Intestinal Metaplasia is Present in Most if Not All Patients Who Have Undergone Endoscopic Mucosal Resection for Esophageal Adenocarcinoma.
Smith J, Garcia A, Zhang R, DeMeester S, Vallone J, Chandrasoma P.
Am J Surg Pathol 2016 Apr;40(4):537-43

http://www.ncbi.nlm.nih.gov/pubmed/26813746

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 multi-headed microscope by 4 pathologists. Residual intestinal metaplasia (IM) was defined by the presence of goblet cells in non-dysplastic 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.

Predictors of Treatment Failure After Radiofrequency Ablation for Intramucosal Adenocarcinoma in Barrett Esophagus: A Multi-institutional Retrospective Cohort Study.
Agoston AT, Strauss AC, Dulai PS, Hagen CE, Muzikansky A, Fudman DI, Abrams JA, Forcione DG, Jajoo K, Saltzman JR, Odze RD, Lauwers GY, Gordon SR, Lightdale CJ, Rothstein RI, Srivastava A.
Am J Surg Pathol 2016 Apr;40(4):554-62

http://www.ncbi.nlm.nih.gov/pubmed/26645729

The goal of this multicenter retrospective cohort study was to investigate the rate of intramucosal adenocarcinoma (IMC) eradication when using RFA with or without EMR and to identify clinical and pathologic predictors of treatment failure. The study included 78 patients with biopsy-proven IMC between 2006 and 2012 and at least 1 post-ablative surveillance endoscopy with biopsy. All index pathology slides before RFA+/- EMR were re-reviewed by 2 GI pathologists. The extent of IMC was determined by the number of tissue fragments involved with IMC and also by the percentage of columnar metaplastic area involved by IMC. Complete eradication (CE) [absence of IM or Barrett's esophagus associate dysplasia (DYS) on first follow-up endoscopy] was achieved in 86% of patients, and durable eradication (DE) (CE with no recurrence of IMC/DYS until last follow-up) was achieved in 78% of patients, with a mean follow-up of 2 years. Of the 32 patients with >2 years of follow-up, 29 (91%) achieved a DE. The use of EMR before RFA significantly reduced the risk for treatment

failure for IMC/DYS (p=0.001), whereas IMC involving ≥50% of the columnar metaplastic area on index examination significantly increased the risk for treatment failure (p=0.005).

Histologic Features Associated with Columnar-lined Esophagus (CLE) in Distal Esophageal and Gastroesophageal Junction (GEJ) Biopsies From GERD Patients
Soucy G, Onstad L, Vaughan TL, Odze RD.
Am J Surg Pathol 2016 Feb26 [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/ 26927889

The goal of this study was to determine which histologic features in SCJ biopsies from a prospective cohort of community clinic-based patients with GERD symptoms are associated with the presence of CLE and to determine the histologic features of patients with irregular Z-line. The study group consisted of 544 patients (age 20 to 80 y) from 5 gastroenterology clinics from 1997-2000. Previously diagnosed BE patients were excluded. All patients had separate 4-quadrant biopsies. 2216 mucosal biopsies were evaluated in a blinded manner by 1 of the authors. Of the 544 patients, 269 (49.4%) had a normal appearing Z-line, 58(10.7%) had an irregular Z-line and 217(39.9%) had CLE. Histologic findings were correlated with the endoscopic findings (normal Z-line, irregular Z-line, or CLE) and evaluated by logistic regression and receiver operating characteristic analysis. 5 features were associated with CLE: pure mucous glands, multilayered epithelium (ME), presence of goblet cells, ≥50% of crypts with goblet cells and buried columnar epithelium. Pure oxyntic glands were inversely associated with CLE. ME, squamous island (foci of squamous epithelium surrounded on both sides by columnar epithelium) and buried epithelium were significantly increased in biopsies from patients with irregular Z-line compared with those with normal Z-line. In summary, certain histologic features in biopsies of SCJ are associated with presence of CLE and irregularity of Z-line is a condition probably indicative of very early, or ultrashort, segment CLE instead of being a potential anatomic variation of normal.

Do Ancillary Studies Aid Detection and Classification of Barrett Esophagus (BE)? Special article
Panarelli NC, Yantiss RK.
Am J Surg Pathol 2016 Apr 19. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/27096258

This article is a nice review of ancillary tests in BE, including histochemical, immunohistochemical and molecular tests. The value of IHC in diagnosing BE has been investigated (mainly CDX2, MUC2, MUC1, 45M1, and DAS1 stains). All these stain goblet cells, although none is entirely specific. Unfortunately, these stains can decorate nongoblet columnar epithelium, so the staining reaction alone is not reliable. Zhang et al showed that esophageal brushings from patients with IM in biopsy samples were positive for HepPar1. Some authors have proposed a battery of IHC stains to distinguish IM of the esophagus from that of the stomach; CK7, CK20, MUC1, MUC2, MUC6, HepPar1, MUC5AC, and DAS1. Unfortunately,

these attempts have been largely unsuccessful. AMACR and p53 IHC may be of value in evaluating patients with BE for dysplasia. However, given the available data neither AMACR nor p53 is sufficiently sensitive or specific. Several FISH panels are commercially available (most extensively studied are 4-probe panes that include CDKN2A, CMYC, erbB-2 and 20q13.2). Overall, most studies to date are retrospective in nature and thus prospective data establishing their added value are needed before their use is routinely employed in daily practice.

