ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus.
Shaheen NJ, Falk GW, Iyer PG, Gerson LB.

American College of Gastroenterology Guidelines on Barrett’s esophagus diagnosis, screening, surveillance and therapy. Excellent summary of the full recommendation is in Table 1 of the article. Most relevant to pathologists, recommendations regarding diagnosis of BE include:

“1. BE should be diagnosed when there is extension of salmon-colored mucosa into the tubular esophagus extending ≥1 cm proximal to the gastroesophageal junction with biopsy confirmation of IM (strong recommendation, low level of evidence).

2. Endoscopic biopsy should not be performed in the presence of a normal Z line or a Z line with <1 cm of variability (strong recommendation, low level of evidence)…

5. In patients with suspected BE, at least 8 random biopsies should be obtained to maximize the yield of IM on histology. In patients with short (1–2 cm) segments of suspected BE in whom 8 biopsies are unattainable, at least 4 biopsies per cm of circumferential BE, and one biopsy per cm in tongues of BE, should be taken (conditional recommendation, low level of evidence).”

Therefore, the finding of intestinal metaplasia in an endoscopically abnormal segment less than 1 cm is not diagnostic of BE.

A Prospective Study on the Usefulness of Duodenal Bulb Biopsies in Celiac Disease Diagnosis in Children: Urging Caution.

This prospective study included 22 children with celiac disease (confirmed clinically and histologically) and 22 non-celiac control children. Centralized interpretation of the duodenal bulb biopsies included villous height and crypt depth ratios. IgA deposits targeting transglutaminase 2 were also evaluated. 45% (20 of 44) bulb specimens were inadequate for morphometric measurements, including after reorienting and recutting. Interestingly, 77% (10 of 13) non-celiac control patients has an injured bulb mucosa, including flattened villi (villus height : crypt depth
All celiac patients had ratios <2 (mean 0.2). This finding indicates an increased risk of false-positive diagnosis. IgA deposits were able to separate celiac patients from controls, and may be helpful when the biopsy specimen is inadequate for morphometric analysis. The mean density of intraepithelial lymphocytes was increased in more celiac patients than in controls. Overall, the authors urge caution as to an increased risk of false positive celiac diagnosis if biopsies are restricted to the duodenal bulb in pediatric patients undergoing endoscopy.

**Gastrointestinal Findings in the Largest Series of Patients With Hereditary Biallelic Mismatch Repair Deficiency Syndrome: Report from the International Consortium.**


This multinational study characterizes the GI phenotype in patients with hereditary biallelic mismatch repair deficiency (BMMRD). GI data were available on 24 individuals. Colonic adenomas were found as early as 7 years of age, and small bowel adenomas as early as 11 years of age. The median age of the eight patients who developed colorectal adenocarcinoma was 16.7 years and the median age of the four patients who developed small bowel adenocarcinoma was 18 years. Rapid development of colorectal adenocarcinoma was found, with diagnosis within 6 to 11 months since the last endoscopy. Penetrance of colonic neoplasia was 67% at baseline and 100% at follow-up. Baseline colonoscopy in BMMRD should begin at age 3 to 5, with surveillance every 6 months. Small bowel screening should begin at age 8. The authors note that due to similarities in presentation, patients with suspected familial adenomatous polyposis with uninformative genotyping must be tested for BMMRD.

**Long-Term Outcome of Endoscopic Resection vs. Surgery for Early Gastric Cancer: A Non-inferiority-Matched Cohort Study.**

This prospective trial over a ten year period compared long-term outcomes and perioperative morbidity and mortality rates of endoscopic mucosal resection with those of surgical intervention for early gastric cancer. A total of 1290 patients had endoscopic resection and 1273 patients had surgical resection. The 10 year overall survival, disease specific survival, and recurrence free survival rates were statistically similar between the two groups, but the disease free survival was significantly worse in the endoscopic resection group, because of metachronous recurrence. Early complications were more common in the endoscopic resection group, while late complications were more common in the surgical group. Predictors of overall survival in the endoscopic resection group included old age, male sex, an elevated tumor, and submucosal invasion. In conclusions, the overall 10 year survival for endoscopic resection of early gastric cancers was not found to be inferior to surgical resection.

Are clinicopathological features of colorectal cancers with methylation in half of CpG island methylator phenotype panel markers different from those of CpG island methylator phenotype-high colorectal cancers?

