

**Postobesity surgery esophageal dysfunction: a combined cross-sectional prevalence study and retrospective analysis**

Miller AT, Matar R, Abu Dayyeh BK, Beran A, Vela MF, Lacy BE, Crowell MD, Geno DM, Lavey CJ, Katzka DA, Ravi K

Am J Gastroenterol. 2020;115(10):1669-1680.

<https://pubmed.ncbi.nlm.nih.gov/32558689/>

Post-bariatric surgery patients may develop esophageal dysmotility, but the prevalence of these complications is unknown. The authors sought to define the prevalence of dysphasia and esophageal dysmotility disorders (ie. achalasia) after bariatric surgery. This was a large retrospective review of patients from 3 large tertiary referral sites with history of laparoscopic sleeve gastrectomy or Roux-en-Y gastric bypass who underwent diagnostic high resolution impedance manometry (HRIM) between June 2012 and February 2019. 137 patients were identified of which there were 40 who had undergone HRIM prior to surgery and 97 who had undergone HRIM after sleeve gastrectomy (n=39) and Roux-en-Y (n=58). A manometric pattern consistent with achalasia was identified in 7 (7.2%) postsurgical patients and an achalasia like pattern was seen in an additional 5 (5.2%) postsurgical patients. The incidence of achalasia and achalasia-like pattern was more common in the Roux-en-Y treated patients, however this did not reach statistical significance. No patients in the preoperative group had an achalasia or achalasia-like pattern (p=0.02). Increasing time since surgery was associated with achalasia, achalasia-like pattern, and major motility disorders. Among 271 postbariatric surgery patients contacted for a symptom assessment survey, 13.7% reported dysphasia at a mean 3.9 years after surgery. The authors conclude that postoperative dysphagia is a common long-term complication after bariatric surgery and that esophageal dysmotility may be an important under-recognized complication in these patients.

**Tumor infiltrative growth pattern correlates with the immune microenvironment and is an independent factor for lymph node metastasis and prognosis in stage T1 esophageal squamous cell carcinoma**

Zhao Y, Xu E, Yang X, Zhang Y, Chen H, Wang Y, Jin M

Virchows Arch. 2020;477(3):401-408.

<https://pubmed.ncbi.nlm.nih.gov/32232560/>

This is a retrospective study evaluating the association between the tumor infiltrative growth pattern and tumor immune environment and its predictive value for lymph node metastasis and overall survival in esophageal squamous cell carcinoma (stage 1). The authors grouped tumors into infiltrative, expansive and intermediate based on H&E findings. Tumor infiltrating

lymphocytes were graded based on percentage of tumor stroma infiltrated by inflammatory cells and grouped into low and high grade. In their conclusion, the authors report that the infiltrative pattern is an independent risk factor for lymph node metastasis. They also state that cases with a higher grade of tumor infiltrating lymphocytes along with the expansive/intermediate pattern had the greatest prognosis.

### **Significance of druggable targets (PD-L1, KRAS, BRAF, PIK3CA, MSI, and HPV) on curatively resected esophageal squamous cell carcinoma**

Lee HK, Kwon MJ, Ra YJ, Lee HS, Kim HS, Nam ES, Cho SJ, Park H, Min SK, Seo J, Choe J, Min K, Kang SY

Diagn Pathol. 2020;15:126.

<https://pubmed.ncbi.nlm.nih.gov/33054840/>

This study aims to study for the expression of PDL-1 in surgically resected esophageal squamous cell carcinomas (ESS) and its relationship to molecular markers that are potential therapeutic targets. ESS is an intractable disease with dismal prognosis and limited therapeutic options, and the authors note that, unlike many other tumors, there are no established prognostic or predictive markers. In this study, they included 64 patients with primary esophageal cancers who were chemotherapy- or radiation therapy-naive at the time of the surgery from Hallym University Sacred Heart Hospital (Korea), and they correlated clinicopathological characteristics with IHC for PDL-1 (tissue microarray TMA), microsatellite instability (MSI) by IHC/TMA for mismatch repair (MMR) and PCR for five quasi-monomorphic mononucleotide repeat markers, DNA analysis (*KRAS*, *PIK3CA*, and *BRAF*) and HPV status analysis (PANA RealTyper™ HPV Kit). The rate PD-L1-positive cases was 35.9%, and they showed favorable overall survival and better disease free survival. In addition, *PIK3CA* and MSI were detected in less than a fifth of cases, 1 patient had high-risk HPV68 infection, and none of the studied cases had *KRAS* and *BRAF* mutations. PD-L1 status did not correlate with *PIK3CA* nor MSI. *PIK3CA* mutations were associated with worse outcomes in PD-L1 negative patients, but there was no difference in overall survival and disease free survival for PD-L1+ and PD-L1- with or without MSI. The authors concluded that *PIK3CA* mutation status can help as prognostic biomarker in PD-L1 negative patients.

### **Review of pathological findings in laparoscopic sleeve gastrectomy specimens performed for morbid obesity**

Nowak K, DiPalma A, Serra S, Queresby F, Jackson T, Okrainec A, Chetty R

J Clin Pathol. 2020;73(10):618-623.

<https://pubmed.ncbi.nlm.nih.gov/32591353/>

This is a review of the English literature for the spectrum of pathological findings in laparoscopic sleeve gastrectomy (LSG) specimens for obesity patients. The prevalence of

obesity is increasing, and it has a negative impact on health. In addition, LSG is becoming a more popular procedure as treatment for obesity and it is at the discretion of the pathology laboratories to determine specimens that will be examined by pathologists. The authors reviewed all case series and studies for weight loss or comorbidities in LSG patients up to 11/30/2019 (12923 patients) using the Cochrane Library and PubMed that were published in English. They reviewed the histologic findings and divided the cases into clinically indolent (did not require medical intervention) versus clinically actionable (non-neoplastic lesions, premalignant and malignant). The rate of clinically actionable histological findings was 17.0% (2226), and the majority were due to *H. pylori* gastritis. On the other hand, malignant lesions were rare (44 cases of GIST, 1 MALT lymphoma, 2 adenocarcinoma, 1 metastatic carcinoma and 2 G1 neuroendocrine tumor). The authors concluded that LSG specimens may show significant/clinically actionable findings in approximately one-fifth of cases.

### **Use of p53 immunohistochemistry in conjunction with routine histology improves risk stratification of patients with Barrett's oesophagus during routine clinical care**

Tokuyama M, Geisler D, Deitrick C, Fasanella KE, Chennat JS, McGrath KM, Pai RK, Davison JM  
Histopathology. 2020;77(3):481-491.  
<https://pubmed.ncbi.nlm.nih.gov/32431062/>

Risk stratification of patients with Barrett esophagus (BE) remains an important clinical challenge. The development of abnormalities in *TP53* is a known driver of progression to adenocarcinoma in patients with BE, and there are multiple reports that an aberrant expression pattern of p53 in BE biopsies is associated with an increased risk of progression to high-grade dysplasia (HGD) and adenocarcinoma. The use of immunohistochemical (IHC) stains for p53 is not, however, used during routine clinical practice in the United States. In this study, the authors evaluate the use of p53 IHC stains in patients under surveillance for BE over a 6 year period. Their study cohort included patients with non-dysplastic Barrett esophagus (BENEG), Barrett esophagus indefinite for dysplasia (IND), or Barrett esophagus with low-grade dysplasia (LGD) that had sufficient clinical follow up, no prior diagnosis of HGD or adenocarcinoma, no ablation procedures performed prior to the diagnosis of HGD or adenocarcinoma, and were not referred for treatment of HGD or adenocarcinoma. Utilizing these inclusion criteria, 78 patients with BENEG had biopsies that were tested with IHC stains for p53, while 892 were evaluated by morphology alone. There were similar demographic features between the two groups, although patients tested with p53 tended to be older than those that were not tested. IHC testing for p53 was significantly more likely to be done in cases interpreted as IND or LGD (79.5% of p53 tested cases) compared to those that were not tested. Univariate analysis revealed that abnormal p53 expression was associated with a significantly higher risk of progression to HGD or adenocarcinoma (46.9%) over a 5-year follow-up period compared to 7.6% of patients who were not tested and 5.9% of patients with wildtype p53. This association remained in multivariate analysis but was influenced by grade of dysplasia. While there was no difference in the rate of progression for patients with IND who were selected for p53 IHC compared with those who were not, abnormal p53 expression in the IND group was a significant risk factor for

progression to HGD or adenocarcinoma. Based on these data, the authors conclude that p53 IHC may assist in the risk stratification of patients with IND who are at risk for progression to more advanced lesions.

### **Squamous lesions of the stomach**

AbdullGaffar B, Quraishi H  
Int J Surg Pathol. 2020;28(6):647-648.  
<https://pubmed.ncbi.nlm.nih.gov/31822146/>

This is very brief discussion of rare squamous lesions of the stomach including squamous cell carcinoma and squamous metaplasia.

