GIPS Journal Watch
November & December 2020

Intestinal metaplasia around the gastroesophageal junction is frequently associated with antral reactive gastropathy: implications for carcinoma at the gastroesophageal junction

Vyas M, Celli R, Singh M, Patel N, Aslanian HR, Boffa D, Deng Y, Ciarleglio MM, Laine L, Jain D
Hum Pathol. 2020;105:67-73.
https://pubmed.ncbi.nlm.nih.gov/32941964/

The hypothesis of this retrospective histopathologic study is that bile reflux, rather than gastric acid alone, causes the mucosal injury and resulting intestinal metaplasia seen at the gastroesophageal (GE) junction. In order to test this hypothesis, the authors compare a group of patients who have "reactive" antral gastropathy in the absence of a known medication injury (often assumed to be secondary to bile reflux) to a group of patients without antral mucosal changes. They then look at the GE junction biopsies from these patient cohorts to see if the incidence of inflammation and intestinal metaplasia is also different between groups. They find that the patients who had reactive (presumed bile reflux-related) gastropathy were more likely to have endoscopic features of Barrett esophagus (18% vs. 7%) as well histologic confirmation of intestinal metaplasia (33 % vs. 5%). They conclude that bile reflux may play an important etiologic role of GE junction malignancy.

Early esophageal squamous cell carcinoma in a Western series is not associated with active HPV infection

Kanaan C, Lorenzo D, Barret M, Audebourg A, Leblanc S, Chaussade S, Prat F, Terris B
Virchows Arch. 2020;477(5):697-704.
https://pubmed.ncbi.nlm.nih.gov/32524184/

In this study the authors examined P16 and P53 expression by immunohistochemistry, as well as HPV in situ hybridization, in esophageal squamous cell carcinomas. While the authors found that 21% of their 86 cases demonstrated reactivity for P16, none were found to be positive for HPV by ISH. Instead, these cases appeared to correlate with alcohol or tobacco consumption and histologically exhibited marked inflammatory infiltrates. This study found no association between esophageal SCC and active HPV infection in their Western cohort.

Mouse double minute 2 amplification in oesophageal squamous cell carcinoma is associated with better outcome

Jiang D, Chen L, Huang J, Wang H, Song Q, Shi P, Wang H, Hou Y
Histopathology. 202;77(6):963-973.

https://pubmed.ncbi.nlm.nih.gov/32652667/

Esophageal squamous cell carcinoma has a relatively low 5-year survival rate and there is increased interest in the identification of biomarkers that would assist in the risk stratification of these patients. Mouse double minute 2 (*MDM2*) amplification has been reported in a subset of esophageal squamous cell carcinomas but its clinical significance is uncertain. In these study, the authors attempt to determine the frequency of *MDM2* amplification in their population, as well as to assess the prognostic significance of this amplification. A tissue microarray was created from resected esophageal squamous cell carcinomas from 515 Chinese patients. Fluorescent in situ hybridization studies for *MDM2* were performed on all 515 tumors. *MDM2* amplifications were identified in 37 cases (7.2%). A total of 3.1% showed high-level amplification. Amplification of *MDM2* was negatively associated with tumor size, disease progression, and death. Multivariate analysis demonstrated that *MDM2* amplification was an independent prognostic factor for improved outcome. Stratifying these data based upon clinical stage demonstrates that the prognostic significance of *MDM2* amplification with regard to disease-free and overall survival is restricted to early stage tumors. The authors conclude that *MDM2* amplification is correlated with improved patient outcomes in stage 1 and stage 2 esophageal squamous cell carcinomas and may assist in the risk stratification of patients who may be poor candidates for intensive chemotherapy and surgical resection.

Helicobacter pylori antigen but not the organism is occasionally present within germinal centers: implications for patient management and biology

Nelson ND, Tondon R, Fortuna D, Westerhoff M, Swanson PE, Furth E
Am J Surg Pathol. 2020;44(11):1528-1534.
https://pubmed.ncbi.nlm.nih.gov/32657781/

The authors have encountered multiple cases in which immunohistochemical (IHC) staining for *Helicobacter pylori* (*H. pylori*) showed reticular immunoreactivity in germinal centers without organisms on the overlying gastric surface. To this end, the authors aimed to determine the prevalence and clinical significance of this germinal center pattern of immunoreactivity and to understand the mechanism underlying this pattern. A retrospective evaluation of the frequency of *H. pylori* germinal center immunoreactivity via evaluation of 367 gastric specimens (over a 54-month period) was performed. *H. pylori* germinal center immunoreactivity was observed in 5% of cases with germinal centers. Nine of 11 (81%) patients with *H. pylori* germinal center immunoreactivity had concurrent or recent *H. pylori* infection. Only 2 patients (18%) had neither concurrent nor recent *H. pylori* infection. This was in contrast to 36% (9/25) patients with germinal centers but no immunoreactivity (P = 0.03). None of the patients with germinal center immunoreactivity developed mucosa-associated lymphoid tissue lymphoma. In situ hybridization for *H. pylori* performed on 3 cases with positive germinal center IHC were negative for *H. pylori* nucleic acids within those germinal centers, demonstrating that only the antigen is present. These findings support a link between germinal center immunoreactivity for *H. pylori* and infection with this organism. The authors recommend reporting all germinal

center *H. pylori* IHC staining, and accompanied by a note with a recommendation for ancillary *H. pylori* testing, such as a stool antigen test or urea breath test when organisms are not identified in overlying foveolar or surface epithelial cells.

Gastrin staining in inflamed stomach biopsies labeled as "antral" rarely detects atrophic gastritis

Dunn ALJ, Drage MG, Whitney-Miller CL, McMahon LA, Gonzalez RS
Am J Clin Pathol. 2020;154(6):761-766.
https://pubmed.ncbi.nlm.nih.gov/32632455/

Histologically, well-developed autoimmune metaplastic atrophic gastritis (AMAG) is characterized by a diffuse lymphoplasmacytic infiltrate with loss of oxyntic glands that may be replaced by intestinal, pyloric, or pancreatic glands. In this study, the authors evaluated whether AMAG could be overlooked in tissue samples not explicitly noted as being from the gastric body or fundus. They assessed whether the use of gastrin immunohistochemistry would increase sensitivity for diagnosing early AMAG. Any case with absence of gastrin-positive endocrine cells in this study was reflexed to chromogranin immunohistochemistry. The 298-patient study cohort comprised 222 females (mean age, 47 years) and 76 males (mean age, 49 years). Biopsies were designated as "antral/antral nodules" (61%), and the rest were labeled "gastric/random stomach" (39%). The majority of the specimens (289/298; 97%) demonstrated G cells on gastrin immunohistochemistry, confirming that the antral-appearing mucosa on H&E indeed arose from the gastric antrum. The remaining 9 specimens (3%) demonstrated absence of gastrin immunostaining in at least some inflamed antral- appearing fragments, indicating that those tissue samples arose from the body of the stomach; one of those showed endocrine cell hyperplasia by chromogranin staining. Therefore, this study emphasizes the importance of meticulously analyzing the histologic appearance regardless of specimen labeling. The authors conclude that occasionally specimens designated as “antrum” are not from antrum, and such labeling can bias pathologists against consideration of AMAG as a diagnosis. Pathologists should be aware of the histologic features of early AMAG and should meticulously analyze tissue regardless of specimen labeling. Gastrin immunostain can be used as a supplemental diagnostic tool when encountering inflamed antral-appearing specimens.

