GIPS Journal Watch
March & April 2021

Utility of routine esophageal biopsies in patients with refractory reflux symptoms

Nijhuis RABO, Curvers WL, van der Ende M, Herregods TVK, Schuitenmaker JM, Smout AJPM, Bredenoord AJ
Am J Gastroenterol. 2021;116(4):816–820.
https://pubmed.ncbi.nlm.nih.gov/33982953/

Current Rome criteria recommend esophageal biopsies for all patients with refractory reflux symptoms to rule out eosinophilic esophagitis (EoE). The authors assessed the yield of routine esophageal biopsies in these patients to determine the clinical factors (dysphagia, vomiting, symptoms of food impaction, history of endoscopic bolus removal, atopy, endoscopic EoE features, Schatzki ring) associated with EoE diagnosis. In this prospective cross-sectional study, consecutive patients (n=301) with refractory reflux symptoms underwent upper endoscopy and biopsy per standardized protocol. Fourteen patients met the clinicopathological diagnostic definition of EoE. All 14 patients had dysphagia (among n=153 with dysphagia). Endoscopic EoE features were present in 9 (64.3%) of 14 patients. Dysphagia was 100% sensitive in identifying EoE, with a diagnostic yield of 9.2%. The authors argue that routine esophageal biopsy in all patients with refractory reflux symptoms is of low yield, and dysphagia should be used to screen patients requiring biopsy.

Global prevalence of Barrett's oesophagus and oesophageal cancer in individuals with gastro-oesophageal reflux: a systematic review and meta-analysis

Eusebi LH, Cirota GG, Zagari RM, Ford AC
Gut. 2021;70(3):456-463.
https://pubmed.ncbi.nlm.nih.gov/32732370/

This is a systematic review and meta-analysis of data to estimate global prevalence of Barrett’s esophagus (BE) in individuals with reflux. They evaluated 4963 citations from MEDLINE, Embase and Embase Classic to identify cross-sectional surveys that reported prevalence of BE or esophageal adenocarcinoma in adults with gastroesophageal reflux. Prevalence of BE among individuals with gastroesophageal reflux varied according to different geographical regions ranging from 3% to 14% for histologically confirmed BE. Prevalence of BE was significantly higher in men, both for endoscopically suspected and histologically confirmed BE. Dysplasia was present in 13.9% (95% CI 8.9% to 19.8%) of cases of histologically confirmed BE, 80.7% of which was low-grade. In conclusion, the prevalence of Barrett's esophagus among individuals with gastroesophageal reflux varied strikingly among countries and it was significantly higher in men.

Perineural invasion predicts for locoregional failure in patients with oesophageal adenocarcinoma treated with neoadjuvant chemoradiotherapy

Patel AK, Pan X, Vila DM, Frankel WL, Chen W, Perry KA, Merritt RE, D'Souza DM, Wuthrick EJ, Williams TM
J Clin Pathol. 2021;74(4):228-233.
https://pubmed.ncbi.nlm.nih.gov/32317290/

This study evaluates the prognostic significance of perineural invasion (PNI) in esophageal adenocarcinoma (EAC) patients who were treated with neoadjuvant chemo- radiotherapy (nCRT) and surgery. PNI is an important pathological factor in many malignancies, but there is still conflicting data about the significance of PNI in some instances. In addition, few papers have studied its significance in nCRT patients and the impact on locoregional recurrence. This study is retrospective, and 73 patients from the University of Ohio were included (1996-2015). PNI is defined as the presence of neoplastic cells in the perineural space and was identified using H&E staining. A total of 29 patients (39.7%) had PNI at resection. In comparison to PNI-negative patients, these patients had statistically significant higher stage (T3-T4), positive lymph nodes (pN), tumor size, lymphovascular invasion, positive circumferential margin and tumor regression grade of 3. PNI + patients had more recurrence (locoregional or distant) and worse disease free survival, but there was no statistical difference in median survival among the two groups. The authors concluded that the presence of PNI is a significant prognostic factor in nCRT EA patients with locally advanced EAC, including higher locoregional recurrence.

Salvage endoscopic resection after definitive chemoradiotherapy for esophageal cancer: a Western experience

Al-Kaabi A, Schoon EJ, Deprez PH, Seewald S, Growth S, Giovannini M, Braden B, Berr F, Lemmers A, Hoare J, Bhandari P, van der Post RS, Verhoeven RHA, Siersema PD
Gastrointest Endosc. 2021;93(4):888-898.
https://pubmed.ncbi.nlm.nih.gov/32763242/

In Japan, salvage endoscopic resection (ER) is offered for superficial residual or recurrent esophageal squamous cell carcinoma (ESCC) following definitive chemoradiotherapy (CRT), with promising outcomes. This is first international collaborative initiative to investigate salvage ER in Western population. In this case series, 80 endoscopists from Europe and the United States shared their data on salvage ER for local failure following definitive CRT for esophageal/gastroesophageal junction adenocarcinoma or squamous cell carcinoma without distant metastasis. The overall survival was comparable with that reported in Japan, and no severe adverse events were reported. In carefully selected Western patient populations, salvage ER seems to be effective for the management of local residual or recurrent esophageal cancer following definitive CRT with a favorable safety profile.

Tumor budding assessed according to the criteria of the International Tumor Budding Consensus Conference determines prognosis in resected esophageal adenocarcinoma

Lohneis P, Hieggelke L, Gebauer F, Ball M, Bruns C, Büttner R, Löser H, Quaas A
Virchows Arch. 2021;478(3):393-400.
https://pubmed.ncbi.nlm.nih.gov/32761393/

This is a retrospective study that looked at tumor budding in 104 cases of resected esophageal adenocarcinoma. They used the published consensus criteria (ITBCC criteria) for colorectal tumor budding and looked at hematoxylin and eosin (H&E) and cytokeratin (AE1/AE3) stained slides. They analyzed the mean count of tumor buds in one high power field and assigned to budding groups Bd1-3. They found that tumor budding was significantly associated with a worse overall survival and that an increased number of tumor buds was significantly associated with reduced overall survival. Thus they concluded that tumor budding is an independent prognostic factor in resected esophageal adenocarcinoma.

SMARCA4/SMARCA2-deficient carcinoma of the esophagus and gastroesophageal junction

Horton RK, Ahadi M, Gill AJ, Said S, Chen ZE, Bakhshwin A, Nichols M, Goldblum JR, Graham RP
Am J Surg Pathol. 2021;45(3):414-420.
https://pubmed.ncbi.nlm.nih.gov/33027072/

The authors cumulatively collected 14 cases of SMARCA4/SMARCA2-deficient undifferentiated carcinoma of the gastroesophageal junction and esophagus. All cases showed sheets of dyscohesive tumor cells exhibiting a rhabdoid appearance with large nuclei, prominent macronucleoli, and brisk mitotic activity. Adjacent intestinal metaplasia and high-grade dysplasia was seen in a subset of cases. Immunohistochemically, tumors showed variable expression of keratins along with loss of expression of SMARCA4 in 12 cases and SMARCA2 in 7 cases. Immunostain for p53 showed a mutant pattern in 4 of 4 cases of invasive carcinoma and associated dysplasia, when present. Limited clinical follow-up was available, but 3 patients died of disease within less than a year of diagnosis, indicating that these tumors likely have a poor prognosis. They also suggest that these tumors may be part of a group of neoplasms which may be responsive to novel immune checkpoint inhibition.

Survival times of patients with Menetrier's disease and risk of gastric cancer

Almazar AE, Penfiel JD, Saito YA, Talley NJ
Clin Gastroenterol Hepatol. 2021;19(4):707-712.
https://pubmed.ncbi.nlm.nih.gov/32184187/

This is a case-control study of Menetrier's disease, assessing the outcomes and characteristics of these patients. Menetrier's disease is a rare acquired disorder that often presents with

severe protein-losing enteropathy. As most literature on this entity is limited to case reports, the current understanding of etiology and epidemiology is limited. The authors assessed a cohort of 76 Menetrier's disease patients, and compared clinical, histologic, and survival characteristics with non-Menetrier's disease patients (matched for sex, age, and geographic region) who had undergone gastric biopsy for dyspepsia. Menetrier's disease is more associated with symptoms of vomiting, abdominal pain, postprandial fullness, or weight loss of at least 10 lbs, as well as smoking; alcohol use, *H. pylori* infection, and inflammatory bowel disease were not significantly associated. Gastric cancer was more common in the setting of Menetrier's disease (8.9%, vs 3.7% controls over 10 years after diagnosis), with a median time to development of gastric cancer of 3.8 months. Menetrier's disease patients had decreased survival (72.7% and 65 % survival at 5 and 10 years, vs 100% of controls). The overall findings suggest that Menetrier's disease is associated with increased risk of gastric cancer and overall increased mortality.