### **Histological changes associated with pyloric and pseudopyloric metaplasia after *Helicobacter pylori* eradication**

Wada Y, Kushima R, Kodama M, Fukuda M, Fukuda K, Okamoto K, Ogawa R, Mizukami K, Okimoto T, Murakami K  
Virchows Arch. 2020;477(4):489-496.  
<https://pubmed.ncbi.nlm.nih.gov/32356024/>

This study evaluated pyloric metaplasia and pseudopyloric metaplasia in the gastric oxyntic mucosa caused by *Helicobacter pylori* infection. Pyloric metaplasia was characterized as MUC6 positive and pepsinogen negative while pseudopyloric metaplasia was MUC6 positive and pepsinogen positive. Through this work, the authors conclude that these types of metaplasia are different modulations of the same line of differentiation and that they are both reversible. They also concluded that pyloric metaplasia may potentially emerge from pseudopyloric metaplasia.

### **USF1 defect drives p53 degradation during *Helicobacter pylori* infection and accelerates gastric carcinogenesis**

Costa L, Corre S, Michel V, Le Luel K, Fernandes J, Ziveri J, Jouvion G, Danckaert A, Mouchet N, Da Silva Barreira D, Torres J, Camorlinga M, D'Elis MM, Fiette L, De Reuse H, Galibert MD, Touati E  
Gut. 2020 ;69(9):1582-1591.  
<https://pubmed.ncbi.nlm.nih.gov/31822580/>

*Helicobacter pylori* reduces the expression of the transcription factor USF1 shown to stabilize p53 in response to stress. This study examined the role of USF1 in gastric carcinogenesis. In

their conclusion, the authors suggest that the depletion of USF1 and its de-localization in the vicinity of cell membranes are essential events promoting gastric carcinogenesis.

### **Histopathologic analysis of signet-ring cell carcinoma in situ in patients with hereditary diffuse gastric cancer**

Tsugeno Y, Nakano K, Nakajima T, Namikawa K, Takamatsu M, Yamamoto N, Fujisaki J, Nunobe S, Kitagawa M, Takeuchi K, Kawachi H  
Am J Surg Pathol. 2020;44(9):1204-1212.  
<https://pubmed.ncbi.nlm.nih.gov/32520759/>

Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant syndrome characterized by increased risk of developing Laurén's diffuse-type gastric carcinoma and lobular breast carcinoma. Germline mutation of *cadherin-1* (*CDH1*), the gene encoding E-cadherin, has been detected in 30% to 50% of HDGC patients. The authors aimed to study the incidence, distribution, histologic, and immunohistochemical characteristics, as well as diagnostic implications of signet-ring cell carcinoma (SRCC) in situ (SRCC-pTis) in HDGC cases with *CDH1* germline mutation. The study group consisted of gastrectomy specimens from 6 Japanese HDGC patients. In total, 274 carcinoma foci (range: 8 to 107; mean 45.7 foci) were detected in mucosa measuring 40.18m in length (range: 2.93 to 10.51; mean 6.70m). Of the 274 foci, 225, 3, and 46 were diagnosed with intramucosal SRCC (SRCC-pT1a), intramucosal poorly differentiated adenocarcinoma, and SRCC-pTis, respectively. All SRCC-pTis foci were observed in the fundic mucosa, with no foci detected in the pyloric or cardia mucosal areas. All SRCC-pTis foci exhibited a pagetoid pattern type in this study. Immunohistochemically, E-cadherin expression was lost more frequently in SRCC-pTis (96.4%) when compared to SRCC-pT1a (48.2%;  $P < 0.001$ ). No SRCC-pTis were identified in 60 samples from gastric cancer cases analyzed as controls. The authors conclude that SRCC-pTis (especially pagetoid type), is highly specific for HDGC patients with *CDH1* germline mutation, and its characteristic histopathologic features can assist diagnostic pathologists to identify SRCC-pTis lesions in daily practice.

### **Frozen section diagnosis of gastrointestinal poorly cohesive and signet-ring cell adenocarcinoma: useful morphologic features to avoid misdiagnosis**

Zhu X, Bledsoe JR  
Virchows Arch. 2020;477(4):497-506.  
<https://pubmed.ncbi.nlm.nih.gov/32215719/>

This is a retrospective study on 50 frozen sections of poorly differentiated adenocarcinoma with signet-ring cells to characterize useful histologic features to distinguish carcinoma from inflammatory/stromal cells. Features with 100% specificity and positive predictive value (PPV) for carcinoma were cells with a single distinct cytoplasmic mucin vacuoles, focal gland formation, and perineural invasion. Features with high specificity, sensitivity, PPV (> 75%) were

irregular nuclear contours, large nuclear size with many nuclei > 4× the size of a small lymphocytes, and disruption/obliteration of normal structures. Other features with high specificity and PPV (≥ 85%) but relatively low sensitivity and NPV were crescent-shaped/indented nuclei, prominent nucleoli, anisonucleosis (> 4:1 difference in nuclear size), multinucleation, and the presence of mitotic figures.

### **Analysis of clinicopathological and molecular features of crawling-type gastric adenocarcinoma**

Fujita Y, Uesugi N, Sugimoto R, Eizuka M, Toya Y, Akasaka R, Matsumoto T, Sugai T  
Diagn Pathol. 2020;15:111.  
<https://pubmed.ncbi.nlm.nih.gov/32943104/>

The purpose of this retrospective study is to compare the clinicopathologic and molecular features of crawling-type adenocarcinoma (CRA) with those of conventional differentiated adenocarcinoma (CDA). The authors noted that CRA has attracted more attention as a subtype of gastric carcinoma and is said to demonstrate subtle cytological atypia but with a complex architecture “shaking-hands pattern”, resembling the shapes of the letters W, H, Y or X. It is reported that these lesions may be mistaken for benign intestinal metaplasia. The authors examined 51 CRA patients and 126 CDA patients with tubular or papillary formation who underwent surgical or endoscopic resection for GC at Iwate Medical University Hospital (Iwate, Japan 2010-2018). They performed IHC (MUC5Ac, MUC6, MUC2, CD10, CDX2, MLH-1, p53, β-catenin), molecular analysis (*TP53*, *KRAS*, *BRAF*), analysis of allelic imbalance (AI), MSI and DNA methylation. In comparison to CDA, CRA was more frequent in the middle 1/3 of the stomach, more commonly had a component of mixed or poorly differentiated carcinoma, and showed a lower frequency of β-catenin expression and loss of MLH-1. There was no difference in mucin phenotype or CDX2 expression between the 2 groups. The *TP53* mutation frequency was higher for CRA (37.3%) and 10 cases of CRA had the specific *TP53* mutation c.529\_546del. There was no significant difference in MSI frequency between the two groups, but AIs were more often appreciated in CRA compared to CDA. The authors suggest that CRA is an independent histological subtype of GC in terms of clinicopathological and molecular findings.

### **Distinct clinicopathological differences between early gastric cardiac and non-cardiac carcinomas: a single-center retrospective study of 329 radical resection cases**

Wang Y, Li X, Gao L, Wang C, Zhang Y, Huang Q  
BMC Gastroenterol. 2020;20(1):351.  
<https://pubmed.ncbi.nlm.nih.gov/33087057/>

The clinicopathologic differences between early gastric cardiac carcinoma (EGCC) and early gastric non-cardiac carcinoma (EGNCC) remain elusive. In this study, the authors studied 329 early gastric carcinoma radical gastrectomies with 70 EGCCs and 259 EGNCCs. Compared to the

EGNCC antrum-angularis-pylorus subgroup (n = 181), but not fundus-corporis subgroup (n = 78), EGCC was associated with significantly older patient age, better tumor differentiation, and higher percentage of tubular/papillary adenocarcinoma. EGCC was associated with a lower frequency of mixed poorly cohesive carcinoma with tubular/papillary adenocarcinoma, pure poorly cohesive carcinoma, grossly depressed pattern, and absence of lymph node metastasis in tumors with only superficial submucosal invasion. No significant differences were found between EGCC and EGNCC sub-groups in gender, tumor size, *H. pylori* infection rate, and lymphovascular/perineural invasion. Additionally, EGCC with esophageal invasion had a higher percentage of tumor size > 2 cm and tubular differentiation compared to EGCC without esophageal invasion. However, there is no significant difference in the rate of *H. pylori* infection and esophageal columnar, intestinal, or pancreatic metaplasia between them. The authors concluded that there are distinct clinicopathologic differences between EGCC and EGNCC sub-groups.

### **Perineural invasion as a predictive factor for survival outcome in gastric cancer patients: a systematic review and meta-analysis**

Zhao B, Lv W, Mei D, Luo R, Bao S, Huang B, Lin J  
J Clin Pathol. 2020;73(9):544-551.  
<https://pubmed.ncbi.nlm.nih.gov/31980559/>

This is a meta-analysis study about the prognostic significance of perineural invasion (PNI) in gastric carcinoma (GC) patients. PNI is known to be a negative prognostic indicator for pancreatic, colorectal and prostatic carcinoma, and there is conflicting literature about its significance in GC. Authors defined positive PNI as the presence of tumor cells along the perineurium or the neural fascicles in surgically resected specimens, and they included 13 studies (7004 GC patients underwent surgical treatment) out of 254 potentially relevant papers using PubMed and Embase databases, selecting papers that had clinicopathological characteristics or follow up. In this study, the rate of PNI was 35.9%, and it was significantly associated with undifferentiated histology type, diffuse type, higher stage and lymph node metastasis, and showed a negative impact on survival. The authors concluded that the rate of PNI is high in GC patients, and the status of PNI provides additional prognostic information to GC patients.

