Soucy G, Onstad L, Vaughan TL, Odze RD.

The goal of this study was to determine which histologic features in SCJ biopsies from a prospective cohort of community clinic-based patients with GERD symptoms are associated with the presence of CLE and to determine the histologic features of patients with irregular Z-line. The study group consisted of 544 patients (age 20 to 80 y) from 5 gastroenterology clinics from 1997-2000. Previously diagnosed BE patients were excluded. All patients had separate 4-quadrant biopsies. 2216 mucosal biopsies were evaluated in a blinded manner by one of the authors. Of the 544 patients, 269 (49.4%) had a normal appearing Z-line, 58 (10.7%) had an irregular Z-line and 217 (39.9%) had CLE. Histologic findings were correlated with the endoscopic findings (normal Z-line, irregular Z-line, or CLE) and evaluated by logistic regression and receiver operating characteristic analysis. 5 features were associated with CLE: pure mucous glands, multilayered epithelium (ME), presence of goblet cells, \( \geq 50\% \) of crypts with goblet cells, and buried columnar epithelium. Pure oxyntic glands were inversely associated with CLE. ME, squamous island (foci of squamous epithelium surrounded on both sides by columnar epithelium), and buried epithelium were significantly increased in biopsies from patients with irregular Z-line compared with those with normal Z-line. In summary, certain histologic features in biopsies of SCJ are associated with presence of CLE and irregularity of Z-line is a condition probably indicative of very early, or ultrashort segment CLE instead of being a potential anatomic variation of normal.

**Barrett's Esophagus: A Comprehensive and Contemporary Review for Pathologists.**
Naini BV, Souza RF, Odze RD.

This review provides a summary of the current understanding and controversies surrounding the diagnosis, pathogenesis, histopathology, natural history and molecular biology of Barrett’s esophagus (BE) and associated neoplasia. The histologic subtypes of dysplasia in BE are covered. The pathologic issues related to treatment and its complications are also discussed.

**Post-ablation lymphocytic esophagitis in Barrett esophagus with high grade dysplasia or intramucosal carcinoma.**
Kissiedu J, Thota PN, Gohel T, Lopez R, Gordon IO.
This study looks at post ablation changes in squamous mucosa in patients with a history of ablation, cryotherapy or both for dysplasia in the setting of Barrett’s Esophagus. The authors looked for evidence of eosinophilic esophagitis or an emerging entity called lymphocytic esophagitis. The criteria used for the diagnosis of lymphocytic esophagitis were 1) greater than 20 peripapillary lymphocytes per high power field 2) peripapillary lymphocytosis with spongiosis 3) absence of significant neutrophils or eosinophils. While the authors did find intraepithelial eosinophils in some post ablation biopsies, they did not find diagnostic eosinophilic esophagitis. The authors did find that there was an increased incidence of the histologic features of lymphocytic esophagitis. Cases of lymphocytic esophagitis correlated with smoking, hyperlipidemia and treatment by cryotherapy.

**Impact of peritumoral and intratumoral budding in esophageal adenocarcinomas**

The aim of this multicenter study was to investigate the role of tumor budding in esophageal adenocarcinomas. Tumor budding was defined similar to that of the colon: detached isolated single cell or small cell clusters up to 5 cells at the invasive front (peritumoral budding) or within the tumor (intratumoral budding). With the aid of pancytokeratin immunohistochemistry, 200 primarily resected esophageal adenocarcinomas with intestinal phenotype were scored by two pathologists for peritumoral and intratumoral budding (reported across 10 high-power fields). The results showed that peritumoral and intratumoral budding correlated with each other. In addition, higher rates of budding were seen in more advanced tumor categories, tumors with lymph node metastases, lymphovascular and perineural invasion, and high tumor grade. High grade intratumoral, but not peritumoral, budding showed an association with worse survival, and whereas lymph node and resection status were independent prognostic parameters in multivariate analysis, tumor budding was not. The authors conclude that high grade budding is associated with aggressive tumor phenotype and an assessment of tumor budding may provide prognostic information about tumor behavior and stratification for patients.

**SMYD3 stimulates EZR and LOXL2 transcription to enhance proliferation, migration, and invasion in esophageal squamous cell carcinoma**

In this retrospective immunohistochemical microarray study, 131 cases of esophageal squamous cell carcinomas were stained for SET and MYND domain-containing protein 3 (SMYD3), a methyltransferase that plays a role in transcriptional regulation during human cancer progression. High expression of SMYD3 in primary tumors correlates with low overall survival (P = 0.008), is an independent prognostic factor for poor overall survival, and is associated with lymph node
metastasis. SMYD3 was further explored in cell lines of esophageal squamous cell carcinoma and nude mice. The authors showed that RNAi-mediated knockdown of SMYD3 suppressed cancel cell proliferation, migration, and invasion in vitro and inhibited local tumor invasion in vivo. The study also identified EZR and LOXL2 as new target genes of SMYD3 in esophageal squamous cell carcinoma cells by confirming that protein levels of EZR and LOXL2 positively correlate with SMYD3 expression.

