GIPS Journal Watch November & December 2019

Budesonide Oral Suspension Significantly Improves Eosinophilic Esophagitis Histology Scoring System Results: Analyses From a 12-Week, Phase 2, Randomized, Placebo-controlled Trial.
Collins MH, Dellon ES, Katzka DA, Hirano I, Williams J, Lan L.
Am J Surg Pathol. 2019 Nov;43(11):1501-1509.
https://www.ncbi.nlm.nih.gov/pubmed/31498177

The aim of this study was to use the previously validated Eosinophilic Esophagitis Histology Scoring System (EoE HSS) to assess the effect of Budesonide Oral Suspension (BOS) (n=49) and placebo (n=38) over 12 weeks on the severity (grade) and extent (stage) of 8 histopathologic features in patients with EoE. Mean (SD) EoE HSS grade and stage total scores at baseline for placebo and BOS groups were grade :0.42 (0.16) and 0.49 (0.14), respectively; stage: 0.38 (0.14) and 0.46 (0.11), respectively. These scores significantly decreased from baseline for patients receiving BOS versus placebo (grade: $P<0.0001$; stage: $P<0.0001$). EoE HSS total scores improved for 6 of the 8 and 5 of the 8 histopathologic features for grade and stage, respectively, in BOS versus placebo. Change in EoE HSS total scores correlated moderately with change in endoscopic severity and correlated weakly with change in Dysphagia Symptom Questionnaire scores. Based on these findings, authors concluded that EoE HSS provides a comprehensive analysis of EoE histopathology and is a valuable endpoint of treatment response in randomized clinical trials.

Loss of ARID1A expression is associated with DNA mismatch repair protein deficiency and favorable prognosis in advanced stage surgically resected esophageal adenocarcinoma.
Lowenthal BM, Nason KS, Pennathur A, Luketich JD, Pai RK, Davison JM, Ma C.
Hum Pathol. 2019 Dec;94:1-10.
http://www.ncbi.nlm.nih.gov/pubmed/31655170

This tissue microarray study applied immunohistochemistry for ARID1A and MMR proteins to 316 surgically resected treatment-naïve esophageal adenocarcinomas. ARID1A-loss was detected in 13%. MMR deficiency was identified in 5% but was more frequent in ARID1A-loss than ARID1A-retained adenocarcinomas. The whole section slides of the ARID1A-loss adenocarcinomas were evaluated morphologically and these showed significant peritumoral lymphoid aggregates (90%) and tumor infiltrating lymphocytes (51%). In patients with stages III or IV (n = 169), patients with ARID1A-loss adenocarcinomas had longer overall survival (median 26 vs. 16 months). In these patients, ARID1A-loss correlated with a 56% reduction in mortality independent of other prognostic factors ($P = .007$). The authors conclude that loss of ARID1A expression in esophageal adenocarcinoma is associated with DNA MMR protein deficiency (a finding that is similar to data for colorectal and gastric adenocarcinoma) and is independently associated with a more favorable prognosis for patients with locally advanced or metastatic esophageal adenocarcinomas.

Isolated tumor cells in regional lymph nodes in patients with adenocarcinoma of the esophagogastric junction might represent part of true metastases.
Fiehn AK, Jepsen DNM, Achiam MP, Ugleholdt H, Federspiel B.
Hum Pathol. 2019 Nov;93:90-96.
http://www.ncbi.nlm.nih.gov/pubmed/31445841

Isolated tumor cells (ITCs), defined as single tumor cells or small clusters of tumor cells not exceeding 0.2 mm, were examined in the regional lymph nodes of 126 resections containing adenocarcinoma of the EGJ. Deeper sections (six 200-micron levels with two 4-micron sections per level) were performed to determine how often a true metastasis is revealed. ITCs were detected in 41 (32.5%) of 126 patients (or 59 (1.7%) of 3454 total lymph nodes). In 29 (49.2%) lymph nodes with ITCs on the primary slide, deeper sections changed the ITCs to a metastasis. In 7 (17.1%) of 41 patients, the pN category was changed. The study shows ITCs are common among patients with adenocarcinoma of the EGJ and the authors encourage additional deeper sections when ITCs are encountered.

