GIPS Journal Watch July & August 2019

Ciliated columnar epithelium in the esophagus and gastroesophageal junction: A different perspective from study of a North American population.
Scott B, Cottreau J, Oviedo A, Arnason T.
Ann Diagn Pathol. 2019 Aug;41:90-95.
https://www.ncbi.nlm.nih.gov/pubmed/31200216

Ciliated columnar epithelium in the distal esophagus and GEJ biopsies are rarely report in Western population, though it has been reported in up to 30-40% of Japanese population in the literature. These authors retrospectively review 1048 GEJ biopsies and no ciliated columnar epithelium was identified. In a prospectively review of 971 cases, 3 cases of ciliated columnar epithelium were identified with a prevalence of <0.5%. The origin of ciliated columnar epithelium in the GEJ remains controversial. Some cases were related to the margination of lung bronchial epithelium due to post-surgical fistula tract or developmental disorder. In the absence of a fistula, others thought that the ciliated epithelium of the GEJ might be a metaplastic change in the spectrum of multilayered epithelium and Barrett's esophagus and was evidenced by negative TTF1 expression. Overall, the finding of ciliated epithelium at the GEJ seems to have no apparent clinical significance.

Multinucleated stromal giant cells in the gastroesophageal junctional and gastric mucosa: a retrospective study.
Sachak T, Frankel WL, Arnold CA, Chen W.
Diagn Pathol 2019 Jul;14(1):83.
https://www.ncbi.nlm.nih.gov/pubmed/31351475

This retrospective morphologic and immunohistochemical study of stomach and gastroesophageal junction (GEJ) biopsies (n=361) and resection (n=1) sought to identify the origin and significance of multinucleated stromal giant cells (MSGCs). Six percent (22/362) cases contained MSGCs, which included 7 gastric biopsies, 14 GEJ biopsies, and the one GEJ resection. Statistically significant clinical correlations included reflux (p=0.03), but not acute or chronic inflammation, intestinal metaplasia, or pancreatic acinar cell metaplasia in the GEJ cases, and in the stomach biopsies, although reactive gastropathy was more commonly seen in MSGC positive cases, it was not statistically significant, nor was acute or chronic inflammation or intestinal metaplasia. Most cases had one or two MSGCs, with a median of 5 nuclei, predominantly in the subepithelial zone, with three morphologic arrangements described: “wreath”, “caterpillar”, and “morular”. MSGCs were positive for SMA, variably positive for desmin, and negative for CD68, AE1/3, S100, chromogranin, and CD117, consistent with smooth muscle/myofibroblast differentiation. The authors conclude that MSGCs represent reactive/regenerative stromal changes associated with mucosal inflammation/injury, such as reflux.

Sarcoidosis Involving the Gastrointestinal Tract: Diagnostic and Therapeutic Management.
Brito-Zerón P, Bari K, Baughman RP, Ramos-Casals M.
Am J Gastroenterol. 2019 Aug;114(8):1238-1247.
https://www.ncbi.nlm.nih.gov/pubmed/30865014

This review evaluates the current literature regarding gastrointestinal (GI) involvement by sarcoidosis. In large series, GI manifestations are appreciated in <2% of sarcoidosis patients yet this review is able to

assess the features of 305 cases comprising 238 patients. As the paper is written in such a way that each luminal organ is discussed separately, comparisons can be readily made. In brief, esophageal involvement (reported in 14% of cases) tends to present with dysphagia when it involves the upper portion of the esophagus but can also present with achalasia-like symptoms when the predominant disease involves the lower esophagus. Rare cases of extrinsic compression by robust mediastinal adenopathy have also been reported. The stomach was the most common site of involvement in the GI tract, being reported in 51% of cases, with this finding being the first manifestation of the disease in 49% of these patients. The most frequent pattern of involvement was extensive diffuse infiltration (58% of cases). This led to a linitis plastica-like appearance in several cases. A smaller subset of gastric sarcoidosis patients presented with ulcerative disease (29%). Small bowel sarcoidosis was reported in 17% of cases while colonic involvement was noted in 10%. Clinical presentations in these cases varied widely and included abdominal pain, diarrhea, weight loss, iron deficiency anemia, constipation, and hematochezia. Similar variability was also reported in the endoscopic appearance with cases demonstrating multiple features such as ulcers, thickened folds, friable mucosa, plaque-like lesions, submucosal masses, and polyps among others. The authors conclude by noting that sarcoidosis appears to involve the GI tract with an oral-anal gradient such that the upper GI tract is more commonly involved.

Esophageal Lichen Planus Is Associated With a Significant Increase in Risk of Squamous Cell Carcinoma.
Ravi K, Codipilly DC, Sunjaya D, Fang H, Arora AS, Katzka DA.
Clin Gastroenterol Hepatol. 2019 Aug;17(9):1902-1903.e1.
https://www.ncbi.nlm.nih.gov/pubmed/30342260

This brief research correspondence examined a substantial cohort of patients with esophageal lichen planus (ELP) (n= 132) and evaluated the incidence of esophageal squamous cell carcinoma (ESCC). The authors note that lichen planus has already been associated with an increased risk of esophageal cancer in other studies. Of their cohort, 55 (42%) patients had histologic confirmation of their ELP while the remaining individuals were diagnosed as such based on clinical and endoscopic findings. Eight patients (6.1%) developed ESCC and two of these were considered prevalent as they occurred within three months of their initial ELP diagnosis. The remaining six cases had a median time to progression of 44.3 months. A thorough examination of clinical and endoscopic features found no risk factors which identified ELP patients at risk of subsequent ESCC. The authors conclude that individuals with ELP may benefit from surveillance for ESCC.

MDM2 copy number increase: a poor prognostic, molecular event in esophageal squamous cell carcinoma
Sawada R, Maehara R, Oshikiri T, Nakamura T, Itoh T, Kodama Y, Kakeji Y, Zen Y.
Hum Pathol. 2019 Jul;89:1-9.
http://www.ncbi.nlm.nih.gov/pubmed/31004651

This tissue microarray study applied in situ hybridization for MDM2 and immunohistochemistry for p53 to 399 esophageal squamous cell carcinoma (ESCC) resections. 5% were found to have MDM2 amplification and 4% showed chromosome 12 polysomy, the latter of which were strongly associated with pre-operative chemotherapy. Half of these MDM2 positive cases showed diffuse alterations (defined as positive results in all related tissue cores) and correlated with advanced pT stage and

lymphovascular invasion. The authors conclude that ESCCs with MDM2 alterations indicate worse prognosis but may be treated with targeted MDM2 therapy. No significant associations were seen between p53 mutations and MDM2 amplification.