Categorizing CpG island methylator phenotype (CIMP) into categories of CIMP-0 (0/8 methylated markers), CIMP-low (1/8 to 3/8 methylated markers), and CIMP-high (5/8 to 8/8 methylated markers) this study analyzed 17 colorectal cancers with 4/8 methylated markers as compared with 1164 cases in the other CIMP categories. CIMP-4/8 were closer to CIMP-high regarding sex distribution, mucin production, serration, nodal metastasis, CK7 expression, CK20 loss, CDX2 loss, and overall survival. CIMP-4/8 were similar to CIMP-low with frequent right side location and poor differentiation. Interestingly, CIMP-4/8 had the shortest overall survival compared to any of the other CIMP categories. Overall, the authors suggest CIMP-4/8 be categorized as CIMP-high.

CD3 immunohistochemical staining in diagnosis of lymphocytic colitis.
Fiehn AM, Engel U, Holck S, Munck LK, Engel PJ.

This retrospective review of biopsies diagnosed as lymphocytic colitis or lymphocytic colitis incomplete (i.e. histology similar to lymphocytic colitis but with fewer intraepithelial lymphocytes) showed that supplementary CD3 staining leads to improved diagnostic agreement among four pathologists (full agreement in 60 cases (38%) improved to 78 cases (50%)) and a change in diagnosis (in 44 of 131 cases, 34%), 13 of which were from lymphocytic colitis incomplete to lymphocytic colitis. The addition of the CD3 stain resulted in 18% to 44% of H&E only diagnoses being changed, depending on the pathologist. Cases originally diagnosed as lymphocytic colitis on H&E alone were rarely changed after review of CD3. Therefore, the authors suggest using a CD3 before making a diagnosis of lymphocytic colitis incomplete.
Integrin α5 promotes tumor progression and is an independent unfavorable prognostic factor in esophageal squamous cell carcinoma.

This retrospective immunohistochemical tissue microarray study on 147 samples of esophageal squamous cell carcinoma show heterogeneous intensity and distribution of integrin α5, however, high expression was significantly correlated with lymph node metastasis, tumor size, and poor overall survival, as well as being an independent prognostic factor. Decreased growth, migration, and invasion of esophageal squamous cancer cells were all decreased in vitro with RNAi-mediated knockdown of integrin α5.


This study included 26 endoscopists at tertiary care centers who had undergone standard narrow-band imaging (NBI) training and performed 1451 colonoscopies. They made 3012 diagnostic predictions using NBI on diminutive polyps with high-confidence in 74.3%. Surveillance interval predictions were also made, 898 of which were made immediately post-procedure, and 505 of which were made with histology input. The negative predictive value for high-confidence diagnosis in the rectosigmoid was 94.7% with 91.2% surveillance agreement, which meets the American Society for Gastrointestinal Endoscopy recommended thresholds. Negative predictive value and accuracy were lower for diminutive polyps proximal to the rectosigmoid. High-confidence diagnosis was a statistically significant predictor of accuracy. Although performance improved over time, only 7 endoscopists (27%) identified adenomas with sufficient sensitivity so as not to require further auditing. The authors point out that a complete cost analysis of the “characterize, resect, and discard strategy” should include not only decreased pathology costs, but also increased gastroenterology costs related to auditing, surveillance, and implications of low-confidence diagnoses.

Association Between Response to Etrolizumab and Expression of Integrin αE and Granzyme A in Colon Biopsies of Patients With Ulcerative Colitis.
This retrospective analysis of 110 ulcerative colitis patients in a phase 2 placebo-controlled trial of etrolizumab and 21 controls found that those who had a clinical response to etrolizumab expressed significantly higher levels of T cell associated genes than nonresponders. Also, clinical remission and mucosal healing were achieved in a significantly higher proportion of patients with high levels of granzyme A mRNA or integrin αE mRNA as compared with those with low levels of these mRNAs. Therefore, tissue levels of granzyme A mRNA or integrin αE mRNA can predict which UC patients are most likely to benefit from etrolizumab therapy.

Suspicious Cytologic Diagnostic Category in Endoscopic Ultrasound-guided FNA of the Pancreas: Follow-up and Outcomes.

Alston EA, Bae S, Eltoum IA.