### **Gastric adenocarcinoma of the fundic gland type: clinicopathological features of eight patients treated with endoscopic submucosal dissection**

Li C, Wu X, Yang S, Yang X, Jin Yao J, Zheng H  
Diagn Pathol. 2020; 23;15(1):131.  
<https://pubmed.ncbi.nlm.nih.gov/33097069/>

This paper reviews eight cases of gastric adenocarcinoma of the fundic gland type (GA-FG) that were diagnosed at Zunyi Medical University (2017-2019) and were completely removed by endoscopic submucosal dissection (ESD). This entity was first described in 2007, and the latest WHO classification divided it into 3 subcategories (chief cell predominant [most common type], parietal cell predominant [~1% of cases], and mixed phenotype). The majority of reported cases are from Asia. The authors recorded the endoscopic findings, the pathologic features with immunostaining, and follow up. Initially, 4 cases were diagnosed as GA-FG and the rest were called oxyntic gland adenoma due to the superficial nature of biopsies. In this cohort, the mean size was 6 mm, and 7 cases arose in the upper third of stomach. The majority were superficially elevated macroscopically (6/8) with a normal background mucosa in most cases. Histologically, all tumors were chief cell-predominant and arose from the deep mucosal layer with an infiltrative growth pattern. Submucosal invasion was appreciated in 6 cases, but the overlying foveolar epithelium was normal in most cases. There was no evidence of lymphatic or venous invasion in this series, and no disease progression nor metastasis were noted in a mean follow up of 17 months. The authors concluded that GA-FG is a well-differentiated type of adenocarcinoma, and it can be completely removed using ESD, with a favorable prognosis in patients.

### **Diffuse MIST1 expression and decreased $\alpha$ 1,4-linked N-acetylglucosamine ( $\alpha$ GlcNAc) glycosylation on MUC6 are distinct hallmarks for gastric neoplasms showing oxyntic gland differentiation**

Yamada S, Yamanoi K, Sato Y, Nakayama J.  
Histopathology. 2020;77(3):413-422.  
<https://pubmed.ncbi.nlm.nih.gov/32502322/>

Gastric neoplasms showing oxyntic gland differentiation (GAOG) are challenging neoplasms that were initially described as gastric adenocarcinomas with chief cell differentiation and are currently categorized in by the WHO as either oxyntic gland adenomas or the invasive counterpart gastric adenocarcinoma of the fundic gland type. The protein  $\alpha$ GlcNAc is thought to serve as a tumor suppressor, as mice lacking the enzyme that catalyzes its biosynthesis spontaneously develop gastric tumors. Likewise, typical gastric adenocarcinomas in humans, as well as pyloric gland adenomas with high-grade dysplasia frequently exhibit reduced  $\alpha$ GlcNAc expression. In this study, the authors investigate the expression of  $\alpha$ GlcNAc, along with MUC6, MUC5AC, MUC2, the gastric gland markers MIST1, PG1, H/K-ATPase, and Ki67 in 13 GAOGs. They report that all of the GAOGs express MIST1 and PG1, often at high levels. While, like normal mucous neck cells, all GAOGs expressed MUC6, only 23% of these lesions expressed  $\alpha$ GlcNAc and typically in less than 1/3rd of the lesional cells. The Ki-67 proliferative index was less than 5% in all lesions. The authors suggest that expression of MUC6 and MIST1 with loss of or decreased expression of  $\alpha$ GlcNAc may aid in the diagnosis of these lesions, particularly in submucosal dissections where it may be challenging to distinguish them from non-neoplastic gastric oxyntic glands.



## **An LCM-based genomic analysis of SPEM, gastric cancer and pyloric gland adenoma in an Asian cohort**

Srivastava S, Huang KK, Rebbani K, Das K, Fazreen Z, Yeoh KG, Tan P, Teh M  
Mod Pathol. 2020;33(10):2075-2086.  
<https://pubmed.ncbi.nlm.nih.gov/32269290/>

Pyloric gland adenoma (PGA) and spasmolytic polypeptide-expressing metaplasia (SPEM) are both lesions in which gastric body glands are replaced by pyloric glands, and both are associated with autoimmune gastritis (AIG). The authors hypothesized that SPEM might be related to PGA at the genomic level, and also related to intestinal metaplasia (IM) and intestinal type gastric cancer (GC). The authors performed a retrospective analysis of 13 gastrectomies showing PGA with or without dysplasia, GC, and SPEM. IHC for MUC5AC, MUC6, gastrin, and TFF2 were performed, as well as exome sequencing for 49 commonly dysregulated genes in GC. The authors found that SPEM showed fewer genomic variations than GC and PGA, and was genomically distinct from PGA. Progression of PGA from non-dysplastic to dysplasia/adenocarcinoma was associated with an increase in mutations. The authors conclude that SPEM appears to be more genomically similar to GC than PGA.

## **Integrated characterisation of cancer genes identifies key molecular biomarkers in stomach adenocarcinoma**

Wang H, Shen L, Li Y, Lv J  
J Clin Pathol. 2020 Sep;73(9):579-586.  
<https://pubmed.ncbi.nlm.nih.gov/32034058/>

This study aimed to perform a comprehensive analysis for the driver genes in gastric adenocarcinoma (GA) and to search for molecular biomarkers associated with more aggressive behavior. The genomic mutations in GA have been largely studied by next-generation studies such as The Cancer Genome Atlas (TCGA) project that classified GA based on molecular signature. However, the molecular mechanisms of tumorigenesis and progression are not completely understood with few studies having identified some driver genes such as *TP53*, *ARID1A* and *CDH1*. The authors included 208,012 somatic mutations of 387 GA samples from the TCGA database, and used five computational methods (MutSigCV, OncodriveCLUST, OncodriveFM, dendrix and edriver) to predict the driver genes. They did further analysis for gene pathway enrichment, weighted gene co-expression network for hub genes (i.e. genes that showed high intramodular connectivity), protein-protein interaction network analysis, and copy number variation. 376 driver genes were predicted by these 5 tools, and *PIK3CA* was the overlapping gene predicted by all five tools. They identified the 10 most commonly mutated

genes (*TTN*, *TP53*, *LRP1B*, *CSMD3*, *OBSCN*, *ARID1A*, *FAT4*, *FLG*, *PCLO* and *CSMD1*), top 5 hub genes (*PIK3CD*, *NLRC3*, *FMNL1*, *TRAF3IP3* and *CR1*) that correlated with tumor stage and lymph node stage, three groups of GA based on copy number variation of driver genes and subset genes associated with more mortality such as *DNER*, *LHCGR*, *NLRP14*, *OR4N2*, *PSG6*, *TTC29* and *ZNF568* genes. The authors in this study provided a comprehensive list of genes involved in tumorigenesis of GA and found some genes that have prognostic significance.

### **Duodenal bulb biopsy in the diagnostic work-up of coeliac disease**

Özakıncı H, Kırmızı A, Tural M, Kiremitçi S, Savaş B, Kuloğlu Z, Kansu A, Ensari A  
Virchows Arch. 2020;477(4):507-515.  
<https://pubmed.ncbi.nlm.nih.gov/32405928/>

This study looks at distribution of celiac disease (CD) in the duodenum. The authors looked at cases of CD with which there was serologic evidence of disease and both duodenal bulb and distal duodenal biopsies were obtained. They found that 15% of CD cases show patchy disease in these two locations with 13% demonstrating involvement limited to the duodenal bulb. In their conclusion, the authors state that if the duodenal bulb is not biopsied during an evaluation for CD the diagnostic features may be missed in up to 13% of cases.

### **Probiotics for celiac disease: a systematic review and meta-analysis of randomized controlled trials**

Seiler CL, Kiflen M, Stefanolo JP, Bai JC, Bercik P, Kelly CP, Verdu EF, Moayyedi P, Pinto-Sanchez MI  
Am J Gastroenterol. 2020;115(10):1584-1595.  
<https://pubmed.ncbi.nlm.nih.gov/32740074/>

Probiotics have been proposed as an adjuvant treatment for celiac disease (CD). The authors performed a systematic review and meta-analysis to evaluate the efficacy of probiotics in improving GI symptoms and quality of life (QOL) in patients with CD. After screening, 7 articles describing 6 RCTs (n=5,279 participants) were eligible for quantitative analysis. The authors found that probiotics improved GI symptoms when assessed by the GI Symptoms Rating Scale (mean difference symptom reduction:228.7%; 95% CI 243.96-213.52; p=0.0002). *Bifidobacteria* levels increased after probiotics. No difference in adverse events was observed between probiotics and placebo. However, the overall certainty of the evidence ranged from very low to low. The authors conclude that probiotics may improve GI symptoms in CD, but high quality clinical trials (establishing the optimal species, timing, and dosage of probiotics) are needed to improve the certainty of the evidence.

