Journal Watch – July and August, 2015

Evaluation of mutational testing of preneoplastic Barrett's mucosa by next-generation sequencing of formalin-fixed, paraffin-embedded endoscopic samples for detection of concurrent dysplasia and adenocarcinoma in Barrett's esophagus

El Portillo A, Lagana SM, Yao Y, Uehara T, Jhala N, Ganguly T, Nagy P, Gutierrez J, Luna A, Abrams J, Liu Y, Brand R, Sepulveda JL, Falk GW, Sepulveda AR

J Mol Diagn. 2015; 17(4): 412-419.

http://www.ncbi.nlm.nih.gov/pubmed/26068095

The authors of this paper used next-generation sequencing to detect mutations in biopsies and mucosal resections of Barrett's esophagus in an attempt to identify biomarkers that may predict the presence of concurrent high-grade dysplasia or adenocarcinoma in patients whose biopsy samples reveal only nondysplastic intestinal metaplasia. The authors studied two groups of patients: 1)patients with Barrett's esophagus who did not progress to a more advanced lesion after two years of follow up and 2) patients with Barrett's esophagus and concurrent high-grade dysplasia or superficial adenocarcinoma. They studied a panel of 50 oncogenes and tumor suppressor genes. They report that no nonsynonymous mutations were detected in group 1, whereas the most common mutations in group 2 were in *TP53*, *CDKN2A*, and *APC.* Mutations in *TP53* and *APC* were also detected in nondysplastic Barrett's mucosa from the same patients. Based on these results, the authors postulate that mutations in these genes may serve as biomarkers of concurrent high-grade dysplasia or intramucosal adenocarcinoma in patients whose biopsies do not reveal dysplasia.

Chromoendoscopy for Surveillance in Inflammatory Bowel Disease Does Not Increase Neoplasia Detection Compared With Conventional Colonoscopy With Random Biopsies: Results From a Large Retrospective Study.
Mooiweer E, van der Meulen-de Jong AE, Ponsioen CY, Fidder HH, Siersema PD, Dekker E, Oldenburg B.
Am J Gastroenterol. 2015 Jul;110(7):1014-21.

http://www.ncbi.nlm.nih.gov/pubmed/25823770

This retrospective study included patients with ulcerative colitis and Crohn's disease undergoing surveillance at three referral centers. A total of 440 colonoscopies in 401 patients using chromoendoscopy were compared to 1802 colonoscopies in 772 patients using shite light endoscopy with random biopsies every 10 cm over a 14 year period. The percent of cases in which dysplasia was detected was similar between the two groups (11% in chromoendoscopy

vs 10% in random biopsy). Looking only at targeted biopsies, there was no significant difference between yield of dysplastic lesions between the two methods. The authors also noted that there was no significant learning curve effect for the two endoscopists when chromoendoscopy was implemented. Overall, these findings cast doubt on previous randomized controlled studies reporting superior dysplasia detection for chromoendoscopy.

Forty-Year Analysis of Colonoscopic Surveillance Program for Neoplasia in Ulcerative Colitis: An Updated Overview.
Choi CH, Rutter MD, Askari A, Lee GH, Warusavitarne J, Moorghen M, Thomas-Gibson S, Saunders BP, Graham TA, Hart AL.
Am J Gastroenterol. 2015 Jul;110(7):1022-34.

http://www.ncbi.nlm.nih.gov/pubmed/25823771

This retrospective study provides an update on trends in ulcerative colitis and associated neoplasia. Included were 1375 ulcerative colitis patients followed for a median of 11 years per patient over a 42 year span. The incidence rate of colorectal cancer was 4.7 per 1000 patient-years and there was a decrease in the incidence rate of advanced colorectal cancer and of interval colorectal cancer. Early colorectal cancer incidence rate increased 2.5-fold in the current decade as compared with the past decade but with a 10 year survival rate of almost 80%. In contrast to the retrospective study by Mooiweer et al, this study reported that chromoendoscopy was more effective at detecting dysplasia compared with white light endoscopy. The authors also reported a significant decrease in incidence of colectomy performed for dysplasia over time, and that there was no significant increase in colorectal cancer risk in patients with “indefinite” as compared to low grade dysplasia. The median age of patients diagnosed with colorectal cancer was 55 years and median duration of ulcerative colitis at the time of cancer diagnosis was 23 years. Sixty-one percent of patients in surveillance with cancer had preceding dysplasia.