Young Adults With Esophageal Adenocarcinoma Present With More Advanced Stage Tumors and Have Shorter Survival Times.
Sawas T, Manrique GC, Iyer PG, Wang KK, Katzka DA.
Clin Gastroenterol Hepatol. 2019 Aug;17(9):1756-1762.
https://www.ncbi.nlm.nih.gov/pubmed/30267861

This study investigated the occurrence of esophageal adenocarcinoma (EAC) in young adult patients (younger than 50 years old) and compared the clinicopathologic features of these cases with those of older patients. The authors note that the incidence of EAC is rising however there is little data on the development of these tumors in younger individuals. They performed a single center retrospective study which evaluated all patients diagnosed with EAC over a period of four years. These patients (n=682) were then further subdivided into age groups of less than 50 years (n=105), 51-70 years (n=383), and greater than 70 years (n=194). The clinical, pathologic, and outcome data from these cases were then compared. The authors found that 15% of EAC occurred in young patients and that these tumors tended to present at later stages compared to older individuals, with 77% presenting with either stage II or IV disease. The mean time of survival following diagnosis was also statistically different among the age groups with those individuals younger than 50 years having the shortest time interval (mean 4+/-4.2 years compared to 5+/-3.9 years in the 51-70 year group). Younger individuals were also less likely to have documented intestinal metaplasia associated with their EAC. The authors conclude by postulating that perhaps the more aggressive clinical course of EAC in young patients is due to a late recognition of these tumors as screening guidelines often don't apply to persons younger than 50 years of age. Therefore, they may only be appreciated once they have become more advanced.

Tumor Budding and Other Risk Factors of Lymph Node Metastasis in Submucosal Early Gastric Carcinoma: A Multicenter Clinicopathologic Study in 621 Radical Gastrectomies of Chinese Patients.
Du M, Chen L, Cheng Y, Wang Y, Fan X, Zhang Y, Zhou X, Guo L, Xu G, Zou X, Huang Q.
Am J Surg Pathol. 2019 Aug;43(8):1074-1082.
https://www.ncbi.nlm.nih.gov/pubmed/31094925

The authors systematically investigated the prognostic significance of tumor budding and other risk factors for lymph node metastasis (LNM) in 621 radical gastrectomies with submucosal gastric carcinomas (pT1b) from 4 medical centers in one of the endemic high-risk regions for gastric cancer in China. LNM was identified in 172 cases (27.7%). Overall, the significant independent high-risk factors for LNM are lymphovascular invasion ($P<0.01$), tumor budding ($P<0.01$), mixed tubular/ papillary adenocarcinoma with poorly cohesive carcinoma ($P<0.05$), and female sex ($P<0.05$). The significant low-risk factor for LNM was the gastric cardiac location ($P<0.05$). In 276 well/moderately differentiated tubular or papillary carcinomas, independent risk factors were tumor budding, deep submucosal (SM2) invasion and lymphovascular invasion. In 174 cases without tumor budding and lymphovascular invasion, no LMN was identified in 47 cardiac tumors, and 15 tumors <1.0 cm in size. Based on these findings authors concluded that tumor budding and lymphovascular invasion as the most important risk factors of LNM in submucosal early gastric carcinomas, while tumors in the gastric cardia were at a significantly lower risk of LNM.

Low Frequency of Lymph Node Metastases in Patients in the United States With Early-stage Gastric Cancers That Fulfill Japanese Endoscopic Resection Criteria.
Hanada Y, Choi AY, Hwang JH, Draganov PV, Khanna L, Sethi A, Bartel MJ, Goel N, Abe S, De Latour RA, Park K, Melis M, Newman E, Hatzaras I, Reddy SS, Farma JM, Liu X, Schlachterman A, Kresak J, Trapp G, Ansari N, Schrope B, Lee JY, Dhall D, Lo S, Jamil LH, Burch M, Gaddam S, Gong Y, Del Portillo A, Tomizawa Y, Truong CD, Brewer Gutierrez OI, Montgomery E, Johnston FM, Duncan M, Canto M, Ahuja N, Lennon AM, Ngamruengphong S.
Clin Gastroenterol Hepatol. 2019 Aug;17(9):1763-1769.
https://www.ncbi.nlm.nih.gov/pubmed/30471457

This multicenter retrospective study examined the frequency of lymph node metastases (LNM) in early gastric cancers (EGC) in a large cohort of patients from the United States. The authors note that endoscopic resection techniques, modalities which were originally adopted more readily in Asian countries, are becoming more popular in Western populations. While much has been published on the rate of LNM in EGC in Asian populations, this has not been extensively clarified in Western societies. This information would be pertinent to determine whether the currently available Asian guidelines for endoscopic resection can be applied to the US population. In this study, 176 patients undergoing surgical resection for EGC (defined as Tis or T1a, or T1b) were evaluated for the presence of LNMs as well as other clinicopathologic features such as lesional size, differentiation, and the presence or absence of lymphovascular invasion. These findings were correlated with the presence of absence of LNM. The data demonstrated that the rate of LNM in overall EGC in the cohort was 20.5%, a number which is substantially higher than that reported in Asian cohorts. However, those cases which fulfilled the Japanese standard criteria for endoscopic resection (differentiated tumor, nonulcerated, intramucosal cancers ≤ 2 cm) (n=10) exhibited a LNM rate of 0%. Using the expanded criteria, which allows for larger lesions or smaller lesion with ulceration or undifferentiated histology, the rate of LNM was 7.5%. A multivariate analysis demonstrated that submucosal invasion and the presence of lymphovascular invasion were associated with an increased risk of LNM. The authors conclude by saying that the rate of LNM in EGC in the US is higher than in Asian populations. However, by utilizing the standard Japanese criteria for endoscopic resection a subset of patients with whom mucosal resections could be recommended can be safely identified.

Liquid biopsies to track trastuzumab resistance in metastatic HER2-positive gastric cancer.
Wang DS, Liu ZX, Lu YX, Bao H, Wu X, Zeng ZL, Liu Z, Zhao Q, He CY, Lu JH, Wang ZQ, Qiu MZ, Wang F, Wang FH, Li YH, Wang XN, Xie D, Jia WH, Shao YW, Xu RH.
Gut. 2019 Jul;68(7):1152-1161.
https://www.ncbi.nlm.nih.gov/pubmed/30269082

This retrospective study included 78 cases of gastric cancer that had matched pairs of tissue and blood samples, on which targeted sequencing was performed, and also included 97 serial plasma samples from 24 patients with HER2+ metastatic gastric cancer, on which longitudinal analysis was performed to validate identified trastuzumab candidate resistance genes. Somatic copy number alterations (SCNA) of the *HER2* gene were high in patients with trastuzumab resistance and decreased in those who acquired resistance. Patients with resistance also had PIK3CA, ERBB2/4, and NF1 mutations. Resistance was overcome by combined HER2 and MEK/ERK blockade.

An association between crypt apoptotic bodies and mucosal flattening in celiac disease patients exposed to dietary gluten.
Lee M, Betman S, Iuga A, Yang HM, Fleming J, Green PHR, Lebwohl B, Lagana SM.
Diagn Pathol. 2019 Aug 31;14(1):98.
https://www.ncbi.nlm.nih.gov/pubmed/31472694

This retrospective study included 23 newly diagnosed adults with celiac disease, who had both a positive diagnostic biopsy and a follow-up biopsy after gluten free diet. The maximum number of apoptotic bodies (as defined by the German-Austrian-Swiss Consortium "liberal" criteria) per ten consecutive crypts was recorded by three gastrointestinal pathologists. The authors found a direct correlation between crypt apoptotic body count (ABC) and the degree of villous atrophy (as measured by Marsh score) in the active celiac biopsies. Crypt ABC decreased but not back to normal with gluten free diet. Mean maximum ABC in active celiac disease was 5.44 per crypt and decreased to 2.60 with gluten free diet ($p = <.0001$). The authors suggest that counting and tracking crypt ABC may be useful in assessing response to gluten free diet, and indicate that further study is needed to determine whether crypt ABC predicts villous recovery.