The objective of the study was to assess how the suspicious category is followed up in a large EUS-FNA service, its outcomes, and the predictors that are likely to be associated with the subsequent diagnosis of a neoplastic process. Of a total of 3822 EUS-FNA cases, 116 were diagnosed with suspicious cytology. Median follow-up was 131 days and 18 patients were lost to follow-up. The final outcome was based on surgical diagnosis, repeat FNA, or clinical follow-up. The rates of neoplasm detection were compared among the different methods using chi-square test. After a cytologic diagnosis of suspicious, a total of 90 of 98 neoplasms (92%) were identified, including 72 carcinomas. Similar rates of neoplasia were detected after repeat FNA (34 of 37 neoplasms, 92%) and subsequent biopsy/surgical resection (44 of 46 neoplasms, 97%), but fewer neoplasms were detected among patients with clinical follow-up (18 of 23 neoplasms, 78%). In summary, the diagnostic category of “suspicious” was associated with a high-risk of benign and malignant neoplasms, regardless of follow-up method. The only clinical factor found to be significantly associated with ductal carcinoma was a history of weight loss. The presence of a mass was significantly associated with a higher rate of diagnosis of a neoplasm.

Endoscopic Ultrasound-guided FNA and ProCore biopsy in sampling pancreatic and intra-abdominal masses
The aim of this study was to evaluate EUS-guided sampling of intraabdominal masses and compare the diagnostic utility of conventional EUS-FNA aspiration sampling (FNA) and ProCore fine-needle biopsy (FNB). EUS-guided biopsy samples (FNA and/or FNB) were retrospectively retrieved over the course of 23 months. All cell blocks were reviewed, and their cellularity was scored (range, 0-3). 56 masses from 58 cases were acquired and included 40 pancreatic sites and 16 other intraabdominal sites. Among the 31 FNB-only cases, 71% were satisfactory, 65% were positive for malignancy at final diagnosis, and their cell blocks were moderately cellular. For the cases with both FNB and FNA performed, more FNB samples than FNA samples were satisfactory (83% vs 76%) and were positive for malignancy (65% vs 48%) at final diagnosis, and the former had more cellular cell blocks (mean score, 1.58 vs 1.29); however, the differences were not statistically significant. Significantly more FNB samples were used for immunostains (48% vs 10%; \(p=.005\)).

**Cytopathologic Diagnosis of Oncocytic Type Intraductal Papillary Mucinous Neoplasm: Criteria and Clinical Implications of Accurate Diagnosis**

*Cancer Cytopathol.* 2016;124(2):122-34.
Reid MD, Stallworth CR, Lewis MM, Akkas G, Memis B, Basturk O, Adsay V.

In this study 5 oncocytic variant IPMNs (aka IOPNs) were described (2 men, 3 women, mean age: 66 years). 4 in pancreatic head and 1 in body/tail. Radiologic diagnoses included pancreatic ductal adenocarcinoma (PDAC)(n=2), invasive cancer associated with IPMN (n=1), IPMN vs mucinous cystic neoplasm (n=1) and cystic mass (n=1). Cytologic findings included: hypercellular smears (4/5) containing well formed clusters of oncocytic cells (5/5) with prominent, slightly eccentric nucleoli (4/5), predominantly arranged in sheets/papillary units (5/5), with punched-out intercytoplasmic spaces (4/5), and with occasional 3-dimensional groups and focal necrosis (3/5). Very limited intracytoplasmic mucin and thick extracellular mucin were observed only in 2 cases. Resections included 4 pancreaticoduodenectomy and 1 distal pancreatectomy. 4 cases were pure oncocytic IPMNs whereas 1 had an additional gastric-foveolar-type epithelial component. All IOPNs were graded (by default) as high-grade and 3 out of 5 cased had an invasive carcinoma of the tubular type. In summary, it is crucial to be aware of the cytomorphologic findings of IOPNs because radiologically they typically form complex
masses interpreted as PDAC. Unlike other IPMNs, they tend to have low/normal carcinoembryonic antigen levels. Accurate recognition on FNAB can prevent unnecessary chemoradiation, especially in those with noninvasive disease.

**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 of the biology and pathophysiology of Barrett’s esophagus (BE) and associated cancer development, with an accent on the pathologic role in evaluating patients with this disease and the difficulty and limitations of doing so. Despite many recent advances in our understanding of the pathogenesis, molecular biology, and pathology of BE and associated neoplastic lesions, there remains many ongoing controversies and challenges that need to be solved.