Of note, an editorial discussing these two papers in light of the SCENIC Consensus statement can also be found in the same issue (Higgins, P.D.R. *Am J Gastroenterol* 2015; 110:1035–1037)

Low Prevalence of Colon Polyps in Chronic Inflammatory Conditions of the Colon.
Sonnenberg A, Genta RM.
Am J Gastroenterol. 2015 Jul;110(7):1056-61.

http://www.ncbi.nlm.nih.gov/pubmed/25916222

This case-control study of 130,204 patients undergoing colonoscopy for diarrhea found reduced prevalence of hyperplastic polyps, serrated adenomas, and tubular adenomas in patients with histologic

evidence of microscopic colitis, inflammatory bowel disease, and active colitis, but not in patients with diverticulitis or ischemic colitis. This finding was present overall and in three different age groups (less than 50 years old, 55-64 years old, and older than 65 years old). Due to the nature of the database examined, the possibility that the patients included in the study may have had prior polypectomy could not be determined. The diversity of the endoscopists contributing to the database and the fact that the pathologic diagnosis was made in a clinical setting are noted as strengths of the study to diffuse bias. Overall, the authors conclude that chronic mucosal inflammatory conditions of the colon are associated with decreased colon polyp prevalence.

Evidence for Neuronal and Structural Changes in Submucous Ganglia of Patients With Functional Dyspepsia.
Cirillo C, Bessissow T, Desmet AS, Vanheel H, Tack J, Vanden Berghe P.
Am J Gastroenterol. 2015 Aug;110(8):1205-15.

http://www.ncbi.nlm.nih.gov/pubmed/26077177

This study utilized recently developed live optical recording techniques to directly test submucosal plexus nerves of the duodenum in histologically normal biopsies from symptomatic patients clinically diagnosed with functional dyspepsia. Submucosal plexus nerves from 18 newly diagnosed functional dyspepsia patients were examined by calcium imaging, immunofluorescent staining for counts of ganglia, neurons per ganglion, and individual neurons, and for expression of the HuCD neuron protein, S100, and VIP. Eosinophils and mast cells were also counted. The authors found decreased calcium response, gliosis, altered architecture of ganglia and neurons, all consistent with impaired neuronal function. Correlation with increased eosinophils and mast cells was also found. These findings will be helpful for diagnosis, prognosis, and treatment planning in this patient population.

The Clinical Utility of a Novel Blood-Based Multi-Transcriptome Assay for the Diagnosis of Neuroendocrine Tumors of the Gastrointestinal Tract.
Modlin IM, Kidd M, Bodei L, Drozdov I, Aslanian H.
Am J Gastroenterol. 2015 Aug;110(8):1223-32.

http://www.ncbi.nlm.nih.gov/pubmed/26032155

This study prospectively tested for blood biomarker chromogranin A and NETest in 81 gastrointestinal tumor cases and 98 pancreatic tumor cases, to determine the sensitivity and selectivity of the NETest, a PCR-based test including 51 neuroendocrine tumor markers. The NETest was 93% accurate for intestinal carcinoids, and 94% accurate for pancreatic NETs. The NETest was also significantly more sensitive than chromogranin A blood test for detection of small intestinal and pancreatic NETs. The authors suggest that the superior performance of the NETest as compared to the chromogranin A test, could help with earlier and more precise NET detection, as well as in prediction of therapeutic efficacy.

Traditional serrated adenoma: an update.
Bettington ML, Chetty R.
Hum Pathol. 2015 Jul;46(7):933-8.

http://www.ncbi.nlm.nih.gov/pubmed/26001333

Excellent review of traditional serrated adenomas in light of relationship with other serrated polyps and molecular pathways of development and progression to carcinoma.

Outcome of "indefinite for dysplasia" in inflammatory bowel disease: correlation with DNA flow cytometry and other risk factors of colorectal cancer.
Choi WT, Rabinovitch PS, Wang D, Westerhoff M.
Hum Pathol. 2015 Jul;46(7):939-47.

http://www.ncbi.nlm.nih.gov/pubmed/25962315

Eighty-four patients with inflammatory bowel disease and biopsies indefinite for dysplasia who also had follow-up biopsies were included to determine subsequent histologic detection of any neoplasia, although due to statistical constraints only subsequent LGD was used in the final analysis. Concurrent flow cytometric DNA content was available in 63% of patients and DNA aneuploidy was significantly associated with increased risk of any neoplasia within 1 year of follow-up. Overall, 13% of IND cases had LGD on follow-up. The authors suggest that flow cytometry could improve identification of which IBD patients indefinite for dysplasia are most at risk to develop subsequent neoplasia.