**Chief cell-predominant gastric polyps: a series of 12 cases with literature review.**

This multi-site case series identified 12 gastric lesions composed of a combined proliferation of chief and oxyntic cells. In the past, such lesions were designated as adenocarcinoma of fundic gland type or as oxyntic gland polyp/adenoma. In this series, all lesions were located in the fundus and seven of eight were polyloid on endoscopy. Most lesions were solitary, averaged 4.6 mm in diameter, and made up mostly of chief cells. Architectural patterns included anastomosing, solid, clustered, or a mixture of these patterns. Most were mucosal lesions, though two had submucosal involvement, and none had known metastatic disease. CDX2 was negative in the five cases in which it was performed. These lesions have low-grade cytology and low Ki-67 proliferative index (<2% on at least 500 cells evaluated per lesion).

**Gastric crypt dysplasia: a distinct subtype of gastric dysplasia with characteristic endoscopic features and immunophenotypic and biological anomalies.**

Gastric crypt dysplasia (GCD) is a precursor to adenocarcinoma; typically, dysplasia is diagnosed when the full length of the pit and surface epithelium is abnormal. However, in GCD, there can be various degrees of dysplasia-like atypia without surface involvement. This study explores whether GCD is endoscopically identifiable, and included 1196 consecutive endoscopic resections of gastric epithelial dysplasia (GED) with immunohistochemical analysis for various mucins, CD10, Ki-67, and p53. 51 (4.3%) lesions contained GCD, and these were elevated mucosal lesions (66.7%) with similarity in color and texture to the adjacent mucosa. GCD tends to have an antr pyloric location and a higher grade than the adenomatous type (P < 0.05). A gastric immunophenotype was more common in GCD compared to adenomatous GED (P < 0.05). GCD contains more Ki-67 and p53 expression compared to adjacent gastric mucosa. The authors discuss that GCD could be a precursor of classic GED of foveolar or hybrid type, and that it is difficult to identify endoscopically and difficult to diagnose on biopsy.

**Reduced MUTYH, MTH1, and OGG1 expression and TP53 mutation in diffuse-type adenocarcinoma of gastric cardia**
This study compared gastric diffuse-type adenocarcinomas arising in the cardia (strictly defined as in the stomach within 2cm of the esophagogastric junction) to those of the pylorus. The authors compared immunohistochemical expression of inducible nitric oxide synthase; 8-hydroxy-deoxyguanosine; and base excision repair enzymes such as MUTYH, MTH1, and OGG1 and TP53 mutational status. Compared to tumors of the pylorus, adenocarcinoma of the gastric cardia occurred in younger patients (P = 0.0227) and showed more frequent venous invasion (P = 0.0106). In addition, these tumors accumulated 8-hydroxy-deoxyguanosine and showed decreased MUTYH, the latter finding of which was associated with diffuse-type morphology. Lower expressions of OGG1 correlated with aggressive features such as higher T-stage, lymphatic invasion, and lymph node metastasis. TP53 mutation was associated with worse survival in adenocarcinoma of the gastric cardia. Based on these findings, the authors suggest that oxidative stress accumulation and down regulation of base excision repair enzymes may play a role in the pathogenesis of diffuse-type adenocarcinoma of the gastric cardia, which may therefore involve different molecular pathways from those of other gastric cancer subsets.

Jejunoileal Neuroendocrine Tumors Complicated by Intestinal Ischemic Necrosis Are Associated With Worse Overall Survival.
Landau M, Wisniewski S, Davison J.
Arch Pathol Lab Med. 2016 May;140(5):461-6

Jejunoileal neuroendocrine tumors (JINETs) usually present at an advanced stage, in contrast to neuroendocrine tumors of the stomach and other GI sites. Their 5-year overall survival is about 60%. Occasionally, these tumors come to clinical attention because of tumor-induced intestinal ischemia, with resection specimens showing intestinal ischemic necrosis (IIN) in the non-neoplastic small bowel. In this study, 10 JINETs with IIN were identified and studied against a control group of 52 JINETs without IIN. At 1 year post-surgery, only 40% (4/10) of the patients with IIN were alive, compared to 94% (49 of 52) of those without IIN (P < 0.001). Patients with IIN were significantly older than those without IIN (median age 83 years versus 65.5 years, P = 0.001). When controlling for age, advanced stage, tumor grade, and synchronous carcinoma, IIN showed a trend toward prognostic significance (2.31-fold increased risk of death, 95% CI 0.85-6.27, P = 0.10). JINETs often spread to mesentery to form bulky masses near mesenteric vasculature, and they elicit abundant stromal fibrosis, which could have a role in causing IIN. When IIN is identified in association with JINETs, it could portend a significantly worse overall survival.

