Dysplasia in Barrett’s oesophagus: p53 immunostaining is more reproducible than haematoxylin and eosin diagnosis and improves overall reliability, while grading is poorly reproducible.

72 cases spanning the spectrum of Barrett’s esophagus were circulated to 10 pathologists pre-trained on p53 interpretation. Cases were classified on H&E using the four-tier Vienna system (negative, indefinite, low-grade, high-grade) and then by p53 staining using a qualitative system (significant or not significant staining pattern, and the two distinct aberrant patterns of expression, strong or absent). For the Vienna system, average unweighted kappa was 0.30; weighted kappa averaged 0.47. For definite dysplasia versus no definite dysplasia, average kappa was 0.55, but kappa for LGD versus HGD was only 0.31. For p53, using qualitative assessment, unweighted kappa was 0.6. Using both H&E and p53, average kappa was 0.61 for definite dysplasia versus other categories. The authors advocate the use of p53 as an ancillary marker in difficult cases to help categorize dysplasia as present, indefinite, or absent. However, there is no marker at present (including p53) which helps distinguish LGD from HGD.

Histologic intestinal metaplasia and endoscopic atrophy are predictors of gastric cancer development after Helicobacter pylori eradication.

In this retrospective long-term Japanese cohort study, the authors aimed to evaluate the relationship between the distribution of intestinal metaplasia (IM) and the degree of endoscopic atrophy at the initial endoscopy and the incidence of gastric cancer on follow-up in 749 consecutive patients, who underwent successful H. pylori eradication therapy. Patients were classified according to the distribution of IM as follows: no IM (IM group A), IM in the antrum only (IM group B), and IM in the corpus with or without IM in the antrum (IM group C). Atrophy was assessed by reviewing endoscopic images according to the Kimura-Takemoto classification system. A total of 573 eligible patients (mean age-58 y; F:M-1:1.2; median time to eradication 0.2 y, range 0.08-0.38 y; mean follow-up 6.2±4.8; mean EGD 4.7±4.2) with follow-up endoscopy were analyzed. They were characterized histologically as: IM group A – 399 (70%), IM group B – 117 (20%), and IM group C – 57 (10%). Endoscopically: none/mild atrophy – 168 (29%), moderate atrophy – 296 (52%), and severe atrophy – 109 (19%). 21(3.7%) patients developed gastric cancer (20 intestinal type; 1 diffuse type) during the study period. The cumulative 5-year incidences of gastric cancer were 3.2% overall, with 1.5%, 5.3%, and 9.8% in
IM groups A, B, and C, and 0.7%, 1.9%, and 10% in the none/mild, moderate, and severe endoscopic atrophy groups, respectively. Compared with IM group A, the hazard ratio for IM group B was 3.6 (95% CI, 1.2-11), and that for IM group C was 3.7 (95% CI, 1.1-12) by multivariate analysis. Compared with the none/mild endoscopic atrophy group, the hazard ratio for severe atrophy was 9.3 (95% CI, 1.7-174) by multivariate analysis. Based on these findings, the authors concluded that patients with histologic IM or severe endoscopic atrophy are at increased risk for gastric cancer development after *H. pylori* eradication, after which they require intensive follow-up.

**Risk of Gastric Cancer Among Patients With Intestinal Metaplasia of the Stomach in a US Integrated Health Care System.**
Reddy KM, Chang JI, Shi JM, Wu BU.

This retrospective cohort study sought to determine the incidence of gastric cancer among patients diagnosed with intestinal metaplasia of the stomach and to assess any associations with other risk factors including age, ethnicity, *H. pylori* status, family history and tobacco use.

The authors note that most previous studies assessing such relationships have been performed on high-risk patients and the literature provides little in the way of such studies in the United States population. While not explicitly stated, the text of the article suggests the authors were evaluating the incidence of gastric carcinoma as opposed to other stomach malignancies. By reviewing cases spanning an 11 year period, the authors identified 923 cases of patients with gastric intestinal metaplasia. Within this cohort, 25 individuals were noted to have developed gastric cancer (2.7%), with the majority (17) being diagnosed concurrently with the diagnosis of gastric intestinal metaplasia. For those patients who developed cancer after the diagnosis of intestinal metaplasia (8), the median time to diagnosis was 4.6 years. Of the risk factors evaluated, only a family history of gastric cancer and the presence of extensive intestinal metaplasia on initial testing were associated with an increased risk of gastric cancer when compared to age and sex matched control patients. The authors conclude that targeted surveillance of such patients may be prudent.

**PD-L1 expression is associated with massive lymphocyte infiltration and histology in gastric cancer**

This study aimed to explore the correlations among PD-L1, Epstein-Barr virus (EBV) infection, lymphocyte infiltration, HER2 expression, HER2 gene status, histology, and other clinicopathological factors in gastric cancer (GC). A total of 44 GCs with massive lymphocyte infiltration (GC-MLI), defined as the average number of tumor infiltrating lymphocytes (TILs)
>80%, and 93 cases of GC controls (<10% TILs) were studied with the following parameters: IHC expression levels of PD-L1 and HER2; FISH for HER2-positive cases with a score of 2+; EBER to test for EBV infection. In univariate analysis, PD-L1 expression was significantly associated with GC-MLI (P<.001), lower age (P=.019), EBV infection (P<.001), lower HER2 expression (P=.011), and diffuse/mixed type histology (P=.022). EBER-positive cases were significantly associated with GC-MLI (P<.001), lower age (P=.016), diffuse/mixed type of histology (P=.011), and lower HER2 expression (P=.032). In the multivariate logistic regression model, GC-MLI and the diffuse/mixed type histology were identified as 2 independent factors that affected PD-L1 expression (P<.001). PD-L1-positive cases had worse overall survival than PD-L1-negative cases (P=.011). Further study is necessary to determine whether PD-L1 inhibitory treatment may be beneficial in tumors with massive lymphocyte infiltration and the diffuse/mixed type histology.

**High Tumor Vascular Endothelial Growth Factor Expression Is Associated with Poorer Clinical Outcomes in Resected T3 Gastric Adenocarcinoma**


In this study the authors evaluated 453 T3 gastric cancers from patients from a single institution in China for expression of vascular endothelial growth factor (VEGF) by immunohistochemistry. The levels of expression were then correlated with outcomes. VEGF expression was scored using a five tiered system (Negative (less than 10%); 1+ (10-25%); 2+ (25-50%); 3+ (50-75%); and 4+ (>75%)). Low expression (2+ or less) tumors were compared with high expression (3+ or greater) and it was found that high expression was significantly associated with poorer median recurrence-free survival, poorer median overall survival time, higher overall recurrence, poorer overall survival time, and increased risk of recurrence.