Investigation of the clinical significance and pathological features of lanthanum deposition in the gastric mucosa

Nishida S, Ota K, Hattori K, Iwatsubo T, Kawaguchi S, Kojima Y, Takeuchi T, Maeda T, Masahiro Sakaguchi M, Higuchi K
BMC Gastroenterol. 2020;23;20(1):396.
https://pubmed.ncbi.nlm.nih.gov/33228604/

This retrospective study aimed to investigate the clinical significance of lanthanum (La) deposition in the gastric mucosa, and the association between endoscopic features and histologic findings in the same population. The study compared background factors in patients taking lanthanum carbonate (LaC) with and without La deposition in their gastroscopic biopsy specimen. There was a significant difference in the total dose of LaC between the La-positive and La-negative groups. In 27 biopsy specimens with specific whitish mucosa, 10 showed mild histiocytic infiltration and 17 showed severe infiltration. In contrast, among 24 specimens with non-whitish mucosa, 5 showed no histiocytic infiltration, 10 showed mild infiltration, and 9 showed severe infiltration. There was a significant relationship between endoscopic features and the degree of histiocytic infiltration. The authors concluded that La deposition in the gastric mucosa depended on the total dose of LaC and was not affected by background factors. The specific endoscopic features of La deposition are associated with the infiltration of histiocytes.

The clinicopathological and molecular features of sporadic gastric foveolar type neoplasia

Sugai T, Uesugi N, Habano W, Sugimoto R, Eizuka M, Fujita Y, Osakabe M, Toya Y, Suzuki H, Matsumoto T
Virchows Arch. 2020;477(6):835-844.
https://pubmed.ncbi.nlm.nih.gov/32533343/

This study evaluated the clinicopathological characteristics and molecular alterations contributing to the development of gastric intraepithelial foveolar type neoplasia (IEFN) compared to intestinal type neoplasia (IEIN) with low grade dysplasia. They looked at CDX2, P53 nuclear β-catenin expression, microsatellite instability (MSI), DNA methylation status (low methylation epigenotype [LME], intermediate ME, or high ME), allelic imbalances (AIs), and *APC* promoter 1B mutations. There were no differences in the frequencies of CDX2, P53 expression, and MSI between IEFN and IEIN cases. Nuclear expression of β-catenin was significantly higher in IEIN than in IEFN. In addition, although the rate of LME was significantly higher in IEFN cases than in IEIN cases, IEFN was characterized by AIs at multiple foci. Finally, mutation of the *APC* promoter 1B was detected in only one IEFN case. Their findings suggests that IEFN may be an independent entity in terms of molecular alterations including the presence of multiple AIs and LME.

Gastric neuroendocrine tumours from long-term proton pump inhibitor users are indolent tumours with good prognosis

Trinh VQ, Shi C, Ma C
Histopathology. 2020;77(6):865-876.
https://pubmed.ncbi.nlm.nih.gov/32702178/

Gastric neuroendocrine tumors can be subtyped depending upon whether they develop in the setting of autoimmune metaplastic atrophic gastritis (type I), multiple endocrine neoplasia type

I or Zollinger-Ellison syndrome (type II), or sporadically in the absence of hypergastrinemia (type III). Type III gastric neuroendocrine tumors are relatively aggressive compared to the other subtypes. Proton pump inhibitors (PPI) are commonly used medications in the United States and associated with persistent hypergastrinemia. Gastric neuroendocrine tumors have only rarely been reported in the setting of PPI use. It is unclear whether or not gastric neuroendocrine tumors arising in this setting should be characterized as sporadic (type III), which has important management implications. In this study, the authors investigate whether neuroendocrine tumors developing in the setting of chronic PPI use exhibit an indolent clinical course or behave like more aggressive type III tumors. Their cohort consists of 66 patients with gastric neuroendocrine tumors but no clinical or pathologic evidence of atrophic gastritis, MEN 1, or Zollinger-Ellison syndrome. Long-term PPI use, defined as at least one year, was seen in 58% of their cohort, with the remaining 42% either having had PPI use for less than one year or no PPI use. Though not statistically significant, neuroendocrine tumors developing in the setting of PPI use tended to be smaller, confined to the mucosa and submucosa, and lacked lymphovascular invasion. Perhaps more importantly, there were no instances of distance metastasis or death in PPI users, while seven (25%) of the patients with sporadic gastric neuroendocrine tumors died. The authors conclude from these data that gastric neuroendocrine tumors developing in long-term PPI users are indolent and should not be classified as sporadic type III tumors.

Chromosomal and molecular pathway alterations in the neuroendocrine carcinoma and adenocarcinoma components of gastric mixed neuroendocrine-nonneuroendocrine neoplasm

Sun L, Zhang J, Wang C, Zhao S, Shao B, Guo Y, Liu Y, Sun Y
Mod Pathol. 2020;33(12):2602-2613.
https://pubmed.ncbi.nlm.nih.gov/32461621/

The authors analyzed high resolution copy number profiling data on neuroendocrine carcinoma (NEC) and adenocarcinoma components of eight gastric mixed adenoneuroendocrine carcinoma (MANEC). Common copy number variations (CNVs) were frequently detected in both components, supporting the likelihood of single clonal origin of morphologically heterogenous tumor cells. The authors also found some CNVs to be specific for the NEC component such as MAPK1 loss.

Looking into digestive mixed neuroendocrine – nonneuroendocrine neoplasms: subtypes, prognosis, and predictive factors

Uccella S, La Rosa S
Histopathology. 2020;77(5):700-717.
https://pubmed.ncbi.nlm.nih.gov/32538468/

In this review, the authors begin by discussing the historical terminology used to describe epithelial neoplasms with mixed neuroendocrine and nonneuroendocrine components. They go on to review the concept of mixed neuroendocrine – nonneuroendocrine neoplasms (MiNEN), a term that more accurately captures the diverse histologic features of these tumors and facilitates clinically relevant discussion with the treating oncologist. They discuss the histologic features of MiNENs, specifically the intermingling of neoplastic cells with neuroendocrine and nonneuroendocrine histologic features at least focally. They also highlight the importance of confirmatory immunohistochemical studies while warning against the over interpretation of these markers in tumors lacking classical neuroendocrine histology. A brief review of the genetics of MiNENs is also provided, along with a discussion of MiNENs at different sites within the tubular gut, pancreas, extrahepatic biliary tree, gallbladder, and liver. They end the review with a discussion of unresolved issues with regard to the diagnosis of MiNENs such as the classification of amphicrine carcinomas that are made up of a single population of cells showing a hybrid morphology, the currently accepted but arbitrary 30% cutoff for each component in order for a tumor to be considered mixed, and the identification of neuroendocrine differentiation following neoadjuvant therapy.

Comparison of metastasis between early-onset and late-onset gastric signet ring cell carcinoma

Zhou QP, Ge YH, Liu CY
BMC Gastroenterol. 2020;14;20(1):380.
https://pubmed.ncbi.nlm.nih.gov/33189128/

This is a retrospective study using the Surveillance, Epidemiology, and End Results (SEER) database and data from a local hospital to determine if a difference exists between metastases from early-onset (EOGC) and late-onset gastric signet ring cell carcinoma (SRCC). A total of 2052 EOGC patients from the SEER database and 403 patients from the local hospital were retrieved. Late-onset SRCC patients had worse survival than early-onset patients, but late-onset SRCC patients were less likely to have distant metastases. The study also found that an age of 45 or younger was an independent risk factor for distant metastases. The authors concluded that distant metastases were more common in early-onset SRCC than in late-onset SRCC.

p53 immunostaining cannot be used to predict *TP53* mutations in gastric cancer: results from a large Central European cohort

Schoop I, Maleki SS, Behrens HM, Druger S, Haag J, Rocken C
Hum Pathol. 2020;105:53-66.
https://pubmed.ncbi.nlm.nih.gov/32971129/