The Significance of So-Called Equivocal Immunohistochemical Staining for Cytomegalovirus in Colorectal Biopsies.
Ambelil M, Saulino DM, Ertan A, DuPont AW, Younes M.
Arch Pathol Lab Med. 2019 Aug;143(8):985-989.
https://www.ncbi.nlm.nih.gov/pubmed/30702332

The authors aimed to determine the clinical significance of equivocal CMV staining in colorectal biopsies. 221 consecutive cases of colorectal biopsies that were stained for CMV by immunohistochemistry were retrieved. Staining results were recorded as negative (completely negative nuclear staining), unequivocal (when at least 1 large nucleus positively stained), or equivocal (only occasional or rare small positively stained nuclei, similar in size to adjacent negative nuclei). A total of 83 of the 221 cases (38%) showed nuclear staining for CMV by IHC in at least 1 cell. Fifty-two cases (24% of all tested, 63% of positive cases) showed equivocal staining for CMV, and of these, 41 had follow-up information. Polymerase chain reaction for CMV was performed largely on blood samples and was not found to be sensitive for the detections of CMV proctocolitis. Even when only unequivocally positive cases by IHC (the gold standard) were considered, 75% of these cases had negative PCR results. Of 25 patients with equivocal CMV who received antiviral treatment and had follow-up information available, 21 (84%) had complete resolution of symptoms, compared with 8 of 16 (50%) who did not receive antivirals ($p= .02$), supporting that patients with equivocal CMV-IHC are more likely to have symptomatic improvement when they receive specific antiviral treatment for CMV. There was no statistically significant difference in response to antiviral drugs in patients with equivocal and unequivocal CMV staining. The authors suggest that any positive nuclear stain for CMV in colorectal biopsies, regardless of the size or shape of the nucleus, should be reported to the clinicians, as equivocal CMV staining likely represents true CMV proctocolitis; however, prospective studies are needed to confirm these findings.

Cytomegalovirus reactivation in inflammatory bowel disease: an uncommon occurrence related to corticosteroid dependence.
Hissong E, Chen Z, Yantiss RK.
Mod Pathol. 2019;32(8):1210-1216.
https://www.ncbi.nlm.nih.gov/pubmed/30952971

The hypothesis for this study is that decreased detection of CMV in patients with inflammatory bowel disease is due to less frequent use of long-term corticosteroids in the maintenance of the disease. The authors looked retrospectively at cases of patients with severe flairs in established inflammatory bowel disease between 2002 and 2017 and corticosteroid-dependent vs. corticosteroid-independent patient cases were compared. All cases of CMV (most diagnosed between 2002 and 2009) in the study set were from corticosteroid dependent patients. The authors conclude that decreasing rates of CMV related colitis may reflect a shift away from corticosteroid based therapy in inflammatory bowel disease.

Meta-analysis of Histological Margin Positivity in the Prediction of Recurrence After Crohn's Resection.

Ryan JM, Rogers AC, O'Toole A, Burke JP.
Dis Colon Rectum 2019; 62: 882–892
https://www.ncbi.nlm.nih.gov/pubmed/31162377

The authors of this study performed meta-analysis through literature searches to ascertain the effect of positive histologic margins at the time of initial resection on recurrence of Crohn's disease. Crohn's disease is challenging to manage with medication alone and up to 78% require resection. Within 10 years, 19% of those patients will require a second surgical resection for recurrence. Currently accepted risk factors for recurrence include smoking, perforating disease, restoration of the fecal stream, ileocolic involvement, previous surgical resection. Margin status has not been an emphasis and recently the presence of inflammation within the enteric nervous system or "plexitis" has been reported to have an association with increased risk of disease recurrence. To that end, this study reviewed a total of 176 citations with the following inclusion criteria (original publication, histologically proven Crohn's disease with histologic margin status included, reported outcome measures of recurrence) and exclusion criteria (English language, unavailable or uninterpretable data, initial surgery involved stricturoplasty, children under 16 years of age). Ultimately 18 studies were included with a mean rate of positive margins of 41.7 ± 17.4% and a pooled mean follow-up of 69 ± 39 months. The definition of margin status differed between studies. 72% reported margin positivity as inflammation, granulomas, or plexitis found at either the proximal or distal margin. One study did not specify how the margins were assessed. The remaining studies reported proximal margin status only. Nonspecific or mild inflammation was considered a negative margin in 5 studies and a positive margin in 4 studies. 4 studies did not provide a histologic definition of inflammation. The remainder of the studies focused on myenteric plexitis only. 4 studies reported on plexitis at the resection margins, of which 2 also reported separately on inflammation at the margins. Plexitis was defined as "at least one chronic inflammatory cell contiguous to or within a ganglion or nerve bundle" in 3 of the 4 studies that reported it. In one study, this definition was modified to greater than 2 mastocytes contiguous to or within a ganglion or nerve bundle. Positive margins were associated with a higher rate of overall recurrence (OR, 1.7; 95% CI, 1.3–2.1; $p < 0.001$), clinical recurrence (OR, 1.7; 95% CI, 1.0–2.8; $p = 0.04$), and anastomotic recurrence (OR, 1.6; 95% CI, 1.0–2.3; $p = 0.03$). When plexitis was specifically reported at the margin, there was an increase in recurrence (OR, 2.3; 95% CI, 1.1–4.9; $p = 0.02$). Overall, the authors conclude that the presence of involved histological margins at the time of index resection in Crohn's disease is associated with recurrence, and plexitis shows promise as a marker of more aggressive disease. The authors emphasize the need for standardized histological scoring of margin status and recurrence reporting in future studies.

Responsiveness of histological disease activity indices in ulcerative colitis: a post hoc analysis using data from the TOUCHSTONE randomised controlled trial.
Jairath V, Peyrin-Biroulet L, Zou G, Mosli M, Vande Casteele N, Pai RK, Valasek MA, Marchal-Bressenot A, Stitt LW, Shackelton LM, Khanna R, D'Haens GR, Sandborn WJ, Olson A, Feagan BG, Pai RK.
Gut. 2019 Jul;68(7):1162-1168.
https://www.ncbi.nlm.nih.gov/pubmed/30076171

In this post-hoc analysis of 197 patients with moderately to severely active ulcerative colitis who had colon biopsies performed as part of a multicenter randomized, placebo-controlled, phase II trial of ozanimod for induction and maintenance of remission, four gastrointestinal pathologists read digital images of H&E stained sections and applied four histologic disease activity index ratings after reviewing standardized training materials on each. The indices were: Geboes score (GS) and modified Riley score (MRS) scores, the Robarts Histopathology Index (RHI) and Nancy Histological Index (NHI). Inter-rater reliability of the histological indices was substantial to almost perfect (ICC>0.61) for all four indices. Responsiveness was moderate to large (SES estimates>0.5) for all four indices for the detection of treatment effect in this set. Specifically, all four indices were able to discriminate between patients treated with ozanimod and those given placebo. The authors conclude that further study may help identify which index could be best in different patient populations and treatment scenarios.