A Model Based on Pathologic Features of Superficial Esophageal Adenocarcinoma Complements Clinical Node Staging in Determining Risk of Metastasis to Lymph Nodes.
Davison JM, Landau MS, Luketich JD, McGrath KM, Foxwell TJ, Landsittel DP, Gibson MK, Nason KS.
Clin Gastroenterol Hepatol. 2016;14(3):369-377.

http://www.ncbi.nlm.nih.gov/pubmed/26515637

The objective of this study was to develop a mathematical model based on specific pathologic findings to estimate the risk of lymph node metastasis in superficial adenocarcinomas of the esophagus. A total of 210 esophagectomy specimens were examined for the presence or absence of tumor size ≥2 cm, high grade features, angiolymphatic involvement and submucosal invasion. High grade features were defined as <50% tubular, papillary or gland forming histology or the presence of extensive tumor budding. These elements were used to develop a logistic model to produce 4 risk categories of associated lymph node metastasis (<5%, 5-10%, 15-20%, >20% risk). A separate cohort of 163 patients were used to validate the subsequent model. Although univariate analysis revealed that the only independent predictor of lymph node metastasis was the presence of high tumor grade, the other pathologic features modified this risk. The ability to risk stratify cases appeared most applicable in cases of T1b disease. Only 2/27 (7.1%) T1b validation cases judged to have a <5% risk of lymph node involvement by the statistical model did in fact have lymph node disease. This was in contrast to T1b cases in which the model yielded a high estimated probability of nodal metastasis, where 30/73 (41%) had confirmed lymph node metastasis.

Incidence and Severity of Prepouch Ileitis: A Distinct Disease Entity or a Manifestation of Refractory Pouchitis?
Samaan MA, de Jong D, Sahami S, Morgan S, Fragkos K, Subramaniam S, Kok K, Makanyanga J, Barnova I, Saravanapavan H, Parisi I, Di Caro S, Vega R, Rahman F, McCartney S, Bloom SL, van den Brink GR, Löwenberg M, Ponsioen CY, Buskens CJ, Tanis PJ, de Buck van Overstraeten A, D'Hoore A, Bemelman WA, D'Haens GR.
Inflamm Bowel Dis. 2016 Mar;22(3):662-8.

http://www.ncbi.nlm.nih.gov/pubmed/26383915

This retrospective study from three European tertiary inflammatory bowel disease referral centers found that pre-pouch ileitis (PI) occurred in 33 of 546 (6%) histologically confirmed ulcerative colitis patients who underwent ileal pouch-anal anastomosis. All of these patients also had pouchitis. Nine of the 33 patients (27%) responded to antibiotic therapy and 18 (54%)

needed escalation to steroids/immunomodulators or anti-tumor necrosis factor agents. Significantly more PI patients required escalation therapy than did patients with pouchitis alone. Patients who developed PI were significantly younger than controls (no pouch inflammation) at the time of UC diagnosis and at the time of colectomy. Backwash ileitis and primary sclerosing cholangitis were also significantly associated with PI. Of note, PI included patients with both endoscopic and histologic evidence of inflammation in the afferent limb, and six patients were excluded due to histologic inflammation alone; patients were also excluded if the afferent limb could not be visualized or was not biopsied. The authors conclude that their findings support the theory that PI is an extension of pouchitis, rather than a type of Crohn's disease.

Treatment and Survival of Small-bowel Adenocarcinoma in the United States: A Comparison With Colon Cancer

Young J, Mongoue-Tchokote, S, Wieghard, N, Motomi M mori, Vaccaro, GM, Sheppard BC, Tsikitis, VL.
Dis Colon Rectum 2016; 59: 306–315

http://www.ncbi.nlm.nih.gov/pubmed/26953989

This retrospective cohort study compared surgical and adjuvant treatment of small-bowel adenocarcinoma (SBA) to colon adenocarcinoma (CA) to determine overall survival and cancer specific survival. 2123 patients with SBA and 248,862 patients with CA were identified from 1992-2010. Patients with duodenal tumors were excluded. The 5 year overall survival rates for SBA were 35% and for CA 51%. Similar proportions of patients underwent surgery and chemotherapy. However, chemotherapy did not improve survival for patients with SBA and those who underwent chemotherapy alone had worse outcomes. Poor outcome predicators were advanced age, African American race, advanced stage, poor differentiation, multiple comorbidities and distal location. Although not well characterized, APC mutations are reported less frequently in SBA. Therefore, distinct pathways may be responsible for the development of neoplasia in the small bowel and colon. The authors conclude that SBA is unique entity, despite some similarities to CA, and should be treated and managed as such.

Large Sessile Serrated Polyps Can Be Safely and Effectively Removed by Endoscopic Mucosal Resection.