**A Consensus for Classification and Pathologic Reporting of Pseudomyxoma Peritonei and Associated Appendiceal Neoplasia: The Results of the Peritoneal Surface Oncology Group International (PSOGI) Modified Delphi Process.**

Carr NJ, Cecil TD, Mohamed F, Sobin LH, Sugarbaker PH, González-Moreno S, Taflampas P, Chapman S, Moran BJ.  

71 participants (34 pathologists) from 13 different countries achieved a modified Delphi consensus process about terminology in pseudomyxoma peritonei (PMP) and appendiceal neoplasia. It was agreed that “mucinous adenocarcinoma” should be reserved for lesions with infiltrative invasion characterized by tumor budding, discohesive cells, angulated glandular structures and desmoplastic response. It was agreed that “cystadenoma” should no longer be recommended. A new term of “high-grade appendiceal mucinous neoplasm” (HAMN) was proposed for lesions without infiltrative invasion but with high-grade cytologic atypia. Serrated polyp with or without dysplasia was preferred (instead of SSA/P) for tumors with serrated
features confined to the mucosa with an intact muscularis mucosae. Consensus was achieved on the pathologic classification of PMP with 3 categories: low-grade (LG), high-grade (HG) and HG with signet ring cells. Acellular mucin should be classified separately. It was agreed that LG and HG mucinous carcinoma peritonei should be considered synonymous with disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis, respectively. It was also agreed that the grading of PMP should be of the peritoneal disease (ie, the PMP) rather than the primary tumor. The concept of “adenocarcinoma ex goblet cell carcinoid” (Tang et al) was preferred to the WHO term mixed adenoneuroendocrine carcinoma “MANEC”.

**Intraductal Papillary Mucinous Neoplasms Often Contain Epithelium From Multiple Subtypes and/or Are Unclassifiable.**

Schaberg KB, DiMaio MA, Longacre TA. 

In this study 72 pancreatic IPMN resections (from 2008 to 2014) were retrospectively evaluated by 2 GI pathologists. All noninvasive IPMNs were entirely submitted. There were 41 gastric (57%), 8 intestinal (11%), 4 pancreatobiliary (6%) and 1oncocytic (1%). 18 (25%) IPMNs were either unclassifiable due to ambiguous morphology (n=7) or contained >10% epithelium from >1 subtype (“mixed”, n=11). Most mixed IPMNs featured gastric epithelium with either pancreatobiliary or intestinal epithelium. Immunohistochemistry for CDX-2, MUC2 and MUC5AC was performed on cases where histologic subtype could not be determined on H&E stain. Staining was considered positive if >5% of tumor cells show staining. 2 IPMNs initially unclassifiable on H&E stains, were classified as intestinal by immunohistochemical stains. Immunohistochemistry for another 7 IPMNs did not allow for definite classification. In conclusion, one quarter of IPMNs cannot be subtyped due to mixed or unclassifiable epithelium. In the problematic cases on H&E stain, immunohistochemistry adds little value.

**Loss of Hes1 Differentiates Sessile Serrated Adenoma/Polyp From Hyperplastic Polyp.**

Hes1 is a downstream target of Notch-signaling pathway and plays an important role in intestinal development by regulating differentiation of enterocytes. Hes1 is ubiquitously expressed in the nuclei of normal colonic epithelial cells. A total of 63 SSA/P (45 right colon, 18 left colon), 35 HPs (27 left colon, 8 right colon), 15 TAs, 10 TSA and 3 SSA/P with dysplasia were included in this study with consensus diagnosis among 3 pathologists. Comparison of the Hes1 expression rates among HP and SSA/P was done using the Fisher exact test (2-tailed). The complete loss or a very weak expression of Hes1 was observed in 58/63 SSA/Ps (92%), compared with the normal expression of Hes1 in HPs (35/35,100%). In SSA/P with dysplasia, the dysplastic areas demonstrated cytoplasmic and/or nuclear staining for Hes1. TA and TSA showed patchy staining. In conclusion, in this study, loss of Hes1 expression had a sensitivity of 92% and specificity of 100% in differentiating SSA/P from HP.

**Perineural Invasion Is a Strong Prognostic Factor in Colorectal Cancer: A Systematic Review.**

Knijn N, Mogk SC, Teerenstra S, Simmer F, Nagtegaal ID. 

