplastic islet cells, recapitulating the ductoinsular complex. We define this phenomenon as tumor-insular complex (TIC). Herein, we describe the clinicopathologic characteristics of TIC in neoadjuvant treated PDAC cases for the first time. We retrospectively reviewed the pathology of 105 cases of neoadjuvant treated PDAC resected at our institution. TIC was noted in 35 cases (33.3%), the mean tumor bed size was 2.7 ± 1.0 cm, mean percentage of residual tumor $40 \pm 28\%$ and mean Residual Tumor Index (RTI) (an index previously established as a prognostic parameter by our group) was 1.1 ± 1.0 . TIC was significantly associated with perineural invasion ($P=0.001$), higher tumor bed size ($P=0.007$), percentage of residual tumor ($P=0.009$), RTI ($P=0.001$), ypT stage ($P=0.045$), and poor treatment response, grouped by a previously established criteria ($P=0.010$). Using our prior binary reported prognostic cutoff for RTI of 0.35 and >0.35 , TIC was associated with a RTI >0.35 ($P=0.002$). Moreover, patients who did not receive neoadjuvant radiation were associated with a higher frequency of TIC ($P=0.003$). In this cohort, RTI but not TIC was also shown to be a significant independent prognosticator for recurrence-free survival and overall survival on multivariate analysis. In conclusion, TIC is significantly associated with a more aggressive neoplasm which shows a poor treatment response. Further studies will be needed to better understand the tumor biology of TICs.

doi: <https://doi.org/10.1097/PAS.0000000000001454>

- **Insulinoma-associated protein 1 (INSM1) is a robust marker for identifying and grading pancreatic neuroendocrine tumors**

Cancer cytopathology 2020 04;128(4):269-277

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31977134>

BACKGROUND: Pancreatic neuroendocrine tumor (PNET) is a diagnostic challenge with limited samples in not only identification but grading. Prior studies have shown insulinoma-associated protein 1 (INSM1) to be a robust marker in identifying PNETs from other solid pancreatic tumors on resection specimens. In this study, we investigated the utility of INSM1 not only for identifying PNETs but also for grading in cell blocks (CBs) and surgical resections (SRs). **METHODS:** A search for PNET cases between 2000 and 2019 identified 55 samples (26 CBs and 29 SRs) that were further separated into high (2 CBs, 3 SRs), intermediate (4 CBs, 7 SRs), and low (20 CBs, 19 SRs) grades based on their final pathology report and Ki-67 level. Immunohistochemical (IHC) staining for INSM1 (C-8, Santa Cruz Biotechnology [1:100]) was performed and quantified using an H score of 0 to 300. Non-PNET solid pancreatic tumors were compared and included acinar cell carcinoma, solid pseudopapillary neoplasm, and ductal adenocarcinoma. **RESULTS:** All 55 cases of PNET demonstrated nuclear INSM1 staining. The average H scores for INSM1 staining of

PNET were 254 and 252 in CB and SR, respectively. The H scores decreased with increasing tumor grade, with low-grade (G1), intermediate-grade (G2), and high-grade (G3) tumors showing average INSM1 H scores of 229 and 253, 266 and 253, and 30 and 33 in both CB and SR, respectively. CONCLUSION: IHC with INSM1 plays a role in identifying and potentially grading PNETs.

doi: <https://doi.org/10.1002/ency.22242>

- **Microscopic size measurements in post-neoadjuvant therapy resections of pancreatic ductal adenocarcinoma (PDAC) predict patient outcomes**

