GIPS Journal Watch
March & April 2020

The diagnosis of clinically significant oesophageal Candida infections: a reappraisal of clinicopathological findings.

Hissong E, Schechter S, Mowers J, Yantiss RK, Slavik T, Cheng J, Lamps LW.
Histopathology. 2020 Apr;76(5):748-754.
https://www.ncbi.nlm.nih.gov/pubmed/31944368

Esophageal *Candida* infection is a common cause of esophagitis in immunosuppressed patients and typically presents with odynophagia. While often white plaques and exudates are commonly encountered at upper endoscopy, this is not a specific finding and definitive diagnosis relies on pathologic confirmation. Distinguishing true esophageal infection from oropharyngeal contamination may be clinically important. Historically, the presence of pseudohyphae, fungal invasion, and intraepithelial neutrophils have been presumed to represent clinically significant infection, but this has not been well-studied. In this work, the authors investigate a cohort of 271 biopsy samples in which *Candida* was detected. They report that most patients experienced upper gastrointestinal symptoms, with 36% exhibiting dysphagia. Likewise, the majority (73%) of patients had abnormal findings at upper endoscopy. Histological findings included desquamated epithelial cells and pseudohyphae in the vast majority of cases. Invasive yeasts were only seen in 37% of patients and did not correlate with the presence of clinical symptoms or with the endoscopic findings. More importantly, there was no relationship between the histologic identification of epithelial invasion by fungi and a clinical response to treatment with antifungal agents. Based on these data, the authors conclude that the detection of *Candida* in esophageal biopsies should always be considered to be potentially clinically significant and that the presence of neutrophilic inflammation and tissue invasion are not required to establish a diagnosis of fungal infection.

Correlation of endoscopic signs and mucosal alterations in children with eosinophilic esophagitis

Girish Hiremath, Hernan Correa, Sari Acra, Evan S. Dellon.
Gastrointest Endosc 2020;91:785-94.
https://www.ncbi.nlm.nih.gov/pubmed/31785273

This is a retrospective study investigating the endoscopic score (including edema, rings, exudates, furrows, and strictures), histological score (including eosinophilic inflammation, basal zone hyperplasia, eosinophilic abscess, eosinophilic surface layering, dilated intercellular space, surface epithelial alteration, dyskeratotic epithelial cells, and lamina propria fibrosis), and peak eosinophilic count (PEC) in pediatric patients with eosinophilic esophagitis (EoE). They found that the relationship between the total endoscopic score and histological score was moderate

with Rho (r) of 0.61, although this was slightly stronger than the relationship between the endoscopic score and PEC (r=0.55). Histological score had significantly higher area under the curve to predict active EoE than endoscopic score. However, a combination of endoscopic and histological findings to include furrows, eosinophilic inflammation, basal zone hyperplasia, eosinophilic abscess, and dilated intercellular space had the highest under the curve area of 0.97 with an accuracy of 98%, sensitivity of 97%, and specificity of 98% to predict active EoE in pediatric patients. The data emphasized the need to measure multiple endpoints including the clinical symptoms, endoscopic findings, and histological features to fully assess the course of EoE.

Isolated tumor cells in the regional lymph nodes in patients with squamous cell carcinoma of the esophagus are rarely observed but often represent part of a true metastasis

Jepsen DNM, Fiehn AMK, Svendsen B, Achiam MP, Federspiel B
Ann Diagn Pathol. 2020 Apr;45:151478.
https://www.ncbi.nlm.nih.gov/pubmed/32135481

Isolated tumor cells (ITCs) are rare and not well characterized in esophageal carcinomas; this finding is defined as single tumor cells or tumor cell clusters not exceeding 0.2 mm in extent using the 8th edition of the UICC TNM classification, and is not addressed specifically in the 8th edition of the AJCC cancer staging manual. The aim of this study was to determine the prevalence of ITCs in esophageal squamous cell carcinoma (SCC) and investigate how often these ITCs comprised part of a larger metastatic deposit on deeper sections. This series evaluated 100 esophagogastrectomies (neoadjuvant and non-neoadjuvant) containing 2460 lymph nodes performed between March 2014 to March 2019. 10 lymph nodes (9% of patients, 0.4% of total evaluated lymph nodes) contained ITCs; these blocks had 6 deeper levels with 2 sections per level (H&E and AE1/AE3 + 5D3) and 0.2 mm between levels cut. 5 lymph nodes from 4 patients was upstaged from ITCs to a true metastasis, and resulted in a higher pN stage in 2 patients. These findings suggest that, if staging using the UICC 8th edition system, additional sections may be warranted before classification of a tumor as pN0(i+).

HER2 expression and relevant clinicopathological features in esophageal squamous cell carcinoma in a Chinese population
Rong L, Wang B, Guo L, Liu X, Wang B, Ying J, Xue L, Lu N.
Diagn Pathol. 2020 Mar 24;15(1):27.
https://www.ncbi.nlm.nih.gov/pubmed/32209107

This multicenter study from China evaluated 857 consecutive esophageal squamous cell carcinoma (ESCC) patients who underwent a radical esophagectomy without neoadjuvant therapy (from years 2014-2015). A total of 1.5% were found to be 3+ positive for HER2 IHC with 100% concordance with DISH (using the established criteria for evaluation of breast carcinomas). Equivical HER2 (2+) was identified in 6.1% of cases by IHC with 18.2% of these

select cases demonstrating HER2 gene amplification by DISH. The authors found no significant correlations between HER2 status (IHC or gene amplification) and age, tumor differentiation, pT stage, pN stage, pM stage and pTNM stage ($P > 0.05$). The authors conclude by suggesting that these findings may have future implications in the treatment of ESCC.

Real-time use of artificial intelligence in the evaluation of cancer in Barrett's oesophagus.

Ebigbo A, Mendel R, Probst A, Manzeneder J, Prinz F, de Souza LA Jr, Papa J, Palm C, Messmann H.
Gut. 2020 Apr;69(4):615-616.
https://www.ncbi.nlm.nih.gov/pubmed/31541004

This article is on a real-time deep learning artificial intelligence (AI) system to evaluate cancer in Barrett's esophagus. While an expert endoscopist conducts the endoscopic assessment of BE, the AI system captures random images from the real-time camera livestream and provides a global prediction (classification), as well as a dense prediction (segmentation) differentiating accurately between normal BE and early oesophageal adenocarcinoma (EAC). The AI system showed an accuracy of 89.9% on 14 cases with neoplastic BE.

Topography, morphology, and etiology of lymphocytic gastritis: a single institution experience.

Yip RHL, Lee LH, Lee LH, Schaeffer DF, Horst BA, Yang HM.
Virchows Arch. 2020 Apr;476(4):551-559.
https://www.ncbi.nlm.nih.gov/pubmed/31897816

This article summarizes the findings of 27 cases of lymphocytic gastritis collected at Vancouver general hospital between August 2011 and September 2017. Gluten-sensitive enteropathy (GSE) was the main reported cause of LG followed by NSAID injury. Cases of LG associated with gluten-sensitive enteropathy were antral predominant, those associated with *H. pylori* were body predominant, and those occurring in the setting of NSAID injury show pangastritis. Glandular microabscesses were observed in all cases of LG associated with *H. pylori*, and not in the setting of GSE or NSAID injury. In addition, a case of LG associated with melanoma immunotherapy was reported. The authors concluded that topography and morphology of lymphocytic gastritis may point to the cause of injury, allowing for proper treatment of the underlying disease.

Sarcina Organisms in the Upper Gastrointestinal Tract: A Report of 3 Cases With Varying Presentations.

Propst R, Denham L, Deisch JK, Kalra T, Zaheer S, Silva K, Magaki S.

Int J Surg Pathol. 2020 Apr;28(2):206-209.
https://www.ncbi.nlm.nih.gov/pubmed/31496372

Sarcina species are anaerobic gram-positive cocci rarely seen in the upper gastrointestinal tract and associated with delayed gastric emptying. This is a report of 3 cases of *Sarcina* infection with varying clinical presentations including the first reported case of *Sarcina* in a patient with eosinophilic esophagitis. Although the pathogenesis of *Sarcina* is unclear, awareness of the bacteria is important as they can usually only be detected on histopathologic examination of upper gastrointestinal biopsies. The authors suggest that treatment in symptomatic patients may prevent severe complications such as emphysematous gastritis and gastric perforation.

Dissecting Expression Profiles of Gastric Precancerous Lesions and Early Gastric Cancer to Explore Crucial Molecules in Intestinal-Type Gastric Cancer Tumorigenesis.

Zhang Y, Wu X, Zhang C, Wang J, Fei G, Di X, Lu X, Feng L, Cheng S, Yang A.
J Pathol. 2020 Mar 24 [published online ahead of print].
https://www.ncbi.nlm.nih.gov/pubmed/32207854

The authors sought to investigate the RNA expression changes participating in intestinal type gastric cancer (IGC) tumorigenesis and identify related prognostic information by comparing precancerous lesions to early gastric cancer (EGC) and normal controls. RNA expression profiles of 94 gastroscopic biopsies from 47 patients, including gastric precancerous lesions (GPL: low-grade intraepithelial neoplasia [LGIN] and high-grade intraepithelial neoplasia [HGIN]), EGC and paired controls, were detected by Agilent Microarray. During IGC tumorigenesis from LGIN through HGIN to EGC, the number of activity-changed tumor hallmarks increased. LGIN and HGIN had similar expression profiles when compared to EGC. There was an increase in the stemness of gastric epithelial cells in LGIN, HGIN and EGC, and 27 consistent genes that might contribute to dedifferentiation, including 5 driver genes. Remarkably, the immune microenvironment was more active in EGC than in GPL, especially in the infiltration of lymphocytes and macrophages. A 5-gene signature from the gastric tumorigenesis process could independently predict the overall survival and disease-free survival of GC patients (log rank test: $p < 0.0001$), and the robustness was verified in an independent cohort ($n > 300$) and by comparing with two established prognostic signatures in GC. The authors concluded that cancer-like changes occur in LGIN and accumulate in HGIN and EGC. The immune microenvironment is more active in EGC than in LGIN and HGIN. The identified signature from the tumorigenesis process has robust prognostic significance for GC patients.

Morphological spectrum of immune check-point inhibitor therapy-associated gastritis.