Autoimmune Gastritis
Hall SN, Appelman HD.
Arch Pathol Lab Med. 2019 Nov; 143:1327-1331.
https://www.ncbi.nlm.nih.gov/pubmed/31661309

In this short review, the authors review the pathogenesis, clinical features, diagnostic criteria, differential diagnoses, sequelae, and surveillance recommendations for autoimmune gastritis.
Autoimmune gastritis is an important disease characterized by a loss of oxyntic mucosa and presence of metaplastic epithelium such as mucous cell or intestinal metaplasia and enterochromaffin-like cell hyperplasia. It is associated with intrinsic factor deficiency, either with or without pernicious anemia. Sequelae include indolent gastric carcinoids and a small risk of gastric adenocarcinoma .The guidelines' recommendation is endoscopic follow-up every 3 to 5 years to assess for epithelial dysplasia, carcinoid tumors, and gastric adenocarcinoma in patients with autoimmune gastritis. Awareness and proper diagnosis are critical to prevent mismanagement of patients.

Epstein-Barr virus is absent in gastric superficial neoplastic lesions
Ribeiro J, Malta M, Galaghar A, Afonso LP, Libânio D, Medeiros R,
Dinis-Ribeiro M, Pimentel-Nunes P, Sousa H.
Virchows Archiv 2019 Dec;475(6):757-762.
https://www.ncbi.nlm.nih.gov/pubmed/31673776

EBV has been reported in approximately 10% of all gastric adenocarcinomas, mainly the intestinal (The Lauren classification) and modularly types. However, gastric carcinogenesis related to EBV infection remains controversial in the literature. In this study, the authors investigated EBV expression using in situ hybridization (EBER) in a total of 242 gastric lesions including 27 low-grade dysplasia, 100 high-grade dysplasia, and 05 early gastric adenocarcinomas (78 intramucosal, and 27 submucosal adenocarcinomas). None of the 242 lesions had EBV infection in current study, which is contradictory to a few previous reports showing the presence of EBV in the gastric premalignant conditions. Rare EBV-positive lymphocytes were found in 4 of 242 lesions and higher number of EBV-positive lymphocytes was found in 1 of 242 cases. These findings suggest that EBV infection may be a late event in the gastric carcinogenesis.

Predictive value of WHO classification for PD-L1 and Her2/Neu expression and distinct associations with protein expression based classification in gastric carcinoma.
Setia N, Ahn S, Han HS, Park DY, Lauwers GY.
Hum Pathol. 2019 Dec;94:64-70.
http://www.ncbi.nlm.nih.gov/pubmed/31676362

This study looked at 486 gastric carcinomas which have been classified into protein expression-based groups. The authors found low positive predictive value of any single morphologic pattern for biomarker-expression and conclude that morphologic patterns alone cannot predict PD-L1, Her2/neu expression and EBV- or MSI-gastric cancer. However, they suggest that targeting a combination of WHO patterns for testing can achieve high positive predictive values (nearly 100%) among certain tests, which can be a useful screening strategy. These include performing PD-L1 testing for all WHO gastric cancer patterns of:

a. Tubular
b. Carcinoma with lymphoid stroma
c. Undifferentiated
d. Poorly cohesive

And, Her2/neu testing for all WHO gastric cancer patterns of:

e. Tubular
f. Mixed
g. Papillary
h. Mucinous

More detailed associations are described in the article. For example, while carcinoma with lymphoid stroma was highly associated with EBV-gastric carcinoma, other morphologic subtypes were also seen, including tubular, papillary, and undifferentiated carcinoma. Other protein-expression groups not previously mentioned, but specifically characterized in this study include E-cadherin and p53.

Intratumoral heterogeneity and loss of ARID1A expression in gastric cancer correlates with increased PD-L1 expression in Western patients.
Tober JM, Halske C, Behrens HM, Krüger S, Röcken C.
Hum Pathol. 2019 Dec;94:98-109.
http://www.ncbi.nlm.nih.gov/pubmed/31704366

This immunohistochemical study reviewed whole-slide staining of 450 treatment naïve gastric adenocarcinoma resections with IHC staining of ARID1A. 5.1% of cases showed heterogeneous staining while 9.6% showed complete loss of ARID1A staining; the latter was associated with Epstein-Barr virus and microsatellite unstable gastric adenocarcinomas, as well as intestinal- and undifferentiated-types by Lauren classification. There was no significant association with HER2 or MET status, but loss of ARID1A correlated inversely with PD-L1 and PD-1 expression. The authors suggest that loss of ARID1A can serve as a surrogate marker for PD-L1 in determining immune therapy potential. While loss of ARID1A did not correlate with patient survival, nodal metastases preferentially stemmed from the ARID1A-negative subclones.