Incidence of metachronous cancer after endoscopic submucosal dissection: a comparison between undifferentiated-type and differentiated-type early gastric cancer

Ishioka M, Yoshio T, Miyamoto Y, Namikawa K, Tokai Y, Yoshimizu S, Horiuchi Y, Ishiyama A, Hirasawa T, Tsuchida T, Fujisaki J
Gastrointest Endosc. 2021;93 (3):557-564.
https://pubmed.ncbi.nlm.nih.gov/32621817/

Endoscopic submucosal dissection (ESD) is indicated for a subset of differentiated type (D-type; papillary and well to moderately differentiated tubular adenocarcinoma) mucosal cancers (early gastric cancer; EGC). Expanded indication includes a subset of undifferentiated type (UD-type; poorly differentiated adenocarcinoma or signet ring cell carcinoma) mucosal cancer. Data regarding metachronous (cancer detected >1 year after the index ESD) gastric cancer occurring after ESD for UD-type are limited. In this retrospective cohort study, 175 UD-type gastric cancer patients who underwent curative ESD and have been followed over 3 years were analyzed and compared with controls from D-type EGC (n=350). Compared to D-group, the cumulative incidence of metachronous gastric cancer in the UD-group was significantly lower (approximately 0.9% per year), and it occurred only in those with *Helicobacter* infection (Hp+). However, a higher percentage (57.1%; 4/7) of metachronous cancers from UD-group could not be cured by ESD and additional gastrectomy was required with their deeper invasion and ulcerative findings, compared to those from D-group. The authors conclude that routine surveillance should be conducted more carefully following ESD for UD-type EGC, especially in Hp+ patients.

Clinical outcomes of early gastric cardiac cancer treated with endoscopic submucosal dissection in patients with different indications

Fan T, Sun Q, Cao S, Fan X, Huang Q, Zhang S, Lv Y, Zhang X, Ling T, Wang L, Zou X, Xu G

BMC Gastroenterol. 2021;21(1):119.
https://pubmed.ncbi.nlm.nih.gov/33711944/

The authors evaluate a series of 495 Chinese patients undergoing endoscopic submucosal dissection of cancers in the gastric cardia under 'absolute', 'expanded', and 'beyond expanded' indications, using the Japanese Gastric Cancer Association classification. Namely, absolute indications were defined as differentiated intramucosal cancers less than or equal to 2 cm in diameter without ulceration, while expanded indications include cancers that were 1) intramucosal, nonulcerated and differentiated, of any size, 2) intramucosal, ulcerated, differentiated EGCs <30 mm, 3) differentiated EGCs <30 mm with superficial submucosal invasion (SM1; <500 microns below the muscularis mucosae), and 4) undifferentiated intramucosal EGCs without ulceration less than or equal to 2 cm. Prior cohort studies from Asia have demonstrated that ESD for early gastric adenocarcinomas that meet expanded criteria is associated with high curative rates (comparable with gastrectomy). The goal of this study was to evaluate the short and long term outcomes of all early gastric cancer patients. The authors found that patients in their 'beyond extended indication (BEI)' group (which included combinations of size >30 mm, deep submucosal invasion, and presence of lymphovascular invasion, among others) were more likely to experience early delayed bleeding as a short term complication, and to undergo a subsequent gastrectomy. In addition, BEI patients had a shorter disease-specific survival. The authors conclude that, while endoscopic resection of EGCs achieves favorable outcomes for patients under the current absolute and expanded indications, patients who underwent endoscopic resection beyond these indications often experience poorer outcomes, and need to be followed carefully.

Association of tumor-infiltrating T lymphocytes with intestinal-type gastric cancer molecular subtypes and outcome

Mansuri N, Birkman EM, Heuser VD, Lintunen M, Ålgars A, Sundström J, Ristamäki R, Lehtinen L, Carpén O
Virchows Arch. 2021;478(4):707-717.
https://pubmed.ncbi.nlm.nih.gov/32954467/

This study investigated the subtypes of T lymphocytic infiltration in intestinal-type gastric cancer. They looked at the presence of CD3, CD8, and FOXP3 T lymphocytes in a cohort of 190 intestinal gastric and gastroesophageal adenocarcinomas with four distinct molecular subtypes: Epstein-Barr virus-positive (EBV+), mismatch-repair-deficient (MMR-D), aberrant TP53, and the "other" subtype. Although, there was a large variation in the amount of infiltrating T lymphocytes, EBV+ cancers showed increased lymphocyte infiltration and high CD8+/FOXP3+ ratio. While the TP53 aberrant subtype did not differ in the absolute amount of T lymphocytes, the ratio of CD8+/FOXP3+ and CD3+/FOXP3+ cells was highest in this subtype, possibly reflecting immunosuppression associated with genomic instability. They also found that increased CD3+ and CD8+ T lymphocyte infiltrates were associated with better survival, and remained as independent prognostic factors in a multivariate analysis.

Neuroendocrine carcinoma and mixed neuroendocrine–non-neuroendocrine neoplasm of the stomach: a clinicopathological and exome sequencing study

Ishida S, Akita M, Fujikura K, Komatsu M, Sawada R, Matsumoto H, Saegusa J, Itoh T, Kakeji Y, Zen Y
Hum Pathol. 2021;110:1-10.
https://pubmed.ncbi.nlm.nih.gov/33359239/

The purpose of this cross-sectional study was to analyze the gene mutation profiles of gastric neuroendocrine carcinomas (NEC) and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN). Recent molecular analysis in neuroendocrine tumors (NETs) of lung/pancreas has showed that NET-associated genes (*MEN1*, *ATRX*, *DAXX*) are not present in NEC, suggesting that NET and NEC are biologically distinct, but the driver mutations of NEC appear to be specific to individual organs. In an effort to assess the molecular pathology of NEC and MiNEN in the stomach, the authors performed clinicopathologic correlation (with immunohistochemistry and whole exome sequencing) on 7 gastric NEC and 6 gastric MiNEN. NEC cases consisted of 2 small cell NEC and 4 large cell NEC, where all MiNEN cases showed large cell NEC with tubular adenocarcinoma (with no components of well-differentiated NET). Tumors were all positive for neuroendocrine markers by IHC (2 for chromogranin, 5 for synaptophysin, and 6 for both), and the majority of cases show microscopic invasion, deep invasion (at least muscularis propria), and lymph node metastasis. Abnormal p53 by IHC was present in 9 cases, and only one case of MiNEN was found to be MSI-H. Whole exome sequencing on the NEC components identified recurrent *TP53* mutations in 8 cases (62%), more commonly in MiNEN than in NEC (100% vs 29%), and one case of large cell NEC had a frameshift mutation with loss of heterozygosity in *Rb1*. Two MiNEN cases showed frameshift *APC* mutations, and the MSI-H MiNEN showed mutations in NET-related genes (*MEN1* and *ATRX1*). Separate sequencing of the adenocarcinoma component of MiNEN found the same *TP53* mutations (all cases) and *APC* mutations (when present) in both the NEC and adenocarcinoma components. The overall findings suggest that *TP53* is the most frequently mutated gene in both gastric NEC and MiNEN, and that gene mutations observed in well-differentiated NET were uncommon but not exclusive.

Next-generation sequencing demonstrates the rarity of short kinase variants specific to quadruple wild-type gastrointestinal stromal tumours

Wong N, Gigerv OT, Hoopen RT, Casey RT, Russell K, Faulkner C
J Clin Pathol . 2021;74(3):194-197.
https://pubmed.ncbi.nlm.nih.gov/32646927/

This study aims to characterize the short kinase variants in quadruple wild-type gastrointestinal stromal tumours (qWT GIST). Wild type GIST cases account for 10% of GISTs and they often

show a poor response to TKI therapy. Molecularly defined, qWT GIST refers to WT GIST cases (*KIT*-/*PDGFRA*-) that do not show succinate dehydrogenase (SDH) deficiency, *BRAF* or *KRAS* mutations, nor are they associated with neurofibromatosis 1 (NF1). Previous studies have demonstrated the presence of short kinase variants such as *FGF1R* or *NTRK3* alterations in a small subset of qWT GISTs. In this study, the authors included 11 wild-type GISTs (4 SDH deficient, 2 NF1-related, 2 *BRAF* mutated and 3 qWT GISTs), 3 *KIT* mutated GISTs and 2 *PDGFRA* mutated GISTs from Bristol Royal Infirmary. DNA sequencing was performed to cover 672 kinase genes, and 26 gene variants were detected in the three qWT. No short variants of *FGFR1* or *NTRK3* kinase were found among these tumors. Among these 26 variants detected, six in silico-classified deleterious variants (*CSNK2A1*, *MERTK*, *RHEB*, *ROCK1*, *PIKFYVE* and *TRRAP*) were found after exclusion of the likely common population variants. None of these six variants were present in two or more qWT GISTs, and they were not found among anther tested cohort of four qWT GISTs. A few, in silico-classified deleterious variants were found among the other wild-type GIST subgroups (*COL1A1*, *CHEK2*, *MTOR*, *ERBB4*, *MAPKAPK5*, *MLH1*). The authors concluded that qWT GISTs are possibly a heterogonous group in which there are no universal short kinase variants that can be detected.