Evaluating Intestinal Infections: A Systematic Approach
Barbieri A, West AB.
In this review article, the authors provide a systematic approach to evaluating infections involving the large and small intestines. The authors divide intestinal mucosal biopsies into 5 main anatomic compartments: epithelium, histiocytes, lamina propria, non-neoplastic macroscopic lesions and intestinal lumen. These compartments are further subdivided and the commonly associated pathogens are categorized by compartment, described by histologic pattern, compared to differential diagnoses, and captured in 32 photomicrographs that demonstrate examples of various entities (including H&E stain, special stains, and immunohistochemistry). The article also includes 4 electron microscopy photos of microorganisms and a useful reference table. This is a helpful article for those studying GI biopsies in residency or fellowship training, any pathologist who sees non-neoplastic GI mucosal biopsies infrequently, or anyone who wants a refresher on pathogens affecting the GI tract.

Clinical Significance of Metastatic Lymph Nodes in the Gut of Patients with Pure and Mixed Primary Appendiceal Carcinoids
Ciarrocchi A, Pietroletti R, Carlei F, Amicucci G.

This retrospective comparative study reviewed resected specimens for appendiceal carcinoids over a 10-year period. Of the 613 patients reviewed, follow up was available through 2012. The authors state that published data shows no significant difference in survival rates among patients who undergo appendectomy alone vs. hemicolectomy. Therefore, the aim of this study was to investigate the impact of positive lymph nodes on survival rates while controlling for potential confounding factors: sex, tumor size, histology group, and surgical intervention. Tumor size was defined as greater than 2cm or less than 2cm, as tumors greater than 2cm are associated with an increased risk of lymph node metastases. The histologic group was divided into “pure carcinoid” and “mixed carcinoid”. In the “pure carcinoid” group “148 were malignant carcinoid tumors, 4 were enterochromaffin cell carcinoids, and 40 were low- and medium-grade neuroendocrine cell carcinomas”. The “mixed carcinoid” group consisted of “224 goblet cell carcinoids, 66 composite carcinoids, 122 adenocarcinoid tumors, 2 atypical carcinoid tumors, and 7 high-grade or undifferentiated neuroendocrine cell carcinomas”. Tumor size was similar between the two groups. Ultimately, the comparison of survival curves revealed that the pure carcinoid group had a better prognosis than those with mixed variants (P < 0.001). However both groups had high 10-year survival rates: 88% for pure carcinoids and 73% for mixed carcinoids. Furthermore, after controlling for age, sex, tumor size, surgical intervention, a Cox proportional hazards model showed histologic type to be an independent predictor of overall survival (P = 0.004). Therefore, the authors reiterate that “mixed carcinoids” are biologically more aggressive, but reinforce that metastatic spread to lymph nodes remains an important factor in survival regardless of histologic type.

Histopathology of Graft-vs-Host Disease of Gastrointestinal Tract and Liver: An Update.
Salomao M, Dorritie K, Mapara MY, Sepulveda A.
This review article is a practical and useful overview of the diagnosis of gastrointestinal and liver graft-vs-host disease (GVHD) with an emphasis on histopathologic evaluation of luminal GI and liver biopsies. The article discusses pathogenesis and clinical manifestations as well as specific histopathologic findings and their differential diagnosis.

Clinicopathologic Threshold of Acute Colorectal Graft-versus-Host Disease.

This study examines crypt apoptotic bodies (CAB) in the context of “rule-out GVHD” with chart review to assess outcome and management. 81 biopsies for suspected GVHD from 74 patients were stratified based on their pre-study diagnoses (no significant abnormality, grade 1 GVHD, and descriptive diagnoses mentioning increased apoptosis). Chart review was performed to assess clinical and endoscopic findings at the time of biopsy and to check subsequent management and outcome. Number of crypt apoptotic bodies was counted in areas of highest histologic severity. Density of crypt apoptosis (number of apoptotic cells per crypt) was counted in areas of highest histologic severity with up to a maximum of 10 contiguous crypts evaluated. True negative cases included 26 biopsies with an average of 3 CAB. True positive cases were 32 biopsies with an average of 9.75 CAB (P < 0.001). True negative cases had an average density of 1.36 CAB per crypt and true positive cases had an average density of 2.97 CA per crypt (P < 0.001). A threshold of 7 or more CAB per 10 contiguous crypts leads to appropriate treatment of grade 1 acute GVHD after other diagnoses are excluded. This threshold is 100% specific to grade 1 acute GVHD after other mimics are excluded, but this threshold has a low sensitivity (59.4%) as less than 7 CAB per 10 contiguous crypts results in heterogeneous clinical findings.