Histopathology 2020 Jul;77(1):144-155

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31965618>

AIMS: Pancreatic ductal adenocarcinomas (PDACs) are increasingly being treated with neoadjuvant therapy. However, the American Joint Committee on Cancer (AJCC) 8th edition T staging based on tumour size does not reflect treatment effect, which often results in multiple, small foci of residual tumour in a background of mass-forming fibrosis. Thus, we evaluated the performance of AJCC 8th edition T staging in predicting patient outcomes by the use of a microscopic tumour size measurement method. METHODS AND RESULTS: One hundred and six post-neoadjuvant therapy pancreatectomies were reviewed, and all individual tumour foci were measured. T stages based on gross size with microscopic adjustment (GS) and the largest single microscopic focus size (MFS) were examined in association with clinicopathological variables and patient outcomes. Sixty-three of 106 (59%) were locally advanced; 78% received FOLFIRINOX treatment. The average GS and MFS were 25 mm and 11 mm, respectively; nine cases each were classified as T0, 35 and 85 cases as T1, 42 and 12 cases as T2, and 20 and 0 cases as T3, based on the GS and the MFS, respectively. Higher GS-based and MFS-based T stages were significantly associated with higher tumour regression grade, lymphovascular and perineural invasion, and higher N stage. Furthermore, higher MFS-based T stage was significantly associated with shorter disease-free survival (DFS) ($P < 0.001$) and shorter overall survival (OS) ($P = 0.002$). GS was significantly associated with OS ($P = 0.046$), but not with DFS. CONCLUSIONS: In post-neoadjuvant therapy PDAC resections, MFS-based T staging is superior to GS-based T staging for predicting patient outcomes, suggesting that microscopic measurements have clinical utility beyond the conventional use of GS measurements alone.

doi: <https://doi.org/10.1111/his.14067>

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

Archives of pathology & laboratory medicine 2020 Jun;144(6):755-763

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>

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

Gastroenterology 2020 02;158(3):573-582.e2

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 CCAs 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 also were found in corresponding invasive PDACs and intrahepatic CCAs, 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>

- **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 2020 04;33(4):648-656

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 oncocyctic morphology: three cases were diagnosed as intraductal oncocyctic papillary neoplasms, and three as intraductal papillary mucinous neoplasms with mixed oncocyctic and pancreatobiliary or gastric features. Four cases had an invasive carcinoma component composed of oncocyctic 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>

- **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 2020 04;33(4):657-664

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.

doi: <https://doi.org/10.1038/s41379-019-0373-y>

- **Whole-genome sequencing reveals distinct genetic bases for insulinomas and non-functional pancreatic neuroendocrine tumours: leading to a new classification system**

Gut 2020 May;69(5):877-887

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31462556>

OBJECTIVE: Insulinomas and non-functional pancreatic neuroendocrine tumours (NF-PanNETs) have distinctive clinical presentations but share similar pathological features. Their genetic bases have not been comprehensively compared. Herein, we used whole-genome/whole-exome sequencing (WGS/WES) to identify genetic differences between insulinomas and NF-PanNETs. **DESIGN:** The mutational profiles and copy-number variation (CNV) patterns of 211 PanNETs, including 84 insulinomas and 127 NF-PanNETs, were obtained from WGS/WES data provided by Peking Union Medical College Hospital and the International Cancer Genome Consortium. Insulinoma RNA sequencing and immunohistochemistry data were assayed. **RESULTS:** PanNETs were categorised based on CNV patterns: amplification, copy neutral and deletion. Insulinomas had CNV amplifications and copy neutral and lacked CNV deletions. CNV-neutral insulinomas exhibited an elevated rate of YY1 mutations. In contrast, NF-PanNETs had all three CNV patterns, and NF-PanNETs with CNV deletions had a high rate of loss-of-function mutations of tumour suppressor genes. NF-PanNETs with CNV alterations (amplification and deletion) had an elevated risk of relapse, and additional DAXX/ATRX mutations could predict an increased relapse risk in the first 2-year period. **CONCLUSION:** These WGS/WES data allowed a comprehensive assessment of genetic differences between insulinomas and NF-PanNETs, reclassifying these tumours into novel molecular subtypes. We also proposed a novel relapse risk stratification system using CNV patterns and DAXX/ATRX mutations.

doi: <https://doi.org/10.1136/gutjnl-2018-317233>

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

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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>

- **New Nodal Staging for Primary Pancreatic Neuroendocrine Tumors: A Multi-institutional and National Data Analysis**