A morphologic reappraisal of endoscopically but not histologically apparent polyps and the emergence of the overlooked goblet cell--rich hyperplastic polyp.
Sethi A, Hanson JA.
Hum Pathol. 2015 Aug;46(8):1147-52.

http://www.ncbi.nlm.nih.gov/pubmed/26004372

The authors hypothesized that overlooked goblet cell-rich hyperplastic polyps may lead to underdiagnosis of serrated polyposis syndrome. They performed two blinded reviews on 160 endoscopically but not histologically apparent polyps by a single gastrointestinal pathologist with an intervening 6 month wash-out period. Medical record evaluation was also performed to determine whether the addition of a goblet cell-rich hyperplastic polyp would result in a new diagnosis of serrated polyposis syndrome. Fourteen (9%) polyps were reclassified to goblet cell-rich hyperplastic polyps, of which 12 (86%) were originally diagnosed as “colonic mucosa with surface hyperplastic change”. This change in diagnosis did not result in any new cases of serrated polyposis syndrome.

A Hereditary Form of Small Intestinal Carcinoid Associated With a Germline Mutation in Inositol Polyphosphate Multikinase.
Sei Y, Zhao X, Forbes J, Szymczak S, Li Q, Trivedi A, Voellinger M, Joy G, Feng J, Whatley M, Jones MS, Harper UL, Marx SJ, Venkatesan AM, Chandrasekharappa SC, Raffeld M, Quezado MM, Louie A, Chen CC, Lim RM, Agarwala R, Schäffer AA, Hughes MS, Bailey-Wilson JE, Wank SA.
Gastroenterology. 2015 Jul;149(1):67-78.

http://www.ncbi.nlm.nih.gov/pubmed/25865046

This prospective study included 33 families with at least 2 cases of small intestinal carcinoid tumor and found that most familial cases had multiple synchronous primary tumors. They also found occult tumors in 34% of asymptomatic relatives greater than 50 years old. Determination of disease-associated mutations was performed in a single large family by linkage analysis, whole-exome sequencing, and copy number analysis of germline and tumor DNA, which revealed an autosomal dominant germline deletion in the gene inositol polyphosphate multikinase (IPMK) resulting in a truncated protein. The authors recommend that family members should be screened and that 22%-35% of cases previously considered sporadic may actually be familial.

Predictors of Disease Recurrence and Survival in Esophageal Adenocarcinomas with Complete Response to Neoadjuvant Therapy

Agoston AT, Zheng Y, Bueno R, Lauwers GY, Odze RD, Srivastava A

Am J Surg Pathol. 2015 Aug;39(8):1085-92.

http://www.ncbi.nlm.nih.gov/pubmed/26076061

The purpose of this retrospective study was to determine predictors of disease recurrence and survival in patients with esophageal adenocarcinomas (EAC) who obtained complete pathologic response (pCR) after neoadjuvant chemoradiation. A total of 93 esophagectomies were studied for different variables. Complete histologic examination of the tumor bed was the most significant predictor of favorable outcome for both disease recurrence and disease-specific mortality. The presence of high-grade EAC component (moderately to poorly or poorly differentiated EAC, or those with a signet ring cell or mucinous component) in pretreatment biopsies was also associated with a higher disease-specific mortality. Involvement of the gastroesophageal junction (GEJ) on pretreatment endoscopic examination was associated with a higher rate of disease recurrence. This may be explained by previously documented presence of skip metastasis with positive cervical lymph nodes without any thoracic involvement in a subset of deeply invasive tumors of the GEJ. These 3 variables (adequacy of histologic examination, high tumor grade and GEJ involvement) can explain the heterogeneity in outcomes for EAC patients with pCR to therapy (22.2% of all EAC patients in this study).

Germline MLH1 Mutations Are Frequently Identified in Lynch Syndrome Patients with Colorectal and Endometrial Carcinoma Demonstrating Isolated Loss of PMS2 Immunohistochemical Expression

Dudley B, Brand RE, Thull D, Bahary N, Nikiforova MN, Pai RK

Am J Surg Pathol. 2015 Aug;39(8):1114-20

http://www.ncbi.nlm.nih.gov/pubmed/25871621

This study analyzes clinical and pathologic features of patients with isolated loss of PMS2 IHC expression in colorectal (CRC) and endometrial (End) cancer following a prospective examination of MMR IHC. 32 tumors (16/3213 CRC and 16/215 End) showed isolated loss of PMS2. MSI PCR done in 29/32 tumors revealed 28 MSI-H and 1 MSI-L. 17 patients underwent germline mutation analysis for PMS2 and additionally for MLH1 (if no PMS2 mutation was identified), showing 24% (n=4) MLH1 mutations, 35% (n=6) MSH2 mutations, 12% (n=2) with PMS2 variants of undetermined significance and 29% (n=5) with no mutations in either MLH1 or PMS2. 3 out of 4 patients with MLH1 mutations demonstrated immunogenic but functionally inactive MLH1 protein (falsely preserved MLH1 protein expression in IHC). Diminished or weak MLH1 staining may be a clue that underlying germline MLH1 mutation is the cause of the abnormal MMR expression. The high frequency of MLH1 germline mutations identified in this study supports that patients with isolated loss of PMS2 without PMS2 germline mutation must have MLH1 mutation analysis performed. Is it important to distinguish both mutations since PMS2 mutations are associated with a lower cumulative lifetime risk of CRC and extracolonic malignancies as compared to MLH1 mutations.