### **Long-term consequences of undiagnosed celiac seropositivity**

Kårhus LL, Skaaby T, Petersen J, Madsen AL, Thuesen BH, Schwarz P, Rumessen JJ, Linneberg A  
Am J Gastroenterol. 2020;115(10):1681-1688.  
<https://pubmed.ncbi.nlm.nih.gov/32558687/>

Little is known about the long-term consequences of undiagnosed celiac disease (CD). The authors aimed to investigate the long term consequences of undiagnosed CD for mortality, chronic diseases, and cancer incidence. Biobank serum samples were screened for IgA and IgG TTG and IgG deamidated gliadin peptide in a study of 8 population-based cohort studies comprising 16,776 participants examined between 1976-2012 and followed with >99% complete follow up in Danish nationwide registries until 12/31/2017. Undiagnosed CD was defined as antibody positivity in those without a recorded diagnosis of CD. The authors found the prevalence of undiagnosed CD to be 1%, with no statistically significant increase over time. Undiagnosed CD was significantly associated with increased risk of incident cancer overall (HR 1.57; 95% CI 1.16-2.11) and an increased risk of incident cardiovascular disease (HR 1.37; 95% CI 1.01-1.85). No significant association with mortality was found. The authors conclude that undiagnosed CD has serious long term health consequences.

### **Intestinal graft versus host disease involving Brunner's glands**

Kreft A, Wagner DC, Neumann H  
Int J Surg Pathol. 2020;28(7):772-773.  
<https://pubmed.ncbi.nlm.nih.gov/31918610/>

Case report: According to authors, this is the first reported case of GVHD involving the Brunner's glands. It is worth to say that in this case, GVHD also involved the overlying intestinal mucosa.

### **Macroscopic and microscopic characteristics of low grade appendiceal mucinous neoplasms (LAMN) on appendectomy specimens and correlations with pseudomyxoma peritonei development risk**

Hegg KS, Mack LA, Bouchard-Fortier A, Temple WJ, Gui X  
Ann Diagn Pathol. 2020;48:151606  
<https://pubmed.ncbi.nlm.nih.gov/32889392/>

This series evaluated the microscopic and macroscopic features associated with concurrent and subsequent development of pseudomyxoma peritonei. The authors retrospectively reviewed 154 low-grade appendiceal mucinous neoplasms (LAMNs) to describe select gross and

histologic associations with pseudomyxoma. They found that LAMNs with pseudomyxoma often had a smaller luminal diameter, thicker wall, and microscopic perforation. They corroborated previous studies showing that both acellular and cellular extra-appendiceal mucin were associated with the development of pseudomyxoma. Similar to previous studies, they also found that the presence of neoplastic cells or acellular mucin at the surgical resection margin was not associated with development of pseudomyxoma.

### **The role of bile acids in chronic diarrhea**

Camilleri M, Vijayvargiya P

Am J Gastroenterol. 2020;115(10):1596-1603.

<https://pubmed.ncbi.nlm.nih.gov/32558690/>

In this review, the authors discuss the disease states and mechanisms underlying bile acid malabsorption. Clinical features, diagnosis and potential therapeutic targets are also summarized.

### **Topographical distribution of microscopic colitis and the importance of orientation of paraffin-embedded biopsies**

Kanstrup Fiehn AM, Heiberg Engel PJ, Lanzarotto F, Goudkade D, Landolfi S, Munck LK, Villanacci V

Hum Pathol. 2020;103:63-71.

<https://pubmed.ncbi.nlm.nih.gov/32673680/>

In this study, the authors reviewed colonic biopsies from 96 patients who met clinical criteria for microscopic colitis in order to determine how many biopsy samples should be taken to make this diagnosis by histology, whether right or left colonic biopsies are more sensitive, and what effect tissue orientation has on the diagnosis of microscopic colitis. In the manuscript, the proportion of diagnostic biopsies are broken down by the clinical center where they were obtained. Overall, 70% of the biopsy samples taken had features of microscopic colitis, although patients with lymphocytic colitis tended to have more diffuse involvement of tissue fragments than patients with collagenous colitis. The authors confirmed that biopsies of the right colon were more likely to have histologic changes of microscopic colitis than those from the left colon. When looking at tissue embedding, the diagnostic rate was higher for tissue oriented perpendicularly with precut cellulose acetate filters when compared to non-oriented biopsy fragments, although this difference is not said to be statistically significant. Based on this work, the authors recommend that 4 biopsy sites proximal to the rectum should be sampled by endoscopy in order to rule in microscopic colitis. The manuscript includes tables that clearly specify diagnostic criteria used by the pathologists in this study as well as the diagnostic rate broken down by clinical site, diagnosis, and colonic site sampled.

### **Complete resolution of mucosal neutrophils associates with improved long-term clinical outcomes of patients with ulcerative colitis**

Pai RK, Hartman DJ, Rivers CR, Regueiro M, Schwartz M, Binion DG, Pai RK  
Clin Gastroenterol Hepatol. 2020;18(11):2510-2517  
<https://pubmed.ncbi.nlm.nih.gov/31843598/>

Current IBD working group and Gastroenterology guidelines recommend treatment for ulcerative colitis (UC) patients to achieve endoscopic remission, and histologic evaluation is not recommended in these guidelines. In this study, the authors investigated histologic findings using three existing scoring systems: Geboes score (GS), Robarts histological index (RHI) and Nancy histological index (NHI) in 281 UC patients. Their results demonstrated that histologic activity was significantly associated with systemic corticosteroid use, colectomy and hospitalization in different analyses. For patients who had endoscopic remission, only histologic activity but not histologic normalization, mucosal eosinophilic infiltration, or basal lymphoplasmacytic inflammation was an independent prognostic parameter associated with the use of systemic corticosteroids in multivariate analyses. These data emphasized the importance of assessment of histologic activity for clinical treatment decision and clinical recommendations.

### **Automatic, computer-aided determination of endoscopic and histological inflammation in patients with mild to moderate ulcerative colitis based on red density**

Bossuyt P, Nakase H, Vermeire S, de Hertogh G, Eelbode T, Ferrante M, Hasegawa T, Willekens H, Ikemoto Y, Makino T, Bisschops R  
Gut. 2020;69(10):1778-1786.  
<https://pubmed.ncbi.nlm.nih.gov/31915237/>

In this study the authors tested an operator independent computer based tool to evaluate UC activity based on endoscopic imaging. The authors conclude that their algorithm can accurately assess disease activity and that it correlated well with endoscopic and histological findings.

### **Histologic healing is more strongly associated with clinical outcomes in ileal Crohn's disease than endoscopic healing**

Christensen B, Erlich J, Gibson PR, Turner JR, Hart J, Rubin DT  
Clin Gastroenterol Hepatol. 202;18(11):2518-2525  
<https://pubmed.ncbi.nlm.nih.gov/31812654/>

Symptomatic remission and endoscopic mucosal healing have been the recommended goals for the treatment of inflammatory bowel disease (IBD). In patients with ulcerative colitis (UC), previous studies have shown that histologic assessment should also be included in the analysis

of disease outcomes in standard care. Due to the patchiness of Crohn's disease (CD), it is believed that histologic assessment may be biased and difficult. Therefore, the role of histologic assessment in CD remains largely unexplored. In this study, the authors aimed to examine the prognostic value of histologic healing (HH) using a modified Ileal Global Histologic Disease activity (IGHAS) score compared with endoscopic healing (EH) in relation to clinical outcomes, hospitalization, corticosteroid use, and medication escalation in 101 patients with ileal restricted CD. The authors' results demonstrated that 63% of patients had EH, in comparison to 55% of patients with HH with kappa coefficient ( $\kappa$ ) of 0.225. Only HH but not EH was significantly associated with decreased clinical relapse, medication escalation, and corticosteroid use on multivariate analyses. These data emphasized the importance of histologic assessment in managing patients with CD.

### **An update on the medical management of inflammatory pouch complications**

Quinn KP, Raffals LE

Am J Gastroenterol. 2020;115(9):1439-1450.

<https://pubmed.ncbi.nlm.nih.gov/32453044/>

The authors review inflammatory complications involving ileal pouch and include a focused approach to diagnosis and management. While most patients undergoing total proctectomy with ileal pouch-anal anastomosis (IPAA) have a good outcome, several early and late complications may occur, with pouchitis being most common (50% incidence at 10 years, 80% at 30 years). Most pouchitis is idiopathic, but several secondary causes should be considered including Crohn's Disease (CD) of the pouch. Endoscopically, primary/idiopathic pouchitis is classically characterized by diffuse inflammation of the pouch with sparing of the prepouch ileum proximal to the pouch inlet. Prepouch ileitis tends to occur more often in PSC-associated pouchitis than idiopathic pouchitis. Extensive prepouch ileitis (>10cm proximal to the pouch) especially in the presence of other features like deep ulceration, fistula, and nonanastomotic strictures should raise concern for CD. Asymmetric, sharply demarcated inflammation, on the other hand, may suggest ischemic pouchitis. Histology usually shows nonspecific active and chronic changes, likely representing adaptive changes to fecal stasis, but can be useful in identifying secondary causes of pouchitis such as CMV pouchitis or granulomas (present in up to 12% of CD of the pouch). Most episodes of pouchitis respond to antibiotic treatment, though 10-20% will develop chronic pouchitis that requires long term treatment or is refractory to conventional therapy. These patients may have significant morbidity and chronic pouchitis carries an increased risk of pouch failure. A multidisciplinary approach to managing these patients is often necessary.