Targeted mutational analysis of inflammatory bowel disease–associated colorectal cancers
Alpert L, Yassan L, Poon R, Kadri S, Niu N, Patil SA, Mujacic I, Montes D, Galbo F, Wurst MN, Zhen CJ, Cohen RD, Rubin DT, Pekow JR, Weber CR, Xiao SY, Hart J, Segal J, Setia N.
Hum Pathol. 2019 Jul;89:44-50.
http://www.ncbi.nlm.nih.gov/pubmed/31054900

Fifty-five IBD-CRCs from 48 patients underwent molecular analysis with a 50 gene hot spot solid tumor panel (OncoScreen ST2.0) and were compared to controls of sporadic colorectal cancers and The Cancer Genome Atlas data. The most common mutation was TP53, which was similar in frequency in both IBD-CRC and sporadic CRC (69% & 70%). By comparison, APC and KRAS mutations were less frequent in IBD-CRC than sporadic, and IDH1 R132 mutations were seen in 7% of IBD-CRC compared to 1% of sporadic, suggesting some IBD-CRCs may be amenable to targeted treatment. There was no significant association between any mutations and age, sex, tumor location, mucinous or signet ring cell histology, lymphovascular invasion, pT stage, or presence of lymph node metastases. Other findings include a 5% MMR deficiency rate among IBD-CRC, a smaller percentage than reported in other studies. The data support diverging pathways of carcinogenesis between IBD-CRC and sporadic CRC.

Whole Exome Sequencing of Ulcerative Colitis-associated Colorectal Cancer Based on Novel Somatic Mutations Identified in Chinese Patients.
Yan P, Wang Y, Meng X, Yang H, Liu Z, Qian J, Zhou W, Li J.
Inflamm Bowel Dis. 2019 Jul 17;25(8):1293-1301.
https://www.ncbi.nlm.nih.gov/pubmed/30794281

This study analyzed 10 cases of UC- associated CRC patients at high- risk of carcinogenesis, and found 25 deleterious mutations involved in apoptosis, epigenetics regulation, cell adhesion, PI3K-Akt pathway and autophagy. In comparison to genetic alterations in sporadic primary CRC (223 cases from The Cancer

Genome Atlas), 11/25 mutated genes were significantly different from sporadic CRC. 78% our ulcerative colitis–associated CRC patients harbored at least 1 non-silent somatic mutation involved in epigenetic regulation, and several genes encoding epigenetic regulators—such as SUPT6H, NCOR2, and MECP2—were more frequently harbored mutations in the ulcerative colitis–associated CRCs than in the sporadic CRCs. The TP53 somatic mutations were marginally less prevalent in ulcerative colitis–associated CRCs than in sporadic CRCs (61% vs 80%). This study of 10 patients showed distinct genomic alteration profiles of deleterious somatic mutations were found in their cohort ulcerative colitis–associated and sporadic CRCs.

Association Between Cigarette Smoking and Alcohol Consumption and Sessile Serrated Polyps in Subjects 30 to 49 Years Old.
Lee JY, Chang HS, Kim TH, Chung EJ, Park HW, Lee JS, Lee SM, Yang DH, Choe J, Byeon JS.
Clin Gastroenterol Hepatol. 2019 Jul;17(8):1551-1560.e1.
https://www.ncbi.nlm.nih.gov/pubmed/30476586

The study sought to examine the prevalence of sessile serrated polyps (SSPs) in young adults and to evaluate the association of these lesions with modifiable lifestyle factors such as cigarette smoking and alcohol consumption. The authors state that prior studies have identified both of these practices as risk factors for SSPs in adults over the age of 50 but little work has been done on younger individuals. This cross-sectional study evaluated a large cohort of asymptomatic patients (n=49,646) from Seoul, Korea who had voluntarily underwent screening colonoscopies. A total of 13,618 individuals were aged 30 to 49 years. The authors found the prevalence of SSPs to be 2.0% in this population, which was similar to their second cohort of patients aged 50 to 75 years. Just as has been shown in older adults, cigarette smoking (20 or more pack-years) was determined to be a significant risk factor of overall SSPs, large (greater than 1.0 cm) SSPs, and multiple SSPs. Alcohol consumption was found to have a similar association. The authors also showed that this SSP risk was reduced in patients who had ceased smoking for 5 years. Furthermore, the association between smoking and SSPs was said to be statistically stronger for distal SSPs compared to proximal SSPs. The authors conclude by saying that just as in older adults, smoking and alcohol consumption appear to be associated with the development of SSPs in young adults and that modifying these risk factors may reduce the risk of developing these lesions.

EIF3E-RSPO2 and PIEZO1-RSPO2 fusions in colorectal traditional serrated adenoma.
Hashimoto T, Ogawa R, Yoshida H, Taniguchi H, Kojima M, Saito Y, Sekine S.
Histopathology. 2019 Aug;75(2):266-273.
https://www.ncbi.nlm.nih.gov/pubmed/30916365

Traditional serrated adenoma (TSA) is an uncommon type of colorectal serrated polyp with abundant eosinophilic cytoplasm, elongated nuclei, ectopic crypt formation, and slit like serrations. RSPO fusions, which potentiate WNT signaling, are common and characteristic genetic alterations in TSA. In the present study, the authors analyzed 99 TSAs by quantitative polymerase chain reaction (PCR) and identified RSPO fusions in 33 of 99 TSAs (33%); 29 of which had previously reported PTPRK–RSPO3 fusions, demonstrating that PTPRK–RSPO3 is the predominant RSPO fusion in TSAs. They found overexpression of RSPO2 in 6 lesions. Among the six lesions with RSPO2 overexpression, two overexpressed full-length RSPO2. In addition, EIF3E–RSPO2 and PIEZO1–RSPO2 fusions were identified in three and one TSAs, respectively. All of the four TSAs with RSPO2 fusions concurrently had KRAS mutations and showed the classic histological features. In summary, the present study identified EIF3E–

RSPO2 and PIEZO1–RSPO2 in a subset of TSAs. The TSAs with these fusions showed conventional clinic-pathological and molecular features. These observations expand the spectrum of RSPO fusions in TSAs, and suggest that TSAs are precursors of colorectal cancers with these RSPO2 fusions.