KIT, PDGFRA, and BRAF Mutational Spectrum Impacts on the Natural History of Imatinib-Naive Localized GIST: a Population-based Study

Rossi S, Gasparotto D, Miceli R, Toffolatti L, Gallina G, Scaramel E, Marzotto A, Boscato E, Messerini L, Bearzi I, Mazzoleni G, Capella C, Arrigoni G, Sonzogni A, Sidoni A, Mariani L, Amore P, Gronchi A, Casali PG, Maestro R, Dei Tos AP.

Am J Surg Pathol. 2015 Jul;39(7):922-30.

http://www.ncbi.nlm.nih.gov/pubmed/25970686

This paper focuses on the relevance of KIT, PDGFRA, and BRAF mutation status of naive localized surgically resected primary GISTs (n=451) with a median follow-up of 10 years. Inclusion criteria: GIST >2cm; GISTs yielding DNA suitable for molecular diagnosis, any age who had been surgically treated, no neoadjuvant therapy, no other malignant tumor beside GIST and no history of NF1. Mutation analysis was performed by Sanger sequencing. Multivariable Cox regression models identified 3 molecular risk groups: Group 1 (best outcome) included PDGFRA exon 12, BRAF, and KIT exon 13-mutated cases; Group 2 (intermediate outcome) included triple negative (KIT, PDGFRA, BRAF wild-type cases), KIT exon 17, PDGFRA exon 18 D842V, and PDGFRA exon 14-mutated cases; Group 3 (worst outcome) comprised KIT exon 9 and exon 11 and PDGFRA exon 18 mutations apart from D842V. These results may be useful in decision making for adjuvant therapy, complementing the conventional clinicopathologic stratification.

Distinctive Spatiotemporal Stability of Somatic Mutations in Metastasized Microsatellite-Stable Colorectal Cancer

Jesinghaus M, Wolf T, Pfarr N, Muckenhuber A, Ahadova A, Warth A, Goeppert B, Sers C, Kloor M, Endris V, Stenzinger A, Weichert W.

Am J Surg Pathol. 2015 Aug;39(8):1140-7.

http://www.ncbi.nlm.nih.gov/pubmed/25786087

This retrospective study analyzes through ultradeep sequencing 24 MSS CRC cases, each comprising the primary tumor, matched normal tissue, and metastatic sites from node, lung, liver, or brain. Using an in-house developed gene panel covering hot-spot regions of 30 CRC-related genes, a high concordance between CRC-specific genetic alterations of the primary and secondary sites was noted (100% concordance in the genotype for *APC, KRAS, FBXW7, PIK3CA, BRAF, SMAD4, and ACVR2A)* with only modest, non-significant changes in allele frequency. The somatic mutations were not only stable over various distant sites but also over time, with a median follow-up of 36.96 months. Except for true de novo mutations in 4 cases (16.6%) affecting *SYNE1, CTNNB1, TP53, and PTEN*, all remaining cases (84.4%) shared the genetic lesions of the primary tumors. In summary, in this study, the mutational profile of metastatic sites was not significantly influenced by the location or by systemic therapy or by the date of origin of the metastasis and intervals between diagnosis of the primary tumor and secondary site involvement.

The Impact of the New Proposed Papanicolaou Society of Cytopathology Terminology for Pancreaticobiliary Cytology in Endoscopic US-FNA: A Single-Institutional Experience

Saieg MA, Munson V, Colletti S, Nassar A.

Cancer Cytopathology 2015;123:488-494

http://www.ncbi.nlm.nih.gov/pubmed/25994860

This retrospective study applies the new proposed Papanicolau Society of Cytopathology terminology for pancreatobiliary cytology in 155 pancreatic endoscopic US-FNA obtained over a 12-month period. The proposed terminology scheme recommends a 6-tiered system: Non-diagnostic, negative, atypical, neoplastic [benign or other], suspicious and positive. Unique to this scheme is the "neoplastic" category separated into "benign" (serous cystadenoma) or "other" (premalignant mucinous cysts, neuroendocrine tumors and SPNs. The positive or malignant category is reserved for high-grade, aggressive malignancies. The new terminology had a greater impact among specimens classified as atypical and suspicious, with minimal influence of negative or positive samples. As an example, 11 samples previously classified as negative and 3 as non-diagnostic with CEA levels> 192 ng/mL were reclassified as neoplastic:other. All positive specimens remained within their same categories in the revised classification. 16 patients (10.3%) had surgical resection specimens available, and complete or partial agreement with FNA results was achieved in 13 (reasons for discrepancy sampling error (n=5) and interpretation error (n=1)).