Prognostic and predictive values of the KIT11 mutated grading system in patients with gastrointestinal stromal tumors: a retrospective study

Song L, Ge H, Shi X, Shen W
Hum Pathol. 2021;110:31-42.
https://pubmed.ncbi.nlm.nih.gov/33476644/

This is a retrospective study analyzing the correlation between types of *KIT* exon 11 mutations in gastrointestinal stromal tumors (GISTs) and response to adjuvant therapy with imatinib. It has well documented that approximately 75% of GISTS have an oncogenic mutation in *KIT* (followed by 10% with *PDGFRA* mutations) and that many patients respond to targeted adjuvant therapy. There are several *KIT* mutations that have described, most commonly *KIT* exon 11 (87% of *KIT* mutations) and *KIT* exon 9 (11% of *KIT* mutations). The prognostic prediction between type of mutation and response to imatinib is not currently well understood. The authors collected a cohort of 106 patients with GISTs that were treated with imatinib and classified them as low/intermediate/high risk based on the modified NIH histologic criteria from 2008 (which includes tumor size, mitosis count, tumor rupture, and site). The tumors were sequenced for *KIT* (exons 9, 11, 13, and 17) and *PDGFRA* (exons 12 and 18). Based on the mutational analysis of the high risk tumors classified by NIH criteria, the authors devised a mutational grading system for *KIT* exon 11 based on mutational site (codon involved) and mutation type (insertion, duplication, deletion). The 5 year disease free survival (DFS) was significantly worse in grade 3 KIT11-mutated GISTs (42%) compared to grade 1 (93%) and grade 2 (71%), but there was no difference in overall survival. Multivariable analysis suggests that KIT11 mutation type is an independent risk factor for DFS. The overall findings suggest that type of KIT11 mutation can be used to stratify survival in GIST patients treated with imatinib, in that KIT11 mutations in codons 561-570, 550-555, or 555-561 may be more resistant to imatinib.

Duodenal intraepithelial lymphocytosis in *Helicobacter pylori* gastritis: comparison before and after treatment

Bosch DE, Liu YJ, Truong CD, Lloyd KA, Swanson PE, Upton MP, Yeh MM
Virchows Arch. 2021;478(4):805-809.
https://pubmed.ncbi.nlm.nih.gov/33025296/

The aim of this study was to assess the performance of duodenal intraepithelial lymphocyte counting for diagnosis of *Helicobacter pylori* (*H. pylori*) gastritis, and effects of eradication therapy on intraepithelial lymphocytosis. They looked at duodenal and gastric biopsies from subjects with *H. pylori* gastritis. They found higher duodenal intraepithelial lymphocyte counts in cases with *H. pylori* gastritis (26 ± 5 per villus) than subjects negative for *H. pylori* (12 ± 2 per villus). They also found that duodenal lymphocytosis decreases significantly after successful eradication therapy but remains elevated when treatment fails. In conclusion, they propose that intraepithelial lymphocyte counts of > 15 per villus or > 10 per 100 enterocytes were predictive of infection.

Proton pump inhibitors reduce duodenal eosinophilia, mast cells, and permeability in patients with functional dyspepsia

Wauters L, Ceulemans M, Frings D, Lambaerts M, Accarie A, Toth J, Mols R, Augustijns P, De Hertogh G, Van Oudenhove L, Tack J, Vanuytsel T
Gastroenterology. 2021;160(5):1521-1531.
https://pubmed.ncbi.nlm.nih.gov/33346007/

The effect and mechanism of proton pump inhibitors (PPIs) on duodenal alterations in the pathophysiology of functional dyspepsia (FD) is unclear. The authors performed a prospective interventional study assessing symptoms (Patient Assessment of Gastrointestinal Symptom Severity Index), duodenal alterations, and systemic factors in patients with FD ("FD-starters") and healthy volunteers (HVs) before and after PPI therapy. Duodenal eosinophils, mast cells, and permeability were quantified. Procedures were also performed on patients with PPI-refractory FD ("FD-stoppers") before and 8 weeks after PPI withdrawal. Thirty HV, 27 FD-starters, and 18 FD-stoppers completed the study. PPIs not only reduced symptoms, but also duodenal eosinophils, mast cells, and permeability in the FD-starters. In contrast, immune cells and permeability increased in HVs on PPIs. Dyspeptic symptoms correlated with eosinophils before and during PPI therapy. The authors conclude that this study provides the first prospective evidence for eosinophil reducing effects as a therapeutic mechanism of PPIs in FD.

Classification of intestinal T-cell receptor repertoires using machine learning methods can identify patients with coeliac disease regardless of dietary gluten status

Foers AD, Saad Shoukat M, Welsh OE, Donovan K, Petry R, Evans SC, FitzPatrick MEB, Collins N, Klenerman P, Fowler A, Soilleux EJ
J Pathol. 2021;253(3):279-291.
https://pubmed.ncbi.nlm.nih.gov/33225446/

The purpose of this sequencing study was to use machine learning to analyze the T cell receptor repertoire in celiac disease biopsies for definitive classification of celiac disease, even in indeterminate biopsies or biopsies from patients on gluten free diets. Celiac disease is known to have CD4+ T cell-mediated gluten recognition and CD8+/γδ T cell mediated inflammation, with increased numbers of γδ T cells that persist through treatment. The authors carried out genomic sequencing for the T-cell receptor (TCR)-γ and TCR-δ, and used a machine learning-based analysis to classify biopsies. The algorithm was able to correctly classify 100% of cases by TCR- γ and 95% of cases by TCR-δ, including classification of biopsies from patients on strict gluten-free diets. This finding confirms that the known changes in duodenal TCR- γδ repertoire may be permanent in celiac disease, even when adequately treated and in the absence of histologic abnormalities. As such, analysis of TCR repertoire may be a useful adjunct in indeterminate cases.

Parechovirus infection in early childhood and association with subsequent celiac disease

Tapia G, Chuda K, Kahrs CR, Stene LC, Kramna L, Marild K, Rasmussen T, Rønningen KS, Cinek O, Størdal K
Am J Gastroenterol. 2021;116(4):788–795.
https://pubmed.ncbi.nlm.nih.gov/33177347/

Carrying HLA DR4-DQ8/DR3-DQ2 genotype confers an increased risk of celiac disease (CD), however environmental triggers of CD are unknown. Viral infection may play a role in CD development. In this case-control study, over 45,000 newborns in Norway were screened for HLA DQ2/DQ8 genotype and carriers of the genotype (1.9%) were followed with repeated questionnaires, plasma and stool samples. CD group (n=25) was identified by questionnaire and screening for transglutaminase 2 (TG2) antibodies in the most recent blood samples. Two controls per case were matched for follow-up duration, date of birth and county of residence. Available stool samples were tested with real-time PCR for parechovirus and anellovirus; two candidate viruses identified using metagenomic virome sequencing. Parechovirus, but not anellovirus, was more frequent (found in 11.1% of stool samples) in case children before the development of TG2 antibodies (adjusted odds ratio 1.67, 95% CI 1.14-2.45, p=0.01). The authors conclude that early-life parechovirus infection may be one of the environmental triggers of CD in genetically susceptible children.

The prevalence of small-bowel polyps on video capsule endoscopy in patients with sporadic duodenal or ampullary adenomas

Awadie H, Klein A, Tate D, Jideh B, Bar-Yishai I, Goodrick K, Ahlenstiel G, Bourke MJ
Gastrointest Endosc. 2021;93 (3):630-636.
https://pubmed.ncbi.nlm.nih.gov/32717365/

Patients with sporadic duodenal adenoma (DA)s are at significantly increased risk of developing colonic polyps. The authors hypothesized that those with DA will also have a higher prevalence of additional small bowel polyps compared to those without DA. In this single-center prospective study, 95 DA patients without syndromic conditions underwent video capsule endoscopy (VCE) for evaluation of the small bowel. A total of 101 age-matched patients without DA who underwent VCE for occult gastrointestinal bleeding or iron deficiency anemia served as controls. Colonoscopy reports within the past 5 years was reviewed for all patients. No small bowel polyp was found in either group. Colonic polyps of any histology and advanced adenomas (high-grade dysplasia, >10 mm, villous histology) were more frequent in the DA group compared with the control group. The authors conclude that patients with DAs do not need VCE to screen for small bowel polyps, however colonoscopy is mandated in this group.