Rao AK, Soetikno R, Raju GS, Lum P, Rouse RV, Sato T, Titzer-Schwarzl D, Aisenberg J, Kaltenbach T.
Clin Gastroenterol Hepatol. 2016;14(4):568-74.

http://www.ncbi.nlm.nih.gov/pubmed/26499926

While this retrospective analysis largely focused on clinical and endoscopic characteristics and outcomes, it may influence the types of specimens institutions should expect to receive in the future. This study aimed to assess the efficacy and safety of inject-and-cut endoscopic mucosal resections (EMR) of sessile serrated polyps (SSP) measuring greater than 10 mm. Of the 138 patients who had a qualifying lesion (proximal to the descending colon, size greater than 10 mm,

pathologic diagnosis of SSP, removal via EMR) only 5 had local recurrences (3.6%). Recurrences were identified after a median follow-up of 17.8 months (±15.4 months) and were typically small in size (median size of 4 mm). Although only 1.2% of SSPs contained dysplasia on the initial EMR, 20% (1 of 5) of recurrent lesions had this feature on the original resection. No recurrent lesions subsequently developed dysplasia if this feature was not present on initial EMR. No adverse safety events were noted. The authors concluded that inject-and-cut EMR is an effective and safe method for the resection of large SSPs.

Clinical and endoscopic predictors of cytological dysplasia or cancer in a prospective multicentre study of large sessile serrated adenomas/polyps.
Burgess NG, Pellise M, Nanda KS, Hourigan LF, Zanati SA, Brown GJ, Singh R, Williams SJ, Raftopoulos SC, Ormonde D, Moss A, Byth K, P'Ng H, McLeod D, Bourke MJ.
Gut. 2016 Mar;65(3):437-46.

http://www.ncbi.nlm.nih.gov/pubmed/25731869

In comparison to conventional adenomas, sessile serrated adenomas/polyps are difficult to detect endoscopically. 268 SSA/Ps at least 20 mm in size were removed via EMR (overall, 13.4% of patients with colonic lesions were found to have SSA/Ps). 32.4% of these SSA/Ps harbored dysplasia, associated with increasing lesion size, increasing age, adenomatous pit pattern, and any Paris 0-Is or nodular component. Prediction of dysplasia was poorer if the lesion endoscopically resembled a conventional adenoma.

Serrated tubulovillous adenoma of the large intestine.
Bettington M, Walker N, Rosty C, Brown I, Clouston A, McKeone 1, Pearson SA, Klein K, Leggett B, Whitehall V.
Histopathology. 2016 Mar;68(4):578-87.

http://www.ncbi.nlm.nih.gov/pubmed/26212352

A subset of tubulovillous adenomas with prominent serration (serrated TVAs) were analyzed as a distinct group from conventional TVAs and traditional serrated adenomas. 48 serrated TVAs, 50 conventional TVAs, and 66 BRAF wild-type TSAs were analyzed via clinic-pathologic assessment, BRAF and KRAS mutation status, CpG island methylation, MGMT methylation, and immunohistochemical analysis for MLH1, p16, p53, beta-catenin, Ki-67, CK7, and CK20. Compared to conventional TVAs, serrated TVAs are larger, more often proximal, histologically more advanced, contain more CpG island methylation, and show more frequent KRAS mutation. Compared to TSAs, serrated TVAs are more often proximal, show less CpG island methylation, more frequent MGMT methylation, and more frequent nuclear beta-catenin staining. Serrated TVAs are a precursor of KRAS mutated, microsatellite-stable CRC.

Diagnostic Challenges Caused by Endoscopic Biopsy of Colonic Polyps: A Systematic Evaluation of Epithelial Misplacement With Review of Problematic Polyps From the Bowel Cancer Screening Program, United Kingdom.
Panarelli NC, Somarathna T, Samowitz WS, Kornacki S, Sanders SA, Novelli MR, Shepherd NA, Yantiss RK.
Am J Surg Pathol 2016 Mar 11. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/26975041

The aim of this study was to describe the spectrum of histologic features in adenomas with epithelial misplacement due to endoscopic manipulation. The clinical and morphologic features of 16 polyps with biopsy-related misplaced epithelium (all of them with dysplastic epithelium in the submucosa) were compared with 10 adenomas with pseudoinvasion and 10 adenomas with invasive adenoca. Ki-67 and p53 IHC was performed in all cases. From the 16 polyps, (12 men and 4 women), 69% of these polyps were located proximal to the splenic flexure. All of the study polyps were interpreted to be adenomas on prior sampling. These lesions were large and most (81%) had a sessile appearance. Endoscopic manipulations produced 2 morphologic patterns of misplacement: circumscribed (5; 31%) and ill-defined aggregates of epithelium in submucosa (11;69%). Features that aid distinction of biopsy-related epithelial misplacement from invasive adenoca included the presence of lamina propria (88%) and muscularis mucosae (44%) around the submucosal epithelium, low-grade cytologic features (none of the 16 polyps had HGD in the submucosal epithelium), and concomitant nondysplastic epithelium in submucosa (38%). Misplaced epithelium was associated with extruded mucin (75%) and tattoo pigment (63%). All of the study polyps showed a similar patchy distribution of Ki67 in the misplaced epithelium compared with surface adenoma and none showed strong p53 staining in submucosal epithelium. Inv. adenoca showed malignant cytology and desmoplasia; most (70%) lacked features of trauma. Ki67 and p53 showed increased staining for 1 or both markers.