Histology Grade Is Independently Associated With Relapse Risk in Patients With Ulcerative Colitis in Clinical Remission: A Prospective Study.
Zenlea T, Yee EU, Rosenberg L, Boyle M, Nanda KS, Wolf JL, Falchuk KR, Cheifetz AS, Goldsmith JD, Moss AC.

This study sought to prospectively examine the association of baseline endoscopic, histologic and laboratory findings with subsequent symptomatic relapse in ulcerative colitis (UC) patients in clinical remission. The observational cohort consisted of 179 patients initially in clinical remission who were followed over a period of 12 months. Baseline Mayo endoscopy scores, Geboes histology grades, complete blood counts, erythrocyte sedimentation rates and C-reactive protein were recorded. These measures were compared to a primary outcome of clinical relapse, which was defined by a number of factors discussed in the article. The only significant predictor of future relapse in these patients after multivariate analysis was the presence of histologic evidence of inflammation, particularly epithelial neutrophilic infiltrates, crypt destruction,
erosions or ulcers. The relative risk of clinical relapse was 3.5 in subjects with such findings while 7% of patients in clinical, endoscopic and histologic remission at baseline had a clinical relapse. Endoscopic impressions of mucosal inflammation were not found to be independently predictive of future relapse.

**Risk of Neoplasia After Colectomy in Patients With Inflammatory Bowel Disease: A Systematic Review and Meta-analysis.**
Derikx LA, Nissen LH, Smits LJ, Shen B, Hoentjen F.

This literature review with meta-analysis was conducted to determine the prevalence, incidence and risk factors for colorectal neoplasia in inflammatory bowel disease patients who had previously undergone a colectomy. Data was extracted from 16 articles which included patients who had undergone a permanent ileostomy with rectal stump, 68 articles including patients who had ileorectal anastomosis (IRA) and 56 articles comprising patients who had undergone an ileal pouch-anal anastomosis (IPAA). The meta-analysis revealed prevalence values of subsequent colorectal carcinomas of 2.1%, 2.4% and 0.5% for these groups respectively. Factors that were found to increase this risk included the presence of residual rectum and a history of colorectal carcinoma. The authors postulate that the presence of residual rectum following surgery is the major determinate for carcinoma development. This was supported by the significantly lower cancer prevalence in the IPAA group compared with the individuals with residual rectal tissue. Importantly, the prevalence in all post-colectomy groups was less than the lifetime risk in the general population.

**Traditional serrated adenoma with BRAF mutation is associated with synchronous/metachronous BRAF-mutated serrated lesions.**
Tsai JH, Cheng CH, Chen CC, Lin YL, Lin LI, Chen ML, Liau JY.

111 patients with an index TSA were studied as to synchronous/metachronous serrated lesions, including hyperplastic polyps, SSAs, additional TSAs, and CRCs. 27% of TSAs showed a precursor serrated polyp at the periphery and were strongly correlated with BRAF mutation (P < 0.001). Serrated polyps were more common in patients with BRAF-mutated index TSAs than in patients with KRAS-mutated index TSAs. BRAF-mutated index TSAs were strongly associated with right-sided location (P = 0.013) and BRAF mutation of synchronous/metachronous serrated polyps (P = 0.005). 17 CRCs were identified, characterized by a high BRAF mutation rate of 59%, a positive CpG island methylator phenotype (59%) and microsatellite stability or low levels of MSI (77%). The authors conclude that BRAF-mutated TSA and KRAS-mutated TSA are distinct in their predisposition to subsequent serrated neoplasia.
Frequent PTPRK-RSPO3 fusions and RNF43 mutations in colorectal traditional serrated adenoma.
Sekine S, Yamashita S, Tanabe T, Hashimoto T, Yoshida H, Taniguchi H, Kojima M, Shinmura K, Saito Y, Hiraoka N, Ushijima T, Ochiai A.

In an effort to further examine the molecular mechanisms involved in the pathogenesis of traditional serrated adenomas (TSAs), these authors performed targeted next generation sequencing and RT-PCR on 70 such lesions and compared those findings to identical testing in 26 hyperplastic polyps, 34 sessile serrated adenoma/polyps, 27 tubular adenomas and 31 tubulovillous adenomas. Similar to previous studies, the authors noted a percentage of TSAs with BRAF and KRAS mutations (60% and 36% respectively). Novel findings included the detection of RNF43 mutations in 24% of TSAs, which were found in only 6% of SSA/Ps and no other polyps. RT-PCR detected PTPRK-RSPO3 fusions in 31% of TSAs, a finding which was not appreciated in any other polyp type. This later finding was more frequent in TSAs that harbored high-grade dysplasia versus not (11/22 to 5/44). The authors note that a small percentage of colorectal carcinomas have been shown to harbor PTPRK-RSPO3 fusions and suggest that TSAs may be the precursor lesions to these specific malignancies.

Risk of Metachronous Advanced Neoplastic Lesions in Patients with Sporadic Sessile Serrated Adenomas Undergoing Colonoscopic Surveillance.