### **Vasculitis involving the gastrointestinal system is often incidental but critically important**

Zhang X, Furth EE, Tondon R

Am J Clin Pathol. 2020;154(4):536-552.

<https://pubmed.ncbi.nlm.nih.gov/32789454/>

The authors aimed to investigate the importance of encountering unexpected vasculitis identified in gastrointestinal (GI) specimens. They investigated the prevalence, correlation with clinical outcomes, as well as the rate of the timely communication to the clinician with its impact on clinical management. The authors identified 29 (0.02%) cases showing histologic evidence of GI vasculitis, of a total of 131,367 GI pathology cases received over a 10-year study period in their tertiary care hospital. Twenty of 29 cases (69%) of vasculitis were not clinically suspected. Four of the 20 patients (20%) were subsequently diagnosed with systemic vasculitis. On clinical follow-up (mean: 34 months), 4 of 17 patients (24%) with unexpected vasculitis died as the result of direct complications of this disease. In this study, the authors also found that most (95%) of these cases were communicated in a timely manner to the clinician, and this necessitated additional workup in 85% of these patients. The authors conclude that although rare, an unexpected diagnosis of vasculitis in the GI tract carries a notable clinical significance with a high mortality rate, and urgent communication with the clinical team is important for the early diagnosis and treatment of this disease. The results of this study highlight the importance of examining the vasculature in every GI specimen for the recognition of vasculitis and communicating its presence to the clinician in a timely manner.

### **PHOX2B immunostaining: a simple and helpful tool for the recognition of ganglionic cells and diagnosis of Hirschsprung disease**

Drabent P, Bonnard A, Guimiot F, Peuchmaur M, Berrebi D  
Am J Surg Pathol. 2020;44(10):1389-1397.  
<https://pubmed.ncbi.nlm.nih.gov/32604166/>

Hirschsprung disease (HD) is a complex multigenic congenital disease of enteric innervation characterized by the complete absence of ganglionic cells (GC) in the myenteric and submucosal plexuses of the intestine. Patients undergo a rectal suction biopsy (RSB), which remains the gold standard, for the assessment or diagnosis of HD with the diagnosis resting on the absence of GC. The fact that the GCs may be immature and hard to recognize in very young or preterm born children the histologic diagnosis may be challenging. Ancillary techniques, such as acetylcholinesterase histochemistry and calretinin immunostaining are commonly used as a diagnostic adjunct; however these techniques focus mainly on the changes in nerve fibers, but not on GCs themselves. PHOX2B is a major transcription factor responsible for the differentiation and survival of GCs of the enteric nervous system. In this study, the authors aimed to assess the staining of PHOX2B in immature enteric ganglia and the utility of this stain in recognizing GCs in rectal suction biopsies with suspicion for HD. A series of 68 consecutive children with a suspicion of HD were included prospectively for the study, during a 2 year study period. The criteria for diagnosis of HD included: (i) compatible morphology on H&E-stained sections with no GC with or without submucosal nerve fiber hyperplasia and/or hypertrophy, (ii) hyperplasia and/or hypertrophy of nerve fibers in the muscularis mucosa and lamina propria on AChE histochemistry, and (iii) absence of calretinin-stained nerve fibers in the

muscularis mucosa and lamina propria. Of the 68 RSBs included in the study, 29 were diagnosed as HD, 3 were inadequate due to lack of submucosa, and 36 were diagnosed as non-HD. PHOX2B immunostaining was positive in 97% of the non-HD RSB (35/36 cases) and entirely negative in 97% (28/29 cases) of the HD RSB, yielding a 97% specificity and 97% sensitivity. The only non-HD case in which PHOX2B was negative was a superficial RSB with scarce submucosa. The authors suggest that the use of PHOX2B immunostaining is of great help in the recognition of GCs on RSBs and therefore in the diagnosis of HD. The high sensitivity averts any overdiagnosis of HD, especially in cases with undifferentiated or poorly differentiated GCs, which can be hard to recognize on standard H&E.

### ***Enterobius vermicularis* in a tubulovillous adenoma**

Coyne JD, Charan V, Ganjifrockwala A  
Int J Surg Pathol. 2020;28(6):651-652.  
<https://pubmed.ncbi.nlm.nih.gov/31865817/>

Case report: This is purported to be the first case report of *Enterobius* in a tubulovillous adenoma.

### **Clinicopathologic and molecular characteristics of familial adenomatous polyposis-associated traditional serrated adenoma**

Okamura T, Hashimoto T, Naka T, Yoshida T, Tanabe N, Ogawa R, Yamada M, Saito Y, Yatabe Y, Sekine S  
Am J Surg Pathol. 2020;44(9):1282-1289.  
<https://pubmed.ncbi.nlm.nih.gov/32384323/>

Familial adenomatous polyposis (FAP) is an autosomal dominant cancer predisposition syndrome, caused by inactivating germline mutations in *APC*, the most frequently mutated tumor-suppressor gene in sporadic colorectal cancer, and FAP patients develop numerous conventional adenomas. In this study, the authors aimed to clarify the clinicopathologic and molecular features of FAP-associated traditional serrated adenomas (TSAs) by analyzing the clinicopathologic and molecular features of 37 TSAs retrieved from 21 FAP patients. Histologically, a majority of the TSAs (97%) showed typical cytology, characterized by a brightly eosinophilic cytoplasm and small elongated nuclei, in >50% of the area examined. Slit-like serration was seen in >10% of the area of most of the lesions. However, ectopic crypt formation was infrequent and only focally seen in 16% of cases. Precursor polyps (6 hyperplastic polyps, and 1 sessile serrated lesion) were seen in seven TSAs (19%). Immunohistochemically, 89% showed focal or diffuse nuclear  $\beta$ -catenin accumulation and annexin A10 expression was variably detectable in 76% of cases. Forty nine percent and 38% of TSAs showed *KRAS* and *BRAF* V600E mutations respectively, via next-generation sequencing and Sanger sequencing. Somatic *APC* mutations were detected in 84% of analyzed cases. Three lesions had *BRAF* non-V600E



mutations, and 2 of them had a concurrent *KRAS* mutations. All TSAs (19%) associated with a precursor polyp showed *BRAF* V600E mutations. None of the lesions showed the high CpG island methylation phenotype. These results indicate that although FAP-associated TSAs share many histologic, immunohistochemical, and molecular features with sporadic TSAs, they show infrequent ectopic crypt formation, highly prevalent *APC* mutations, and the absence of the CIMP-high phenotype.

### **Long-term colorectal cancer incidence after adenoma removal and the effects of surveillance on incidence: a multicentre, retrospective, cohort study**

Cross AJ, Robbins EC, Pack K, Stenson I, Kirby PL, Patel B, Rutter MD, Veitch AM, Saunders BP, Duffy SW, Wooldrage K  
Gut. 2020;69(9):1645-1658.  
<https://pubmed.ncbi.nlm.nih.gov/31953252/>

This is a large study (> 28 k cases) on postpolypectomy colonoscopy surveillance and its effectiveness in reducing CRC. The UK surveillance guideline is based on risk: low risk group surveillance at 5-10 years, intermediate at 3 years and high risk every 1 year. The authors found that postpolypectomy surveillance is associated with a reduction in CRC risk. However, even without surveillance, CRC risk in some low and intermediate-risk patients is not higher than the general population and these patients could potentially be managed by screening rather than surveillance.

### **Poorly differentiated clusters in colorectal cancer: a current review and implications for future practice**

Shivji S, Conner JR, Barresi V, Kirsch R  
Histopathology. 2020;77(3):351-368.  
<https://pubmed.ncbi.nlm.nih.gov/32358792/>

Poorly differentiated clusters are defined as clusters of 5 or more tumor cells without gland formation and have garnered increased interest recently as a prognostic factor that may dictate the biologic behavior of colorectal cancers. In this review, the authors discuss current evidence regarding the prognostic significance of poorly differentiated clusters in comparison to conventional histologic grading and the assessment of tumor budding. In particular, they review the relationships between clinical outcome and poorly differentiated cluster grade in stage 2 colon cancers, reporting that the presence of poorly differentiated clusters is associated with outcome and may assist in identifying patients with node-negative disease that could benefit from adjuvant therapy. They also review data regarding the presence of poorly differentiated clusters in endoscopically resected pT1 cancers, reporting that higher poorly differentiated cluster grades are associated with an increased risk for lymph node metastasis. The relationship

between poorly differentiated clusters and tumor budding, as well as issues regarding the assessment of poorly differentiated cluster grading and reproducibility are also discussed.