Interlaboratory Variability in the Histologic Grading of Colorectal Adenocarcinomas in a Nationwide Cohort.
Kuijpers CC, Sluijter CE, von der Thüsen JH, Grünberg K, van Oijen MG, van Diest PJ, Jiwa M, Nagtegaal ID, Overbeek LI, Willems SM.
Am J Surg Pathol. 2016 Mar 11. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/26975039

This study investigates the variability in the histologic grading of CRC. Using data extracted from PALGA (the nationwide network and registry of histopathology and cytopathology in Netherlands), all synoptically reported CRC resections from 2010-2013 were identified. The overall nationwide proportion of poorly differentiated (PD) adenocarcinomas (adenoca) was determined and compared between 35 laboratories by univariable and multivariable logistic regression analyses. Reports of patients who received neoadjuvant treatment were excluded. 11,719 resections (11,681 patients) were included, of which 1427 (12.2%) were PD (range in 35 laboratories: 5.0% to 33.2%). After adjustment for case mix, 4 (11%) laboratories still reported a significantly lower (n=2) or higher (n=2) proportion of PD adenoca compared with the reference laboratory. 7 of 8 investigated laboratories showed considerable intralaboratory variation

between pathologists as well. In the subgroup of 2812 patients who could have been eligible for adjuvant chemotherapy solely based on differentiation (stage 2 colon cancer without other high-risk factors), 258 (9.2%) were PD (range between laboratories: 0% to 22.7%). In conclusion, there is considerable inter/intra-laboratory variation in the histologic grading of CRC.

Adverse histological features in malignant colorectal polyps: a contemporary series of 239 cases.
Brown IS, Bettington ML, Bettington A, Miller G, Rosty C
J Clin Pathol. 2016;69:292–299

http://www.ncbi.nlm.nih.gov/pubmed/26424814

This retrospective study examined the clinical and histologic features of 239 "malignant colorectal polyps" (MCP's) and 140 colectomy specimens performed as subsequent treatment for high-risk MCP's. The purpose of this review was to define adverse histologic features associated with high-risk for residual disease, either within the colonic wall or regional lymph nodes. Eleven histologic features were reviewed: 1)Polyp configuration 2)Polyp size 3)Invasive tumor size 4) Haggitt level 5) Kikuchi level 6) Vascular space invasion 7) Tumor differentiation 8) Cribriform architectural pattern 9) Distance to deep resection margin 10) Presence of tumor budding and focal dedifferentiation 11) Presence and type of any pre-existing lesion. The features associated with the highest risk of residual disease were poor tumor differentiation and increased tumor size. The authors concluded that surgical resection should be recommended if ≥2 of the adverse features were present and may be warranted if only one feature is identified. They also stated that a positive margin may only require local resection if none of the above adverse histologic features were present.

Prevalence of Advanced Histological Features and Synchronous Neoplasia in Patients with Flat Adenomas.
Naravadi V, Gupta N, Early D, Jonnalagadda S, Wani SB, Gaddam S, Sharma P, Edmundowicz SA, Bansal A, Rastogi A.
Gastrointest Endosc. 2016 Apr;83(4):795-9

http://www.ncbi.nlm.nih.gov/pubmed/26341856

The aims of this study were to determine whether flat adenomas harbor advanced histology more than polypoid adenomas and whether the presence of flat adenomas is an independent predictor of synchronous adenomas. This was a post hoc analysis of data from 3 prospective trials investigating the impact of novel imaging techniques on polyp detection and/or polyp histology prediction. The studies were conducted at the VA Medical Center in 3 different cities between 2008 and 2013. A total of 2931 polyps were removed in 1340 patients. Of the 1911 adenomas (65.2%), 293 (15.3%) were flat and 1618 (84.7%) were polypoid. The prevalence of advanced histology did not differ between flat and polypoid adenomas (1.4% vs 3.1%). Multivariate analysis confirmed that the presence of at least 1 flat adenoma was a predictor of the presence of a large adenoma ($P < .01$), advanced adenoma ($P < .01$), and 3 or more adenomas ($P < .01$). This

study has some limitations, including the majority of subjects being veterans who were white males and the study population underwent colonoscopy with different methods.

CA11-19: a Tumor Marker for the Detection of Colorectal Cancer (CRC)
Overholt BF, Wheeler DJ, Jordan T, Fritsche HA.
Gastrointest Endosc 2016 Mar;83:545-551

http://www.ncbi.nlm.nih.gov/pubmed/26318832

The goal of this study was to evaluate the diagnostic accuracy on an enzyme-linked immunosorbent assay for the CA11-19 serologic tumor antigen in the detection of CRC. Serum specimens were obtained from 522 colonoscopy-confirmed subjects, ranging from 20 to 87 years of age, with an average of 56.6. Specimens were blind coded. Subjects were assigned to 1 of 5 groups: (1) normal, (2) hyperplastic polyps, (3) other benign GI disease, (4) adenomatous polyps and (5) CRC. Group 3 included subjects with hemorrhoids, diverticulosis, GI bleeds, positive fecal occult blood test results, and those who reported a change in bowel habits. When a cutoff of 6.4 units/mL for normal was used, the CA11-19 level was elevated in 128 of 131 of CRC subjects. Normal levels were found in 87% of normal subjects (90/103) and 83% of those with benign GI diseases (185/223). CA11-19 showed a sensitivity of 98% and specificity of 84% for the diagnosis of CRC.