Driver mutations occur frequently in metastases of well-differentiated small intestine neuroendocrine tumours

Samsom KG, Levy S, van Veenendaal LM, Roepman P, Kodach LL, Steeghs N, Valk GD, Wouter Dercksen M, Kuhlmann KFD, Verbeek WHM, Meijer GA, Tesselaar MET, van den Berg JG
Histopathology. 2021;78(4):556-566.
https://pubmed.ncbi.nlm.nih.gov/32931025/

Well-differentiated neuroendocrine tumors (NETs) are clinically and histologically distinct from neuroendocrine carcinomas and harbor relatively few genetic alterations. In this work, the authors investigate the presence of driver mutations in metastatic small intestinal NETs and assess the clinical significance of these alterations. Whole genome sequencing was performed on 35 metastatic small intestine NETs and identified 23 driver mutations in 17 discrete patients (49%). 74% of these mutations occurred in tumor suppressor genes including *TP53*, *RB1*, *ATM*, *CDKN1B*, and *SMAD2*, and 22% were in protooncogenes like *KRAS*, *NRAS*, and *CTNNB1*. None of the metastatic small intestine NETs were microsatellite unstable and all showed a low tumor mutational burden. 63% of tumors showed allelic loss of chromosome 18. Clinically validated next-generation sequencing interrogating hotspots in 58 cancer-associated genes was performed on 8 patients. Driver mutations were identified in 4 (50%) of these tumors and again included alterations in *TP53* and *CTNNB1*. There was a significant association with the number of variants detected and the Ki67 proliferative index, but not with disease specific survival. The authors conclude from this work that approximately 50% of metastatic small intestinal NETs exhibit variants in known cancer driver genes. The presence of these clinically significant variants make these patients potentially eligible for targeted therapies such as CDK4/6 inhibitors, PARP inhibitors, and RAS/REF/MEK/ERK inhibitors.

Molecular and clinicopathological features of appendiceal mucinous neoplasms

Yanai Y, Saito T, Hayashi T, Akazawa Y, Yatagai N, Tsuyama S, Tomita S, Hirai S, Ogura K, Matsumoto T, Wada R, Yao T
Virchows Arch. 2021;478(3):413-426.
https://pubmed.ncbi.nlm.nih.gov/32821969/

This is a molecular study on appendiceal mucinous tumors. They looked at 51 lesions (LAMN: 34, HAMN: 8, mucinous adenocarcinoma [MAC]: 9) and analyzed a subset of the tumors by next-generation sequencing (11 pure LAMN, 4 HAMN, and 3 MAC cases). They found that *KRAS* and *GNAS* are the most frequently mutated genes. They did Sanger sequencing to detect *KRAS*, *GNAS*, and *TP53* mutations in the remaining 31 cases and *RNF43* mutations in all cases. *KRAS*/*GNAS* and *TP53* mutations occurred exclusively in pure LAMNs whereas *RNF43* mutations almost exclusively occurred with *KRAS*/*GNAS* mutations. In MAC and HAMN, *KRAS*/*GNAS* mutation status was nearly preserved between lower-grade areas. *RNF43* mutations were detected in both components of MAC with lower-grade areas. *RNF43* mutations were detected in only one of the eight HAMN patients, which was the sole case without pseudomyxoma peritonei (PMP). None of the four MAC patients with *RNF43* mutations showed PMP. They suggest that *RNF43* mutations occur at a later stage of MAC development and do not associate with PMP. Furthermore, they propose that a gradual transition from LAMN to MAC via HAMN could be considered.

An international multicenter real-life prospective study of electronic chromoendoscopy score PICaSSO in ulcerative colitis

Iacucci M, Smith SCL, Bazarova A, Shivaji UN, Bhandari P, Cannatelli R, Daperno M, Ferraz J, Goetz M, Gui X, Hayee B, De Hertogh G, Lazarev M, Li J, Nardone OM, Parra-Blanco A, Pastorelli L, Panaccione R, Occhipinti V, Rath T, Tontini GE, Vieth M, Villanacci V, Zardo D, Bisschops R, Kiesslich R, Ghosh S
Gastroenterology. 2021;160(5):1558-1569.
https://pubmed.ncbi.nlm.nih.gov/33347880/

Endoscopic and histological remission are important targets to achieve in patients with ulcerative colitis (UC). In this prospective multicentric study, the authors used virtual chromoendoscopy techniques for optical assessment of colonic mucosa and reported the diagnostic and prognostic performance of their PICaSSO (Paddington International virtual Chromoendoscopy scOre). A total of 11 endoscopists performed tandem white light and virtual chromoendoscopy with PICaSSO in 302 patients with UC. Subsequently, they performed targeted biopsies from the most inflamed regions and blinded readers scored the inflammation using the Nancy Index and Robarts Histopathology Index. The PICaSSO scores were more strongly correlated with histologic activity as compared with the Mayo endoscopy score (MES) and UC Endoscopic Index of Severity (UCEIS). The PICaSSO score was also better that the MES

and UCEIS at predicting histologic remission at 6 and 12 months, similar to histology. The authors conclude that PICaSSo can be a useful endoscopic tool in the therapeutic management of UC.

Pyloric gland metaplasia: Potential histologic predictor of severe pouch disease including Crohn's disease of the pouch in ulcerative colitis

Li H, Arslan ME, Lee EC, Qualia CM, Mikula MW, Fu Z, Petchers A, Arker SH, M Kmeid, Boguniewicz A, Lee H
Pathol Res Pract. 2021; 220:153389.
https://pubmed.ncbi.nlm.nih.gov/33640710/

Approximately 5-25% of ulcerative colitis (UC) patients undergoing ileal pouch-anal anastomosis (IPAA) develop Crohn's disease (CD)-like conditions of the pouch (CDP), clinically. Histologic predictors of CDP and its association with family history of inflammatory bowel disease (IBD) and smoking history is unknown. 114 UC patients who underwent IPAA with at least 20 months of follow-up were identified and charts were reviewed to identify patients (n=26) that developed clinical CDP during the follow-up period. 26 UC patients with similar severity of pouchitis with CDP group determined by PDAI (Pouch Disease Activity Index) and 34 random UC patients regardless of pouchitis served as matched and random UC controls, respectively. Proctocolectomies, ileostomies, and post-IPAA specimens (pouch, pre-pouch ileum and rectal cuff biopsy and small bowel resection) from the 3 groups were reviewed for the presence of pyloric gland metaplasia (PGM) and granulomas. Family history of IBD and smoking history were reviewed for all patients. The frequency of PGM was similar between the CDP group and matched UC control group, however was lower in the random UC control group. Granulomas were found in the CDP group only. Family history of CD, but not smoking history, was associated with CDP development. Finding PGM in any specimens generated from UC patients may warrant close follow-up for severe pouch disease. Some of these patients, especially those with a family history of CD, may progress and meet the clinical diagnostic criteria for CDP.

Active margins, plexitis, and granulomas increase postoperative Crohn's recurrence: systematic review and meta-analysis

Tandon P, Malhi G, Abdali D, Pogue E, Marshall J, van Overstraeten A, Riddell R, Narula N
Clin Gastroenterol Hepatol. 2021;19(3):451-462.
https://pubmed.ncbi.nlm.nih.gov/32801016/

This is a systematic review and meta-analysis assessing the association of specific histologic features with postoperative recurrence of Crohn's disease. The majority of Crohn's disease patients require bowel resection for management, but in spite of advances in biologic therapy, postoperative recurrence continues to occur at a high rate. Identification of patients at high risk

for recurrence may be beneficial to allow for close monitoring or early therapeutic intervention. Out of a total search of 734 abstracts identified (up to February 2020), the authors included 39 studies in their meta-analysis to analyze the effect of resection margin status, plexitis, and granulomas on clinical recurrence (disease on radiology or endoscopy), endoscopic recurrence (endoscopic findings), or surgical recurrence (need for repeated resection). Positive resection margins increased the risk of clinical and surgical recurrence, with a trend towards endoscopic recurrence. Plexitis (mostly assessed at the margin) increased the risk of endoscopic recurrence, with a trend towards clinical recurrence. In particular, myenteric plexitis (but no submucosal plexitis) increased the risk of endoscopic recurrence. Granulomas increased the risk of clinical, and endoscopic recurrence, with a trend towards surgical recurrence. The overall findings suggest that positive resection margins, myenteric plexitis at the margin, and granulomas within the resection specimen are associated with increased risk of postoperative Crohn's disease recurrence.

Clinicopathologic features of chronic intestinal schistosomiasis and its distinction from Crohn disease

Cai L, Chen Y, Xiao SY
Am J Surg Pathol. 2021;45(3):430-438.
https://pubmed.ncbi.nlm.nih.gov/32991343/

The authors evaluated the clinical, endoscopic, imaging, gross, and histologic features of 40 cases of chronic intestinal schistosomiasis (CIS) and compared them to 40 cases of Crohn's disease (CD). The most common location for CIS was found to be rectum and/or left colon (67.5%); and endoscopically polyps were seen most commonly (57.1%), followed by yellow granular hyperplasia (40%). In contrast, most CD resections were terminal ileum and ascending colon. Grossly, mural thickening or stricture with segmental erosions or ulcerations were seen in CIS (50%), but were significantly more common in CD (100%). Histologically, CIS showed the presence of calcified ova in the submucosa, variably accompanied by fibrosis, granulomas, or multinucleated giant cells. Crypt distortion, ulceration, and transmural lymphoid aggregates were seen, but were significantly less frequent in CIS than CD. Pyloric gland metaplasia was not seen in CIS in this study, and eosinophilic counts were not significantly increased in CIS when compared with CD. The authors conclude that clinico-pathologic manifestations of CIS are not specific, and increased awareness of this disease, especially in patients from endemic regions, and rigorous search for parasitic eggs in tissue is recommended to facilitate a correct diagnosis.