Although gastric carcinoma in general has a poor prognosis, the malignancy is genetically heterogeneous, and certain molecular subtypes may have different outcomes or respond

differently to certain therapies. The Tumor Cancer Genome Atlas (TCGA) has proposed four molecular subgroups of gastric carcinoma, one of which is the chromosomal instable (CIN) subtype. The authors of this study recognized that CIN gastric cancers are likely to be resistant to therapy because of intratumoral heterogeneity; they therefore sought a readily available diagnostic technique to identify these CIN cancers. The authors hypothesized that, because *TP53* mutations were one of the characteristics of CIN in the TCGA analysis, diffuse expression or complete loss of p53 by immunohistochemistry may correlate with CIN. Immunohistochemistry for p53 was performed in 467 unique gastric carcinomas, and only 53 (11%) had a heterogenous staining pattern. Twenty-five (5%) were p53 negative, and the remaining cases had what is described as a "homogenous" staining pattern. Several algorithms were constructed to "bin" these various p53 expression patterns. When p53 expression was compared to the mutation status of *TP53* by Sanger sequencing in a subset of cases (n=111), there was an overall correlation between staining and mutation, but individual cases would have been misclassified if IHC had been the only tool for determination of CIN. The authors conclude that they could not confidently use p53 immunohistochemistry to predict the *TP53* mutational status in gastric cancer.

Claudin-18 as a marker for identifying the stomach and pancreatobiliary tract as the primary sites of metastatic adenocarcinoma

Li WT, Jeng YM, Yang CY
Am J Surg Pathol. 2020;44(12):1643-1648.
https://pubmed.ncbi.nlm.nih.gov/32925194/

The authors examined claudin-18 immunostaining as a marker for identifying the primary site of metastatic adenocarcinoma in the stomach and pancreatobiliary tract. The authors stained tissue arrays containing 575 carcinomas from different anatomic sites and representative sections of 157 metastatic adenocarcinomas with claudin-18 immunostain. In the group of primary tumors, claudin-18 was frequently expressed in gastric, pancreatic, and pulmonary mucinous adenocarcinomas. Membranous staining of claudin-18 was present in 82% (54/66) of gastric adenocarcinomas, 68% (30/44) of pancreatic ductal adenocarcinomas, 40% (8/20) of cholangiocarcinomas, 73% (8/11) of mucinous pulmonary adenocarcinomas, 52% (19/35) of ovarian mucinous carcinomas, 14% (9/64) of colorectal adenocarcinomas, and 8.6% (5/58) of nonmucinous pulmonary adenocarcinomas. Diffuse staining of claudin-18 was noted in >50% of tumor cells in most cases of gastric and pancreatic adenocarcinoma, while the staining pattern was more heterogeneous (ranging from <10% to >50%) in other types of adenocarcinoma. For metastatic adenocarcinoma, 88% (15/17) of gastric adenocarcinomas, 78% (18/23) of pancreatic adenocarcinomas, and 57% (4/7) of cholangiocarcinomas and gallbladder adenocarcinomas were positive for claudin-18. Only 4 tumors that originated outside the stomach and pancreatobiliary tract were positive for claudin-18. The authors conclude that claudin-18 has an acceptable sensitivity (79%) and excellent specificity (93%) as a marker of gastric and pancreatobiliary adenocarcinoma and can aid pathologists and clinicians in narrowing down the primary cancer sites to these anatomic sites.

Upper gastrointestinal cancer risk and surveillance outcomes in Li-Fraumeni Syndrome

Katona BW, Powers J, McKenna DB, Long JM, Le AN, Hausler R, Zelley K, Jennings S, Domchek SM, Nathanson KL, MacFarland SP, Maxwell KN
Am J Gastroenterol. 2020;115(12):2095-2097.
https://pubmed.ncbi.nlm.nih.gov/32969947/

The authors assessed upper gastrointestinal (UGI) cancer risk and surveillance outcomes in Li-Fraumeni Syndrome (LFS) using the International Agency for Research on Cancer database and a single-center adult LFS cohort. UGI cancer was found to be present in 7.2% of families and 3.9% of individuals with *TP53* mutation in the International Agency for Research on Cancer; 29% occurred before age 30. In the LFS cohort, 35 individuals (31%) had upper endoscopies (n=48), of which 3 (8.5%) had concerning UGI findings. The authors conclude that UGI cancer occurs in LFS and state that upper endoscopy should be part of the LFS surveillance program.

Gastric cancer among American Indian and Alaska Native populations in the United States, 2005-2016

Melkonian SC, Pete D, Jim MA, Haverkamp D, Wiggins CL, Bruce MG, White MC
Am J Gastroenterol. 2020;115(12):1989-1997.
https://pubmed.ncbi.nlm.nih.gov/32740090/

In the United States, American Indian and Alaska Native (AI/AN) populations have some of the highest rates of gastric cancer and death. The authors in this study reviewed population based cancer registry data from 2005-2016. They compared gastric cancer incidence rates for AI/AN vs. white populations in the United States. Age-adjusted gastric cancer incidence rates were expressed per 100,000 per year. The authors found that incident rates for gastric cancer were disproportionately high in AI/AN populations, especially in Alaska. However, the rates in AI/AN populations varied by region and sex. The overall incidence rates decreased over time in both the AI/AN and white populations, nevertheless, decreases in rates in AI/AN males in some regions, including Alaska, were not significant. The high incidence of carcinoma in the central/distal portions of the stomach in these populations likely reflects a high prevalence of *H. pylori* infection. The authors conclude that these data could be used to develop interventions to reduce risk factors and improve access to healthcare among AI/AN people at high risk for gastric cancer.

Orientation precedes interpretation: comparison of different tissue handling techniques to attain well-oriented small-intestinal endoscopic biopsy

Garg N, Majumdar K, Sakhuja P

J Clin Pathol. 2020;73:769-771.
https://pubmed.ncbi.nlm.nih.gov/32561523/

This study aimed to evaluate whether using albumin and lens paper during the processing of endoscopic small bowel biopsies could improve tissue orientation. Several studies previously showed that meticulous tissue handing in the pathology laboratory could help to decrease fragmentation of tissue and achieve a more desirable orientation. The authors included 150 consecutive small intestinal biopsies from patients suspected of having non-neoplastic disorders over a duration of 6 months and they recorded the percentage length of well-oriented tissue among 4 groups (Whatman paper, Whatman paper + albumin, lens paper, lens paper + albumin). The highest median and mean percentage orientation was found among the lens paper+ albumin group. Multiple pairwise comparison between any two groups showed significantly lower percentage only in Whatman paper when compared to any other group, but there was no significant difference in paired comparison between non- Whatman groups. The authors concluded that using lens paper +/- albumin can provide better orientation, and the addition of albumin to Whatman paper can improve the orientation as well.

Diagnosis and prognostic significance of extramural venous invasion in neuroendocrine tumors of the small intestine

Liu Q, Polydorides AD
Mod Pathol. 2020;33(11):2318-2329.
https://pubmed.ncbi.nlm.nih.gov/32514164/

Extramural venous invasion (EMVI) is an independent prognostic factor in colorectal carcinoma, but has not be studied in small intestinal neuroendocrine tumors (NETs). This study reviewed primary small bowel NETs from 104 patients. EMVI was found in 58 cases and on univariate analysis was associated with lymphovascular and perineural invasion, tumor stage, and lymph node and distant metastases. However, on multivariate analysis, only distant metastases remained significant. Liver metastases were present in 55 cases and on univariate analysis were associated with lymphovascular and perineural invasion, tumor stage, lymph node metastasis and EMVI. However, on multivariate analysis, only EMVI remained significant. The authors conclude that EMVI is common in small bowel NETs and strongly correlated with the development of liver metastases and suggest the inclusion of EMVI in pathology reporting guidelines.