Histological assessment of stromal maturity as a prognostic factor in surgically treated gastric adenocarcinoma.
Kemi NA, Eskuri M, Pohjanen VM, Karttunen TJ, Kauppila JH.
Histopathology. 2019 Dec; 75:882-889.
https://www.ncbi.nlm.nih.gov/pubmed/31173384

The prognostic relevance of stromal maturity based on analyzing H&E-stained slides is unknown in gastric cancer. In this study, the authors aimed to evaluate the reproducibility and prognostic significance of assessing stromal maturity in gastric adenocarcinoma. This was a retrospective study consisting of a cohort of 583 gastric adenocarcinoma patients treated surgically in Finland between 1983 and 2016. Patients were divided into mature stroma and immature stroma groups, and stromal maturity was analyzed in relation to 5-year and overall survival (OS). Stromal maturity was analyzed from scanned H&E stained slides using Aperio ImageScope independently by two researchers blinded to the clinical and outcome data. The maturity of tumor-associated stroma was analyzed from the intratumoral stroma of the invasive tumor and the desmoplastic reaction in front of the invasive edge of the tumor. Immature stroma was defined as the presence of thick, hypocellular collagen bundles with eosinophilic hyalinization, also described as "keloid like collagen". If there were no keloid-like collagen bundles or if they were present only in fewer than 5% of the intratumoral stromal area and desmoplastic stromal area in front of the tumor, combined, the stroma was considered mature. The kappa-coefficient for interobserver agreement was 0.609. Patients with immature stroma had worse 5-year survival compared to patients with mature stroma [adjusted hazard ratio (HR) = 1.32]. Stromal maturity was significantly associated with 5-year survival in intestinal-type subgroup (adjusted HR = 0.63, 95%), but not in the diffuse-type subgroup (adjusted HR = 1.21). The authors conclude that the stromal maturity might be an independent clinically applicable prognostic factor in gastric cancer, although moderate interobserver agreement reached in this study might limit its usefulness. Additional larger retrospective and prospective studies, and including studies in neoadjuvant-treated patients and early-stage gastric cancer are needed to better understand more clearly the prognostic value of stromal maturity in gastric cancer.

Clinical and Histopathologic Predictors of Disaccharidase Deficiency in Duodenal Biopsy Specimens.
Reed RC, Pacheco MC.
Am J Clin Pathol. 2019;152(6):742-746.
https://www.ncbi.nlm.nih.gov/pubmed/31332425

This study was performed to investigate potential strategies for optimizing, and reducing the use of disacharidase (DS) activity testing, while still maintaining clinical sensitivity for the detection of DS deficiency. DS deficiency, congenital or acquired, falls in the differential diagnosis of pediatric diarrhea and abdominal pain. The gold standard test for DS deficiency is a quantitative spectrophotometric measurement of glucose released by hydrolysis of different disaccharide substrate by the DS present in a sample of the patient's duodenum obtained by biopsy, which requires a separate biopsy placed on ice and flash frozen to retain enzyme integrity. Frequently the test is a send out to a reference lab. The authors of the article looked retrospectively at a series of cases from two institutions, and after reviewing DS activity testing results, clinical information, and associated histologic findings on biopsy developed a proposed testing algorithm. In the flow chart, the frozen tissue from biopsy is retained until histology results are available. If any significant inflammation or evidence of other mucosal injury is seen (i.e. probable celiac disease or other histology that could explain symptoms), the DS activity testing is not performed. Only normal biopsies or those with minimal change in patients who have continued clinical suspicion for DS deficiency are tested, leading to significant cost savings when compared to testing all samples.

Histological, immunohistochemical and mRNA gene expression responses in coeliac disease patients challenged with gluten using PAXgene fixed paraffin-embedded duodenal biopsies.
Taavela J, Viiri K, Popp A, Oittinen M, Dotsenko V, Peräaho M, Staff S, Sarin J, Leon F, Mäki M, Isola J.
BMC Gastroenterol. 2019 Nov 15;19(1):189.
https://www.ncbi.nlm.nih.gov/pubmed/31730447