Annals of surgery 2019 Jul;():

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31356277>

OBJECTIVE: To determine the prognostic role of metastatic lymph node (LN) number and the minimal number of LNs for optimal staging of patients with pancreatic neuroendocrine tumors (pNETs). **BACKGROUND:** Prognosis relative to number of LN metastasis (LNM), and minimal number of LNs needed to evaluate for accurate staging, have been poorly defined for pNETs. **METHODS:** Number of LNM and total number of LN evaluated (TNLE) were assessed relative to recurrence-free survival (RFS) and overall survival (OS) in a multi-institutional database. External validation was performed using Surveillance, Epidemiology and End Results (SEER) registry. **RESULTS:** Among 854 patients who underwent resection, 233 (27.3%) had at least 1 LNM. Patients with 1, 2, or 3 LNM had a comparable worse RFS versus patients with no nodal metastasis (5-year RFS, 1 LNM 65.6%, 2 LNM 68.2%, 3 LNM 63.2% vs 0 LNM 82.6%; all $P < 0.001$). In contrast, patients with 4 LNM (proposed N2) had a worse RFS versus patients who either had 1 to 3 LNM (proposed N1) or node-negative disease (5-year RFS, 4 LNM 43.5% vs 1-3 LNM 66.3%, 0 LNM 82.6%; all $P < 0.05$) [C-statistics area under the curve (AUC) 0.650]. TNLE 8 had the highest discriminatory power relative to RFS (AUC 0.713) and OS (AUC 0.726) among patients who had 1 to 3 LNM, and patients who had 4 LNM in the multi-institutional and SEER database ($n = 2764$). **CONCLUSIONS:** Regional lymphadenectomy of at least 8 lymph nodes was necessary to stage patients accurately. The proposed nodal staging of N0, N1, and N2 optimally staged patients.

doi: <https://doi.org/10.1097/SLA.0000000000003478>

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

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

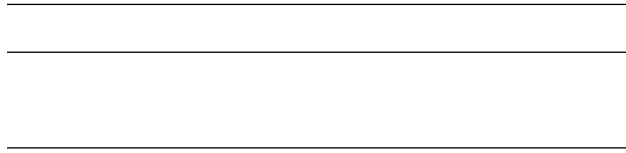
PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31025231>

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

patient prognosis. In the near future, a more precise mutational analysis of IPMNs might help to better tailor their management.

doi: <https://doi.org/10.1245/s10434-019-07389-6>

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1.3 Gallbladder

- **Neuroendocrine Carcinomas of the Gallbladder: A Clinicopathologic and Immunohistochemical Analysis of 34 Resected Cases**

The American journal of surgical pathology 2020 Jul;():

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=32739935>

Neuroendocrine carcinoma (NEC) is an aggressive malignant tumor that rarely arises from the gallbladder. Here, we investigated the clinicopathologic and immunohistochemical characteristics of 34 NECs of the gallbladder. The patients were predominantly women (68%) with a median age of 63 years (range, 37 to 82 y). NECs frequently occurred in the fundus (44%) as mass-forming lesions (66%). Histologically, 17 tumors were of small cell type, and another 17 were of large cell type. Twenty-three cases (68%) were associated with biliary intraepithelial neoplasia (38%) and intracholecystic papillary neoplasm (29%). The majority of tumors exhibited a diffuse growth pattern (74%), followed by organoid (24%) or scirrhous (2%) growth patterns. Histologic features related to neuroendocrine differentiation, such as nuclear molding (56%), perilobular pseudopalisading (18%), and rosette formation (15%), were identified. Immunohistochemically, cytokeratin 7 and 20 were expressed in 19 (56%) and 8 (24%) cases, respectively. Loss of Rb1 expression and concomitant overexpression of p16 were observed in 25 (74%) cases. No BRAF mutations were identified in any of the 34 NECs. For survival analysis, the 1-, 3-, and 5-year overall survival rates were 64%, 35%, and 19%, respectively. In a multivariate analysis, the receipt of adjuvant chemoradiation therapy was identified as the only independent prognostic factor associated with the overall survival rate. The 1- and 3-year overall survival rates of patients with NECs were poorer for patients with poorly differentiated adenocarcinoma of the gallbladder ($P < 0.001$). The complete resection and application of postoperative adjuvant therapy may influence a better clinical outcome in patients with NEC of the gallbladder.