Local PEComatosis of the appendix: new insights into the histogenesis of nodular granular muscle degeneration and granular cells/granular cell lesions of the appendix

Tran TAN, Fanaian N
Int J Surg Pathol. 2020;28(8):899-905.
https://pubmed.ncbi.nlm.nih.gov/32423259/

This is a case report of nodular granular muscle degeneration (NGMD) of the appendix with dual immunopositivity for myogenic and melanocytic markers. Thus, the authors propose that this is a form of perivascular epithelioid cell proliferation. NGMD is a rare histologic finding characterized by distinctive nests of polygonal epithelioid cells with abundant pale-pink eosinophilic granular cytoplasm, in the inner layer of the muscularis propria or submucosa of the appendix. Although the nature of this finding has not been elucidated, it is believed that they are degenerative smooth muscle cells of the appendiceal muscularis propria. The authors analyzed the old medical literature on granular cells/granular cell lesions of the appendix to shed some light on this ill-defined morphologic finding and its relationship to NGMD of the appendix. They conclude that since NGMD of the appendix appears to be a lesion of perivascular epithelioid cells, the term NGMD is a misnomer, and thus they propose to designate them as "local PEComatosis of the appendix".

Clinicopathologic features of low-grade appendiceal mucinous neoplasm: a single-institution experience of 117 cases

Bell PD, Huber AR, Drage MG, Barron SL, Findeis-Hosey JJ, Gonzalez RS
Am J Surg Pathol. 2020 ;44(11):1549-1555.
https://pubmed.ncbi.nlm.nih.gov/32796173/

The authors studied the clinical and pathologic features of 117 low-grade appendiceal mucinous neoplasms (LAMN) over a period of 24 years (1994-2018) from a single institution (potentially eliminating the bias from extramural consults), including its staging distribution using current American Joint Committee on Staging (AJCC) criteria. LAMN was present in 0.6% of appendices in this study (76 females and 41 males; mean age: 60 years old). The diagnosis of LAMN was confirmed, using Peritoneal Surface Oncology Group International (PSOGI) criteria. The criteria were mucinous neoplasm with low-grade cytologic atypia, plus at least 1 of 7 subcriteria, namely, loss of muscularis mucosae (seen in 99% cases); fibrosis of submucosa (seen in 78% cases); pushing invasion (seen in 32% cases); dissection of acellular mucin in wall; undulating or flattened epithelial growth (seen in 100% cases); rupture of appendix (seen in 6% cases); mucin and/or cells outside appendix (27% cases). Ninety-two cases (79%) demonstrated epithelial denudation; these were often markedly dilated and contained intraluminal or mural micro- calcifications. Thirty-two (27%) had a mucosal Schwann cell proliferation. Per the AJCC 8th edition cancer staging manual, a majority (66%) were staged as pTis, 9% as pT3, 24% as pT4a, and 2% as pT4b. Ten cases (9%) were associated with histopathologic evidence of disseminated pseudomyxoma perionei (PMP). Only 1 patient died of disease, while 3 were alive with disease at last follow-up. The findings in their study confirms that LAMNs are bland and indolent neoplasms when confined to the appendix, without complicating factors such as rupture or PMP.

Clinicopathologic analysis of appendiceal goblet cell adenocarcinoma with peritoneal metastasis: World Health Organization grade predicts survival following cytoreductive surgery with intraperitoneal chemotherapy

Shyu S, Choudry H, Hall L, Pingpank J, Holtzman M, Bartlett D, Pai RK
Histopathology. 2020;77(5):798-809.
https://pubmed.ncbi.nlm.nih.gov/32557796/

Peritoneal dissemination of goblet cell adenocarcinoma is the most common route of metastasis, as well as the most common cause of death in patients with these appendiceal neoplasms. Several grading systems exist to subclassify goblet cell adenocarcinomas (most recently the three-tiered WHO 5th edition grading scheme), but focus primarily on grading the primary appendiceal neoplasm rather than the peritoneal metastasis. In this work, the authors investigate the prognostic significance of applying the WHO 5th edition grading criteria to peritoneal disease. They evaluate a cohort of 63 patients with peritoneal metastasis of goblet cell adenocarcinoma that had been subjected to cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion (CRS-HIPEC). The majority of the patient's in their cohort had peritoneal metastasis at the time of initial presentation, and most were treated with neoadjuvant chemotherapy prior to CRS-HIPEC. Application of the WHO 5th edition grading criteria to peritoneal metastasis resulted in 73% of cases being classified as WHO G3, 16% as WHO G2, and 11% as WHO G1. Approximately 95% of cases had complete cytoreduction (CC0, no residual macroscopic disease). Patients with WHO G3 peritoneal disease exhibited significantly reduced overall survival from both the date of diagnosis and the date of CRS-HIPEC when compared to WHO G1/G2 peritoneal tumors. There was, however, no differences in overall survival when the peritoneal tumors were graded with the Tang system. Multivariate analysis confirmed the poor survival associated with peritoneal WHO G3 goblet cell adenocarcinomas compared with WHO G1/G2 tumors, and also indicated that >50% extracellular mucin was also associated with a worse prognosis. The authors conclude that grading peritoneal metastasis of goblet cell adenocarcinomas using the WHO 5th edition grading criteria is clinically relevant and may assist in risk stratification/aid in the selection of patients most likely to benefit from CRS-HIPEC.

Non-neoplastic colorectal disease biopsies: evaluation and differential diagnosis

Moore , Feakins RM, Lauwers GY
J Clin Pathol. 2020;73(12):783-792.
https://pubmed.ncbi.nlm.nih.gov/32737191/

This is a review article that provides an overview on the histopathological characteristics of colitis with a focus on entities other than inflammatory bowel disease. The authors describe normal histologic findings in colonic biopsies, and then provided a pattern- based approach that integrates clinical and endoscopic findings to yield more focused pathologic diagnoses. The patterns of injury were based on the prominent type of inflammatory cells (neutrophils,

eosinophils, histiocytes and intraepithelial lymphocytosis), fibrosis, apoptosis, subepithelial collagenosis, pseudomembrane, and basal plasmacytosis. The paper also highlights the key features of multiple entities, including infection, ischemia, medication injury….etc.

Lymphocytic and collagenous colitis in children and adolescents: Comprehensive clinicopathologic analysis with long-term follow-up

Windon AL, Almazan E, Oliva-Hemker M, Hutchings D, Assarzadegan N, Salimian K, Montgomery EA, Voltaggio L
Hum Pathol. 2020;106:13-22.
https://pubmed.ncbi.nlm.nih.gov/32991931/

Microscopic colitides are classically taught as diseases that present in older patients. Rarely, though, histologic features consistent with lymphocytic or collagenous colitis are identified in a pediatric population. The purpose of this retrospective histopathologic study was to identify any atypical features in pediatric patients diagnosed with microscopic colitis and to provide clinical follow-up. Overall, 27 patients aged 3-18 were identified with a microscopic colitis. The majority (85%) had lymphocytic colitis, and most (67%) were females. While watery diarrhea is the most common complaint among adults and children, 67% of children also complained of abdominal pain. Eleven (41%) patients had known immune dysregulation, including six with common variable immune deficiency or IgA deficiency, three with celiac diseases, and two with juvenile arthritis. One patient was found to have LRBA deficiency which results in loss of CTLA-4 protein. The histologic features in this pediatric cohort were largely typical of microscopic colitis, but 9 patients also had increased crypt apoptosis. No patients had features of chronic injury as defined by crypt distortion, Paneth cell metaplasia, or basal plasmacytosis on initial diagnosis. Clinical follow-up was available for 23 (85%) of the patients, and 17 of these responded to therapy. Six patients did not respond to any form of therapy (diet change, medication cessation, or steroids). Only one patient went on to develop inflammatory bowel disease. Interestingly, there was no histologic difference in initial biopsies between the patients who did and not respond to therapy. The authors conclude that children with microscopic colitis by histology may have an underlying immune-dysregulation syndrome. It does not appear that this population is at high risk of developing inflammatory bowel disease.