**Immunohistochemistry as a surrogate for molecular subtyping of gastric adenocarcinoma**


The Cancer Genome Atlas Research Network recently classified gastric adenocarcinoma into 4 molecular subtypes: Epstein-Barr virus-positive tumors, microsatellite-unstable tumors, tumors with chromosomal instability, and genomically stable tumors. The authors stained 104 gastric adenocarcinomas for MLH1, p53, and EBER in situ hybridization. Cases were grouped based on staining patterns: Group 1 (EBER positive), 7 cases (7%); Group 2 (MLH1 deficient), 17 cases (16%); Group 3 (aberrant p53 staining, EBER negative, retained MLH1), 40 cases (38%); Group 4 (unremarkable staining), 40 cases (38%). This distribution was comparable to that found by the Research Network after accounting for the TP53 mutation rate in the chromosomal instability group. Group 1 patients had significantly longer follow-up times
(median, 70 months versus 13 months for other groups; \( P = .0324 \)). No group 2 cases overexpressed HER2. In group 3, 3 of 40 cases were HER2 immunohistochemistry positive, but 7 of 27 were HER2 positive by fluorescence in situ hybridization. The authors conclude that staining offers an efficient, reasonably accurate alternative for molecular subtyping of gastric adenocarcinoma, although some cases with chromosomal instability cannot be identified. They also postulate that the findings have potential prognostic and therapeutic implications.

**Comprehensive Mutation Profiling of Mucinous Gastric Carcinoma.**

In this paper, the authors investigated the molecular profiles of mucinous subtype of gastric carcinomas, and compared their findings to the molecular underpinnings that have been reported in non-mucinous gastric carcinomas. A total of 68 mucinous tumors were studied with an initial group of 16 carcinomas undergoing whole-exome sequencing. Targeted sequencing was performed on the remainder of the cases based on 114 genes identified during the aforementioned broader sequencing. The most frequently mutated gene was \( TP53 \) (55.9%), followed by \( ARID1A \) (20.6%), \( CDH1 \) (20.6%), \( MLL2 \) (19.1%), \( RBMXL3 \) (19.1%), and \( MLL3 \) (14.7%). The authors noted frequent mutations in genes associated with chromatin/histone modification including \( MLL \) genes and \( ARID1A \) (32/68 cases). This frequency is greater than that reported in other gastric cancers. Several other genes that are rarely reported to be mutated in other gastric carcinomas were identified in this cohort including \( RBMXL3 \) (n=13), \( MYH9 \) (n=9), and \( SDK1 \) (n=9). Several alterations of possible therapeutic importance were identified including \( MTOR \) (6/68; 8.8%), \( BRCA2 \) (6/68; 8.8%), \( BRCA1 \) (5/68; 7.4%) and \( ERBB3 \) (4/68; 5.9%). When the cohort was split into cases of differentiated and undifferentiated types of mucinous carcinoma, \( MYH9 \) mutations clustered in the latter group (9/46 cases) with no such mutations being identified on the former group. Furthermore, the authors noted that a comparative analysis of driver mutations in the differentiated mucinous carcinoma group was similar to intestinal-type gastric carcinoma. In contrast, the undifferentiated mucinous group appeared unrelated to either intestinal-type or diffuse-type gastric carcinomas. The authors postulated that undifferentiated mucinous carcinomas of the stomach may represent a distinct clinicopathologic entity.

**Dysregulated Wnt signalling and Recurrent Mutations of the Tumour Suppressor RNF43 in Early Gastric Carcinogenesis.**
The authors of this study sought to investigate the genomic and transcriptomic landscape among multiple points in the carcinogenesis pathway within the stomach. This paper included 39 cases of early gastric neoplasia from Korea and Japan, which were composed of 17 well- or moderately-differentiated adenocarcinomas with mucosal or submucosal invasion, 10 cases of high-grade dysplasia (HGD), and 12 cases of low-grade dysplasia (LGD). Transcriptome sequencing and identification of differentially expressed genes was performed on the aforementioned cases of neoplasia as well as adjacent areas of normal gastric mucosa. Overall, the expression patterns were notably different among normal mucosa, LGD and early gastric carcinoma (EGC). Cases of HGD exhibited overlapping features with LGD and EGC. Globally, genes related to cell-to-cell adhesion and extracellular matrix interactions were preferentially altered in EGC compared to LGD while Wnt signaling genes were downregulated in EGC. Given these initial findings, the authors evaluated the cases for mutations in a number of genes and found several alterations to be exclusive to EGC including TP53 (64.7%) and ARID1A (11.8%). Mutations in RNF43, ERBB2 and ERBB3 were present in cases of HGD and EGC, but not LGD. The authors pointed out that RNF43 and APC mutations were almost mutually exclusive and alterations in the latter gene were infrequently encountered in EGC (17.6%) while more common in LGD (66.7%). The authors concluded that their findings, including the presence of RNF43 mutations, might be useful in deciding on further therapy for gastric neoplasia.

**FGFR2 in gastric cancer: protein overexpression predicts gene amplification and high H-index predicts poor survival**


*Mod Pathol.* 2016 Sep;29(9):1095-103.


The authors of this study set out to correlate the expression of FGFR2b measured by a specific immunohistochemistry antibody (FPR2-D) with FGFR2 amplification measured by FISH. Previous reports of FGFR2 immunohistochemistry did not show good correlation with FGFR2 amplification; however, the FPR2-D antibody is described in the article as being specific for the FGFR2b isoform that is predominantly overexpressed in FGFR2 amplified cancers. In the initial discovery set and subsequent cohort there was a high correlation between immunohistochemistry and FISH results. A second aim of the study was to compare FGFR2b protein expression between primary and metastatic sites. Results of this part of the study showed that FGFR2b protein expression was more frequently seen in the metastatic focus than in the primary tumors. High levels of FGFR2b expression (define semi-quantitatively by H-score) were seen more frequently in diffuse type cancers, higher N stage, and was associated with a worse prognosis.

**Pathologic Response of HER2-positive Gastric Cancer to Trastuzumab-based Chemotherapy.**

Urabe M, Ushiku T, Seto Y, Fukayama M.

The goal of this study was to characterize the histologic response of gastric cancer to trastuzumab-based chemotherapy and its correlation with HER2 status. The authors identified 10 surgically resected cases and 11 biopsy specimens from inoperable patients after trastuzumab therapy. Histologic findings were characterized and compared with 10 surgically resected specimens from patients who underwent chemotherapy without trastuzumab (control group). HER2 status post-trastuzumab therapy was evaluated by immunohistochemistry (IHC) and dual-color in-situ hybridization (DISH) as per the standard scoring system in the treated resection and biopsy specimens. In surgically resected specimens, complete response was found in 2 and partial response (5% to 80%) to trastuzumab therapy was noted in 8. Histologically, the proportion of viable tumor cells was more in the superficial layers (mucosa/submucosa) when compared to deep layers. HER2+ (by IHC) tumor cells were noted in all the 8 cases with higher proportion of HER2+ tumor cells in the superficial layers. In 3 specimens, HER2+ tumor cells were noted exclusively in the superficial layers of which 2 cases showed only intravascular viable HER2+ tumor cells. The proportion of HER2+ tumor cells was higher in the primary tumor when compared to metastatic tumor in 6 of 7 cases. There was no significant difference in the HER2/CEP17 ratio (by HER2-DISH) between the preoperative biopsy and the post-trastuzumab surgical resection specimens. In contrast to the trastuzumab treatment group, the control group demonstrated more viable tumor cells in the deeper layers. 8 of 11 (73%) post-trastuzumab treatment biopsies were HER2+. Based on these findings, the authors concluded that there is selective survival of HER2+ tumor cells in the superficial areas and intravascular spaces post-trastuzumab therapy and that this may lead to underestimation of therapeutic effect of trastuzumab-based therapy, especially when evaluating HER2 status in post-trastuzumab treatment mucosal biopsies. The authors postulated that this selective difference in tumor survival can be secondary to heterogeneous distribution of monoclonal antibody within the tumor due to high affinity binding of the antibody to the tumor cells closer to the feeding vessels, which are located in the deeper layers (binding-site barrier).