Colonoscopy Surveillance After Colorectal Cancer Resection: Recommendations of the US Multi-Society Task Force on Colorectal Cancer (USMSTF)
Kahi CJ, Boland RC, Dominitz JA, Giardiello FM, Johnson DA, Kaltenbach T, Lieberman D, Levin TR, Robertson DJ, Rex DK.
Gastrointest Endosc. 2016 Mar;83(3):489-498

http://www.ncbi.nlm.nih.gov/pubmed/26802191

This document updates the USMSTF 2006 consensus guidelines and focuses on the role of colonoscopy in patients after CRC resection. The evidence shows that postoperative colonoscopy has no effect on cancer-specific death. The role of postoperative colonoscopy is confined primarily to perioperative clearing and prevention of metachronous colon cancer. It is recommended that CRC patients undergo high-quality perioperative clearing with colonoscopy. The procedure should be performed preoperatively, or within a 3- to 6-month interval after surgery in case of obstructive CRC. It was recommended that patients who have undergone curative resection receive their first surveillance colonoscopy 1 year after surgery (or 1 year after the clearing preoperative colonoscopy). The interval to the next colonoscopy should be 3 years and then 5 years. Subsequent colonoscopies should occur at 5-year intervals. The 2006 USMSTF guidelines suggested sigmoidoscopy or rectal EUS every 3 to 6 months for the first 2 or 3 years after surgery, in addition to colonoscopic surveillance for metachronous neoplasms, and this suggestion was maintained in the current document. In patients with obstructive CRC precluding complete colonoscopy, computed tomographic colonography is recommended as the best alternative to exclude synchronous neoplasms. Finally, there is insufficient evidence to recommend routine use of FIT or fecal DNA for surveillance after CRC resection.

The expression and prognostic significance of bcl-2-associated transcription factor 1 in rectal cancer following neoadjuvant therapy.
Brown GT, Cash B, Alnabulsi A, Samuel LM, Murray GI.
Histopathology. 2016 Mar;68(4):556-66.

http://www.ncbi.nlm.nih.gov/pubmed/26183150

bcl-2 associated transcription factor 1 is a nuclear protein that binds bcl-related proteins to induce apoptosis and autophagy. Microarray analysis of 248 rectal cancers, 76 lymph node metastases, and 73 non-neoplastic rectal mucosal samples showed increased cytoplasmic and nuclear BCLAF1 expression post-neoadjuvant therapy. Negative and weak nuclear BCLAF1 expression are both associated with poor prognosis.

Pathologic Complete Response in Rectal Cancer: Can We Detect It? Lessons Learned From a Proposed Randomized Trial of Watch-and-Wait Treatment of Rectal Cancer
Nahas SC, Nahas CSR, Marques CFS, Ribeiro U, Cotti GC, Imperiale AR, Capareli FC, Chen ATC, Hoff PM, Cecconello I.
Dis Colon Rectum 2016; 59: 255–263

http://www.ncbi.nlm.nih.gov/pubmed/26953983

This prospective study sought to determine if patients undergoing neoadjuvant chemoradiation and surgery for rectal adenocarcinoma could be identified accurately for a complete clinical response (cCR). To this end the authors compared clinical and radiologic criteria to pathologic findings in patients who either underwent total mesorectal excision (TME) or observation only (Watch-and-Wait). Patients were staged and restaged by digital examination, colonoscopy, pelvic MRI, and chest and abdominal CT scans. All of the patients who did not achieve a cCR by 8 weeks were submitted to TME. Patients who did achieve cCR were randomly assigned 1:1 to TME in 2 weeks or observation. Out of 160 consecutive patients only 6 were considered complete responders. 2 were selected for surgery and 4 were observed. Of those 4, 3 maintained cCR at 12 months and 1 was found to have local recurrence and underwent TME. Of the 112 non-cCR patients who underwent immediate TME, 18 had a pathologic complete response (pCR) upon resection. The sensitivity of identifying patients with a cCR in this study was 18.2%, lower than previously reported studies. The authors state several limiting factors for their inability to accurately correlate cCR with pCR. Therefore they recommend identifying better methods for assessing patients for cCR before employing a watch-and-wait tactic for patients with rectal cancer.