Mitochondrial impairment drives intestinal stem cell transition into dysfunctional Paneth cells predicting Crohn's disease recurrence

Khaloian S, Rath E, Hammoudi N, Gleisinger E, Blutke A, Giesbertz P, Berger E, Metwaly A, Waldschmitt N, Allez M, Haller D
Gut. 2020;(11):1939-1951.
https://pubmed.ncbi.nlm.nih.gov/32111634/

Reduced number of Paneth cells (PC) and their impaired function has contributed to the ileal Crohn's disease (CD) pathogenesis. Paneth cells reside in proximity to Lgr5+ intestinal stem cells (ISC) and mitochondria are critical for ISC-renewal and differentiation. In this study they characterize ISC and PC under inflammatory conditions and described the role of mitochondrial function for ISC niche-maintenance by using ileal tissue from CD patients and mouse model for mitochondrial dysfunction and CD-like ileitis. They found out that in patients with CD and mouse models with CD-like ileitis, inflammation correlated with reduced numbers of Lysozyme-positive granules in PCs and decreased Lgr5 expression in crypts. These changes were also present in non-inflamed regions and were associated with the risk of recurrence. They show that inhibition of mitochondrial respiration linked mitochondrial function to the aberrant PC phenotype. Consistent with reduced stemness in vivo, crypts from inflamed CD-like ileitis mice failed to grow into organoids ex vivo. They also showed that Dichloroacetate-mediated inhibition of glycolysis, forced cells to shift to mitochondrial respiration, improved ISC niche function and rescued the ability of mice with CD-like ileitis crypts to form organoids.
In summary, they provide evidence that inflammation-associated mitochondrial dysfunction in the intestinal epithelium triggers a metabolic imbalance, causing reduced stemness and acquisition of a dysfunctional PC phenotype. They further showed that blocking glycolysis might be a novel drug target to antagonize PC dysfunction in CD patients.

Hyperplastic polyp or sessile serrated lesion? The contribution of serial sections to reclassification

Jaravaza DR, Rigby JM
Diagn Pathol. 2020;15(1):140.
https://pubmed.ncbi.nlm.nih.gov/33298116/

This is a retrospective study to assess the rate of reclassification of previously diagnosed cases as hyperplastic polyp into sessile serrated lesion (SSL) after obtaining additional histologic sections. Since the first description of SSL in 2003, many cohorts studied the rate of reclassification of hyperplastic polyps, and the authors sought to study the rate of reclassification using the 2019 WHO criteria, which is less stringent than 2010 criteria. They reviewed all 147 hyperplastic polyps of adult patients from Tygerberg Academic Hospital (2016-2017) with documented site of polyp, but no history of polyposis syndrome or carcinoma. Initial H&E review reclassified 9/147 cases as SSL and ~24% of case as others (mainly non- diagnostic mucosa, inflammatory/ prolapse polyp or conventional adenoma). After obtaining 8 serial sections on cases with initially confirmed HP (n=103), 11 were reclassified as SSL. All were less than 5 mm and the majority were distally located (10/11). A mean of 3.6 additional serial sections were required to reach a change in diagnosis. The authors found additional serial sections helpful in identifying SSL, even when the size of polyp was less than 5 mm.

Long term outcomes of colon polyps with high grade dysplasia following endoscopic resection.

Chang JJ, Chien CH, Chen SW, Chen LW, Liu CJ, Yen CL
BMC Gastroenterol. 2020;10;20(1):376.
https://pubmed.ncbi.nlm.nih.gov/33172387/

This is a clinical cohort study with patients who underwent polypectomy during screening colonoscopy to assess recurrent colonic adenoma risk factors. A total of 11,565 patients at the authors' facility underwent screening colonoscopy between September 1998 and August 2007. Data from 211 patients with colon polyps with high-grade dysplasia (HGD) who had undergone follow-up colonoscopy were included for analysis. Rates of metachronous adenoma and advanced adenoma at follow-up were 58% and 20%, respectively. The mean follow-up period was 5.5 ± 1.8 (3-12) years. Univariate logistic regression analysis revealed that an adenoma count of ≥ 3 at baseline colonoscopy was strongly associated with overall recurrence, multiple recurrence, advanced recurrence, proximal recurrence, and distal adenoma recurrence. Multivariate analysis revealed gender (male) and adenoma count ≥ 3 at index colonoscopy to be significantly associated with recurrence of advanced adenoma. The authors concluded that the recurrence of colonic adenoma at time of follow-up colonoscopy is common in patients who undergo polypectomy for HGD colonic adenomas during baseline colonoscopy. Risk of further developing advanced adenomas is associated with gender and the number of colon adenomas present.

Evaluation of *KRAS*, *NRAS* and *BRAF* mutational status and microsatellite instability in early colorectal carcinomas invading the submucosa (pT1): towards an in-house molecular prognostication for pathologists?

Bourhis A, De Luca C, Cariou M, Vigliar E, Barel F, Conticelli F, Marcorelles P, Nousbaum JB, Robaszkiewicz M, Samaison L, Badic B, Doucet L, Troncone G, Uguen A
J Clin Pathol. 2020;73(11):741-747.
https://pubmed.ncbi.nlm.nih.gov/32273401/

This is a case- control study to assess the value of microsatellite instability (MSI) and 3 other mutations in the risk assessment of early colorectal carcinoma (CRC) patients (i.e. pT1 involving submucosa). Over the past 2 decades, early CRC has been treated with endoscopic resection among patients who are low- risk based on histopathologic evaluation (margins, tumor differentiation, vascular invasion, invasion depth and tumor budding), and the use of molecular alterations is still debated in these patients. The authors investigated the significance of molecular mutations in predicting aggressive behavior of early CRC given the interobserver variability in histopathologic evaluation. They included 20 pT1 patients whom developed locoregional recurrence and/or metastatic disease during the 5 years following initial treatment (2009-2013) and 40 matched control cases without recurrence/metastasis. They recorded the histopathologic features associated with increased risk of recurrence, and performed the following: IHC for microsatellite instability (MSI), NGS (*KRAS*, *NRAS* and *BRAF*), and Idylla testing for MSI, *NRAS*, *BRAF*, and *KRAS* mutations. *KRAS* alterations were the most commonly detected mutations (found in approximately half of the cases), and there was no statistically significant

difference for molecular alterations among *KRAS*, *NRAS* and *BRAF* as well as for MSI/MSS between cases with or without metastatic evolution. Furthermore, the mutational status did not correlate with the histoprognostic parameters associated with an increased risk of tumor recurrence. In addition, there was very good agreement between Idylla tests and NGS results (*KRAS*, *NRAS* and *BRAF* status) and between Idylla MSI status and IHC result, and there were only 5 discrepant cases between NGS and Idylla. The authors concluded the molecular testing of *KRAS*, *NRAS*, *BRAF* and MSS/MSI status does not seem useful for prognostic purposes in pT1 CRC.