Johncilla M, Grover S, Zhang X, Jain D, Srivastava A.
Histopathology. 2020 Mar;76(4):531-539.
https://www.ncbi.nlm.nih.gov/pubmed/31692018

The majority of patients treated with immune check-point inhibitors experience immune-related adverse events that most frequently involve the skin and gastrointestinal tract, among other organs. The histologic features of lower gastrointestinal tract injury in patients treated with various immune check-point inhibitors is well-characterized but, to this point, there has been only limited investigation of patterns of injury to the upper gastrointestinal tract. In this study, the authors identify 12 patients treated with immune check-point inhibitors who underwent endoscopy with gastric biopsies for evaluation of upper gastrointestinal symptoms. While the majority of patients in their cohort had metastatic malignant melanoma (7), single patients with hepatocellular carcinoma, breast carcinoma, colorectal adenocarcinoma, renal cell carcinoma, Hodgkin lymphoma, and sclerosing epithelioid fibrosarcoma were also included. Patient's received various combinations of the immune check-point inhibitors ipilimumab, nivolumab, and pembrolizumab. Evaluation of gastric biopsies revealed that 8 of the 12 cases exhibited a diffuse chronic active gastritis pattern of injury with full-thickness mucosal involvement. Intraepithelial lymphocytosis involving the surface foveolar and deep glandular epithelium with prominent apoptosis was seen in 7 of the cases with a chronic active gastritis pattern of injury. The remaining cases showed a focally enhancing gastritis pattern of injury reminiscent of Crohn disease with cuffs of lymphohistiocytic aggregates around actively inflamed gastric glands. Ten patients were treated with corticosteroids in addition to medication withdrawal which resulted in symptom resolution in the majority of cases, though two were eventually treated with infliximab for refractory symptoms. The authors claim that immune check-point inhibitor associated gastritis frequently manifests as a diffuse chronic active gastritis pattern of injury with increased intraepithelial lymphocytes and frequent apoptosis in the proper clinical context. A subset of patients show a focally enhancing gastritis pattern of injury, including a single patient homozygous for an *ATG16L1* polymorphism strongly associated with Crohn disease. They raise the possibility that patients with IBD-associated genetic polymorphisms may be more likely to develop immune related adverse events of the gastrointestinal tract in the setting of check-point inhibition.

Demographic and Lifestyle Risk Factors for Gastric Intestinal Metaplasia Among US Veterans.

Tan MC, Mallepally N, Liu Y, El-Serag HB, Thrift AP.
Am J Gastroenterol. 2020 Mar;115(3):381-387
https://www.ncbi.nlm.nih.gov/pubmed/31899705

This cross sectional study aimed to identify the demographic and lifestyle factors independently associated with the risk of noncardiac gastric intestinal metaplasia (IM). Patients attending primary care and endoscopy clinics at a VA hospital in Houston completed questionnaires and underwent endoscopy with gastric mapping biopsies. The authors identified 423 cases with IM and 1,796 controls without IM. Older age (>60 years), male sex, nonwhite race/ethnicity, and current smoking status were the nonendoscopic factors independently associated with IM. These risk factors remained statistically significant after adjusting for *H. pylori* infection and

their effect sizes were larger for associations with extensive gastric IM (antrum and corpus involvement) compared with focal IM.

Next-generation sequencing identifies 2 genomically distinct groups among pyloric gland adenomas.

Setia N, Wanjari P, Yassan L, Niu N, Kadri S, Ritterhouse L, Misdraji J, Brown I, Segal J, Hart J. Hum Pathol. 2020 Mar;97:103-111.
https://www.ncbi.nlm.nih.gov/pubmed/31783043

In this retrospective study, next generation sequencing using the UCM-OncoPlus panel was performed on pyloric gland adenomas (PGA) in order to identify any previously undescribed molecular alterations in these lesions and to correlate molecular-histologic findings. Overall, 14 PGAs and 1 adenocarcinoma arising from a PGA with high-grade dysplasia were sequenced as cases, and 4 samples of autoimmune gastritis were sequenced as controls. In the PGA group, one patient was known to have attenuated familial adenomatous polyposis, and one had autoimmune gastritis. Ten PGAs were considered to have low-grade dysplasia, and the remaining 5 had high-grade dysplasia and/or carcinoma. All 10 low-grade PGAs had at least one concurrent mutation present in each of the *APC, KRAS,* and *GNAS* genes. Other mutations were infrequent in this group. In contrast, the 4 high-grade PGAs and PGA with adenocarcinoma had variable mutations including *KRAS* (n=2), *GNAS* (n=1), *APC* (n=1), *CTNNB1* (n=1), *TP53* (n=1), *CDKN2A* (n=1), *PIK3CA* (n=1), *EPHA5*(n=1). Chromosomal gains and losses were also more common in this group. No significant pathogenic mutations were present in the 4 autoimmune gastritis controls. The authors suggest that PGAs with high grade dysplasia and/or carcinoma may represent a distinct group of dysplastic lesions or a distinct pathway of dysplasia development because they lack the *APC/KRAS/GNAS* mutational triad characteristic of the low-grade adenomas.

Thirty years of Epstein-Barr virus-associated gastric carcinoma.

Fukayama M, Abe H, Kunita A, Shinozaki-Ushiku A, Matsusaka K, Ushiku T, Kaneda A. Virchows Arch. 2020 Mar;476(3):353-365.
https://www.ncbi.nlm.nih.gov/pubmed/31836926

This review article presents a portrait of EBV-associated gastric carcinoma (accounting for 10% of gastric carcinoma worldwide) from initiation to maturity defined as the 'gastritis-infection-cancer sequence', followed by its molecular abnormalities and interactions with immune checkpoint molecules and the microenvironment. EBV non-coding RNAs (microRNA and circular RNA) and exosomes derived from EBV-infected cells that were previously behind the scenes are now recognized for their roles in EBV-associated gastric carcinoma. The virus utilizes cellular machinery skillfully to control infected cells and their microenvironment.

Preservation of Epstein-Barr virus status and mismatch repair protein status along the metastatic course of gastric cancer.

Dislich B, Blaser N, Berger MD, Gloor B, Langer R.
Histopathology. 2020 Apr;76(5):740-747.
https://www.ncbi.nlm.nih.gov/pubmed/31898331

Four distinct molecular gastric cancer types were proposed by the Cancer Genome Atlas project and include Epstein-Barr virus (EBV)-positive cancers and those exhibiting microsatellite instability (MSI), among other subgroups. The identification of EBV-positive and mismatch repair deficient (MMR) subtypes may be important in clinical practice as these tumors are potentially targeted with immune check-point inhibitors. In this study, the authors investigate whether changes in the EBV and MMR status of gastric cancers occur during metastasis to lymph nodes and other sites. This retrospective study included a cohort of 415 treatment-naïve resected gastric carcinomas. Distant metastatic material was present for evaluation in 111 cases, while 297 cases had lymph node metastasis in the primary resection material. The authors created tissue microarrays and performed immunohistochemical staining for MLH1, PMS2, MSH2, and MSH6, and chromogenic *in situ* hybridization studies for the Epstein-Barr virus (EBER) on all cases. Of the 415 cases in their cohort, 2.7% of the gastric cancers were EBER+ and MMR proficient, and 11.8% were EBER- and MMR deficient. All MMR deficient cases showed a loss of MLH1 and PMS2. All examined distant and lymph node metastases showed complete concordance with the primary tumors with regard to MMR protein status and EBER reactivity, though not every metastatic case was examined. The authors claim that these results suggest that molecular subtyping can be reliably performed on either primary or metastatic gastric carcinomas.

Meta-analysis of genome-wide association studies and functional assays decipher susceptibility genes for gastric cancer in Chinese populations.

Yan C, Zhu M, Ding Y, Yang M, Wang M, Li G, Ren C, Huang T, Yang W, He B, Wang M, Yu F, Wang J, Zhang R, Wang T, Ni J, Chen J, Jiang Y, Dai J, Zhang E, Ma H, Wang Y, Xu D, Wang S, Chen Y, Xu Z, Zhou J, Ji G, Wang Z, Zhang Z, Hu Z, Wei Q, Shen H, Jin G.
Gut. 2020 Apr; 69(4):641-651.
https://www.ncbi.nlm.nih.gov/pubmed/31383772

This article aimed to identify new susceptibility genes and elucidate their mechanisms in gastric cancer (GC) development. This is a meta-analysis of four genome-wide association studies (GWASs) encompassing 3771 cases and 5426 controls. After targeted sequencing and functional annotation, they performed in vitro and in vivo experiments to confirm the functions of genetic variants and candidate genes. They identified three loci at 1q22, 5p13.1 and 10q23.33 associated with GC risk at $p<5\times10-8$ and replicated seven known loci at $p<0.05$. At 5p13.1, the risk rs59133000[C] allele enhanced the binding affinity of NF-κB1 (nuclear factor kappa B

subunit 1) to the promoter of *PRKAA1*, resulting in a reduced promoter activity and lower expression. The knockout of *PRKAA1* promoted both GC cell proliferation and xenograft tumour growth in nude mice. At 10q23.33, the rs3781266[C] and rs3740365[T] risk alleles in complete linkage disequilibrium disrupted and created, respectively, the binding motifs of POU2F1 and PAX3, resulting in an increased enhancer activity and expression of *NOC3L*, while the *NOC3L* knockdown suppressed GC cell growth. Overall, they identified 12 loci to be associated with GC risk in Chinese populations and deciphered the mechanisms of *PRKAA1* at 5p13.1 and *NOC3L* at 10q23.33 in gastric tumourigenesis.

A deep learning convolutional neural network can recognize common patterns of injury in gastric pathology

Martin DR, Hanson JA, Gullapalli RR, Schultz FA, Sethi A, Clark DP
Arch Pathol Lab Med. Mar 2020; 144:370-378
https://www.ncbi.nlm.nih.gov/pubmed/31246112

The application of deep learning, characterized by the ability to perform unsupervised learning from either labeled or unlabeled data sets, is new to non-neoplastic pathology despite its success in neoplastic pathology across various organ systems. This study evaluated the ability of deep learning to distinguish between 3 common patterns of injury in gastric biopsy specimens: *Helicobacter* gastritis, reactive gastropathy, and normal mucosa. The authors assessed 200 cases each of *Helicobacter* gastritis (obtained from 2018), reactive gastropathy, and normal gastric mucosa (each obtained 2016-2018), and conducted the study in 2 phases. In phase 1, biopsies with classical histology of *Helicobacter* gastritis, reactive gastropathy, and normal gastric mucosa were scanned at 40 X magnification, imported into a computer, and annotated by 2 GI pathologists. 1-3 representative, full tissue fragments were selected per case, excluding any fragments with prominent intestinal metaplasia. Each of the 3 patterns (*Helicobacter* gastritis, reactive gastropathy, and normal mucosa) were assigned separate labels. In phase 1, 210 of 300 cases were randomly selected for the training set (70 each of *Helicobacter* gastritis, reactive gastropathy, and normal biopsies), and the remainder were saved for the testing set. In the first phase, the algorithm correctly assigned the correct digital diagnosis to a majority of tissue fragments. The sensitivity, specificity, and accuracy values were 96.7%, 86.7%, and 90.0% for normal, 100%, 98.3%, 98.9% for *Helicobacter* gastritis, and 96.7%, 96.7%, and 96.7% for reactive gastropathy. The positive predictive value and negative predictive value for *Helicobacter* gastritis were both 100%. In phase 2, the algorithm was evaluated on its ability to classify non-classical examples of *Helicobacter* gastritis, reactive gastropathy, and normal gastric mucosa. To do this, the authors selected an additional 130 cases from different patients, representing the last 130 consecutive gastric biopsies (excluding gastric polyps, malignancies, autoimmune gastritis, cases with extensive intestinal metaplasia, and histologically suspected *Helicobacter* gastritis cases with negative immunohistochemistry); a final set of 106 cases were scanned and annotated for phase 2. In this new set, the sensitivity, specificity, and accuracy were 73.7%, 79.6%, and 76.4% for normal gastric mucosa, 100%, 62.5%, and 71.7% for reactive gastropathy, and 95.7%, 100%, and 99.1% for *Helicobacter* gastritis. A subset of cases previously

diagnosed as ‘mild chronic inactive gastritis’ was most often categorized as ‘normal’, followed by ‘reactive gastropathy’ according to this algorithm, suggesting that mildly inflamed cases are unlikely to be diagnosed as *Helicobacter* gastritis according to the algorithm.
This study was significant for the application of deep learning to inflammatory gastrointestinal pathology as a proof of concept. In addition, the authors suggested a potential use as a screening tool to select cases for up-front *Helicobacter* immunohistochemistry.