The aim of this meta-analysis was to investigate the role of perineural invasion (PNI) as a prognostic factor in CRC. For that purpose, a literature search was performed using PubMed database from inception to 1/1/2014. Articles published in English and studies with at least 100 patients were selected. Studies with and without (neo)adjuvant treatment were included. A total of 58 articles with 22,900 patients were used. The incidence of PNI was 18.2% in the overall cohort, 20.6% in rectal cancer, and 14.1% in colon cancer studies. PNI was correlated with increased local recurrence (LR)(RR 3.22, 95% CI,2.33-4.44) and decreased 5-year disease free survival (5yDFS) (RR 2.35, 95% CI, 1.66-3.31), 5-year cancer specific survival (5yCSS)(RR 3.61, 95% CI,2.76-4.72), and 5-year overall survival (5yOS)(RR 2.09, 95% CI, 1.68-2.61). In multivariate analysis, PNI remained an independent prognostic factor for 5yDFS, 5yCSS, and 5yOS. In summary, this meta-analysis shows that PNI is a pathologic feature in CRC with a strong impact on prognosis. The impact of PNI on prognosis is similar to well-established prognostic factors such as depth of invasion, presence of lymph node metastases, lymphatic invasion, vascular invasion and differentiation grade.
Intestinal Metaplasia is Present in Most if Not All Patients Who Have Undergone Endoscopic Mucosal Resection for Esophageal Adenocarcinoma.


In this article, 27 endoscopic mucosal resections (EMR) performed in 21 patients were retrospectively reviewed. Of the 27, 1 had high-grade dysplasia only, 17 had intramucosal adenocarcinoma (adenoca) (T1a) and 9 had adenoca involving submucosa (T1b). The sections were retrieved and examined under a multiheaded microscope by 4 pathologists. Residual intestinal metaplasia (IM) was defined by the presence of goblet cells in nondysplastic columnar epithelium. No special stains were used. Residual IM was absent in 10/27 (37%) of EMR specimens. An in-depth study of those 10 cases showed that 3 had IM in a concurrent EMR specimen, 4 had IM in prior biopsy in their unit, and 2 had IM in an esophagectomy that followed the EMR. The 1 patient in whom they did not demonstrate IM had a cancer involving a large part of a short segment of Barrett esophagus (BE). She had a 40-year history of GERD, with >20 years of surveillance for BE, which makes it certain that she had IM. In summary, this study concludes that the frequent absence of residual IM around an adenoca in an EMR specimen is the result of sampling error, indicating that IM is a necessary precursor to adenoca of the esophagus.

Endoscopic Overestimation of Colorectal Polyp Size

Anderson BW, Smyrk TC, Anderson KS, Mahoney DW, Devens ME, Sweetser SR, Kisiel JB, Ahlquist DA. Gastrointest Endosc 2016;83:201-8

In this study, colonoscopy and pathology reports were reviewed from the 2012 medical records at a large institution. Only polyps resected in toto with both endoscopic estimates and pathology measurements were included. From 6067 polyps resected, both endoscopic and pathology sizes were available on 1528. Colonoscopies were performed by 50 staff gastroenterologists and 12 gastroenterology fellows. Among 99 polyps endoscopically called 1 cm, 72% were <1 cm on pathology. Of 222 polyps estimated as ≥1 cm on endoscopy, 46% were <1 cm on pathology. Endoscopic overestimation was more common in women (54%) than in men (40%) (p=0.03) and with proximal (56%) than distal (40%) sites (p=0.02). By configuration, 61% of flat polyps were overcalled by endoscopy (p=0.014). The presence of a fellow during endoscopy had no
association with overcall/undercall rates. In summary, almost half of polyps called advanced on endoscopic estimates of size ≥1 cm fell below this threshold on actual pathology measurements.