Associations of non-pedunculated T1 colorectal adenocarcinoma outcome with consensus molecular subtypes, immunoscore, and microsatellite status: a multicenter case-cohort study

Haasnoot KJC, Backes Y, Moons LMG, Kranenburg O, Trinh A, Vermeulen L, Noë M, Tuynman JB, van Lent AUG, van Ginneken R, Seldenrijk CA, Raicu MG, Trumpi K, Ubink I, Milne AN, Boonstra JJ, Groen JN, Schwartz MP, Wolfhagen FHJ, Geesing JMJ, Ter Borg F, Brosens LAA, van Bergeijk J, Spanier BWM, de Vos Tot Nederveen Cappel WH, Kessels K, Seerden TCJ, Vleggaar FP, Offerhaus GJA, Siersema PD, Elias SG, Laclé MM; Dutch T1 CRC Working Group
Mod Pathol. 2020;33(12):2626-2636.
https://pubmed.ncbi.nlm.nih.gov/32581367/

The authors used a case-cohort approach to study the outcomes of non-pedunculated T1 CRC with respect to their consensus molecular subtypes (CMS) and immunoscore. A total of 651 patients with non-pedunculated T1 CRC treated with surgery were identified. All patients with lymph node metastasis (LNM) or recurrence were included along with a randomly selected subgroup of 223 patients. Tissue microarrays were constructed to determine microsatellite instability (MSI) as well as CMS (MSI/CMS1, CMS2/3, CMS4). In the case-cohort, patients with CMS4 tumors had increased risk for LNM or recurrence compared to patients with tumors with other CMSs. The authors concluded that immunoscore and MSI were not significantly associated with adverse outcome after surgery, while CMS4 substantially increased the risk of adverse outcome.

Optimal criteria for G3 (poorly differentiated) stage II colon cancer: prospective validation in a randomized controlled Study (SACURA trial)

Ueno H, Ishiguro M, Nakatani E, Ishikawa T, Uetake H, Matsui S, Teramukai S, Murotani K, Ajioka Y, Shimazaki H, Maeda A, Takuma K, Yoshida T, Kambara T, Matsuda K, Takagane A, Tomita N, Sugihara K; SACURA Study Group
Am J Surg Pathol. 2020;44(12):1685-1698.
https://pubmed.ncbi.nlm.nih.gov/32868525/

An appropriate pathologic diagnosis of grade 3 (G3, poorly differentiated) colorectal carcinoma (CRC) is important, especially for stage II tumors because G3 is regarded as an essential risk

factor for recurrence according to the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology guidelines and is used to identify a subgroup of stage II CRC patients that may benefit from post- operative adjuvant therapy. According to a previous study, an intratumoural poorly differentiated area with no glandular formation (POR) that fills the microscopic field of a ×40 objective lens was an essential factor that defined G3. The authors aimed to prospectively validate this in a randomized controlled study of adjuvant chemotherapy (SACURA trial). The SACURA (Surgical Adjuvant Chemotherapy with UFT for Curatively Resected Stage II Colon Cancer) trial is a multicenter, randomized controlled study that evaluated the superiority of 1 year of adjuvant treatment with oral tegafururacil (UFT) compared with surgery alone for stage II colon cancer. They aimed to determine the accuracy of the prognostic stratification power of the grading system and to verify its superiority to the conventional tumor grading system by enrolling 991 stage II colon cancer patients. POR was graded according to the ×40 objective lens rule and the intensity of poorly differentiated clusters (GradePOR), and its prognostic power was compared with that of the conventional tumor grade (Gradeconv). A total of 313, 526, and 152 tumors were classified according to GradePOR as G1POR, G2POR, and G3POR, respectively, and the 5-year relapse-free survival (RFS) rates were 91.1%, 82.9%, and 74.7%, respectively (P<0.0001). When G3POR and G3conv were alternatively added to the prognostic model consisting of 8 conventional factors, only G3POR was a significant factor for RFS. The adverse impact of G3POR on RFS was greater in the microsatellite stable/microsatellite instability-low subset than that in the full analysis set. The authors conclude that G3POR, which is characterized by a simple definition for POR and the least differentiation policy with the ×40 objective lens rule, is expected to have an advantage in the objectiveness of the criteria compared with G3 defined by the UICC/TNM or the WHO classification, also especially given the robust prognostic value of G3POR validated in their study.

Clinical–pathologic characteristics and long-term outcomes of left flexure colonic cancer: a retrospective analysis of an international multicenter cohort

Pedrazzani C, Turri G, Park SY, Hida K, Fukui Y, Crippa J, Ferrari G, Orig M, Spolverato G, Zuin M, Bae SU, Baek SK, Costanz A, Maggioni D, Son GM, Scala A, Rockall T, Guglielmi A, Choi GS, Larson DW
Dis Colon Rectum. 2020;63(12):1593-1601.
https://pubmed.ncbi.nlm.nih.gov/33149021/

This is a retrospective analysis of left flexure tumors (LFT) of colonic adenocarcinoma from 10 tertiary referral centers in Europe, Asia, and the USA. LFT are uncommon and the prognostic significance of tumors is still controversial, with some authors reporting worse survival rates compared to other colonic sites. The authors defined LFT as those lesions arising among the last third of the transverse colon, the splenic flexure itself, and the first 10 cm of the descending colon. They studied 641 consecutive adult patients (3% of total CRC patients) with LFT with a minimum follow up of 24 months, and they paired them in a 1 to 1 fashion with right-sided tumors (RT) and sigmoid tumors (ST). The study excluded any tumor other than

adenocarcinoma, synchronous CRC, and presence of tumors other than CRC. In comparison to other groups, LFT patients more frequently presented with stenosis and showed higher rates of peritoneal recurrence. In comparison to RT patients, LFT patients had higher rates of systemic metastasis at the time of surgery and lower rates of harvested lymph nodes. In comparison to ST, LFT had a higher rate of mucinous histology and more commonly infiltrated serosa/ other organs ($p< 0.05$). There was no difference in the 5- year overall survival and cancer specific survival based on tumor location. The authors demonstrated that there is no evidence of independent prognostic value of LFT compared to RT and ST, but there is a higher rate of peritoneal carcinomatosis at recurrence in LFT patients.

Evaluating the impact of lymph node resampling on colorectal cancer nodal stage

Tran C, Howlett C, Driman DK
Histopathology. 2020;77(6):974-983.
https://pubmed.ncbi.nlm.nih.gov/32654207/

The accurate evaluation of lymph nodes for metastasis in colorectal cancer specimens has important prognostic and therapeutic implications. A minimum of 12 lymph nodes is used as a benchmark for adequate dissection in most institutions, with additional tissue sampling performed to reach this benchmark. In this study, the authors investigate whether resampling identifies additional lymph node metastasis and tumor deposits, as well as whether it has a clinical impact. Their cohort consisted of 395 oncologic colorectal carcinoma resections where additional sections were submitted to increase the lymph node yield if the initial count was less than 12. Over the 10 year study period, resampling increased the proportion of colorectal cancer specimens with lymph node counts greater than or equal to 12 from 84.9% to 92.5%. A total of 119 of the 395 cases had lymph node metastasis and/or tumor deposits. Resampling identified additional nodal metastasis and/or tumor deposits in 30 cases (7.6%), which resulted in upstaging in 20 cases. The identification of additional positive lymph nodes and/or tumor deposits resulted in 4 cases being reclassified as pN1a, 1 case as pN1b, and 3 cases as pN1c. The identification of additional positive lymph nodes did no change the N-stage for 10 cases. Logistic regression analysis failed to identify any patient, specimen, or prosector specific factors that predicted the identification of additional lymph nodes containing metastasis or tumor deposits following the submission of additional tissue. Sixty-one (52.1%) of the 117 stage II colorectal carcinomas initially had low lymph node yield, a high-risk factor that potentially influences the oncologists decision regarding whether or not to initiate adjuvant chemotherapy. Following resampling, the discovery of additional lymph nodes resulted in 33 of these 65 Stage II cases (50.8%) being classified as having no high-risk features. The authors conclude from this work that resampling in cases with initially inadequate lymph node dissections has an impact on nodal staging and may impact adjuvant treatment decisions.