This study aims to evaluate the morphometric, immunohistochemical, and mRNA expression changes in duodenal biopsies fixed in PAXgene from celiac disease patients challenged with gluten. A total of 15 patients with celiac disease and 24 patients without celiac disease were included in the study. Fifteen coeliac disease patients were challenged with 4 g of gluten per day for 10 weeks. Digital quantitative villous height: crypt depth ratio (VH: CrD) measurements revealed significant duodenal mucosal deterioration in all celiac disease patients on gluten challenge. In contrast, the Marsh-Oberhuber class worsened in only 80% of celiac patients. We showed that measuring the intraepithelial CD3+ T-lymphocyte and lamina propria CD138+ plasma cell densities simultaneously is a new effective measurement of inflammation. Staining for γδ T cells and IgA deposits, which needed frozen samples previously, was successful in PAXgene fixed paraffin-embedded samples. mRNA extraction from the PAXgene fixed paraffin-embedded block was successful and allowed large-scale qRT-PCR and RNAseq analyses for gene expression. The mRNA expression ratio of villous epithelium-specific gene APOA4 to crypt proliferation gene Ki67, showed significant distinction between paired baseline and post-gluten challenged biopsies. The authors concluded that using PAXgene fixation, digitally measured histologic and molecular markers for gluten challenge studies can be obtained from a single paraffin-embedded biopsy specimen. Molecular morphometry seems to be a promising new tool in assessing duodenal mucosal health in celiac patients. In addition, evaluation of IgA deposits is more accessible in routine clinics when stained in paraffin-embedded specimens.

Mutational profiling and immunohistochemical analysis of a surgical series of ampullary carcinomas.
Harthimmer MR, Stolborg U, Pfeiffer P, Mortensen MB, Fristrup C, Detlefsen S.
J Clin Pathol. 2019 Nov;72(11):762-770.
https://www.ncbi.nlm.nih.gov/pubmed/31256008

This retrospective study assessed 59 surgically resected ampullary adenocarcinomas (AC) for 1) clinicopathological features and frequency of the histological subtypes, 2) IHC expression of IMP3, maspin, MUC5AC and S100P and 3) NGS (315 gene panel Illumina platform including TMB and MSI). Intestinal-type adenocarcinomas (INT-AC), pancreatobiliary-type adenocarcinomas (PB-AC) and mixed type adenocarcinomas (MIX-AC) subtypes were included and both IHC and H&E were used determine subtype. When histological and IHC typing differed tumors were classified as MIX-AC. Ultimately 83.1% of ACs were classified as adenocarcinomas: 45.8% PB-AC, 23.7% INT-AC and 13.6% MIX-AC. Maspin had an IHC score ≥2 in 94.9% of ACs . S100P had a score ≥2 in 39.0% and MUC5AC in 18.6% of ACs, both with the highest expression in PB-AC. *TP53* was the most frequently altered gene (59.3%), followed by *KRAS* (40.7%), *APC* (27.8%), *SMAD4* (20.4%), *CDKN2A* (16.7%) and *ARID2*/*PIK3CA* (each in 11.1%). Amplifications of MDM2 as well as ERBB2 and ERBB4 were seen infrequently. Interestingly, APC mutations differed according to subtype (53.8% of INT-AC had mutations compared to only 8.7% of PB-AC). SOX9 alterations were exclusively seen in INT-AC and MDM2 and FRS2 alterations were only detected in PB-AC. *ARID2* and *ERBB2* were more frequently altered in MIX-AC. Four cases showed high-TMB (>20 muts/ Mb): two MIX-ACs, one PB-AC and one mucinous adenocarcinoma. 87.8% of cases were MSI-stable, two MSI-intermediate (both PB-AC) and four MSI-high (two MIX-ACs, one PB-AC and one mucinous adenocarcinoma). All 4 MSI-H tumors were also high-TMB and all showed loss of MLH-1 and PMS2 by IHC. Given the lack of germline

mutations in MMR genes, MLH-1 promoter hypermethylation was assumed to be the etiology for the microsatellite instability. Overall, the authors state that the use of comprehensive mutational profiling in this European study showed similar results to studies performed in the US and Japan. They also found that PB-AC was the most frequent subtype of AC and that maspin and IMP3 were the most frequently expressed tumor markers. The authors agree that their data supports the use of additional testing to subtype AC's and provide guidance for targeted treatment options.

A novel collagen area fraction index to quantitatively assess bowel fibrosis in patients with Crohn's disease.

Li XH, Fang ZN, Guan TM, Lin JJ, Sun CH, Huang SY, Mao R, Lu BL, Cao QH, Feng ST, Li ZP.
BMC Gastroenterol. 2019 Nov 11;19(1):180.
https://www.ncbi.nlm.nih.gov/pubmed/31711420

This study aims to establish a new index to quantify the severity of bowel fibrosis in patients with Crohn's disease-associated fibrostenosis. The histopathological data of 31 patients with Crohn's disease strictures undergoing surgical resection were analyzed. The most representative sections of resected strictured segments were stained with Masson trichrome to manifest bowel fibrosis. Collagen area fraction strongly correlated with histological fibrosis scores ($r = 0.733$, $P < 0.001$). It showed a stronger correlation ($r = 0.561$, $P < 0.001$) with the degree of bowel strictures than the histological fibrosis score did ($r = 0.468$, $P < 0.001$). It was also shown to be more accurate for diagnosing Crohn's disease strictures (area under the receiver operating characteristic curve = 0.815, $P < 0.001$) compared with the histological fibrosis score (area under the curve = 0.771, $P < 0.001$). High repeatability was observed for the collagen area fraction, with an intra-class correlation coefficient of 0.915 ($P < 0.001$). The authors concluded that collagen area fraction is a simple and reliable index to quantify the severity of bowel fibrosis in patients with Crohn's disease-associated fibrostenosis.