Analysis of Biopsies from Duodenal Bulbs of All Endoscopy Patients Increases Detection of Abnormalities but has a Minimal Effect on Diagnosis of Celiac Disease.

This retrospective analysis evaluated the diagnostic yield of distal and duodenal bulb biopsies in the diagnosis of celiac disease. Unlike similar studies which concentrated on patients with established diagnosis or positive serologies, this investigation evaluated the role of these biopsies in a low-probability population. Data from 679 patients who had undergone an upper endoscopy with targeted biopsies of the distal duodenum and duodenal bulb were assessed for a number of clinical, laboratory and pathologic parameters, including age, sex, indications for biopsy, serologic findings and the presence of intraepithelial lymphocytes or villous blunting. A
A diagnosis of celiac disease was made if patients had positive serology and compatible histology. A total of 16 patients (2%) were identified as having celiac disease with a single case (0.1%) having histologic changes limited to the bulb. Abnormal histologic findings were identified in 265 (39%) of patients with chronic peptic duodenitis, active chronic peptic duodenitis, gastric heterotopia and Brunner gland hyperplasia being more common in the bulb as opposed to the distal duodenum. The authors concluded that targeted sampling of the duodenal bulb had minimal effect on celiac disease detection but did increase detection of histologic abnormalities.

Duodenal Bacteria From Patients With Celiac Disease and Healthy Subjects Distinctly Affect Gluten Breakdown and Immunogenicity

This study investigated gluten metabolism by opportunistic pathogens and commensal duodenal bacteria and characterized the capacity of the produced peptides to activate gluten-specific T-cells from CD patients. Germ-free C57BL/6 mice were colonized with bacteria isolated from the small intestine of CD patients or healthy controls, selected for their in vitro gluten-degrading capacity. After gluten force-feeding, gliadin amount and proteolytic activities were measured in intestinal contents. Peptides produced by bacteria used in mouse colonization from the immunogenic 33-mer gluten peptide were characterized by liquid chromatography tandem mass spectrometry and their immunogenic potential was evaluated using peripheral blood mononuclear cells from celiac patients after receiving a 3-day gluten challenge. Bacterial colonization produced distinct gluten-degradation patterns in the mouse small intestine. Pseudomonas aeruginosa, an opportunistic pathogen from CD patients, exhibited elastase activity and produced peptides that better translocated the mouse intestinal barrier. P. aeruginosa-modified gluten peptides activated gluten-specific T-cells from CD patients. In contrast, Lactobacillus spp. from the duodenum of non-CD controls degraded gluten peptides produced by human and P. aeruginosa proteases, reducing their immunogenicity. Small intestinal bacteria exhibit distinct gluten metabolic patterns in vivo, increasing or reducing gluten peptide immunogenicity. This microbe-gluten-host interaction may modulate autoimmune risk in genetically susceptible persons and may underlie the reported association of dysbiosis and CD.

A Cross-Sectional Study of the Prevalence of Gastrointestinal Symptoms and Pathology in Patients with Common Variable Immunodeficiency.
The authors performed a cross-sectional study to investigate the prevalence of gastrointestinal (GI) symptoms and histologic findings among a group of patients with common variable immunodeficiency (CVID). While similar studies have been previously published, this investigation was novel as it included individuals irrespective of GI symptoms. 112 CVID patients were invited to participate in this study of which 103 completed a detailed questionnaire regarding GI related symptoms and 53 agreed to undergo upper and lower endoscopic examinations. Additional laboratory testing was performed including analysis of a variety of soluble inflammatory markers as well as viral PCR and gene expression profiling studies on tissue. The most commonly reported symptoms included bloating (34%), pain (30%) and diarrhea (26%). Histologic findings which were most frequently encountered included decreased mucosal plasma cells (62%), increased intraepithelial duodenal lymphocytes (46%) and lymphoid hyperplasia (38%). While decreased plasma cells were not associated with increased GI symptoms, it was related to markers of increased systemic inflammation. Cases of CVID associated with increased intraepithelial lymphocytes, while microscopically resembling celiac disease, exhibited differential gene expression profiles compared to true celiac disease. Finally, in contrast to recently published literature, the authors found no significant evidence of involvement by a number of viral pathogens, including norovirus.

**Demonstration of Trophozoites of *G. Lamblia* in Ileal Mucosal Biopsy Specimens May Reveal Giardiasis in Patients With Significantly Inflamed Parasite-free Duodenal Mucosa.**
Oberhuber G, Mesteri I, Kopf W, Müller H.

The authors in this study described the clinicopathologic findings in 11 immunocompetent patients (5 Females, 6 Males, Median age 45y, range 35-62y) with chronic Giardiasis in which the trophozoites were only identified in the terminal ileum and the duodenal biopsies showed significant inflammation without any organisms. Clinical symptoms included severe diarrhea of at least 4 weeks duration (n=10), weight loss (n=4), and nausea with vomiting (n=4). Only one patient was asymptomatic. Biopsies from 10 patients showed significant villous architectural abnormalities with 7 patient biopsies showing total villous atrophy (grade IIIc), 2 biopsies with mild villous blunting (IIla), and 1 biopsy with marked villous blunting. All the duodenal biopsies showed increased number of plasma cells and lymphocytes in the lamina propria and varying numbers of neutrophils in the epithelium. The duodenal biopsy from one patient had significantly increased intraepithelial lymphocytes (IELs ) (>40/100 epithelial cells) mimicking celiac disease. *Giardia* trophozoites were not identified in the duodenal biopsies, but were identified in all biopsies from the ileum. Only two ileal biopsies demonstrated mild villous blunting. Epithelial neutrophilic infiltrate was noted in 6 ileal biopsies. >40 lymphocytes /100 epithelial cells were noted in ileal biopsies from 2 patients. One biopsy had associated acute colitis pattern of injury with rare trophozoites in the ascending colon. Based on these findings,
the authors concluded that giardiasis may be associated with significant duodenal pathology without discernible parasites in the biopsy specimens and that ileal biopsies were helpful in demonstrating the organisms in these patients. The authors postulated that inflammatory response in the duodenum led to reduced number of trophozoites, which were difficult to detect in duodenal biopsies.