Unique clinicopathologic and genetic alteration features in early onset colorectal carcinoma compared with age-related colorectal carcinoma: a large cohort next generation sequence analysis

Escobar D, Jones R, Gao J, Sun L, Liao J, Guang-Yu Y
Hum Pathol. 2020;105:37-46.
https://pubmed.ncbi.nlm.nih.gov/32916163/

Although the overall incidence of colorectal carcinoma is decreasing in the United States, the incidence of sporadic colorectal carcinoma in younger patients (<40 years old) has been increasing. Patients with early-onset colorectal carcinoma (eCRC) fall outside of the age recommendation for population-based screening tests, and they often present with advanced disease. The authors of this study compare two years of genetic data compiled from two patient cohorts, one of patients with eCRC (n=42), and one of patients over 70 years old with CRC (n=164). In general, they found that eCRC was more likely to be left-sided and high clinical stage than conventional CRC. Immunohistochemistry for mismatch repair proteins was performed on all tumors, and there was no statistically significant difference in the rates of protein expression between groups. Next generation sequencing was performed on the CRC at the Northwestern Memorial Hospital Diagnostic Molecular Biology Lab using a solid tumor panel that screens of 1825 hotspot mutations in 22 genes. Although the most frequently mutated genes were similar between cohorts, the relative proportion of the genes mutated were different. For example, *PIK3CA* was mutated in 29.3% of age-related CRC, but only 9.5% of eCRC. Mutations in *CTNNB1* were more common in eCRC (11.9%) than age-related CRC (2.4%). Finally, the rate of *BRAF* mutations was 4.8% in eCRC but 5 times that (19.5%) in age-related CRC. The lower prevalence of *BRAF* mutations in eCRC is explained by the patients in this cohort who were found to have MSI-H disease related to Lynch syndrome. In older adults, MSI-H disease was more often *BRAF* mutated with MLH methylation. The authors find that their cohort supports the hypothesis that early onset colorectal carcinoma differs both clinically and genetically from conventional, age-related colorectal carcinoma.

B7-H3 immune checkpoint expression is a poor prognostic factor in colorectal carcinoma

Lu Z, Zhao ZX, Cheng P, Huang F, Guan X, Zhang MG, Chen HP, Liu Z, Jiang Z, Zheng ZX, Zou SM, Wang XS
Mod Pathol. 2020;33(11):2330-2340.
https://pubmed.ncbi.nlm.nih.gov/32514163/

Metastatic colorectal cancer patients are not as responsive to PD-1/PD-L1 immunotherapy as some other tumors. Therefore, the authors investigated the expression of B7-H3 (another target for immunotherapy) in 805 primary tumors and matched metastases. They used tissue microarrays to evaluate B7-H3, B7-H4 and PD-L1 protein levels as well as differential lymphocyte infiltration. B7-H3 was the most commonly detected protein (50.9%) and coexpression with B7-H4 or PD-L1 was uncommon. Elevated expression of B7-H3 was

associated with advanced overall stage and was significantly related to decreased disease-free survival. B7-H3 expression was positively correlated with high density CD45RP T cells in primary tumors, while B7-H4 and PD-L1 overexpression were related to CD3 T-cell infiltration. The authors conclude that B7-H3 expression exhibited a higher prevalence and was related to aggressiveness, worse prognosis, and CD45RO T cell infiltration.

The prognostic role of tissue TLR2 and TLR4 in colorectal cancer

Beilmann-Lehtonen I, Böckelman C, Mustonen H, Koskensalo S, Hagström J, Haglund C
Virchows Arch. 2020;477(5):705-715.
https://pubmed.ncbi.nlm.nih.gov/32424768/

This study explored the prognostic value of Toll-like receptors, TLR2 and TLR4 in colorectal cancer (CRC) patients by immunohistochemistry. They found that among patients with lymph node-positive disease and no distant metastases, strong TLR2 immunoactivity associated with a better prognosis. Among patients with local disease, a strong TLR4 immunoactivity was associated with a worse disease-specific survival. Thus they are proposing to use TLR2 and TLR4 as new prognostic factors to indicate which CRC patients require adjuvant therapy and which could be spared unnecessary follow-up.

Colonoscopy and reduction of colorectal cancer risk by molecular tumor subtypes: a population-based case-control study

Hoffmeister M, Bläker H, Jansen L, Alwers E, Amitay EL, Carr PR, Kloor M, Herpel E, Roth W, Chang-Claude J, Brenner H
Am J Gastroenterol. 2020;115(12):2007-2016.
https://pubmed.ncbi.nlm.nih.gov/32858564/

Colonoscopy is associated with stronger risk reduction for distal colorectal cancers (CRC) than for proximal CRC. This study aimed to investigate whether reduction of CRC risk through colonoscopy varies according to different tumor markers and pathways of CRC. The authors performed a German population-based case-control study with 2,132 patients with first diagnosis of CRC and 2,486 control patients without CRC. They observed a strong risk reduction in CRC after colonoscopy that was weaker for microsatellite instable (MSI), *BRAF* mutated, proximal colon CRC classified into the sessile serrated pathway, especially after colonoscopy with detection of proximal adenomas or hyperplastic polyps. The authors state that this study extends the molecular understanding of differences in risk reduction of proximal and distal CRC.

Smoking and colorectal cancer risk, overall and by molecular subtypes: a meta-analysis

Botteri E, Borroni E, Sloan EK, Bagnardi V, Bosetti C, Peveri G, Santucci C, Specchia C, van den Brandt P, Gallus S, Lugo A
Am J Gastroenterol. 2020;115(12):1940-1949.
https://pubmed.ncbi.nlm.nih.gov/32773458/

This systematic review and meta-analysis looked at the association between cigarette smoking and colorectal cancer (CRC) risk. The authors found that smoking increases the risk of CRC in a dose dependent manner, while quitting smoking reduces CRC risk. In addition, smoking was associated with a higher risk of CRC developing through the microsatellite instability pathway (CpG island methylator phenotype positive, *BRAF* mutation positive).

Chromogranin A expression in rectal neuroendocrine tumors is associated with more aggressive clinical behavior and a poorer prognosis

Kim J, Kim JY, Oh EH, Yoo C, Park IJ, Yang DH, Ryoo BY, Ryu JS, Hong SM
Am J Surg Pathol. 2020;44(11): 1496-1505.
https://pubmed.ncbi.nlm.nih.gov/32735108/

The authors investigated the correlation between tissue chromogranin A expression in their cohort of 538 endoscopically or surgically rectal neuroendocrine tumors (NETs) with the clinicopathologic features and long-term disease-free survival (DFS) outcomes. Rectal NET cases with focal (5% to 50%) or diffuse (> 50%) labeling were classified as positive, and those with no or spotty (> 1% and <5%) chromogranin A labeling as negative. All of the rectal NETs in this study were synaptophysin positive, but chromogranin A positivity was detected in 111 cases (20.6%). Rectal NETs with chromogranin A expression were associated with an older age (≥50 y; P = 0.013), male sex (P = 0.002), radical resection (P = 0.003), larger tumor size (≥ 1 cm; P = 0.038), muscularis propria invasion (P=0.002), lymphovascular (P=0.014) and perineural (P<0.001) invasion, involved resection margin (P=0.028), lymph node metastasis (P=0.003), and had higher plasma chromogranin A levels (P = 0.023) when compared to those with negative chromogranin A expression during follow-up. There was no significant correlation between chromogranin A expression and histologic grade (P = 0.422), or synchronous distant metastasis (P = 0.638). The 10-year disease-free survival rate in patients with chromogranin A expression was also significantly shorter than the negative cases by both univariate (HR 14.438; 95% CI: 2.911-71.598; P < 0.001) and multivariate (HR 12.099; 95% CI: 2.044-71.608; P = 0.006) analyses. The authors concluded that chromogranin A protein correlates with more aggressive clinical behavior and is also a prognostic indicator of higher recurrence risk for patients with resected rectal NET, and these patients may require closer follow-up irrespective of the tumor grade, size, or invasion depth.