**Impact of Next-generation Sequencing on the Clinical Diagnosis of Pancreatic Cysts**


The objective of this study was to investigate the impact of next generation sequencing (NGS) on the clinical diagnosis based on imaging features and cyst fluid analysis in a prospective cohort of 79 patients (92 pancreatic cysts). CEA levels were recorded and the imaging diagnosis was further classified based on CEA levels < or > 192 ng/ml. 39 cancer genes were targeted. 14 cysts had follow-up histology. Overall there were 40 cysts of the wild type (43%), *KRAS* mutation in 43 cysts (47%), *GNAS* mutations in 22 cysts (24%), and *VHL* mutation in 2 cysts (2%). 19/92 (21%) had an elevated CEA level (>192 ng/ml) supporting a mucinous cyst etiology. A total of 73 cysts did not demonstrate an elevated CEA level, and of these, 35(48%) had mutations by NGS. Of the 53 cysts classified as mucinous by imaging, 36 (68%) did not have an elevated CEA level. NGS confirmed a mucinous etiology in 26/36 cysts (72%) and demonstrated a *VHL* mutation in 2 (changing the clinical impression from branch-duct IPMN to serous cystadenoma). A *KRAS* or *GNAS* mutation supported an IPMN by imaging with nonmucinous CEA in 71% of cases. In conclusion, NGS analysis of pancreatic cyst fluid changed the imaging impression in 12% of patients and was most valuable in identifying mucinous cysts with low CEA levels.

**Long-term Outcomes of a Primary Complete Endoscopic Resection (CER) Strategy for Short-segment Barrett’s Esophagus (BE) with High-grade Dysplasia (HGD) and/or Early Esophageal Adenocarcinoma (EEA)**


The goal of this study was to describe long-term outcomes of a primary CER strategy of BE with HGD/EEA. Patients with biopsy-proven HGD and EEA in short-segment BE (≤3 cm in circumferential length and ≤5 cm in maximal length) underwent staged CER by multiband
mucosectomy or the cap method. 138 patients were included. CER was technically successful in all patients and was established after a median of 2 sessions. Covert synchronous EEA was found in 1 patient. At a mean follow-up of 40.7 months by intention-to-treat analysis, CER of HGD/EEA, dysplasia and intestinal metaplasia was achieved in 98.5%, 89.1% and 71%, respectively. Esophageal dilation was performed in 36.8% in a mean of 2.5 sessions. At the end of follow-up, 96.4% of patients had no or minimal dysphagia. In conclusion, this study demonstrated that a primary CER strategy for short segment HGD/EEA is a safe, well-tolerated and highly effective treatment with a durable response. This study has some limitations. It was a single-arm observational study with no control group, concerning only short-segment BE.

Diagnostic yield of EUS-guided FNA for Malignant Biliary Stricture: a Systematic Review and Meta-analysis.


The aim of this meta-analysis was to determine the diagnostic yield of EUS-FNA in malignant extrahepatic biliary strictures. A comprehensive literature review was carried out by 2 reviewers for studies evaluating the accuracy of EUS-FNA in biliary stricture. 20 studies involving 957 patients met inclusion criteria. The pooled sensitivity and specificity of EUS-FNA was 80% and 97% respectively. The pooled positive likelihood ratio was 12.35 and the negative likelihood ratio was 0.26. The pooled diagnostic odds ratio for diagnosing a malignant biliary stricture was 70.53. The area under the receiver-operating characteristic curve was 0.97. This meta-analysis demonstrates that EUS-FNA is sensitive and highly specific for diagnosing malignancy in biliary strictures. There were not enough studies to reliably compare the pooled diagnostic odds ratio for distal versus proximal biliary strictures.

Initial Experience of EUS-guided Radiofrequency Ablation of Unresectable Pancreatic Cancer

This study aimed to assess the technical feasibility and safety of EUS-RFA for unresectable pancreatic cancer. The inclusion criteria were: 1) histologically confirmed pancreatic cancer, 2) unresectable stage due to locally advanced or metastatic disease, and 3) resistance to a previous treatment modality. A total of 6 consecutive patients were included. EUS-RFA was performed successfully in all 6 patients (5 females, 1 male, median age: 62 years). Pancreatic cancer was located in the head (n=4) or body (n=2) of the pancreas. The median diameter of masses was 3.8 cm. 4 patients had stage 3 disease and 2 patients had stage 4 disease. An 18-gauge endoscopic RFA electrode and a radiofrequency generator were used for the procedure. After insertion of the RFA electrode into the mass, the radiofrequency generator was activated to deliver 20 to 50 W ablation power for 10 seconds. Depending on tumor size, the procedure was repeated to sufficiently cover the tumor. After the procedure 2 patients experienced mild abdominal pain. To avoid major vessel injury real-time Doppler imaging was used. Because the follow-up duration was limited (max 6 months), this study could not evaluate long-term survival.