**Mesenteric Arteriovenous Dysplasia/Vasculopathy Is Distinct From Fibromuscular Dysplasia.**


The authors of this study identified unique vascular changes that mimic fibromuscular dysplasia (FMD) in intestinal resection specimens for suspected cases of ischemia or Crohn’s disease. FMD is a rare idiopathic, noninflammatory, nonatherosclerotic vascular disorder that affects medium sized arteries, primarily renal, extracranial carotid and vertebral, which commonly occurs in children and young adults. FMD can rarely involve celiac and mesenteric arteries leading to intestinal ischemia. Changes similar to FMD have been identified by the authors in some intestinal resection specimens; however, these changes were identified in both arteries and veins. In this article, the authors characterized this unique form of mesenteric dysplasia/vasculopathy, which appears to be distinct from typical FMD. The authors identified 11 cases (8 females and 3 males, mean age 63 years), which fit the description of FMD-like vascular changes after systematically reviewing the pathology reports of 1016 cases of intestinal resections performed between 1982 and 2014 at their institution. Chronic abdominal pain (>1 year) was the most common presenting symptom. Two patients presented with acute abdomen requiring emergency surgical resection. The working clinical diagnosis was Crohn’s disease (CD) (45%), mass/lesion (27%), ileal conduit obstruction (9%), acute ischemia (9%) and rectal prolapse (9%). Seven patients had prior history of surgery. The authors categorized the pathologic findings as CD-like pattern of injury (n=5), ischemic pattern of injury (n=4) and others (n=2). In specimens with CD-like pattern of injury (3 ileal, 2 colonic), grossly there were multiple strictures and common mucosal changes included multifocal fissuring-type ulcers (100%), architectural distortion (80%), pyloric gland metaplasia (100%), submucosal lymphoid aggregates (100%), and submucosal fibrosis (80%). However, characteristic changes of CD, including basal plasmacytosis, transmural lymphoid aggregates, and granulomas were not identified. In four (4) cases (2 ileal, 2 ileocolonic) with ischemic pattern of injury, two cases showed diffuse hemorrhagic necrosis and 2 cases showed multifocal ulcers with features of chronic ischemic injury. The remaining 2 cases displayed small bowel carcinoids and rectal prolapse changes without any features of chronic or ischemic mucosal injury. Most importantly, the vascular changes identified mainly in the subserosal vessels included (1) concentric/eccentric smooth muscle collarette (9 cases well developed; 2 cases thin and irregular) around the tunica media of both the artery and the vein in ≥2 foci, (2) varying degrees of intimal and medial hyperplasia and adventitial fibrosis, and (3) lack of inflammation or thrombi. Movat stain was helpful in confirming these changes. In all cases, the vascular changes corresponded to the segment of bowel with abnormal mucosa. Unlike FMD, surgery appeared
to be curative since most patients (n=8) were asymptomatic on follow-up (mean 32 mo). Based on these findings, which are different from FMD, the authors proposed the term “mesenteric arteriovenous dysplasia/vasculopathy” (MAVD/V). Most importantly, the histologic findings can lead to misdiagnosis as CD.

Increased Proliferation of the Ileal Epithelium as a Remote Effect of Ulcerative Colitis.

The authors sought to determine whether the homeostasis of the ileal mucosa is altered in patients with ulcerative colitis. A new experimental mouse ulcerative colitis model was used (Il10/Nox1<sup>dKO</sup>). They also studied 9 UC patients who underwent resection, 4 of whom had cecal inflammation, but none with “backwash ileitis”, although it was not stated how they defined this. In paraffin embedded sections of the patient samples, Ki67 was significantly higher than controls and crypt length was also significantly longer. The mouse model revealed increased proliferation in the ileal crypts using Ki67 and BrdU after chronic, but not acute, TNBS induced colitis, which did not correlate with the severity of colonic inflammation. Mouse studies also identified increased ileal epithelial cell apoptosis, and activation of MAP kinase and Wnt/β-catenin pathways. Histology revealed no ileal inflammation and no inflammatory (pro- or anti-) cytokines were different from controls by mRNA or protein analysis. Peyer’s patch naïve CD4+ T cells were significantly higher and effector CD4+ T cells were significantly lower, possibly due to involvement of the IL-22 pathway. The authors conclude that a chronic colitis, such as UC, can affect the ileal mucosa homeostasis.

Prospective Evaluation of Terminal Ileitis in a Surveillance Population of Patients with Ulcerative Colitis.

This prospective case-control study of UC patients with inactive or mildly active disease who underwent colonoscopy examined the endoscopic and histologic features of the terminal ileum and found that 16 of 72 (22%) UC patients had ileitis which was significantly different from healthy controls (4 of 90, 4%, P < 0.001). Significant associations were found with colonic involvement of the ileocecal valve (P = 0.02) and alcohol use in the week prior to colonoscopy (P = 0.02). One UC case with ileitis was subsequently reclassified as Crohn’s disease. There were no associations with bowel preparation, UC medications, smoking, or NSAID use. The authors note that backwash was not likely the cause of the ileitis even in cases with colon-side
Involvement of the ileocecal valve because the valve was not endoscopically patulous or distended. The authors discuss their findings in light of prior studies, and note that clinicians should not use terminal ileal involvement alone to change a patient’s diagnosis from UC to Crohn’s disease.

Crypt apoptotic body counts in normal ileal biopsies overlap with graft-versus-host disease and acute cellular rejection of small bowel allografts

In intestinal transplant pathology, 2 or fewer apoptotic bodies per 10 consecutive crypts are considered normal, whereas 6 or more is consistent with mild acute cellular rejection (ACR). Three to 5 apoptotic bodies are often classified as indeterminate for ACR. The minimum diagnostic threshold for GVHD is controversial but also depends on the apoptotic body count (ABC). The authors reviewed 40 cases of normal ileal biopsies from healthy subjects (native intestines, no bone marrow transplant) who underwent screening colonoscopy with ileal biopsy to confirm complete colonoscopy. The authors recorded the number of biopsy pieces per specimen and the maximum ABC in 10 consecutive crypts. Twenty-six of 40 patients (65%) had an ABC of 3 or more in 10 crypts, thus only 35% were "normal." Using the current guidelines, 55% of normal small bowel biopsies could conceivably be diagnosed as indeterminate for ACR, while 10% could potentially be diagnosed as mild ACR; 60% meet NIH criteria for GVHD. The authors share that large and meticulous clinical pathologic studies will be needed to establish better diagnostic criteria for ACR and GVHD in the small intestine.

Comparative incidence of rejection occurring in small intestinal and colonic mucosal biopsies of patients undergoing intestinal transplantation.