Distinct Disease Phenotype of Ulcerative Colitis in Patients With Coincident Primary Sclerosing Cholangitis: Evidence From a Large Retrospective Study With Matched Cohorts.

Cordes F, Laumeyer T, Gerß J, Brückner M, Lenze F, Nowacki T, Rijcken E, Tepasse P, Schmidt H, Kucharzik T, Bettenworth D.
Dis Colon Rectum. 2019 Dec;62(12):1494-1504.
https://www.ncbi.nlm.nih.gov/pubmed/31725582

This retrospective review studied 705 patients with ulcerative colitis (UC) and 77 patients with ulcerative colitis and concurrent PSC (UC-PSC) to determine differences in age of onset, disease activity and development of CRC. Clinical characteristics, extent of disease using Montreal classification, surgical history, and neoplasia history were recorded. Results were similar to previously published reports that age of UC onset was significantly lower in patients who had UC-PSC compared to those with UC without PSC (23.3 vs 29.3 years; $p < 0.001$). Extensive colitis was significantly more frequent in UC-PSC at the time of diagnosis than in UC without PSC (73.3% vs 48.7%; $p < 0.001$). There was a significantly higher risk for CRC occurrence in UC-PSC (5/59; 8.5%) than in UC without PSC (3/174; 1.7%; $p = 0.027$). However, differences in disease progression from distal to extensive UC were not seen. Interestingly, the average disease activity during acute flares was significantly higher in patients who had UC without PSC than in patients with UC-PSC (7.3±2.3 vs 6.2±2.1; $p < 0.001$) and there was significantly higher disease activity in patients with UC than in patients with UC-PSC during the first decade after diagnosis. As such the need for biologic therapy with infliximab, adalimumab, golimumab, or vedolizumab was less in the UC-PSC

group. Overall, the authors observed a distinct phenotype in UC-PSC patients characterized by earlier disease onset, lower disease activity, extensive disease manifestation, and increased incidence of CRC. They postulate that subclinical disease activity, only detected histologically, could result in delay of medical treatment and ultimately an increase in disease duration that has a known association with the development of neoplasia. Therefore, the authors stress the need for careful dysplasia surveillance in patients with UC-PSC, as recommended by current guidelines. As this is an observational study only the authors address the many limitations and need for further investigation.

Spectrum of gastrointestinal tract pathology in a multicenter cohort of 43 Cowden syndrome patients.
Borowsky J, Setia N, Rosty C, Conrad R, Susman R, Misdraji J, Hart J, Lauwers GY, Brown IS.
Mod Pathol. 2019 Dec;32(12):1814-1822.
https://www.ncbi.nlm.nih.gov/pubmed/31273317

The purpose of this retrospective study was to report the spectrum of gastrointestinal pathologic findings in a series of 43 patients with Cowden syndrome who underwent at least one upper GI endoscopy or colonoscopy with biopsy, with the aim to raise awareness among pathologists of the characteristic admixture of lesions seen in the syndrome so that they can help identify appropriate patients for additional genetic testing and counseling. In the large bowel, the most common polyp was reported to be hamartomatous with one or more stromal components described as lymphoid aggregates, lipomatous, ganglioneuromatous, and/or fibrous rich. Serrated polyps and conventional adenomas were also identified. In the Upper GI biopsies, the most common finding was gastric hamartomatous/inflammatory polyps and esophageal glycogenic acanthosis.