Prognostic factors for advanced colorectal neoplasia in inflammatory bowel disease: systematic review and meta-analysis

Wijnands AM, de Jong ME, Lutgens MWMD, Hoentjen F, Elias SG, Oldenburg B; Dutch Initiative on Crohn and Colitis (ICC)
Gastroenterology. 2021;160(5):1584-1598.

https://pubmed.ncbi.nlm.nih.gov/33385426/

Patients with inflammatory bowel disease (IBD) have an increased risk of colorectal cancer (CRC). This is a systematic review and meta-analysis to identify all prognostic factors for advanced colorectal neoplasia in patients with IBD. A systematic literature search was conducted which yielded 164 studies, allowing a pooled analysis of 31 potential prognostic factors. In univariate analysis, the evidence for extensive disease was classified as “strong” while evidence for low grade dysplasia, strictures, primary sclerosing cholangitis, post-inflammatory polyps, family history of CRC and ulcerative colitis vs Crohn’s disease was considered “moderate.” Histological inflammation was identified as a risk factor in multivariable analysis (weak evidence). Evidence for the protective factors of colonoscopic surveillance, 5-ASA, thiopurines, and smoking was “moderate” in univariable analysis. In all, the authors identified 12 risk factors and 5 protective factors for advanced colorectal neoplasia in IBD patients.

Medication-specific variations in morphologic patterns of injury in immune check-point inhibitor-associated colitis

Isidro RA, Ruan AB, Gannarapu S, Raj D, Rahma O, Grover S, Srivastava A
Histopathology. 2021;78(4):532-541.
https://pubmed.ncbi.nlm.nih.gov/32931028/

Gastrointestinal symptoms occur in approximately 30% of patients undergoing treatment with immune check-point inhibitors (ICIs). Historically, the presence of active colitis, increased intraepithelial lymphocytes, and epithelial cell apoptosis has been regarded as the triad of histologic findings that are helpful in making the diagnosis of ICI colitis. It is clear, however, that other pathologic findings are also encountered in biopsies derived from patients with lower gastrointestinal tract symptoms, including the chronic active colitis pattern, active colitis pattern, microscopic colitis pattern, and GVHD-like pattern of injury. In this work, the authors evaluate the spectrum of histologic changes associated with ICI colitis and assess whether or not different patterns of injury are associated with specific medications. Their study cohort includes 86 patients with biopsy confirmed colitis and a final clinical diagnosis of ICI-induced GI tract toxicity. Fourteen (14) patients were treated with ipilimumab, 29 with ipilimumab + nivolumab, 20 with nivolumab, and 23 with pembrolizumab. Overall, a diffuse active colitis pattern of injury was seen in 25.6% of patients, chronic active colitis in 25.6% of patients, lymphocytic colitis in 18.6% of patients, collagenous colitis in 16.3% of patients, and GVHD-like colitis in 8.1% of patients. A mixed pattern of injury was seen in a minority of the patients in the cohort. Importantly, the histologic findings tended to be diffuse, involving all biopsy fragments derived from each patient 77.9% of the time. With regard to specific medications, patients treated with ipilimumab monotherapy more frequently demonstrated diffuse active colitis and less frequently demonstrated lymphocytic colitis than those treated with other agents or combinations of agents. Patients treated with nivolumab monotherapy more frequently showed a chronic active colitis pattern of injury and tended to receive more doses of ICI over a

longer period of time than those treated with other agents. Lymphocytic colitis and collagenous colitis were also detected more frequently in patients treated with nivolumab than those treated with ipilimumab. Similarly, lymphocytic colitis and collagenous colitis were also seen more frequently in patients treated with pembrolizumab. The GVHD-like pattern of colitis was most frequently encountered in those treated with ipilimuab + nivolumab combination therapy. The authors conclude from this work that ICI colitis shows a more diverse spectrum of morphologic changes than those captured by the classic triad of active colitis, increased intraepithelial lymphocytes, and increased apoptotic activity. ICI colitis should be considered in the differential diagnosis of a variety of different inflammatory patterns, though there are some medication-specific patterns of injury.

Histopathologic features and fragmentation of polyps with cold snare defect protrusions

Ishii T, Harada T, Tanuma T, Yamazaki H, Tachibana Y, Aoki H, Shinohara T, Katanuma A
Gastrointest Endosc. 2021;93(4):952-959.
https://pubmed.ncbi.nlm.nih.gov/32730821/

While cold snare polypectomy (CSP) is generally indicated for 3-9 mm lesions, it carries a risk for cold snare defect protrusions (CSDPs) involving the muscularis mucosae (MM) and submucosa layers. The authors studied whether the occurrence of CSDPs is associated with polyp fragmentation. In this retrospective study (1026 eligible polyps), the authors assessed the presence or absence of a CSDP by evaluating endoscopic images of polypectomy defects and reviewed corresponding pathology reports and slides. They assessed polyp fragmentation and measured the proportion of the MM with a cutoff of 50%. Polyp fragmentation and the proportion of MM<50% was significantly associated with the occurrence of CSDPs. Risk factors for CSDPs included size ≥ 6mm, resection time ≥5 seconds and serrated lesions. The authors conclude that CSDPs may be good indicators of polyp fragmentation which may lead to suboptimal pathologic examination.

***RNF43* mutation analysis in serrated polyposis, sporadic serrated polyps and Lynch syndrome polyps**

van Herwaarden YJ, Koggel LM, Simmer F, Vink-Börger EM, Dura P, Meijer GA, Nagengast FM, Hoogerbrugge N, Bisseling TM, Nagtegaal ID
Histopathology. 2021;78(5):749-758.
https://pubmed.ncbi.nlm.nih.gov/33098683/

RNF43 negatively regulates the Wnt pathway and has been proposed as a candidate gene in the pathogenesis of serrated polyposis syndrome. Pathogenic variants of *RNF43* have only rarely been reported in the literature, however. Somatic *RNF43* mutations can be found in approximately 18% of colorectal adenocarcinomas, as well as in a variety of precursor lesions, including sessile serrated lesions, traditional serrated adenomas, and hyperplastic polyps. In

this work, the authors investigate the role of the *RNF43* in serrated polyposis syndrome and in sporadic serrated polyps. No germline pathogenic variants of *RNF43* were detected in the 26 serrated polyposis syndrome patients included in their cohort. They also investigated 99 sporadic serrated polyps (25 hyperplastic polyps, 35 sessile serrated lesions, and 38 traditional serrated adenomas) for pathogenic variants in *RNF43*. Sanger sequencing identified *RNF43* mutations in 2 TSAs, both at known hotspots composed of homopolymeric tracts of C-G pairs (p.Arg117fs and p.Gly659fs). Both of these lesions showed loss of MSH6 nuclear immunoreactivity and were ultimately demonstrated to be derived from patients with known Lynch syndrome. Additional sequencing with broader gene coverage was performed on these sporadic serrated lesions and identified additional variants not detected by hotspot testing in another TSA and in 1 sessile serrated lesion. A third cohort included 37 hyperplastic polyps, 11 sessile serrated lesions, and 61 adenomas from patients with known Lynch syndrome. Hotspot mutations in *RNF43* were detected in 7 serrated polyps and 12 conventional adenomas in the Lynch syndrome cohort. Eight of these polyps did not exhibit microsatellite instability. The authors conclude from this work that *RNF43* mutations are uncommon in serrated polyposis syndrome. They are however present in sporadic serrated lesions, as well as serrated lesions and adenomas in patients with Lynch syndrome. Alterations in *RNF43* are, therefore, not specific for serrated polyp subtypes and are not an early driver event in tumorigenesis.