BRAF V600E immunohistochemistry demonstrates that some sessile serrated lesions with adenomatous dysplasia may represent collision lesions.
Bettington M, Liu C, Gill A, Walker N, Leggett B, Whitehall V, Rosty C.
Histopathology. 2019 Jul;75(1):81-87.
https://www.ncbi.nlm.nih.gov/pubmed/30825335

Sessile serrated lesions (SSL) with dysplasia (SSLD) are biologically high-grade with a high risk of rapid malignant transformation. Most of these have a BRAF mutation and 75% show loss of MLH1 expression in their dysplastic component. The authors hypothesized that a subset of SSLs with adenomatous dysplasia may represent a collision lesion between an ordinary SSL and a conventional adenoma. BRAF mutation analysis was performed using molecular testing and BRAF-V600E immunohistochemistry on 80 SSLDs. These included 19 with adenomatous dysplasia, 18 with serrated dysplasia and 43 with dysplasia not otherwise specified (NOS). The overall BRAF-V600E mutation rate was 84% in all lesions, 68% in SSLs with adenomatous dysplasia, 89% in SSLs with serrated dysplasia and 88% in SSLs with dysplasia NOS. Out of the BRAF-V600E mutation positive 63 SSLs with dysplasia , a negative BRAF-V600E immunostaining was observed in the dysplastic component of 83% of SSLs with adenomatous dysplasia, 0% of SSLs with serrated dysplasia and 3% of SSLs with dysplasia NOS ($P < 0.001$).The authors suggest that a small subset of SSLDs are likely to represent collision lesions. The dysplasia in these SSLs mimics dysplasia seen in conventional adenomas and is not associated with loss of MLH1 expression. These collision lesions can be identified by judicious use of BRAF-V600E immunohistochemistry in cases with the appropriate morphology. These findings have clinical relevance as true SSLDs are high-risk polyps with a propensity to rapid malignant transformation, justifying complete removal of the primary polyp with close endoscopic surveillance. In contrast, a collision lesion between an SSL and a conventional adenoma is a low-risk lesion. The authors also suggest a need for updating the current terminology surrounding the morphological patterns of SSLDs, as cases with adenomatous dysplasia are unlikely to represent true SSLDs.

Association Between Endoscopist Personality and Rate of Adenoma Detection.
Ezaz G, Leffler DA, Beach S, Schoen RE, Crockett SD, Gourevitch RA, Rose S, Morris M, Carrell DS, Greer JB, Mehrotra A.
Clin Gastroenterol Hepatol. 2019 Jul;17(8):1571-1579.e7.
https://www.ncbi.nlm.nih.gov/pubmed/30326300

If you're perhaps interested in a little break from more serious literature this paper may suffice. The authors of this work evaluated the adenoma detection rate (ADR; proportion of all colonoscopies in which any adenoma or carcinoma was identified) for 117 endoscopists whom also completed surveys. These questionnaires inquired about perceptions of their colonoscopy quality, personality traits, and financial motivations. Respondents included both private practice physicians as well as those employed in an academic setting. Their results were consistent with prior literature which found that female sex of physician, gastroenterology specialty training, and fewer years in practice were associated with higher ADRs. There were no significant differences in ADRs between physicians paid via several methods including salary, fee-for-service, or salary with volume incentive. ADRs were found to be higher in

individuals who self-reported as being “more compulsive than their peers” and “more thorough relative to their peers”. Interestingly, the authors also found that endoscopists who reported feeling rushed, having difficulty pacing themselves, or difficulty in accomplishing goals also had statistically higher ADRs. These latter findings were also associated with longer withdrawal times. The authors conclude by postulating that perhaps performing more thorough endoscopies is taxing and can make a physician feel rushed or have less time to accomplish personal goals. They also state that it is unclear how these findings can be utilized to improve colonoscopy quality as it is unclear whether compulsiveness or thoroughness can be taught.

Optical Technologies for Endoscopic Real-Time Histologic Assessment of Colorectal Polyps: A Meta-Analysis.
Mason SE, Poynter L, Takats Z, Darzi A, Kinross JM.
Am J Gastroenterol. 2019 Aug;114(8):1219-1230.
https://www.ncbi.nlm.nih.gov/pubmed/30848728

This meta-analysis was conducted to investigate the current status of enhanced optical technologies in the diagnosis of colorectal polyps. The authors note that there has been an impetus to develop technologies which can provide accurate and real-time endocopic assessments of such lesions to reduce the number of unnecessarily removed benign polyps and to better identify those which may harbor more advanced lesions. A total of 102 studies were evaluated as part of this analysis which included works investigating such technologies as digital chromoendoscopy (including narrow band imaging), dye chromoendoscopy, spectral analysis of autofluorescence, endomicroscopy, and computer-aided diagnosis. While the sensitivities and specificities of these techniques varied to a small degree (ranging from 88.4%-94.4% and 50.9%-92.5% respectively) the negative predictive value for adenoma detection in these techniques largely fell short of 90%. This benchmark is often considered to be the threshold that would have to be reached before these technologies could have any potential clinical utility. The exception was in the digital chromoendoscopy analysis of small rectosigmoid colon polyps. The authors also analyzed the studies to determine whether improvements have been made over time and determined that they have not. They conclude by stating that current technologies are insufficient to support strategies by which polyps may be discarded following resection and that major advances will be required before advanced optical technologies can replace conventional histologic assessment.

A Review of Current Challenges in Colorectal Cancer Reporting.
Dawson H, Kirsch R, Messenger D, Driman D.
Arch Pathol Lab Med. 2019 Jul;143(7):869-882.
https://www.ncbi.nlm.nih.gov/pubmed/30672337

High-quality pathology reporting is essential for prognostication and management of patients with colorectal cancer (CRC). This detailed review addresses challenging areas in CRC pathology and provides an overview of the literature, current guidelines, and expert recommendations for the handling of colorectal cancer resection specimens in everyday practice. The review talks in depth about the issues of gross assessment of total mesorectal excision specimens, radial margin evaluation, serosal involvement including staging challenges of T3 vs. T4a, and staging issues revolving around nodal metastases. Other topics discussed are tumor deposits, tumor budding, venous and perineural invasion and risk stratification of stage II CRC patients.

Budding, tumor-infiltrating lymphocytes, gland formation: scoring leads to new prognostic groups in World Health Organization low-grade colorectal cancer with impact on survival
Lang-Schwarz C, Melcher B, Haumaier F, Schneider-Fuchs A, Lang-Schwarz K, Krugmann J, Vieth M, Sterlacci W.
Hum Pathol. 2019 Jul;89:81-89.
http://www.ncbi.nlm.nih.gov/pubmed/ 31054898

This study identified features separating WHO low-grade colorectal cancer cases (a majority of colorectal cases) into additional subgroups using features such as gland formation, budding and tumor infiltration lymphocytes. 576 cases representing all stages were divided into low risk, intermediate risk and high risk groups via a proposed "Bayreuth score" system which is applied only to WHO low-grade CRC of no special type, as below:
Gland formation:
1 point >95%
2 points 95% - 50%
Budding:
1 point Low (0-4 buds)
2 points Intermediate or high (≥5 buds)
Tumor infiltrating lymphocytes:
1 point >5%
2 points ≤5% =
Total score 3-4 = "low risk"
Total score 5 = "intermediate risk"
Total score 6 = "high risk"
The 3 groups resulted in differing pT, pN, M, stage, lymphovascular invasion and overall survival.