Colonic Manifestations and Complications Are Relatively Under-Reported in Systemic Sclerosis: A Systematic Review.
Brandler JB, Sweetser S, Khoshbin K, Babameto M, Prokop LJ, Camilleri M.
Am J Gastroenterol. 2019 Dec;114(12):1847-1856.
https://www.ncbi.nlm.nih.gov/pubmed/31805016

This review article covers, as the title suggests, the colonic manifestations of systemic sclerosis (SSc). The authors note that while effects on other portions of the tubular gut have been well explored, predominately including the esophagus with still others examining small bowel and anorectal manifestations, a comprehensive evaluation of colonic involvement has not been performed. Data from 74 articles, which included 59 case reports or series, were included in this review. A majority of the patients were female (84%) and had limited versus diffuse SSc (65.6% vs 26.2%). The most common gastrointestinal organs to be covered in these articles included the esophagus (32%), colon (24%), small intestine (19%), and stomach (17%). This review evaluates the most frequently covered colonic manifestations including constipation, dysmotility, volvulus, megacolon, diverticulosis, and inflammatory bowel disease. Only one study appeared to include histologic manifestations of colonic SSc disease and noted that all cases demonstrated muscularis atrophy with a majority also exhibiting fibrosis (63%) or myenteric plexus hypertrophy (75%). In regards to inflammatory bowel disease, studies associating ulcerative colitis with SSc were most commonly encountered with patients frequently being diagnosed with the former prior to the latter (67%). It was also noted that most patients' inflammatory bowel disease was uncontrolled at the time of SSc diagnosis (80%). The authors conclude by stating that colonic manifestations of SSc constitute a large proportion of published reports covering gastrointestinal tract involvement and can lead to serious complications in these patients.

Rosai-Dorfman Disease of the Digestive System-Beware Vasculopathy: A Clinicopathologic Analysis.
Alruwaii ZI, Zhang Y, Larman T, Miller JA, Montgomery EA.
Am J Surg Pathol. 2019 Dec;43(12):1644-1652.
https://www.ncbi.nlm.nih.gov/pubmed/31414989

The authors of this study aimed at characterizing the digestive tract manifestations of Rosai-Dorfman Disease (RDD) in, 12 specimens (1 appendix, 2 right colon, 6 left colon, 2 pancreas, and 1 liver) from 11 patients (8 female and 3 male; age range 17 to 76 y). Two patients had coexistent nodal disease, and 1 had bone and soft-tissue involvement. The average size of colonic lesions was 4.9 and 2.8 cm for pancreatic lesions. Resected masses were firm, with white-tan cut surfaces and ill-defined-borders. Histologically, the lesions showed sheets of polygonal to spindle-shaped histiocytes with eosinophilic to clear cytoplasm with variable lymphoplasmacytic infiltrate and fibrosis. Lymphoid aggregates were seen in 7 cases. Scattered neutrophils were seen in 6 cases. Novel features included small vessel wall thickening (n= 9), arteritis of medium sized arteries (n =5), and phlebitis (n= 2). All cases showed strong S100 positive histiocytes. Increased IgG4-labeled plasma cells was noted in one case but not in the ductcentric pattern characteristic of autoimmune pancreatitis. In 5 patients with follow up, one developed IgA nephropathy and died of renal failure. Overall, the authors concluded that RDD involving the digestive organs is rare and can be seen in middle-aged females in association with immunologic or hematologic conditions. Vasculopathy, usually affecting arteries rather than veins, can lead to the diagnosis of IgG4-related disease. S100-protein staining is useful in reaching the correct diagnosis.

Identification of a novel PRR15L-RSPO2 fusion transcript in a sigmoid colon cancer derived from superficially serrated adenoma.
Mizuguchi Y, Sakamoto T, Hashimoto T, Tsukamoto S, Iwasa S, Saito Y, Sekine S.
Virchows Archiv 2019 Nov;475(5):659-663.
https://www.ncbi.nlm.nih.gov/pubmed/31209633

Colorectal serrated lesions including the sessile serrated adenomas and traditional serrated adenomas have been recognized as the precursors of 30% of all colorectal adenocarcinomas. However, hyperplastic polyp, one histological type of the serrated lesions is thought to have no malignant potential. Recently, the authors proposed a novel subtype of serrated lesions, called superficially serrated adenoma (SuSA) mainly located in the rectosigmoid colon with mixed adenomatous and serrated features confined to the superficial epithelium. Since SuSA was frequently associated with TSA, it was expected that SuSA may be a precursor to colorectal cancer. In this brief study, the authors reported a case of a sigmoid adenocarcinoma associated with adjacent SuSA that only had superficial serration but no TSA component was found in this lesion. Molecular studies showed KRAS mutation and a novel fusion gene transcript PRR15L-RSPO2 found in the SuSA, adenocarcinoma and the metastasis, but not in the normal mucosa. More investigations may be necessary to recognize SuSA as a new potential precursor to colorectal cancers.