Colorectal adenocarcinomas diagnosed following a negative faecal immunochemical test show high-risk pathologic features in a colon screening programme

Steel MJ, Bukhari H, Gentile L, Telford J, Schaeffer DF
Histopathology. 2021;78(5):710-716.
https://pubmed.ncbi.nlm.nih.gov/33037645/

Fecal immunochemical testing (FIT) measures human hemoglobin in stool and is utilized as a screening testing for colorectal adenocarcinoma in average risk populations. Despite relatively good sensitivity, a proportion of patients diagnosed with colorectal cancer have had a recent negative FIT. It is unclear if these negative FIT results represent false-negatives where FIT failed to detect the presence of malignancy or a precursor lesion, or that these cancers arose in the interval period following the initial negative screening test. In this work, the authors investigate the histologic characteristic of these FIT-interval cancers. They evaluate a cohort including 876 screen-detected and 50 FIT-interval carcinomas with available pathology reports. The FIT-interval cancers showed a higher rate of poorly and undifferentiated cancers, as well as cancers with signet ring cell or mucinous morphology than those detected by the screening program. The FIT interval cancers also tended to be a higher pathologic stage at the time of resection, those these results were not significant. The authors postulate that the FIT negativity of these interval cancers can likely be explained by low test sensitivity. However, they cannot exclude that possibility that a proportion of these FIT interval carcinomas were not present at the time of initial screening and developed in the interval period, especially since some of these cancers have high-risk morphologic features. They advocate for further study in larger colorectal cancer

screening cohorts to better characterize the morphologic features and genetic drivers of these interval carcinomas.

Current dilemmas in the pathologic staging of colorectal cancer: the results of a national survey

Wong NACS, Bracey TS, Mozayani B, Bateman AC, Novelli MR, Shepherd NA
Histopathology. 2021;78(4):634-639.
https://pubmed.ncbi.nlm.nih.gov/33001486/

The accurate and reproducible staging of colorectal adenocarcinomas has important prognostic and therapeutic implications. Adjuvant chemotherapy is often considered for pT4 colorectal adenocarcinomas, as well as for those with nodal metastasis or positive resection margins (R1). Pathologic staging is based upon the TNM manual of the Union for International Cancer Control (UICC TNM 8) in much of the world, and by the Royal College of Pathologists' dataset for histopathological reporting of colorectal cancer in the UK. There remain, however, challenging staging scenarios that yield discordant opinions despite these published guidelines. In this work, the authors conducted an anonymous survey to assess whether such discordant opinions regarding pT stage and margin status exist in the setting of acellular mucin lakes at the resection margin following neoadjuvant short-course radiotherapy, the nature of the carcinoma at the resection margin or peritoneal surface, and microscopic evidence of perforation. Fifteen distinct scenarios were evaluated. Only 2 scenarios (extramural tumor nodule in the main specimen and extending to less than 1 mm from a circumferential resection margin as R1, and carcinoma macroscopically adherent to another organ but not microscopically invading organ as pT3) were staged the same by greater than 90% of survey respondants. Monospecialty GI pathologists were also significantly more likely to interpret carcinoma free-floating within a vessel lumen in the main specimen and located less than 1 mm from the circumferential resection margin as R1, and no macroscopic perforation and carcinoma greater than 1 mm from the circumferential resection margin but separated from the margin by microscopically evident perforation as R0 than non-monospecialty pathologists. They conclude from this work that there are several issues in staging that can potentially influence clinical decision making but are not addressed by current UICC TNM and RCPath dataset guidelines, and advocate for their inclusion in future versions.

Germline and tumor sequencing as a diagnostic tool to resolve suspected Lynch syndrome

Pope BJ, Clendenning M, Rosty C, Mahmood K, Georgeson P, Joo JE, Walker R, Hutchinson RA, Jayasekara H, Joseland S, Como J, Preston S, Spurdle AB, Macrae FA, Win AK, Hopper JL, Jenkins MA, Winship IM, Buchanan DD
J Mol Diagn. 2021;23(3):358-371.
https://pubmed.ncbi.nlm.nih.gov/33383211/

The authors performed germline whole-genome sequencing (WGS) and targeted and genome-wide tumor sequencing on samples from 14 cancer-affected patients with suspected Lynch syndrome (SLS); the latter defined as patients in whom mismatch repair (MMR)-deficient cancer develops in the absence of pathogenic variants of germline MMR genes or somatic hypermethylation of the MLH1 gene promoter. Germline WGS identified three carriers of MMR pathogenic variants (21.4%), including a 9.5-Mb inversion in multiple family members. After excluding these 3 cases, tumor sequencing identified at least two somatic MMR gene mutations in 8 of 11 tumors tested (72.7%). Double somatic MMR gene mutations, and therefore a likely sporadic etiology, were identified as the cause of tumor MMR deficiency in more than 70% of the SLS cases in this study (excluding the three identified LS carriers) in whom germline WGS confirmed the absence of other novel germline complex MMR gene variants.

Taking tumour budding to the next frontier – a post International Tumour Budding Consensus Conference (ITBCC) 2016 review

Studer L, Blank A, Bokhorst JM, Nagtegaal ID, Zlobec I, Lugli A, Fischer A, Dawson H
Histopathology. 2021;78(4):476-484
https://pubmed.ncbi.nlm.nih.gov/33001500/

A standardized and evidence-based method for scoring and reporting tumor budding in colorectal adenocarcinomas came out of the International Tumour Budding Consensus Conference (ITBCC) in 2016. In this review, the authors discuss the rationale for adopting the scoring system proposed by Ueno in 2004, as well as for reporting both the degree of budding in a three-tiered system and the absolute budding count. Because of significant interobserver variation in the assessment of tumor budding, there has been much interest in the development of automated methods for the detection of tumor buds. The review goes on to discuss the current state of the published literature regarding image analysis and automated budding assessment. While most of the reviewed literature focuses on tumor budding in colorectal adenocarcinoma, they also include works evaluating automated systems for detecting buds in the context of cancers of the oral cavity, bladder, and breast. They discuss differences in methodology between these works, including the reliance upon immunohistochemistry and variable degrees of human input. Because the currently developed systems differ significantly in terms of techniques and results, validation and standardization will be necessary before these methods can be integrated into routine clinical practice.

ACG clinical guidelines: colorectal cancer screening 2021

Shaukat A, Kahi CJ, Burke C, Rabeneck L, Sauer BG, Rex DK
Am J Gastroenterol. 2021; 116(3):458-479.
https://pubmed.ncbi.nlm.nih.gov/33657038/

This is an update of the 2009 colorectal cancer (CRC) screening guideline from the American College of Gastroenterology. The strength of recommendations are stratified into strong vs. conditional depending on the grade of quality of evidence. Outcomes are CRC incidence, CRC mortality, incidence of colorectal advanced neoplasia (adenomas or SSL ≥10 mm, ≥3 adenomas/SSL, any villous histology, high-grade dysplasia or submucosal cancer in a colonic polyp or a traditional serrated adenoma), and harms of screening. A few notable strong recommendations that are relevant to pathologists are: 1) in average-risk individuals, CRC screening is recommended between ages 50 and 75; 2) colonoscopy (interval: every 10 years) and FIT (fecal immunochemical testing; interval: every 1 year) are recommended as the primary screening modalities. A few notable conditional recommendations are: 1) for average-risk individuals between ages 45 and 49 years, CRC screening is suggested; 2) for individuals with CRC or advanced polyp in 1st degree relative (FDR) at age <60 years, or CRC or advanced polyp in ≥2 FDR at any age, initiating CRC screening with a colonoscopy at age 40 or 10 year before the youngest affected relative, whichever is earlier, is suggested; 3) for individuals with CRC or advanced polyp in 1 FDR at age ≥ 60 years, initiating CRC screening at age 40 or 10 years before the youngest affected relative and then resuming average-risk screening recommendations is suggested. In addition, recommendations on the role of aspirin for chemoprevention, quality indicators for colonoscopy, approaches to organized CRC screening, and improving adherence to CRC screening are provided.

Calculation of stop ages for colorectal cancer screening based on comorbidities and screening history

Cenin DR, Tinmouth J, Naber SK, Dubé C, McCurdy B, Paszat L, Rabeneck L, Lansdorp-Vogelaar I Clin Gastroenterol Hepatol. 2021;19(3):547-555.
https://pubmed.ncbi.nlm.nih.gov/32450362/

This is a model that estimates the harms and benefits of screening colonoscopy, with particular attention paid to the role in which comorbidities and screening history play a role. Currently, routine screening guidelines for patients at average risk of colon cancer is screening coloscopies between the ages of 50 and 74 years, with more recent guidelines that have suggested that screening in older patients may be useful in specific clinical situations (based on comorbidities or screening history). Guidelines for implementing such more personalized screening recommendations has not been well elucidated. The authors use a simulation model to investigate the impact that age, sex, comorbidities, and screening history may have on guidelines for colorectal screening cessation in assessing harms (false positives, overdiagnosed cancer, complications from colonoscopy) and benefits (appropriate early treatment of carcinoma). The model found benefit in providing initial screening in unscreened patients without comorbidities (up to 88-90 years old). However, as screening adherence improved or comorbidities increased, the optimal age at which to cease screening decreased; patients with severe comorbidities and perfect screening history should stop screening at around 66 years old. The overall findings suggest that individuals with lower comorbidity and less intensive screening history will benefit from screening past the recommended stop age, but patients with

high comorbidity and perfect screening history would stop benefitting from screening at an age earlier than recommended.