Incidence of Celiac Disease Is Increasing Over Time: A Systematic Review and Meta-analysis.

King JA, Jeong J, Underwood FE, Quan J, Panaccione N, Windsor JW, Coward S, deBruyn J, Ronksley PE, Shaheen AA, Quan H, Godley J, Veldhuyzen van Zanten S, Lebwohl B, Ng SC, Ludvigsson JF, Kaplan GG.
Am J Gastroenterol. 2020 Apr;115(4):507-525.
https://www.ncbi.nlm.nih.gov/pubmed/32022718

The authors conducted a systematic review and meta-analysis to define the worldwide incidence of celiac disease (CD) and examine temporal trends. Populations based studies reporting the incidence of CD in adults and children were included. Studies solely examining at risk populations (ie. patients with type 1 diabetes) were excluded. The authors identified 50 suitable studies for analysis (of 11,189 citations). They note that the incidence of CD has been widely studied in Europe, North America and Oceania, however, population based studies on the incidence of CD are lacking from Africa, Asia, and Latin America. Based on the 50 studies they identified, the authors report that in the 21st century, the pooled female incidence of CD was 17.4 per 100,000 person-years compared with 7.8 in males. Child specific incidence was 21.3 per 100,000 person years compared with 12.9 in adults. In addition the incidence of CD was found to be increasing by 7.5% per year over the past several decades. The authors conclude that the incidence of CD is highest in females and children and that the overall incidence has been significantly rising throughout the Western world.

Management of Small Bowel Villous Atrophy in Patients Seronegative for Celiac Disease.

Jansson-Knodell CL, Murray JA, Rubio-Tapia A.
Am J Gastroenterol. 2020 Apr;115(4):492-497.
https://www.ncbi.nlm.nih.gov/pubmed/32141915

In this short report, the authors provide a practical approach to the workup and management of seronegative villous atrophy (villous atrophy without positive celiac serology): (1) Check for celiac disease considering clinical, serologic, and histologic features. (2) Scrutinize the biopsy. Villi may appear atrophic due to artifact; a pitfall leading to overdiagnosis and unnecessary treatment. A pathologist with gastrointestinal expertise should rereview the biopsies in light of the suspicion of nonceliac causes of atrophy to seek clues to an alternative diagnosis and

consider the use of special stains. The endoscopist should ask about features such as intraepithelial lymphocytosis, goblet cells (decreased in autoimmune enteropathy), plasma cells (sometimes absent in common variable immunodeficiency), foamy macrophages (Whipple disease), and collagen (collagenous sprue). If careful analysis does not reveal a diagnosis, reassess the patient's symptoms and history. (3) Reassess the patient's recent medication (NSAIDs, immunosuppressants, and angiotensin II receptor blockers are culprits for drug-associated enteropathy). In particular, omesartan has been associated with severe sprue-like enteropathy. Check for recent travel to countries at risk of tropical sprue, environmental enteropathy, or infections. Infections noted by the authors include giardiasis, tuberculosis, tropical sprue, HIV, viral gastroenteritis, and Whipple disease. (4) Test for a mimicker via lab testing (folate, vitamin B12, immunoglobulins, HIV, antienterocyte antibody), stool testing (giardia antigen, stool ova and parasite), biopsy staining (PAS, Congo red, CD3, CD4, and CD8), and molecular diagnostics (T cell receptor clonal rearrangement). A thoughtful approach with selected testing is recommended, as opposed to ordering all studies. (5) Management of uncertainty. The authors state that when there is no definitive diagnosis, seronegative CD remains a significant consideration. Symptoms improve within weeks of starting a gluten free diet in patients with seronegative CD, although the response alone should not be considered definitive. Patients with severe symptoms often respond to steroids. Spontaneous resolution is possible. The authors conclude by noting that there are many histologic mimickers of CD and that the pathologist is an expert resource whose help may expedite correct diagnoses and prompt treatment.

Malignant Gastrointestinal Neuroectodermal Tumor: Clinicopathologic, Immunohistochemical, and Molecular Analysis of 19 Cases.

Chang B, Yu L, Guo WW, Sheng WQ, Wang L, Lao I, Huang D, Bai QM, Wang J.
Am J Surg Pathol. 2020; 44:456-466.
https://www.ncbi.nlm.nih.gov/pubmed/31651526

The authors studied the clinical, pathologic, immunophenotypic, and molecular features of malignant gastrointestinal neuroectodermal tumor (GNET) in their cohort of 19 patients along with clinical treatment and response, particularly to targeted therapy. The mean tumor size was 4.2 cm (range 3-8 cm), and the sites of tumor origin were small intestine (57.9%), followed by the stomach (15.8%), colon (10.5%), ileocecal junction (5.3%), lower esophagus (5.3%), and anal canal (5.3%). Histologically, the tumors were composed of epithelioid cells with eosinophilic or clear cytoplasm arranged in variable patterns (nests/solid/ papillary/ trabecular/ microcystic/ pseudoalveolar) and/or spindle tumor cells with eosinophilic cytoplasm arranged in a fascicular pattern. Immunohistochemically, the tumors showed positivity for S100 (100%), SOX10 (93.3%), vimentin (100%), synaptophysin (41.2%), CD56 (30.8%), CD99 (20%), and CD117 (6.7%). The tumor cells were negative for HMB45, Melan A, DOG1, CD34, AE1/AE3, CAM5.2, chromogranin A, smooth muscle actin, and desmin. 93.3% (14 of 15 cases) showed split Ewing sarcoma breakpoint region 1 gene (*EWSR1*) signals consistent with a chromosomal translocation involving *EWSR1*. One case showed <10% tumor cells positive for *EWSR1* split signals, and was

evaluated as negative. During follow-up (15 patients; mean 29.7 months, range 3-63 months), 13.3% (2/15) died of GNET, 33.3% (5/15) patients were alive with tumor; of these, 4 had liver metastasis and 2 had lymph node metastasis and/ or local recurrence (one patient had both liver and nodal metastases), and 53.3% (8/15) had no evidence of disease. Two and 1 patient(s) showed partial response to apatinib and anlotinib, respectively. The authors conclude that GNET has distinctive morphologic, immunohistochemical, and molecular genetic features and should be distinguished from other gastrointestinal (GI) tract malignancies with epithelioid and/or spindled morphology such as carcinoma, melanoma, GISTs amongst others. GNET should be suspected in cases of a GI tract tumor depicting epithelioid cells arranged in various patterns and/or sheets of spindle cell tumor cells. Positive S100 and SOX10 expression along with molecular detection of involvement of *EWSR1* chromosomal rearrangement is recommended to confirm the diagnosis of GNET. Apatinib and anlotinib might be effective for the treatment of advanced GNET and could prolong patient survival.

Acellular mucin in pseudomyxoma peritonei of appendiceal origin: what is adequate sampling for histopathology?

Al-Azzawi M, Misdraji J, van Velthuysen MF, Shia J, Taggart MW, Yantiss RK, Svrcek M, Carr N.
J Clin Pathol. 2020 Apr;73(4):220-222.
https://www.ncbi.nlm.nih.gov/pubmed/31611287

This is a prospective study concerning the yield of additional sampling in cases of extraappendiceal mucin found in association with mucinous appendiceal neoplasia. A total of 12 cases were identified where initial sampling of extraappendiceal mucin yielded no evidence of associated neoplastic cells. In these cases, additional mucin was submitted for histologic evaluation including the mucin in its entirety or up to 30 blocks. Of the 12 cases, 2 revealed evidence of extraappendiceal mucinous epithelium on further sampling. The authors conclude by recommending that additional sampling of cases in which only acellular mucin is appreciated on initial sections should be strongly considered.

Appendix Cyst.

Handra-Luca A, Ben Romdhane MH.
Int J Surg Pathol. 2020 Apr;28(2):176-177.
https://www.ncbi.nlm.nih.gov/pubmed/31232137

This is a case report of an apparent mesoappendix squamoid cyst.

SATB2 protein expression by immunohistochemistry is a sensitive and specific marker of appendiceal and rectosigmoid well differentiated neuroendocrine tumours.

Hoskoppal D, Epstein JI, Gown AM, Arnold Egloff SA, Gordetsky JB, Shi CJ, Giannico GA.
Histopathology. 2020 Mar;76(4):550-559.
https://www.ncbi.nlm.nih.gov/pubmed/31595536

Neuroendocrine neoplasms (both well and poorly differentiated) arise in a variety of organ systems with clinical courses ranging from indolent to extremely aggressive. The metastatic involvement of the liver and lymph nodes may dominate the clinical picture before the primary lesion is detected. As treatment protocols vary based upon the site of origin, the identification of the primary site may have important ramifications for patient management. In this study, the authors evaluate the expression of the special AT-rich sequence-binding protein 2 (SATB2) in neuroendocrine neoplasms arising in various primary sites. Immunohistochemical staining for SATB2 was performed on their cohort of 266 neuroendocrine neoplasms arising in the lung, genitourinary tract, pancreas, and luminal gastrointestinal tract. In most instances, whole slides were utilized for immunohistochemistry, but tissue microarrays were employed for the investigation of 13 bladder, 31 prostatic, and 15 lung small cell carcinomas, as well as for 35 small bowel well-differentiated neuroendocrine tumors (WDNET). Nuclear reactivity for SATB2 in greater than 10% of the tissue was defined as positive and staining intensity was scored from 0-3+. For the lung, a single carcinoid tumor (3%) showed weak (1+) staining intensity for SATB2, while 8 of the 39 (21%) small cell carcinomas were positive for the marker with an intensity ranging from weak to strong. In the genitourinary tract, 32% of prostatic and 38% of bladder small cell carcinomas stained with SATB2, again with varying intensity. A total of 124 WDNETs arising in the luminal gastrointestinal tract and pancreas were investigated. All appendiceal (22) and rectosigmoid (15) WDNETs were immunoreactive for SATB2, while none of the tumors arising in the stomach, duodenum/ampulla, small bowel, or pancreas stained with the marker. Conversely, SATB2 expression was detected in only 4 of the 21 (19%) poorly differentiated neuroendocrine carcinomas of the gastrointestinal tract and pancreas. Collectively, these data show that SATB2 is a sensitive and specific marker for rectal (100%; 83.6%) and appendiceal (100%; 88%) WDNETs. Although expressed to some degree in neuroendocrine neoplasms arising outside of the gastrointestinal tract (notably small cell carcinomas of the genitourinary system and lung), the authors claim these results show that SATB2 is a highly sensitive and specific marker for WDNETs of the appendix and rectum, supporting its application in clinical practice for the classification of WDNETs of unknown origin.