doi: <https://doi.org/10.1097/PAS.0000000000001536>

- **Intracholecystic tubular non-mucinous neoplasm (ICTN) of the gallbladder: a clinicopathologically distinct, invasion-resistant entity**

Virchows Archiv : an international journal of pathology 2020 Jul;():

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=32691142>

Preinvasive tumor-forming gallbladder neoplasms that are composed of small, non-mucinous tubules with complex architecture remain a poorly characterized group. Here, we evaluated the clinicopathological characteristics of this entity. Twenty-eight examples were analyzed. Tumors were invariably pedunculated polyps with thin stalks, often presented as loosely attached intraluminal nodules, with cauliflower architecture (akin to cholesterol polyps) comprised of compact, back-to-back acinar-like, small tubular units with minimal/no cytoplasm showing variable complexity, creating a picture distinct from the other tubular type dysplasia in the gallbladder. Their limited stroma showed distinctive amorphous amyloid-like hyalinization (39%). While some had round nuclei with single prominent nucleoli, others exhibited slightly more elongated nuclei with washed out chromatin reminiscent of papillary thyroid carcinoma. Squamoid/meningothelial-like morules (71%) and subtle neuroendocrine cell clusters (39%) were frequent. The level of cytoarchitectural atypia qualified as high-grade dysplasia (HGD) in all cases, but none were invasive. The background mucosa showed no dysplasia, but cholesterosis. The majority ($n = 8/12$) showed diffuse MUC6 expression and lacked MUC5AC expression. Based on these observations, 635 gallbladder carcinomas were re-analyzed for residual/adjacent lesions with entity-defining characteristics disclosed here, and none could be identified. Preinvasive tubular non-mucinous neoplasm of the gallbladder, which we propose to classify as intracholecystic tubular non-mucinous neoplasm, is a clinicopathologically discrete entity, which tends to occur in uninjured gallbladders and in association with cholesterol polyps. By being tubular, non-mucinous and MUC6-positive, it is akin to intraductal tubulopapillary neoplasms of pancreatobiliary tract, but it is also

different in many other aspects. Although their cytoarchitectural complexity warrants an HGD/carcinoma classification, they do not show invasion and their distinct characteristics warrant their separate classification.

doi: <https://doi.org/10.1007/s00428-020-02877-7>

- **Long-term outcomes of surgical resection for T1b gallbladder cancer: an institutional evaluation**

BMC cancer 2020 Jan;20(1):20

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=31907021>

BACKGROUND: There is no comprehensive agreement concerning the overall performance of radical resection for T1b gallbladder cancer (GBC). This research focused on addressing whether T1b GBC may spread loco-regionally and whether radical resection is necessary. **METHODS:** A retrospective analysis was conducted of 1032 patients with GBC who underwent surgical resection at our centre and its affiliated institutions between January 1982 and December 2018. A total of 47 patients with T1b GBC, 29 (62%) of whom underwent simple cholecystectomy and 18 (38%) of whom underwent radical resection with regional lymph node dissection, were enrolled in the study. **RESULTS:** GBC was diagnosed pre-operatively in 16 patients (34%), whereas 31 patients (66%) had incidental GBC. There was no blood venous or perineural invasion in any patient on histology evaluation, except for lymphatic vessel invasion in a single patient. There were no metastases in any analysed lymph nodes. The open surgical approach was more prevalent among the 18 patients who underwent radical resection (open in all 18 patients) than among the 29 patients who underwent simple cholecystectomy (open in 21; laparoscopic in 8) ($P = 0.017$). The cumulative 10- and 20-year overall survival rates were 65 and 25%, respectively. The outcome following simple cholecystectomy (10-year overall survival rate of 66%) was akin to that following radical resection (64%, $P = 0.618$). The cumulative 10- and 20-year disease-specific survival rates were 93 and 93%, respectively. The outcome following simple cholecystectomy (10-year disease-specific survival rate of 100%) was equivalent to that following radical resection (that of 86%, $P = 0.151$). While age (> 70 years, hazard ratio 5.285, $P = 0.003$) and gender (female, hazard ratio 0.272, $P = 0.007$) had a strong effect on patient overall survival, surgical procedure (simple cholecystectomy vs. radical resection) and surgical approach (open vs. laparoscopic) did not. **CONCLUSIONS:** Most T1b GBCs represent local disease. As pre-operative diagnosis, including tumour penetration of T1b GBC, is difficult, the decision of radical resection is justified. Additional radical resection is not required following simple cholecystectomy provided that the penetration depth is restricted towards the muscular layer and that surgical margins are uninvolved.