A Multicenter Study of the Prognostic Value of Desmoplastic Reaction Categorization in Stage II Colorectal Cancer.
Ueno H, Kanemitsu Y, Sekine S, Ishiguro M, Ito E, Hashiguchi Y, Kondo F, Shimazaki H, Kajiwara Y, Okamoto K, Mochizuki S, Tsujimoto H, Shinto E.
Am J Surg Pathol. 2019 Aug;43(8):1015-1022.
https://www.ncbi.nlm.nih.gov/pubmed/31094924

This multi institutional study aimed at clarifying the prognostic significance of desmoplastic reaction (DR) categorization based on the hyalinized collagen bundles and myxoid stroma classified as mature, intermediate, or immature in stage II colorectal cancer patients. The first cohort included 679 stage II CRC patients from a single institution between 1980 and 2005. To validate the results from the first cohort, 446 patients with stage II CRC diagnosed between 2007-2008 from 4 institutions were enrolled as second cohort. 430, 180, and 69 tumors from first cohort and 235, 142, and 69 tumors from second cohort were classified into the mature, intermediate, and immature groups, respectively. In the first cohort, recurrence rate at 5 years were 9.1%, 12.8%, and 30.7% in the mature, intermediate, and immature groups, respectively ($P < 0.0001$). Five-year recurrent free survival (RFS) was most favorable in the mature group (85.2%), followed by intermediate (77.1%) and immature groups (60.9%) ($P<0.0001$). Similar results were observed in the second cohort. Multivariate analyses showed that the immature pattern as an independent factor, adversely affecting RFS in both cohorts. Additional analysis of all the known prognostic factors revealed that DR categorization was the most effective factor for RFS, followed by tumor budding in both cohorts. Based on these findings the authors concluded that DR categorization could be a new useful prognostic factor in stage II CRC patients.

CDX2 and Muc2 immunohistochemistry as prognostic markers in stage II colon cancer
Cecchini MJ, Walsh JC, Parfitt J, Chakrabarti S, Correa RJ, MacKenzie MJ, Driman DK.
Hum Pathol. 2019 Aug;90:70-79.
http://www.ncbi.nlm.nih.gov/pubmed/31121192

This immunohistochemical study investigated staining patterns of CDX2, CDX1, Muc2, GPX2 and villin on 210 cases of stage II colorectal cancer without adjuvant therapy, utilizing whole slide staining on 3 sections from each patient. Results were stained from 0-4 based on intensity and positive staining included scores 2-4. Compared to prior studies showing that loss of CDX2 has a worse prognosis, this study found that CDX2 expression can be patchy (23% of cases) or lost (11%) without impact on survival. Muc2 expression showed reduced survival, but no outcome differences were seen with CDX1, GPX2 or villin.

Confirmation that somatic mutations of beta-2 microglobulin correlate with a lack of recurrence in a subset of stage II mismatch repair deficient colorectal cancers from the QUASAR trial.
Barrow P, Richman SD, Wallace AJ, Handley K, Hutchins GGA, Kerr D, Magill L, Evans DG, Gray R, Quirke P, Hill J.
Histopathology. 2019 Aug;75(2):236-246.
https://www.ncbi.nlm.nih.gov/pubmed/31062389

Beta2-microglobulin (B2M) mutations occur frequently in mismatch repair-deficient colorectal cancer (dMMR CRC), with limited data suggesting they may protect against recurrence. The aim of this study was to determine the frequency of somatic B2M mutations by performing Sanger sequencing for the three coding exons of B2M in a sample of 121 dMMR and 108 proficient MMR (p MMR) CRC specimens from a large randomised controlled clinical trial (QUASAR) and correlate mutation status with B2M protein expression and recurrence. B2M protein expression was assessed by immunohistochemistry. Deleterious B2M mutations were detected in 39 of 121 (32%) dMMR tumors. None of the 39 B2M-mutant tumors recurred, compared with 14 of 77 (18%) B2M-wild-type tumors (p = 0.005) (median follow-up :7.4 years). Sensitivity and specificity of IHC in detecting B2M mutations was 87 and 71%, respectively. Significantly fewer (2.9%) of the 108 pMMR CRCs demonstrated deleterious B2M mutations. These results indicate that patients with dMMR CRC who have a B2M mutation are protected from developing recurrent disease following resection, and B2M mutation status has potential clinical utility as a prognostic biomarker in stage II dMMR CRC.

Prognostic value of microvessel density in stage II and III colon cancer patients: a retrospective cohort study.
den Uil SH, van den Broek E, Coupé VMH, Vellinga TT, Delis-van Diemen PM, Bril H, Belt EJT, Kranenburg O, Stockmann HBAC, Belien JAM, Meijer GA, Fijneman RJA.
BMC Gastroenterol. 2019 Aug 16;19(1):146.
https://www.ncbi.nlm.nih.gov/pubmed/31420015

Microvessel density (MVD) has been associated with poor outcome in several types of cancer. This study aimed to evaluate the prognostic value of MVD in stage II and III colon cancer and its relation to tumor-stroma-percentage (TSP) and expression of HIF1A and VEGFA. 53 stage II and 54 (5-fluorouracil-treated) stage III colon cancer patients were included. MVD was scored by digital morphometric analysis of CD31-stained whole tumor sections. TSP was scored using hematoxylin-eosin stained slides. Protein

expression of HIF1A and VEGFA was determined by immunohistochemical evaluation of tissue microarrays. The study found that the median MVD was higher in stage III compared to stage II colon cancers (11.1% versus 5.6%, $p < 0.001$). High MVD in stage II patients tended to be associated with poor disease free survival (DFS) in univariate analysis ($p = 0.056$). In contrast, high MVD in 5FU-treated stage III patients was associated with better DFS ($p = 0.006$). Prognostic value for MVD was observed in multivariate analyses for both cancer stages. The authors concluded that MVD is an independent prognostic factor associated with poor DFS in stage II colon cancer patients, and with better DFS in stage III colon cancer patients treated with adjuvant chemotherapy.

Traditional Serrated Pathway-associated Colorectal Carcinoma: Morphologic Reappraisal of Serrated Morphology, Tumor Budding, and Identification of Frequent PTEN Alterations.
Tsai JH, Jeng YM, Yuan CT, Lin YL, Cheng ML, Liau JY.
Am J Surg Pathol. 2019 Aug;43(8):1042-1051.
https://www.ncbi.nlm.nih.gov/pubmed/31094930

This study was aimed at morphologic assessment of 27 colorectal carcinomas arising from TSA (TSA-CRCs) and 53 BRAF-mutated/ microsatellite-stable colorectal carcinomas (BRAF-mut/MSS CRCs). *PTEN*, a tumor suppressor gene commonly mutated in microsatellite-unstable CRCs was also analyzed. 90% of TSA-CRCs and BRAF-mut/MSS CRCs exhibited a constellation of serrated morphology, including epithelial serrations, abundant eosinophilic cytoplasm, and discernible/vesicular nuclei. 78% (21/27) of TSA-CRCs and 59% (31/53) of BRAF-mut/MSS CRCs were diagnostic for serrated adenocarcinoma (Makinen's Criteria), while 11% (3/27) of TSA-CRCs and 34% (18/53) of BRAF-mut/MSS CRCs were equivocal for serrated adenocarcinoma. About 70% (19/27) of TSA-CRCs were BRAF mutated and 30% (8/27) were KRAS mutated. High-grade tumor budding (n=43) was closely associated with serrated morphology and was a significant independent factor for poor patient survival in multivariate analysis (P=0.008). 44 tumors had aberrant PTEN expression by immunohistochemistry and 8 harbored PTEN somatic mutations without hotspot clustering, 12 had promoter hypermethylation, and 14 had deleted alleles. Based on these findings the authors concluded that there are morphologic and molecular similarities between TSA-CRCs and BRAF-mut/MSS CRCs which may well constitute the TSA pathway.