Can Microscopic Ileitis in Patients with Clinically Suspected Inflammatory Bowel Disease Predict the Future?

Baker FA, Z'cruz De La Garza JA, Nafrin S, Mari A, Suki M, Ovadia B, Gal O, Kopelamn Y.
BMC Gastroenterol, 2020 Mar 5; 20 (1): 52.
https://www.ncbi.nlm.nih.gov/pubmed/32138683

This study aims to determine the prognostic yield of biopsy findings of microscopic ileitis in patients with normal endoscopy findings but clinically suspected IBD, and to evaluate the

correlation of microscopic ileitis with long-term clinical outcome. A total of 439 patients were included. Sixty-four (14.6%) showed inflammation on biopsy and were included in the microscopic ileitis group. Age range and gender figures did not differ significantly between the microscopic ileitis group and normal group. Overall follow-up period was 6.1 ± 2.3 years. Patients in the microscopic ileitis group were significantly associated with Crohn's diagnosis during the follow-up period compared with the normal group (19% vs 2%, OR = 11.98, 95%CI = 4.48-32.01; $p < 0.01$). Patients with granuloma or moderate-severe ileitis on biopsy were significantly associated with Crohn's development (100% vs 11%; $P < 0.01$) compared with mild or nonspecific inflammation. The authors conclude that the discovery of microscopic ileitis in clinically suspected IBD patients is associated with increased risk of future diagnosis of Crohn's disease.

Prominence of ileal mucosa-associated microbiota to predict postoperative endoscopic recurrence in Crohn's disease.

Sokol H, Brot L, Stefanescu C, Auzolle C, Barnich N, Buisson A, Fumery M, Pariente B, Le Bourhis L, Treton X, Nancey S, Allez M, Seksik P; REMIND Study Group Investigators.
Gut. 2020 Mar;69(3):462-472.
https://www.ncbi.nlm.nih.gov/pubmed/31142586

This study investigated the role of the ileal mucosa-associated microbiota in postoperative endoscopic recurrence of Crohn’s disease (CD). Ileal mucosa-associated microbiota was analyzed by 16S sequencing at the time of surgery and/or of endoscopic evaluation in 201 patients prospectively recruited in France. Ileal mucosa-associated microbiota exhibits profound changes following surgery in CD. Compared with non-recurrence setting, endoscopic recurrence is associated with strong changes in ileal mucosa-associated microbiota that are highly reminiscent of those observed generally in ileal CD compared with healthy subjects with a reduction in alpha diversity, an increase in several members of the Proteobacteria phylum and a decrease in several members of the Lachnospiraceae and the Ruminococcaceae families within the Firmicutes phylum. At the time of surgery, they identified several bacterial taxa associated with endoscopic recurrence that can better predict relapse than usual clinical risk factors. They conclude that gut microbiota has the potential to predict postoperative evolution and recurrence of CD.

Modulation of cytokine patterns and microbiome during pregnancy in IBD.

van der Giessen J, Binyamin D, Belogolovski A, Frishman S, Tenenbaum-Gavish K, Hadar E, Louzoun Y, Peppelenbosch MP, van der Woude CJ, Koren O, Fuhler GM.
Gut. 2020 Mar;69(3):473-486.
https://www.ncbi.nlm.nih.gov/pubmed/31167813

This study investigates the effects of pregnancy on IBD using fecal and serum samples (46 IBD patients and 179 healthy controls during first, second and third trimester of pregnancy, and prepregnancy and postpartum). Proinflammatory serum cytokine levels in patients with IBD decrease significantly on conception. Reduced interleukin (IL)-10 and IL-5 levels but increased IL-8 and interferon (IFN)γ levels compared with healthy controls were seen throughout pregnancy. Microbial diversity in pregnant patients with IBD was reduced compared with that in healthy women, and significant differences existed between patients with UC and CD in early pregnancy. However, these microbial differences were no longer present during middle and late pregnancy. Serum proinflammatory cytokine levels markedly improve on conception in pregnant patients with IBD, and intestinal microbiome diversity of patients with IBD normalizes during middle and late pregnancy. Thus they conclude that pregnancy is safe and even potentially beneficial for patients with IBD.

Interleukin-22 orchestrates a pathological endoplasmic reticulum stress response transcriptional programme in colonic epithelial cells.

Powell N, Pantazi E, Pavlidis P, Tsakmaki A, Li K, Yang F, Parker A, Pin C, Cozzetto D, Minns D, Stolarczyk E, Saveljeva S, Mohamed R, Lavender P, Afzali B, Digby-Bell J, Tjir-Li T, Kaser A, Friedman J, MacDonald TT, Bewick GA, Lord GM.
Gut. 2020 Mar;69(3):578-590.
https://www.ncbi.nlm.nih.gov/pubmed/31792136

This study challenges perceptions of IL22 as a predominantly beneficial cytokine in IBD and provide novel insights into the molecular mechanisms of IL22-mediated pathogenicity in chronic colitis and as therapeutic strategies in patients with colitis. They employed a three-dimensional mini-gut epithelial organoid system, in vivo disease models and transcriptomic datasets in human IBD to investigate the functional role of IL22. In the colon of patients with active colonic Crohn's disease (CD), there was enrichment of IL22-responsive transcriptional modules and ER stress response modules. Strikingly, in an IL22-dependent model of chronic colitis, targeting IL22 alleviated colonic epithelial ER stress and attenuated colitis. Pharmacological modulation of the ER stress response similarly impacted the severity of colitis. In patients with colonic CD, antibody blockade of IL12p40, which simultaneously blocks IL12 and IL23, the key upstream regulator of IL22 production, alleviated the colonic epithelial ER stress response.

Histopathologic Patterns of Colitis in Patients With Impaired Renal Function.

Qiu L, Volk E, Mais DD.
Am J Clin Pathol. 2020; 153:380-386.
https://www.ncbi.nlm.nih.gov/pubmed/31679016

The authors characterized the histopathologic features in patients with impaired renal function who underwent colonoscopic evaluation of colitis between 2011 and 2015. A total of 413 patients (185 males, 228 female), with 75.5% (312 patients) having normal renal function and 24.5% (101 patients) showing impaired renal function of varying severity (mild, moderate, and severe impairment groups) were included in the study. The most common patterns seen in patients with impaired renal function were ischemic colitis (58%, 59/101), followed by infectious colitis/ acute self-limited colitis (20.8%; 21/101) and then medication -induced injury (10.9%, 11/101), with crystal-associated injury being the exclusive pattern found in this study. *Clostridium difficile* and cytomegalovirus infections were more frequent etiologies amongst the infectious colitis group. Notably, features of idiopathic inflammatory bowel disease were only observed in the normal renal function group ($P < .001$), accounting for 33% (103 cases) of the patients examined, in whom this was the most frequent diagnosis. Similarly, lymphocytic colitis was identified in 9.6% in patients with normal renal function. The authors conclude that colitis in patients with impaired renal function is etiologically distinct from that seen in patients with normal renal function, and is most commonly caused by ischemia, certain forms of infections, and medications.

Assessment of Tumor-infiltrating Lymphocytes Using International TILs Working Group (ITWG) System Is a Strong Predictor of Overall Survival in Colorectal Carcinoma: A Study of 1034 Patients.

Fuchs TL, Sioson L, Sheen A, Jafari-Nejad K, Renaud CJ, Andrici J, Ahadi M, Chou A, Gill AJ. Am J Surg Pathol. 2020; 44:536-544.
https://www.ncbi.nlm.nih.gov/pubmed/31743129

The presence of increased tumor-infiltrating lymphocytes (TILs), a marker of immune activation by a tumor, is considered as a positive predicting factor across a range of malignancies, including colorectal carcinoma (CRC). No studies have evaluated the prognostic value of TILs in CRCs using the standardized International TILs Working Group (ITWG) scoring method. The authors used the ITWG system to assess the density of stromal TILs in an unselected cohort of 1034 CRC patients undergoing primary tumor resection. Per ITWG methodology, the density of TILs was assessed within the stromal compartment of the tumor mass, and scored as a percentage of stromal area, rounded to the nearest 5%. Scores were based on the average across the whole slide (not hotspots). Only TILs within the border of invasive tumors were assessed. All mononuclear cells (eg, lymphocytes and plasma cells) were included as TILs, whereas other inflammatory cells (ie, neutrophils/granulocytes) were excluded. Areas of necrosis, including the central “dirty necrosis” characteristic of CRC, were excluded from the assessment, and only stromal TILs were assessed, so that TILs within nests of epithelial cells were excluded. The percentage TILs score was categorized into 3 groups: low (0% to 10%), intermediate (15% to 50%), and high (55% to 100%). Overall survival ($P = 0.0001$) was best in the high-TIL group (mean survival: 75 months), followed by the intermediate-TIL group (mean survival: 67 months), and then the low-TIL group (mean survival: 53 months). This survival benefit remained statistically significant in subgroup analyses for mismatch repair (MMR)

proficient cases (P = 0.0001), MMR deficient cases (P = 0.031), *BRAF* V600E wild-type cases (P = 0.0001), and *BRAF* V600E-mutant cases (P = 0.001). TILs were significantly correlated with overall survival within the group of combined stages II and III tumors (P < 0.0001). The predictive value of TILs assessed using the ITWG system was superior to the assessment of intraepithelial lymphocytes performed prospectively using a standard system requiring ≥5 lymphocytes per high-powered field in direct contact with tumor cells or between tumor clusters. The authors conclude that the ITWG system for assessing TILs shows good interobserver concordance after minimal training, has superior prognostic value when compared with other methods of scoring tumor-associated lymphocytic inflammation in clinical practice, and predicts all-cause survival independent of mismatch status, tumor stage, and a range of other patient and tumor factors.

Tumour budding/T cell infiltrates in colorectal cancer: proposal of a novel combined score.