doi: <https://doi.org/10.1186/s12885-019-6507-2>

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

The American journal of surgical pathology 2020 04;44(4):467-476

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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1.4 Bile Ducts

- **Biliary intraductal tubule-forming neoplasm: a whole exome sequencing study of MUC5AC-positive and -negative cases**

Histopathology 2020 Jun;76(7):1005-1012

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=32181510>

AIMS: Biliary intraductal tubular neoplasms that are non-mucinous and negative for mucin 5AC (MUC5AC) are called intraductal tubulopapillary neoplasms (ITPNs). Intraductal tubular neoplasms with mucinous cytoplasm and MUC5AC positivity also occur and their nature remains unclear, although some pathologists may classify these as ‘intraductal papillary neoplasms of the bile duct (IPNBs) of gastric type’. This study aimed to elucidate genetic features of biliary intraductal tubular neoplasms. METHODS AND RESULTS: Six resected cases of biliary intraductal neoplasm with >70% tubular configuration were characterised by clinicopathological examination and whole exome sequencing, and the findings obtained were compared between MUC5AC-negative (n = 2) and -positive cases (n = 4). The intraductal tumours consisted of the pancreatobiliary-type epithelium with high-grade dysplasia arranged in back-to-back tubules. Both of the two MUC5AC-negative cases were non-invasive neoplasms and developed in the liver, whereas all MUC5AC-positive cases had invasive carcinoma and were present in the intrahepatic (n = 2), perihilar (n = 1) and distal bile ducts (n = 1). In an exome-sequencing study, MUC5AC-negative cases harboured mutations in CTNNB1, SF3B1, BAP1 and BRCA1 (one case each). KRAS mutations were observed in three of four MUC5AC-positive cases (75%) but none of the MUC5AC-negative neoplasms. Compared to published data, known driver genes of other intraductal neoplasms of the pancreatobiliary system (e.g. APC, CTNNB1, STK11, GNAS and PIK3CA) were wild-type in all but one MUC5AC-negative case with CTNNB1 mutation. Chromatin modifiers (ARID1A, BAP1 and KMT2C) were also altered in MUC5AC-positive cases, similar to usual cholangiocarcinomas. CONCLUSIONS: This exome-sequencing study suggested that MUC5AC-negative biliary ITPNs are genetically distinct from pancreatic ITPNs and IPNBs. They may also biologically differ from MUC5AC-positive tubular neoplasms despite morphological resemblance.

doi: <https://doi.org/10.1111/his.14103>

- **Intraductal papillary neoplasms of the bile duct consist of two distinct types specifically associated with clinicopathological features and molecular phenotypes**