### **Reproducibility of AJCC criteria for classifying deeply invasive colon cancers is suboptimal for consistent cancer staging.**

Panarelli NC, Hammer STG, Lin J, Gopal P, Nalbantoglu I, Zhao L, Cheng J, Gersten AJ, McHugh JB, Parkash V, Lucas E, Westerhoff M  
Am J Surg Pathol. 2020;44(10):1381-1388.  
<https://pubmed.ncbi.nlm.nih.gov/32931163/>

Despite the latest 8th edition of American Joint Committee on Cancer (AJCC) staging manual guidelines for staging the depth of invasion in colorectal cancers, staging of deeply invasive T3 vs. T4a colorectal cancers remains challenging and a source of diagnostic confusion, especially when the tumors closely approach the serosal surface. To this end, the authors in this study assessed interobserver agreement among pathologists, including six gastrointestinal (GI) pathologist and 4 pathologists focused in non-GI subspecialties, from different institutions in the application of this AJCC 8th edition criteria. They classified 47 deeply invasive colonic adenocarcinomas  $\leq 1$ mm from the serosal surface into pT3 or pT4a, by examining low-magnification and high-magnification images of the most deeply invasive area. They also identified morphologic patterns that produce diagnostic confusion. The cases were divided into three different histologic patterns at the advancing edge of the tumor- continuous invasion through an inflammatory focus (pattern 1), pushing border (pattern 2), and infiltrative glands and cell clusters with serosal reaction (pattern 3). For pattern 1, GI pathologists achieved slight ( $\kappa=0.16$ ) agreement and the non-GI pathologists achieved fair (0.31) agreement. For pattern 2, GI pathologists achieved moderate ( $\kappa=0.46$ ) agreement and the non-GI pathologists achieved fair (0.39) agreement. For pattern 3, both GI and non-GI pathologists achieved moderate agreement ( $\kappa=0.51$ , and 0.57, respectively). The distinction between pT3 and pT4a would have changed the overall clinical stage in 10 (21%) cases. The authors show the lack of interobserver agreement when staging deeply invasive colonic adenocarcinomas close to the serosal surface, and call out for clarification of these criteria to ensure uniform reporting of tumor stage.

### **Colorectal endoscopic submucosal dissections: an analysis of 279 cases with emphasis on the importance of multidisciplinary work and establishing examination protocols**

Taşkın OÇ, Aslan F, Kulaç İ, Yılmaz S, Adsay V, Kapran Y  
Int J Surg Pathol. 2020;28(6):600-608.  
<https://pubmed.ncbi.nlm.nih.gov/32349582/>

This retrospective study looked at 279 endoscopic submucosal dissection specimens and evaluated the histopathologic challenges. They found various histopathologic difficulties and make the recommendation that specimens should be prepared in the endoscopy suite,

submitted to the pathology laboratory oriented, pinned, and placed in copious amount of fixative. They also recommend total sampling, gross photography, mapping, and proper fixation.

### **Colorectal adenocarcinomas harboring *ALK* fusion genes: a clinicopathologic and molecular genetic study of 12 cases and review of the literature.**

Lasota J, Chłopek M, Wasąg B, Kowalik A, Christiansen J, Lamoureux J, Kuźniacka A, Felisiak-Gołębek A, Liu Y, Reyes TAR, Saha R, Agaimy A, Behenska K, Biernat W, Cattaneo L, Centonze G, Daum O, Daumova M, Domagała P, Dziuba I, Geppert CE, Gózdź S, Nasierowska-Guttmejer A, Hałoń A, Hartmann A, Inaguma S, Iżycka-Świeszewska E, Kaczorowski M, Kołos M, Kopczyński J, Michal M, Milione M, Okoń K, Pęksa R, Pyzlak M, Ryś J, Waloszczyk P, Wejman J, Miettinen M. *Am J Surg Pathol.* 2020;44(9):1224-1234.  
<https://pubmed.ncbi.nlm.nih.gov/32804454/>

The authors present a comprehensive clinicopathologic, immunohistochemical, and molecular evaluation of 12 *anaplastic lymphoma kinase (ALK)* fusion–driven tumors (0.15%) identified from a large cohort of 8150 colorectal carcinomas (CRCs) screened with ALK immunohistochemistry. ALK immunoreactivity showed 3 patterns of staining: diffuse (cytoplasmic or membrane), focal, and luminal. No nuclear staining was seen. All 12 CRCs characterized by diffuse ALK staining harbored *ALK* fusion genes, and no *ALK* fusions, rearrangements, and/or mutations were identified in tumors showing focal or exclusively luminal ALK positivity. A RNA based next-generation sequencing assay showed that the *ALK* fusion partner genes included *CAD*, *DIAPH2*, *EML4*, *LOC101929227*, *SLMAP*, *SPTBN1*, and *STRN* in this study. *ALK* fusion carcinomas showed a median age of 72y, a female predominance (F: M=3:1), and a propensity to involve the right colon (11 cases). Seven tumors were stage T3 and 2 were stage T4. The tumors showed moderate (n=6) or poor (n=3) glandular differentiation, solid medullary growth pattern (n=2), and pure mucinous morphology (n=1). DNA mismatch repair–deficient phenotype was identified in 10 cases, with tumor-infiltrating lymphocytes prominent in 9 cases. Three cases showed strong focal programmed death-ligand 1 immunoreactivity and 1 case showed diffuse expression. Local lymph node and distant metastases were seen at presentation in 9 and 2 patients respectively. Four patients died of disease within 3 years, and 7 were alive with follow-up ranging from 1 to 8 years. No mutations in *BRAF*, *RAS*, and in genes encoding components of PI3K-AKT/MTOR pathway were identified. However, 1 tumor had a loss-of-function *PTEN* mutation. Aberration of p53 signaling, *TP53* mutations, and/or nuclear accumulation of p53 protein was seen in 9 cases. The authors conclude that *ALK* fusion colorectal carcinomas are a distinct and rare subtype of colorectal cancers which display some features of mismatch repair–deficient tumors, i.e. female predominance and right colon location and MMR-deficiency identified in 83% of tumors analyzed in this study. In CRC, diffuse cytoplasmic or membranous ALK expression by immunohistochemistry predicts an *ALK* fusion and separation of *ALK* fusion tumors into a new molecular subtype is indicated due to the presence of additional therapeutic options.

## **Molecular and clinicopathological features of colorectal adenocarcinoma with enteroblastic differentiation**

Yamashiro Y, Saito T, Hayashi T, Murakami T, Yanai Y, Tsuyama S, Suehara Y, Takamochi K, Yao T  
Histopathology. 2020;77(3):492-502.  
<https://pubmed.ncbi.nlm.nih.gov/32438490/>

Gastric adenocarcinoma with enteroblastic differentiation is a primitive epithelial neoplasm with clear cytoplasm and expression of one or more of the oncofetal proteins. The lower gastrointestinal counterpart has been referred to as colorectal adenocarcinoma with enteroblastic differentiation and is extremely rare. It is, however, purported to be associated with an aggressive clinical course. In this study, the authors investigate the expression of the oncofetal proteins glypican 3, SALL4, and AFB in a tissue microarray containing 971 colorectal adenocarcinomas. They find that 39 tumors exhibited expression of at least one of the enteroblastic markers (most commonly SALL4) and were subsequently confirmed on histologic sections of these tumors. They combined these 39 cases with 3 previously diagnosed pure colorectal adenocarcinomas with enteroblastic differentiation for subsequent analysis. Colorectal adenocarcinomas with enteroblastic differentiation occurred in a slightly younger population (63.3 versus 67.2 years), more commonly showed lymphatic invasion, and presented with TNM stage 4 disease. This resulted in a 3-year overall survival of only 66%, compared to 85% for colorectal adenocarcinomas lacking enteroblastic differentiation. Next-generation sequencing studies identified frequent *TP53* mutations, which appeared to be enriched in tumors with clear cytoplasm. Of the colorectal adenocarcinomas with enteroblastic differentiation, 9.5% were HER2 positive, slightly higher than the 5% reported in conventional colorectal carcinomas. Conversely, 12.2% of these tumors are MSI-H, which is similar to the frequency of microsatellite instability seen in conventional colorectal carcinomas. The authors conclude that colorectal adenocarcinomas with enteroblastic differentiation can be identified by the expression of one or more of the previously mentioned oncofetal proteins, regardless of the presence of clear cytoplasm, and frequently exhibit an aggressive clinical course. The higher frequency of HER2 expression in these tumors may make targeted therapies an option for patients with these tumors.