Dawson H, Christe L, Eichmann M, Reinhard S, Zlobec I, Blank A, Lugli A.
Histopathology. 2020 Mar;76(4):572-580.
https://www.ncbi.nlm.nih.gov/pubmed/31560788

The assessment of tumor budding and of the T cell host response have emerged as complementary modalities to traditional TNM staging in the risk stratification of colorectal carcinomas. While previous studies have investigated tumor budding and immune cell infiltrates in isolation, the authors of this retrospective study attempt to assess tumor budding in conjunction with the T cell infiltrate, creating a unifying budding/T cell score that is a better predictor of aggressive tumor biology and correlates with patient outcomes. To achieve this, they assembled a cohort of 345 primary colorectal carcinoma patients and collected demographic and survival data. Histologic features, including histologic subtype, TNM staging, tumor grade, lymphovascular and perineural invasion, budding, and MMR status were also assessed, and tissue microarrays constructed with cores taken from the tumor center, invasive front, and areas at the tumor/host interface containing tumor buds and non-tumoral cells. Double immunohistochemical staining for the pankeratin cocktail AE1/AE3 was performed along with CD8, CD3, or CD45RO on the TMA, and tumor budding and T cell infiltrates were quantified on scanned slides using Scorenado and QuPath, respectively. The budding/T cell score (BTS) was then calculated by dividing the number of tumor buds by the number of lymphocytes. Similar to previous studies, T cell counts in the tumor center were associated with lower pT and pN stages, as well as the absence of lymphovascular invasion, higher KM-score, and lower tumor budding counts. Similarly, tumor budding in all tumor areas was positively associated with an underlying aggressive biology. BTS scores from the tumor center were calculated for both CD3+ and CD8+ T cells and both were associated with a higher pT, pN, and pM stage, as well as the presence of lymphovascular and perineural invasion. In their analysis, center CD8+ BTS scores performed better than all other parameters at predicting nodal metastasis. Likewise, in multivariate analysis, only a higher center CD3+ BTS was significantly associated with a poorer overall survival. The authors believe that combining tumor budding with T cell counts into the BTS reflects and integrates the aggressive (budding) and protective

(immune response) forces in colorectal carcinoma, and claim that BTS may be a stronger predictor of survival and nodal metastasis than either metric in isolation. They envision that BTS may serve a complementary role to traditional TNM staging, the assessment of tumor budding, and imunoscore in early stage colorectal cancers and in preoperative rectal biopsies.

Artificial intelligence-guided tissue analysis combined with immune infiltrate assessment predicts stage III colon cancer outcomes in PETACC08 study.

Reichling C, Taieb J, Derangere V, Klopfenstein Q, Le Malicot K, Gornet JM, Becheur H, Fein F, Cojocarasu O, Kaminsky MC, Lagasse JP, Luet D, Nguyen S, Etienne PL, Gasmi M, Vanoli A, Perrier H, Puig PL, Emile JF, Lepage C, Ghiringhelli F.
Gut. 2020 Apr;69(4):681-690.
https://www.ncbi.nlm.nih.gov/pubmed/31780575

In this study, the authors developed a software to detect colon tumor, healthy mucosa, stroma and immune cells on CD3 and CD8 stained slides. The lymphocyte density and surface area were quantified automatically in the tumor core (TC) and invasive margin (IM). Using a LASSO algorithm, DGMate (DiGital tuMor pArameTErs), they detected digital parameters within the tumour cells related to patient outcomes. Within the dataset of 1018 patients, they observed that a poorer relapse-free survival (RFS) was associated with high IM stromal area (HR 5.65; 95% CI 2.34 to 13.67; p<0.0001) and high DGMate (HR 2.72; 95% CI 1.92 to 3.85; p<0.001). Higher CD3+ TC, CD3+ IM and CD8+ TC densities were significantly associated with a longer RFS. Analysis of variance showed that CD3+ TC yielded a similar prognostic value to the classical CD3/CD8 Immunoscore (p=0.44). A combination of the IM stromal area, DGMate and CD3, designated 'DGMuneS', outperformed Immunoscore when used in estimating patients' prognosis (C-index=0.601 vs 0.578, p=0.04) and was independently associated with patient outcomes following Cox multivariate analysis. A predictive nomogram based on DGMuneS and clinical variables identified a group of patients with less than 10% relapse risk and another group with a 50% relapse risk. Thy conclude that artificial intelligence can potentially improve patient care by assisting pathologists in better defining stage III colon cancer patients' prognosis.

High-dimensional cytometric analysis of colorectal cancer reveals novel mediators of antitumour immunity.

de Vries NL, van Unen V, Ijsselsteijn ME, Abdelaal T, van der Breggen R, Farina Sarasqueta A, Mahfouz A, Peeters KCMJ, Höllt T, Lelieveldt BPF, Koning F, de Miranda NFCC.
Gut. 2020 Apr;69(4):691-703.
https://www.ncbi.nlm.nih.gov/pubmed/31270164

In this study, they characterized the immune profiles in patients with colorectal cancer (CRC). Thirty-six immune cell markers were simultaneously assessed at the single-cell level by mass

cytometry in 35 CRC tissues, 26 tumor-associated lymph nodes, 17 colorectal healthy mucosa and 19 peripheral blood samples from 31 patients with CRC. Additionally, functional, transcriptional and spatial analyses of tumor-infiltrating lymphocytes were performed by flow cytometry, single-cell RNA-sequencing and multispectral immunofluorescence. They discovered that a previously unappreciated innate lymphocyte population ($Lin^{-}CD7^{+}CD127^{-}CD56^{+}CD45RO^{+}$) was enriched in CRC tissues and displayed cytotoxic activity. This subset demonstrated a tissue-resident ($CD103^{+}CD69^{+}$) phenotype and was most abundant in immunogenic mismatch repair (MMR)-deficient CRCs. Their presence in tumours was correlated with the infiltration of tumour-resident cytotoxic, helper and γδ T cells with highly similar activated ($HLA\text{-}DR^{+}CD38^{+}PD\text{-}1^{+}$) phenotypes. Remarkably, activated γδ T cells were almost exclusively found in MMR-deficient cancers.

Neutrophils Expressing Lysyl Oxidase-Like 4 Protein Are Present in Colorectal Cancer Liver Metastases Resistant to Anti-Angiogenic Therapy.

Palmieri V, Lazaris A, Mayer TZ, Petrillo SK, Alamri H, Rada M, Jarrouj G, Park WY, Gao ZH, McDonald PP, Metrakos P.
J Pathol, 2020 Apr 16. [Epub ahead of print].
https://www.ncbi.nlm.nih.gov/pubmed/32297656

This study used RNA sequencing to identify differentially expressed genes between colorectal cancer liver metastases (CRCLM) with a replacement histopathological growth pattern (HGP) and those with a desmoplastic HGP. The authors stated that the replacement HGP is more resistant to neoadjuvant therapy and preoperative identification of these patients is important. The authors demonstrate that lysyl oxidase-like 4 (LOXL4) is transcriptionally upregulated in replacement HGP CRCLM compared to desmoplastic HGP CRCLM and the adjacent normal liver. Interestingly, LOXL4 protein was expressed by neutrophils present in the tumor microenvironment in replacement HGP CRCLM. LOXL4 expression is higher in circulating neutrophils of cancer patients compared to healthy control patients and its expression can be induced by stimulation with lipopolysaccharide and tumor necrosis factor alpha. This study shows for the first time the expression of LOXL4 in neutrophils and reveals the potential for LOXL4-expressing neutrophils to support the replacement HGP phenotype and to serve as a surrogate biomarker for this subtype of CRCLM.

Loss of microfibril-associated protein 5 (MFAP5) expression in colon cancer stroma.

Zhao L, Westerhoff M, Hornick JL, Krausz T, Antic T, Xiao SY, Hart J.
Virchows Arch. 2020 Mar;476(3):383-390.
https://www.ncbi.nlm.nih.gov/pubmed/31422503

The aim of this study was to confirm the reduced expression of MFAP5 in colonic tumor stroma using immunohistochemistry and to explore the utility of MFAP5 as a marker to facilitate

diagnosing an invasive component versus pseudoinvasion in colon polyps. In all 19 colon cancer resection cases evaluated, while there was intact MFAP5 immunoreactivity in the uninvolved normal connective tissue, there was marked reduction of MFAP5 immunoreactivity in the desmoplastic stroma surrounding the invasive component. The difference in MFAP5 expression levels was most pronounced within the tumor, while a more heterogeneous expression pattern was observed at the tumor invasive front. Reduction of MFAP5 staining was also observed in the stroma around mucin pools in 6 out of 9 sections from mucinous adenocarcinomas and in areas with high-grade dysplasia. For the polypectomy cases, intact expression of MFAP5 was seen in the stroma surrounding the displaced adenomatous glands in 9 out of 12 polyps with pseudoinvasion. Loss of expression of MFAP5 was observed in the stroma surrounding small foci of invasive adenocarcinoma in 8 of 10 malignant polyps. They conclude MFAP5 is a useful marker to distinguish normal connective tissue from stroma within invasive colonic adenocarcinoma and can facilitate the distinction between pseudoinvasion and true invasive cancer in polyps with a sensitivity of 80% and a specificity of 75%.

Cancer gland rupture as a potential risk factor for lymph node metastasis in early colorectal adenocarcinoma with deep submucosal invasion.

Oishi K, Ito T, Sakonishi D, Uchida K, Sekine M, Negi M, Kobayashi D, Miura K, Akashi T, Eishi Y. Histopathology. 2020 Mar;76(4):603-612.
https://www.ncbi.nlm.nih.gov/pubmed/31643099

An increasing proportion of patients with early stage colorectal adenocarcinomas (T1-CRAC) are initially treated endoscopically, with salvage surgical resection and lymph node dissection reserved for patients with histologic risk factors for nodal metastasis. The guidelines put forth by the Japanese Society for Cancer of the Colon and Rectum suggest that high-risk groups include endoscopically resected poorly differentiated adenocarcinomas, as well as mucinous and signet ring cell histologic types, and tumors with submucosal invasion of greater than 1mm. Despite these guidelines, the majority of patients undergoing salvage surgery for T1-CRACs do not have lymph node metastasis and better risk assessment models are needed. In this study, the authors evaluate cancer gland rupture (CGR), defined as C-shaped cancer glands with a discontinuous epithelial lining at the invasive front, as a risk factor for lymph node metastasis in T1-CRACs. This retrospective study group consisted of 217 patients with well and moderately differentiated, early stage adenocarcinomas who either underwent oncologic surgical resection without preceding therapeutic endoscopic resection, and 49 patients undergoing salvage surgery. Cases were reviewed for traditional high-risk histologic features in addition to CGR, which was identified in 77% of the study cases with good interobserver concordance (K-value 0.61-0.80). All twenty of the cases with lymph node metastasis in their cohort were positive for CGR. Conversely, 49 of the 197 cases negative for lymph node metastasis were negative for CGR. While high-grade tumor budding, lymphovascular invasion, and depth of submucosal invasion greater than 1 mm were all significantly associated with lymph node metastasis, the odds ratio for nodal metastasis was highest for CGR (13.7). Lymph node metastasis was not detected in any of the 40 cases without deep submucosal invasion, regardless of the presence

of CGR or other risk factors. Likewise, lymph node metastasis was not detected in any of the 29 cases with deep submucosal invasion but no CGR. Of the 148 remaining cases exhibiting both deep submucosal invasion and CGR, 14% exhibited lymph node metastasis, which constituted every case of metastasis in this cohort. Based upon these results, the authors devised a risk classification system where cases without deep invasion, and cases with deep invasion but no CGR were classified as low-risk, cases with deep invasion, CGR, and the presence of lymphovascular invasion or high-grade tumor budding were classified as high-risk, and those with deep invasion and CGR but no lymphovascular invasion or budding as moderate risk. The authors claim that utilizing CGR as a component of the risk stratification algorithm may help to identify lower risk patients with deeply invasive T1-CRACs that are less likely to benefit from salvage surgery.