SATB2 Expression Distinguishes Ovarian Metastases of Colorectal and Appendiceal Origin from Primary Ovarian Tumors of Mucinous or Endometrioid Type

Moh M, Krings G, Ates D, Aysal A, Kim GE, Rabban JT

Am J Surg Pathol. 2016 Mar;40(3):419-32

http://www.ncbi.nlm.nih.gov/pubmed/26551622

SATB2, a transcriptional regulator involved in osteoblastic and neuronal differentiation, is a sensitive marker for normal colorectal (CRC) epithelium and CRC adenocarcinoma (adenoca). The purpose of this study was to test SATB2 as a possible marker in distinguishing ovarian metastases of CRC adenoca from primary ovarian mucinous tumors and from primary ovarian endometrioid tumors. Among primary ovarian tumors, SATB2 staining was observed in 0/22 mucinous cystadenomas that lacked a component of mature teratoma, 4/12 mucinous cystadenomas with mature teratoma, 1/60 mucinous borderline tumors, 0/17 mucinous adenoca, 0/3 endometrioid borderline tumors, and 0/72 endometrioid adenoca. Among ovarian metastases, SATB2 staining was observed in 24/32 (75%) colorectal adenoca, 8/10 (80%) low-grade appendiceal mucinous neoplasms and 4/4 (100%) high-grade appendiceal adenoca. No SATB2 staining was observed in any ovarian metastasis of pancreatic, gastric, gallbladder, or endocervical origin. Evaluation of primary extraovarian tumors showed the highest incidences of SATB2 staining among primary CRC adenoca (71%), primary appendiceal low-grade mucinous neoplasms (100%), and primary appendiceal high-grade adenoca (100%). None of the primary pancreatic or gastric adenoca showed any SATB2 staining. In a subset of tumors for which CK7, CK20, and CDX2 were available, SATB2 was never positive in any tumor of any origin that was CK7+CK20-CDX2-. Among tumors that co-expressed all 3 markers (CK7+CK20+CDX2+), 6/7 SATB2+ tumors were of CRC or appendiceal origin, and 1/7 was a primary ovarian borderline tumor. Probably, the most helpful role for SATB2 may be in ovarian mucinous tumors that co-express all 3 traditional markers as that phenotype can be displayed by tumor of either ovarian or extraovarian origin. In that setting SATB2 expression was highly predictive of a CRC or appendiceal origin.

A Practical Approach to the Evaluation of Gastrointestinal Tract Carcinomas for Lynch Syndrome.
Pai RK, Pai RK.
Am J Surg Pathol 2016 Apr;40(4):17-34

http://www.ncbi.nlm.nih.gov/pubmed/26974895

This excellent special article reviews evolving concepts in Lynch syndrome diagnostics, including the growing clinical problem of individuals with Lynch-like syndrome, constitutional MMR protein deficiency, and the importance of MMR protein expression patterns in tumors in informing strategies for germline MMR and EPCAM gene-sequencing. It also provides algorithms for detecting patients at risk for Lynch syndrome in the setting of colorectal carcinoma. It reviews the screening recommendations for Lynch syndrome on other gastrointestinal tract tumors (stomach, small bowel, ampulla and appendix). Screening for Lynch syndrome in special circumstances (such as in colorectal adenomas, inflammatory bowel disease and synchronous intestinal neoplasia) is also covered in this article. It finalizes with the emerging theranostic implications of MMR deficiency in gastrointestinal tract carcinoma, including the

latest clinical trial investigating MSI status and response to monoclonal antibodies blocking the PD-1 pathway.

Significance of Paneth cells in Histologically Unremarkable Rectal Mucosa
Pezhouh MK, Cheng E, Weinberg AG, Park JY.
Am J Surg Pathol 2016 Feb 19 [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/26900817

This study examined the frequency and clinical correlates of rectal Paneth cells in 245 rectal biopsies (195 endoscopic pinch biopsies and 52 rectal suction biopsies) with normal endoscopic and histologic evaluations. The biopsies were obtained from patients between the ages of 2 weeks to 20 years in a pediatric tertiary care facility from 2010 to 2011. Mean follow-up was 2.1 years. Paneth cells were present in 42 cases (17.1%). Only 1 out of 42 patients with rectal Paneth cells (this patient had 1 Paneth cell in 100 crypts) was diagnosed with Crohn disease 2 years after the initial rectal biopsy. The number of Paneth cells per 100 crypts ranged from 1 to 14. Paneth cells were identified more often in suction biopsies than pinch biopsies (40.4% vs. 10.9%, $p<0.0001$). The finding of Paneth cells was associated with young age. Constipation was the most common presenting symptom in patients with rectal Paneth cells. In the pinch biopsies, Paneth cell cases still had a higher rate of constipation (28.6% vs. 7.6%, $p=0.002$). Overall, the identification of isolated Paneth cells in a histologically unremarkable rectum is histologically nonspecific and in most cases may be regarded as clinically insignificant. In this pediatric group, isolated Paneth cells in the rectum were associated with young age and clinical constipation and did not appear to have an association with current or future development of IBD.