Investigating Endoscopic Features of Sessile Serrated Adenomas/Polyps by Using Narrow-Band Imaging with Optical Magnification

Yamada M, Sakamoto T, Otake Y, Nakajima T, Kuchiba A, Taniguchi H, Sekine S, Kushima R, Ramberan H, Parra-Blanco A, Fujii T, Matsuda T, Saito Y.

Gastrointest Endosc. 2015 Jul;82(1):108-17

http://www.ncbi.nlm.nih.gov/pubmed/25840928

This retrospective study investigates endoscopic images obtained by using narrow-band imaging with optical magnification from 242 lesions (124 HPs and 118 SSA/Ps). The images were independently evaluated by 2 endoscopists. The study suggests that dilated and branching vessels (DBVs), defined as thickened capillary vessels with branching that is observed on the surface, is a potentially unique endoscopic feature of a colorectal SSA/P.

Barrett's oesophagus patients with low-grade dysplasia can be accurately risk-stratified after histological review by an expert pathology panel.

Duits LC, Phoa KN, Curvers WL, Ten Kate FJ, Meijer GA, Seldenrijk CA, Offerhaus GJ, Visser M, Meijer SL, Krishnadath KK, Tijssen JG, Mallant-Hent RC, Bergman JJ.

Gut. 2015 May;64(5):700-6.

http://www.ncbi.nlm.nih.gov/pubmed/25034523

This study of 264 Barret's low-grade dysplasia patient with available follow-up examines the effect of expert pathologist review on the diagnosis low-grade dysplasia (LGD). A panel of experts downgraded 73% of community LGD diagnoses to either Barrett's esophagus negative for dysplasia or indefinite for dysplasia. Those cases confirmed by the experts as LGD showed an increased risk of progression to malignancy (9.1% per patient-year, 5-year cumulative high-grade dysplasia/adenocarcinoma incidence of 33.3%). The authors generally recommend expert pathology review of the diagnosis of LGD, as such review identifies a subgroup with a high risk of progression to malignancy.

Immunohistochemical panel for the diagnosis of Hirschsprung's disease using antibodies to MAP2, calretinin, GLUT1 and S100.

Bachmann L, Besendörfer M, Carbon C, Lux P, Agaimy A, Hartmann A, Rau TT.

Histopathology. 2015 Mar;66(4), 467-469.

http://www.ncbi.nlm.nih.gov/pubmed/25123159

Using 69 specimens from 37 patients, a panel approach to workup of Hirschsprung disease is presented (rather than the traditional identification of acetylcholinesterase-positive hypertrophic submucosal nerve fibers). In Hirschsprung's, there is gain of GLUT1 and S100 expression (intensely stained perineurium around nerve fibers by GLUT1 staining and thicker S100-positive nerve fibers) and loss of calretinin and MAP2 (i.e., general lack of calretinin- or MAP2-positive ganglia and neurons in the myenteric and submucosal plexuses). The authors propose a scoring system for Hirschsprung's requiring at least five submucosal HPFs to be

counted with assessment of ganglia/HPF by MAP2 and calretinin, thickness of nerve fibers by S100, and expression of GLUT1 by perineurium, and they provide ranges for normal tissue, transition zone or suspicious for Hirschsprung's, and definite Hirschsprung's.

Inflammatory pseudotumours of the oesophagus – histological and immunohistochemical findings.

Sy K, Parfitt J, Marginean C, Riddell RH, Streutker CJ.

Histopathology. 2015 Jun;66(7):1003-9.

http://www.ncbi.nlm.nih.gov/pubmed/25393329

Case series of 12 inflammatory esophageal pseudotumors occurring with roughly equal sex distribution with a mean patient age of 57.3 years. Characteristic endoscopic findings include distal esophageal nodules or masses. Characteristic microscopic features include inflammation and granulation tissue in the lamina propria, mucosal ulceration and acute inflammation of the epithelium, and markedly atypical pleomorphic stromal cells with prominent nucleoli. 11/11 cases showed uniform vimentin positivity and 2/7 cases showed weak focal smooth muscle actin expression. In similar reports in the literature, there is generally no expression of S100, CD31/34, c-kit, or desmin. The authors found no expression of melanoma or lymphocyte markers, and they urge consideration of inflammatory pseudotumor in cases with stromal atypia in an inflammatory background.

Archives of pathology

Note: The June issue contains a special section from the Houston Society of Clinical Pathologists 55th Annual Spring Symposium in April 2014. Reviews include the topics of esophagitis (Grin A and Streutker CJ), serrated polyps (Yang H-M, Mitchell JM, Sepulveda JL, Sepulveda AR), IgG4 disease in the GI tract (Deshpande V), and GI neuroendocrine tumors (Grin A and Streutker A).