The Impact of Extramural Venous Invasion in Colorectal Cancer: A Detailed Analysis Based on Tumor Location and Evaluation Methods.

Shin YM, Pyo JS, Park MJ.
Int J Surg Pathol. 2020 Apr;28(2):120-127.
https://www.ncbi.nlm.nih.gov/pubmed/31544653

This study aimed to elucidate the prognostic implications of extramural venous invasion (EMVI) in colorectal cancer (CRC) through a meta-analysis. Eighteen eligible studies were included in this meta-analysis. Data on the prevalence of EMVI and the correlation between EMVI and survival were collected from these studies. In addition, a subgroup analysis was conducted based on tumor location and evaluation methods. The estimated prevalence of EMVI was 28.3% (95% confidence interval [CI] = 23.1% to 34.0%) in patients with CRC. The estimated prevalence of EMVI in patients with colon cancer and rectal cancer was 23.0% (95% CI = 17.6% to 29.6%) and 35.7% (95% CI = 22.3% to 51.6%), respectively. Based on the evaluation method, the estimated prevalence of EMVI were 28.3% (95% CI = 23.2% to 34.1%) and 27.3% (95% CI = 8.4% to 60.6%) in pathologic and radiologic examinations, respectively. The correlation of EMVI with worse overall and disease-free survival rates was significant (hazard ratio = 1.773, 95% CI = 1.483-2.120, and hazard ratio = 2.059, 95% CI = 1.683-2.520, respectively). However, in the subgroup analysis with radiologic examination, there was no significant difference in survival rates between patients with and without EMVI. This study showed that EMVI was frequently detected in 28.3% of patients with CRC and was correlated to worse survival. The detection of EMVI can be useful for predicting the prognosis of patients with CRC.

Significance of Radial Margin in Patients Undergoing Complete Mesocolic Excision for Colon Cancer.

Lee JM, Chung T, Kim KM, Simon NSM, Han YD, Cho MS, Hur H, Lee KY, Kim NK, Lee SB, Kim GR, Min BS.
Dis Colon Rectum. 2020 Apr;63(4):488-496.

https://www.ncbi.nlm.nih.gov/pubmed/31977585

This retrospective study evaluated the prognostic impact of a positive radial margin in 834 patients who underwent complete mesocolic excision for colon adenocarcinoma. Radial margin was defined as the adventitial soft tissue margin from the cut edge of the mesentery or retroperitoneal surface to the deepest tumor infiltration. Patients with radial margin <1 mm (21% of patients) showed reduced overall survival and disease-free survival. This study supports the importance of evaluating the distance of closest tumor to radial margin.

A Proposal for Novel Standards of Histopathology Reporting for D3 Lymphadenectomy in Right Colon Cancer: The Mesocolic Sail and Superior Right Colic Vein Landmarks.

Garcia-Granero A, Pellino G, Giner F, Frasson M, Grifo Albalat I, Sánchez-Guillén L, Valverde-Navarro AA, Garcia-Granero E
Dis Colon Rectum. 2020 Apr;63(4):450-460.
https://www.ncbi.nlm.nih.gov/pubmed/31996584

In this study, surgeons and pathologists collaborated to standardize the examination and reporting for D3 lymphadenectomies in oncologic right hemicolectomy specimens. Similar to the concept of evaluating the completeness of the mesorectal excision in rectal carcinoma, complete D3 lymphadenectomy involves removal of the lympho-adipose tissue along the superior mesenteric vein and head of the pancreas. The authors used two reproducible anatomic structures (the mesocolic sail and superior right colic vein) to define complete D3 excision. They showed that D3 removal increased the total number of lymph nodes procured and suggested that this removal enhanced the rate of complete removal of lymph nodes that may harbor tumor cells.

Pure Discrete Punctate Nuclear Staining Pattern for MLH1 Protein Does Not Represent Intact Nuclear Expression.

Zhang Q, Young GQ, Yang Z.
Int J Surg Pathol. 2020 Apr;28(2):146-152.
https://www.ncbi.nlm.nih.gov/pubmed/31566049

This study was designed to investigate whether “a discrete punctate nuclear staining pattern of staining” represents intact nuclear expression of MLH1. The study was done on 161 colorectal adenocarcinoma cases. Pure discrete punctate nuclear staining pattern for MLH1 was observed in 11 tumors and completely negative staining was seen in 13 tumors. Those 24 tumors invariably showed loss of PMS2. Three patients whose biopsies showed pure punctate staining for MLH1 underwent repeat testing on resections: 1 retained the punctate staining and 2 showed complete loss of MLH1. Nine with loss of PMS2 and pure punctate MLH1 staining underwent molecular testing: 4 had *BRAF* V600E mutations and 1 had a *MLH1* gene mutation.

Pure discrete punctate staining pattern is paired with loss of PMS2 expression and may be associated with *BRAF* or *MLH1* gene mutation, thus it should not be interpreted as intact nuclear expression.

Should you repeat mismatch repair testing in cases of tumour recurrence? An evaluation of repeat mismatch repair testing by the use of immunohistochemistry in recurrent tumours of the gastrointestinal and gynaecological tracts.

Aird JJ, Steel MJ, Chow C, Ho J, Wolber R, Gilks CB, Hoang LN, Schaeffer DF. Histopathology. 2020 Mar;76(4):521-530.
https://www.ncbi.nlm.nih.gov/pubmed/31677289

Universal screening for mismatch repair deficiency (dMMR) is recommended for all patients with colorectal and endometrial cancer. Recently, mismatch repair testing has evolved into a predictive biomarker, as the FDA has approved the use of immune checkpoint inhibitors for solid tumors with dMMR, irrespective of site. While repeat molecular testing for some biomarkers is currently recommended for recurrent or metastatic tumors, it is unclear if additional MMR testing on metastatic tissue adds value when the initial tumor was mismatch repair proficient. In this study, the authors investigate how frequently mismatch repair testing by immunohistochemistry shows discordant results between the primary tumor and tumor recurrence/metastasis. They evaluated 137 patients with MMR-proficient and 13 patients with dMMR tumors of the gastrointestinal and gynecological tracts that had either local recurrence or distant metastasis at least 30 days after the resection of the primary tumor. Tissue microarrays were constructed and immunohistochemical stains for MLH1, PMS2, MSH2, and MSH6 performed and interpreted without knowledge of the original tumor's MMR status. All 13 patients with primary tumors that were dMMR showed concordant dMMR in the recurrent/metastatic material tested. Conversely, 3 of the 137 primary tumors that were initially categorized as MMR-proficient showed loss of staining for at least one of the mismatch repair proteins in the recurrence (two cases showed loss of MLH1 and PMS2, and one case showed loss of MSH6). Review of the original material showed subclonal loss of MLH1 in two endometrial carcinomas that was not identified initially and confirmed to be the result of promoter hypermethylation. In the other discordant case, the patient's original rectal adenocarcinoma was confirmed to be proficient for the mismatch repair proteins. However, a chart review revealed that the tested metastatic site had been previously irradiated and the MSH6 loss was interpreted as aberrant loss of staining secondary to radiotherapy. The authors of this study, therefore, report no true instances of discordance between the MMR status of primary gastrointestinal and gynecological carcinomas and tumor recurrences. They claim that repeat MMR testing on tumor recurrences may not be warranted.

Clinical performance of the Idylla MSI test for a rapid assessment of the DNA microsatellite status in human colorectal cancer

Zwaenepoel K, Duelund JH, Winne KD, Maes V, Weyn C, Lambin S, Dendooven R, Broeckx G, Steiniche T, Pauwels P
J Mol Diagn. Mar 2020; 22(3): 386-395
https://pubmed.ncbi.nlm.nih.gov/31881332

Assessment for microsatellite instability (MSI) and mismatch repair (MMR) protein deficiency in colorectal cancers is important, both to screen for Lynch syndrome, and for its therapeutic and prognostic implications. In a subset of cases, immunohistochemical findings are either equivocal or difficult to interpret. The purpose of this paper was to demonstrate the sensitivity, specificity, and overall agreement of a rapid MSI test (Idylla), with immunohistochemical findings and another MSI analysis system (Promega). The study group consisted of 330 colorectal cancer patients referred for mismatch repair protein immunohistochemistry between 2009 and 2018. 10 consecutive FFPE sections were cut, the first and last slides were H&E stained, and the area enriched for tumor was manually designated. In comparison to Promega, the Idylla MSI test shows 99.7% concordance, 98.7% sensitivity, and 100% specificity; in addition, the Idylla MSI test shows 98.7% concordance, 94.4% sensitivity, and 100% specificity in comparison to mismatch repair protein immunohistochemistry. In cases of discordance between immunohistochemistry and the Idylla MSI test, tumor mutational burden analysis agreed with the Idylla MSI test in the majority of instances. The authors note that a limitation of this study is that patient-specific controls were not evaluated for the Promega assay, possibly resulting in spurious classification of some markers as unstable. The authors note that the advantages of the Idylla test include rapid turnaround time (the assay takes <2.5 hours, allowing for a turnaround time of <1 day), no requirement for sample batching, and a limited number of manual steps, decreasing the possibility of human error. Importantly, the Idylla test has no requirement for non-neoplastic patient tissue in comparison to the Promega assay.