This prospective study aimed to examine the risk of metachronous advanced neoplastic lesions during surveillance colonoscopy following endoscopic resection of sessile serrated adenomas/polyps (SSA/Ps). Factors associated with these subsequently developed lesions, including the presence or absence of synchronous adenomatous lesions at the time of SSA/P resection, were also examined. Of 185 patients presenting with at least 1 resected SSA/P, 75 patients were included in the final cohort after the majority were excluded for a number of explicit reasons including lack of endoscopic follow-up. This group was related to a comparison cohort of 564 patients who presented with non-SSA/P adenomatous lesions or negative colonoscopies. The incidence rate of subsequent advanced neoplastic lesions was remarkably similar among the groups of patients presenting with SSPs alone, SSPs with synchronous low-risk adenomas and with low-risk adenomas alone (1.41, 0 and 1.47 per 1000 person-months respectively). This is in contrast to the incidence rate of metachronous advanced lesions among patients who initially presented with an SSA/P and synchronous high-risk adenoma (12.96 per 1000 person-months), which was higher than patients presenting with a high-risk adenoma alone (5.07 per 1000 person-months). The authors suggest that surveillance colonoscopy recommendations for low-risk adenomas are likely appropriate for patients with SSA/Ps alone or those with synchronous SSA/Ps and low-risk adenomas. However, they propose that patients with synchronous SSA/Ps and high-risk adenomas require closer surveillance.
Early Outcomes of Endoscopic Submucosal Dissection for Colorectal Neoplasms According to Clinical Indications
Youk, E, Sohn DK, Hong WC, Lee, SD, Han Sk, Kim CB, Chang HJ, Kim MJ

This prospective, multicenter study assesses the outcomes of endoscopic submucosal dissection (ESD) for patient’s with 1) early colorectal cancer 2) laterally spreading tumors >2 cm and 3) submucosal neoplasms. ESD differs from endoscopic mucosal resection (EMR) in that the submucosa is dissected under the lesion with a specialized knife. Curative resection is defined as en block resection (one-piece) and no pathologic requirement for additional surgery. 319 patients were enrolled and the mean tumor size was 24 mm. Submucosal fibrosis was identified within 41 patients, which is considered a high risk factor for ESD. 71.8% of patients had histologically confirmed curative ESD and 4.7% required radical surgery following ESD for risk of lymph node metastasis. The complications were perforation (10%) and muscle injury (7%), all of which were managed through endoscopic clipping. There was a lower rate of clear margins for patients who had laterally spreading tumors (LST). The authors conclude that colorectal ESD yields acceptable early outcomes and confirms that submucosal fibrosis increases complication rates. They re-emphasize that ESD and EMR are procedures only appropriate for neoplasms without risk of lymph node metastasis. One of the limitations of this study was the lack of standardized pathologic review by a single pathologist and the fact that submucosal fibrosis and tumor budding were not validated by grading and scoring systems.

Tumor eosinophil infiltration and improved survival of colorectal cancer patients: Iowa Women’s Health Study.

This study looks at the issue of whether tumor eosinophil infiltration might be a prognostic factor in colorectal cancer. The authors cite several recent studies that have investigated this issue, with the majority suggesting that higher peritumoral eosinophils may indicate improved survival. This study, using colon cancer patients from the Iowa Women’s Health study, evaluated paraffin embedded tissue with immunohistochemistry that the authors state has been validated to discriminate between eosinophil peroxidase stored in intact eosinophils and proteins secreted from degranulated eosinophils. The authors original hypothesis was that eosinophil accumulation in the stroma as well as degranulation might be associated with better survival times. While the authors did not observe an association with degranulation and increased survival or stage at diagnosis, their findings did support the previous observations that high tumor stromal eosinophil count was correlated with decreased risk and that this may become an important prognostic factor in colorectal cancer.
SOX9 expression predicts relapse of stage II colon cancer patients
Marcker Espersen ML, Linnemann D, Christensen IJ, Alamili M, Troelsen JT, Høgdall E.

This goal of this retrospective immunohistochemical study was to investigate if protein expression of sex-determining region y-box 9 (SOX9) in primary tumors could predict relapse of stage II colon cancer patients. In addition to SOX9, the 144 patients with stage II primary colon cancer were also evaluated for mismatch repair status by IHC and promoter hypermethylation assay. The study found that high SOX9 expression at the invasive front was significantly associated with lower risk of relapse, and low SOX9 associated with high risk of relapse. The authors posit that SOX9 may have important value as a biomarker to predict relapse in stage II colon cancer.

Distal intramural and tumor spread in the mesorectum after neoadjuvant radiochemotherapy in rectal cancer: about 124 consecutive patients
Guedj N, Maggiori L, Poté N, Norkowski E, Cros J, Bedossa P, Panis Y.