The July issue contains a special section that is part 2 from the Houston Society of Clinical Pathologists 55th Annual Spring Symposium in April 2014. Reviews include the topics Difficult Diagnostic Problems in Pancreatobiliary Neoplasia (Bledsoe JR, Shinagare SA, Deshpande V) and Pathophysiology and Diseases of the Proximal Pathways of the Biliary System (Nakanishi Y, Saxena R).

Goblet Cell Carcinoid Tumor, Mixed Goblet Cell Carcinoid-Adenocarcinoma, and Adenocarcinoma of the Appendix: Comparison of Clinicopathologic Features and Prognosis.

Taggart MW, Abraham SC, Overman MJ, Mansfield PF, Rashid A.

Arch Pathol Lab Med. 2015 Jun;139(6):782-90.

http://www.ncbi.nlm.nih.gov/pubmed/26030247

The behavior of goblet cell carcinoid tumor (GCT) of the appendix is studied (is there a difference in behavior of GCTs with a minor component (less than 50%) of adenocarcinoma versus those with more than 50% adenocarcinoma?). The authors also wanted to evaluate if the prognosis of patients with appendiceal adenocarcinoma with a GCT component was better than that of patients with carcinoma lacking a GCT component. They compare the spectrum of GCTs with poorly differentiated appendiceal adenocarcinomas, which can be confused with GCT or mixed adenoneuroendocrine tumor due to presence of a neuroendocrine component [WHO 2010 identifies mixed adenoneuroendocrine carcinomas arising from GCT but no category is available for mixed tumors in population-based tumor registries, leading to unclear classification.] The authors find in this study of 142 appendiceal tumors that the amount of carcinoma correlates with clinical features and disease stage and is a major predictor of survival. There is no survival difference for patients with poorly differentiated adenocarcinomas with or without GCT. The surgical management of patients with GCT on appendectomy is controversial; some studies recommend further surgery in all cases, while other studies recommend additional surgery for patients with specific features such as positive marging, significant atypia, or increased mitoses (among other features). In this study, 14/30 patients with tumors containing a GCT component had residual disease upon right colectomy, either in the intestinal wall, peri-intestinal soft tissue, and/or lymph nodes, and the authors generally support right colectomy for all patients with GCT-related tumors. The role of systemic chemotherapy for GCT and mixed GCT/adenocarcinoma remains controversial.

HepPar-1 and Arginase-1 Immunohistochemistry in Adenocarcinoma of the Small Intestine and Ampullary Region.

Lagana S, Hsiao S, Bao F, Sepulveda A, Moreira R, Lefkowitch J, Remotti H.

Arch Pathol Lab Med. 2015 Jun;139(6):791-5.

http://www.ncbi.nlm.nih.gov/pubmed/26030248

The authors study 20 nonampullary small bowel adenocarcinomas and 32 ampullary adenocarcinomas (intestinal, pancreatobiliary, and unclassifiable types) to assess patterns of HepPar-1 and arginase-1 expression. HepPar-1 but not arginase-1 tends to be positive in small bowel adenocarcinomas and ampullary adenocarcinomas with intestinal morphology (positive HepPar-1 in 12/20 and 11/15 cases, respectively, whereas arginase-1 was positive only in 1 duodenal adenocarcinoma and 2 ampullary carcinomas). HepPar-1 positivity in metastatic adenocarcinoma with intestinal morphology should suggest an upper GI primary site.

Colestipol granules in the colon: macroscopic and microscopic findings.

Gonzalez RS, Schwartz DA, Shi C.

Histopathology. 2015 Jul;67(1), 141-142.

An abstract is not available; this is correspondence to the editor delineating the endoscopic and biopsy appearance of the bile acid sequestrant colestipol, found in association with polyps in a patient with well-controlled Crohn disease. The patient had a 5-year history of colestipol granule intake, and the rounded granules seen on biopsy appear different from crystalline fragments in patients taking colestipol tablets. Direct evidence of mucosal injury was not seen.

Endoscopic biopsies from gastrointestinal carcinomas and their suitability for molecular analysis: a review of the literature and recommendations for clinical practice and research.

Hale MD, Gotoda T, Hayden JD, Grabsch HI.

Histopathology. 2015 Aug;67(2):147-157.

http://www.ncbi.nlm.nih.gov/pubmed/25431371

This review and meta-analysis outlines recommendations for using endoscopic biopsy specimens from gastrointestinal carcinomas for molecular analysis in clinical and research settings. The authors propose a minimum data set of pathology and endoscopy data to be reported for biomarker research studies (e.g., tumor content estimated as percentage of biopsy area involved, time between tissue removal and formalin fixation if known, etc.).

New insights into the lymphovascular microanatomy of the colon and the risk of metastases in pT1 colorectal cancer obtained with quantitative methods and three-dimensional digital reconstruction.