Biomarker alterations associated with distinct patterns of metastatic spread in colorectal cancer

Michl M, Taverna F, Kumbrink J, Schiergens TS, Heinemann V, Engel J, Kirchner T, Neumann J
Virchows Arch. 2021;478(4):695-705.
https://pubmed.ncbi.nlm.nih.gov/33300106/

This a study of different metastatic patterns of colorectal carcinoma. They looked at 246 patients with either exclusive lung metastasis (N = 82), exclusive liver metastasis (N = 82) or non-metastatic colorectal cancer (N = 82). They examined mutations in the *RAS* and *RAF* genes and expression of β-catenin and CD133. They found that MAPK pathway mutations in either the *KRAS*, *NRAS* or *BRAF* genes were associated with the development of lung metastasis (63.4%) compared to the control group. They also noted that MAPK pathway alterations plus high β-catenin expression was associated with metastasis to the lungs but not to the liver. On the other hand, high CD133 expression correlated with the development of liver metastasis compared to the control group. The authors suggest that their data indicates that different patterns of distant spread are associated with specific biomarker alterations and may represent different molecular subtypes of colorectal cancer.

An update on the epidemiology, molecular characterization, diagnosis, and screening strategies for early-onset colorectal cancer

Burnett-Hartman AN, Lee JK, Demb J, Gupta S
Gastroenterology. 2021;160(4):1041-1049.
https://pubmed.ncbi.nlm.nih.gov/33417940/

In this review, the authors provide an update on early-onset colorectal cancer (CRC) in patients <50 years, with a focus on epidemiology, molecular characterization, red flag signs and symptoms, and screening. *Epidemiology*: The incidence of early-onset CRC has increased during the past 3 decades, and mortality rates among adults <50 years of age with CRC have increased by 1.3% per year from 2008-2017. These tumors are predominantly distal colon and rectal and are more likely to be higher stage. The incidence is similar in men and women, though there is geographic variation (ie. highest incidence in the southern and rural parts of the United States). As for risk factors, there are conflicting results as to whether obesity and diabetes are risk factors, though metabolic syndrome has been associated with early onset CRC and a Western diet is associated with early onset high-risk adenomas. *Molecular/Tumor markers*: Early onset CRC is more likely to exhibit global hypomethylation and somatic *CTNNB1* mutations and less likely to have somatic *APC* and *BRAF* mutations. *COMP* is over-expressed in early onset CRC and may be a potential target for treatment. Somatic *POLE* mutations are also more common in

early onset CRC and may have implications for better response to immune checkpoint inhibitors due to association with higher tumor mutation burden. MSI-high early onset CRC is mostly due to Lynch syndrome and accounts for <20% of all early onset CRC. *Red flag signs or symptoms* precede 70-95% of early onset CRC cases and include rectal bleeding, abdominal pain, change in bowel habits, unexplained weight loss and anemia. *Screening*: Recent research suggests models incorporating genetic risk scores, lifestyle and other factors may identify candidates for early initiation of screening. New draft recommendations by the USPSTF support the initiation of screening at age 45 instead of 50 for individuals of average risk.

Systematic review of prevalence, risk factors, and risk for metachronous advanced neoplasia in patients with young-onset colorectal adenoma

Enwerem N, Cho MY, Demb J, Earles A, Heskett KM, Liu L, Singh S, Gupta S
Clin Gastroenterol Hepatol. 2021 Apr;19(4):680-689.
https://pubmed.ncbi.nlm.nih.gov/32428708/

This is a systematic review of early onset colorectal cancer (< 50 years old) and its clinical features, as well as its risk for metachronous neoplasia. While overall the incidence and morality of colorectal cancer has decreased among older adults, the incidence of adenoma and cancer is increasing in younger adults, raising the question of whether earlier detection and surveillance may be beneficial in the younger population. The authors did a systematic search through multiple electronic databases (through February 2019) to identify studies of individuals 18-49 years old with adenoma and identified 24 studies comprising 23,142 patients. The overall prevalence of young-onset adenoma was 9%, but there was substantial heterogeneity, and associated risk factors were increasing age, male sex, increased BMI, and smoking. In patients with early adenoma, the pooled risk for metachronous advanced neoplasia on follow up is estimated at 6%, again with substantial heterogeneity; however, across all these studies, there was only 1 case of colorectal carcinoma (0.01%). The overall findings suggest increasing prevalence of young onset adenoma (compared to decades prior) that increases with age, with a risk for metachronous advanced neoplasia.

Artificial Intelligence System to Determine Risk of T1 colorectal cancer metastasis to lymph node

Kudo SE, Ichimasa K, Villard B, Mori Y, Misawa M, Saito S, Hotta K, Saito Y, Matsuda T, Yamada K, Mitani T, Ohtsuka K, Chino A, Ide D, Imai K, Kishida Y, Nakamura K, Saiki Y, Tanaka M, Hoteya S, Yamashita S, Kinugasa Y, Fukuda M, Kudo T, Miyachi H, Ishida F, Itoh H, Oda M, Mori K
Gastroenterology. 2021;160(4):1075-1084.
https://pubmed.ncbi.nlm.nih.gov/32979355/

Most patients with T1 colorectal cancers (CRCs) undergo surgical resection with lymph node dissection, though the incidence of lymph node metastases in these patients is low (~10%). The authors sought to use artificial intelligence to build a model to identify higher risk T1 lesions in

order to reduce unnecessary surgical resections. They then validated this model on a separate set of patients. A total of 3134 patients with T1 CRC formed the training cohort. The authors developed a machine learning artificial neural network (ANN) using data on patients' age, sex, tumor size, location, morphology, lymphovascular invasion, and histologic grade. The model was externally validated using 939 patients. The authors reported lymph node metastases in 319 (10.2%) of patients in the training cohort and 79 (8.4%) of 939 patients in the validation cohort. In the validation cohort, the ANN model identified patients with lymph node metastases with an AUC of 0.83, whereas following Unites States guidelines identified patients with lymph node metastases with an AUC of 0.73 ($p<0.001$). Similarly, when analysis was limited to patients with initial endoscopic resection (n=517), the ANN model outperformed guidelines in identifying patients with lymph node metastases (AUC 0.84 vs. 0.77; $p =0.005$). The authors conclude that this model might be useful in determining which patients require additional surgery after endoscopic resection of T1 CRCs.

Expressions of TWIST1 and CD105 markers in colorectal cancer patients and their association with metastatic potential and prognosis

Fattahi F, Zanjani LS, Vafaei S, Shams ZH, Kiani J, Naseri M, Gheytanchi E, Madjd Z
Diagn Pathol. 2021;16(1):26.
https://pubmed.ncbi.nlm.nih.gov/33752711/

This study evaluates the prognostic significance of TWIST1 and CD105 as biological markers in surgically treated colorectal carcinoma (CRC) patients who did not receive chemotherapy or radiotherapy. TWIST1 mediates cell migration and differentiation, but its significance in CRC is still controversial. CD105 is a neoangiogenesis-related protein, and increased expression has been reported in aggressive and metastatic CRC patients. In this study, tissue microarrays were constructed for TWIST1 (223 patients) and CD105 (208 patients). Patients with high nuclear expression of TWIST1 (136 individuals) were more likely to have distant metastasis, shorter disease- specific survival (DSS), and lower progression- free survival (PFS). A total of 164 patients had cytoplasmic expression of CD105 in tumor cells which was found to be associated with advanced TNM stage and metastatic disease, but no significant association with the other clinicopathological parameters (tumor size, LVI, PNI and recurrence). In addition, there was no difference in DSS or PFS between high and low expression levels of CD105. The authors concluded that nuclear TWIST1 and cytoplasmic CD105 expression in tumor cells is associated with more aggressive tumor behavior and more advanced disease in CRC cases.

Incidental secondary findings in hemorrhoidectomy specimens: a 16-year experience from a single academic center

Navale P, Gonzalez RS, Vyas M
Hum Pathol. 2021 Mar;109:12-20.
https://pubmed.ncbi.nlm.nih.gov/33245989/

The purpose of this retrospective study was to describe the spectrum of incidental anal pathology identified in hemorrhoidectomy specimens. Incidental findings in hemorrhoidectomy specimens are rare and have led to debate regarding the utility of routine pathologic examination, but no large systematic study has yet detailed the variety and frequency of clinically significant pathology in these specimens. The authors reviewed hemorrhoid specimens over a 16 year period and found that 4.5% (72/1612 cases) had a clinically significant finding. The range of findings included: 7 incidental malignancies (SCC, verrucous carcinoma, adenocarcinoma, mixed adenocarcinoma and neuroendocrine carcinoma, poorly differentiated neuroendocrine carcinoma, melanoma); 54 anal intraepithelial neoplasias (3.3% of total cases including HSIL in 2.6% of total cases); and 11 benign findings (including 1 case with a sexually transmitted infection). In 72% of patients, the incidental finding was a first diagnosis. The authors conclude that systematic evaluation of hemorrhoidectomy specimens may be good practice, as clinically significant findings may be masked by or mistaken for infarcted or thrombosed hemorrhoids.