This is an observational prospective study aimed to assess the distribution of intramural and mesorectal tumor spread in mid/low rectal cancer after neoadjuvant radiochemotherapy. A total of 124 consecutive surgical specimens were evaluated for the distribution of mesorectal metastatic lymph nodes, mesorectal extranodal cancer tissue, and distal intramural tumor spread. The authors found that distal intramural or mesorectal spread was a rare event independent of neoadjuvant therapy. Based on this finding, the authors suggest that the 1-cm distal margin recommendation for patients with low rectal carcinoma could be reduced and still ensure a negative margin.

The Performance of Anal Cytology as a Screening Test for Anal HSILs in Homosexual Men.

This study reports the performance of liquid-based anal cytology in the detection of histological HSILs at the time of the baseline visit among a cohort of HIV-negative and HIV-positive homosexual men in Sidney, New South Wales, Australia. Biopsies were obtained for histological assessment if lesions suspicious for HPV infection were visible during high-resolution anoscopy. Using any cytological abnormality as the threshold, the sensitivity, specificity, and positive and negative predictive values were calculated against histologically diagnosed HSILs. Among 617
men recruited (median age: 49 y, 35.7% positive for HIV), sensitivity of cytology was 83.2%, specificity 52.6%, PPV 45.8%, and NPV 86.7%. Specificity improved with increasing age. Sensitivity was significantly higher in men with more extensive HSILs (>1 anal octant of biopsy-confirmed HSIL (92.9% vs 77.7%; P = .010)) and in those with metaplastic cells present on cytology (≥10 metaplastic cells present on cytology slides (87.5% vs 70.2%; P = .007)).

Assessment of Melanocyte Density in Anorectal Mucosa for the Evaluation of Surgical Margins in Primary Anorectal Melanoma.
Tse JY, Chan MP, Zuckerberg LR, Nazarian RM.

This study examines the distribution and density of melanocytes in normal anorectal mucosa vs. anal mucosa adjacent to primary colorectal melanoma with the aid of immunohistochemistry for microphthalmia transcription factor (MITF) and HMB45 with the goal to help evaluate surgical margins for “trailing” melanoma in situ (MIS) in cases of primary anal melanoma. The authors found that the immunohistochemistry, especially MITF, helped to distinguish “trailing” MIS and benign melanocyte hyperplasia but only when also taking melanocyte density, nuclear atypia, and growth pattern together into consideration. A third element of the study involved evaluating the utility of BRAF V600E immunohistochemistry (VE1) in this setting but the authors found that it showed non-specific staining in glandular epithelium and was not useful to identify MIS.

Conventional Risk Stratification Fails to Predict Progression of Succinate Dehydrogenase-(SDH) deficient Gastrointestinal Stromal Tumors: A Clinicopathologic Study of 76 Cases.
Mason EF, Hornick JL.
http://www.ncbi.nlm.nih.gov/pubmed/27340750

The goal of this study was to prove that conventional risk stratification criteria does not predict outcome for SDH deficient GISTs. A total of 76 SDH-deficient GISTs (45 female/31 male, mean age at diagnosis 32 y; range 11 to 71 y;10 patients 50 y of age or above) diagnosed from 2005 to 2015 were identified on the basis of histologic features (multinodular/plexiform architecture, multifocality of the primary tumor, or compelling personal or family history). The clinical, histologic and genetic findings were described. Risk stratification for progressive disease was assigned to 59 patients for whom complete data on primary resection and clinical follow-up were available. Using conventional criteria (primary tumor size and mitotic rate), 17 patients were at high risk, 17 were at moderate risk, 10 were at low risk, 12 were at very low risk and 3 were at no risk. Conventional risk stratification failed to predict disease progression, as 60% to 82% of patients with tumors ranging from very low risk to high risk for progressive disease developed distant metastases. Of the 3 patients categorized as having no risk for progressive disease by conventional risk stratification, 1 (33%) developed distant metastases.
Clinicopathologic Spectrum of Gastrointestinal T-cell Lymphoma: Reappraisal Based on T-cell Receptor Immunophenotypes.

This is a retrospective clinicopathologic analysis of 42 cases of GITCL especially addressing their TCR phenotype, including TCRβ and γ expression. The cases were obtained from Nagoya University Hospital and 38 collaborating hospitals in Japan. The criteria for inclusion were positivity for at least 1 of the T-cell antigens (CD3, CD4, CD5, CD8, TCR β and γ) determined either by IHC or flow cytometry and the absence of B-cell markers. EBER+ or ALK+ cases were excluded. No patient had a history of celiac disease. 42 cases of GITCL were identified. 9 of 42 (21%) GITCL were positive for TCR γ protein expression. Of note, 5 of these 9 patients also had TCR β+. 24 patients (57%) were negative for TCR β and γ. TCR β positivity without TCR γ expression was seen in 9 GITCL patients (21%). There was no significant difference in clinicopathologic parameters between TCR γ+β- and γ+ β+. Compared with TCR β+γ- or β-γ-, TCR γ+ cases were characterized by exclusive involvement of intestinal sites but not of stomach. Notably, TCR γ positivity was an independent unfavorable prognostic factor (P<0.001) and all of the TCR γ+ cases treated with chemotherapy were refractory to the initial treatment. Multivariate analysis showed that thrombocytopenia, TCR γ positivity, and presence of GI tract perforation were adverse prognostic factors. Considering these results, the authors support that TCR γ+ GITCL appear to constitute a distinct disease entity.