This retrospective study looked at all intestinal transplants (ITx) with colon at a single center between 2009 and 2014. Paired biopsies in small bowel and colonic grafts were evaluated blindly by two experienced GI subspecialists and were graded based on international consensus criteria, with modifications for colon biopsies. Each biopsy was assessed as negative or positive for acute cellular rejection (ACR). 15 patients underwent paired biopsies. Agreement for the grade of ACR in the small bowel biopsies (kappa) was 0.62; kappa for colon biopsies was 0.65. Inter-rater agreement was better for biopsies negative for ACR and for higher grades of ACR. Overall, about 75% of paired biopsies were concordant for presence or absence of ACR, with modest agreement for the presence or absence of ACR between small bowel and colon biopsies (kappa of 0.44). The authors suggest that colon biopsy alone may not be sufficient to exclude ACR after ITx. [Modified criteria used in the colon are as follows: mild ACR in graft colon
biopsies was defined as at least 6 apoptotic bodies per 10 crypt cross-sections if the apoptotic bodies were of a larger “popcorn” type, or at least 10 apoptotic bodies per 10 crypt cross-sections if the apoptotic bodies were of a smaller “pinpoint” type.]

**Ileal “carcinoid” tumors—small size belies deadly intent: high rate of nodal metastasis in tumors ≤1 cm in size**


Although 2 cm is a general cut-off point for risk of lymph node metastasis in intestinal NETs in the absence of other high-risk features, metastases have been reported in 12% of tumors of small (1cm or less) tumors in the jejunum and ileum. Twenty-one small (≤1 cm) ileal NETs were identified from 2 institutions; six (29%) were multifocal and 7 (33%) had distant metastasis at diagnosis. Regional lymph nodes were examined in 14 cases (67%), and 10 of these cases (71%) showed lymph node metastasis. Mean primary tumor size in cases with nodal metastasis was 7.3 mm. In this series of ileal NETs ≤1 cm in size, the rate of lymph node metastasis was 48% overall and 71% for cases with regional lymph node resections. In addition, 33% showed distant metastasis at the time of diagnosis. Tumors as small as 3 mm and those confined to the submucosa can give rise to nodal metastasis; the authors emphasize the need for consideration of local resection with regional lymphadenectomy, even for subcentimeter ileal NETs.

**The Significance of Sessile Serrated Polyps in Inflammatory Bowel Disease.**


This retrospective review included 134 IBD patients with a total of 147 serrated polyps on biopsy or resection. The first serrated polyp was designated as the index polyp, and all serrated polyps were categorized as sessile serrated poly (SSP), hyperplastic polyp (HP), or serrated polyp unclassifiable (SPU) based on H&E. Similar to sporadic serrated polyps, 76% of SSPs were in the right colon, as compared to 42% of SPUs and 28% of HPs (P = 0.002). Interestingly, about one-third of patients in each group had a focus of synchronous visible dysplasia, however, multifocal synchronous visible dysplasia was significantly more common in SSP (45%) and SPU (67%) compared to HP (12%) (P = 0.031). In 13 IBD patients with SSP who underwent followup, a larger index SSP size was associated with a higher risk of developing metachronous visible dysplasia (10% increased risk for every 1 mm increase in size, P = 0.028) but not for developing subsequent SSP. The authors suggest that an index SSP in an IBD patient is a marker for higher risk of developing visible neoplasia.
High frequency of KRAS mutation in early onset colorectal adenocarcinoma: implications for pathogenesis  
Watson R, Liu TC, Ruzinova MB.  

This study identified 68 consecutive sporadic early onset colorectal cancer cases with available molecular data treated between 2007 and 2014. Consistent with previous reports, the majority of sporadic early onset colorectal cancer patients had left-sided tumors, which were predominately of low histologic grade, but advanced clinical stage. A subset of tumors (<40%) contained mucinous or signet ring cell features. DNA mismatch repair pathway, commonly associated with Lynch syndrome, was abnormal only in a minor subset of cases. In contrast to the low prevalence (<30%) of KRAS mutations reported by previous studies, this study found a significantly higher proportion (54%) of early onset colorectal cancer cases harbored KRAS mutations independent of tumor stage. The high prevalence of KRAS mutation in early onset colorectal cancer suggests that it shares common genetic initiating events with colorectal cancer in older patients.

Loss of INI1 expression in colorectal carcinoma is associated with high tumor grade, poor survival, BRAFV600E mutation, and mismatch repair deficiency  

SMARCB1 is a tumor suppressor gene that encodes for the protein INI1. SMARCB1 is commonly inactivated and INI1 correspondingly shows loss of expression in a range of malignant neoplasms including rhabdoid tumors, renal medullary carcinomas, and epithelioid sarcomas. Loss of INI1 expression has recently been reported in occasional gastrointestinal adenocarcinomas. The authors sought to investigate the incidence and clinicopathological significance of INI1 loss in colorectal adenocarcinoma (CRC). Immunohistochemistry for INI1 was performed in tissue microarray (TMA) format on a well-characterized and unselected cohort of CRCs undergoing surgical resection. If staining was negative or equivocal in the TMA sections, immunohistochemistry was repeated on whole sections. Focal or widespread negative staining for INI1 was identified in whole sections from 14 (0.46%) of 3051 CRCs. In 7 (50%) of 14 negative cases, the loss of staining was focal, whereas the remainder were characterized by negative staining in all neoplastic cells in whole sections. In the cases with focal staining, loss of staining was frequently found in areas of poor differentiation. Global or focal INI1 loss was strongly associated with higher histological grade, larger tumor size and poor overall survival (P<.001). The authors conclude that INI1 loss occurs rarely (0.46% when screened by TMA) in CRC, where it is associated with higher grade, larger tumor size, poorer survival, mismatch repair deficiency, and BRAFV600E mutation.
Significant Individual Variation Between Pathologists in the Evaluation of Colon Cancer Specimens After Complete Mesocolic Excision
Munkedal DL, Laurberg S, Hagemann-Madsen, R, Stribolt K, Krag S, Quirke P, West N,
Dis Colon Rectum 2016; 59: 953-961

This exploratory study aimed to validate the pathologic evaluation of 100 complete mesocolic excisions (CME) for colon carcinoma. CME involves dissection within the mesocolic plane when separating the colon and mesocolon from the retroperitoneum. The goal is removal of the entire tumor and all tumor draining lymph nodes within an intact facial and peritoneal lined specimen. The pathologists role is to grade the quality of the resection in the mesocolic plane by assessing the degree of a smooth and intact surface. In this study, 4 GI pathologists and 2 abdominal surgeons reviewed pictures of the gross specimens in two rounds. The first 50 were used to determine a detailed grading procedure. The results from an experienced pathologist from round 1 served as the reference standard. This system was then applied to the second round of 50 specimens. Grading was based on the whether the specimen was resected in the mesocolic plane (good-quality: fascial and peritoneal lined with little or no defects), the intramesocolic plane (moderate quality: moderate amount of mesocolon and defects deeper than 5mm but does not reach the muscularis propria) or the muscularis propria plane (poor quality: at least one defect reaching the muscularis propria). The results showed poor intraobserver and interobserver variability between pathologists, but improvement after a grading system was implemented. The authors state the use of photos instead of the actual specimen and small sample size, in particular very few CME specimens resected within the muscularis propria plane, as limitations to this study. In conclusion, the authors caution using current grading criteria of CME’s for clinical studies.