Assessment of two different HER2 scoring systems and clinical relevance for colorectal cancer.
Virchows Arch. 2020 Mar;476(3):391-398.
Liu F, Ren C, Jin Y, Xi S, He C, Wang F, Wang Z, Xu RH, Wang F.
https://www.ncbi.nlm.nih.gov/pubmed/31720832

The study evaluates HER2 status and its correlation with clinicopathological characteristics and survival according to the HER2 diagnostic criteria for gastroesophageal adenocarcinoma (GEA criteria) and the HERACLES diagnostic criteria (HERACLES criteria) in a large cohort of Chinese colorectal carcinoma patients. The HER2 positivity was 2.9% (43/1490) and 2.6% (39/1490) in CRCs based on the GEA criteria and the HERACLES criteria, and 3.7% (9/243) in mCRC according to both criteria. HER2 status was associated with primary tumor location (P = 0.037), regional lymph node metastasis (P = 0.035), and TNM stage (P = 0.022) in CRCs based on the HERACLES criteria. No such association was found based on the GEA criteria. Furthermore, HER2 positivity only presented in patients with *RAS* gene wild type (P = 0.001). Significant difference was only observed between the HER2-positive and HER2-negative groups in terms of disease-free

survival for stage II-III CRCs (P = 0.048) according to the HERACLES criteria, but not based on the GEA criteria. These findings suggest that the frequency of HER2 overexpression or amplification was low in Chinese CRC patients, and provide a rationale for further evaluation of HER2 in CRC based on the HERACLES criteria and the HER2 diagnostic criteria for gastroesophageal adenocarcinoma.

Assessing the diagnostic yield of targeted next-generation sequencing for melanoma and gastrointestinal tumors

Garg S, Grenier S, Misyura M, Sukhai MA, Thomas M, Kamel-Reid S, Stockley T
J Mol Diagn. Apr 2020; 22(4): 467-475
https://pubmed.ncbi.nlm.nih.gov/32036084

Multigene, next generation sequencing (NGS) panels are increasingly being used to evaluate various tumor types for the rationale of obtaining more diagnostic information using a single test. The purpose of this study was to evaluate whether NGS-based assays increase diagnostic yield in melanomas, colorectal carcinomas, and gastrointestinal stromal tumors (GISTs). The authors evaluated 1041 total samples obtained between January 2015 and October 2016, including 687 melanomas, 73 GISTs, and 281 colorectal carcinomas, using a 26-gene NGS panel. A subset of variants were verified using orthogonal means. Variants were classified on a 5-tier system; tiers 1 to 3 were classified as being clinically informative. In melanomas, 64% of the detected variants were clinically informative; the NGS panel improved *BRAF* variant detection by 24%, and enhanced diagnostic yield by 20% (i.e. variants that would not have been identified using non-NGS assays). In colorectal carcinomas, 42% of variants were clinically informative; NGS improved diagnostic yield in colorectal carcinomas by 36% compared to single gene assays. However, there was no added benefit of NGS panels to molecular testing for GISTs.
The authors suggest that the utility of NGS depends on the tumor type and the variants to be identified.

Multiclonal colorectal cancers with divergent histomorphological features and *RAS* mutations: one cancer or separate cancers?

Lin MT, Zheng G, Tseng LH, Zhang P, Ling H, Azad N, Gocke CD, Montgomery E, Eshleman JR.
Hum Pathol. 2020 Apr;98:120-128.
https://www.ncbi.nlm.nih.gov/pubmed/32171651

In colorectal carcinoma (CRC) tumorigenesis, it has been thought that *NRAS, KRAS,* and *BRAF* mutations are mutually exclusive, although some larger cohort studies have previously reported co-existing *NRAS* and *KRAS* mutations in <1% of CRC. The authors report three cases of colorectal adenocarcinoma with multiple *RAS* mutations and interrogate various regions of these tumors in an attempt to elucidate a mechanism for simultaneous but different *RAS* mutations during tumor progression. Subareas of different areas of the invasive

adenocarcinoma and any adjacent non-invasive adenomatous lesion were microdissected, and next generation sequencing was performed using the AmpliSeq Cancer Hotspot Panel. From the original colorectal carcinoma blocks, the authors found that one case contained different *KRAS* mutations between the adenoma and adenocarcinoma, one case had a *KRAS* mutation in one region of the adenocarcinoma but an *NRAS* mutation in another invasive region, and the third case had an *NRAS* mutation in the adenocarcinoma but co-existing *NRAS* and *KRAS* mutations within the adenoma. *APC* mutations were preserved across these subareas, indicating a common clonal *APC*-mutated founder lineage in each case. All cases were microsatellite stable. The authors present these cases as evidence for parallel evolution of distinct subpopulations of colorectal adenocarcinoma, rather than the usual stepwise model of mutagenesis. They suggest that the presence of disparate *RAS* mutations within a single colorectal carcinoma could have therapeutic implications as targeted therapies become the norm but single regions of tumor are generally selected for molecular testing.

Overexpression of TP53 protein is associated with the lack of adjuvant chemotherapy benefit in patients with stage III colorectal cancer.

Williams DS, Mouradov D, Browne C, Palmieri M, Elliott MJ, Nightingale R, Fang CG, Li R, Mariadason JM, Faragher I, Jones IT, Churilov L, Tebbutt NC, Gibbs P, Sieber OM.
Mod Pathol. 2020 Mar;33(3):483-495.
https://www.ncbi.nlm.nih.gov/pubmed/31471586

The authors in this study sought to examine the predictive utility of TP53 overexpression in patients with stage III colorectal adenocarcinoma. The authors note that TP53 alterations have been associated with poor prognosis and resistance to chemotherapy, but that the data remains controversial. The association between TP53 and 5-year-disease-free-survival was tested in a prospective cohort of 264 patients with resected stage III tumors, grouped by adjuvant treatment. They validated their findings in an independent retrospective cohort of 274 stage III patients. The authors found overexpression of TP53 by immunohistochemical stain in 53% of the cases from the prospective cohort and 52% of the cases from the retrospective cohort. In patients receiving adjuvant therapy, TP53+ status was associated with shorter disease free survival. This finding was not seen in patients treated with surgery alone. The authors use these data to suggest that adjuvant chemotherapy benefit in stage III colorectal cancer may be restricted to cases with low level TP53 expression and that patients with TP53+ tumors may need more aggressive treatment or follow-up.

Non-coding RNAs in GI cancers: from cancer hallmarks to clinical utility.

Dragomir MP, Kopetz S, Ajani JA, Calin GA.
Gut. 2020 Apr;69(4):748-763.
https://www.ncbi.nlm.nih.gov/pubmed/32034004

This review is on the biology and translational value of three of the most studied categories on non-coding RNAs, the microRNAs, the long non-coding RNAs and the circular RNAs. They also focus on some aspirational concepts that can help in the development of clinical applications related to non-coding RNAs, including using pyknons to discover new non-coding RNAs, targeting human-specific transcripts which are expressed specifically in the tumour cell and using non-coding RNAs to increase the efficiency of immunotherapy.

The inhibitory receptor CD94/NKG2A on CD8+ tumor-infiltrating lymphocytes in colorectal cancer: a promising new druggable immune checkpoint in the context of HLAE/β2m overexpression.

Eugène J, Jouand N, Ducoin K, Dansette D, Oger R, Deleine C, Leveque E, Meurette G, Podevin J, Matysiak T, Bennouna J, Bezieau S, Volteau C, Thomas WEA, Chetritt J, Kerdraon O, Fourquier P, Thibaudeau E, Dumont F, Mosnier JF, Toquet C, Jarry A, Gervois N, Bossard C. Mod Pathol. 2020 Mar;33(3):468-482.
https://www.ncbi.nlm.nih.gov/pubmed/31409873

The authors begin by referencing their prior study which demonstrated that HLA-E/β2m overexpression in colorectal cancer occurs in 20% of cases and is associated with unfavorable prognosis. The current study, in a retrospective cohort of 234 colorectal cancer patients, seeks to assess (i) the expression profile of HLA-E/β2m on tumor cells and the density of CD94+ tumor infiltrating lymphocytes (TILs) in relation to clinicopathological and molecular features; (ii) the nature (T and/or NK cells), phenotype (co-expression of inhibitory NKG2A or activating NKG2C), and biologic function of CD94+ TILs; and (iii) their prognostic influence. To answer these questions, they assessed the expression of HLA-E, β2m, CD94, CD8, and NKp46 by immunohistochemistry on tissue microarray. Expression of HLA-E/β2m and TIL density were correlated to clinicopathological and molecular features (microsatellite status, *BRAF*, and *RAS* mutations). The authors then used flow cytometry to characterize CD94+ TILs in a set of 27 prospective colorectal cancer cases. The authors report that HLA-E/β2m is preferentially overexpressed in microsatellite instable tumors compared to microsatellite stable ones (45% vs 19%, respectively), irrespective of *RAS* or *BRAF* mutational status. Interestingly, both microsatellite instable and stable HLA-E/β2m+ colorectal cancers were significantly enriched in CD94+ TILs (predominantly CD8+ αβ T cells). In addition, a high number of CD94+ TILs in close contact to tumor cells was independently associated with worse prognosis. The authors conclude that the HLA-E/β2m-CD94/NKG2A axis represents a new inhibitory immune checkpoint, which could be targeted with the recently generated anti-NKG2A monoclonal antibody, adding a new prospect to our arsenal of colorectal cancer immunotherapies.

Varying practices in tumor regression grading of gastrointestinal carcinomas after neoadjuvant therapy: results of an international survey.

Westerhoff M, Osecky M, Langer R.

Mod Pathol. 2020 Apr;33(4):676-689.
https://www.ncbi.nlm.nih.gov/pubmed/31673084

The authors report the results of a survey of gastrointestinal pathologists on the topic of tumor regression grading in neoadjuvantly treated gastrointestinal cancer specimens. The 23 question online survey was announced at the 107th annual meeting of the United States and Canadian Academy of Pathology (2018) and the 30th European Congress of Pathology (2018). It was also distributed online via communication through national and international communities of gastrointestinal pathologists. Topics addressed included grossing, histological work up, tumor regression grading systems, and degree of difficulty identifying and estimating residual cancer within treatment effect. A total of 203 responses were received, 173 of which were participants who completed the entire questionnaire. Half of the respondents were from Europe, 29% from North America, 10% from Australia, with the remaining 11% from other continents. Overall, the authors found that 95% report a tumor regression grade. A minority (27%) always embed the entire tumor bed while 54% embed the complete tumor site if not a grossly apparent large mass. A total of 59% use hematoxylin and eosin stain alone, while the remaining use additional stains. This study identified regional differences in the use of staging systems. In North America and Australia, the AJCC/CAP/Ryan system is routinely used for gastroesophageal (71%) and rectal carcinomas (77%). However, in Europe, for gastroesophageal tumors, 36% use the Mandard system, 22% use AJCC/CAP/Ryan, and 10% use Becker; for rectal tumors 30% use Dworak system, 24% use AJCC/CAP/Ryan, and 14% use Mandard. Overall, 51% of participants prefer a four-tiered system and 66% believe that tumor regression in lymph nodes should be included in regression grade. The authors conclude that this survey provides an overview of tumor regression in gastrointestinal cancers with respect to grossing, work up, and grading, with regional differences identified particularly between North America and Europe.