Monocentric Study of Bile Aspiration Associated with Biliary Brushing Performed During Endoscopic Retrograde Cholangiopancreatography in 239 patients With Symptomatic Biliary Stricture.
Cancer Cytopathol .2016 May;124(5):330-9

The objective of this study was to assess the diagnostic performance of bile aspiration (3 to 10 mL of bile collected above the stenosis) associated with biliary brushing during therapeutic ERCP. Among 239 patients with symptomatic biliary stricture from 2004 to 2009, 143 were men and 96 women (mean age: 67 and 68 y). Samples were evaluated by an experienced cytopathologist. The 289 cytologic samples were divided in 3 groups: bile aspiration alone (26%), biliary brushing alone (20%) and bile aspiration combined with brushing (54%). The cytologic diagnoses were as follows: 149 samples were benign (50%), 114 were malignant (38%), 34 had atypia (12%), and 1 had no diagnostic value. The final diagnoses were assessed by histology, FNA or long-term clinical follow-up (up to 4 years). The procedure output values were as follows: for bile aspiration alone, sensitivity was 56.4%, specificity was 93.9%, PPV was 91.7%, and NPV was 64.6%; for brushing alone, sensitivity was 62.5%, both specificity and the PPV were 100%, and the NPV was 73%; and, for bile aspiration and brushing combined,
sensitivity was 81%, both specificity and the PPV were 100%, and the NPV was 75%. Therefore, a combination of bile aspiration and brushing is best.

**Evaluation of Indeterminate Biliary Strictures: Is it Time to FISH or Cut Bait?**
Singhi AD, Slivka A.

This editorial article reviews the role of adjunct modalities that have been attempted to improve the sensitivity for diagnosing cholangiocarcinomas. Brush cytology, intraductal biopsy sampling and FNA performed alone are associated with low sensitivities, usually at or below 50%. FISH has been developed that uses fluorescent probes to hybridize to regions of chromosomes 3, 7, 17 and 9, locations that harbor some genetic alterations associated with cholangiocarcinoma. More recently next generation sequencing (NGS) can explore the genetic mutations with reduced costs and complexity, representing a potential replacement for FISH. Dudley et al used an NGS panel of 39 genes on a cohort of 81 bile duct brushings. Overall, NGS was superior to both cytology and FISH in detecting advanced neoplasia with 74% sensitivity and 98% specificity. Further, the combination of NGS and cytology yielded an increased sensitivity of 85% and maintained a high specificity of 96%. However, the sensitivity of NGS testing is still a limiting factor and a multimodal approach that integrates clinical, radiographic, cytologic, and molecular findings is still needed.

**Cystoisospora belli Infection of the Gallbladder in Immunocompetent Patients: A Clinicopathologic Review of 18 Cases.**
Lai KK, Goyne HE, Hernandez Gonzalo D, Miller KA, Tuohy M, Procop GW, Lamps LW, Patil DT

This study represents the largest series of cystoisosporiasis in immunocompetent patients and of cystoisosporiasis affecting the gallbladder. It describes the clinicopathologic features of 18 cases of Cystoisospora infection affecting the gallbladder (diagnosed over a 7-year period), compared with a control group (n=16). Mean age of infection: 33 years and male to female ratio 1:4.3. Cholecystectomy was performed for biliary dyskinesia (n=7), abdominal pain (n=7), suspected cholelithiasis (n=5), and cholecystitis (n=3). In 2 cases, Cystoisospora was found in donor gallbladders resected at liver transplantation. Calculi were identified in 2 cases and 11 controls. Surface and crypt epithelial disarray was present in 17/18 cases. 15/18 cases showed rare IELs. Mild chronic cholecystitis was documented in 13/18 cases. None of the cases showed acute cholecystitis, intramucosal eosinophilia, mural thickening, or serosal inflammation. Of the 11 cases with follow-up (average 15 months), none had evidence of disease related to Cystoisospora infection within the biliary tract or elsewhere in the GI tract. On the basis of the clinical follow-up, gallbladder cystoisosporiasis in immunocompetent individuals appears to be a self-limited infection.
American Gastroenterological Association Guidelines are Inaccurate in Detecting Pancreatic Cysts with Advanced Neoplasia: a Clinicopathologic Study of 225 patients with Supporting Molecular Data.
Gastrointest Endosc. 2016 Jun;83(6):1107-1117