Characterization and Identification of Colorectal Cancer in Persons Younger Than 50 Years.
Strum WB, Boland CR.
Clin Gastroenterol Hepatol. 2019 Nov;17(12):2600-2602.
https://www.ncbi.nlm.nih.gov/pubmed/30543950

This is a brief research correspondence but covers the currently evolving topic of early onset colorectal carcinoma (EOCRC). The authors note that the incidence of EOCRC, defined as cancers occurring in individuals younger than 50 years of age, has been increasing over the last several decades while there has been a concurrent decrease in CRC occurring in patients older than this threshold. This brief report analyzed the clinical features and mismatch repair (MMR) enzyme status of a cohort of EOCRC patients who initially presented at a single community hospital. Using the institution's registry, 127 cases of EOCRC were identified spanning approximately a 10 year period. This included individuals aged 20-49 years of which 53% were women. Deficiencies in MMR were detected in 10 of 99 cases evaluated (10%). A majority of these individuals were found to have germline defects indicative of Lynch syndrome or suspected deleterious mutations. By comparing the EOCRC cohort to two other previously established cohorts of CRC patients aged 50 or older, the authors noted a significant difference in the location of the associated carcinomas. A majority of the EOCRC cohort had distal tumors (79%) and 44% were rectal in origin. This was significantly different from the comparison groups in which 49% and 53% were found to have distal tumors. The EOCRC cohort was also found to have a significantly higher number of non-Caucasians.

Clinical and Molecular Features of Post-Colonoscopy Colorectal Cancers.
Samadder NJ, Neklason D, Snow A, Samowitz W, Cessna MH, Rowe K, Sandhu I, Boucher K, Pappas L, Smith KR, Wong J, Curtin K, Provenzale D, Burt RW.
Clin Gastroenterol Hepatol. 2019 Dec;17(13):2731-2739.e2.
https://www.ncbi.nlm.nih.gov/pubmed/30930275

This retrospective cross-sectional study of colorectal carcinoma was performed to evaluate the clinical and pathologic features of interval or post-colonoscopy colorectal cancers (PCCRCs). PCCRCs were defined as carcinomas detected within 6-60 months of colonoscopy and were compared to tumors appreciated within 6 months of a colonoscopy, termed detected CRCs (DCRCs). Using statewide databases in Utah, 2659 cases of CRC were noted of which 159(6%) were defined as PCCRCs. PCCRCs were noted to more frequently occur in the proximal colon (64% vs 44%) and were more often of an early stage (86% vs 69%). Accompanying this spatial differential, MSI was more frequent in PCCRCs compared to DCRCs (32% vs 13%). Interestingly, the occurrence of other specific molecular alterations such as *BRAF* or *KRAS* mutations were not found to be significantly different between the two groups (26% vs 24% and 29% vs 30% respectively). This lack of differential was also appreciated in rates of CpG island methylation. The authors conclude by stating that this population-based study corroborates similar efforts in the past which have demonstrated that interval or PCCRCs are more frequently right sides and MSI.

Histologic Evaluation of Malignant Polyps and Low-Stage Colorectal Carcinoma.
Hagen CE, Farooq A.
Arch Pathol Lab Med. 2019 Dec; 143:1450-1454.
https://www.ncbi.nlm.nih.gov/pubmed/31509454

In this short review, the authors discuss and review several histopathologic features in malignant colorectal polyps and low-stage colorectal carcinoma that need to be accessed and communicated to the

clinical team to allow for proper management and triage patients who may be candidates for subsequent lymph node dissections. Poor prognostic factors for malignant polyps include high tumor grade, presence of lymphovascular invasion, tumor less than 1 mm from resection margin, submucosal invasion deeper than 1 mm, and high tumor budding.When this information is provided to the clinical colleagues, patients can appropriately be triaged to undergo additional surgical resection with lymph node dissection as necessary.

CDX2 Loss with Microsatellite Stable Phenotype Predicts Poor Clinical Outcome in Stage II Colorectal Carcinoma.
Slik K, Turkki R, Carpén O, Kurki S, Korkeila E, Sundström J, Pellinen T.
Am J Surg Pathol. 2019 Nov;43(11):1473-1482.
https://www.ncbi.nlm.nih.gov/pubmed/31490234

The authors aimed at studying the prognostic relevance of loss of CDX2 expression in colorectal carcinomas (CRC) and its association with epithelial mesenchymal transition (EMT). Tissue microarrays constructed from tumor center and invasive front areas from 232 stage II CRC were evaluated for CDX2 expression. 18 (8.6 %) tumors showed loss of CDX2 in the tumor center and 22 (10.9 %) tumors showed loss at the tumor front. Loss of CDX2 either in the tumor center or front areas was associated with shorter disease-free survival (DFS) and disease-specific survival (DSS). Overall, loss of CDX2 predicted survival independently of other stage II risk factors including tumor budding. Most patients with CDX2 loss in the tumor center or front had MSI-high phenotype (76% and 64% respectively). Loss of CDX2 predicted DSS and DFS only in the MSS patient group (P<0.001; P=0.019), but not in the MSI-high group (P=0.21; P=0.14). CDX2 loss was associated with EMT related phenotypic changes of low E-cadherin expression, tight junction disruption, and high expression of ezrin protein. Based on these findings, authors concluded that loss of CDX2 is an independent risk factor in stage II CRC and lined to EMT.