**Histopathology**

**Adenoma-like adenocarcinoma: a subtype of colorectal carcinoma with good prognosis, deceptive appearance on biopsy and frequent KRAS mutation.**


The authors describe a subtype of colorectal carcinoma (CRC) that appears malignant endoscopically but shows only fragments of dysplastic tissue on biopsy without evidence of stromal invasion. Even on resection, some of these tumors resemble villous adenoma rather than overt carcinoma. 35 such carcinomas, here termed “adenoma-like adenocarcinoma” were obtained, defined as containing “areas demonstrating villiform architecture, no more than rare foci of high-grade nuclear atypia and either the absence of desmoplasia or limited zones of desmoplasia closely outlining infiltrating glands, rather than forming expansive regions of fibrous tissue.” Tumors with intraluminal dirty necrosis, tumor budding, or conventional well-differentiated CRC with unambiguous malignant features were excluded. 24 tumors (~66%) had advanced T-category but only 7 tumors (20%) shows nodal metastasis and only 5 patients (15%) shows distant metastasis. All but one case with nodal metastasis were pT3 or pT4. 15 cases (43%) were called adenoma on biopsy. 21 resections (60%) showed no residual associated adenoma, of which 9 had been called adenoma on biopsy. Over median follow-up of 44 months, 4 patients (12%) had died of disease and 22 were alive at last follow-up. 14/24 cases showed KRAS mutation (58%) and 4/17 (24%) were microsatellite unstable. In comparison to
conventional CRC, survival is significantly better (P=0.011). [Note: this subtype has been termed villous adenocarcinoma or papillary adenocarcinoma in some prior reports.]

**Loss of RNA-binding motif protein 3 expression is associated with right-sided localization and poor prognosis in colorectal cancer.**

RNA-binding motif protein 3 (RBM3) is a glycine-rich protein transcriptionally induced by low temperature and hypoxia. Its expression was studied by immunohistochemistry on a microarray of 1800 CRCs. Of interpretable cases, 95.9% showed nuclear RBM3 expression. Loss of RBM3 was associated with advanced tumor stage (P<0.0001), right-sided tumor location (P<0.0001) and poor prognosis (P=0.0003). Tumor stage and nodal status are independent prognostic markers (P<0.0001 each) but prognostic impact of RBM3 is not significant (P=0.2655).

**The number and ratio of positive lymph nodes affect pancreatic cancer patient survival after neoadjuvant therapy and pancreaticoduodenectomy (pages 210–220).**

This study examines prognostic significance of number of positive lymph nodes and lymph node ratio (number of positive lymph nodes:total) in pancreatic ductal adenocarcinoma (PDAC) patients who received neoadjuvant therapy with subsequent pancreaticoduodenectomy (PD). As context, the authors reported in the past about 240 PDAC patients who received neoadjuvant therapy with subsequent PD versus 60 patients who underwent surgery first. In the prior study, neoadjuvant therapy resulted in better overall survival and lower frequency of lymph node metastasis. In the current study, 398 neoadjuvant/PD patients were studied. Lymph node status was categorized as ypN0, ypN1 (1-2 positive nodes) or ypN2 (at least 3 positive nodes). Status of ypN0 was present in 183 (46.0%) of patients, ypN1 in 117 (29.4%) and ypN2 in 98 (24.6%). 162 patients (40.7%) had a LNR of ≤0.19 and 53 (13.3%) had a LNR >0.19. Higher N status was associated with shorter disease-free survival and overall survival, as was LNR>0.19. The
authors advise that subclassification of post-therapy node-positive tumors into yPN1 and ypN2 groups should be incorporated into future AJCC staging.

**Discordant human epidermal growth factor receptor 2 overexpression in primary and metastatic upper gastrointestinal adenocarcinoma signifies poor prognosis.**

Hedner C, Tran L, Borg D, Nodin B, Jirström K, Eberhard J.


The prognostic value of HER2 overexpression in gastric cancer is unclear, though targeted therapy with trastuzumab has been effective for patients with HER2 overexpression in gastric cancer. 174 patients with esophageal or gastric adenocarcinoma were studied for tumor HER2 overexpression and gene copy alterations via immunohistochemistry and silver in-situ hybridization on microarrays. Positive conversion from primary tumor to lymph node metastasis was seen in 7.8% of cases (from 0 or 1 to 2 or 3) or 5.6% of cases (0, 1, or 2 to 3). HER2 expression or intratumoral heterogeneity were not prognostic, but primary-metastatic conversion independently predicted shorter overall survival (hazard ratio=4.93).