PD-L1 expression in colorectal cancer is associated with microsatellite instability, BRAF mutation, medullary morphology and cytotoxic tumor-infiltrating lymphocytes
Rosenbaum MW, Bledsoe JR, Morales-Oyarvide V, Huynh TG, Mino-Kenudson M.
Mod Pathol. 2016 Sep;29(9):1104-12.

This study looks at the expression of PD-L1 in colorectal cancer and its clinicopathologic features and molecular features including microsatellite instability status. PD-1 and its ligand (PD-L1) related therapy has recently become important in treatment for other malignancies (e.g. melanoma and lung cancers). In contrast colorectal cancer has shown a very low overall response rate, with the exception of a subset of tumors with microsatellite instability and increased intra-tumoral lymphocytes. In this study a set of tumors with known microsatellite status were evaluated by immunohistochemistry for PD-L1. The findings showed PD-L1 expression was associated with increased CD8 positive infiltrating lymphocytes, medullary phenotype, poor differentiation, and microsatellite instability. PD-L1 expression was not predictive of survival overall, but within the microsatellite subgroup it was associated with worse disease free survival. The authors conclude that the findings may explain why PD-L1
related therapy may be more effective in microsatellite unstable tumors and that PD-L1 immunohistochemistry may play a predictive and prognostic role in colorectal cancer.

**Albumin expression distinguishes bile duct adenomas from metastatic adenocarcinoma.**
Moy AP, Arora K, Deshpande V.

Branched-chain ISH was used to study albumin reactivity in bile duct adenomas. BRAF mutation status was studied, as well as the ability to detect the BRAFV600E mutation with IHC. Entire sections of bile duct adenomas (26 total) were stained for BRAF and albumin, as well as 3 cases of bile duct hamartoma. 158 pancreatic ductal adenocarcinomas were studied for albumin expression by bISH on a tissue microarray, including whole sections from 30 cases) and IHC for BRAFV600E was performed on 49 of these cases. Albumin expression was performed on tissue microarrays from an assortment of primary GI adenocarcinomas (esophageal, gastric, periampullary, and colonic). 23/25 (92%) of bile duct adenomas stained positive for albumin by bISH, of which 18 (78%) showed diffuse staining and five (~22%) showed focal staining. Two of 3 bile duct hamartomas stained positive for albumin (one with focal staining); the third case was not evaluable due to background staining. In contrast to the adenomas, albumin staining was absent in all pancreatic ductal adenocarcinomas whether on whole section or on microarray (P<0.0001). Albumin was not detected in the esophageal, gastric, periampullary, and colonic adenocarcinomas. BRAFV600E expression was detected by IHC in 7/16 (~44%) of bile duct adenomas, including one case with focal cytological atypia (the other was not stained for BRAFV600E). Only 5 of 106 (4.7%) of pancreatic ductal adenocarcinomas were positive for BRAFV600E (P<0.001). Both bile duct hamartomas lacked BRAFV600E staining by IHC. This study indicates the significant utility of albumin bISH and BRAFV600E IHC on distinguishing bile duct adenomas from metastatic adenocarcinomas.

**Progression From Perianal High-Grade Anal Intraepithelial Neoplasia to Anal Cancer in HIV-Positive Men Who Have Sex With Men**
Tinmouth J, Peeva V, Amare H, Blitz S, Raboud J, Sano M, Steele L, Salit, I
Dis Colon Rectum 2016; 59: 836-842

This prospective cohort study screened 550 HIV-positive men who have sex with men (MSM) to determine the rate of progression from high grade anal intraepithelial neoplasia (HGAIN) to invasive squamous cell carcinoma. HIV positive MSM have the highest reported risk of developing anal cancer. Therefore, the purpose of this study was to understand the rate of progression from dysplastic lesions to invasive cancers as well as identify factors associated with this progression. Of the 550 patients who underwent high resolution anoscopy (HRA) by experienced clinicians 48 showed HGAIN on biopsy of either internal or external lesions. 3 patients were lost to follow up. Therefore, the final cohort consisted of 38 patients. In this
study the prevalence of HGAIN was 8%. The median age was 48 years old, the average CD4 count was 330 cells/ml and 68% had undetectable viral loads. The majority of patients had symptoms such as anal discharge, anal bleeding and anal pain. The authors state that the gross appearance of the lesions was variable and that histology was essential for a definitive diagnosis of HGAIN. HGAIN was treated by a variety of methods based on personal preference and burden of disease: local excision, thermocoagulation, topical treatment with either 5-flourouracil or imiquimod and close monitoring. Of the 35 patients without a previous history of anal cancer, 5 progressed from HGAIN to invasive SCC (14%), which correlates with a rate of progression of 5.2 cases per 100 person-years. The authors note that the rate of local excision was lower in this cohort than in others and acknowledge that those treated less aggressively tended to have a higher rate of progression. Overall, the study reports that HIV-positive MSM are at increased risk of progression from HGAIN to invasive SCC and should undergo HRA with biopsy for a definitive diagnosis and treatment.

**Adenocarcinoma ex-goblet cell carcinoid (appendiceal-type crypt cell adenocarcinoma) is a morphologically distinct entity with highly aggressive behavior and frequent association with peritoneal/intra-abdominal dissemination: an analysis of 77 cases**


This study describes a series of aggressive adenocarcinomas arising from the less aggressive goblet cell carcinoma, adenocarcinoma ex-goblet cell carcinoid. The authors describe various patterns, usually seen in combination, that they claim are somewhat recognizable even in metastatic sites. The seven patterns described are: 1) ordinary goblet cell carcinoid; 2) poorly cohesive goblet cell; 3) poorly cohesive non-mucinous cell; 4) microglandular; 5) mixed “other” carcinoma; 6) goblet cell carcinoid with high-grade morphology; 7) solid sheet-like pattern punctuated by goblet cells/microglandular units. The authors also noted that, in contrast to intestinal type adenocarcinoma, adenocarcinoma ex goblet cell carcinoid occurs predominantly in women and is often mistaken for a gynecologic malignancy.