## **Unexpected expression of mismatch repair protein is more commonly seen with pathogenic missense than with other mutations in Lynch syndrome**

Chen W, Hampel H, Pearlman R, Jones D, Zhao W, Alsomali M, Knight D, Frankel WL  
Hum Pathol. 2020;103:34-41.  
<https://pubmed.ncbi.nlm.nih.gov/32652087/>

In rare cases of colorectal carcinoma, patients who have a pathogenic mutation in a mismatch repair gene may still show retained expression of the corresponding protein by immunohistochemistry. The authors of this retrospective study wanted to further interrogate

this subset of colorectal carcinoma with “unexpected MMR expression.” A total of 82 patients with colorectal carcinoma and a known MMR deficiency (not methylation) had slides available for review. Intact MMR staining was defined as at least 5% of tumor cells staining with stain intensity at least as strong as internal positive control cells (lymphocytes). Sixteen (20%) of the 82 patients had unexpected MMR expression: 4 patients with Lynch syndrome and a missense mutation, 5 with Lynch syndrome and a truncating mutation, and 7 with double somatic MMR mutations. All four MMR genes were found to be involved in these cases of unexpected MMR expression. Of the 16 cases, only 6 (37%) had “diffuse strong” tumor staining; the remaining had staining weaker than that of the internal control. The authors reiterate the importance of IHC controls, especially now that MMR IHC is generally the tool for universal Lynch syndrome screening.

### **Prognostic significance of mesothelin expression in colorectal cancer disclosed by area-specific four-point tissue microarrays**

Shiraishi T, Shinto E, Nearchou IP, Tsuda H, Kajiwara Y, Einama T, Caie PD, Kishi Y, Ueno H  
Virchows Arch. 2020;477(3):409-420.  
<https://pubmed.ncbi.nlm.nih.gov/32107600/>

Mesothelin expression is often associated with an unfavorable prognosis. This study examined the prognostic significance of mesothelin in different areas of colorectal cancers (submucosal, subserosal, central and rolled edge of each tumor). The authors concluded that mesothelin expression was relatively homogeneous and high expression was associated with an unfavorable prognosis regardless of the tumor area.

### **Endoscopic and clinicopathological characteristics of colorectal T/NK cell lymphoma**

Ishibashi H, Nimura S, Hirai F, Harada N, Iwasaki H, Kawauchi S, Oshiro Y, Matsuyama A, Nakamura S, Takamatsu Y, Yonemasu H, Shimokama T, Takeshita M  
Diagn Pathol. 2020;15(1):128.  
<https://pubmed.ncbi.nlm.nih.gov/33087157/>

This is a retrospective review of 27 T/NK cell lymphoma (TNKCL) patients with colorectal involvement. TNKCL of the GI tract is not common, and often involves the small bowel and rarely the colon. The main types of lymphoma that involve the GI tract are enteropathy-associated T-cell lymphoma (EATL) that is associated with celiac disease in European populations, and monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) that is more common in East Asia. Secondary involvement by other types may occur, such as adult T-cell leukemia/lymphoma (ATLL). All TNKCL cases were retrieved from the Department of Pathology at Fukuoka University (1990-2018), and classified according to the 2017 WHO classification and staged according to the Lugano classification. In this series, ATLL was the most common type (41%) while 33% were MEITL. In addition, they found 1 anaplastic large cell lymphoma, two indolent TLPD, 1 EBV+ CD56+ TNKCL and 3 EBV+ CD56 negative TNKCL. The most frequent

symptoms were chronic diarrhea and abdominal pain, and up to ~ 2/3 of MEITL patients and ATLL showed more than two colorectal lesions involved by lymphoma cells. Six patients were considered as primary colorectal TNKCL while the small intestine was involved in 6 MEITL patients and 4 ATLL patients. As expected, blood involvement was most frequently encountered in ATLL patients (75%) compared to other patients. Endoscopically, a diffuse infiltrating pattern was the most common finding in MEITL and ATLL, and ulceration was more common in non- MEITL patients. Some cases showed aphthous lesions, edematous mucosa or polypoid lesions. Most MEITL and 60% of ATLL showed increased atypical intraepithelial lymphocytes, and almost half of MEITL patients had lymphocytic proctocolitis. The 50% OS of MEITL patients was 9.5 months and for ATLL was 9 months. The authors concluded that awareness of endoscopic and pathologic features including lymphocytic proctocolitis may help in detecting early-stage colorectal TNKCL/ (i.e. prodromal findings of MEITL), and patients with advanced stage often have a worse prognosis.

### **Glomus tumor of the colon: a rare case report and review of literature**

Chen IY, Fazili BG, Liao X  
Int J Surg Pathol. 2020;28(6):691-695  
<https://pubmed.ncbi.nlm.nih.gov/32188316/>

Case report: This is a case report of glomus tumor involving the colon. According to the authors this is the sixth such cases in literature.

### **Gastrointestinal bleeding in patients with coronavirus disease 2019: a matched case-control study**

Martin TA, Wan DW, Hajifathalian K, Tewani S, Shah SL, Mehta A, Kaplan A, Ghosh G, Choi AJ, Krisko TI, Fortune BE, Crawford CV, Sharaiha RZ  
Am J Gastroenterol. 2020 Oct;115(10):1609-1616.  
<https://pubmed.ncbi.nlm.nih.gov/32796176/>

The risk and type of gastrointestinal bleeding (GIB) in patients with COVID-19 is not well characterized. The authors conducted a matched case-control study with 41 cases of GIB (31 upper and 10 lower) in patients with COVID-19 and 81 matched controls of patients with COVID-19 without GIB in order to characterize bleeding etiologies, outcomes, and therapeutic approaches. The authors found no significant differences in initial presenting symptoms or severity of COVID-19 manifestations. The most common GIB etiologies were gastric or duodenal ulcers (80%) and rectal ulcers related to rectal tubes (60%). Anticoagulation and rectal tube usage trended toward being a risk factor for GIB, but did not reach statistical significance. The

authors conclude that conservative management seems to be a reasonable approach in managing these complex cases, and that larger studies are needed.

### **Gastrointestinal malakoplakia: clinicopathologic analysis of 26 cases**

Zhang Y, Byrnes K, Lam-Himlin D, Pittman M, Pezhouh M, Gonzalez RS, Alruwaih Z, Larman T, Miller JA, Matoso A, Oshima K, Epstein JI, Montgomery EA, Voltaggio L  
Am J Surg Pathol. 2020;44(9):1251-1258.  
<https://pubmed.ncbi.nlm.nih.gov/32301754/>

Malakoplakia is an inflammatory process driven by defects in the bactericidal ability of macrophages, especially gram-negative organisms such as *Escherichia coli*. The gastrointestinal (GI) tract is the second most commonly affected site after the genitourinary system. The authors discuss the clinicopathologic manifestations of 26 cases of GI malakoplakia, identified from 6 institutions. A majority of patients were women (16/26; 62%) with a mean patient age of 64 years (range: 24 to 83 years). A majority involved the colorectum (n=23 cases), and then stomach (2 cases) and appendix (1 case). In the current study, malakoplakia was an incidental finding on routine screening in 63% of the cases, usually manifesting as colonic polyps. All cases were characterized by histiocytic-rich infiltrates containing intracytoplasmic concretions with a targetoid appearance known as Michaelis-Gutman (MG) bodies with a size range from 2 to 10µm. The process most frequently involved the mucosa (n=19), with architectural distortion in 13 cases. It appeared that the distortion was due to an inflammatory response in most cases but in a minority, it was related to the malakoplakia itself. Lymphoid aggregates were present in 18 cases, and were prominent or obscuring in 11 (all colon) biopsies. Clinical associations in this study included colonic neoplasia, organ transplantation, colitides, history of malignancy, gastric hyperplastic polyps and chemical gastritis. Michaelis-Gutman bodies were positive for Periodic Acid-Schiff with diastase, Von Kossa, and iron stains. Although 2 cases were positive for *Tropheryma whipplei* antibody, no *T. whipplei* transcripts were detected on real-time polymerase chain reaction. The H&E differential diagnosis included *T. whipplei* infection (Whipple disease), crystal-storing histiocytosis, *Mycobacterium avium* complex infection, and Langerhans cell histiocytosis. All patients with available follow-up were alive and well with no additional instances of malakoplakia in this study, suggesting that it was a benign, incidental finding.

### **Intestinal angiolipofibroma: clinicopathologic characteristics of 11 cases**

Agostini-Vulaj D, Bsirini C, Drage MG, Huber AR  
Int J Surg Pathol. 2020;28 (6):609-615.  
<https://pubmed.ncbi.nlm.nih.gov/32362158/>

This is a report of 11 cases of angiolipofibroma involving the GI tract. A majority were identified on biopsy specimens (8; 73%) with a mean patient age of 49. Most cases occurred in the colon (7; 64%) with the remaining involving the small intestine (2) or ileocecal valve (1). All lesions involved the submucosa with 3 (27%) cases showing extension into the overlying lamina propria. No incidences of recurrence were noted.