**MET in gastric cancer – discarding a 10% cutoff rule.**

Metzger ML, Behrens HM, Böger C, Haag J, Krüger S, Röcken C.


470 gastric cancer (GC) cases were studied for hepatocyte growth factor receptor (MET) expression and gene amplification via immunohistochemistry (IHC) and chromogenic in-situ hybridization (CISH). Percentage area of MET-amplified tumor cell clones was measured by virtual microscopy. Whether in primary or metastatic GC, MET expression was heterogeneous. MET-IHC of 2+ or 3+ correlated with MET amplification. Positive MET status was defined as MET-IHC 2+ or 3+ with MET amplification or as MET-IHC 3+ without MET amplification. Prognostic significance of MET status was independent of the percentage of positive tumor cells (hence the article title advising dropping the 10% cutoff). MET-positive GCs were microsatellite stable, wild-type for KRAS/PIK3CA, and had poor prognosis with median survival of 5.4 months.
Reappraisal of Serosal Invasion in Patients With T3 Colorectal Cancer by Elastic Stain: Clinicopathologic Study of 139 Surgical Cases With Special Reference to Peritoneal Elastic Lamina Invasion.
139 cases of pT3 CRC were examined in comparison to 30 cases of pT4a CRC. Elastic staining was performed on pT3 cases on the areas containing the deepest invasive tumor partially or entirely covered with peritoneum. Peritoneal elastic lamina invasion (PELI) was identified in 23% (32 of 139) of pT3 cases. PELI was associated with lymph node metastasis (P<0.001), LVI (P<0.001), recurrence (P=0.007) and age (P=0.002). Percentage of patients with a 4-year recurrence-free period were 90.3% (negative PELI), 66.7% (positive PELI), and 28.9% (pT4a tumor). The authors advocate for elastic staining to evaluate serosal invasion of CRC. Positive PELI is a significant predictive factor for lymph node metastasis and recurrence-free survival in patients with pT3 CRC and may help stratify patients who would benefit from more aggressive therapy similar to that for pT4a patients.

Impact of the angulus biopsy for the detection of gastric preneoplastic conditions and gastric cancer risk assessment

The authors evaluated biopsies from the gastric antrum (2), incisura angulus (1) and corpus (2) of 213 patients according to the updated Sydney system for classification of chronic gastritis in order to assess the added value of angulus biopsies. Histologic assessment was performed using the updated Sydney System, the operative link on gastritis assessment (OLGA), and operative link on gastritis assessment using intestinal metaplasia (OLGIM) systems. Particular attention was paid to the diagnosis of intestinal metaplasia and atrophy (preneoplastic conditions). Seventeen (8%) of the cases with atrophic gastritis and six (3%) with intestinal metaplasia would have been missed without the incisura angulus biopsy. More patients were diagnosed with a preneoplastic condition when the angulus biopsy was considered (13.1% versus 18.4%). OLGA and OLGIM scores dropped significantly when recalculated without the angulus biopsies. However, the number of patients classified as high-risk (OLGA and OLGIM stages III and IV) did not change significant when the angulus biopsy was added.

Next-Generation Sequencing and Fluorescence in Situ Hybridization Have Comparable Performance Characteristics in the Analysis of Pancreaticobiliary Brushings for Malignancy
The authors evaluated 81 bile duct brushings from by cytology analysis, FISH using the UroVysion probe set, and targeted next generation sequencing (NGS) interrogating mutation hotspots on 39 genes. Specimens were cytologically classified as negative/ataypical (negative) or suspicious/positive (positive) and negative or positive categories on the basis of FISH and NGS results. Clinical follow-up revealed that there were 33 patients with high-risk neoplasia/malignant strictures (41%) and 48 with benign disease (59%). Using clinical outcome as the gold standard, cytology had a sensitivity of 67% and a specificity of 98%. Next-generation sequencing increased the sensitivity to 85%, whereas FISH increased the sensitivity to 76%. The authors suggest that NGS may be a useful adjunct to cytologic evaluation of bile duct strictures, particularly when cytology reveals negative findings.
Reviewers

Raga Ramachandran, MD, PhD; University of California San Francisco
Steven D Hart, MD; University of California Los Angeles
Ilyssa Gordon, MD, PhD; Cleveland Clinic
Nicole Panarelli, MD; Cornell University Medical Center
David Hernandez; University of Florida Gainsville
Michael Torbenson, MD; Mayo Clinic Rochester