**Prevalence of Sclerosing Cholangitis Detected by Magnetic Resonance Cholangiography in Patients With Long-term Inflammatory Bowel Disease**


The prevalence of primary sclerosing cholangitis (PSC) among patients with inflammatory bowel disease (IBD) is unclear. Patients with IBD might be screened for PSC using magnetic resonance cholangiography (MRC). The authors aimed to estimate the frequency and distribution of MRC-detected lesions that indicate PSC in patients with IBD 20 years after their initial diagnosis and to identify clinical characteristics associated with these findings. Follow-up analysis was performed on a population-based cohort of 756 patients in South-Eastern Norway diagnosed with IBD from January 1, 1990 through December 31, 1993. Of these subjects, 470 attended a follow-up evaluation 20 years later in which they were offered routine clinical blood testing and ileocolonoscopy; 322 were screened by MRC (222 with ulcerative colitis and 100 with Crohn’s disease). Two radiologists independently evaluated results from the MRC examinations. In the MRC examination, 24 patients (7.5%) were found to have PSC-like lesions; only 7 of these patients (2.2%) were known to have PSC. One patient was initially missed and 1 had small-duct PSC, so the final prevalence of PSC was 8.1%. Extensive colitis, a high prevalence of colectomy, and chronic and continuous symptoms of IBD occurred in significantly more patients with suspected PSC than without PSC (P = .029, P = .002, and P = .012, respectively). Among patients with subclinical features of PSC, the MRC progression score for PSC increased when they were re-examined after a median 3.2 years (P = .046). Using MRC analysis of patients with long-term IBD, the prevalence of PSC was 3-fold higher than that detected based on symptoms. Sixty-five percent of patients had subclinical PSC associated with progressive IBD, with no biochemical abnormalities and mild disease, based on radiology findings. PSC appears to progress in patients with subclinical disease, but long-term outcomes are not known.

Development and Validation of a Template-Independent Next-Generation Sequencing Assay for Detecting Low-Level Resistance-Associated Variants of Hepatitis C Virus
Wei B, Kang J, Kibukawa M, Chen L, Qiu P, Lahser F, Marton M, and Levitan D
J Mol Diagn 2016,18: 643-656

Both traditional treatment with pegylated interferon alpha/ribavirin and direct acting antiviral (DAA) drugs have varying responses to different genotypes and subtypes of HCV. The genetic variability of HCV has been classified into four hierarchical strata, which show geographical variation: genotypes, subtypes, isolates, and quasispecies. In one individual infected with HCV, the virus exists as a mixture of genetically distinct but closely related genomes described as a quasispecies. The development of quasispecies is believed to be secondary to high viral load and error-prone RNA replication machinery leading to treatment resistance-associated variants (RAV). Therefore, these authors describe a method of whole HCV genome, template-independent (TI) next generation sequencing (NGS) utilizing a RNA-seq method of random primed cDNA synthesis combined with a unique RNA extraction and human rRNA depletion procedure. The advantage of TI-NGS is the ability to sequence variants that may not be represented in the public nucleotide sequence databases. Therefore, rare, geographically related sequences of all subtypes and treatment RAV’s do not need to be known ahead of time. The specimens used in this study were 1) 3 high viral load HCV plasma cells and 2 HCV serum
samples purchased from commercial companies 2) Negative controls from pooled plasma samples from 5 normal healthy volunteers 3) 17 clinical plasma samples collected from a clinical trial with DAA drugs, of which 2 patients were resistant 4) In vitro assays using plasmids to determine resistance variants associated with NS3/4A protease inhibitor grazoprevir and NS5A replication inhibitor elbasvir. All NGS libraries were run on a MiSeq instrument with Illumina MiSeq Reagent kit v3 with 260x260 cycles. The results show that viral loads from the commercial samples had less correlation than the viral loads performed on the clinical samples. The authors suggest this is likely due to the fact that viral loads from the commercial samples were determined by different methods. HCV subtypes were found to have high accuracy, 100% when compared to the NS5B small amplicon sequencing-based phylogenetic analysis. In determining low-level genotype/subtype in mixed infections, TI-NGS had a lower sensitivity than expected, also thought to be related to initial viral loads being determined by different assay methods. The in-vitro transcribed HCV RNA samples showed excellent correlations with expected variant allele fraction’s (VAF’s) and measured VAFs. Estimated sensitivity, specificity, and NPV for in vitro samples depleted of human plasma RNA were stated as excellent (>0.95) starting at 1% VAF cutoff. PPV improved at the 3% VAF cutoff. Sanger confirmation of 2 samples revealed some discrepancies. The authors explain challenges included lack of publically available GT6 sequences to design primers. Since TI-NGS called variants that the Sanger confirmation did not, the authors suggested that primers were designed on top of those variants and were therefore missed. This hypothesis was confirmed by designing template-dependent NGS assays to confirm the variants found on the TI-NGS assay and subsequently missed by Sanger confirmation. In conclusion, the authors admit higher viral loads (greater than 10⁶) are required to achieve acceptable sensitivity, specificity, NPV and PPV with TI-NGS. However, they state that for less well-known subtypes and for DAA related variants, TI-NGS has the advantage of detecting variants that are not yet known. Therefore, TI-NGS is best applied in a research setting for HCV subtyping, genotype/subtype infection detection and the detection of low level DAA-treatment resistant variants.

The expression of arginase-1, keratin (K) 8 and K18 in combined hepatocellular cholangiocarcinoma, subtypes with stem-cell features, intermediate-cell type
J Clin Pathol 2016;0:1–6

The WHO defines two main types of CHC; classical type and subtypes with stem-cell features which is further divided into 1) typical subtype 2) intermediate-cell subtype (CHC-INT) and 3) cholangiolocellular subtype. A previous study by this same group reported low HepPar1 expression in cholangiocarcinomas, intermediate-cell type (CHC-INT) and therefore sought to discover more sensitive hepatocyte markers within this tumor subtype. This paper interrogates 32 CHC-INT with a series of immunohistochemical markers: Arginase-1, HepPar-1, keratin 8, keratin 7 and keratin 18 and keratin 19. Protein expression was scored from 0-4 where a score
of 0 correlated with no staining; 1 with 1-5% positive cells; 2 6-25% positive cells; 3 26-50% positive cells; and 4 >50% positive cells. Cases with a score >3 were placed into a high expression group and those with <2 into a low expression group. The authors summarized that 9 cases showed high Arg-1 expression and 23 cases revealed low expression. Arg-1 was significantly higher than HepPar1 and significantly lower than keratin 18, 19 and 7 in CHC-INT’s. Arg-1 was more frequently expressed in trabecular structures, whereas Keratin 8 was more frequently expressed in glandular structures. Keratin 18 showed diffuse expression throughout the tumor. In terms of clinical correlation with pathologic findings, Arg-1 high expression tumors showed a significantly smaller size than those with low Arg-1 expression. Therefore, the authors suggest Arg-1 expression to be associated with a less aggressive phenotype. In conclusion, the authors state that although IHC is not essential for making a diagnosis, keratin 8 and Arg-1 are helpful in identifying intermediate cells between hepatocytes and cholangiocytes in CHC-INT.

A Practical Approach to the Classification of WHO Grade 3 (G3) Well-differentiated Neuroendocrine Tumor (WD-NET) and Poorly Differentiated Neuroendocrine Carcinoma (PD-NEC) of the Pancreas.
Tang LH, Basturk O, Sue JJ, Klimstra DS.