The purpose of this study is to determine the short-term accuracy of the AGA guidelines in detecting advanced neoplasia (IPMN with adenocarcinoma, IPMN with HGD and cystic pancreatic NET). The study group consisted of 225 consecutive symptomatic and asymptomatic patients who were evaluated by EUS-guided FNA and had molecular analysis (KRAS, GNAS, VHL, TP53, PIK3CA and PTEN) for pancreatic cysts between 2014 and 2015. The AGA guidelines were retrospectively applied to the study cohort. Diagnostic pathology results were available for 41 patients (18%), with 13 (6%) harboring advanced neoplasia. Among these cases, the AGA guidelines identified advanced neoplasia with 62% sensitivity, 79% specificity, 57% PPV, and 82% NPV. Moreover, the AGA guidelines missed 45% of IPMNs with adenocarcinoma or HGD. For cases without confirmatory pathology, 27 of 184 patients (15%) with serous cystadenomas (SCAs) based on EUS findings and/or VHL alterations would have continued costly and unnecessary MRI surveillance. An alternative novel algorithmic pathway is proposed by the authors including molecular testing of pancreatic cyst fluid detecting advanced neoplasias with 100% sensitivity, 90% specificity, 79% PPV and 100% NPV.

The spectrum of histopathological changes encountered in pancreatectomy specimens after neoadjuvant chemoradiation, including subtle and less-well-recognized changes
Kalimuthu SN, Serra S, Dhani N, Chetty R

This paper reviews resected, borderline, pancreatic ductal adenocarcinomas with the aim of cataloging pancreas specific histologic features associated with neoadjuvant chemoradiation therapy (NCRT). In this review, cases were selected from patients who underwent a variety of different NRCT regimens. Therefore, unique morphologic findings are not associated with specific NRCT protocols. The authors grouped histologic features into two main categories: those associated with the residual tumor and those associated with the background non-neoplastic parenchyma. Many histologic features are well described and organized including nuclear and cytoplasmic changes as well as architectural aberrations (Table 1). A few points of emphasis include, 1) importance of identifying unique features of residual tumor cells within a desmoplastic fibrotic stoma and 2) recognizing the difference between atrophic, fibrotic changes within the non-neoplastic pancreatic parenchyma and residual tumor. In summary, this paper categorizes a wide range of morphologic changes within the neoplastic and non-neoplastic pancreatic parenchyma following NCRT.
Performing molecular biomarker studies on limited FFPE material from small biopsies or cell blocks made from fine-needle aspiration (FNA’s) are limited by low total tumor DNA and low percentage of tumor DNA compared to wild type. This paper describes a technique to utilize neoplastic cells directly from stained cytology smears. They performed qClamp xenonucleic technology and quantitative RT-PCR to detect common mutations and translocations in non-small cell lung carcinomas (NSCLC) and thyroid lesions from Diff-Quick and Papanicolaou (PAP) stained cytology smears. QClamp technology involves sequence specific wild-type template xenonucleic acid to suppress PCR amplification of wild-type template DNA and, therefore, allows selective PCR amplification of mutant templates only. The downside to this technology is that specific base changes, insertion and deletion sequences are unknown. For NSCLC the following mutations were interrogated: EGFR point mutations in exons 20 and 21, and in-frame deletions in exon 19; KRAS point mutations in codons 12, 13, and 61; and EML-4-ALK translocation. For papillary thyroid carcinomas the BRAF V600E point mutation was targeted. The authors found a 1% molecular alteration detection rate for these common mutations in as few as 50 cells with at least 90% tumor cellularity. The stated advantages are rapid turnaround time, with results between 1-2 days, and better quality of DNA/RNA from alcohol fixed slides in comparison to FFPE material.

The May issue of Archives of Pathology & Laboratory Medicine contains articles from the KOPANA (Korean Pathologists Association of North America) 2015 Spring Seminar. Numerous practical topics are reviewed in GI pathology, including practical points in gastric pathology, molecular subtypes of CRC, and clinical aspects of idiopathic IBD, to name a few. We refer the reader to the Archives website for this material.

http://www.archivesofpathology.org/toc/arpa/140/5

Journals Reviewed (May And June 2016)
Histopathology
Archives of Pathology and Lab Medicine
Modern Pathology
American Journal of Clinical Pathology
Journal of Pathology
Journal of Clinical Pathology
American Journal of Pathology
Human Pathology
Cancer Cytopathology
American Journal of Surgical Pathology
Advances in Anatomic Pathology
Journal of Molecular Diagnostics
Gastrointestinal Endoscopy
Gastroenterology Clinics of North America
Gastroenterology
Gut
American Journal of Gastroenterology
Clinical Gastroenterology Hepatology
Inflammatory Bowel Diseases
Diseases of the Colon and Rectum

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