### **Clinical and histological features of secondary carcinomas in gastrointestinal tract biopsies**

Rosty C, Pai RK, Graham RP  
Histopathology. 2020;77(4):622-630.  
<https://pubmed.ncbi.nlm.nih.gov/32590886/>

The gastrointestinal tract is an uncommon site for metastatic carcinoma and may be encountered in endoscopic biopsies. Establishing an accurate diagnosis is particularly challenging for poorly differentiated carcinomas that lack defining histologic features, especially when the pathologist is not aware of a previously diagnosed carcinoma of another site, or that diagnosis is remote. In this work, the authors investigate the clinical, endoscopic, and histologic features of metastatic carcinomas to the gastrointestinal tract that were sampled via endoscopic biopsy. Their cohort was assembled across three institutions over an 11-year period and included 197 cases derived from 190 patients. The median age of the patients in their cohort was 67 years and included 109 women (57%) and 81 men (43%). The most common histologic type of metastatic tumor were carcinomas of the breast (38%), followed by kidney (13%), lung (12%), prostate (8%), and ovary (7%). The stomach was the most common site of involvement (34%), followed by colon (27%), rectum (18%), duodenum (13%), esophagus (5%), jejunum (3%), and anus (0.5%). While breast and renal cell cancers can involve any portion of the GI tract, they are most commonly seen in the stomach and large bowel in this cohort. Conversely, prostatic carcinomas and high-grade serous carcinomas most frequently involve the rectum and left colon. The diagnosis of the primary carcinoma was not known to the pathologist in 16% of cases. The endoscopic impression frequently suggested the presence of a neoplastic process, with 54% of cases demonstrating a mucosal mass, a suspicious ulcer in 9%, a stricture in 8%, thickened or nodular mucosa in 9%, or extrinsic compression by a mass lesion in 4%. Thirteen percent of cases with histologically identified metastatic disease either showed non-specific inflammation or were endoscopically normal. Infiltration of the mucosa was common across all tumor types (76%), followed by submucosal infiltration (41%), invasion of lymphatic spaces (14%), and epithelial colonization (8%). Obstructive-type changes, namely lamina propria edema, lymphatic dilation, and crypt/foveolar hyperplasia, were most commonly seen for carcinomas of the prostate (53%). Most cases utilized immunohistochemical stains to assist in rendering a diagnosis. The authors emphasize that a high degree of awareness is necessary in order to diagnosis secondary carcinomas of the small and large bowel, including the absence of a definitive precursor lesion or preneoplastic process or growth patterns centered in the submucosa or deeper layers of the bowel wall.



## **Reappraisal of primary Epstein-Barr virus (EBV)-positive diffuse large B-cell lymphoma of the gastrointestinal tract: comparative analysis among immunosuppressed and nonimmunosuppressed stage I and II-IV patients**

Miyagi S, Ishikawa E, Nakamura M, Shimada K, Yamamura T, Furukawa K, Tanaka T, Mabuchi S, Tsuyuki Y, Kohno K, Sakakibara A, Satou A, Kato S, Fujishiro M, Nakamura S  
Am J Surg Pathol. 2020;44(9):1173-1183.  
<https://pubmed.ncbi.nlm.nih.gov/32349049/>

The authors studied 36 cases of primary Epstein-Barr virus (EBV)-positive diffuse large B-cell lymphomas (DLBCLs) of the gastrointestinal (GI) tract. The median age in this series was 69.5 years (range, 35 to 84 y), and there was a slight female preponderance (16 men and 20 women). The 36 patients were divided into 3 groups on the basis of the available clinical information: 8 immunosuppressed patients, 7 non-immunosuppressed patients with Lugano stage I disease, and 21 non-immunosuppressed patients with Lugano stage II1/II2/III/IV disease. There was a higher incidence of intestinal involvement ( $P=0.001$ ) and perforation ( $n=2$ ) in immunosuppressed patients when compared to advanced stage non-immunosuppressed patients. Among non-immunosuppressed stage I patients, lesions were restricted to the stomach, and none showed multiple lesions or elevated serum lactate dehydrogenase. The overall survival curve plateaued in these cases. Immunosuppressed patients also exhibited intestinal lesions and had advanced stage disease; however, delineation of prognoses was not statistically significant ( $P=0.0581$ ). The authors suggest that non-immunosuppressed stage I cases without bulky masses may be considered EBV mucocutaneous ulcer with local progression. The authors conclude that primary EBV+ GI DLBCL cases could be delineated into 3 groups based on their immune status and clinical stage, and this may serve as a useful guide for diagnostic and therapeutic approaches.

## **Prognostic impact of combined progression index based on peritoneal grading regression score and peritoneal cytology in peritoneal metastasis**

Benzerdjeb N, Durieux E, Tantot J, Isaac S, Fontaine J, Harou O, Glehen O, Kepenekian V, Alyami M, Villeneuve L, Laplace N, Traverse-Glehen A, Shisheboran-Devouassoux M, Bakrin N  
Histopathology. 2020;77(4):548-559.  
<https://pubmed.ncbi.nlm.nih.gov/32060943/>

Pressurized intraperitoneal chemotherapy (PIPAC) has been proposed as a modality to treat patients with peritoneal metastasis who are not eligible for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). The assessment of therapeutic response to PIPAC is challenging, however. Currently, therapeutic response is assessed with either peritoneal cytology or the 4-tiered peritoneal grading regression score (PRGS). However, positive peritoneal cytology or an increase in the PRGS between the first and third cycles of PIPAC (iPRGS) fail to identify non-responders to PIPAC with regards to overall survival. It is suspected, however, that this lack of significance is at least partially attributable to a lack of

statistical power in prior studies. In the current work, the authors perform the largest study to date in order to assess the prognostic impact of iPRGS and peritoneal cytology alone, or combined as the novel combined progression index (CPI), on progression free and overall survival. A positive CPI was defined as an increase in PRGS between the first and third cycles of PIPAC and/or positive peritoneal cytology at the time of the third cycle of PIPAC. Their study cohort included 112 patients (median age 58.9 years) with a median follow-up of 39.1 months. Gastric cancer was the most common peritoneal disease in their cohort, accounting for 49.1% of cases, while colorectal (13.4%), ovarian serous (12.5%), appendiceal (7.1%), and small bowel adenocarcinomas (2.7%) were also represented, along with smaller numbers of pancreatobiliary carcinomas and mesotheliomas. When CPI was assessed using the highest PRGS of the biopsy samples (rather than the mean PRGS from all biopsy samples), it was found to be associated with a worse overall and progression free survival in the setting of peritoneal metastasis. The authors conclude that CPI should be implemented in the therapeutic decision making process during PIPAC.

### **Gastrointestinal tissue-based molecular biomarkers: a practical categorization based on the 2019 World Health Organization classification of epithelial digestive tumours**

Quezada-Marín JI, Lam AK, Ochiai A, Odze RD, Washington KM, Fukayama M, Rugge M, Klimstra DS, Nagtegaal ID, Tan PH, Arends MJ, Goldblum JR, Cree IA, Salto-Tellez M  
Histopathology. 2020;77(3):340-350.  
<https://pubmed.ncbi.nlm.nih.gov/32320495/>

In this concise review, the authors extract information regarding molecular biomarkers for epithelial neoplasms of the gastrointestinal tract from the 5<sup>th</sup> edition of the World Health Organization classification of tumours, Digestive system tumours. Preinvasive and invasive neoplasms of the esophagus, stomach, small intestine/ampulla, appendix, colorectum, and anal canal are discussed with regard to diagnostic, predictive, and prognostic biomarkers, including those just entering routine pathologic analysis (such as PD-L1 and MSI in esophageal and gastric adenocarcinomas), as well those still under preclinical investigation. Several easy to reference tables divided by site are provided.

### **Assessment of a highly curated somatic oncology database to aid in the interpretation of clinically important variants in next-generation sequencing results**

Yaung SJ, Krishna S, Xi L, Ju C, Palma JF, Schmid M  
J Mol Diagn. 2020;22(11):1356-1366  
<https://pubmed.ncbi.nlm.nih.gov/32961319/>

Although this manuscript did not specifically work with GI tumors, the results and discussion are likely applicable. Next-generation sequencing is frequently requested by treating oncologists to aid in selecting treatment regimens and in assessing eligibility for targeted

therapies. Although there are many databases available to aid in variant interpretation, the content of these databases only partly overlap; as such, collating information from multiple databases is often needed for comprehensive evaluation. The authors evaluated a tertiary software (NAVIFY) that has a curated database of clinically important variants. The results of the software's interpretation was compared with previous manual variant curation results obtained on 37 lung cancer cases. All cases have documented treatment regimens (10 chemotherapy, 5 EGFR TKI, 22 ALK TKI), and were previously sequenced retrospectively. Accuracy of interpretation, validity of content with updates, and agreement with public databases was evaluated. The authors found that NAVIFY correctly identified targeted therapy options in cases with targetable mutations. Resistance mutations to crizotinib were also detected in patients with ALK-rearranged lung cancer. Annotations for all mutations were also correct using NAVIFY, compared to OncoKB and COSMIC. There was substantial agreement between NAVIFY and OncoKB for classifying actionable mutations. Finally, suggested targeted therapies were also accurate across different geographic regions and remained up to date.

**Journals Reviewed September-October  
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  
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Clinical Gastroenterology Hepatology  
Diagnostic Pathology  
Diseases of the Colon and Rectum

Gastrointestinal Endoscopy  
Gut  
Histopathology  
Human Pathology  
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Journal of Pathology  
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