Papillary Immature Metaplasia of the Anal Canal: A Low-grade Lesion That Can Mimic a High-grade Lesion

Roberts JM, Cornall AM, Ekman D, Law C, Poynten IM, Jin F, Hillman RJ, Templeton DJ, Tabrizi SN, Garland SM, Thurloe JK, Grulich AE, Farnsworth A
Am J Surg Pathol.2016 Mar;40(3):348-353

http://www.ncbi.nlm.nih.gov/pubmed/26551619

This case series provides the first analysis of anal papillary immature metaplasia (PIM) of the anal canal in a longitudinal cohort study of 518 homosexual men aged ≥35 y/o both HIV+ and HIV- from Sidney community based settings. All cytologic and histologic specimens were referred to a specialist anogenital unit with 3 pathologists. PIM previously described in the cervix is a subset of exophytic low-grade squamous intraepithelial lesion (eLSIL) composed of slender papillae with fibrovascular cores. The surface of each papilla is covered by a layer of immature and uniform metaplastic cells with little to no maturation. In this study, a total of 15 cases of PIM were identified from 12 men (5 HIV+), aged 40 to 61. A warty or papillary gross appearance was always noted. PIM was characterized by closed proximity to conventional eLSIL (14 out of 15 cases show admixture of both) and negativity for p16 expression. HPV genotyping revealed the presence of a single low-risk HPV (either 6 in 8/12 cases or 11 in 4/12 cases). The

clinical significance of recognizing PIM lies in preventing misdiagnosis as HSIL (both cytologically and histologically) due to the morphologic immaturity of the cell population. Cytologic findings in the ThinPrep vial did not predict a diagnosis of PIM on biopsy. Although there is no evidence that anal or cervical PIM are premalignant conditions, there are reports of anal SCC associated with HPV 6 and 11.

Basaloid Squamous Cell Carcinoma of the Anus Revisited.
Graham RP, Arnold CA, Naini BV, Lam-Himlin DM.
Am J Surg Pathol 2016 Mar;40(3):354-60

http://www.ncbi.nlm.nih.gov/pubmed/26866355

This retrospective study evaluated cases originally diagnosed as basaloid SCC, cloacogenic carcinoma (Ca) or poorly differentiated SCC from 1994 to 2013 at 3 different institutions. 10 (27%) of these 37 cases were misclassified (reclassified as BCC of the perianal skin (n=6), malignant melanoma (n=2) and neuroendocrine ca (large cell type)(n=2). Basaloid SCC (n=27) had a female/male ratio of 4:1. Histologic material included 19 resections, 6 biopsies and 2 liver metastases. Morphologically, basaloid SCC could be categorized into 4 groups: transitional ca like (n=10, resembling urothelial ca), basaloid with peripheral palisade (n=13), adenoid cystic ca-like (n=3) and mucinous microcystic (n=1, admixture of clear and eosinophilic neoplastic cells, resembles mucoepidermoid ca). In 19 cases the histologic patterns were pure. IHC showed positivity of CK5/6 (27/27), p40 (26/27) and strong and diffuse p16 (27/27). SOX2 was positive in 18/22 (82%) of cases and 6/18 with focal staining (<50% of cells). The tumor showing mucinous microcystic morphology was positive for mucicarmine and negative for MAML2 FISH (seen in 80% of mucoepidermoid ca of salivary glands). High-risk HPV DNA in situ hybridization was positive in all cases. Clinical follow-up was available on 60% of cases; 9 patients (53%) developed local recurrence or metastasis and 5(29%) died of disease.

Clinicopathologic Spectrum of Gastrointestinal T-cell Lymphoma (GITCL): Reappraisal Based on T-cell Receptor Immunophenotypes.
Tanaka T, Yamamoto H, Elsayed AA, Satou A, Asano N, Kohno K, Kinoshita T, Niwa Y, Goto H, Nakamura S, Kato S.
Am J Surg Pathol 2016 Mar 11. [Epub ahead of print]

http://www.ncbi.nlm.nih.gov/pubmed/26975035

This study conducted a retrospective clinicopathologic analysis of 42-cases of GITCL especially addressing their TCR phenotype, including TCRβ and γ expression. The cases were obtained from Nagoya University Hospital and 38 collaborating hospitals in Japan. The criteria for inclusion were positivity for at least 1 of the T-cell antigens (CD3, CD4, CD5, CD8, TCRβ and γ) determined either by IHC or flow cytometry and the absence of B-cell markers. EBER+ or ALK+ cases were excluded. No patient had a history of celiac disease. 42 cases of GITCL were

identified. 9 (21%) of 42 GITCL were + for TCRγ protein expression. Of note, 5 of these 9 patients with TCR β+. 24 patients (57%) were negative for TCR β and γ. TCR β positivity without TCR γ expression was seen in 9 GITCL patients (21%). There was no significant difference in clinicopathologic parameters between TCR γ+β- and γ+ β+. Compared with TCR β+γ- or β-γ-, TCRγ+ cases were characterized by exclusive involvement of intestinal sites but not of stomach. Notably, TCRγ positivity was an independent unfavorable prognostic factor ($p<0.001$) and all of the TCR γ+ cases treated with chemotherapy were refractory to the initial treatment. Multivariate analysis showed that thrombocytopenia, TCR γ positivity and presence of GI tract perforation were adverse prognostic factors. Considering these results, the authors support that TCR γ+ GITCL appear to constitute a distinct disease entity.