Clinicopathological factors associated with BRAF-V600E mutation in colorectal serrated adenomas.
Travaglino A, D'Armiento FP, Cassese G, Campanino MR, Borrelli G, Pignatiello S, Luglio G, Maione F, De Palma GD, D'Armiento M.
Histopathology. 2019 Aug;75(2):160-173.
https://www.ncbi.nlm.nih.gov/pubmed/30815911

This study is a systematic review and meta-analysis assessing the association of clinical and pathological factors with BRAF mutation in colorectal serrated adenomas. Forty studies assessing 3511 serrated adenomas (2375 sessile serrated adenoma (SSAs) and 1136 traditional serrated adenoma (TSAs)) were included. The authors confirmed the association of BRAF mutation with proximal localization in the colon and with CIMP-H status in both SSA and TSA, but not with sex, age, sessile shape, serrated dysplasia, invasive cancer, nuclear β-catenin expression and p53 overexpression. BRAF mutation was significantly associated with polyp size <10 mm in TSA, and with endoscopic pit pattern II-O and expression of gastric-type mucins at least in SSA.

Colorectal large-cell neuroendocrine carcinoma with lymphoid stroma: further evidence confirming a unique subtype associated with MLH1/PMS2 loss, BRAF mutation, Epstein-Barr virus negativity, and the possibility of a better prognosis.
Chetty R, Capo-Chichi JM, Serra S.
Histopathology. 2019 Aug;75(2):247-253.
https://www.ncbi.nlm.nih.gov/pubmed/30990915

The authors aim to highlight a unique subtype of colorectal pure large-cell neuroendocrine carcinoma (LCNEC). Three patients (ages 79, 85 and 89 years) with large, ulcerated, polypoid masses (average size 72 mm, pT3N2) are described. Two presented with ascending colon masses and one with a rectal mass. Histologically, the tumors were composed of large cells arranged in sheets of cells as well as packets and nests of cells with rosettes, all with high mitotic counts (>20/10 HPFs) and high Ki67 proliferative indices (95%, 100%, and 80%). All cases contained mainly peritumoral lymphoid aggregates. No associated adenocarcinoma component was identified. Synaptophysin, chromogranin (less intense) and epithelial markers were expressed in all cases in the majority of the tumor cells. All tumors were characterized by immunohistochemical loss of MLH1 and PMS2, while both MSH2 and MSH6 were retained. The tumors were EBER-ISH-negative. BRAF was mutated in all tumors and all three were MSI-H and showed methylation of MLH1. Two patients survived for 48 and 72 months, whereas the third is alive after 12 months without evidence of recurrence. In summary, these unusual primary colorectal LCNECs with an accompanying lymphoid component are characterized by loss of MLH1/PMS2, BRAF mutation, microsatellite instability, and Epstein-Barr virus negativity. The authors suggest that LCNECs with a lymphoid component may behave better than other LCNECs lacking an accompanying lymphoid infiltrate, likely owing to a combination of the lymphoid component and the MSI status (high) of these cases. The authors also suggest that reporting of these cases as such is warranted to accumulate more cases in order to confirm whether they do indeed have a better prognosis and represent a distinct morphological variant of neuroendocrine carcinoma.

Mutation in BRAF and SMAD4 associated with resistance to neoadjuvant chemoradiation therapy in locally advanced rectal cancer.
Jiang D, Wang X, Wang Y, Philips D, Meng W, Xiong M, Zhao J, Sun L, He D, Li K.
Virchows Arch. 2019 Jul;475(1):39-47.
https://www.ncbi.nlm.nih.gov/pubmed/31056731

Using next generation sequencing, the authors investigated 59 genes in 74 patients with locally advanced rectal cancer who received neoadjuvant chemoradiation therapy (nCRT). Higher rate of BRAF mutation was identified in tumor regression score of 2-3 than tumor regression of 0-1. SMAD4 was mutated more frequently in tumor regression score of 3 than score of 0-2. Patients with BRAF or SMAD4 mutations showed worse prognosis than those with wild type genes. Other genes including KRAS, PIK3CA, TP53, and MMR status failed to predict tumor response to the nCRT. BRAF and SMAD4 might be useful predictive molecular markers for patients with advanced rectal cancer underwent neoadjuvant chemoradiation therapy.

Detection of ERBB2 Amplification by Next-Generation Sequencing Predicts HER2 Expression in Colorectal Carcinoma
Odise Cenaj, MD, Azra H Ligon, PhD, Jason L Hornick, MD, PhD, Lynette M Sholl, MD
American Journal of Clinical Pathology, Volume 152, Issue 1, July 2019, Pages 97–108
https://www.ncbi.nlm.nih.gov/pubmed/31115453

Her2 inhibitory therapy has been shown to be useful in treating some patients with pretreated, KRAS wild type, cetuximab resistant metastatic colorectal cancers (CRCs). The aim of this study was to investigate the concordance between the amplification of Her2 Gene (ERBB3) identified through targeted next-generation sequencing (NGS) and overexpression identified by immunohistochemistry (IHC) in a retrospectively identified set of CRCs. The authors found a high correlation between overexpression, identified by NGS, and immunohistochemistry positivity using criteria from the HER2 Amplification for Colorectal Cancer Enhanced Stratification [HERACLES] trial (intense membrane staining in 50% or more of tumor cells by IHC as per the HER2). They suggest NGS may be useful as a screening test to identify cases for further testing by IHC.

Prevalence of recurrent oncogenic fusion in mismatch repair-deficient colorectal carcinoma with hypermethylated MLH1 and wild-type BRAF and KRAS.
Wang J, Yi Y, Xiao Y, Dong L, Liang L, Teng L, Ying JM, Lu T, Liu Y, Guan Y, Pang J, Zhou L, Lu J, Zhang Z, Liu X, Liang X, Zeng X, Yi X, Zhou W, Xia X, Yang L, Zhang J, Kopetz S, Futreal PA, Wu H, Liang Z
Mod Pathol. 2019;32(7):1053-1064.
https://www.ncbi.nlm.nih.gov/pubmed/30723297

This retrospective study set out to investigate molecular genetic alterations in colorectal carcinoma based on DNA mismatch repair status. The authors found that targetable oncogenic fusions were more frequently detected in DNA mismatch repair deficient tumors with MLH1 hypermethylation and wild type BRAF and KRAS. The authors propose that this finding may be of use in an easy to perform cost effective strategy in screening for targetable alterations. The authors state that further investigation is warranted.