The Journal of pathology 2020 May;251(1):38-48

PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=32100878>

Intraductal papillary neoplasm of the bile duct (IPNB) is a grossly visible papillary biliary neoplasm with morphological variations and occasional invasion. Recently a new classification of IPNB into type 1 and type 2 was proposed in which the type 1 IPNBs consist of fine papillary neoplastic glands and the type 2 IPNBs consist of complex branching glands, seldom with foci of solid-tubular components. However, clinicopathological and molecular characteristics of these types of IPNBs are yet to be identified. We aimed to uncover clinicopathological and molecular characteristics of the types of IPNBs. Thirty-six IPNBs were studied retrospectively. Clinicopathological features as well as molecular alterations of 31 genes were evaluated by means of targeted next-generation sequencing and immunohistochemical examination of expression of mucin and cancer-associated molecules. The 36 IPNBs were classified into 22 of type 1 and 14 of type 2. The type 1 IPNBs were associated with a non-invasive phenotype, intestinal and oncocytic subtypes, development in the intrahepatic bile duct, overt mucin production, and a relatively good prognosis. The type 2 IPNBs were associated with an invasive phenotype, the pancreatobiliary subtype, development within the extrahepatic bile duct, and worse prognosis compared with the type 1 IPNBs. In the molecular analysis, recurrent mutations were found in TP53 (34.3%), KRAS (31.4%), STK11 (25.7%), CTNNB1 (17.1%), APC (14.3%), SMAD4 (14.3%), GNAS (11.4%), PBRM1 (11.4%), ELF3 (8.6%), KMT2C (8.6%), NF1 (8.6%),

PIK3CA (8.6%), ARID1A (5.7%), ARID2 (5.7%), BAP1 (5.7%), BRAF (5.7%), EPHA6 (5.7%), ERBB2 (5.7%), ERBB3 (5.7%), KMT2D (5.7%), and RNF43 (5.7%). Mutations in KRAS and GNAS were enriched in the type 1 IPNBs, whereas mutations in TP53, SMAD4, and KMT2C were enriched in the type 2 IPNBs. These results indicate that IPNBs consist of two distinct types of neoplasms specifically associated with clinicopathological features and molecular phenotypes. © 2020 Pathological Society of Great Britain and Ireland. Published by John Wiley & Sons, Ltd.

doi: <https://doi.org/10.1002/path.5398>

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- **Testing for ROS1, ALK, MET, and HER2 rearrangements and amplifications in a large series of biliary tract adenocarcinomas**

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PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/?term=32447492>

Biliary tract carcinomas are divided into intrahepatic, perihilar, distal extrahepatic cholangiocarcinomas, and gallbladder adenocarcinomas. Therapies targeting ROS1, ALK, MET, and HER2 alterations are currently evaluated in clinical trials. We assessed ROS1 and ALK translocations/amplifications as well as MET and HER2 amplifications for each tumor subtype by fluorescent in situ hybridization (FISH) and immunohistochemistry (IHC) in 73 intrahepatic, 40 perihilar bile duct, 36 distal extrahepatic cholangiocarcinomas, and 45 gallbladder adenocarcinomas (n = 194). By FISH, we detected targetable alterations in 5.2% of cases (n = 10): HER2 and MET amplifications were found in 4.1% (n = 8) and 1.0% (n = 2), respectively. The HER2-amplified cases were mostly gallbladder adenocarcinomas (n = 5). The MET- and HER2-amplified cases were all positive by IHC. Fourteen cases without MET amplification were positive by IHC, whereas HER2 over-expression was detected by IHC only in HER2-amplified cases. We detected no ALK or ROS1 translocation or amplification. Several alterations were consistent with aneuploidy: 24 cases showed only one copy of ROS1 gene, 4 cases displayed a profile of chromosomal instability, and an over-representation of centromeric alpha-satellite sequences was found in five cases. We confirm a relatively high rate of HER2 amplifications in gallbladder adenocarcinomas and the efficacy of IHC to screen these cases. Our results also suggest the value of IHC to screen MET amplification. Contrary to initial publications, ROS1 rearrangements seem to be very rare in biliary tract adenocarcinomas. We confirm a relatively high frequency of aneuploidy and chromosomal instability and reveal the over-representation of centromeric alpha-satellite sequences in intrahepatic cholangiocarcinomas.

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1.5 Ampulla

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

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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.

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