Brown PJ, Toh E-W, Smith KJE, Jones P, Treanor D, Magee D, Burke D, Quirke P.

Histopathology. 2015 Aug;67(2):167-175.

http://www.ncbi.nlm.nih.gov/pubmed/25557923

This study investigates the paradigm that risk of tumor metastasis in the gut is predicted by depth of invasion and access to deep lymphovascular channels. The authors studied 30 samples of CD31-positive vessels in the deep mucosa and submucosa of normal large bowel wall. Samples were serially sectioned and ultimately a 3D reconstruction was generated to look at number, circumference, and area of vessels (all of which showed significant differences between submucosal layers, $P<0.001$). Blood vessels were most numerous in the mucosa but smaller than in deeper layers, in contrast to their hypothesis that the number and size of blood vessels increases with depth of submucosa. They suggest that tumor metastasis could depend on area or volume of submucosal invasion rather than depth.

Gastric Cancers Missed During Endoscopy in England.

Chadwick G1, Groene O2, Riley S3, Hardwick R4, Crosby T5, Hoare J6, Hanna GB7, Greenaway K8, Cromwell DA2.

Clin Gastroenterol Hepatol. 2015 Jul;13(7):1264-1270.

http://www.ncbi.nlm.nih.gov/pubmed/25645877

The authors perform a population based study, from England, to determine the frequency and correlates of gastric carcinomas missed on upper endoscopy. They retrospectively study a cohort of 2727 individuals with a diagnosis of gastric cancer. Of these, 225 had an endoscopy that was interpreted as negative for carcinoma within the 3 years preceding their diagnosis of gastric cancer, giving a frequency of 8.3% of gastric carcinomas that were apparently missed initially on endoscopy. Of this group of 225 individuals, 102 had endoscopies that failed to detect cancer within 3-12 months of diagnosis. Also of note, a subcohort analysis

of this group of 102 cases with endoscopy within 12 months of diagnosis showed that gastric ulcers were found in 64% of individuals, but had been interpreted as benign. The authors conclude that individuals with suspicious lesions should be re-scoped and undergo another biopsy until either the lesion heals or a diagnosis of cancer is made.

Endoscopic Mucosal Impedance Measurements Correlate With Eosinophilia and Dilation of Intercellular Spaces in Patients With Eosinophilic Esophagitis.

Katzka DA1, Ravi K2, Geno DM2, Smyrk TC3, Iyer PG2, Alexander JA2, Mabary JE4, Camilleri M2, Vaezi MF5.

Clin Gastroenterol Hepatol. 2015 Jul;13(7):1242-1248. Epub 2015 Jan 13.

http://www.ncbi.nlm.nih.gov/pubmed/25592662

The authors study mucosal impedance in a small group of individuals with eosinophilic esophagitis (10 with more than 15 eosinophils per hpf and 10 with less than 15 eosinophils per hpf). Impedance is basically a measure of how easily an electric current can pass through the esophageal tissue. They find that impedance drops as tissue is more spongiotic and has more intraepithelial eosinophils. By statistical analysis, impedance showed significant negative correlation with both eosinophil count and spongiosis. Statistical analysis also showed that about 30% of the variability in eosinophils could be explained by impedance. The authors conclude that esophageal mucosal impedance might be accurate enough to measure disease activity to replace the need for biopsies in patients with eosinophilic esophagitis.

Persistence of Human Papillomavirus, Overexpression of p53, and Outcomes of Patients After Endoscopic Ablation of Barrett's Esophagus.

Rajendra S1, Wang B2, Pavey D3, Sharma P4, Yang T5, Lee CS6, Gupta N7, Ball MJ8, Gill RS9, Wu X5.

Clin Gastroenterol Hepatol. 2015 Jul;13(7):1364-1368.

http://www.ncbi.nlm.nih.gov/pubmed/25460562

The data on HPV's role, if any, in Barrett's esophagus remains controversial. This study examines whether individuals thought to have HPV infection of Barrett's mucosa would clear the virus after ablation therapy. The authors' report that before endoscopic therapy, 15/43 individuals were positive for active HPV. All but two individuals cleared the virus after ablation therapy.

Celiac Disease: Ten Things That Every Gastroenterologist Should Know.

Oxentenko AS, Murray JA.

Clin Gastroenterol Hepatol. 2015 Aug;13(8):1396-404.

http://www.ncbi.nlm.nih.gov/pubmed/25051511

A very nice summary of key clinical points in managing individuals with possible and confirmed celiac disease.

Increased Risk of Esophageal Eosinophilia and Eosinophilic Esophagitis in Patients With Active Celiac Disease on Biopsy.

Jensen ET, Eluri S, Lebwohl B, Genta RM, Dellon ES.