Endoscopic Removal of Colorectal Lesions: Recommendations by the US Multi-Society Task Force on Colorectal Cancer.
Kaltenbach T, Anderson JC, Burke CA, Dominitz JA, Gupta S, Lieberman D, Robertson DJ, Shaukat A, Syngal S, Rex DK.
Am J Gastroenterol. 2020 Mar;115(3):435-464.
https://www.ncbi.nlm.nih.gov/pubmed/32058340

Note – this article was also published in Gastroenterology as well as American Journal of Gastroenterology

This report summarizes the evidence and consensus based recommendations from the MSTF on best practices for endoscopic resection of precancerous colorectal lesions. Some important highlights for pathologists: (1) The MSTF recommends that endoscopists use the Paris classification to describe the macroscopic surface morphology of lesions (type 0 corresponds to superficial lesions, and types 1-5 with advanced cancers). Most type 0 lesions are polypoid, and although depressed (0-IIc) lesions are uncommon, their risk of submucosal invasion is highest (27-35.9% vs. 0.7-2.4% in flat 0-IIa lesions). More than 40% of small (6-10mm) depressed 0-IIc

lesions contain submucosal invasive cancer, and virtually all large (>20mm) depressed (0-IIc) lesions have submucosal invasion. (2) The subtle endoscopic appearance of large sessile serrated lesions has been associated with high rates of incomplete removal compared to conventional adenomas (31% vs. 7.2%) with even higher rates in large lesions (47.5%). Ineffective resection appears to be the cause of some interval cancers. Within a serrated lesion, endoscopic areas of distinct surface pattern change or nodular component are suggestive of cytologic dysplasia. (3) The authors recommend that non-pedunculated lesions with endoscopic features suggestive of submucosal invasive cancer are resected en bloc to be retrieved and pinned to a flat surface before submitting the specimen to pathology to facilitate sectioning (2mm intervals) perpendicular to the resection plan. (4) For non-pedunculated colorectal lesions resected en block with submucosal invasion, they recommend that pathologists measure and report the depth of invasion, distance of the cancer from the vertical and lateral resection margin, in addition to prognostic features (differentiation, lymphovascular invasion, tumor budding). (5) For pedunculated colorectal lesions resected en block with submucosal invasion, they recommend that pathologists report distance of the cancer from cautery line, degree of differentiation, lymphovascular invasion, and tumor budding.

Receptor Tyrosine Kinase Fusions Act as A Significant Alternative Driver of the Serrated Pathway in Colorectal Cancer Development.

Chan AW, Pan Y, Tong JH, Lung RWM, Kwan JSH, Chow C, Tin EKY, Chung LY, Li H, Wong SSY, Chau SL, Chan YY, Mak TWC, Ng SSM, To KF.
J Pathol, 2020 Mar 11 [published online ahead of print].
https://www.ncbi.nlm.nih.gov/pubmed/32162306

The authors combined multiple approaches to analyze the genetic alterations in 86 colorectal adenomas (including 35 sessile serrated lesions, 15 traditional serrated adenomas, and 36 conventional adenomatous polyps). The authors also investigated the in vitro and in vivo oncogenic properties of a novel variant of the *NCOA4-RET* fusion gene. Molecular profiling revealed that sessile serrated lesions and traditional serrated adenomas have distinct clinicopathological and molecular features. The receptor tyrosine kinase translocations were exclusively found in sessile serrated lesions (17%), and the observation was validated in a separate cohort of 34 sessile serrated lesions (15%). The kinase fusions as well as the *BRAF* and *KRAS* mutations were mutually exclusive to each other. Ectopic expression of a novel variant of the *NCOA4-RET* fusion gene promoted cell proliferation in vitro and in vivo, and the proliferation was significantly suppressed by RET kinase inhibitors. In addition, the authors found that the kinase fusion may occur early in the precursor lesion and subsequent loss of *TP53* may drive the transformation to carcinoma during serrated tumorigenesis. The authors concluded that kinase fusions are a significant alternative driver of the serrated pathway in colorectal cancer development, and detecting their presence may serve as a biomarker for the diagnosis of sessile serrated lesions.

A Streamlined Mass Spectrometry-Based Proteomics Workflow for Large Scale FFPE Tissue Analysis.

Coscia F, Doll S, Bech JM, Schweizer L, Mund A, Lengyel E, Lindebjerg J, Madsen GI, Moreira JMA, Mann M.
J Pathol, 2020 Mar 10 [Epub ahead of print].
https://www.ncbi.nlm.nih.gov/pubmed/32154592

The authors described a mass spectrometry (MS)-based proteomic workflow for quantitative profiling of large FFPE tissue cohorts directly from histopathology glass slides. The authors demonstrated broad applicability of the workflow to clinical pathology specimens and variable sample amounts, including low-input cancer tissue isolated by laser microdissection. Using state-of-the-art data dependent acquisition (DDA) and data independent (DIA) MS workflows, the authors consistently quantified a large part of the proteome in 100 min single-run analyses. In an adenoma cohort comprising more than 100 samples, total work up took less than a day. A moderate trend towards lower protein identifications was observed in long-term stored samples (>15 years) but clustering into distinct proteomic subtypes was independent of archival time. The results underline the great promise of FFPE tissues for patient phenotyping using unbiased proteomics and prove the feasibility of analyzing large tissue cohorts in a robust, timely and streamlined manner.

Traditional serrated adenoma-like lesions in patients with inflammatory bowel disease.

Miller GC, Liu C, Bettington ML, Leggett B, Whitehall VLJ, Rosty C.
Hum Pathol. 2020 Mar;97:19-28.
https://www.ncbi.nlm.nih.gov/pubmed/31917154

The authors of this retrospective study set out to understand the significance of traditional serrated adenomas (TSA) or TSA-like lesions in the setting of inflammatory bowel disease (IBD). They hypothesized that TSA-like lesions that required surgical removal (colectomy) were more likely to represent true IBD-associated dysplasia than those that were removed endoscopically. In total, 52 lesions from 30 patients were identified in nine years, representing 2.7% of all IBD patients who had a polyp or lesion during this time. The study patients were predominately men (67%) with underlying ulcerative colitis (87%) and an average age of 56 years. Twelve (40%) patients underwent surgical resection, while the remaining 18 (60%) had endoscopic removal of the TSA lesion. Twenty-three (77%) patients had follow-up available (median: 30 months). Overall, patients with TSA-like lesions that required surgical removal were present throughout the colon and were more likely to have plaque-like growth with ill-defined borders, cytologic (serrated) dysplasia, abnormal p53 expression by IHC, and *KRAS* mutations. In contrast, lesions removed endoscopically were predominately left-sided, discrete polyps, and cytologic (serrated) dysplasia was uncommon (8%). Abnormal p53 was present in only one case and *KRAS* and *BRAF* mutations were identified in equal proportions. Of interest, MLH1 and SATB2 expression by IHC were normal in all 52 lesions, regardless of size, location, or dysplasia.

During follow-up, four patients were diagnosed with advanced colorectal dysplastic lesions, two in the surgical group and two in the endoscopic resection group. All four patients had serrated dysplasia in their index TSA-like lesions. The authors conclude that TSA-like lesions with atypical endoscopic features (non-polypoid, ill-defined borders) or with histologic features of serrated dysplasia (cytologic atypia) likely represent a form of IBD-related dysplasia in contrast to the left-side predominate, sporadic TSA lesions without serrated dysplasia.

Perianal Paget's disease: a clinicopathological and immunohistochemical study of 13 cases

Liao X, Liu X, Fan X, Lai J, Zhang D.
Diagn Pathol. 2020 Mar 24;15(1):29.
https://www.ncbi.nlm.nih.gov/pubmed/32209119

This multi-center study reports the clinico- pathologic features of 13 perianal Paget disease (PPD) patients. Four cases were primary and nine (69%) were secondary. Secondary Paget's cells were more mucinous, frequently with eccentric nuclei and signet ring cell appearance, resembling the underlying carcinomatous cells. GCDFP-15 and CDX2 were helpful in distinguishing primary vs secondary Paget's in the examined cases, unlike CK7, CK20, CEA, MUC1, and MUC2. Recurrence, metastasis, and a single death due to disease were noted only in secondary Paget's. This study supports the indolent course of primary PPD, and highlights the importance CDX2 and GCDFP-15.

Primary gastrointestinal liposarcoma—a clinico-pathological study of 8 cases of a rare entitiy

Gajzer DC, Fletcher CD, Agaimy A, Brcic I, Mhanlari M, Rosenberg AE.
Hum Pathol. 2020 Mar;97:80-93.
https://www.ncbi.nlm.nih.gov/pubmed/31884085

This case series highlights eight patients with a rare gastrointestinal liposarcoma arising distal to the esophagus. These eight lesions arose in the submucosa or muscularis propria of the luminal GI tract; none were exophytic or mesenteric. Six (75%) of the tumors were dedifferentiated liposarcomas, and the remaining two (25%) were considered well-differentiated liposarcomas, lipomatous type. All 8 lesions had strong nuclear expression of MDM2 and CDK4 by immunohistochemistry. The authors also include a table of 37 well-documented primary gastrointestinal liposarcomas of the stomach and intestines, including the 8 from this manuscript. Although follow-up information is not available for all 37 patients, the authors note that 12 patients with well-differentiated liposcarcoma were not known to have metastatic disease or to have died from their disease. In contrast, several patients with dedifferentiated liposarcoma had been reported to experience metastatic disease and/or death from disease.

An organ system-based approach to differential diagnosis of amyloid type in surgical pathology
Giannini G, Nast CC
Arch Pathol Lab Med. Mar 2020; 144: 379-387
https://www.ncbi.nlm.nih.gov/pubmed/31697170

This is a useful review on the organ system-oriented identification of amyloid type, and the implications for clinical management. 5 types of amyloid account for 95% of cases: light chain (AL), transthyretin (ATTR), serum amyloid A (AA), beta-2-microglobulin (Abeta-2-M), and leukocyte chemotactic factor-2 (ALECT-2), all of which have clinical associations. Of these, light chain amyloid comprises approximately 78% of all amyloid cases. While data in the gastrointestinal system is limited, the most common types of amyloid include AL, AA, and ATTR. Abeta-2-M is infrequent and rarer subsets include apolipoprotein A1 (ApoA1) and lysozyme (ALys). Deposition can be found anywhere in the gastrointestinal tract, and can manifest as macroglossia or gastrointestinal symptoms. In one series by Freudenthaler et al, 66.4% of all gastrointestinal amyloid biopsies were AL amyloid, 16.2% were ATTR amyloid, 10.7% were AA amyloid, and other subsets accounted for <1% of amyloid types. The authors also noted a predilection of different microscopic sites: AL amyloid deposits form a mass or nodule in the submucosa or muscularis propria, ATTR and Abeta-2-M distribute in nerves and vessels, and AA amyloid deposits in lamina propria and submucosa.

Journals Reviewed March-April 2020

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