The primary goal of this study is to determine the utility of a selected panel of immunohistochemical stains comprised of DAXX, ATRX, SMAD4, RB, and p53 to improve the classification of WHO Grade 3 neuroendocrine neoplasms into well-differentiated neuroendocrine tumor (WD-NET) and poorly differentiated neuroendocrine carcinoma – small cell and large cell types (PD-NEC, PD-NEC-SCC and PD-LEC-LCC respectively), which are not well defined histologically. Loss of DAXX or ATRX protein expression is identified in WD-NET. PD-NECs commonly show mutations in TP53, RB1 and SMAD4 leading to loss of expression of SMAD4 and RB1 and overexpression of p53. A total of 33 cases (mean age 57y±16y, range 13 to 81y; M:F - 17:16; Ki67 index >20%, mean 60%±20%, range 26%-93%), which fit the current criteria of WHO grade 3 neuroendocrine neoplasms, were identified. Three expert pathologists independently attempted to classify them into WD-NET, PD-NEC-SCC and PD-NEC-LCC based on histology in a single representative section from each case without knowledge of Ki67 proliferation fractions. A consensus diagnosis based on morphology alone was achieved in 11/33 (33%) – 6 WD-NET, 3 PD-NEC-SCC, and 2 PD-NEC-LCC. In 2 cases of PD-NEC, reviewers were conflicted between PD-NEC-SCC and PD-NEC-LCC. 20 cases, in which consensus was not reached, were classified as ambiguous. Ki67 could not accurately distinguish between WD-NET and PD-NEC as 35% (7/20) of the WD-NET cases showed Ki67>55%; and 33% (4/12) of the PD-NEC cases showed Ki67<55%. Looking at the surrogate markers for WD-NET and PD-NEC, IHC confirmed 3/6 cases with morphologic consensus diagnosis of WD-NET (either loss of DAXX or ATRX) and 6/7 PD-NEC cases (abnormal expression of p53, Rb, and/or SMAD4). 12/20 cases (60%) with no consensus were defined as WD-NET (7) or PD-NEC (5) based on IHC alone. Additional histologic findings after review of slides from all specimens in each case was helpful
in further classification of 11 cases, WD-NET (10) and PD-NEC (1), in which IHC had failed to
demonstrate abnormalities. 1 case remained undetermined with normal expression of all
markers and no evidence of entity-defining histologic findings in other slides. Using the final IHC
and clinicopathologic classification, the disease-specific survival was 75 and 11 months for the
WD-NET and PD-NEC groups, respectively (p<0.0001). Based on these findings, the authors
concluded that morphologic diagnosis of high-grade pancreatic neuroendocrine neoplasms is
challenging, especially when limited pathologic materials are available; this necessitates better
defined criteria and knowledge of the histology of prior specimens or other sites of disease.
Ancillary IHC can facilitate accurate diagnosis and prognosis in the majority of cases, thus
providing guidance for appropriate clinical management.

Undifferentiated Carcinoma With Osteoclastic Giant Cells of the Pancreas: Clinicopathologic
Analysis of 38 Cases Highlights a More Protracted Clinical Course Than Currently Appreciated.
Muraki T1, Reid MD, Basturk O, Jang KT, Bedolla G, Bagci P, Mittal P, Memis B, Katabi N,
Bandypadhyay S, Sarmiento JM, Krasinskas A, Klimstra DS, Adsay V.

This multi-institutional study aimed to investigate the clinicopathologic characteristics and
prognosis of undifferentiated carcinomas with osteoclastic giant cells of the pancreas (OGC), a
rare and distinct tumor of pancreas regarded as sarcomatoid carcinoma with poor prognosis.
The authors reviewed the clinicopathologic features of 38 OSCs and contrasted those with 725
resected ductal adenocarcinomas (PDCs). The mean age at resection of OSCs was a close to a
decade younger than PDCs (mean, 57.9 y; vs. mean, 65.0 y P=0.0059). Grossly, OSCs were
significantly larger than PDCs (mean, 5.3 vs. 3.2 cm, respectively, P=0.0004). About a third
(36.1%) of resected OGCs occurred in the body/tail (36.1% vs. 16.0% for PDCs, respectively,
P=0.0004). Histologically, these tumors were composed of 3 distinct cell populations, including
osteoclastic giant cells (range 5-100%, mean 57.1%), histiocyte-like sarcomatoid cells (HSC) and
pleomorphic giant carcinoma cells (PCs). Twenty-nine (76%) OGCs were associated with an
invasive PDC. 8 OGCs arose in tumoral intraepithelial neoplasms, 4 in mucinous cystic
neoplasms with high grade dysplasia and 4 in intraductal papillary mucinous neoplasms with
high grade dysplasia. 23 (61%) OGCs showed prominent intraductal/intracystic growth. Lymph-
vascular invasion was present in 22 (62.9%). However, in OSCs, the frequency of lymph node
metastasis was significantly less than observed in PDCs (22.6% vs. 64.0%, respectively,
P<0.0001). The incidence of perineural invasion was significantly lower than seen in PDCs (31.6
% vs 85.5%, P<0.0001). High-grade PanIN-3/carcinoma in situ was identified in 18 (47%) cases.
Osteoid formation was present in 12 cases. Follow-up biopsy of 8 cases with distant metastatic
tumors showed adenocarcinoma pattern in 4 and sarcomatoid OGC pattern in the other 4.
Immunohistochemistry was performed on 24 OGC cases. CD68 expression was only noted in
osteoclastic giant cells. The background spindle cells and pleomorphic/giant carcinoma cells
often showed p53 expression and lacked cytokeratin expression. Clinically, the survival at 3
years of OGCs was significantly better than that of PDCs (59.1% vs. 15.7%, respectively,
P=0.0009). By applying a modified version of the grading system used for osseous OGC tumors
by Netherlands Committee on Bone Tumors, pancreatic grade I/II (n=26) OGCs had a better survival at 5 years (73.1%) than those that qualified as grade III/IV (n=12) (28.6%, Log-rank test P=0.0288). Based on these findings, the authors concluded that pancreatic OGCs present with larger tumor size and in slightly younger patients than PDC. They are associated with mucinous cystic neoplasms/intraductal papillary mucinous neoplasms. Importantly, OGCs have a significantly better prognosis than is currently reflected in the literature.

The October 2016 issue of Archives of Pathology & Laboratory Medicine includes a special section with based on case presentations from the 2015 New Frontiers in Pathology, an annual seminar led by Univ. of Michigan faculty. The following three review articles are of particular relevance to the GIPS membership.

Cytologic and Immunohistochemical Evaluation of Low-Grade Spindle Cell Lesions of the Gastrointestinal Tract.
Virani N, Pang J, Lew M.

Intraductal Tubulopapillary Neoplasm of the Pancreas: An Update From a Pathologist's Perspective.
Rooney SL, Shi J.

A Historical Perspective and Exposé on Serrated Polyps of the Colorectum.
Choi EY, Appelman HD.
https://www.ncbi.nlm.nih.gov/pubmed/27684980
Journals Reviewed (September and October 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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