Assessing the reliability and positive predictive value of p16 as a surrogate for human papillomavirus-mediated E6/7 mRNA expression in squamous cell carcinoma of the anal canal

Frankart AJ, Criss BE, McKillip KD, Wise-Draper T, Takiar V, Kharofa J
Dis Colon Rectum. 2021;64(4):459-465.
https://pubmed.ncbi.nlm.nih.gov/33394778/

This study aims to assess the concordance rate between p16 immunohistochemistry (IHC) and E6/7 mRNA in squamous cell carcinoma of the anal canal (SCCA). Human papilloma virus (HPV) is a key risk factor in many types of carcinoma, and the presence of HPV E6/7 mRNA is the current standard to identify HPV-induced carcinogenesis. In addition, although the correlation between p16 expression by IHC and E6/7 mRNA has been studied in head and neck carcinoma, there is limited literature in SCCA. In this study, a tissue microarray (TMA) was prepared to evaluate p16 and E6/7 mRNA expression from 25 patients SCCA patients at the University of Cincinnati. E6/7 mRNA was positive in 24 patients, and immunoreactivity for P16 was observed in 23 cases. Concordance between E6/7 ISH and P16 was observed in 24 cases, and only 1 case was discordant between E6/7 mRNA (+) and P16 (-), which demonstrates the high sensitivity, specificity and positive predictive value of P16 expression. The authors concluded that P16 is a reliable marker of HPV-mediated carcinogenesis in SCCA in comparison with E6/7 mRNA ISH.

Non-conventional dysplasias of the tubular gut: a review and illustration of their histomorphologic spectrum

Pereira D, Kővári B, Brown I, Chaves P, Choi WT, Clauditz T, Ghayouri M, Jiang K, Miller GC, Nakanishi Y, Kim KM, Kim BH, Kumarasinghe MP, Kushima R, Ushiku T, Yozu M, Srivastava A, Goldblum JR, Pai RK, Lauwers GY

Histopathology. 2021 Apr;78(5):658-675.
https://pubmed.ncbi.nlm.nih.gov/33124049/

The diagnosis of non-conventional (non-adenomatous) dysplasia in the tubular gastrointestinal tract is challenging and generally associated with less than ideal interobserver agreement. Moreover, the biologic behavior of these lesions has not been fully characterized. In this review, the authors explore the various types of non-traditional dysplasia that have been described at different sites in the tubular gastrointestinal tract. They discuss the histologic features of these lesions, what is known about their molecular phenotype, association with cancer syndromes, risk for progression, and treatment guidelines. Many different types of dysplasia are discussed at each site including foveolar, serrated, and crypt dysplasia in the esophagus, pyloric gland and oxyntic gland adenomas in the stomach, and hypermucinous and serrated dysplasia in the colon in the setting of inflammatory bowel disease. Many nice photomicrographs are included with the review.

Clinicopathological study of blue nevi of the gastrointestinal tract: first case series

Assarzadegan N , Salimian K , Hutchings D , Windon AL , Voltaggio L , Montgomery EA
J Clin Pathol. 2021;74(3):167-170.
https://pubmed.ncbi.nlm.nih.gov/32631943/

This study reports cases of blue nevi (BN) in the gastrointestinal tract from Johns Hopkins Hospital files (1984-2019). While BN typically arise in the skin, there are rare case reports of mucosal BN, including involvement of the rectum. In this study, the authors report six cases of mucosal blue nevi, with 5/6 involving the colorectum and 1 case arising within the stomach. Lesions were identified incidentally during screening endoscopy, and most appeared as superficial hyperpigmented foci. Two patients had bleeding from hemorrhoids. All lesions involved the mucosa, and they showed typical BN microscopic features. Only one case extended to the submucosa. There were no aggressive features nor epithelioid morphology identified. On a median follow- up of 1 year, no evidence of recurrence was found in the 5 cases in which the data was available. The authors concluded that these lesions seem to be similar to their dermatologic counterparts with no major histological differences.

Clinicopathologic features and diagnostic implications of pyloric gland metaplasia in intestinal specimens

Tokuyama M, Dhingra S, Polydorides AD
Am J Surg Pathol. 2021;45(3):365-373.
https://pubmed.ncbi.nlm.nih.gov/33105158/

The authors evaluated the significance of pyloric gland metaplasia (PGM) in intestinal specimens by evaluating 601 specimens (38% biopsies and 62% resections) from 567 different

patients; of these, 511 patients (90%) were diagnosed with inflammatory bowel disease (IBD; 89.4% with Crohn's disease and 10.4% with ulcerative colitis) during clinical follow-up (mean clinical follow-up of 83.5±48.1 months). In multivariate analysis, IBD patients with PGM were younger, and had severely active inflammation when compared with non-IBD patients. Kaplan-Meier analyses depicted that incidental PGM in a biopsy was more likely to predict IBD in patients younger than 50 years without a history of bowel surgery and when identified in the small intestine. The authors conclude that PGM in a small intestinal location and found in patients younger than 50 years without prior intestinal surgery and with severely active inflammation supports an underlying diagnosis of IBD and in particular, Crohn's disease. However, PGM can also be found in patients with ulcerative colitis and in clinical situations other than IBD and its presence should be interpreted with restraint, especially in older patients or those with a history of prior bowel surgery or when identified in biopsy specimens or in samples from the colorectum, particularly when in the absence of severe active or chronic mucosal injury

The diagnostic and clinical significance of granulomas in gastrointestinal biopsies from haematopoietic transplant patients

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Histopathology. 2021;78(5):772-777.
https://pubmed.ncbi.nlm.nih.gov/33217036/

Cord colitis syndrome (UCS) was proposed in 2011 as an entity in patients receiving umbilical cord blood transplants. While all 11 of the patients in this initial series showed chronic active colitis, 7 also had mucosal non-necrotizing granulomas in biopsies derived from either the upper or lower gastrointestinal tracts. Follow-up studies have showed mixed results, but generally have concluded that granulomatous inflammation is not a specific histologic feature of UCS. In this work, the authors explore the controversial association of granulomas with the UCS. They investigate 3 distinct cohorts. The first includes 8 prospectively identified hematopoietic transplant patients with GI biopsies containing granulomas. The second retrospectively identified cohort included 51 biopsies from 14 distinct patients with clinically validated graft-versus-host disease. The third retrospectively identified cohort included 8 patients who received umbilical cord blood transplants and had endoscopic biopsies performed for GI symptoms. Granulomatous inflammation was identified in 3 (21%) of patients with clinically validated GVHD, and 3 (38%) of the patients who received umbilical cord blood transplants. All of the granulomas present in the GVHD patients were cryptolytic in nature. While both cryptolytic and non-cryptolytic granulomas were present in cord blood patients, non-cryptolytic granulomas were exclusively seen in this cohort and were compact and well-defined. Interestingly, loose non-cryptolytic granulomas were only seen in patients with post-transplant lymphoproliferative disorder. The authors conclude from this work that granulomatous inflammation in hematopoietic transplant patients may be seen in association with GVHD and PTLD. Granulomas appear to be more frequently encountered in umbilical cord transplant patients, but do not necessarily imply the presence of UCS. Long-term follow-up of

transplant patients with granulomas showed no association with the development of Crohn disease in this cohort.

The diversity of tumours with microsatellite instability: molecular mechanisms and impact upon microsatellite instability testing and mismatch repair protein immunohistochemistry

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Histopathology. 2021;78(4):485-497
https://pubmed.ncbi.nlm.nih.gov/33010064/

Microsatellite instability (MSI) is a key driver of tumorigenesis that typically produces hypermutated, immunogenic neoplasms which has clear therapeutic implications in the era of immunotherapy. This review article explores the diversity of the MSI phenotype both within and across tumor types. It begins by briefly reviewing the function of the major mismatch repair proteins, as well as commonly encountered pathogenic mechanisms of inactivation and the consequences thereof. It goes on to discuss the historical PCR-based methodologies for the assessment of MSI status, as well as more modern NGS-based approaches including tumor mutational burden. Caveats with these NGS-based methods are also discussed, such as the presence of a low (MSI-I) sensor score (via MSK-IMPACT MSIsensor programme) in non-canonical Lynch syndrome-associated tumors that exhibit loss of mismatch repair protein immunoreactivity. Several clinical vignettes are then presented that discuss the relationship between MSI-status and the immunohistochemical staining pattern for the mismatch repair proteins. In addition to commonly encountered scenarios such as sporadic MMR-deficient colorectal adenocarcinomas developing secondary to MLH1 promoter hypermethylation, rarer clinical situations including POLE driven ultramutated colorectal adenocarcinoma with associated MSH2 deficiency are also discussed. The review ends with a brief discussion, urging caution in the interpretation of mismatch repair protein deficiency in tumors not classically associated with Lynch syndrome, as they may not necessarily be MSI-H and may not respond to immune checkpoint inhibitors.

Journals Reviewed March-April 2021

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