Clin Gastroenterol Hepatol. 2015 Aug;13(8):1426-31.

http://www.ncbi.nlm.nih.gov/pubmed/25724709

The authors' study a very large group of 292,621 patients, 88,517 with both esophageal and duodenal biopsies. Four thousand one hundred one (4.6%) met criteria for eosinophilic esophagitis, while 1203 (1.4%) met criteria for celiac disease. Statistically, the authors found a weak association between celiac disease and eosinophilic esophagitis (OR 1.32 (95% confidence interval, 1.04–1.67). The magnitude of association varied according to the definition of eosinophilic esophagitis, but all definitions showed a weak positive association. In contrast, there was no association between celiac disease and reflux esophagitis or Barrett's esophagus.

UK guidance for the pathological reporting of serrated lesions of the colorectum.

Bateman AC, Shepherd NA.

J Clin Pathol. 2015 Aug;68(8):585-91.

A nice summary of serrated polyps, with a UK perspective on nomenclature.

Hospital autopsy: Endangered or extinct?

J Clin Pathol. 2015 Aug;68(8):601-4.

Turnbull A, Osborn M, Nicholas N.

http://www.ncbi.nlm.nih.gov/pubmed/26076965

Not a purely GI article I know, but an interesting study that documents the decline in UK autopsies, to the point where the authors' conclude that autopsies are on the verge of extinction. While this possible extinction event is unlikely to be equally mourned by all pathologists, it does raise important questions about patient safety and "auditing" hospital care.

Overview of contemporary guidelines in digital pathology: what is available in 2015 and what still needs to be addressed?

Hanna MG, Pantanowitz L, Evans AJ.

J Clin Pathol. 2015 Jul;68(7):499-505.

http://www.ncbi.nlm.nih.gov/pubmed/25979986

The authors' compare the published guidelines for validating and implementing digital pathology systems as published by a number of key organizations, including the Digital Pathology Association, The Royal College of Pathologists, the College of American Pathologists, the Canadian Association of Pathologists, the American Telemedicine Association, and the Society of Toxicologic Pathology. Admittedly, articles comparing guidelines published by professional bureaucracies often makes for grim reading, but the authors do a very nice job of making this material accessible and interesting to the reader.

Utility of Human Papillomavirus Capsid Protein L1 and p16 in the Assessment and Accurate Classification of Anal Squamous Intraepithelial Lesions.

Patil D, Yang B

Am J Clin Pathol. 2015 Jul;144(1):113-21.

http://www.ncbi.nlm.nih.gov/pubmed/26071469

This study looks at the utility of using immunohistochemistry for P16 in combination with HPV capsid protein L1 in the distinction between low grade and high grade squamous intraepithelial lesions in the anal tract. The article states that in the cervix it has been found that the highest production of L1 is in low grade lesions and is nearly absent in high grade lesion. Strong expression of P16 on the other hand is essentially restricted to high grade lesions. 145 anal lesions where reviewed and evaluated and, from the findings, the authors concluded that HPV L1 and P16 expression is mutually exclusive in most anal lesions and can be used to help grade the lesions and stratify risk.

Sequencing of 279 cancer genes in ampullary carcinoma reveals trends relating to histologic subtypes and frequent amplification and overexpression of ERBB2 (HER2).

Hechtman JF, Liu W, Sadowska J, Zhen L, Borsu L1, Arcila ME, Won HH, Shah RH, Berger MF, Vakiani E, Shia J1, Klimstra DS.

Mod Pathol. 2015 Aug;28(8):1123-9.

http://www.ncbi.nlm.nih.gov/pubmed/25975284

The purpose of this study was to look at whether histologic subtype of ampullary carcinoma correlates to genetic mutational and copy number profile in a next-generation sequencing assay that includes 279 cancer related genes (Integrated Mutation Profiling of Actionable Cancer Targets or IMPACT). A study set of 18 pancreatobiliary-type and 14 intestinal-type tumors were evaluated and, among other findings, it was found that KRAS alterations were more common in pancreatobiliary-type and APC mutations were more common in intestinal-type tumors, although the findings did not reach statistical significance. In addition, it was found that ERBB2 was the most frequently amplified gene and the second phase of the study was aimed at validating this observation. Additional ampullary carcinomas, along with the original study set, were evaluated for ERB2 amplification by immunohistochemistry, using gastric cancer scoring criteria, and ISH. Overall 13% (13 of 100 cases) demonstrated amplification by ISH and immunohistochemistry correlated. The authors suggest from this data that patients with ERBB2

amplified ampullary carcinoma may be candidates for targeted therapy and that immunohistochemistry may be a valid screening test.

Journals Reviewed (May and June, 2015 Issues)

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

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Michael Torbenson, MD; Mayo Clinic Rochester