SWI/SNF Complex-deficient Undifferentiated/Rhabdoid Carcinomas of the Gastrointestinal Tract: A Series of 13 Cases Highlighting Mutually Exclusive Loss of SMARCA4 and SMARCA2 and Frequent Co-inactivation of SMARCB1 and SMARCA2

Agaimy A, Daum O, Märkl B, Lichtmannegger I, Michal M, Hartmann A
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http://www.ncbi.nlm.nih.gov/pubmed/26551623

The switch/sucrose-non fermenting (SWI/SNF) complex is a group of interdependent proteins involved in chromatin remodeling. In this study, 13 cases of undifferentiated GI tract carcinomas were tested for expression of SMARCB1(INI1), SMARCA2, SMARCA4, and ARID1A and for the MMR proteins by IHC. Cases with MMR loss were subjected to molecular MSI testing by PCR. Patients included 12 men and 1 woman aged 32 to 81 y. Site of origin was colon (5), small bowel (2), stomach (3), small+large intestine (1), small intestine+ampulla of Vater (1) and EG junction (1). All tumors presented as large exophytic ulcerated and fungating transmural masses with highly anaplastic large cells with variable rhabdoid features and frequent pleomorphic giant cells. A glandular component was observed in 1 case. All but 1 case showed strong vimentin positivity and variable reactivity for panCK. The panCK negative case expressed EMA. In total 12/13 cases showed loss of at least 1 SWI/SNF component. Loss of SMARCB1 (5/13), SMARCA2 (10/13), SMARCA4 (2/13) and ARID1A (2/13) was observed either in combination or isolated. All SMARCB1-deficient tumors showed loss of SMARCA2. Additional 5 tumors showed isolated loss of SMARCA2. Two MMR deficient (MLH1/PMS2) MSI-H cases showed concurrent loss of SMARCB1, SMARCA2 and (1 of them) ARID1A. The SWI/SNF status did not seem to correlate with anatomic sites. Frequent loss of SMARCA2 possibly points to fragility of the SWI/SNF complex as a consequence of lost core subunit SMARCB1. Co-inactivation of SMARCB1 and SMARCA4 or of SMARCA2 and SMARCA4 was not observed.

Cytologic Categorization of Pancreatic Neoplastic Mucinous Cysts With an Assessment of the Risk of Malignancy: A Retrospective Study Based on the Papanicolaou Society of Cytopathology Guidelines
Smith AL, Abdul-Karim FW, Goyal A.
Cancer Cytopathol. 2016 Apr;124(4):285-93

http://www.ncbi.nlm.nih.gov/pubmed/26618476

This study was aimed at using the Pap Society guidelines to categorize pancreatic neoplastic mucinous cysts retrospectively and to stratify the risk of malignancy on the basis of such a categorization. A retrospective database search was performed from 2000 to 2014 for resections of pancreatic mucinous neoplasms (ie, IPMNs and MCNs). Only cases with EUS-FNA within the year preceding the resection were included. The cytology slides from cases that had been initially categorized as negative or nondiagnostic were not reviewed. For cases with atypical, suspicious, or positive cytology diagnoses, the FNA slides were reviewed, blinded to the histologic diagnoses, and were categorized according to the Pap Society guidelines. 127 cases were retrieved (81 IPMNs and 46 MCNs). The sensitivity of cytology for the diagnosis of neoplastic mucinous cysts was 76.4%. The sensitivity, specificity, and accuracy of cytology for the diagnosis of malignancy (high-grade dysplasia or worse) were 48.3%, 94.9%, and 84.3%, respectively. The risk of malignancy was 17.4% for the nondiagnostic category, 0% for the negative category, 13% for the neoplastic category, 63.6% for the atypical category, 80% for the suspicious category, and 100% for a positive diagnosis, confirming that the Pap Society guidelines result in a accurate categorization and that the diagnostic categories (from negative to positive) are associated with an increasing risk of malignancy.

Somatic Mutations of PI3K in Early and Advanced Gallbladder Cancer Additional Options for an Orphan Cancer
Roa I, Garcia H, Game A, de Toro G, de Aretxabala X, Javle M.
J Mol Diagn. 2016 May;18(3):388-94.

http://www.ncbi.nlm.nih.gov/pubmed/26947513

This study used direct sequencing to identify mutations in exons 9 and 20 of the gene PIK3CA (phosphatidylinositol 3-kinase, PI3K) in gallbladder cancer specimens. PI3K is a family of protein kinases that have multiple pathways involved in key cellular functions such as proliferation, cell survival and growth. PIK3CA encodes one of the catalytic subunits critical in downstream PI3K signaling and is the only PIK3 gene reported to have somatic mutations relevant to human neoplasia. Mutations within exons 9 and 20 of PIK3CA result in constitutive activation of downstream signals resulting in aberrant PI3K signaling. The authors hypothesize that mutations in PIK3CA may be important early events as they were found in both early and advanced cancers. As selective inhibitors targeting aberrant PI3K signaling are in use and underdevelopment, identifying patients with GBC who harbor PIK3CA mutations may have important therapeutic implications as well.

Journals Reviewed (Mar and April 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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