Necessity of Genetic Evaluation of Metachronous Metastases of Colorectal Cancer: Quantitative Analysis of Genetic Discordance Between Metachronous Metastases and Radically Resected Primary Colorectal Cancers Using Next-Generation Sequencing.
Lee KH, Kim JS, Kim JY.
Dis Colon Rectum. 2019 Jul;62(7):832-839.
https://www.ncbi.nlm.nih.gov/pubmed/31188184

The presence of pathogenic mutations within RAS and RAF family of genes dictates current treatment options for patients with metastatic colorectal adenocarcinoma. Both intratumoral heterogenicty and clonal evolution within metastasis can result in resistance to therapy. Therefore, this retrospective review analyzed metachronous colorectal metastases following radical primary or palliative resections through next generation sequencing to assess quantitative genetic discordance. 34 patients were included in this study with at least 3 different specimens analyzed per patient with the Ion AmpliSeq Colon and Lung Cancer Research Panel v2 primer pools. This primer set covers 504 mutational hotspot regions in 22 genes (*KRAS*, *EGFR*, *BRAF*, *PIK3CA*, *AKT1*, *ERBB2*, *PTEN*, *NRAS*, *STK11*, *MAP2K1*, *ALK*, *DDR2*, *CTNNB1*, *MET*, *TP53*, *SMAD4*, *FBXW7*, *FGFR3*, *NOTCH1*, *ERBB4*, *FGFR1*, and *FGFR2*). Variants within *KRAS*, *NRAS*, *BRAF*, *PIK3CA*, *MET*, and *PTEN* were analyzed via the provided Ion Torrent Caller plug in and MAF

was used to determine to proportion of mutations within each specimen sequenced. The liver was the most frequent site for the first metachronous metastasis (n = 16), and the lung was second (n = 12). PT53 was the most frequently mutated gene. *KRAS* mutations within the primary tumor was found in 9 patients (27.3%), 1 patient had an *NRAS* mutation and 2 had *BRAF* mutations (3.0% and 6.0%). Ultimately the authors of this study reproduced findings similar to those previously reported: That there can be significant discordance between the primary tumor and metachronous metastases and that the pattern is difficult to predict. Some metastatic lesions show similar mutational profiles while others are different. Therefore, the authors advocate for testing the metastatic disease when possible and suggest using MAF to predict the efficacy of targeted treatment.

SATB2 and CDX2 are prognostic biomarkers in DNA mismatch repair protein deficient colon cancer.
Ma C1, Olevian D1, Miller C1, Herbst C1, Jayachandran P2, Kozak MM2, Chang DT2, Pai RK3.
Mod Pathol. 2019 Jul;32(8):1217-1231.
https://www.ncbi.nlm.nih.gov/pubmed/30962505

This study looks at the prognostic significance of SATB2 and CDX2 expression in a set of colorectal carcinomas, in light of recent evidence that loss of CDX2 and or SATB2 expression is an indicator of poor prognosis. In the study set, which included mismatch repair deficient and proficient tumors, SATB2 negative and/or CDX2 negative expression was more frequently found in mismatch repair protein deficient tumors. Multivariable analysis of survival in patients with mismatch repair protein deficient tumors tumor identified only stage and SATB2 and/or CDX2 negative expression as predictors of survival. SATB2 and CDX2 expression was not predictive in mismatch repair proficient, BRAF mutated, or KRAS mutated tumors. In light of their findings, the authors suggest that SATB2 and CDX2 are prognostic biomarkers in cases of mismatch repair protein deficient tumors, and that immunohistochemistry for these markers may be useful in risk assessment in these cases.

Detection of Tumor NTRK Gene Fusions to Identify Patients Who May Benefit from Tyrosine Kinase (TRK) Inhibitor Therapy.
Hsiao SJ, Zehir A, Sireci AN, Aisner DL.
J Mol Diagn. 2019 Jul;21(4):553-581
https://www.ncbi.nlm.nih.gov/pubmed/31075511

NTRK gene fusions occur in many different tumor types and at different frequencies. Recently, the pan-tyrosine kinase (TRK) inhibitor larotrectinib has been approved as treatment for patients with TRK fusion cancer regardless of tumor subtype and entrectinib is currently being studied in active clinical trials. In certain rare tumors, NTRK fusions are present in most lesions, whereas in more common cancers, the incidence is low, only 0.1% to 2% of tumors. Due to the marked and durable responses achieved with TRK tyrosine kinase inhibitors in patients with pathogenic TRK fusions discovering NTRK gene fusions has become clinically relevant. As such, the authors of this study have proposed a diagnostic algorithm to facilitate the identification of patients with tumors harboring TRK fusions based on a combination of FISH, NGS, and immunohistochemistry assays. Chromosomal rearrangements involving the neurotrophic receptor tyrosine kinase 1, 2, and 3 genes, NTRK1, NTRK2, and NTRK3 lead to functional gene fusions which result in the constitutive activation of single-pass transmembrane receptor tyrosine kinases, high-affinity nerve growth factor receptor (TRKA), BDNF/NT-3 growth factor receptor (TRKB), and NT-3 growth factor receptor (TRKC), respectively. Although other somatic alterations within these genes have been detected, the clinical relevance and response to TKI therapy is currently unclear. Therefore, the

majority of testing is centered around the presence or absence of gene fusions that produce functional, constitutively active oncogenic tyrosine kinases. To this end, the authors propose a strategy to test tumors for NTRK fusions based on how likely those tumors are to have fusions. This study separates tumors into three categories: 1) high incidence of NTRK gene fusions 2) high incidence of TRK expression and low incidence of NTRK gene fusions and 3) low incidence of TRK expression and low incidence of NTRK gene fusions. Tumors with a high incidence of specific NTRK gene fusions include infantile fibrosarcoma, secretory carcinomas of the breast and salivary gland, and cellular and mixed congenital mesoblastic nephroma. These tumors should be routinely analyzed for NTRK gene fusions either by NGS, break-apart FISH, dual-gene FISH, or immunohistochemistry. If tumors are negative in FISH assays, they should be subjected to additional testing, ideally DNA and RNA NGS. Tumor types with a high incidence of TRK expression, (positive pan-TRK immunohistochemistry) and a low incidence of NTRK gene fusions include neuroendocrine tumors, some soft tissue sarcomas, and gastrointestinal stromal tumors. As these tumors will likely have rearrangements other than NTRK driving aberrant tyrosine kinase expression, the authors propose immediate broad-based DNA and RNA NGS analysis. Tumors with a low likelihood of finding NTRK fusions and low incidence of TRK expression by IHC include the most common malignancies including NSCLC, breast cancer, glioma, melanoma, and colorectal cancer. For these tumors, when NGS is already routinely performed per NCCN guidelines, the authors suggest widening the NGS assay to include DNA or RNA interrogation of NTRK fusions. For those where molecular analysis is not routine yet, IHC could help narrow down the specimens that will proceed to NGS analysis. However, IHC is not currently advocated as a screening tool.

Sclerosing Tumors of the Gastrointestinal Tract: A Systematic Approach.
Chelliah A, Kalimuthu SN, Chetty R.
Int J Surg Pathol. 2019 Aug;27(5):468-476.
https://www.ncbi.nlm.nih.gov/pubmed/30955389

Sclerosis can be seen in a variety of settings within the gastrointestinal tract (GIT), ranging from inflammatory/ reactive processes, to benign and malignant neoplasms, and may mask the actual true nature of the lesion. This review highlights several entities occurring in the GIT in which sclerosis is a predominant histological feature. The lesions are categorized according to the anatomical layer of the GIT that is involved primarily, and the histological, immunohistochemical, and molecular features are presented.

Journals Reviewed July-August 2019

Advances in Anatomic Pathology
American Journal of Clinical Pathology
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American Journal of Pathology
American Journal of Surgical Pathology
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