Differential Survival Benefits of 5-Fluorouracil-Based Adjuvant Chemotherapy for Patients With Microsatellite-Stable Stage III Colorectal Cancer According to the Tumor Budding Status: A Retrospective Analysis.
Yamadera M, Shinto E, Kajiwara Y, Mochizuki S, Okamoto K, Hase K, Yamamoto J, Ueno H.
Dis Colon Rectum. 2019 Nov;62(11):1316-1325.
https://www.ncbi.nlm.nih.gov/pubmed/31567925

This retrospective review investigated the impact of tumor budding on survival advantage following adjuvant chemotherapy in patients with MSS stage III colorectal adenocarcinoma. As 5-fluorouracil (5- FU) is a key drug in the neoadjuvant setting, the authors compared patient outcomes with low and high tumor budding grades. MSI-H tumors were excluded as these patients are known to not respond to 5-FU based therapy. 2 data sets of patients undergoing surgery with the intent to cure were studied between 1999 and 2005 (first cohort; n = 203) and between 2006 and 2012 (second cohort; n = 346) due to differences in chemotherapy recommendations. In cohort #1 128 patients received 5-FU–based adjuvant chemotherapy (chemotherapy group) but 75 did not. In cohort #2, there were 203 patients in the chemotherapy group and 143 in the surgery-alone groups. The level of interobserver agreement for evaluation of tumor budding status was substantial (concordance rate, 81% ($\kappa = 0.62$)). Patients who were younger, pT4, pN2, and had high-grade budding received adjuvant chemotherapy more frequently than those who were older, pT2/3, pN1, and had low-grade budding ($p < 0.0001$, $p = 0.006$, $p = 0.049$, and $p = 0.009$). Grade of tumor budding did correlate with T ($p = 0.002$) and N stages ($p = 0.005$). However, it did

not correlate with age, sex, tumor location, histologic type, or venous invasion. Interestingly, patients with low tumor budding CRC's who received 5-FU had increased cancer-specific survival and recurrence-free survival, while those with high-budding CRCs did not. Adjuvant chemotherapy was an independent prognostic factor in low-budding CRC (HR = 0.23; $p < 0.0001$) but not for high-budding CRC. Therefore, tumor budding status may be a consistent marker for predicting the efficacy of 5-FU–based adjuvant chemotherapy. However, given the fact that oxaliplatin based chemotherapy is the current standard of care, the authors agree that additional investigation is necessary prior to implementation in a clinical setting.

Pathological Tumor Regression Grade Classifications in Gastrointestinal Cancers: Role on Patients' Prognosis.
Fanelli GN, Loupakis F, Smyth E, Scarpa M, Lonardi S, Pucciarelli S, Munari G, Rugge M, Valeri N, Fassan M. Int J Surg Pathol. 2019 Dec; 27(8):816-835.
https://www.ncbi.nlm.nih.gov/pubmed/31416371

Neoadjuvant therapy, that is preoperative chemotherapy or combined radiotherapy and chemotherapy (CRT), prior to surgery, represents the standard approach for locally advanced esophageal, gastric, and rectal carcinomas. Several histopathologic tumor regression grade (TRG) scoring systems have been introduced to evaluate the effects of neoadjuvant CRT in the resection specimens. The primary goal of TRG scoring is to allow a reliable prognostic stratification of tumors, identifying patients with a greater risk of tumor recurrence and also influencing subsequent therapeutic decisions. Complete (pathological complete response [pCR]) or subtotal tumor regression is frequently significantly associated with better outcome. However, most TRG systems suffer from poor reproducibility and low interobserver concordance rates. This review paper analyzes the most commonly used TRG systems in esophageal, gastric and colorectal cancers highlighting their pitfalls and usefulness.

Journals Reviewed November-December 2019
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American Journal of Gastroenterology
American Journal of Pathology
American Journal of Surgical Pathology
Annals of Diagnostic Pathology
Archives of Pathology and Lab Medicine
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