CD4/CD8 ratio as a novel marker for increased risk of high-grade anal dysplasia and anal cancer in HIV+ patients: a retrospective cohort study

Geltzeiler B, Xu Y, Carchman E, Ghouse Y, Beczkiewicz J, Son J, Voils CI, Striker R
Dis Colon Rectum. 2020;63(12):1585-1592.
https://pubmed.ncbi.nlm.nih.gov/33149020/

The authors sought to study the use of CD4:CD8 ratio as a marker for advanced anal disease (i.e. high-grade [HG] dysplasia and invasive squamous cell carcinoma [SCC]) in patients living with HIV, given the purported association of low- CD4:CD8 ratios with increased risk of other carcinomas. Immunosuppression is a known risk factor for HPV- related dysplasia such as anal dysplasia, and the screening and surveillance intervals for anal dysplasia are not well defined in HIV+ patients. In this retrospective study, 95 patients had HG- dysplasia and 16 had invasive SCC out of 377 HIV+ patients (2002-2018). Most clinical characteristics were similar between patients with dysplasia/carcinoma and patients without (including age, gender, race, history of sexually transmitted infection, smoking history or anal receptive intercourse), but patients with advanced anal lesions were more likely to have a clinical history of anal condyloma. Female sex and clinical history of anal condyloma were associated with increased odds of advanced disease, while Black race and higher CD4/CD8 ratios were associated with decreased odds of advanced disease. Nadir CD4/CD8 ratio, nadir CD4 count, and CD4/CD8 ratio nearest to the time of screening or diagnosis were lower in patients with advanced disease ($p < 0.001$). Receiver operating characteristic analysis found that the optimal cut off value for using the nadir CD4/CD8 ratio as a risk factor for advanced disease as 0.47 and for nearest CD4:CD8 ratio as 0.95 (sensitivity ~ 56% and specificity ~ 91%). The authors concluded that CD4:CD8 ratio may be able to identify HIV+ patients at greater risk of anal cancer, and suggested that patients with a history of low ratios should be more closely monitored for anal dysplasia and cancer.

CYLD-mutant cylindroma-like basaloid carcinoma of the anus: a genetically and morphologically distinct class of HPV-related anal carcinoma

Williams EA, Montesion M, Sharaf R, Corines J, Patel PJ, Gillespie BJ, Pavlick DC, Sokol ES, Alexander BM, Williams KJ, Elvin JA, Ross JS, Ramkissoon SH, Hemmerich AC, Tse JY, Mochel MC
Mod Pathol. 2020;33(12):2614-2625.
https://pubmed.ncbi.nlm.nih.gov/32461623/

The authors investigated mutations in *CYLD* in anal carcinoma (AC) with histologic features of cylindroma. DNA sequencing was performed on 574 ACs, of which 75 (13%) were found to have *CYLD* mutations (truncating alteration was most common, affecting 67%). The cylindroma-like histomorphology within the *CYLD*-mutant group was striking. Compared to *CYLD*-wildtype ACs, *CYLD*-mutant ACs were significantly more likely to be found in females and the cohort was slightly younger with a lower tumor mutational burden. In addition, there was a near universal detection of HPV-positivity in this cohort. The authors conclude that this previously uncharacterized subtype is a significant subgroup of ACs.

Head-to-head comparison of p63 and p40 in non-neuroendocrine carcinomas of the tubal gut

Bakhshwin AM, Gordon IO, Brown KB, Liu X, Allende DS
Int J Surg Pathol. 2020;28(8):835-843.
https://pubmed.ncbi.nlm.nih.gov/32466705/

An interesting useful study that looked at the diagnostic utility of P40 and P63 immunostains in the classification of GI tract non-neuroendocrine carcinomas. They found that P63 was reactive in 100% of squamous cells carcinomas (SCC) and adenosquamous carcinomas (ASCA) while P40 was reactive in 92.5% of these cases. P63 was reactive in 12% of adenocarcinomas while only 4% of adenocarcinomas stained with P40. Overall, they found that P63 and CK5/6 are more sensitive but less specific than P40 for SCC/ADSCA. They are also suggest using a panel of P63, P40, and CK5/6 to better classify poorly differentiated carcinomas.

Digital whole slide imaging compared with light microscopy for primary diagnosis in surgical pathology: A multicenter, double-blinded, randomized study of 2045 cases

Borowsky AD, Glassy EF, Wallace WD, Kallichanda NS, Behling CA, Miller DV, Oswal HN, Feddersen RM, Bakhtar OR, Mendoza AE, Molden DP, Saffer HL, Wixom CR, Albro JE, Cessna MH, Hall BJ, Lloyd IE, Bishop JW, Darrow MA, Gui D, Jen KY, Walby JAS, Bauer SM, Cortez DA, Gandhi P, Rodgers MM, Rodriguez RA, Martin DR, McConnell TG, Reynolds SJ, Spigel JH, Stepenaskie SA , Viktorova E, Magari R, Wharton KA, Qiu J, Bauer TW
Arch Pathol Lab Med. 2020;144(10): 1245-1253.
https://pubmed.ncbi.nlm.nih.gov/32057275/

A number of studies across organ systems have been conducted evaluating pathologists' use of whole slide imaging (WSI) compared to microscopy for primary diagnosis. The purpose of this study was to determine whether primary diagnoses rendered using WSIs are noninferior to diagnoses rendered by light microscopy in centers that use the Aperio AT2 DX system.
The authors compared concordance of diagnoses rendered on 2045 cases from a variety of organ systems across multiple study sites using light microscopy or WSI, compared to the reference diagnosis (the original diagnosis rendered on the case) using archival slides. Pathologists served in only one role during the duration of the study, ranging from curating study sets, providing study diagnoses, and adjudicating reading pathologist diagnoses with reference diagnoses. Each case was evaluated twice (once by WSI and once by light microscopy) by the same pathologist, who was allowed to defer diagnosis if needed, with a minimum washout time of 31 days (average of 58 days). The study found that the major discrepancy rate (discrepancy between WSI or microscopy and the reference diagnosis) was 3.64% and 3.20%, respectively, with a difference of 0.44% between the two discrepancy rates. The highest major discrepancy rates for both modalities were for urinary bladder biopsies (10.4% for WSI and 9.47% for microscopy), followed by lung, endocrine, soft tissue, and breast. However, the overall differences for major discrepancies between modalities were small. Unbalanced discrepancies (in which one modality was a major discrepancy and the other modality was concordant) made up a small proportion of all cases and occurred with similar frequency for

both modalities. The time to review each case was similar between WSI and microscopy review. The authors conclude that diagnoses made using WSI using the Aperio AT2 DX system are not inferior to traditional light microscopy.

Journals Reviewed November-December 2020

Advances in Anatomic Pathology
American Journal of Clinical Pathology
American Journal of Gastroenterology
American Journal of Surgical Pathology
Annals of Diagnostic Pathology
Archives of Pathology and Lab Medicine
BMC Gastroenterology
Clinical Gastroenterology Hepatology
Diagnostic Pathology
Diseases of the Colon and Rectum
Gastrointestinal Endoscopy
Gut
Histopathology
Human Pathology
International Journal of Surgical Pathology
Journal of Clinical Pathology
Journal of Molecular Diagnostics
Journal of Pathology
Modern Pathology
Virchows Archiv